NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab in combination for untreated, locally recurrent inoperable or metastatic, triple negative breast cancer [ID1546]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab in combination for untreated, locally recurrent inoperable or metastatic, triple negative breast cancer [ID1546]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from MSD
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submissions** from:
   a. Breast Cancer Now
4. **Evidence Review Group report** prepared by ScHARR
5. **Evidence Review Group report – factual accuracy check**
6. **Technical engagement response from company**
7. **Evidence Review Group critique of company response to technical engagement** prepared by ScHARR
   a. Additional ERG document

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab in combination for untreated, locally advanced or metastatic, triple negative breast cancer ID1546

Document B

Company evidence submission

January 2021

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Pembrolizumab 1L mTNBC ID1546 - Document B Final [REDACTED] 11-1-21	Vw.0	No	17-02-2021

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Tables and figures

Tables

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Abbreviations

AE	Adverse events
AIC	Akaike Information Criteria
ASaT	All Subjects as Treated
BC	Breast Cancer
BIC	Bayesian Information Criteria
BICR	Blinded Independent Review Committee
CAA	Commercial Access Agreement
CI	Confidence Interval
CIV	Central imaging vendor
CNS	Central Nervous System
CPS	Combined Positive Score
CR	Complete Response
CrI	Credible interval
CSR	Clinical Study Report
DCR	Disease Control Rate
DoR	Duration of Response
ECOG	Easter Co-operative Oncology Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D-3L	EuroQol 5-dimension 3 level questionnaire
FAS	Full Analysis Set
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
HSUV	Health state utility value
ICER	Incremental cost-effectiveness ratio
ICH	Immunohistochemistry
IMAE	Immune-Medicate AEs
IPD	Induvial patient level data
ITC	Indirect treatment comparison
ITT	Intention to Treat
KM	Kaplan-Meier
LY	Life years
MA	Marketing Authorisation
MAIC	Matching adjusted indirect comparison
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
ORR	Objective Response Rate
OS	Overall Survival
PAS	Patient Access Scheme
PD-1	Programmed cell Death 1 (receptor)

PD-L1	Programmed Death Ligand 1
PD-L2	Programmed Death receptor Ligand-2
PFS	Progression Free Survival
PLD	Patient level data
PPS	Post-progression survival
PR	Partial Response
PRO	Patient Reported Outcome
PSA	Probabilistic sensitivity analysis
Q3W	Every 3 weeks
QALY	Quality adjusted life year
QLQ-C30	Quality of life questionnaire
QoL	Quality of Life
r/m	recurrent / metastatic disease
RCT	Randomised Controlled Trial
RECIST 1.1.	Response Evaluation Criteria on Solid Tumours, version 1.1
RoB	Risk of Bias
SD	Stable Disease
SLR	Systematic Literature Review
SmPC	Summary of Product Characteristics
SoC	Standard of Care
TNBC	Triple Negative Breast Cancer
TOT	Time on Treatment
TPS	Tumour Proportion Score
TTO	Time-trade-off
VAS	Visual analogue scale
WTP	Willingness to pay threshold

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The anticipated marketing authorisation for this indication is: "[redacted] The submission covers part of the anticipated indication.

A summary of the National Institute for Health and Care Excellence (NICE) decision problem can be found in

Table 1.The majority of evidence presented in this submission will focus on the population of patients diagnosed with TNBC whose tumours express PD-L1 CPS ≥10. Subgroup analysis of those treated with pembrolizumab in combination with taxanes (nab-paclitaxel or paclitaxel) are also included.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with previously untreated locally recurrent inoperable or metastatic, triple negative breast cancer.	[redacted]	The population described by MSD reflects the draft licence indication wording.
Intervention	Pembrolizumab (with chemotherapy)	Pembrolizumab (KEYRTUDA ®) in combination with taxanes (nab-paclitaxel or paclitaxel).	To be reflective of KEYNOTE-355 clinical data and to reflect the UK standard of care.
Comparator(s)	• Anthracycline based chemotherapy • Single agent taxane chemotherapy regimens (docetaxel or paclitaxel) For people whose tumours have PD-L1 expression ≥1% • Atezolizumab in combination with nab-paclitaxel	• Paclitaxel • Docetaxel For people whose tumours express PD L1 CPS ≥10 (using the Dako PD-L1 IHC 22C3 pharmDx Assay) • Atezolizumab in combination with nab-paclitaxel	To align with current standard of care in the UK

Outcomes	• overall survival (OS) • progression-free survival (PFS) • response rate (RR) • adverse effects of treatment (AEs) • health-related quality of life (HRQoL)	• overall survival (OS) • progression-free survival (PFS) • response rate (RR) • adverse effects of treatment (AEs) • health-related quality of life (HRQoL) • Duration of response (DoR)	Inclusion of duration of response to reflect clinical trial outcomes and relevant for decision making

B.1.2 Description of the technology being appraised

The draft summary of product characteristics (SmPC) has been included in Appendix C; the European Public Assessment Report (EPAR) was not available at the time of the submission.

The technology being appraised, pembrolizumab, is described in Table 2 below.

Table 2: Technology being appraised

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Mechanism of action	Pembrolizumab (KEYTRUDA®) is a monoclonal antibody (mAb) of the IgG4/kappa isotype designed to exert dual ligand blockade of the PD-1 pathway by directly blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2 which appear on antigen-presenting or tumour cells. By binding to the PD-1 receptor and blocking the interaction with the receptor ligands, pembrolizumab releases the PD-1 pathway-mediated inhibition of the immune response and reactivates both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and anti-tumour immunity [1].
Marketing authorisation/CE mark status	Pembrolizumab was granted marketing authorisation in July 2015 by the European Medicines Agency, covering all European markets including the UK [2].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Pembrolizumab currently has a marketing authorisation (MA) covering the following indications [3]: • KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. • KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection • KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. • KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations. • KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults. • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should

	also have received targeted therapy before receiving KEYTRUDA • KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 • KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1. • KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy • KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults
Method of administration and dosage	Pembrolizumab 200 mg IV on Day 1 of each 21-day cycle plus one of 1) nab-paclitaxel 100 mg/m^2 IV on Days 1, 8 and 15 of each 28-day cycle 2) paclitaxel 90 mg/m^2 IV on Days 1, 8 and 15 of each 28-day cycle 3) gemcitabine1000 mg/m^2 (gemcitabine) and carboplatin AUC 2 on Days 1 and 8 of each 21-day cycle
Additional tests or investigations	Patients with TNBC should be selected for treatment with pembrolizumab and chemotherapy if their tumours expresses PD-L1 ≥10 CPS using a validated test (22C3 pharmDx). The PD-L test is an immunohistochemistry (IHC) test and has become part of routine pathology practice.
List price and average cost of a course of treatment	The list price of pembrolizumab is £2,630 per 100mg vial, the cost of a single administration being £5,260. Based on the KEYNOTE-355 trial, the mean number of pembrolizumab administrations patients received was [redacted] Therefore the average drug acquisition cost per treatment for pembrolizumab is [redacted] at list price (not adjusted for relative dose intensity).

Patient access scheme (if applicable)	A commercial access agreement (CAA) has been arranged with NHS England, with a simple discount in place of [redacted], therefore 200mg administration of pembrolizumab will cost [redacted]

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Triple Negative Breast Cancer: An Overview

Triple negative breast cancer (TNBC) is a subtype of breast cancer, characterised by the lack of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2) expression. Approximately 15 to 20% of breast cancers diagnosed across the globe are TNBC and disproportionately occur in younger, black women and those with Breast Cancer (BRCA) 1 and 2 mutations [4]. It has been described as constituting "a heterogenous group of malignancies that are often aggressive with a poor prognosis" [5].

Patients with TNBC are more likely to have grade 3 tumours and larger tumour size compared with those with other breast cancers [6]. Higher incidence of visceral metastases is observed in TNBC [7] which can lead to a poorer prognosis [8].

TNBC is associated with a high risk of distant recurrence [5]. Studies have found the rate of recurrence for those with TNBC to be between 6.7% and 10.5% compared with a range of 2.1% to 6.4% for all breast cancer patients [9]. Lin et al (2008) retrospectively analysed patients with TNBC and a median disease-free interval (DFI) of 19.9 months was observed in those patients who experienced a recurrence [10]. The most common sites of first distant recurrence are lung (approximately 40%), brain (approximately 30%), liver (approximately 20%) and bone (approximately 10%) [11]. TNBC was associated with a hazard ratio (HR) of 1.87 for Central Nervous System (CNS) metastases compared with HER2 negative/HR positive subtype within the retrospective Epidemiological Strategy and Medical Economics (ESME) metastatic breast cancer study [12].

The five-year overall survival for patients diagnosed with TNBC is between 59%-77% [13] depending on factors such as stage and treatment received. The ESME study, conducted on a cohort of nearly 22,000 patients in France with metastatic breast cancer, reported the overall survival (OS) and progression free survival (PFS). PFS under first line therapy in metastatic TNBC was 4.8 months (95% CI 4.6-5.1) compared to 9.6 months (95% CI 9.4-9.9) for the whole analysis population. The median OS for metastatic TNBC patients (14.8 months, 95% CI 14.1-15.5) compared to HR+/HER2- (43.3, 95% CI 42.2-44.5) and HER2+ (50.1, 95% CI 47.6-53.1) groups was found to be significantly different ($p<0.0001$) [14]. The same study also observed a shorter median time from initial diagnosis to metastatic breast cancer in the TNBC sub-group, 24 months compared with 80 and 46 in HR+/HER2- and HER2+, respectively.

In England there were 48,030 breast cancer cases registered in 2018 [15], which gives an estimated range of TNBC cases of 7,205 to 9,606 (15-20%).

Since 1988, a breast screening programme has been conducted by NHS England [16] with the aim to "reduce mortality by detecting breast cancer at an early stage when there is a better chance of successful treatment" [17]. The core programme invites women between the ages of 50 and 70 for screening every three years. Those outside of this age range can be invited through self/GP referral or part of a research trial [17]. In the financial year 2018-19, there were 19,558 breast cancers detected, 78.8% of which were invasive [17].

B.1.3.2 England clinical care pathway

After consulting with clinical experts, MSD understands that the treatments used in the first line setting for metastatic TNBC patients are dependent on patient factors. For those whose tumours express PD-L1 1% or more using the Ventana PD-L1 (SP142) IHC Assay (used in Impassion130), the choice is atezolizumab with nab-paclitaxel. The PD-L1 expression level is based upon the area that is stained within the tumour sample.

The assay used to establish the level of PD-L1 expression in Impassion130 is different to that utilised within KEYNOTE-355 which is 22C3 pharmDx as well as the method of scoring PD-L1 positivity, see Table 3. Rugo et al have explored the cross over between the two assays [18-20] and this is discussed further in Section 2.9 - Indirect Treatment Comparison.

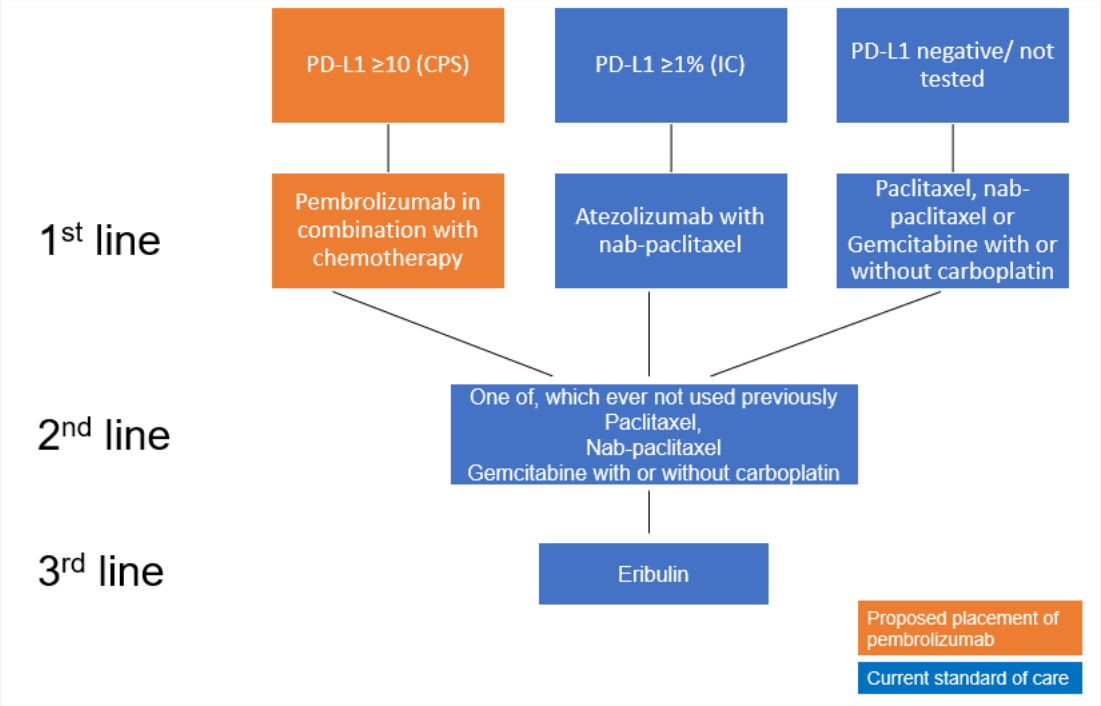
Table 3: Comparison of assays

Trial	KEYNOTE-355	Impassion130
Assay	22C3 pharmDX	SP142
Manufacturer of assay	Dako	Ventana
Calculation of PD-L1 expression	$\text{CPS}=\frac{Number\ of\ PD-L1\ stained\ cells}{(tumour\ cells,lymphocytes,macrophages)}\ \text{x}\ 100$ $Total\ number\ of\ viable\ tumour\ cells$	$\text{IC}=\frac{Tumour\ area\ that\ is\ occupied\ by\ PD-L1\ staining\ immunce\ cells\ of\ any\ \ intensity}{Total\ tumour\ area}$
Expressed as	Whole number	Percentage (%)
Threshold in licence for PD-L1 positivity	≥10	≥1%

References: [21] and [22]

If patients have either not been tested or have a PD-L1 expression less than 1% the options are gemcitabine with or without carboplatin, paclitaxel or, nab-paclitaxel. Clinical experts indicated gemcitabine and carboplatin may be considered for younger fitter patients due to the risk of impaired bone marrow function from gemcitabine, which could lead to leucopoenia, thrombocytopaenia and anaemia [23]. Nab-paclitaxel is used by cancer centres for those who have allergic reaction to paclitaxel or docetaxel [24]. At the time of writing there is the "option to substitute albumin-bound paclitaxel (Abraxane) for paclitaxel or docetaxel to reduce toxicity and potential for admission" under the NICE Interim COVID Guidelines [25]. Pembrolizumab in combination with chemotherapy would be considered as an option for patients with PD-L1 CPS ≥10 as measured using the 22C3 pharmDx assay.

Figure 1: First line treatment options for locally recurrent unresectable or metastatic TNBC and proposed position of pembrolizumab



B.1.4 Equality considerations

MSD does not envisage any equality issues with the use of pembrolizumab in combination with chemotherapy for the treatment of untreated, locally advanced or metastatic, triple negative breast cancer.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

A systemic literature review (SLR) was conducted to identify clinical studies relevant to this submission. The SLR was designed to identify randomised controlled trials (RCTs) relating to the efficacy and safety of pembrolizumab in combination with chemotherapy and relevant comparators (as per final scope described in table 1) in patients with untreated locally recurrent unresectable or metastatic triple negative breast cancer (TNBC).

The SLR was originally conducted on 27th August 2019 and an updated search was conducted on 10th August 2020. As the manufacturer of the technology being appraised, MSD is aware of all relevant RCTs for pembrolizumab in combination with chemotherapy for this indication.

The full SLR methodology and results are presented in Appendix D. In total 12 citations relating to seven RCTs were identified, and of these, one study (IMPassion130) was included in the network meta-analysis to be compared with KEYNOTE-355 (see section 2.9).

The clinical effectiveness evidence presented in this submission is taking from the second interim analysis (IA2) of KEYNOTE-355. The data cut-off date for IA2 was the 11th December 2019. The final analysis of KEYNOTE-355 is currently anticipated in [redacted].

Table 4: Clinical effectiveness evidence

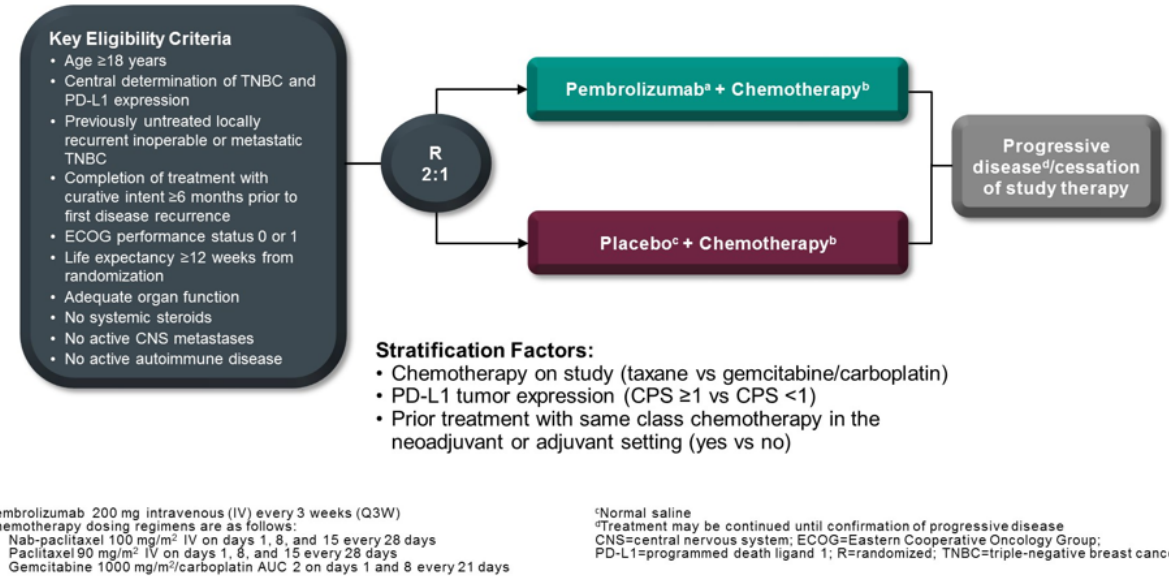
<table>
<tr><td>Study</td><td colspan="5">KEYNOTE-355: Study of Pembrolizumab (MK-3475) Plus Chemotherapy vs. Placebo Plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer [26]</td></tr>
<tr><td>Study design</td><td colspan="5">Phase III Randomised, double blind study</td></tr>
<tr><td>Population</td><td colspan="5">Patients with previously untreated locally recurrent inoperable or metastatic triple negative breast cancer; has a Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; has completed treatment for stage I-III breast cancer, if indicated, and ≥6 months has elapsed between the completion of treatment with curative intent and first documented local or distant disease recurrence.</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Pembrolizumab plus chemotherapy (one of gemcitabine plus carboplatin, nab-paclitaxel or paclitaxel)</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Placebo plus chemotherapy (one of gemcitabine plus carboplatin, nab-paclitaxel or paclitaxel)</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>Y</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>Y</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">KEYNOTE-355 is the pivotal clinical trial in this indication</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• overall survival (OS)
• progression-free survival (PFS)
• response rate (RR)
• adverse effects of treatment (AEs)
• health-related quality of life (HRQoL)
Bolded outcomes are included in the economic model</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">• Time to deterioration (TTD)
• Duration of response
• Patient reported outcomes (PRO)
• Disease control rate (DCR)
Bolded outcomes are included in the economic model</td></tr>
</table>

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 KEYNOTE-355 trial overview

Trial design

Figure 2: KEYNOTE-355 trial design [27]



[a]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W)
[b]Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 every 28 days
Paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 every 28 days
Gemcitabine 1000 mg/m^2/carboplatin AUC 2 on days 1 and 8 every 21 days

[c]Normal saline
[d]Treatment may be continued until confirmation of progressive disease
CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; PD-L1=programmed death ligand 1; R=randomized; TNBC=triple-negative breast cancer

Eligibility criteria

Male and female subject ≥18 years) with locally recurrent inoperable or metastatic TNBC, previously untreated.

Subject inclusion criteria

- Has locally recurrent inoperable breast cancer not previously treated with chemotherapy and which cannot be treated with curative intent OR has metastatic breast cancer not previously treated with chemotherapy.
- Has centrally confirmed TNBC, as defined by the most recent American Society of Clinical Oncology/college of American Pathologists (ASCO/CAP) guidelines.
- Has completed treatment for Stage I-III breast cancer, if indicated, and ≥6 months elapsed between the completion of treatment with curative intent (e.g., date of primary breast tumour surgery or date of last adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence.
- Has been treated with (neo)adjuvant anthracycline, if they received systemic treatment in the (neo)adjuvant setting, unless anthracycline was contraindicated or not considered the best treatment option for the participant in the opinion of the treating physician.
- Has measurable disease based on Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) as determined by local radiology review.
- Has provided recently or newly obtained core or excisional biopsy from a locally recurrent inoperable or metastatic tumour lesion for central determination of TNBC status and PD-L1

expression, unless contraindicated due to site inaccessibility and/or participant safety concerns.

- Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, as assessed within 10 days prior to the start of study drug.
- Has a life expectancy ≥12 weeks from randomisation.
- Demonstrates adequate organ function, within 10 days prior to the start of study drug.
- Female participants of childbearing potential must be willing to use an adequate method of contraception for the course of the study through 120 days (or longer as specified by local institutional guidelines) after the last dose of study drug.
- Male participants of childbearing potential must agree to use an adequate method of contraception starting with the first dose of study drug through 120 days (or longer as specified by local institutional guidelines) after the last dose of study drug.

Subject exclusion criteria

- The subject must be excluded from participating in the trial if the subject:
- Is currently participating in a clinical study and receiving an investigational agent and/or using an investigational device or has participated in a clinical study and received an investigational agent and/or used an investigational device within 4 weeks prior to randomization.
- Has not recovered (e.g., to ≤ Grade 1 or to baseline) from AEs due to a previously administered therapy.
- Has neuropathy ≥ Grade 2.
- Has an active autoimmune disease that has required systemic treatment in the past 2 years (e.g., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs).
- Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to randomization.
- Has a known additional malignancy that progressed or required active treatment within the last 5 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, and in situ cervical cancer.
- Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they have stable brain metastases and did not receive chemotherapy for metastatic breast cancer.
- Has history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
- Has active, or a history of, interstitial lung disease.
- Has a known history of active tuberculosis.
- Has an active infection requiring systemic therapy.
- Has a history of Class II-IV congestive heart failure or myocardial infarction within 6 months of randomization.

- Has a known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
- Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days (or longer as specified by local institutional guidelines) after the last dose of study drug.
- Has received prior therapy with an anti-programmed cell death 1 (anti-PD-1), anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T cell receptor (such as cytotoxic T-lymphocyte-associated protein 4 [CTLA-4], OX-40, CD137) or has previously participated in MSD pembrolizumab (MK-3475) clinical studies.
- Has a known history of human immunodeficiency virus (HIV).
- Has known active hepatitis B or hepatitis C.
- Has received a live vaccine within 30 days prior to randomization.
- Has a known history of hypersensitivity or allergy to pembrolizumab and any of its components and/or to any of the study chemotherapies (e.g., nab-paclitaxel, paclitaxel, gemcitabine, or carboplatin) and any of their components.
- Is receiving any medication prohibited in combination with study chemotherapies as described in the respective product labels, unless medication was stopped within 7 days prior to randomization.

Settings and locations where data were collected

The study was conducted at 251 centres, in 29 countries in North America, Europe, Asia and Australia [26]. There were 82 sites within Europe and of these, nine in the United Kingdom. A total of 259 patients were enrolled in Europe of which 37 were from the UK. All treatments were administered in secondary care setting on an outpatient basis.

Trial drugs and concomitant medication

Trial drugs

Study medications used in this trial are outlined below:

Table 5: Trial treatments

Treatment	Regimen	Route of administration	Duration of treatment	Use in study
Pembrolizumab + chemotherapy combination arm				
Pembrolizumab	200mg Day 1 every 3 weeks (Q3W)	IV infusion	35 cycles	Experimental
Nab-paclitaxel	100mg/m^2 Day 1, 8 and 15 of each 28-day cycle	IV infusion	Until disease progression or cessation of study treatment	Investigator's choice of chemotherapy
Paclitaxel	90mg/m^2 Day 1, 8 and 15 of each 28-day cycle	IV infusion		
Gemcitabine and carboplatin	Gemcitabine: 1000mg/m^2 Carboplatin: AUC2 Day 1 and 8 of each 21-day cycle	IV infusion		
Placebo + chemotherapy combination arm				
Placebo	Day 1 every 3 weeks	IV infusion	Until disease progression or cessation of study treatment	Comparator
Nab-paclitaxel	100mg/m^2 Day 1, 8 and 15 of each 28-day cycle	IV infusion		Investigator's choice of chemotherapy
Paclitaxel	90mg/m^2 Day 1, 8 and 15 of each 28-day cycle	IV infusion		
Gemcitabine and carboplatin	Gemcitabine: 1000mg/m^2 Carboplatin: AUC2 Day 1 and 8 of each 21-day cycle	IV infusion		

Acceptable concomitant medications

All treatments that the Investigator considered necessary for a subject's welfare could be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medications were recorded on the electronic case report form (eCRF), including all prescription, over-the-counter (OTC), and IV medications and fluids. All concomitant medications received within 28 days before randomization, while on study treatment, and up to 30 days after the last dose of study treatment were recorded. After randomization concomitant medications administered beyond 30 days after the last dose of study treatment were recorded when prescribed for serious adverse events (SAEs).

Prohibited concomitant medications

Subjects were prohibited from receiving the following therapies during the screening, and treatment phases of KEYNOTE-355:

- Antineoplastic systemic chemotherapy or biological therapy
    - Immunotherapy not specified in the study protocol
    - Chemotherapy not specified in the protocol
    - Investigational agents other than pembrolizumab
    - Radiation therapy (Could be allowed after consultation with the study sponsor to a single solitary lesion or to the brain)
- Herbal supplements
- Live vaccines within 30 days prior to randomisation and while participating in the study
- Glucocorticoids for any other purpose other than modulation of symptoms from an AE of suspected immunologic etiology, inhaled steroids for management of asthma, physiologic doses of prednisone or prophylactic use of corticosteroids to avoid allergic reactions.

There were no prohibited therapies during the post-treatment follow-up phase.

Outcomes used in the economic model or specified in the scope, including primary outcomes

The outcomes of progression free survival (PFS), overall survival (OS) and HRQoL have been used in the economic model along with time on treatment and adverse events.

KEYNOTE-355 primary and secondary objectives were pre-specified and are as follows.

<u>Primary objectives</u>

1. To compare progression-free survival (PFS) based on RECIST 1.1 as assessed by a blinded central imaging vendor (CIV) of pembrolizumab with chemotherapy versus placebo with chemotherapy.

2. To compare overall survival (OS) of pembrolizumab with chemotherapy versus placebo with chemotherapy.

Both primary outcomes were to be assessed for three groups: all participants, those whose tumours express PD L1 with a CPS ≥1 and those whose tumours express PD L1 with a CPS ≥10.

PFS was defined as the time from randomisation to the first documented disease progression per RECIST 1.1 assessed by a CIV or death due to any cause, whichever occurred first.

OS was defined as the time from randomisation to death due to any cause. Subjects without documented death at the time of the analysis were to be censored at the date of the last follow-up.

Secondary objectives

1. To compare objective response rate (ORR) based on RECIST 1.1 as assessed by a blinded CIV of pembrolizumab with chemotherapy versus placebo with chemotherapy.
2. To compare duration of response (DoR) based on RECIST 1.1 as assessed by a blinded CIV
3. To compare disease control rate (DCR) based on RECIST 1.1 as assessed by a blinded CIV
4. To evaluate the safety and tolerability of the three pembrolizumab and chemotherapy combinations
5. To evaluate changed in health-related quality-of-life (HRQoL) assessment from baseline using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and EORTC Breast Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23).

The secondary objectives numbered one to three, were assessed for three groups: all participants, those whose tumours express PD L1 with a CPS ≥1 and those whose tumours express PD L1 with a CPS ≥10.

ORR was defined as the proportion of the participants in the analysis population who had a complete response (CR) or partial response (PR). DoR was defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurred first. DCR was defined as the percentage of participants who achieved CR or PR or demonstrated stable disease (SD) for at least 24 weeks.

Exploratory objectives

1. To characterize utilities in All Participants and in participants with PD-L1 positive tumours (CPS ≥1 and CPS ≥10) using EuroQol-5 Dimension Questionnaire (EQ-5D™).
2. To investigate association(s) between anti-tumour activity of study treatments and efficacy/resistance biomarkers, utilising tumour and blood specimens obtained before randomisation, during treatment, and at disease progression.

3. To identify molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to pembrolizumab and other treatments in this study, so as to define novel predictive and pharmacodynamic biomarkers and understand the mechanism of action of pembrolizumab.

Participants baseline characteristics KEYNOTE-355

Baseline characteristics of the patients in the intention to treat (ITT) group from KEYNOTE-355 are summarised in Appendix D. The baseline characteristics were well balanced between the pembrolizumab with chemotherapy and placebo with chemotherapy groups and representative of patients with breast cancer. The majority of participants were <65, White, not Hispanic or Latino, post-menopausal, and had a European Co-operative Oncology Group (ECOG) performance score of 0. Most participants entered the study with metastatic TNBC (recurrent [67.1%] or de novo [29.6%] metastatic disease) and a performance score of 0.

Most participants (75.1%) had a tumour tissue PD-L1 expression score of CPS ≥1 and 38.1% of participants had a tumour tissue PD-L1 expression score of CPS ≥10. For participants with PD-L1 positive tumours (CPS ≥1 and CPS ≥10), demographics and other baseline characteristics data were generally well-balanced between the two treatment groups and consistent with those of the ITT population. Table 6 summarises the patient characteristics for those whose tumours expressed PD-L1 with a CPS ≥10.

Table 6: Subject characteristics in those whose tumours express PD-L1 with a CPS≥10

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	220		103		323	
Gender						
Female	220	(100.0)	103	(100.0)	323	(100.0)
Age (Years)						
< 65	[redacted]					
>= 65						
Mean						
SD						
Median						
Range						
Race						
American Indian Or Alaska Native	[redacted]					
Asian						
Black Or African American						
Multiple						
White						
Missing						
Ethnicity						
Hispanic Or Latino	[redacted]					
Not Hispanic Or Latino						
Not Reported						
Unknown						
Missing						
Geographic Region						
Asia	[redacted]					
Europe						
Australia						
North America						
Rest of the World						
Chemotherapy on Study (IVRS)						
Nab-Paclitaxel	[redacted]					
Paclitaxel						
Gemcitabine/ Carboplatin						
Chemotherapy on Study (Actual)						
Nab-Paclitaxel	61	(27.7)	36	(35.0)	97	(30.0)
Paclitaxel	33	(15.0)	11	(10.7)	44	(13.6)

Gemcitabine/ Carboplatin	125	(56.8)	56	(54.4)	181	(56.0)
Missing	1	(0.5)	0	(0.0)	1	(0.3)
Prior Treatment with Same Class Chemotherapy in the Neoadjuvant or Adjuvant Setting (IVRS)						
Yes	[redacted]					
No	[redacted]					
Prior Treatment with Same Class Chemotherapy in the Neoadjuvant or Adjuvant Setting (Actual)						
Yes	[redacted]					
No	[redacted]					
Missing	[redacted]					
Disease Status						
Metastatic, De Novo	[redacted]					
Metastatic, Recurrence	[redacted]					
Locally Recurrent Inoperable	[redacted]					
Missing	[redacted]					
ECOG						
0	[redacted]					
1	[redacted]					
HER2 Status						
0-1+ by IHC	[redacted]					
2+ by IHC	[redacted]					
History of Brain Metastasis						
Yes	[redacted]					
No	[redacted]					
Menopausal Status						
Pre-menopausal	[redacted]					
Post-menopausal	[redacted]					
Disease Free Interval						
de novo metastasis	[redacted]					
< 12 months	[redacted]					
>= 12 months	[redacted]					
Unknown	[redacted]					
Baseline Lactate Dehydrogenase (LDH)						
Normal	[redacted]					
> ULN and < 2 x ULN	[redacted]					
>= 2 x ULN	[redacted]					
Missing	[redacted]					
Sum of Target Lesion Size at Baseline (Central) (mm)						
Subjects with data	[redacted]					
Mean	[redacted]					
SD	[redacted]					
Median	[redacted]					

Range	[redacted]	[redacted]	[redacted]
Sum of Target Lesion Size at Baseline (Investigator) (mm)			
Subjects with data Mean SD Median Range	[redacted]	[redacted]	[redacted]
Database Cut-off Date: 11DEC2019			

B.2.4 KEYNOTE-355: Statistical analysis and definition of study groups

This section reports the relevant statistical methodology of KEYNOTE-355.

Table 7: Statistical analysis plan summary

Study design overview	A randomised, double-blind, phase III study of pembrolizumab plus chemotherapy vs placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic Triple Negative Breast Cancer
Treatment assignment	Approximately 828 subjects to be randomised in a 2:1 ratio between 2 treatment arms: • Arm 1: pembrolizumab + chemotherapy • Arm 2: placebo + chemotherapy. Study is double-blinded. Stratification factors are provided in section 2.3.1.
Analysis populations	Efficacy: Intention-to-Treat Population (ITT) Safety: All Subjects as Treated (ASaT)
Primary endpoints	PFS based on RECIST 1.1 as assessed by a blinded CIV in all subjects, subjects whose tumours express PD L1 with a CPS ≥1 and subjects whose tumours express PD L1 with a CPS ≥10 OS in all subjects, subjects whose tumours express PD L1 with a CPS ≥1 and subjects whose tumours express PD L1 with a CPS ≥10.
Statistical methods for key efficacy analyses	The primary hypotheses will be evaluated by comparing pembrolizumab + chemotherapy vs placebo + chemotherapy in PFS and OS using a stratified log-rank test. The hazard ratio (HR) will be estimated using a stratified Cox model.
Statistical methods for key safety analyses	The analysis of safety will follow a tiered approach. There is no Tier 1 safety endpoint for this trial. Point estimates and 95% confidence intervals (CIs) for between-treatment comparisons via the Miettinen and Nurminen method will be

	provided for Tier 2 safety endpoints; only point estimates by treatment group will be provided for Tier 3 safety endpoints.
Interim and final analyses	Three efficacy interim analyses will be performed. Results will be reviewed by an external Data Monitoring Committee (DMC). Interim analysis 1 (IA1): Timing: Approximately 9 months after first 640 subjects are randomized. Primary purpose: Final ORR analysis, interim PFS and interim OS analysis. IA2: Timing: After approximately 185 OS events among subjects with CPS ≥10 have been observed. Primary purpose: Interim OS analysis and final PFS analysis. IA3: Timing: After approximately 210 OS events among subjects with CPS ≥10 have been observed. Primary purpose: Interim OS analysis. Final analysis (FA): Timing: After approximately 664 OS events among all subjects, approximately 482 OS events among subjects with CPS ≥1, and approximately 240 OS events among subjects with CPS ≥10 have been observed. Primary purpose: Final OS analysis.
Multiplicity	The family-wise type-I error rate over the 6 primary hypotheses and the 2 secondary hypotheses will be strongly controlled at 2.5% (one-sided) with 0.5% allocated to PFS, 1.8% allocated to OS, and 0.2% allocated to ORR hypotheses. An extension of the graphical approach of Maurer and Bretz will be applied to re-allocate alpha between PFS, OS and ORR hypotheses. The Spiessens and Debois method will be used to adjust the nominal alphas in ORR between all subjects and subjects with CPS ≥1. Group sequential methods will be used to allocate alpha between the interim and final analyses for OS endpoints.
Sample size and power	(1) PFS in all subjects: at IA2 the analysis has ~ 89% power at a one-sided 0.111% alpha level, if the true HR is 0.70. At IA2, with ~ 634 events the HR at boundary for success is ~ 0.77 (~ 1.6 months improvement over control median PFS of 5.5 months). At IA2, PFS in all subjects can only be tested if both hypotheses of PFS in subjects with CPS ≥10 and PFS in subjects with CPS ≥1 are supported.

	(2) PFS in subjects with CPS ≥1: at IA2 the analysis has ~ 97% power at a one-sided 0.111% alpha level, if the true HR is 0.62. At IA2, with ~ 463 events the HR at boundary for success is ~ 0.74 (~ 1.9 months improvement over control median PFS of 5.5 months). At IA2, PFS in all subjects with CPS ≥1 can only be tested if the hypothesis of PFS in subjects with CPS ≥10 is supported. (3) PFS in subjects with CPS ≥10: at IA2 the analysis has ~ 86% power at a one-sided 0.411% alpha level, if the true HR is 0.60. At IA2, with ~ 235 events the HR at boundary for success is ~ 0.69 (~ 2.4 months improvement over control median PFS of 5.5 months). (4) OS in all subjects: the trial has ~ 60% power at a one-sided 0.75% alpha level, if the true HR is 0.80. With ~ 664 events, the HR at boundary for success at FA is ~ 0.81 (~ 4.0 months improvement over control median OS of 17.5 months). After IA1, OS in all subjects can be tested if hypothesis of OS in subjects with CPS ≥1 is supported. (5) OS in subjects with CPS ≥1: the trial has ~ 87% power at a one-sided 0.75% alpha level, if the true HR is 0.71. With ~ 482 events, the HR at boundary for success at FA is ~ 0.78 (~ 4.8 months improvement over control median OS of 17.5 months). (6) OS in subjects with CPS ≥10: the trial has ~ 79% power at a one-sided 1.011% alpha level, if the true HR is 0.65. With ~ 240 events, the HR at boundary for success at FA is ~ 0.72 (~ 6.8 months improvement over control median OS of 17.5 months).

The strategy for analysis of key efficacy endpoints is summarised in Table 8, while Table 9 summaries the censoring rules applied for analyses of PFS.

Table 8: Analysis strategy for key efficacy endpoints

Endpoint	Subgroups	Statistical methods	Analysis Population	Missing data approach
<u>Primary endpoints</u>				
PFS based on RECIST 1.1 assessed by a blinded CIV	All subjects	Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Primary censoring rule, Sensitivity analysis 1, Sensitivity analysis 2
	CPS ≥1			
	CPS ≥10			

OS	All subjects CPS ≥1 CPS ≥10	Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Secondary endpoints				
ORR based on RECIST 1.1 assessed by a blinded CIV	All subjects CPS ≥1	Stratified M & N method	The first ~ 640 subjects randomized	Subjects with relevant data missing are considered non-responders
ORR based on RECIST 1.1 assessed by a blinded CIV	CPS ≥10	Stratified M & N method	ITT	Subjects with relevant data missing are considered non-responders
DCR based on RECIST 1.1 assessed by a blinded CIV	All subjects CPS ≥1 and CPS ≥10	Stratified M & N method	ITT	Subjects with relevant data missing are considered non-responders
DOR based on RECIST 1.1 assessed by a blinded CIV	All subjects CPS ≥1 and CPS ≥10	Summary statistics using Kaplan-Meier method	All responders in ITT	See Table 9

Table 9: Censoring rules for primary and sensitivity analysis of PFS

Situation	Primary analysis	Sensitivity analysis 1	Sensitivity analysis 1
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study treatment or completed study treatment.

No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment
PD or death documented after ≤1 missed disease assessment, and before new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death

B.2.5 KEYNOTE-355: Quality assessment

Quality assessment of KEYNOTE-355 was conducted using the Cochrane Risk of Bias (RoB) tool [28]. Based upon this analysis, the study was determined to be at 'low risk' across five out of six domains.

The complete quality assessment is included in Appendix D1.4.

B.2.6 KEYNOTE-355 Clinical effectiveness

B.2.6.1 KEYNOTE-355 results

Interim results are presented from the KEYNOTE-355 study, based upon the second interim analysis (IA2) which had a data cut off of 11th December 2019. The data presented below focuses on those patients whose tumours expressed PD-L1 CPS ≥10, [redacted]. Data for All Subjects population can be found in Appendix D.

For simplicity abbreviated nomenclature for the treatment groups is used in this section as per Table 10.

Table 10: Treatment group nomenclature

Treatment Group	Abbreviated	Table heading
Pembrolizumab with nab-paclitaxel, paclitaxel or gemcitabine and carboplatin	Pembrolizumab in combination with chemotherapy	Pembrolizumab + chemotherapy
Placebo with nab-paclitaxel, paclitaxel or gemcitabine and carboplatin	Placebo in combination with chemotherapy	Placebo + chemotherapy / Control
Pembrolizumab with nab-paclitaxel or paclitaxel	Pembrolizumab in combination with taxanes	Pembrolizumab + taxanes
Placebo with nab-paclitaxel or paclitaxel	Placebo in combination with taxanes	Placebo + taxanes

The IA2 was performed after approximately 185 OS events had been observed among participants with PD-L1 positive tumours (defined as CPS ≥10). The primary endpoints (PFS and OS) and the secondary (ORR and DoR) were analysed for those patients whose tumours expressed PD-L1 with a CPS ≥10. At the IA2 cut-off date, patients had a median duration of follow-up of 16.8 months (range 0. to 35.0), with 8.7% of patients in the pembrolizumab in combination with chemotherapy group and 6.0% in the control group remaining on assigned treatment. Mean duration of exposure was [redacted] weeks (SD [redacted] weeks) in the pembrolizumab in combination with chemotherapy arm compared with [redacted] weeks (SD [redacted] weeks) in the control arm. The mean number of administrations of pembrolizumab in the pembrolizumab in combination with chemotherapy group was [redacted] and [redacted] for placebo in the placebo in combination with chemotherapy group.

Table 11: Summary of drug exposure (CPS ≥10 population)

	Pembrolizumab + Chemotherapy	Placebo + Chemotherapy
Subjects in population	219	103

All Drugs		
Number of Weeks on Therapy (weeks)		
n	219	103
Mean	44.4	35.1
SD	33.9	31.6
Median	35.1	22.6
Range	0.1 to 129.1	0.1 to 133.1
Pembrolizumab/Placebo		
Number of Weeks on Therapy (weeks)		
n	219	103
Mean	42.6	33.4
SD	34.5	30.6
Median	32.9	22.1
Range	0.1 to 126.1	0.1 to 119.3
Number of Administrations		
n	219	103
Mean	14.1	11.1
SD	10.7	9.4
Median	11.0	8.0
Range	1.0 to 35.0	1.0 to 35.0
Nab-Paclitaxel		
Number of Weeks on Therapy (weeks)		
n	62	36
Mean	35.9	30.9
SD	26.1	29.8
Median	29.6	19.6
Range	0.1 to 108.1	5.1 to 130.1
Number of Administrations		
n	62	36
Mean	25.9	23.4
SD	18.4	21.8
Median	23.5	15.0
Range	1.0 to 77.0	5.0 to 96.0
Paclitaxel		
Number of Weeks on Therapy (weeks)		
n	33	11
Mean	37.6	19.0
SD	26.3	15.0
Median	30.6	17.7
Range	6.3 to 102.3	0.1 to 53.7
	Pembrolizumab + Chemotherapy	Placebo + Chemotherapy
Number of Administrations		
n	33	11

Mean	25.8	14.1
SD	16.8	10.7
Median	19.0	14.0
Range	6.0 to 75.0	1.0 to 40.0
Gemcitabine		
Number of Weeks on Therapy (weeks)		
n	125	56
Mean	33.9	32.8
SD	29.2	26.8
Median	22.1	26.7
Range	0.1 to 129.1	0.1 to 133.1
Number of Administrations		
n	125	56
Mean	17.6	17.5
SD	13.5	14.2
Median	13.0	14.0
Range	1.0 to 74.0	1.0 to 85.0
Carboplatin		
Number of Weeks on Therapy (weeks)		
n	125	56
Mean	33.3	32.6
SD	28.3	26.9
Median	22.3	26.7
Range	0.1 to 129.1	0.1 to 133.1
Number of Administrations		
n	125	56
Mean	17.2	17.4
SD	12.9	14.3
Median	13.0	14.0
Range	1.0 to 74.0	1.0 to 85.0
Database Cut-off Date: 11DEC2019		

Summary of clinical efficacy outcomes (IA2)

A summary of the clinical efficacy outcome results from IA2 for patients whose tumours express PD-L1 CPS ≥10 are presented in Table 12, with additional details of each endpoint provided in sub-sections 2.6.2– 2.6.6. Clinical efficacy outcomes for all subjects can be found in appendix D1.5.

Table 12: Summary of clinical efficacy outcomes (IA2) – CPS ≥10 (ITT population)

	Locally recurrent unresectable or metastatic TNBC	
Number of patients	**Pembrolizumab + chemotherapy N=220**	**Placebo + chemotherapy N=103**
Primary endpoints		
PFS (BICR per RECIST 1.1)		
Median (95% CI), [months]	9.7 (7.6, 11.3)	5.6 (5.3, 7.5)
	HR: 0.65 (95% CI 0.49, 0.86); p=0.0012	
PFS rate at 6 months	65.0%	46.9%
PFS rate at 12 months	39.1%	23.0%
OS		
Median (95% CI) [months]	[redacted]	[redacted]
	[redacted]	
OS rate at 6 months	[redacted]	[redacted]
OS rate at 12 months	[redacted]	[redacted]
Secondary endpoints		
ORR (BICR per RECIST 1.1)		
Confirmed ORR % (95% CI)	53.2 (464, 59.9)	39.8 (30.3, 49.9)
Difference in % vs control (95% CI)	13.6 (1.9, 24.8)	
% of patients who achieved a CR (95% CI)	16.8 (12.1, 22.4)	12.6 (6.9, 20.6)
Disease control rate [CR+PR+SD] (95% CI)	65.0 (58.3, 71.3)	54.4 (44.3, 64.2)
Duration of response		

Median (range) [months]	[redacted]	[redacted]
+ Indicates there is no progressive disease by the time of last disease assessment		

B.2.6.2 Overall survival

OS for PD-L1 CPS ≥10 population

Per the multiplicity schema as outlined in the SAP, the primary hypotheses pertaining to OS in All Participants was not formally tested because the success criterion for the primary hypothesis of OS in participants with PD-L1 positive tumours (CPS ≥1) was not met.

Pembrolizumab in combination with chemotherapy [redacted]

[redacted]The median OS [redacted]

Table 13: Analysis of OS (CPS≥10 population)

Treatment	N	Number of events (%)	Person-months	Event rate/100 person-months (%)	Median OS† [months] (95% CI)	OS Rate at month 12 in %† (95% CI)	Vs. control Hazard Ratio (95% CI) p-value§
Pembrolizumab + chemotherapy	220	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo + chemotherapy	103	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

† From product-limit (Kaplan-Meier) method for censored data.

‡ 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) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).

§ One-sided p-value based on log-rank test stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).

Database Cut-off Date: 11DEC2019

Table 14: Summary of OS rate over time (CPS ≥10 population)

	Pembrolizumab + chemotherapy (n=220)	Placebo + chemotherapy (n=103)

	% (95% CI) †	% (95% CI) †
Summary of overall survival rate at time point		
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
† From product-limit (Kaplan-Meier) method for censored data. Database Cut-off Date: 11DEC2019		

Figure 3: KM estimates of OS – CPS ≥10

B.2.6.3 Progression free survival

Progression free survival (PFS) is defined as the time from randomisation to the first documented disease progression per RECIST 1.1 based on blinded CIV or death due to any cause, whichever occurs first.

Per the multiplicity schema as outlined in the SAP, the primary hypotheses pertaining to PFS in All Participants was not formally tested because the success criterion for the primary hypothesis of PFS in participants with PD-L1 positive tumours (CPS ≥1) was not met.

PFS for PD-L1 CPS ≥10 population

Pembrolizumab in combination with chemotherapy demonstrated a statistically significant and clinically meaningful improvement in PFS compared with placebo in combination with chemotherapy in participants with PD-L1 positive tumours (CPS ≥10). The PFS HR of 0.65 (95% CI: 0.49, 0.86, p=0.0012) represents a 35% reduction in the risk of progression or death for participants with PD-L1 positive tumours (CPS ≥10).

Table 15: Analysis of PFS based on BCIV per RECISTS 1.1 (CPS ≥10 Population)

Treatment	N	Number of events (%)	Person-months	Event rate/100 person-months (%)	Median PFS† [months] (95% CI)	PFS Rate at month 12 in % (95% CI)	Vs. control Hazard Ratio‡ (95% CI) p-value§
Pembrolizumab + chemotherapy	220	136 (61.8)	2232.5	6.1	9.7 (7.6, 11.3)	39.1 (32.0, 46.0)	0.65 (0.49, 0.86)
Placebo + chemotherapy	103	79 (76.7)	821.7	9.6	5.6 (5.3, 7.5)	23.0 (14.7, 32.3)	

† From product-limit (Kaplan-Meier) method for censored data.

‡ 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), tumour PD-L1 status (CPS ≥1 vs CPS <1) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).

§ One-sided p-value based on log-rank test stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin), tumour PD-L1 status (CPS ≥1 vs CPS <1) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).

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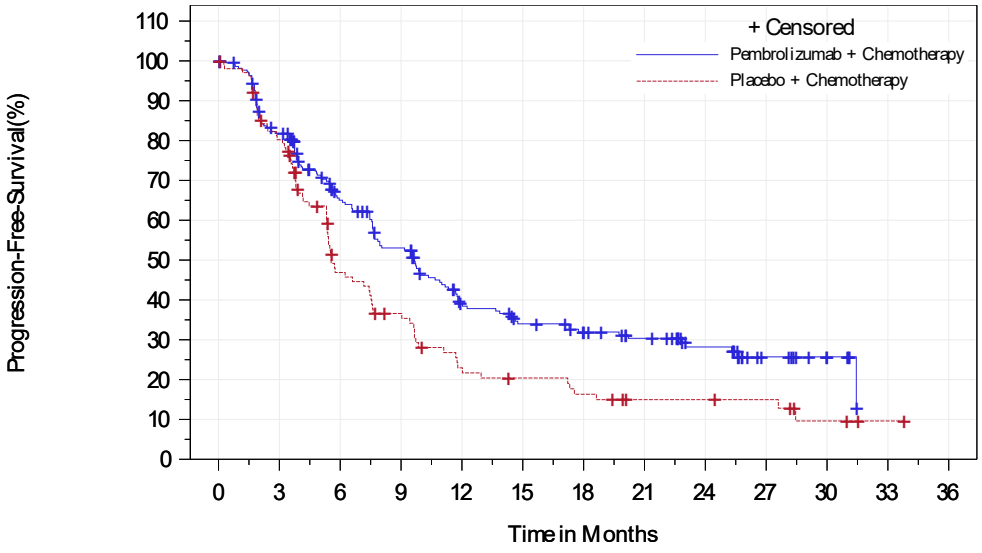
Table 16: Summary of PFS rate over time based on BCIV per RECIST 1.1. (CPS ≥10 Population)

	Pembrolizumab + chemotherapy (n=220) % (95% CI) †	Placebo + chemotherapy (n=103) % (95% CI) †
Summary of overall survival rate at time point		
3 months	81.8 (76.0, 86.4)	80.2 (71.0, 86.8)
6 months	65.0 (58.1, 71.2)	46.9 (36.5, 56.6)
9 months	53.0 (45.8, 59.8)	36.6 (26.9, 46.4)
12 months	39.1 (32.0, 46.0)	23.0 (14.7, 32.3)
† From product-limit (Kaplan-Meier) method for censored data. Database Cutoff Date: 11DEC2019		

Figure 4: KM estimates of PFS based on BICR assessment per RECIST 1.1 - CPS ≥10



Number of subjects at risk

Pembrolizumab + Chemotherapy	220	173	122	96	63	52	44	37	25	12	5	0	0
Placebo + Chemotherapy	103	80	41	30	18	15	12	8	8	7	3	1	0

Database Cutoff Date:11DEC2019

B.2.6.4 Objective response rate

Objective response rate (ORR) is defined as the proportion of the participants in the analysis population who have a complete response (CR) or partial response (PR). Responses were based on RECIST 1.1 as assessed by a blinded CIV. Disease control rate defined as the percentage of participants who have achieved CR or PR or have demonstrated stable disease (SD) for at least 24 weeks.

ORR and DCR in PD-L1 CPS ≥10 population

Pembrolizumab in combination with chemotherapy provided a clinically meaningful improvement in ORR (per RECIST 1.1 by BICR) compared with placebo in combination with chemotherapy in participants whose tumours express PD-L1 CPS ≥10. The ORR (per RECIST 1.1 by BICR) in participants who tumours expressed PD-L1 CPS ≥10 was 53.2% for the pembrolizumab in combination with chemotherapy group versus 39.8% for the placebo in combination with chemotherapy group, with a clinically meaningful difference of 13.6% (95% CI: 1.9, 24.8).

The observed DCR (CR+PR+SD≥24 weeks) was higher for participants with PD-L1 positive tumours (CPS ≥10) in the pembrolizumab in combination with chemotherapy group (65.0% [95% CI: 58.3, 71.3]) than in the placebo in combination with chemotherapy group (54.4% [95% CI: 44.3, 64.2]). This indicates that there was a larger pool of participants with PD-L1 positive tumours (CPS ≥10) who benefited from pembrolizumab in combination with chemotherapy beyond those who experienced CR and PR per RECIST 1.1. The analysis of DCR based on Investigator assessment per RECIST 1.1 in participants with PD-L1 positive tumours (CPS ≥10) was consistent with the results of the analysis by BICR.

Table 17: Analysis of objective response based on BICR assessment per RECIST 1.1 (CPS ≥10 population)

Treatment	N	Number of Objective Responses	Objective Response rate (%) (95% CI)	Difference in % vs. Placebo + chemotherapy	
				Estimate (95% CI) †	p-Value‡
Pembrolizumab + chemotherapy	220	117	53.2 (46.4, 59.9)	13.6 (1.9, 24.8)	0.0115
Placebo + chemotherapy	103	41	39.8 (30.3, 49.9)		

†Based on Miettinen & Nurminen method stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin), tumour PD-L1 status (CPS ≥1 vs CPS < 1) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).

‡ One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

Confirmed responses are included.

Database Cutoff Date: 11DEC2019

Table 18: Summary of best overall response based on BICR assessment per RECIST 1.1. (CPS ≥10 population)

Treatment	Pembrolizumab + chemotherapy (n=220)			Placebo + chemotherapy (n=103		
	N	%	95% CI†	N	%	95% CI†
Complete response (CR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial response (PR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Objective response (CR+PR)	**117**	**53.2**	**46.4, 59.9**	**41**	**39.8**	**30.3, 49.9**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease control (CR+PR+SD ≥24 weeks)	**143**	**65.0**	**28.3, 71.3**	**56**	**54.4**	**44.3, 64.2**
Progressive disease (PD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not evaluable (NE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not assessable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Based on the binomial exact confidence interval method for binomial data.

NE includes subjects with insufficient data for assessment of response per RECIST 1.1.

No Assessment includes subjects without post-baseline assessment on the data cutoff date.

Stable Disease (SD) includes both SD and Non-CR/Non-PD.

Confirmed responses are included.

BICR = Blinded Independent Central Review

Database Cutoff Date: 11DEC2019.Database Cutoff Date: 11DEC2019

B.2.6.5 Duration of response

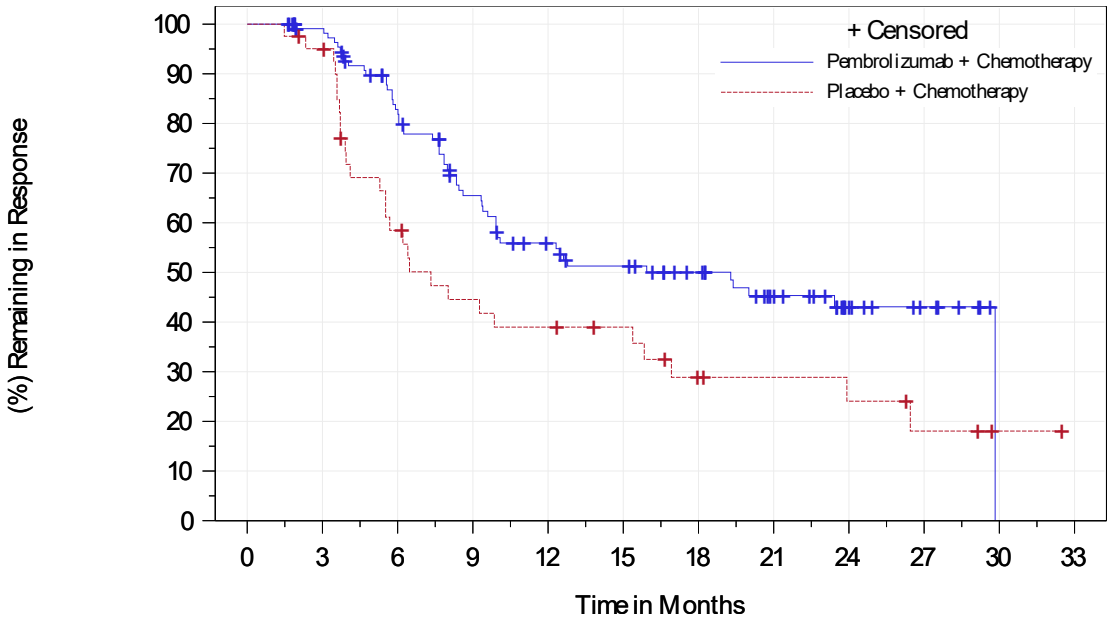
Duration of response (DOR) is defined as the time from first documented evidence of complete response (CR) or partial response (PR) until disease progression or death due to any cause, whichever occurred first.

In responders with PD-L1 positive tumours (CPS ≥10), the responses in the pembrolizumab in combination with chemotherapy group were durable relative to the placebo in combination with chemotherapy group. The median DOR for responders with PD-L1 positive tumours (CPS ≥10) was 19.3 months (range: 1.6+ to 29.8 months) in the pembrolizumab in combination with chemotherapy group and 7.3 months (range: 1.5 to 32.5+ months) in the placebo in combination with chemotherapy group.

Table 19: Summary of DOR for subjects with confirmed response based on BICR per RECIST 1.1 (CPS ≥10 population)

	Pembrolizumab + chemotherapy (n=220)	**Placebo + chemotherapy (n=103)**
Number of subjects with response (%)†	117	41
Response duration (months) Median (range)	19.3 (1.6+ - 29.8)	7.3 (1.5 – 32.5+)
Number (%‡) of subjects with extended response duration		
≥6 months	84 (82.8)	22 (58.3)
≥12 months	49 (55.9)	14 (39.0)
† Includes subjects with confirmed complete response or partial response ‡ From product-limit (Kaplan-Meier) method for censored data. + indicates there is no progressive disease by the time of last disease assessment Database cutoff Date: 11Dec2019		

Figure 5: KM Estimates of DoR Duration of Response in Subjects with CR Based on BICR Assessment per RECIST 1.1 - CPS ≥10



Number of subjects at risk

Pembrolizumab + Chemotherapy	117	107	84	62	49	43	35	24	12	7	0	0
Placebo + Chemotherapy	41	38	22	16	14	12	7	6	5	3	1	0

Database Cutoff Date:11DEC2019

Table 20: Summary of response outcome in subjects with confirmed response based on BICR per RECIST 1.1. (CPS ≥10 Population)

	Pembrolizumab + chemotherapy (n=220)	**Placebo + chemotherapy (n=103)**
Number of subjects with response†	117	41
Subjects who progressed or died (%)‡	[redacted]	[redacted]
Range of DOR (months)	[redacted]	[redacted]
Censored subjects (%)	**63 (53.8)**	**13 (31.7)**
Who missed 2 or more consecutive disease assessments	[redacted]	[redacted]
Who started new anti-cancer treatment	[redacted]	[redacted]

Who were lost to follow-up	[redacted]	[redacted]
Whose last adequate assessment was ≥5 months prior to data cutoff date	[redacted]	[redacted]
Ongoing response§	[redacted]	[redacted]
≥ 6 months	[redacted]	[redacted]
≥ 12 months	[redacted]	[redacted]
Range of DOR (months)	[redacted]	[redacted]

† Includes subjects with a confirmed complete response or partial response.

‡ Includes subjects who progressed or died without previously missing 2 or more consecutive disease assessments.

§ Includes subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, are not lost to follow-up, have not missed 2 or more consecutive disease assessments immediately before progression or death, and whose last disease assessment was <5 months prior to data cutoff date.

For censored subjects who met multiple criteria for censoring and do not have ongoing response, subjects are included in the censoring criterion that occurred earliest.

'+' indicates there was no progressive disease by the time of last disease assessment.

BICR = Blinded Independent Central Review

Database Cutoff 11Dec2019

B.2.6.6 Patient reported outcomes

Three patient reported outcomes (PRO) questionnaires were used to assess patient HRQoL in the study: EORTC QLQ-C30, EORTC QLQ-BR23 and EQ-5D VAS. PRO analyses were based on the PRO full analysis set (FAS) population, defined as all randomised participants who received at least 1 dose of study intervention and had completed at least 1 PRO assessment.

Of particular relevance to this submission is the EQ-5D VAS, which was used to characterise the utility values included in the cost-effectiveness model (see Section B.3). Compliance rates for EQ-5D VAS were [redacted] and [redacted] at baseline for the pembrolizumab in combination with chemotherapy and placebo in combination with chemotherapy groups, respectively, in the FAS population. Completion rates decreased at time points post baseline as more patients discontinued the study.

The analyses of EuroQol-EQ-5D demonstrate that the addition of pembrolizumab to chemotherapy did not result in a decrease in health-related quality of life. Over 15 weeks of

follow-up, participants receiving pembrolizumab in combination with chemotherapy and placebo in combination with chemotherapy had small decreases (worsening) in prespecified EQ-5D VAS scores. The between-group difference in LS mean score changes from baseline at Week 15 in participants with PD-L1 positive tumours CPS ≥10 was [redacted].

Section B.3.4 provides further details of the EQ-5D and utilities data used in the cost-effectiveness model. Further details of the EORTC QLQ-C30 and EORTC QLQ-BR23 are presented in section 11.3 of the KEYNOTE-355 CSR.

Table 21: Analysis of change from baseline in EQ-5D VAS at week 15 - CPS ≥10 (FAS population)

	Baseline		Week 15		Change from Baseline at Week 15	
Treatment	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**LS Mean (95% CI) †**
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise comparison					**Difference in LS Means 95% CI)**	**p-Value**
Pembrolizumab + chemotherapy vs. Placebo + chemotherapy					[redacted]	[redacted]

† Based on cLDA model with the PRO scores as the response variable, and treatment by timepoint interaction, and stratum (defined by stratification factors of chemotherapy on study [taxane vs gemcitabine/carboplatin] and prior treatment with same class of chemotherapy in the (neo)adjuvant setting [yes vs no]) as covariates.

For baseline and Week 15, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group. Two-sided p-value.

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Figure 6: Empirical mean change from baseline in EQ-5D VAS across time (Mean +/- SE) CPS ≥10 (FAS population)

[redacted]

[redacted]

B.2.7 Subgroup analysis

A series of analyses was pre-specified in the KEYNOTE-355 study protocol [29] to determine whether the treatment effect was consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints were estimated and plotted within each category of the following classification variables:

- Chemotherapy on study (nab-paclitaxel vs paclitaxel vs gemcitabine/carboplatin; taxane vs gemcitabine/carboplatin)
    - Detailed data also provided in cost effectiveness section B.3.
- Tumour PD-L1 status (CPS ≥1 vs CPS <1; CPS ≥5 vs CPS <5; CPS ≥10 vs CPS <10; CPS ≥15 vs CPS <15; CPS ≥20 vs CPS <20). *Note: these subgroup analyses will only be conducted in the all subjects population*.
- Prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).
- Prior (neo)adjuvant chemotherapy (yes vs no)
- Prior (neo)adjuvant taxane treatment (yes vs no)
- Prior (neo)adjuvant platinum treatment (yes vs no)
- Menopausal status (for females only; pre- vs post-menopausal)
- Age (<65 years vs ≥65 years)

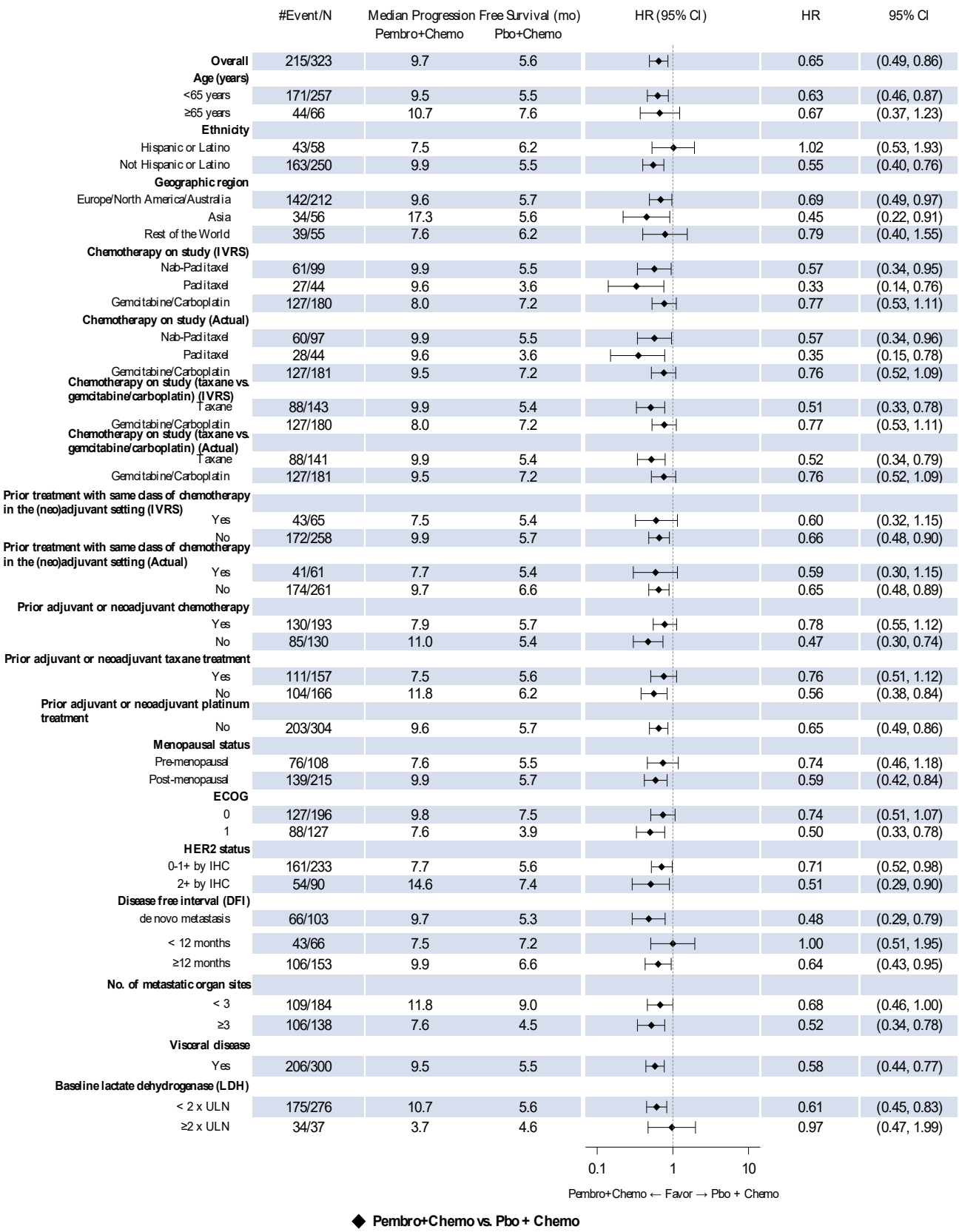
- Geographic region (Europe/Israel/North America/Australia vs Asia vs Rest of World)
- Ethnic origin (Hispanic vs Non-Hispanic)
- ECOG status (0 vs 1)
- HER2 status (2+ by IHC vs 0-1+ by IHC)
- Disease-free interval (de novo metastasis vs <12 months vs ≥12 months)
- Number of metastatic sites (<3 vs ≥3)
- Visceral disease (yes vs no)
- LDH (≥2.0 x Upper Limit of Normal [ULN] vs <2.0 x ULN)

The treatment benefit of pembrolizumab + chemotherapy on PFS, OS, and ORR compared with placebo + chemotherapy in participants whose tumours express PD-L1 CPS ≥10 is consistent across subgroups

The OS and PFS HR forest plots across subgroups for those whose tumours expressed PD-L1 CPS≥10 are presented below. Subgroup analysis for all subjects is in appendix E. Further information on PFS and OS for the subgroups of taxanes and non-taxane (gemcitabine with carboplatin) are also presented in the section below.

Figure 7: Forest Plot of OS hazard ratio by Subgroup Factors - CPS ≥10

Figure 8: Forest plot of PFS Hazard Ratio based on BICR assessment per RECIST 1.1. by subgroup factors - CPS ≥10



Note for OS and PFS Forest plots: Analysis (HR and 95% CI) in the overall population is based on the stratified Cox regression model with Efron's method of tie handling stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin) and 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.

As reported within section 2.3, KEYNOTE-355 study participants were stratified by chemotherapy on study (taxane vs non-taxane), PD-L1 tumor expression (based on CPS ≥1 cut-off) and prior treatment with same class of chemotherapy in earlier disease setting. The results of the taxane subgroup analyses remain valid for the purposes of the HTA since the balance in baseline characteristics and prognostic factors is maintained to a great degree considering that CPS ≥10 is a subset of the original CPS ≥1 population (one of the three stratification factors used). Therefore, the taxane specific subgroup can be leveraged directly within the HTA submission to inform the decision problem and the cost-effectiveness comparisons.

Table 22: Patient characteristics CPS ≥10 who received a taxane

	Pembrolizumab + Taxane		Placebo + Taxane	
	n	%	n	%
Subjects in population	96		47	
Gender				
Female	96	100	47	100
Age (Years)				
< 65	[redacted]	[redacted]	[redacted]	[redacted]
>= 65	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Race				
American Indian Or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Black Or African American	[redacted]	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity				
Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]

Not Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region		0		0
Asia	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]
Australia	[redacted]	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy on Study (IVRS)				
Nab-Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine/Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy on Study (Actual)				
Nab-Paclitaxel	61	63.5	36	76.6
Paclitaxel	33	34.4	11	23.4
Gemcitabine/Carboplatin	1	1	0	0
Missing	1	1	0	0
Prior Treatment with Same Class Chemotherapy in the Neoadjuvant or Adjuvant Setting (IVRS				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Prior Treatment with Same Class Chemotherapy in the Neoadjuvant or Adjuvant Setting (Actual)				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Disease Status				
Metastatic, De Novo	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic, Recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Locally Recurrent Inoperable	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
ECOG				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
HER2 Status				
0-1+ by IHC	[redacted]	[redacted]	[redacted]	[redacted]
2+ by IHC	[redacted]	[redacted]	[redacted]	[redacted]
History of Brain Metastasis				
Yes	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]

Menopausal Status				
Pre-menopausal	[redacted]	[redacted]	[redacted]	[redacted]
Post-menopausal	[redacted]	[redacted]	[redacted]	[redacted]
Disease Free Interval				
de novo metastasis	[redacted]	[redacted]	[redacted]	[redacted]
< 12 months	[redacted]	[redacted]	[redacted]	[redacted]
>= 12 months	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Lactate Dehydrogenase (LDH)				
Normal	[redacted]	[redacted]	[redacted]	[redacted]
> ULN and < 2 x ULN	[redacted]	[redacted]	[redacted]	[redacted]
>= 2 x ULN	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Sum of Target Lesion Size at Baseline (Central) (mm)				
Subjects with data	[redacted]	[redacted]	[redacted]	
Mean	[redacted]	[redacted]	[redacted]	
SD	[redacted]	[redacted]	[redacted]	
Median	[redacted]	[redacted]	[redacted]	
Range	[redacted]	[redacted]	[redacted]	
Sum of Target Lesion Size at Baseline (Investigator) (mm)				
Subjects with data	[redacted]	[redacted]	[redacted]	
Mean	[redacted]	[redacted]	[redacted]	
SD	[redacted]	[redacted]	[redacted]	
Median	[redacted]	[redacted]	[redacted]	
Range	[redacted]	[redacted]	[redacted]	
Database Cut-off Date: 11DEC2019				

Figure 9: Kaplan-Meier Curves of OS - PD-L1 CPS ≥10 Gemcitabine + Carboplatin (ITT population)

Figure 10: Kaplan-Meier Curves of OS - PD-L1 CPS ≥10 Taxanes (ITT population)

Figure 11: Kaplan-Meier Curves of PFS - PD-L1 CPS ≥10 Taxanes (ITT population)

Figure 12: Kaplan-Meier Curves of PFS - PD-L1 CPS ≥10 Gemcitabine + carboplatin (ITT population)

B.2.8 Meta-analysis

The list of chemotherapy comparators within the final scope issued by NICE included paclitaxel and docetaxel [30]. During TA639 clinical experts noted that taxanes (paclitaxel, nab-paclitaxel and docetaxel) are associated with broadly similar efficacy outcomes in advanced breast cancer patients [31]. For the purposes of decision making and based on clinical expert opinion, the Appraisal Committee (AC) accepted that the efficacy of nab-paclitaxel and paclitaxel could be assumed as broadly equivalent. However, since tolerability may differ between amongst the different taxanes, clinical experts noted that weekly paclitaxel would constitute the preferred taxane treatment option for this group of patients in a real world setting due to its improved toxicity profile versus that of docetaxel.

KEYNOTE-355 is the only study that contains data on outcomes [redacted] which can provide clinical and safety evidence supporting the use of pembrolizumab in combination with taxanes in patients with recurrent inoperable or metastatic TNBC. Therefore, a pairwise meta-analysis was not necessary or required to inform the decision problem for the comparisons versus paclitaxel and docetaxel as outlined in the NICE final scope [30].

Since the final list of comparators includes Atezolizumab + nab-paclitaxel (recently approved by NICE for mTNBC PD-L1 positive patents), an indirect treatment comparison (ITC) was necessary to address the decision problem (refer to section 2.9).

B.2.9 Indirect treatment comparison

As noted in section 1.3.2 above, PD-L1 ascertainment differs between KEYNOTE-355 and IMpassion-130. KEYNOTE-355 PD-L1 expression was measured using the PD-L1 IHC 22C3 pharmDx assay (Dako North America, Inc), whereas in IMpassion130, PD-L1 expression was measured with SP142 PD-L1 immunohistochemical assay (Ventana Medical Systems)[32]. These tests differ in both the antibodies, scoring algorithms and cut-off thresholds used to determine the PD-L1 positivity, which may impact upon the comparability and overlap between study populations being considered for the ITC. This may have implications in the robustness of the ITC and therefore assay differences are discussed below for consideration and to ensure ITC reliability.

The KEYNOTE-355 (with Dako 22C3) scoring algorithm uses Combined Positive Score (CPS) and is defined as "the number of PD-L1 staining cells including tumour cells, lymphocytes and macrophages, divided by the total number of viable tumour cells, multiplied by 100" and it is not expressed as a percentage [22]. Whereas in IMpassion130 PD-L1 positivity is based upon tumour infiltrating immune cell (IC) and is calculated as the "presence of discernible PD-L1 staining of any intensity in tumour-infiltrating immune cells covering ≥1% of tumour area occupied by tumour cells, associated intratumoral, and contiguous peritumoral stroma". Therefore, the PD-L1 positivity outcome is subjective and cannot be extrapolated between the two assays due to methodological differences. It should also be noted the [redacted] using the 22C3 pharmDx assay.

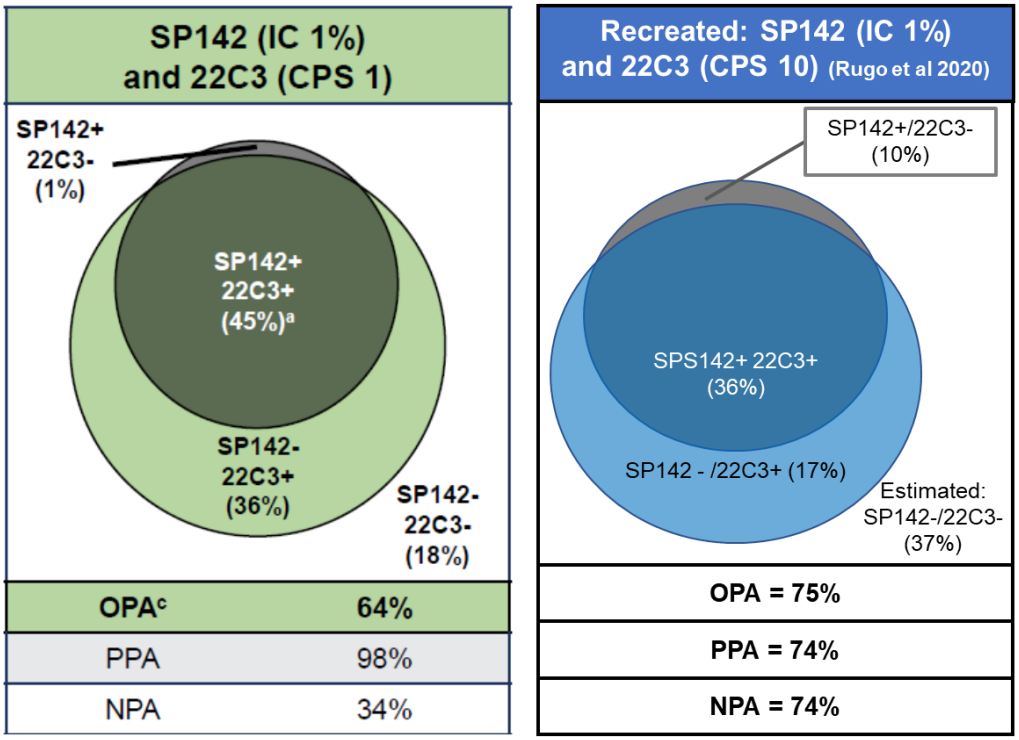
Rugo et al 2020 explored in detail the differences in PD-L1 ascertainment in post-hoc analyses from a subset of the ITT IMpassion-130 population, to understand the feasibility of harmonisation between the different PD-L1 assays available for mTNBC. The authors subsequently provide estimates of PFS and OS for Atezolizumab + nab-paclitaxel for the IMpassion-130 patients testing as PD-L1 +ve using the CPS ≥ 10 cut off and the IHC Dako 22C3 pharmDx assay [19].

To explore assay concordance, the authors retested available samples using both the VENTANA SP142, SP263 and Dako 22C3 assays from a subset of patients from IMpassion-130 patients with sufficient tissues samples available (or Biomarker Evaluable Population (BEP)), comprising of 68% of the original ITT population [18]. The authors then went on to report the PFS and OS estimates from IMpassion-130 by PD-L1 positive subgroup cut-offs as defined by each of the respective assays. For the Dako 22C3 retested samples in particular,

the authors explored the efficacy of Atezolizumab in combination with nab-paclitaxel for subgroups defined as PD-L1 positive using the CPS ≥1 and CPS ≥10 scores, which are presented in two separate publications [18, 20].

Overall, 285 of the 614 patients re-tested as PD-L1 positive based on IC≥1% with the SP-142 Assay (46% versus the original 41% in IMpassion-130 ITT population) [20]. At CPS ≥ 1 22C3 cut-offs, the authors estimated the overall percentage agreement between SP142 and 22C3 (OPA; defined as those testing PD-L1 positive or PD-L1 negative with both Assays) to be equal to 64% (see Figure 13). The authors concluded that the SP142 population was nested within the 22C3 population when exploring the CPS ≥ 1 cut-offs from 22C3 [20], since positive percentage agreement (PPA) between the two assays was 98% (those testing positive with 22C3 divided to those testing positive with SP142). However, only a 45% of the total BEP sample testing positive for PD-L1 status with both SP142+/22C3+ (see Figure 13 below) [19]. According to the authors, analytical concordance between assays requires an OPA ≥ 90% for harmonisation, therefore the assays cannot be harmonised and the populations identified therefore may not be comparable [20]. [redacted]. Evidence of concordance of SP142 and 22C3 using the CPS ≥ 10 is reported in a separate publication by the same authors.

Figure 13: Prevalence and analytical concordance as reported in Rugo et al using CPS ≥ 1 [20] and recreated estimates from CPS ≥ 10 abstract publication in Rugo et al using CPS ≥ 1 [20] and re-created estimates from CPS ≥ 10 abstract publication



A further analysis of analytical concordance between SP142 and 22C3 using the CPS≥10 cut-off for PD-L1 positivity from the Dako 22C3 assay [redacted] has also been presented by Rugo et al 2019 [18].

When looking at the CPS ≥10 cut-off for PD-L1 positivity, the results suggested a reduced PPA between the two assays from 98% to 74% and a negative predictive agreement (NPA) increase from 34% to 74% (see Figure 13 above). In addition, when looking at the CPS ≥10 cut-off for PD-L1 positivity with the Dako 22C3 assay only 36% of patient samples tested was identified as both SP142+/22C3+ (down from 45% at CPS≥1 cut-off reported above), suggesting an even smaller overlap between the two PD-L1 positive populations [19]. Finally, the authors reported an OPA of 75% between the 22C3 and SP142 assays, which again is suboptimal for assay harmonisation.

Evidence of comparison for both CPS ≥ 1 and CPS ≥ 10 with IC≥1% and respective assays demonstrate that the SP142 and 22C3 assays cannot be harmonised, since they may potentially identify different populations with regards to tumour biomarker biology with a very limited overlap[18]. Additional uncertainty around the estimates of the population overlap between the two assays remains since the current effect estimates are based on post-hoc analysis from a subset of the original ITT population (BEP) from IMpassion-130 alone.

The potentially limited population overlap between the two study populations may have implications in the robustness of the ITC and in any subsequent cost-effectiveness estimates produced. Therefore, it needs further consideration at the feasibility assessment stage alongside any other key population differences within IMpassion-130 and KEYNOTE-355.

B.2.9.1 Systematic literature review, feasibility assessment and ITC methodology

A comprehensive Global clinical SLR for the untreated locally recurrent inoperable or metastatic TNBC with a wide range of pharmaceutical interventions was performed in November 2020, to identify all studies potentially relevant for inclusion in evidence synthesis.

The final SLR hits were subsequently filtered based on pre-defined study inclusion/exclusion criteria to identify the studies relevant for inclusion in the evidence synthesis, as per the decision problem and the comparators listed within the final scope issued by NICE.

Of the 1,704 abstracts and 112 full-text publications which were screened, the final evidence base included 16 citations representing 7 unique RCTs. Of these 7 RCTs, only 2 RCTs reported comparators relevant for the UK decision problem [27, 33]. The remaining five trials

were excluded as they were not listed as eligible comparative treatments by NICE. It should be noted that no further studies were identified relevant for the chemotherapy comparison, specific to the PD-L1 positive mTNBC population. The full study identification process including the study inclusion & exclusion criteria and methods for the evidence synthesis are described in detail in Appendix D of this submission.

The final studies retained were KEYNOTE-355 and IMpassion130 by Rugo et al 2020 reporting results of a post-hoc subgroup analysis from PD-L1 CPS ≥ 10 IMpassion130 study population[18, 26]. **Error! Reference source not found.** below outlines the unique studies and publications retained for evidence synthesis.

In order to gauge the appropriateness of proceeding with an NMA, a separate feasibility assessment was conducted for each of the three populations of interest [34, 35]. This feasibility assessment included: 1) assessment of whether the RCT evidence for the interventions of interest do form one evidence network for each research question and outcome of interest, and 2) assessment of the distribution of study and patient characteristics that may affects treatment effects across direct comparisons of the evidence network. Extracted data were evaluated in order to ensure that only trials meeting specific inclusion criteria (e.g. randomized, early stage locally advanced non-metastatic TNBC, previously treated metastatic TNBC, previously untreated locally recurrent inoperable or metastatic TNBC) are included, regardless of the trial phase.

Table 23: Summary of unique studies identified from clinical SLR for evidence synthesis (narrowed down by results reported in CPS ≥ 10 population)

Author	Study	Population	Intervention	Comparator
Rugo et al 2020	IMpassion130	PD-L1 CPS ≥ 10	Atezolizumab + nab-paclitaxel	Placebo + Nab-paclitaxel
MSD (& Cortes et al 2020)	KEYNOTE-355*	PD-L1 CPS ≥ 10	Pembrolizumab + chemotherapy	Placebo + chemotherapy
* KEYNOTE-355 treatment effects used subsequently for the evidence synthesis are specific to the Pembrolizumab + taxanes (paclitaxel + nab-paclitaxel) versus taxanes alone study sub-group to reduce heterogeneity (described below).				

Table 24 below reports the study characteristics, including patient inclusion criteria amongst the studies retained for evidence synthesis. Table 25 presents the baseline characteristics of the trial populations for KEYNOTE-355 PD-L1 CPS ≥ 10 and IMpassion-130 PD-L1 IC ≥ 1%

population for comparison. No baseline characteristics or Kaplan-Meier data are reported within the Rugo et al 2020 abstract publication for patients identified as CPS ≥ 10 PD-L1 positive from IMpassion130 [26, 32, 36]. Figure 14**Error! Reference source not found.** below presents the network formed from the two studies retained.

Table 24: Study characteristics of studies included in the evidence synthesis

Characteristic	KEYNOTE-355 [26]	IMpassion130 [33]
Phase	III	III
Masking	Double-blind	Double-blind
Age	≥ 18	≥ 18
Sex	All	All
Disease stage	Locally recurrent inoperable or metastatic	Locally advanced or metastatic
ECOG performance score	≤ 1	≤ 1
Start date	July 27, 2016	June 23, 2015
TNBC confirmation	Central confirmation	Investigator confirmation
Crossover permitted	No	No
Prior systemic therapy for unresectable locally advanced or metastatic disease	Not permitted	Not permitted
Prior adjuvant/neoadjuvant chemotherapy	Permitted if treatment was completed ≥ 6 months prior to recurrence or ≥ 12 months prior to recurrence if treated with same class of chemotherapy	Permitted if treatment was completed ≥ 12 months prior to randomization
PD-L1 status	Unrestricted	Unrestricted
Assessment of PD-L1 expression	PD-L1 IHC 22C3 pharmDx test (Dako North America, Inc.)	SP142 PD-L1 immunohistochemical assay (Ventana Medical Systems)
Intervention	Pembrolizumab + chemotherapy (comprising of paclitaxel, nab-paclitaxel or gemcitabine/carboplatin)	Atezolizumab + nab-paclitaxel
Comparator	Placebo + chemotherapy (comprising of paclitaxel, nab-paclitaxel or gemcitabine/carboplatin)	Placebo + nab-paclitaxel
Study stratification factors	1. PD-L1 status ≥ CPS 1 score based on 22C3 assay, 2. Prior same class chemotherapy in (neo)adjuvant setting (Yes/No) 3. Chemotherapy on study (taxane versus non-taxane)	1. PD-L1 IC ≥ 1% status based on SP-142 assay 2. Prior taxane use 3. Liver metastases

Primary PFS endpoint assessment	Assessed by blinded independent central review	Assessed by local investigator
Endpoints reported	PFS and OS by all chemotherapies and by chemotherapy backbones (paclitaxel, nab-paclitaxel, gemcitabine/carboplatin)	PFS and OS by nab-paclitaxel alone

Table 25: Patient baseline characteristics

Characteristics	KEYNOTE-355 (PD-L1 CPS ≥ 10) N = 323 [26]	KEYNOTE-355 (PD-L1 CPS ≥ 10 taxane subgroup) n=143[#]	IMpassion130 (PD-L1 IC ≥ 1%) N = 369 [33]
Median age (range)	53 (22-83)	[redacted]	53 (26-85)
Female sex – no. (%)	323 (100)	[redacted]	368 (99.7)
White – no. (%)	223 (69.0)	[redacted]	254 (68.8)
Asian – no. (%)	64 (19.8)	[redacted]	66 (17.9)
Black – no. (%)	15 (4.6)	[redacted]	23 (6.2)
ECOG performance status 0 – no. (%)	196 (60.7)	[redacted]	219 (59.3)
ECOG performance status 1 – no. (%)	127 (39.3)	[redacted]	149 (40.4)
ECOG performance status 2 – no. (%)	0	[redacted]	1 (0.3)
Metastatic disease – no. (%)	309 (95.7)	[redacted]	321 (87.0)
Brain metastases– no. (%)	11 (3.4)	[redacted]	26 (7.0)
Disease Free Interval (DFI) ≥ 6 month but < 12 months	66 (20.4)	[redacted]	0 (0)
# Baseline characteristics from PD-L1 populations were compared between studies during feasibility assessment for the NMA; however, baseline data from PD-L1 CPS 10 population were recreated from Table 22 for population comparability purposes; pooled median age for taxanes could not be estimated without access to PLD.			

KEYNOTE-355 and IMpassion130 enrolled patients irrespective of PD-L1 expression status. However, as discussed, there are notable differences in the PD-L1 ascertainment between the two studies which may limit the population overlap for evidence synthesis (see section 2.9 above). Both studies are international phase III randomized two double-blind studies. KEYNOTE-355 required central histological confirmation of TNBC diagnosis, meanwhile, IMpassion130 allowed local confirmation of TNBC histology. Both studies enrolled previously untreated patients aged 18 years or older with an ECOG performance score of 0 or 1. The primary method for PFS assessment was a blinded independent review committee in KEYNOTE-355, whereas, in IMpassion130 it was based on local investigator-assessment (see Table 24).

Baseline patient characteristics were largely similar between KEYNOTE-355 and IMpassion130 publications (with the exception on DFI in KEYNOTE-355). The same was the case between KEYNOTE-355 taxane subgroup data. However, IMpassion130 only reported baseline characteristics in the PD-L1 IC ≥ 1% group, thus the baseline characteristics of these patients may differ systematically from the modelled CPS ≥ 10 population versus the KEYNOTE-355 CPS ≥ 10 score population (Table 25 above).

Overall, a greater proportion of patients in KEYNOTE-355 had metastatic disease while a greater proportion of patients in IMpassion130 had brain metastases. KEYNOTE-355 permitted prior adjuvant/neoadjuvant chemotherapy if treatment was completed ≥ 6 months prior to recurrence or ≥ 12 months prior to recurrence if treated with same class of chemotherapy. However, IMpassion130 patients were required to have completed prior adjuvant/neoadjuvant chemotherapy for ≥ 12 months prior to randomization. Overall, in KEYNOTE-355 a 20.4% of the CPS ≥ 10 population ([redacted]; see Table 25) had disease-free interval (DFI) prior to study participation of 6 to 12 months (refer to clinical chapter 2.5 and Table 6). Lower DFI has been associated with poorer survival (prognostic factor)outcomes for patients based on clinical expert opinion and upon RWE publications [6, 14]. Therefore, a proportion of patients enrolled in KEYNOTE-355 taxane subgroup may have a more severe disease versus the IMpassion130 patients.

KEYNOTE-355 compared a combination of pembrolizumab and chemotherapy to chemotherapy only. Chemotherapy was investigator's choice of gemcitabine and carboplatin or paclitaxel and nab-paclitaxel. Patients were pre-assigned to investigator's choice of chemotherapy before randomization and then randomized to receive either the assigned chemotherapy alone or the assigned chemotherapy in combination with pembrolizumab [26]. IMpassion130 compared the combination of atezolizumab and nab-paclitaxel to nab-paclitaxel only. Dosing and administration schedule for nab-paclitaxel was identical between KEYNOTE-355 andIMpassion130 (100 mg/m2 IV on Days 1, 8 and 15 of each 28-day cycle) [33]. KEYNOTE-355 taxane subgroup specific treatment effects can be leveraged within the ITC to ensure a more homogeneous common comparator being used in the ITC.

A summary of the quality assessment of included trials in the NMA are provided in Appendix D.1.2.4 of this submission. Quality assessment was conducted for KEYNOTE-355, Rugo et al 2020, and IMpassion130 [18, 32, 33]. Rugo et al 2020 was a post-hoc analysis of

IMpassion130 and as such quality assessment for IMpassion130 was also conducted. Therefore, baseline characteristics used to conduct the feasibility assessment were derived from the IMpassion130 study. KEYNOTE-355 and IMpassion130 can be considered of high quality; however, Rugo et al 2020 is limited by the fact that it is a retrospective post-hoc analysis of IMpassion130.

B.2.9.2 Preferred evidence synthesis method and overview of analyses

Preferred method for evidence synthesis

Both simple and complex evidence synthesis methods were explored including; the Bayesian NMA framework, Matching Adjusted Indirect Comparisons (MAIC) and the simpler Bucher method for comparisons versus atezolizumab + nab-paclitaxel.

Due to absence of baseline characteristics and Kaplan-Meier data specific to the patients identified as CPS ≥ 10 PD-L1 positive from IMpassion-130, it was not deemed feasible to use a MAIC for any further population adjustments (see also section 2.9.2 below) [18]. Therefore, the NMA framework was selected as the preferred method for evidence synthesis based on the evidence base identified and to ensure additional future comparisons or adjustments could be added if the evidence base expanded during the HTA submission if necessary. It should be noted that when indirect comparisons are indirectly assessed through a common comparator, the results from an NMA and a simple Bucher indirect comparison are comparable.

Overview of the analysis and base-case assumptions

As previously discussed in the feasibility assessment, comparisons of study, treatment, and patient characteristics across trials revealed potential key differences that may introduce bias into the NMA. However, NMAs for the base-case analyses were deemed feasible for both PFS and OS to address part of the decision problem. The analysis overview is as following:

1. Baseline patient characteristics for IMpassion130 was only reported in the PD-L1 IC ≥ 1% group, thus the baseline characteristics of these patients may differ systematically from the modelled CPS ≥ 10 population from IMpassion-130 (Rugo et al 2020), which is necessary for this submission and statistical methods cannot be used for any further adjustments of imbalances.

2. In KEYNOTE-355, PD-L1 expression was measured by PD-L1 IHC 22C3 pharmDx test (Dako North America, Inc). Meanwhile for IMpassion130, PD-L1 expression was measured with SP142 PD-L1 immunohistochemical assay (Ventana Medical Systems). These tests have been previously compared and low rates of concordance were found (Rugo et al. 2020)[18].

3. Rugo et al. 2020 used tissue samples from IMpassion130 tested with both SP142 PD-L1 and IHC 22C3 pharmDx to create a model that was used to estimate hazard ratios for OS and PFS in patients with CPS ≥ 10 as measured with IHC 22C3 pharmDx. Because the model used by Rugo et al. 2020 attempted to adjust for this relative treatment effect modifier by estimating survival from IMpassion130 in the same population as KEYNOTE-355, HRs from this study were used as a primary scenario for NMA [18].

4. KEYNOTE-355 included both paclitaxel and nab-paclitaxel as chemotherapy backbones, whereas IMpassion-130 only included nab-paclitaxel as an option. Based on clinical expert opinion and KEYNOTE-355 data showing overlapping 95%CIs for paclitaxel and nab-paclitaxel, the primary analysis assumes equivalent efficacy and pooled HRs for OS and PFS from KEYNOTE-355 in patients who were pre-assigned to paclitaxel or nab-paclitaxel were used in the NMA (pooled taxanes). This is in line with prior AC preferences that taxanes are considered broadly equivalent with regards to survival outcomes noted in TA639[31]. It also increases the data used from KEYNOTE-355 for the estimation of relative treatment, ensuring concordance between treatment effect estimates within the model and the clinical trial. The impact of using nab-paclitaxel alone data from KEYNOTE-355 to inform the estimates of the common comparator for the NMA is explored in sensitivity analysis.

5. HRs for investigator-assessed PFS were used for KEYNOTE-355 in the NMA in order to balance the method of PFS assessment across the network of evidence for the base-case. Blinded independent review committee PFS estimates from KEYNOTE-355 are explored in scenario analysis.

6. Because only one study connected each treatment in the network of evidence, between-study heterogeneity could not be estimated. Therefore, the NMAs were performed with a fixed-effects assumption, which is less plausible than a random effects assumption.

7. Time-varying HR analyses do not rely on the proportional hazards' assumption, and are generally preferred; however, due to the low concordance identified between the

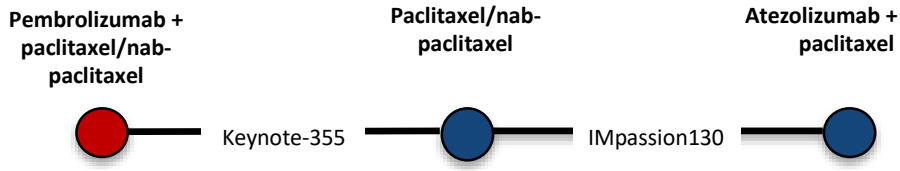
different PD-L1 immunohistochemistry assays, constant OS and PFS HRs obtained from Rugo et al 2020 were used to avoid any further assumptions from being imposed into the ITC. Kaplan-Meier curves for the IMpassion130 population of interest (Rugo et al 2020) was not reported to assess this element, thus, analyses were based on an assumption of constant HRs, which may not reflect a realistic scenario.

8. The Deviance information criterion (DIC) was used to assess competing models (lowest DIC suggests more parsimonious model in general but in this case DIC statistic may be limited due to low number of studies informing analysis and differences described already above).

B.2.9.3 Network of evidence

Figure 14 below shows the base-case network of evidence formed for OS and PFS from the two studies retained for evidence synthesis (using pooled taxanes from KEYNOTE-355). Please refer to Figure 7 Figure 8 and Appendix D.1.2.1 for KEYNOTE-355 effect sizes used in the NMA.

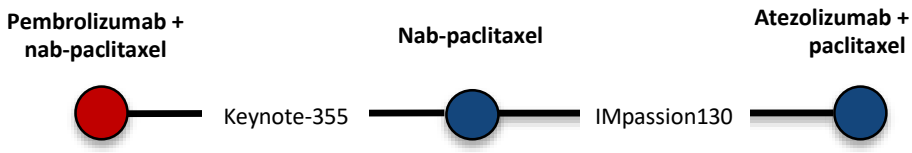
Figure 14: Network of evidence; pooled taxanes (paclitaxel & nab-paclitaxel) as a common comparator from KEYNOTE-355 (PFS & OS) – primary analysis



The structure of the network used in sensitivity analysis with nab-paclitaxel alone as a common comparator from KEYNOTE-355, remains unaltered. This is presented in

Figure 15 below.

Figure 15: Network of evidence; nab-paclitaxel only common comparator only from KEYNOTE-355 (PFS & OS) – sensitivity analysis



B.2.9.3 NMA results for OS and PFS

OS NMA results: pembrolizumab + taxanes vs atezolizumab+ nab-paclitaxel

The results of the base case fixed-effects constant HR NMA are shown in Table 26. Pembrolizumab + taxanes was associated with a [redacted] versus atezolizumab + nab-paclitaxel (HR of [redacted]). Using nab-paclitaxel alone as a common comparator from KEYNOTE-355 also generated a [redacted] in favour Pembrolizumab + nab-paclitaxel versus atezolizumab + nab-paclitaxel of [redacted]). The CrIs associated with this analyses are wider due to the smaller sample size used from KEYNOTE-355 (refer to Figure 7 for OS effect sizes used in the NMA).

Table 26: Hazard ratios fixed-effects constant HR network meta-analysis of OS

Comparison	KEYNOTE-355 PD-L1 expression subgroup	IMpassion130-PD-L1 expression subgroup	HR (95% CrI)	DIC
Base-case – taxanes pooled				
Pembrolizumab + paclitaxel/nab-paclitaxel vs. atezolizumab + nab-paclitaxel	CPS ≥ 10	CPS ≥ 10	[redacted]	3.39
Sensitivity analysis – nab-paclitaxel common comparator from KEYNOTE-355				
Pembrolizumab + nab-paclitaxel vs. atezolizumab + nab-paclitaxel	CPS ≥ 10	CPS ≥ 10	[redacted]	3.40
DIC: Deviance information criterion; lowest DIC statistic results in more parsimonious model; see Figure 7 for OS effect sizes used in the NMA.				

PFS NMA results: pembrolizumab + taxanes vs atezolizumab+ nab-paclitaxel

The results of the base case fixed-effects constant HR NMA are shown in Table 27. Pembrolizumab + taxanes was associated with a numerical PFS benefit versus atezolizumab + nab-paclitaxel [redacted]. The same was seen in the comparison using nab-paclitaxel alone as a common comparator ([redacted] The results remained consistent when BICR PFS data from KEYNOTE-355 were used in the ITC, suggesting a numerical PFS benefit in favour of Pembrolizumab (refer to Appendix D1.2.1 & Figure 8 for PFS effect sizes used in the NMA).

Table 27: Hazard ratios fixed-effect network constant HR meta-analysis of PFS

Comparison	KEYNOTE-355 PD-L1 expression subgroup	IMpassion130-PD-L1 expression subgroup	HR (95% CrI)	DIC
Base-case – using KN-355 INV-assessed PFS & taxanes pooled				
Pembrolizumab + paclitaxel/nab-paclitaxel vs. atezolizumab + nab-paclitaxel	CPS ≥ 10	CPS ≥ 10	[redacted]	3.38
Sensitivity analysis – using KN-355 INV-assessed PFS & nab-paclitaxel as common comparator from KEYNOTE-355				
Pembrolizumab + nab-paclitaxel vs. atezolizumab + nab-paclitaxel	CPS ≥ 10	CPS ≥ 10	[redacted]	3.40
Scenario analyses – using KN-355 BICR-assessed PFS from KEYNOTE-355				
Pembrolizumab + paclitaxel/nab-paclitaxel vs. atezolizumab + nab-paclitaxel	CPS ≥ 10	CPS ≥ 10	[redacted]	3.39
Pembrolizumab + nab-paclitaxel vs. atezolizumab + nab-paclitaxel	CPS ≥ 10	CPS ≥ 10	[redacted]	3.36
DIC: Deviance information criterion; lowest DIC statistic results in more parsimonious model, INV: investigator/local radiology assessed PFS in KN-355. IMpassion130 IA-only reports investigator assessed PFS results; see Appendix D1.2.1 & Figure 8 for PFS effect sizes used in the NMA.				

B.2.9.4 Heterogeneity and inconsistency

Systematic differences in known and unknown effect-modifiers among studies comparing the same interventions in direct fashion may result in between-study heterogeneity. An imbalance in the distribution of effect modifiers between studies comparing different interventions may result in transitivity violations and therefore biased indirect comparison estimates being generated.

As noted above, each connection in the network was only described by a single trial, therefore stable estimates of between-study heterogeneity could not be obtained. Consequently, results are based on fixed-effects model, despite a preference for random effects-model; some of the credible intervals may be narrower than they should be and should be interpreted with caution.

The main difference between studies identified was the impact of PD-L1 ascertainment resulting in a limited population overlap and its impact on population comparability for evidence synthesis. However, this was partially mitigated for by using PFS and OS estimates reported by Rugo et al. 2020 to adjust for this relative treatment effect modifier by estimating survival from IMpassion130 in the same population as KEYNOTE-355, which was subsequently used

in the NMA [18]. Due to data limitations, the impact of other potential treatment effect modifiers could not be ascertained.

B.2.9.5 Interpretation of results and ITC uncertainties

The validity of the findings based on the current NMA depends on the quality of the RCTs and the extent of any violations in the similarity and consistency assumptions across studies. In a NMA of RCTs involving multiple treatment comparisons, the randomisation holds only within the individual trials and not across trials. If the different direct comparisons shows systematic differences in study and patient characteristics, and these differences are treatment effect modifiers, then the estimates of any indirect comparison as obtained with the NMA will be biased. The feasibility assessment to assess heterogeneity in terms of treatment and outcome characteristics as well as the study and patient characteristics was performed which identified several important differences.

In the case of this NMA, key uncertainties arise primarily from differences in PD-L1 ascertainment (including; antibodies, assays, scoring algorithms) between KEYNOTE-355 (pharmDx 22C3 assay by Dako) and IMpassion130 (SP142 Ventana assay) which may limit population comparability for the purposes of the NMA. Rugo et al 2020 demonstrated limited population overlap between the PD-L1 positive populations identified from different PD-L1 assays used in IMpassion130 and KEYNOTE-355 at CPS ≥10 cut-off for PD-L1 positivity with the Dako 22C3 assay only 36 % of patient samples tested was identified as both SP142+/22C3+ whilst 17% was SP142-/22C3+ (Figure 13), concluding that the assays could not be harmonised since they potentially identify different populations with regards to tumour biology.

It was only possible to adjust for PD-L1 ascertainment differences between studies partially since this was reliant upon a post-hoc exploratory analysis conducted in a subset of the IMpassion-130 ITT population [18]. An ITC using IMpassion-130 PD-L1 IC ≥ 1% data (as published by Schmid et al 2018) alongside the KEYNOTE-355 subgroup CPS ≥ 10, would have been suboptimal and a biased comparison considering the limited population overlap [33]. Despite the data limitations, the Rugo et al 2020 post-hoc analysis effect estimates offer a more robust approach in estimating the relative treatment effect between the two comparators.

It was not possible to adjust for any further differences in base-line characteristics between Rugo et al 2020 and the CPS ≥ 10 KEYNOTE-355 population since the Rugo et al 2020 did

not baseline characteristics for patients in the CPS ≥ 10 population. Therefore, some of these characteristics may still differ systematically versus the CPS ≥ 10 KEYNOTE-355 population.

Baseline characteristics and prognostic factors may also differ as a result of differences in the study inclusion criteria between Impassion130 and KEYNOTE-355. KEYNOTE-355 included a more severe population since 20.4% ([redacted]) of enrolled patients had a DFI of 6 to 12 months prior to study enrollment. Since IMpassion130 included patients with DFI $\geq$ 12 months and as such differences cannot be adjusted and may introduce bias against the pembrolizumab + taxane comparison, since a shorter DFI is associated with worse survival outcomes for these patients [37].

Due to lack of Kaplan-Meier curves for the comparator of interest population (CPS ≥ 10 modelled patients by Rugo et al 2020), ITC estimates were based upon the assumption of constant hazards being met, which may not be realistic. This approach was deemed more robust for the ITC to avoid any further uncertainty being introduced.

The limited evidence base meant that between-study heterogeneity could not be estimated. However, a number of steps were carried out to ensure heterogeneity was controlled for is possible, including; the use of investigation based PFS assessment from KEYNOTE-355 to balance out PFS assessment across studies, and the exploration of the impact of common comparator by using nab-paclitaxel data for the evidence synthesis. The decision to use pooled taxanes from KEYNOTE-355 as a common comparator was driven by trial data and clinical expert opinion suggesting no differentiation in survival outcomes between these agents (and in line with prior AC preferences in TA639) [31]. It also increases the data used from KEYNOTE-355, therefore limiting the uncertainty associated with these comparisons.

The SLR did not retrieve any chemotherapy TNBC specific PD-L1 positive CPS ≥ 10 publications for inclusion in the NMA, ensuring that the KEYNOTE-355 RCT contains the most relevant and up-to-date data for comparisons versus the standard chemotherapy comparators of paclitaxel and docetaxel.

In all of the analyses presented the NMA results suggested that Pembrolizumab in combination with taxanes is associated with an [redacted] versus Atezolizumab + nab-paclitaxel. In particular for the OS, the estimates used form KEYNOTE-355 are based on the IA2 dataset, therefore future KEYNOTE-355 data-cuts may [redacted] . Please refer to Appendix D for further information regarding the ITC, including effect sizes used in the NMA .

B.2.10 Adverse reactions

In KEYNOTE-355, safety and tolerability were assessed by clinical review of all relevant parameters including adverse experiences and laboratory tests during the treatment period up to the data cut-off date. The safety analyses were based on the ASaT populations, which consisted of all randomised patients who received at least one dose of study treatment (n=843). Participants were included in the group corresponding to the study intervention actually received. Incidence of, causality and outcome of Adverse Events (AEs), Grade3-5 AEs, serious adverse events (SAEs) and Adverse Events of Special Interest (AEOSI) were collected in the study. AEs were collected up to 30 days after last dose and SAEs up to 90 days after last dose of study medication.

The safety results of KEYNOTE-355 demonstrated that pembrolizumab + chemotherapy was generally well tolerated by participants with locally recurrent inoperable or metastatic TNBC. The safety profile of pembrolizumab + chemotherapy is consistent with the known safety profile of pembrolizumab monotherapy and the chemotherapies (taxane [paclitaxel or nab-paclitaxel] or gemcitabine and carboplatin) administered. No new safety concerns were identified.

The information presented below is for subjects with PD-L1 CPS ≥10. See appendix F for All Subjects population results.

The observed incidence of AEs, drug-related AEs, Grade 3 to 5 AEs, Grade 3 to 5 drug related AEs, deaths, deaths due to drug-related AEs, and any dose modification due to an AE were generally similar between the 2 treatment groups.

There was a higher observed incidence of [redacted].

B.2.10.1 Extent of drug exposure

The median duration of exposure to study intervention for all drugs was [redacted] weeks for pembrolizumab + chemotherapy group (range: [redacted] to [redacted]) and [redacted] weeks for placebo + chemotherapy group (range: [redacted] to [redacted] weeks).

At the time of data cut off, in the pembrolizumab combination, [redacted] of 219 patients ([redacted] person-time) had duration of exposure of 6 months compared with [redacted] of 103 patients ([redacted] person-time) in the placebo + chemotherapy group. [redacted] patients ([redacted] person-time) in the pembrolizumab + chemotherapy group received treatment for over 12 months compared with [redacted] ([redacted] person-time).

Table 28: Summary of drug exposure CPS ≥10 (ASaT Population)

	Pembrolizumab + chemotherapy (n=219)	Placebo + chemotherapy (n=103)
Number of weeks on therapy		
Mean	[redacted]	[redacted]
Median	[redacted]	[redacted]
SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Number of cycles		
Mean	[redacted]	[redacted]
Median	[redacted]	[redacted]
SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Database cut-off 11DEC2019		

Table 29: Exposure by duration CPS ≥10 (ASaT Population)

	Pembrolizumab + Chemotherapy (N=219)		Placebo + Chemotherapy (N=103)	
	n	Person-time	n	Person-time
Treatment Duration				
> 0 m	[redacted]	[redacted]	[redacted]	[redacted]
≥ 1 m	[redacted]	[redacted]	[redacted]	[redacted]
≥ 3 m	[redacted]	[redacted]	[redacted]	[redacted]
≥ 6 m	[redacted]	[redacted]	[redacted]	[redacted]
≥ 12 m	[redacted]	[redacted]	[redacted]	[redacted]
Each subject is counted once on each applicable duration category row. Duration of exposure is the time from the first dose date to the last dose date. Person-time is shown in person-month. Database Cutoff Date: 11DEC2019				

Table 30: Summary of drug exposure CPS ≥10 (ASaT Population)

Administrations	Pembrolizumab + chemotherapy N=219					Placebo + chemotherapy N=103				
	Pembrolizumab	Nab-paclitaxel	Paclitaxel	Gemcitabine	Carboplatin	Placebo	Nab-paclitaxel	Paclitaxel	Gemcitabine	Carboplatin
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Database Cut-off Date: 11DEC2019										

B.2.10.2 Summary of adverse reactions

Subjects with PD-L1 CPS >=10

Comparable proportion of patients in the pembrolizumab + chemotherapy and placebo + chemotherapy groups experienced AEs (98.6% vs 97.1%), grade 3-5 AEs (79.5% vs. 70.9%) and SAEs (28.3% vs. 24.3%). Drug related AEs (96.8% vs. 94.2%), drug related Grade 3 to 5 AEs (70.8% vs. 65.0%) and drug-related SAEs (18.7% vs. 14.6%) were also comparable between the two groups.

Drug related AEs that led to death occurred in [redacted] and [redacted] in the pembrolizumab + chemotherapy and placebo + chemotherapy groups, respectively.

Higher rates of discontinuation of any drug were seen in the pembrolizumab + chemotherapy group compared with the placebo + chemotherapy group ([redacted] which was primarily driven [redacted] ([redacted]. [redacted].

Table 31: Disposition of subjects - CPS ≥10 (ITT population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	220		103		323	
Status for Study Medication in Trial Segment of First Course Treatment						
Started	219		103		322	
Completed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical Progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Complete Response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician Decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive Disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal By Subject	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Status Not Recorded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Status for Trial						
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal By Subject	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Status Not Recorded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Clinical Progression and Progressive Disease are based on Investigator´s assessment and may be different from the data used in the primary analysis.

Progressive Disease refers to disease progression based on RECIST 1.1 and does not include Clinical Progression.

Study medication discontinuation refers to discontinuation of all study medications.

Status Not Recorded: Subjects without a completed study medication discontinuation form or without a completed study disposition form.

Database Cut-off Date: 11DEC2019

Table 32: Adverse event summary - CPS ≥10 (ASaT population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	219		103	
with one or more adverse events	216	(98.6)	100	(97.1)
with no adverse event	3	(1.4)	3	(2.9)
with drug-related† adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]

with serious drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with any dose modification‡ due to an adverse event	[redacted]	[redacted]	[redacted]	[redacted]
pembrolizumab/placebo dose modification	[redacted]	[redacted]	[redacted]	[redacted]
nab-paclitaxel dose modification	[redacted]	[redacted]	[redacted]	[redacted]
paclitaxel dose modification	[redacted]	[redacted]	[redacted]	[redacted]
gemcitabine dose modification	[redacted]	[redacted]	[redacted]	[redacted]
carboplatin dose modification	[redacted]	[redacted]	[redacted]	[redacted]
who died	[redacted]	[redacted]	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued any drug due to an adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued pembrolizumab/placebo	[redacted]	[redacted]	[redacted]	[redacted]
discontinued nab-paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
discontinued paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
discontinued gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
discontinued carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
discontinued any drug due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued pembrolizumab/placebo	[redacted]	[redacted]	[redacted]	[redacted]
discontinued nab-paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
discontinued paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
discontinued gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
discontinued carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
discontinued any drug due to a serious adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued pembrolizumab/placebo	[redacted]	[redacted]	[redacted]	[redacted]
discontinued nab-paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
discontinued paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
discontinued gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
discontinued carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
discontinued any drug due to a serious drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued pembrolizumab/placebo	[redacted]	[redacted]	[redacted]	[redacted]
discontinued nab-paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
discontinued paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
discontinued gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
discontinued carboplatin	[redacted]	[redacted]	[redacted]	[redacted]

† Determined by the investigator to be related to the drug.

‡ Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Grades are based on NCI CTCAE version 4.03.

Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90

days after last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 11DEC2019

2.10.3 Adverse Events

The most frequently reported AEs (incidence ≥30%) were: [redacted].

AEs (incidence ≥10%) with a greater risk difference for pembrolizumab in combination with chemotherapy (ie, the lower bound of the 95% CI for the treatment difference is >0) were [redacted]. These events were primarily Grade 1 or 2 and most did not result in discontinuation of study intervention. There were no AEs with a greater risk difference for placebo in combination with chemotherapy (i.e., the upper bound of the 95% CI for the treatment difference is <0) identified. In both treatment groups, AEs generally occurred within the first 3 months of initiating study intervention with the exposure adjusted event rates decreasing at 3 to 6 months and continuing to decrease through 12 months.

Table 33: Subject with AEs by decreasing incidence – subjects with CPS ≥10 (incidence ≥10% in one or more treatment groups; ASaT population)

	Pembrolizumab + chemotherapy	Placebo + chemotherapy
	n (%)	n (%)
Subjects in population	219	103
with one or more adverse events	216 (98.6)	100 (97.1)
with no adverse events	3 (1.4)	3 (2.9)
Anaemia	[redacted]	[redacted]
Nausea		
Neutropenia		
Alopecia		
Fatigue		
Constipation		
Cough		
Diarrhoea		
Vomiting		
Alanine aminotransferase increased		
Neutrophil count decreased		
Headache		
Thrombocytopenia		
Pyrexia		
Leukopenia		

Aspartate aminotransferase increased	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
Dysgeusia	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
Grades are based on NCI CTCAE version 4.03.
Database Cut-off Date: 11DEC2019.

Drug related AEs

The drug-related AEs observed for participants treated with pembrolizumab in combination with chemotherapy were generally consistent with the known safety profiles of pembrolizumab monotherapy and the chemotherapies (taxane [paclitaxel or nab-paclitaxel] or gemcitabine and carboplatin) administered. The observed incidences of the most frequently reported drug-related AEs (incidence ≥30%) were similar between the 2 treatment groups and included [redacted].

Table 34: Subjects with drug-related AEs by decreasing incidence - CPS ≥10 (incidence ≥5% in one or more treatment groups; ASaT population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	219		103	
with one or more adverse events	212	(96.8)	97	(94.2)
with no adverse events	7	(3.2)	6	(5.8)
[redacted]				
Anaemia				
Nausea				
Neutropenia				
Alopecia				
Fatigue				
Neutrophil count decreased				
Diarrhoea				
Alanine aminotransferase increased				
Vomiting				
Leukopenia				
Platelet count decreased				
Thrombocytopenia				
Decreased appetite				
Aspartate aminotransferase increased				
Hypothyroidism				
White blood cell count decreased				
Rash				
Constipation				
Asthenia				
Arthralgia				
Neuropathy peripheral				
Pyrexia				
Dysgeusia				
Headache				
Peripheral sensory neuropathy				
Stomatitis				
Pruritus				
Myalgia				
Cough				
Oedema peripheral				
Malaise				
Weight decreased				
Dyspepsia				
Rash maculo-papular				

Blood alkaline phosphatase increased	[redacted]	[redacted]	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
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Grade 3 to 5 AEs

The overall incidences of Grade 3 to 5 AEs and drug-related Grade 3 to 5 AEs were similar between the 2 treatment groups. There were no trends noted in the pembrolizumab + chemotherapy group that suggest any new safety concerns. The Grade 3 to 5 AEs and drug-related Grade 3 to 5 AEs observed for participants treated with pembrolizumab + chemotherapy were generally consistent with the known safety profiles of pembrolizumab monotherapy and the chemotherapies (taxane [paclitaxel or nab-paclitaxel] or gemcitabine and carboplatin) administered. The types and frequencies of the most common (incidence ≥5%) Grade 3 to 5 AEs and drug-related Grade 3 to 5 AEs were generally similar between the 2 treatment groups.

Table 35: Subjects with grade 3-5 AEs by decreasing incidence CPS ≥10 (incidence ≥5% in one or more treatment groups; ASaT population)

	Pembrolizumab + chemotherapy	Placebo + chemotherapy
	n (%)	n (%)
Subjects in population	219	103
with one or more adverse events	174 (79.5)	73 (70.9)
with no adverse events	45 (20.5)	30 (29.1)
Neutropenia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the

columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Drug related grade 3-5 AEs

A similar number of patients in each treatment group reported drug related Grade 3 to 5 AEs (pembrolizumab in combination with chemotherapy 70.8%, placebo in combination with chemotherapy 65.0%). The most frequently reported drug-related Grade 3 to 5 AEs were [redacted], known AEs associated with chemotherapy.

Table 36: Subjects with drug related grade 3-5 AEs by decreasing incidence CPS ≥10 (incidence ≥5% in one or more treatment groups; ASaT population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	219		103	
with one or more adverse events	155	(70.8)	67	(65.0)
with no adverse events	64	(29.2)	36	(35.0)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
Grades are based on NCI CTCAE version 4.03.
Database Cut-off Date: 11DEC2019

2.10.4 Serious Adverse Events

The overall incidence of SAEs was higher in the pembrolizumab + chemotherapy group compared with the placebo in combination with chemotherapy group. Except for [redacted], which

was higher in the pembrolizumab in combination with chemotherapy group, the types and incidences of the most frequently reported SAEs (incidence ≥1%) were generally similar between the 2 treatment groups. There were no specific trends noted in the pembrolizumab in combination with chemotherapy group that suggest any new safety concerns. The SAEs observed for participants treated with pembrolizumab in combination with chemotherapy were generally consistent with the known safety profiles of pembrolizumab monotherapy and chemotherapies (taxane [paclitaxel or nab-paclitaxel] or gemcitabine and carboplatin) administered.

Table 37: Subjects with serious AEs up to 90 days after last dose by decreasing incidence (incidence ≥1% in one or more treatment groups; ASaT population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	219		103	
with one or more adverse events	62	(28.3)	25	(24.3)
with no adverse events	157	(71.7)	78	(75.7)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Pyelonephritis	[redacted]	[redacted]	[redacted]	[redacted]
Uterine haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal abscess	[redacted]	[redacted]	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]	[redacted]	[redacted]
Chronic inflammatory demyelinating polyradiculoneuropathy	[redacted]	[redacted]	[redacted]	[redacted]
Drug withdrawal syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Hepatic function abnormal	[redacted]	[redacted]	[redacted]	[redacted]
Hepatotoxicity	[redacted]	[redacted]	[redacted]	[redacted]

Hypocalcaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]
Pancytopenia	[redacted]	[redacted]	[redacted]	[redacted]
Parkinsonism	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia mycoplasmal	[redacted]	[redacted]	[redacted]	[redacted]
Pneumothorax	[redacted]	[redacted]	[redacted]	[redacted]
Scleroderma	[redacted]	[redacted]	[redacted]	[redacted]
Traumatic intracranial haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]
Vascular device infection	[redacted]	[redacted]	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Serious adverse events up to 90 days after last dose are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 11DEC2019

Deaths due to Adverse Events

The overall incidence of deaths was low (≤2.5%) and generally similar between the 2 treatment groups for the all subject population. Of the 14 (2.5%) deaths due to an AE reported in the pembrolizumab in combination with chemotherapy group, the underlying disease, comorbidities and/or use of concomitant medications known to cause the reported AE also likely contributed to the fatal event. Two (0.4%) events were considered related to study medication by the investigator: 1 event (pneumonia) was considered related to pembrolizumab and nab-paclitaxel and 1 event (acute kidney injury) was considered related to pembrolizumab. Of the 5 (1.8%) deaths due to an AE reported in the placebo in combination with chemotherapy group, none were considered related to chemotherapy by the investigator. No new safety signals were identified upon review of these fatal events

2.10.5 Adverse events of special interest

The overall incidence of AEOSIs was higher in the pembrolizumab in combination with chemotherapy group compared with the placebo in combination with chemotherapy group. The incidences of AEOSIs in each AE category, as expected, was higher for pembrolizumab in combination with chemotherapy compared with placebo in combination with chemotherapy. There were no deaths due to an AEOSI.

The most frequently reported AEOSI (≥5%), by category, was [redacted] in the pembrolizumab in combination with chemotherapy group and [redacted] in the placebo in combination with chemotherapy group. The incidence of [redacted] was higher than anticipated in the

pembrolizumab in combination with chemotherapy group based on the known safety profile of pembrolizumab monotherapy and higher than the placebo in combination with chemotherapy group.

Table 38: AEs of special interest by category (incidence >0%; ASaT population)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	562		281	
with one or more adverse events	154	(27.4)	30	(10.7)
with no adverse events	408	(72.6)	251	(89.3)
Adrenal Insufficiency	[redacted]	[redacted]	[redacted]	[redacted]
Colitis	[redacted]	[redacted]	[redacted]	[redacted]
Guillain-Barre Syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Hepatitis	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Infusion Reactions	[redacted]	[redacted]	[redacted]	[redacted]
Myocarditis	[redacted]	[redacted]	[redacted]	[redacted]
Myositis	[redacted]	[redacted]	[redacted]	[redacted]
Nephritis	[redacted]	[redacted]	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thyroiditis	[redacted]	[redacted]	[redacted]	[redacted]
Type 1 Diabetes Mellitus	[redacted]	[redacted]	[redacted]	[redacted]
Uveitis	[redacted]	[redacted]	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included.
Database Cutoff Date: 11DEC2019

B.2.11 Ongoing studies

Results provided in this submission are from IA2 of KEYNOTE-355 clinical trial, based on data cut-off date of 11th December 2019. A paper based upon IA2 has also been published in the Lancet [32]. As described in section B.2.4 the timing of further analyses is event driven and the final analysis is expected to take place in [redacted]

B.2.12 Innovation

Pembrolizumab, a monoclonal antibody, directly blocks the interaction of PD-1 and its ligands PD-L1 and PD-L2 enabling the immune response of both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and anti-tumour immunity.

Until recently there has been limited treatment options for those patients with Triple Negative Brest Cancer compared with those with other types of breast cancer such as HER2 positive and/or hormone receptor positive. Currently, atezolizumab in combination with nab-paclitaxel is recommended by NICE “for treating triple-negative, unresectable, locally advanced or metastatic breast cancer in adults whose tumours express PD-L1 at a level of 1% or more and who have not had previous chemotherapy for metastatic disease” [31].

KEYNOTE-355 demonstrates the additional benefit of pembrolizumab when used in combination with one of three treatments currently used in TNBC within the NHS. The clinical efficacy and safety data presented in this submission show that pembrolizumab, when combined with chemotherapy, [redacted] for Triple Negative Breast Cancer patients whose tumours express PD-L1 CPS ≥10, with an acceptable tolerability profile.

KEYNOTE-355 included patients who had experienced a local or distant recurrent ≥6 months between the competition of treatment with curative intent, whereas in IMPassion 130 this gap was ≥12 months. According to clinical experts approximately one third of patients experience a relapse between 6 and 12 months from last curative intent treatment.

B.2.13 Interpretation of clinical effectiveness and safety evidence

The safety and efficacy data from IA2 of KEYNOTE-355, as presented in this submission, are robust and demonstrate [redacted] in untreated, locally recurrent inoperable or metastatic, triple negative breast cancer. In addition, the safety results from the study are largely consistent with results from previous pembrolizumab trials and affirm an acceptable tolerability profile in the target population.

The key findings from the study are summarised below

Pembrolizumab + chemotherapy is superior to placebo + chemotherapy with respect to PFS in participants with PD-L1 positive tumours (CPS ≥10)

Pembrolizumab + chemotherapy demonstrates a statistically significant and clinically meaningful improvement in PFS compared with placebo + chemotherapy in participants with PD-L1 positive tumours (CPS ≥10); the PFS HR of 0.65 (95% CI: 0.49, 0.86, p=0.0012) represents a 35% reduction in the risk of progression or death for participants with PD-L1 positive tumours (CPS ≥10). The treatment benefit of pembrolizumab + chemotherapy on PFS compared with placebo + chemotherapy in participants with PD-L1 positive tumours (CPS ≥10) is consistent across subgroups.

[redacted]

At the IA2 of KEYNOTE-355 (median duration of follow-up of 16.8 months), [redacted]

[redacted]

The addition of pembrolizumab to chemotherapy does not result in a decrease in health related QoL in participants with PD-L1 positive tumours CPS ≥10

The addition of pembrolizumab to chemotherapy did not result in a decrease in HRQoL. Over 15 weeks of follow-up, participants receiving pembrolizumab + chemotherapy and placebo + chemotherapy had small decreases (worsening) in prespecified EQ-5D VAS scores. The between-group difference in LS mean score changes from baseline at Week 15 in participants with PD-L1 positive tumours (CPS ≥10) was [redacted] (95% CI: -[redacted], [redacted]

Pembrolizumab + chemotherapy has an acceptable tolerability profile which is consistent with the known safety profiles of the therapies administered

The overall incidences of AEs, drug-related AEs, Grade 3 to 5 AEs, Grade 3 to 5 drug-related AEs, deaths, and any dose modification due to an AE were similar between the pembrolizumab in combination with chemotherapy and placebo combination with chemotherapy groups. There were no specific trends noted for the pembrolizumab in combination with chemotherapy group that suggest a safety concern.

For the pembrolizumab in combination with chemotherapy group, the most commonly reported AEs of greater than 30% were [redacted]. The most commonly reported Grade 3 to 5 AEs of greater than 5% included [redacted].

Two of the 14 deaths due to AEs reported in the pembrolizumab in combination with chemotherapy group (pneumonia and acute kidney injury) were considered related to study medication. Of the 5 deaths due to an AE reported in the placebo in combination with chemotherapy group, none were considered related to chemotherapy by the investigator.

Internal validity

KEYNOTE-355 is a robust, multicentre, randomised, active controlled, double blind phase III trial of pembrolizumab in combination with chemotherapy versus placebo in combination with chemotherapy in patients with previously untreated locally recurrent inoperable or metastatic TNBC. The co-primary efficacy endpoints were OS and PFS; both clinically relevant endpoints that were directly reference in the final scope for this appraisal and the decision problem. Moreover, the endpoints selected are consistent with those used in studies of other therapeutic agents in the population of metastatic TNBC. The definition of progression when evaluating the primary endpoint of PFS in KEYNOTE-355 followed an established response evaluation criteria (RECIST 1.1) in the primary efficacy analysis in line with European guidance [38].

In addition to being double blind, with both patients and clinicians blinded to treatment assignment, for PFS analysis, the independent radiologists who performed the central imaging review were also blinded to treatment assignment, in order to minimise bias.

HRQoL was an exploratory endpoint of the KEYNOTE-355 study assessed using EQ-5D as well as cancer specific EORTC QLQ-C30 and breast cancer specific EORTC QLQ-BR23.

Patient demographics and clinical characteristics were similar across both treatment groups in terms of all subject characteristics assessed using gender, age, ethnicity, geography, ECOG performance status, chemotherapy used and tumour PD-L1 status.

External validity

KEYNOTE-355 was a global study conducted in 251 centres in 29 countries. Of the patients participating in the study, 48.1% were enrolled at sites in Europe.

Baseline characteristics of patients enrolled in KEYNOTE-355 were as expected for patients with metastatic TNBC. The majority of patients were white, with a mean age around 53 years old and had recurrent metastatic disease.

The observed safety profile of pembrolizumab + chemotherapy in KEYNOTE-355 was consistent with that seen previously in pembrolizumab trials for other types of tumours.

End-of-life criteria

Based on the clinical trial data from IA2 analysis of KEYNOTE-355, the median OS for the pembrolizumab + chemotherapy group was [redacted] for placebo + chemotherapy in subjects whose tumours expressed PD-L1 CPS ≥10. [redacted] [redacted] as observed directly from the RCT.

Based in the RWE literature available, current chemotherapies are associated with median OS survival below 24 months [14, 39-43], which is consistent with the model outputs; ranging ranges from 1.80 for taxanes to 2.28 Life Years (LYs) for Atezolizumab + nab-paclitaxel.

Finally, the model predicts that pembrolizumab in combination with taxanes will extend the mean OS by 1.99 LYs (versus taxanes) to 1.52 LYs (versus Atezolizumab + nab-paclitaxel).

Based on the evidence presented above, pembrolizumab in combination with taxanes meets the NICE end-of-life criteria for the cost-effectiveness assessment.

Table 39: End-of-life criteria

Criterion	Data available	Reference in submission
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	In the KEYNOTE-355 trial at IA2, median OS in the pembrolizumab in combination with chemotherapy group was [redacted] months compared with [redacted] months for placebo in combination with chemotherapy in subjects whose tumours expressed PD-L1 CPS ≥10. The cost-effectiveness model results predict a mean life years (LY) for patients treated with the current comparators ranges from 1.80 for taxane chemotherapies to 2.28 LYs for Atezolizumab + nab-paclitaxel. Published literature indicates that the median OS estimates with taxane chemotherapies remains below 24 months [14, 39-43].	Clinical section B.2.6.2 and economic results section 3.7.1 to B.3.7.3.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.	Pembrolizumab in combination with chemotherapy offers an extension of life of at least 3 months compared to SoC. The estimated difference in median OS, for those subjects whose tumours expressed PD-L1 CPS ≥10, is [redacted] months in favour of pembrolizumab in combination with chemotherapy. [redacted] Based on model predictions, Pembrolizumab in combination with taxanes is associated with a mean of f 1.99 LYs versus taxanes or 1.52 LYs versus Atezolizumab + nab-paclitaxel.	Clinical section B.2.6.2 and economic results section B.3.7.1 to B.3.7.3.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A comprehensive systematic search was conducted on November 19, to identify relevant cost-effectiveness studies for the treatment of patients in advanced (unresectable or metastatic) triple negative breast cancer. No cost-effectiveness studies evaluating pembrolizumab in combination with chemotherapy in the specified population were identified. Appendix G provides in full detail the SLR search strategy, study inclusion/exclusion criteria and the study identification process.

B.3.2 Economic analysis

Owning to the lack of the cost-effectiveness studies appraising pembrolizumab in combination with chemotherapy for the indication of interest, a *de novo* cost-effectiveness model was developed to inform the decision problem. The model design was based upon the cost-effectiveness studies identified by the economic SLR (Appendix G) alongside TA639, KEYNOTE-355 data availability and clinical expert opinion (see Model Structure section B.3.2.2).

B 3.2.1 Patient population

The patient population included in the economic evaluation consisted of patients with previously untreated locally inoperable r/m TNBC [redacted]Model patient characteristics were based on the KEYNOTE-355 trial, and are specific to the [redacted].

As noted in section B.1.1, a recommendation specific to the use of Pembrolizumab in combination with tanaxes alone is requested for this indication. This is driven by clinical data but also due to taxanes representing the current standard of care chemotherapies in the UK. Therefore, for the purposes of the cost-effectiveness analyses the clinical endpoints (PFS and OS) used to generate cost-effectiveness results are based on the KEYNOTE-355 taxane specific PD-L1 CPS ≥10 score subgroup (confirmed by the IHC pharmDx 22C3 assay), which is subset of the anticipated MA), unless otherwise stated.

Table 40: Baseline characteristics of the population in the cost-effectiveness model

Patient characteristics	Mean Value	Source
Patient Age (years)	[redacted]	KEYNOTE-355 [26]
Age, standard deviation (years)	[redacted]	
Average patient weight (kg)	[redacted]	
Weight, standard deviation (kg)	[redacted]	
Average BSA (m^2)	[redacted]	
BSA standard deviation (m^2)	[redacted]	
Proportion female	[redacted]	
Efficacy data from the taxane subgroup of KN-355 (re-weighted)*		
Pembro + Taxane comprising of:		KEYNOTE-355 [26]
Paclitaxel with Pembro	35.11%	
Nab-paclitaxel with Pembro	64.89%	
Taxane comparator comprising of*:		
Paclitaxel alone	76.60%	
Nab-paclitaxel alone (with paclitaxel costs)	23.40%	
*Efficacy from different taxanes is used directly in the model, however, in the comparator arm costs for nab-paclitaxel are replaced with those of paclitaxel alone to reflect the UK chemotherapies (see section 3.5.1. below).		

B 3.2.2 Model structure

Table 41 provides details of the main features of this economic analysis compared to TA639, the recently approved mTNBC 1L specific guidance for atezolizumab + nab-paclitaxel [31].

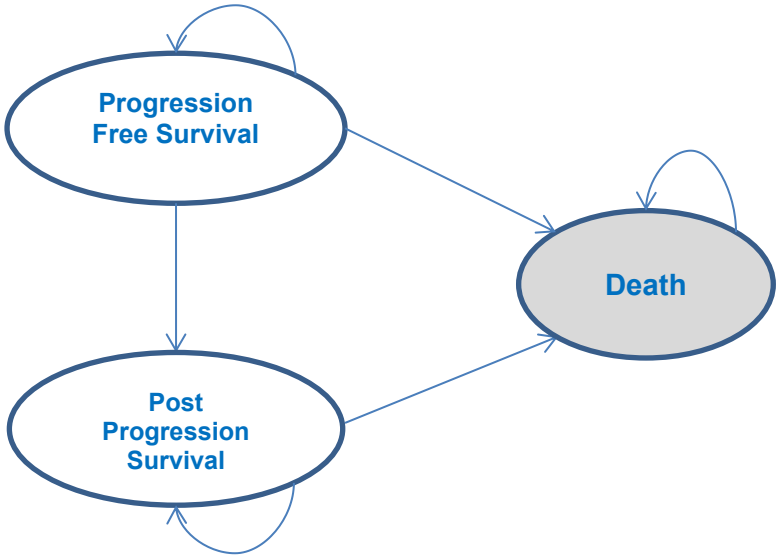
In line with prior NICE submissions for advanced/metastatic breast cancer and the recent DSU guidance, a partitioned survival model (PSM) was developed in Microsoft Excel. The model is structured around the KEYNOTE-355 trial co-primary endpoints (PFS; assessed using a blinded CIV and OS) which are representative of clinical disease progression over time [44]. The model includes three mutually exclusive health states; “progression-free survival (PFS)”, “post-progression-survival (PPS)” and “death”. A model schema is provided in Figure 16 below.

This structure and modelling method is the most commonly used within oncology models including advanced/metastatic breast cancer (BC) and was selected to reduce the number of assumptions necessary when assessing and extrapolating from relatively limited follow up on OS and PFS from KEYNOTE-355 data.

In partitioned survival models, the proportion of patients in each health state is determined using the individual PFS and OS survival curves derived from the clinical data and extrapolated over a sufficiently long time horizon. The PSM modelling approach does not require the calculation of explicit transition probabilities between health states based on limited study follow up data (as in Markov models) and it automatically incorporates time

dependencies in the event rates within the parametric survival functions for PFS and OS. However, the validity of PSM projections within the extrapolation period needs to be assessed for its clinical and biological plausibility to avoid scenarios whereby PFS and OS curves intersect early on or due to lack of relevant (or limited availability) of data that can be used for validation purposes of the long term projections [44].

Figure 16: Cost-effectiveness model structure



How patients move through the different health states

Patients with inoperable r/m TNBC start in the "progression-free survival" health state. At the end of each weekly cycle, patients may remain in the "progression-free" health state, transition to the "post-progression" health state or to death. Upon experiencing a progression, patients can only remain in the "post-progression" health state or move to the death state which is an absorbing health state in which no costs or benefits are accrued. Patients cannot transition to an improved health state (i.e. from post-progression to pre-progression).

Modelling utility

Utilities were derived from the EQ-5D-3L data collected alongside the KEYNOTE-355 study. The model base case uses pooled utilities across both treatment arms with the "the time-to-death approach" to better reflect the deterioration in patient's utility are they near proximity to death, but also to overcome limited PPS EQ-5D collection. Alternative utility estimates by disease status and AE-related disutilities are explored as sensitivity analyses.

Modelling drug costs

In line with the anticipated marketing authorisation for this indication pembrolizumab should be discontinued upon the completing a maximum of 35 administrations or upon achieving a confirmed complete response based on the KEYNOTE-355 trail protocol (refer to section 3.2.3 for more information) [29]. Relevant drug and administration costs have been estimated using KEYNOTE-355 data. Concomitant medications necessary for chemotherapies have also been included in the analyses.

Modelling resource use and associated costs

Resource use was derived from the previous NICE mBC HTAs including the latest mTNBC as well as clinical expert opinion. All costs were extracted from public sources such as the National Schedule of Reference costs, PSSRU, BFN and MIMS and eMIT). Relevant AE management costs were calculated from KEYNOTE-355 clinical data alongside the estimated costs for managing these AEs in the NHS setting and was applied as one-off cost in the first model cycle (see section B.3.5.5).

Modelling subsequent therapies

For patients experiencing a progression, the cost of subsequent therapies that may be used in the UK has been included in the economic model. This was estimated using the subsequent therapy data from KEYNOTE-355, which were considered to be broadly representative of the UK practice following adjustments for subsequent IO therapy use. Adjustments for subsequent IO agent use were implemented by re-distributing patient records across all other subsequent treatments. Relevant dosing schedules were sourced as per SmPC, and the time on treatment was based upon KEYNOTE-355 clinical trial data per line of therapy. Alternative sources of subsequent treatment data derived from UK market research are explored as a sensitivity analysis.

Table 41: Features of the economic analysis

Factor	Previous appraisals	Current appraisal	
	TA639	Base-case	Justification

Time horizon	15 years	20 years	Choice is in line with the reference case and takes into consideration the need to model costs and benefits over sufficiently long time horizon to characterise full impact of the intervention.
Cycle length	7 days	7 days	The maximum number of patients moving between health states based upon this cycle length is always<5% of the starting total; (ii) that the frequency of planned follow-up for disease assessment and quality of life (iii), this cycle length allows for the exploration of weekly taxane chemotherapy (iv) used in recently approved TA639.
Half cycle correction	Yes	Yes	NICE Guide to Methods of technology appraisals, 2013 [45]
Treatment waning effect	Not included	Not included	Treatment waning was not incorporated in the base case. This is consistent with previous BC HTAs and the recent TA639 AC's preferences whereby the AC concluded that there is a lack of data to support this [31].In line with prior HTAs, the impact of this assumption is explored in sensitivity analysis (using data from the SEER registry).
Source of utilities	EQ-5D-5L from IMpassion130 mapped to EQ-5D-3L, literature sources were also explored	EQ-5D-3L utilities collected alongside KN-355 have been used	This approach is consistent with the NICE reference case.[45]
Source of costs	NHS reference Costs, PSSRU BNF, MIMS, eMIT, Published Literature	NHS reference Costs, PSSRU, BNF, MIMS, eMIT, Published literature	Sources for costs used are widely accepted and in-line with guidance in NICE reference case.[45]

Abbreviations: eMIT: electronic market information tool; HTA: health technology appraisal; PSSRU: personal social services research unit; TA: technology appraisals, MIMS: Monthly Index of Medical Specialties

B 3.2.3 Intervention technology and comparators

The final scope intervention for this appraisal is pembrolizumab in combination with chemotherapy as per KEYNOTE-355, including; paclitaxel, nab-paclitaxel or gemcitabine/carboplatin combination. For the purposes of the economic analysis MSD proposes the assessment of Pembrolizumab in combination with taxanes (paclitaxel or nab-paclitaxel) versus taxanes alone. This is reflective of the KEYNOTE-355 clinical data and UK clinical experts suggesting taxane chemotherapies constitute the most relevant Standard of Care (SoC) chemotherapy options in the UK for this population (prior to IO introduction). Clinical experts noted that the gemcitabine/carboplatin high use observed in KEYNOTE-355

would not be expected in the UK setting since it is primarily used in patients who relapse early and were previously treated with taxanes. Market research confirms the very limited gemcitabine/carboplatin use in the UK as 1L mTNBC [redacted] treatment prior to TA639). Based on the above evidence, the decision was taken to position Pembrolizumab in combination with taxanes alone for the decision problem.

The pembrolizumab component cost was applied in the model as per the anticipated licensed dosing regimen (i.e. administered intravenously at a fixed dose of 200mg over 30 minutes every 3 weeks [Q3W]). Paclitaxel (90mg/m^2) and nab-paclitaxel (100mg/m^2) are applied days 1,8 and 15 of each 28 day treatment cycle (3 weeks on treatment, 1 week off treatment).

The final scope specifies the following relevant comparators for this appraisal including: anthracyclines, taxanes (paclitaxel and docetaxel) and the recently approved atezolizumab + nab-paclitaxel for PD-L1 ≥1% expressors [30]. To address the decision problem issued by NICE, the primary comparators for the cost-effectiveness analysis will be taxanes, leveraging on the taxane chemotherapy subgroup specific data from KEYNOTE-355 (paclitaxel or nab-paclitaxel). The analysis versus taxanes will assume equal survival outcomes for taxane chemotherapy comparators as per clinical data and expert opinion during TA639, which is also reflective of prior AC's preferences in TA639 [31].

During TA639, clinical experts noted that paclitaxel was the most relevant chemotherapy comparator in the UK setting vs docetaxel due to its improved toxicity profile [31]. Therefore, the primary chemotherapy comparator will be paclitaxel monotherapy. Docetaxel will be explored as a secondary chemotherapy comparator. Due to a lack of mTNBC specific data identified from the clinical SLR, the assumption that clinical efficacy for docetaxel is equal to that of the taxane comparator subgroup is used in the economic model as per prior AC preferences, adjusting only the drug acquisition costs [31].

Due to the potentially limited population overlap and assumptions necessary to inform the ITC and subsequently cost-effectiveness results, atezolizumab + nab-paclitaxel is also positioned as a secondary comparator for the purposes of the decision problem. In brief, ITC uncertainties arise due to differences in ascertainment of PD-L1 status assays, antibodies and scoring algorithm, study inclusion criteria and reliance on post-hoc exploratory analysis from IMpassion-130 for the ITC, demonstrating a limited overlap between the two study populations identified from the two assays (see section 2.9 above).

Whilst anthracyclines were included in the final scope, owning to the lack of data from studies in this population from the clinical SLR, an ITC was not feasible and therefore cost-effectiveness estimates could not be generated [30]. The AC in TA639 previously agreed that anthracycline use is very limited in this patient population and it was not a relevant comparator.

Discontinuation rules

In line with the KEYNOTE-355 pembrolizumab therapy was continued until RECIST 1.1-defined progression of disease as determined by the investigator, unacceptable toxicity, or for a maximum of 24 months (approximately 35 cycles of therapy). Administration of pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator [29].The model therefore assumes a maximum treatment duration of 35 cycles with pembrolizumab. Taxane chemotherapy treatment could be continued as per clinician's choice upon cessation of pembrolizumab [29].

B.3.3 Clinical parameters and variables

The primary source of clinical data for the economic model is KEYNOTE-355, a phase III pivotal RCT comparing pembrolizumab in combination with chemotherapy (paclitaxel or nab-paclitaxel or gemcitabine/carboplatin) to chemotherapy alone (paclitaxel or nab-paclitaxel or gemcitabine/carboplatin). Patient level data (PLD) from the PD-L1 +ve CPS≥10 score taxane subgroup specific results have been used in the model to generate the UK relevant cost-effectiveness comparisons unless otherwise stated. [redacted].

KEYNOTE-355 provides OS, PFS, Treatment on Treatment (TOT), AE and utility data for the economic model. In KEYNOTE-355 patients were stratified based on the chemotherapy backbone used in the study (taxane versus non-taxane), PD-L1 status positivity at ≥1% cut-off, and prior treatment with same class of chemotherapy in the (neo)adjuvant setting, to ensure similar distribution of patient characteristics across treatment arms. Pre-planned subgroup analyses for taxanes versus gemcitabine/carboplatin, showed differences in the treatment effect for PFS [redacted](see clinical section 2.7 above).

The results of the taxane subgroup analyses remain valid for the purposes of the HTA since the balance in baseline characteristics and prognostic factors is maintained to a great degree

considering that CPS 10 is a subset of the original CPS 1 population (one of the three stratification factors used). Therefore, this subgroup can be leveraged directly within the HTA submission to inform the decision problem and the cost-effectiveness comparisons.

For comparisons versus atezolizumab + nab-paclitaxel whereby an ITC was necessary, the KEYNOTE-355 pooled common comparator ITC results are used assuming equal efficacy of the taxane chemotherapy comparator from KEYNOTE-355 (please refer to ITC section 2.9.2, and for full methodology in modeling outcomes within section B.3.3.4 of the economic chapter).

Table 42: Sources of key clinical evidence used to populate the model

Clinical Evidence	Brief Description	Use in the model
KEYNOTE-355	Phase III clinical trial in recurrent inoperable or metastatic TNBC exploring the efficacy of pembrolizumab 200mg Q3W + chemotherapy (paclitaxel or nab-paclitaxel or carboplatin/gemcitabine combination) compared to chemotherapy alone. As per [redacted] Data specific to the taxane subgroup are used within the economic model to reflect the positioning of the technology into the NHS.	▪ PLD from the taxane specific subgroup of CPS≥10 is used to fit PFS, OS parametric curves for economic modelling ▪ As above, PDL used to fit ToT from the taxane specific subgroup is used to parametric curves for intervention and comparator agents ▪ Used to estimate the dose intensity for cost calculations ▪ EQ-5D-3L trial data derived from the CPS≥10 population were used for trial-based utility analysis to ensure adequate sample size was maintained for the analysis ▪ Modelling of frequency of adverse events ▪ Used for frequency of subsequent treatments used in the base-case
General population mortality	Latest estimates of general population mortality by single year of age from England have been applied from ONS	▪ Used to adjust long-term OS projections ▪ Used to set the minimum threshold of age-matching mortality rates for modelled patients in all treatment arms
SEER mTNBC data	External data sources were used to estimate the impact of waning, which is explored in sensitivity analysis only.	▪ SEER data were used to estimate a timepoint by which the OS hazard changes over time specific to mTNBC patients. ▪ From 4 year onwards the economic model applies this hazard rate for OS across both treatment arms, explored in sensitivity analysis only (refer to Appendix P for more information).

Abbreviations: OS: CPS: Combined Positive Score; Overall survival, ONS: Office of national statistics, PLD: Patient level data, PFS: Progression-free survival; SEER: Surveillance, Epidemiology and End Results Program (USA clinical database); ToT: Time-on-treatment, TNBC; Triple Negative Breast Cancer

Survival analysis methodology outline

Since the follow up in KEYNOTE-355 is shorter than the life-time horizon adopted in the economic model, extrapolation of survival outcomes (OS, PFS, TOT) was necessary to model the outcomes of the patients which had not progressed or died within the follow-up period of the study.

The survival curve fitting was carried out in line with the NICE DSU guidelines [46]. Standard parametric models were fitted to the PLD of PFS and OS data from the pembrolizumab + taxanes and taxanes subgroup in the KEYNOTE-355 trial to extrapolate the endpoints from the trial over a life-time horizon and the analysis was conducted in R Programming language. The following steps were performed for curve fitting:

- First a statistical test of proportional hazard ratio assumption was performed to assess the two approaches: 1) “Joint” models – statistical models including data for both treatment groups, with a term for treatment, and 2) “Separate” models – statistical models that were fitted to each randomized treatment arm separately. A visual inspection of the Schoenfeld residual plot and cumulative hazard plot was also used to guide the decision if joint or separate models should be used.

- If the PH assumption held, a comprehensive range of joint parametric survival models were to be explored. Here, data from both treatment arms were used within the same model. All standard parametric models (i.e. exponential, Weibull, Gompertz, log-logistic, log-normal and generalized gamma) were considered and compared. If the PH assumption did not hold, independent separate survival models were explored., whereby models were separately fitted to each treatment arm using data from the relevant treatment arm. In the separate models, pembrolizumab and SoC could have different parametric models. All parameters of the parametric curves were allowed to vary between pembrolizumab and SoC.

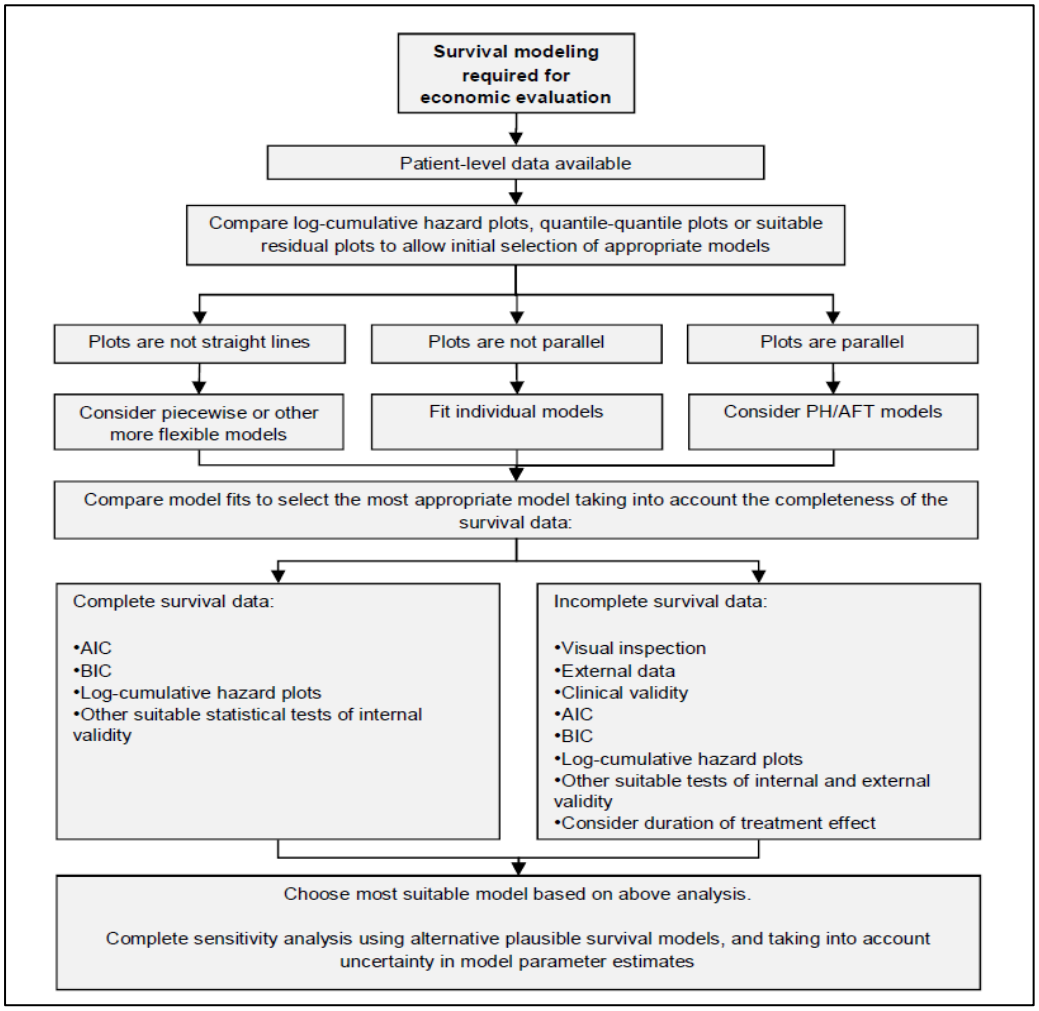
- Within the various parametric survival models explored, visual inspection was used to assess the fit of the fitted curves to the observed clinical trial data. The Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) goodness-of-fit statistics were calculated to help identify the most plausible survival models.

- Lastly, the fit of the alternative models was assessed both by considering internal and external validity (i.e. how well models fitted the observed data) and the clinical plausibility of the extrapolated results for both OS and PFS.

The final model selection for OS and PFS presented below took into account the model selection algorithm by NICE [46] (Figure 17). Validation of long-term extrapolations was performed by cross checking at landmark timepoints the estimates produced by each model versus estimates provided by clinical experts and those reported in the RWE clinical literature

for the mTNBC treated patients. Appendix P provides the full survival methodology and alternative models considered for selection.

Figure 17: Survival Model Selection Process Algorithm (from NICE DSU 14)[46]



B 3.3.1 OS extrapolation for the taxanes subgroup

KEYNOTE-355 is a company sponsored phase III comparative trial for which PLD from both treatment arms are available for analysis. Based on the justifications provided above, this analysis focuses on the taxane alone subgroup results from KEYNOTE-355.

Prior to model fitting, OS cumulative and log-cumulative hazard plots were generated to assess the proportional hazards assumption (see The unique mode of action of a combination of immunotherapy combined with taxanes is not comparable to chemotherapy alone, therefore the underlying hazard assumption for the choice of parametric curve does not need to be the same. Separate models were therefore used to fit the data separately for the projection of the OS.

Figure 18). From inspection of the log-cumulative hazard plots there is a clear separation between the two arms, however, these appear to converge slightly at 25 weeks before separating again thereafter.

Further visual examination of the cumulative hazard plots in suggested week 25, 40 and 52 as potential turning points of the OS curves. Chow statistical tests were used to estimate structural changes to the Kaplan Meier curves to further confirm the identification of cut-off points by detecting structural changes to the slope of the OS cumulative hazard curves [47]. The results of the Chow tests identified optimal cut-off points around weeks 25, 40 and 52 in the taxane subgroup. These were explored further in the model identification process.

The unique mode of action of a combination of immunotherapy combined with taxanes is not comparable to chemotherapy alone, therefore the underlying hazard assumption for the choice of parametric curve does not need to be the same. Separate models were therefore used to fit the data separately for the projection of the OS.

Figure 18: OS cumulative and Log-cumulative hazard plot for Pembrolizumab + taxanes and taxanes chemotherapy comparator based on KEYNOTE-355 (taxanes only)

Alternative parametric models were fitted on the observed OS Kaplan-Meier (KM) data to identify the most appropriate distribution for OS extrapolation following the NICE DSU 14 guidelines[46]. Candidate distributions included individual and piecewise models (based on time points noted above were explored) for all the standard parametric distributions reported

above. The best fitting models are included in the base case for economic modelling (see Appendix P for supplementary analyses including piecewise models).

Full parametric models were deemed more plausible to extrapolate the OS for the taxane comparator arm after considering a number of RWE for validation purposes [14, 39, 40, 43]. In addition, the cumulative hazard plot for Pembrolizumab + taxanes is almost a straight line and the Chow test suggests that all timepoints may be significant for the changes in hazard.

Full parametric models were also selected to extrapolate the OS for Pembrolizumab + taxanes. The best piecewise fitting models for Pembro + taxanes based on goodness of fit statistic (Kaplan-Meier followed by parametric extrapolation) was that of the exponential curve which assumes constant hazards over time. This assumption is simplistic as it contradicts clinical expert opinion and RWE data suggesting that patients remaining alive in the first few years would have lower risk of death from mTNBC. This is also been observed across a number of RWE publications, whereby an OS plateau appears to initiate form year 3 onwards indicating a better prognosis for patients serving beyond 3 years [14, 40, 43]. This is further supported by the immunotherapeutic effect observed with IO agents across a number of tumours including NSCLS, Melanoma and Head & Neck, whereby a % of patients achieves long term survival due to the unique mode of action of IO agents [48-50]. Finally, when piecewise models were applied (regardless of timepoint) predictions over the observed data were inconsistent and/or models generated long term survival projections similar to those reported in chemotherapy RWE studies with which may be considered conservative [14].

Statistical tests based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), combined with visual inspection were used to identify the best-fitted full piece parametric distribution based on internal validity. Short term fit and long term extrapolations are presented in Figure 19 and Figure 20 below. Differences of 5 points or greater are considered important in terms of distinguishing between models. The AIC/BIC statistics for OS presented and visual inspection both suggested that for the OS of pembrolizumab in combination +chemotherapy the best fitting full parametric model was a the log-normal, followed by the log-logistic curve (

Table 43). For the OS of the taxane chemotherapy comparator arm the best fitting full parametric model was the log-logistic curve, followed by the log-normal (

Table 43). Considering the RWE evidence, the full parametric models identified selected result in OS predictions which are not overly aggressive versus current RWE sources.

Figure 19: OS standard full parametric model for Pembrolizumab in combination with taxanes (short term fit and long term projections)

Figure 20: OS standard full parametric model for Taxanes chemotherapy comparator (short term fit and long term projections)

Table 43: Summary of goodness of fit for OS: pembrolizumab + taxanes and taxane chemotherapy comparator arm from KEYNOTE-355

Parametric distribution for OS	Pembrolizumab + taxane				Taxane comparator			
	AIC	BIC	AVRG	Rank	AIC	BIC	AVRG	Rank
Exponential	537.6075	540.1719	538.890	2	398.3883	400.2385	798.627	6
Weibull	537.6084	542.7371	540.173	4	394.6624	398.3627	793.025	2
Log-normal	535.9272	541.0558	538.492	1	394.8131	398.5134	793.327	3
Log-logistic	536.4675	541.5962	539.032	3	394.6040	398.3043	792.908	1
Gen Gamma	539.0803	544.2090	541.645	5	397.0471	400.7474	797.795	5
Gompertz	537.8721	545.5651	541.719	6	396.0407	401.5912	797.632	4

Abbreviations: AIC: Akaike Information Criteria, BIC: Bayesian Information Criteria; AVRG: Average, Ranking is based on the average AIC/BIC statistic.

Table 44 and

Table 45 below presents the OS landmark analysis for the different models versus RWE sources, clinical expert opinion and IMpassion-130 used for external validation purposes.

Table 44: OS landmark analysis and external validation for the pembrolizumab + taxane from KEYNOTE-355

OS options		Pembro + taxanes landmark analysis for OS (Years)								
		0.5	1	1.5	2	3	5	8	10	20
Observed IA2 OS		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical opinion in this TA		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Atezo+N-Pacl TA639 observed*		-	75%	-	49%	-	-	-	-	-
Parametric models	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Atezo+N-Pacl: atezolizumab + nab-paclitaxel; OS: Overall survival, *Observed OS from Primary analysis of Impassion130; table 37 of TA639.

Table 45: OS landmark analysis and external validation for the taxane chemotherapy comparator arm from KEYNOTE-355

OS Options		Taxane comparator landmark analysis for OS (Years)								
		0.5	1	1.5	2	3	5	8	10	20
Observed IA2 OS		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical opinion in this TA		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N-Pacl TA639 modelled estimates*		84.32%	59.23%	39.02%	21.25%	6.97%	1.05%	-	-	-
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%	-
Para	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: N-Pacl: nab-paclitaxel, OS: Overall survival, ** Clinical experts noted high OS estimates vs UK expected OS with SoC chemotherapies,* OS estimates extracted from digitisation of company's preferred model for paclitaxel; observed nab-paclitaxel arm 1Y OS was 64% and 2 year OS at 36.6% (refer to Table 40 of TA639).

Overall survival projections and model selection with limited study follow up, may introduce uncertainty and impact upon the cost-effectiveness results. Therefore clinical expert opinion was sought to select the most plausible parametric survival extrapolations for OS during a UK advisory board [51]. Participants had extensive experience using IO agents across a number of tumours including Lung and Melanoma.

Clinical experts recognised the unique mode of action of IO + chemotherapy in mTNBC, as seen in other tumours, concluding that they would expect an IO effect to be observed over time resulting in a small % of patients experiencing prolonged survival, as seen across a number of patients treated with IO agents [48-50]. Some experts noted that the flattening of the OS KM curve was not yet observed from KEYNOTE-355, suggesting that a longer-term survivorship may be [redacted] [51]. Other estimates for 10 year survival provided by clinical experts ranged [redacted]However, considering the current RWE evidence for survivorship with chemotherapy from Deluche et al 2020, Battisti 2018, Skimmer 2020 and Luhn 2019, these can be considered as very conservative (RWE estimates: 5 Year OS of ~5.8% to 15.9%, 10 year OS of 3.9% to 6.6%) [14, 40, 42, 43].The log-normal was selected for the base-case as it fits the observed data very well and appears to offer plausible long term extrapolations for OS for pembrolizumab considering the immunotherapeutic effect of IO agents and does not result in overly optimistic OS projections versus the current RWE literature (the full exponential model produces estimates equivalent to the RWE literature). As noted above, the best fitting piecewise models (exponential) resulted in long term survival estimates similar to those in for chemotherapies which are unrealistic but also do not factor in that patients which remain alive over the first few years, are likely to have a better prognosis in the longer term as seen in a number of RWE [14, 39, 40, 43].

For the standard chemotherapy arm, clinical experts suggested that survivorship declines rapidly after 3 years. They suggested that an estimated survivorship [redacted]% with chemotherapies assuming optimal management at year 5, followed by a nearly [redacted] year 10 [51]. This is in contrast to the long term survival estimates reported in the EMSE RWE study reporting a Year 5 OS plateau at ~10% maintained throughout year 10 [14] does not reflect the UK clinical practice for standard chemotherapies in the UK. The UK study by Battisti et al 2018 reports OS survivorship with chemotherapies ranging from 5.8% to 13.5% at 5 Years [40]. Therefore, for the taxane comparator arm from KEYNOTE-355 the log-logistic model was selected for the base-case. It was preferred versus the log-logistic considering that the DFI for the majority of KEYNOTE-355 patients is ≥ 12 months and therefore the model with the upper OS range for years 5 and 10 may be more plausible considering RWE. Since the log-normal is also considered plausible based on RWE evidence this is explored in sensitivity analyses (see section B.3.8.3). The final modelled OS curves and OS predictions used in the base case analysis over a 5 year and a 20 year time horizon are presented in Due to their unique mode of action, immunotherapies have been associated with prolonged survival over time in a subset of patients as seen in a number of tumours also known as “immune-therapeutic effect”, observed across a number of tumours including NSCLC and Melanoma [48-50]. The final choice of parametric models used in the base case reflect clinical expert opinion and the real world practice of IO agents to date, accounting for the prolonged survival experienced by these patients.

Figure 21 and Figure 22.

Due to their unique mode of action, immunotherapies have been associated with prolonged survival over time in a subset of patients as seen in a number of tumours also known as “immune-therapeutic effect”, observed across a number of tumours including NSCLC and Melanoma [48-50]. The final choice of parametric models used in the base case reflect clinical expert opinion and the real world practice of IO agents to date, accounting for the prolonged survival experienced by these patients.

Figure 21: OS KM curves vs base-case fitted parametric distributions for OS Pembrolizumab + taxanes and taxanes comparator based on KEYNOTE-355 over a 5 year period (taxane subgroup)

Figure 22: OS KM curves vs base-case fitted parametric distributions for OS Pembrolizumab + taxane and taxane comparator based on KEYNOTE-355 over a 20 year period (taxane subgroup)

B 3.3.2 PFS IRC extrapolation for the taxanes subgroup

Based on the trial protocol of KEYNOTE-355, the first post-randomisation imaging assessment was performed at week 8 (±7 days), with subsequent imaging being performed at week 16 (± 7 days), week 24 (±7 days) and thereafter every 9 weeks (±7 days) post randomisation during the 1st year of follow up. Visual inspection of the KM PFS curves revealed

a steep drop around week 9 in both arms of KEYNOTE-355, likely reflecting the first protocol-scheduled tumour imaging assessment at 8 weeks (± 1 week) from randomisation (section B.2.6 above). Chow tests and log-cumulative hazard plots similarly suggested a break point in the PFS curves at week 9 (refer to appendix P).

The log-cumulative hazard plots of the two treatment arms cross in the middle and diverge at the end, which suggested the implausibility of the proportional hazard assumption (Figure 23). Therefore, separate models were used based upon the pembrolizumab+ chemotherapy and chemotherapy data separately for the projection of the PFS using a 2-piece extrapolation. Parametric models of PFS were therefore derived using a piecewise approach, in which hazard rates of PFS failure were based on the observed Kaplan-Meier curve up to week 9, followed by parametric models fitted thereafter. A comprehensive range of piecewise parametric models were fitted to each treatment arm, following the NICE DSU 14 guidance[52]. Short term fit and long term extrapolations are presented in Figure 24 and Figure 25 below.

Figure 23: PFS cumulative and Log-cumulative hazard plot for Pembrolizumab + taxanes and chemotherapy comparator based on KEYNOTE-355 (taxanes only)

Statistical tests based on the AIC and the BIC, combined with visual inspection were used to help select the best-fitted parametric distribution based on internal validity. The best statistical fit of each model in the observed data is associated with the lowest AIC/BIC, with a difference

of 5 points or greater considered important as important in terms of distinguishing between models.

Figure 24: PFS KM curve (per RECIST v1.1 as assessed by blinded CIV) fit vs fitted piecewise 9 week KM + parametric models for Pembrolizumab in combination with taxanes (short term fit and long term projections)

Figure 25: PFS KM curve (per RECIST v1.1 as assessed by blinded CIV) fit vs fitted piecewise 9 week KM + parametric models for Taxanes chemotherapy comparator (short term fit and long term projections)

.1 as assessed by blinded CIV) is presented in Table 40 below. Summary AIC/BIC statistics and visual inspection both suggested that for the piecewise PFS model, the 2nd best fitting curve for pembrolizumab + taxane was the KM up to week 9+ log-logistic, followed by KM up to week 9+Weibull, with the remaining options demonstrating a poor fit to the observed data

(exponential in particular) or implausible long term projections (Gompertz; best fitting model) (Figure 24).

For the taxane comparator piecewise PFS model, the best fitting curve was the KM up to week 9+ generalised gamma, followed by log-normal and the log-logistic as alternative models based on AIC/BIC statistics (Table 46) and visual inspection. **Error! Reference source not found.** and **Error! Reference source not found.** below present the longer term PFS model predictions for pembrolizumab + taxanes versus taxane chemotherapy alone.

Table 46: Summary of goodness of fit pricewise 9 week BIRC-assessed PFS models: pembrolizumab + taxanes and taxane comparator arm from KEYNOTE-355

Parametric distribution for PFS BICV	Pembro + taxane				Taxane comparator			
	AIC	BIC	AVRG	Rank	AIC	BIC	AVRG	Rank
Exponential	421.5440	423.9135	422.7288	4	255.0779	256.6888	255.8834	5
Weibull	418.7797	423.5186	421.1491	3	255.0463	258.2681	256.6572	6
Log-normal	421.7778	426.5167	424.1472	5	247.0689	250.2907	248.6798	2
Log-logistic	418.1941	422.9330	420.5635	2	247.3357	250.5575	248.9466	3
Gen Gamma	420.6777	427.7860	424.2318	6	245.9182	250.7509	248.3346	1
Gompertz	417.6679	422.4068	420.0374	1	247.5904	250.8122	249.2013	4
Notes: AIC: Akaike Information Criteria, BIC: Bayesian Information Criteria								

Table 47: PFS (per RECIST v1.1 as assessed by BCIV) landmark analysis and external validation for the pembrolizumab + taxanes from KEYNOTE-355

PFS options		Pembro + taxanes landmark analysis for PFS (Years)								
		0.5	1	1.5	2	3	5	8	10	20
Observed IA2 PFS		[redacted]								
Parametric models	Exponential	[redacted]								
	Weibull	[redacted]								
	Log-normal	[redacted]								
	Log-logistic	[redacted]								
	Gen Gamma	[redacted]								
	Gompertz	[redacted]								

Table 48: PFS (per RECIST v1.1 as assessed by blinded CIV) landmark analysis and external validation for the taxane comparator arm from KEYNOTE-355

PFS options		Pembro + taxanes landmark analysis for PFS (Years)								
		0.5	1	1.5	2	3	5	8	10	20
Observed IA2 PFS		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parametric models	Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The final base case for modelling PFS in the taxanes subgroup was a piecewise modelling approach to account for the change in hazard observed. The 9-week cut-off point was determined following review of the log-cumulative hazard plots which showed a significant change in hazard after ~8 weeks. In the base case, the piecewise 9K + Weibull model was used for PFS in the pembrolizumab + taxanes arm. Whilst it ranked as the 3rd best model based on AIC/BIC statistic, it resulted in more conservative PFS extrapolations versus the 2nd best log-logistic model and was therefore preferred for the economic model base-case. The selected model is line with clinical expert opinion sought to validate long term PFS projections (

Table 47 and Table 48), suggesting that at 4 years the PFS [redacted]

[redacted]. Whilst Exponential and Weibull models provide estimates closer to clinical expert opinion, they overpredict PFS during the observed period which is suboptimal for health economic modelling. Further, the Log-logistic model results in long term PFS estimates exceeding those selected for the taxane OS. Considering the plausibility of extrapolations, the piecewise 9KM+ Log-normal model (ranked as 2nd best) was selected for the PFS in the taxane comparator arm as it is overpredicts to a lesser extend in the observed period and results in lower PFS estimates from year 5 onwards, not exceeding the modelled OS. The final modelled PFS curves and PFS predictions used in the base case analysis over a 5 year and a 20 year time horizon are presented in Figure 26 and

Figure 27 below.

Figure 26: PFS KM curves vs 9 week KM + base-case parametric distributions for Pembrolizumab + taxane and taxane comparator based on KEYNOTE-355 over a 5 year period (taxanes only)

Figure 27: PFS KM curves vs 9 week KM + base-case parametric distributions for Pembrolizumab + chemotherapy and chemotherapy comparator based on KEYNOTE-355 over a lifetime horizon (taxanes only)

B 3.3.3 ToT extrapolation for the taxanes subgroup

ToT patient level data from KEYNOTE-355 from the taxane specific subgroup were used to fit parametric curves to the intervention and the comparator arms to ensure the economic model accurately captured associated costs of the treatments.

Parametric curves were fitted to the patient level treatment duration data from KEYNOTE-355 to represent ToT in the economic model the intervention and comparator arms. It should be noted that for the intervention arm, parametric curves were explored on the aggregated data for pembrolizumab and taxanes. This approach differs to that used in TA639, whereby the manufacturer split data between Atezolizumab and nab-paclitaxel TA639 and subsequently estimated ToT for each of the components individually [31].

The different approach followed in this this submission was due to the discontinuation of pembrolizumab beyond a 2 year period (built within the KEYNOTE-355 trial protocol; although subsequent re-treatment is possible under specific clinical criteria) [29]. Therefore, beyond the 2 year timepoint, ToT and discontinuations would only factor in patients continuing to receive chemotherapy. The 2 year pembrolizumab treatment cessation has been factored in the drug cost calculations (see Section 3.2.3).

AIC/BIC based tests combined with visual inspection were used to select the best-fitted parametric distributions

Since the ToT data are fairly mature from the RCT follow up, alternative parametric model selection should not impact greatly the model. However, it should be noted that the pembrolizumab component of KEYNOTE-355 has a maximum treatment duration of 35 cycles (~2 years). The models identified based on AIC/BIC did not exceed the PFS projections (which would be implausible) and were therefore selected for the base-case and sensitivity analyses.

Table 49. The model with the lowest AIC/BIC for pembrolizumab with taxanes was the Weibull whereas the function with lowest AIC/BIC for the taxane comparator arm was the log-logistic.

Alternative plausible scenarios include the log-normal for pembrolizumab +taxane followed by exponential for the taxane comparators.

Since the ToT data are fairly mature from the RCT follow up, alternative parametric model selection should not impact greatly the model. However, it should be noted that the pembrolizumab component of KEYNOTE-355 has a maximum treatment duration of 35 cycles (~2 years). The models identified based on AIC/BIC did not exceed the PFS projections (which would be implausible) and were therefore selected for the base-case and sensitivity analyses.

Table 49: Summary of goodness of fit for ToT for pembrolizumab + taxane and taxane comparator arm from KEYNOTE-355

Parametric distribution for ToT	Pembro + taxane				Taxane comparator			
	AIC	BIC	AVRG	Rank	AIC	BIC	AVRG	Rank
Exponential	856.4326	858.9865	857.7096	6	398.0814	399.9316	399.0065	2
Weibull	849.4653	854.5731	852.0192	1	399.9065	403.6068	401.7566	6
Log-normal	850.1001	855.2079	852.6540	2	398.4189	402.1192	400.2691	3
Log-logistic	852.0750	857.1827	854.6289	4	392.0249	395.7252	393.8751	1
Gen. Gamma	852.6234	857.7311	855.1773	5	399.0846	402.7849	400.9347	4
Gompertz	849.7523	857.4139	853.5831	3	398.1937	403.7442	400.9690	5
Notes: AIC: Akaike Information Criteria, BIC: Bayesian Information Criteria								

Figure 28. ToT KM curve vs fitted one-piece model for pembrolizumab + taxanes based on KEYNOTE-355

Figure 29. ToT KM curve vs fitted one-piece model for chemotherapy comparator based on KEYNOTE-355

B 3.3.4 Comparisons versus Atezolizumab + nab-paclitaxel

For the comparison versus Atezolizumab + nab-paclitaxel the model applies the HR derived from the ITC onto the Pembrolizumab + taxanes parametric models to construct the respective PFS and OS curves. These are subsequently used to infer the cost-effectives for this comparison. Due to data limitations, an assumption that proportional hazards hold is used for the modelling the treatment effect and cost-effectiveness estimates may be associated with high uncertainty. Rugo et al 2020 conclude that the population overlap between Impassion130 and KEYNOTE-355 is very limited since studies potentially identify patients with different tumor biology, therefore, atezolizumab + nab-paclitaxel is not a relevant direct comparator for the decision problem [19]. Considering the limitations associated with this comparison, atezolizumab + nab-paclitaxel is considered as a secondary comparator (full model predictions versus this comparison are presented in Appendix M.1.5.).

B 3.3.5 Final model predictions versus taxane chemotherapies

Figure 30 below presents the final model predictions for OS and PFS for the Pembrolizumab + taxane treatment arm versus the taxanes chemotherapy comparator.

Figure 30: Final model projections for PFS and OS over a 20 year time horizon for Pembrolizumab + taxanes versus Taxane chemotherapy comparators

B 3.3.5 Adverse events within economic model

Adverse events (AEs) experienced by patients were also included in the economic model to factor in the extra costs incurred. The primary source of incidence of AEs was the KEYNOTE-355 study. The model considers all-cause Grade 3+ AEs (incidence rate ≥5% for the CPS ≥10 population taxane subgroup). Additional AEs deemed as clinically relevant for inclusion in the economic modeling included:

- Diarrhea (of Grade 2+)
- Colitis (of Grade 2+)
- Pneumonitis (Grade 3+) included based on Evidence Review Group (ERG) feedback in previous appraisals of immunotherapy HTAs [53, 54]

It should be noted that the incidence rates of Grade 3+ AEs included in the model may be lower than the 5% cut-off used for inclusion since the 5% cut-off is based on AEs of any grade. In line with other IO submissions, the majority of AE costs (at Grade 3+) are associated with hospitalisation costs.

The impact of AEs was incorporated in the base-case by estimating weighted average cost per patient per treatment arm based on the incidence of AEs which is then applied as a one-off cost in the first cycle of the model accordingly.

Table 50: Incidence and duration of modelled AEs from KN-355

All-cause Grade 3+ AEs for the CPS ≥10 population	Grade	Pembrolizumab + taxanes	Taxane comparator	Mean AE duration (days)[#]
Anaemia	3+	[redacted]	[redacted]	[redacted] days
Leukopenia	3+	[redacted]	[redacted]	
Neutropenia	3+	[redacted]	[redacted]	
Thrombocytopenia	3+	[redacted]	[redacted]	
ALT increased	3+	[redacted]	[redacted]	
AST increased	3+	[redacted]	[redacted]	
Neutrophil count decreased	3+	[redacted]	[redacted]	
White blood cell count decreased	3+	[redacted]	[redacted]	
Diarrhoea	3+	[redacted]	[redacted]	
Hypothyroidism	3+	[redacted]	[redacted]	
Vomitting	3+	[redacted]	[redacted]	
Fatigue	3+	[redacted]	[redacted]	
Abdominal abscess	3+	[redacted]	[redacted]	
Pneumonia	3+	[redacted]	[redacted]	
Blood alkaline phosphatase increased	3+	[redacted]	[redacted]	
Lymphocyte count decreased	3+	[redacted]	[redacted]	
Hyperglycaemia	3+	[redacted]	[redacted]	
Lymphopenia	3+	[redacted]	[redacted]	
Pneumonitis (prior IO HTAs)	3+	[redacted]	[redacted]	
Colitis (prior IO HTAs)	2+	[redacted]	[redacted]	
Diahhroea (prior IO HTAs)	2+	[redacted]	[redacted]	

Notes: # used to estimate subsequent QALY decrement based on the selected AE profile which is then applied in the 1st cycle of the economic model

B.3.4 Measurement and valuation of health effects

B 3.4.1 Health-related quality-of-life data from clinical trials

HRQoL was evaluated in the KEYNOTE-355 trial using the EuroQoL EQ-5D-3L. The NICE guidelines stipulate that the EQ-5D is the preferred instrument measuring changes in the HRQoL alongside a clinical trial and that data collected directly from patients alongside a clinical study should be used to estimate the utility weights to populate the economic model [45].

In KEYNOTE-355 the EQ-5D-3L questionnaire was administered on the first day of every 3-week treatment cycle for the first 3 cycles and thereafter until the end of Year 1, every 3rd cycle (or every 9 weeks) during the first year and until PD whilst the treatment is still ongoing. From Year 2 onwards, assessments took place every 4th cycle (or 12 weeks) until PD whilst the treatment was still ongoing. Assessments were also conducted at treatment discontinuation (date of last treatment dose) and at the post-study safety follow up visit after treatment discontinuation (for those patients with treatment discontinuations taking place within 30 days of last dose the PRO collection was not repeated) [29]. Therefore, the utility data for post-progression estimates may be limited and may not be representative of the patient's quality of life in the whole post progression state.

Analysis of the EQ-5D-3L scores reported below was based on the full analysis set (FAS) population using the IA2 data-cut of KEYNOTE-355 CPS ≥ 10 population which took place on 11th of December 2019. UK preference-based scores were used for all patients analysed from the KEYNOTE-355 clinical trial with the UK scoring functions being developed based on the time trade-off (TTO) technique reported by Dolan et al 1997 [55].

Two approaches were considered when estimating utilities for the economic model:

- *Utilities derived based on disease progression status:*

This approach is commonly used across previous oncology submissions, requiring the definition of health states based on the time relative to disease progression. The results can then be leveraged to populate utility estimates by health state within the economic model. However, KEYNOTE-355 collected data up to drug discontinuation or at 30 days post-study follow up, therefore, the number of questionnaires used to inform analyses of post-progression utilities may itself be limited. Previous NICE committees have preferred utilities to be derived from health-state based regression models since utilities would depend upon disease progression status. The date of disease progression was determined based on the RECIST v1.1 blinded CIV from KEYNOTE-355.

  - the progression-free health state utilities: EQ-5D scores collected at all visits before the progression date were used.

  - the progressive health state utilities: EQ-5D scores collected at all visits after the progression date were used.

The analysis by disease progression status was conducted by pooling both treatment arms and by exploring treatment-specific utilities from KEYNOTE-355. The impact on Grade 3+ AEs was also explored by including a covariate for the AE status in the progression free state (this was not performed for the post-progression state due to the very low number of observations informing the analysis).

An alternative method of estimating utilities based on the patient's proximity to death was also explored since a patient's quality of life may experience further deterioration as they reach the terminal phase of their disease [56, 57].

- *Utilities derived based on time to death (TTD):*

This approach overcomes the problem of limited questionnaire availability to inform the PPS health state utility estimates reported above. It has also been deemed acceptable for decision making by NICE previously for a number of recent HTA submissions, including NSCLC, SCLC, RCC and Melanoma [58-62]. The TTD approach is used in the base-case as it was considered more robust for decision making purposes.

Based on KEYNOTE-355, the time to death was categorised as:

- 360 or more days to death
- more than 180 days but less than 360 days
- more than 90 days but less than 180 days
- more than 30 days but less than 90 days
- <30 days to death

Utility analysis results

Compliance to HRQL assessments was very good with [redacted]% of patients completing the questionnaires at baseline for pembrolizumab vs [redacted]% for chemotherapy [redacted]. Compliance rates slowly decreased over time with the lowest reported at Week 42 for pembrolizumab + chemotherapy at [redacted]% vs [redacted]% at week 15 for the chemotherapy arm. Appendix O provides the full methodology, including EQ-5D compliance rates at each assessment time point.

Since patients could have multiple EQ-5D score measurements within each time to death or progression status category, linear mixed-effects model with fixed effects including treatment and one of the following factors including; disease progression status; AE status; or Time-to-

death category, were applied to model EQ-5D scores, assuming compound symmetric structure to account for within-subject correlation due to repeated measurements of EQ-5D over time. The means of the EQ-5D scores in the following by-group of interest were predicted using Least Square (LS) means retrieved from the respective models;

1. By progression status and by treatment arm
2. By AE status within progression-free state and by treatment arm
3. By time-to-death category and by treatment arm

At the baseline assessment, the difference in utility between two arms is not statistically significant or clinically meaningful . EQ-5D utility values were estimated based on progression status (with or without response and treatment status) with further adjustments for the measurement of EQ-5D during a grade 3+ AE incidence rate ≥5%. Using both analyses (by progression status and time to death), no statistical and clinically meaningful differences were identified in the utility values for the between treatment comparisons (coefficient for pembro + chemo versus chemo was not statistically significant) and the associated decrement was < 0.08 (which is defined as minimally important difference (MID) in EQ-5D scores for cancers utility) [63].

The presence of Grade 3+ AE was associated with a statistically significant coefficient in the progression-free status, therefore utilities for Progression free with or without Grade 3+ AEs have also subsequently estimated and have been introduced in the model (see Appendix O). The estimated utilities generated are presented in Table 52, Table 52 and Table 53 below.

For the time to death analysis, the EQ-5D scores collected within each time category were used to estimate the mean utility associated with that category. The analyses of the intervals related to time to death lower than 360 days focused on patients with observed death dates. The justification to exclude patients whose death dates were censored was that their EQ-5D values could not be linked to their time-to-death category. However, for the category of 360 or more days to death, patients with censored death date of 360 days or longer were also included since their EQ-5D data related to a to a survival of at least 360 days, independent of when the death date was censored.

Table 51: Estimates utilities by progression status (pooled treatment arms)

Coefficient	Pooled Value (n=309 patients[#])	SE	95% CI
Progression free	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]		

Notes: [a] Observations after progression-free survival censoring (upon censoring, the patient's health state is unknown and therefore cannot be used in analyses or of interest to the economic model); [#]Number of records analysed per category is provided in the Appendix O – estimates for CPS ≥ 10 population. SE: Standard error, CI: Confidence Interval

Table 52: Estimated utilities from the final regression model (by treatment arm)

Coefficient	Pembro + chemo (n=212 patients[#])			Chemotherapy comparator (n=97 patients[#])		
	Value	SE	95% CI	Value	SE	95% CI
Progression Free during Grade 3+ AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression free no Grade 3+ AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility applied at PFS (calculated)	[redacted]			[redacted]		

Notes: [a] Observations after progression-free survival censoring are not included (upon censoring, the patient's health state is unknown and therefore cannot be used in analyses or of interest to the economic model) [#]Number of records analysed per category is provided in the Appendix O– estimates for CPS ≥ 10 population. SE: Standard error, CI: Confidence Interval

Table 53: EQ-5D health utility scores by time-to-death

Time to death category	Pooled* (N = 183 patients[#])		
	Mean	SE	95%CI
≥ 360 days left	[redacted]	[redacted]	[redacted]
< 360 days ≥ 180 days left	[redacted]	[redacted]	[redacted]
< 180 days ≥ 90 days left	[redacted]	[redacted]	[redacted]
<90 days but ≥ 30 days	[redacted]	[redacted]	[redacted]
< 30 days left	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]		

Notes: *Pooled across both treatment arms (observations without death records were censored) [#]Number of records analysed per category is provided in the appendix O – estimates for CPS ≥ 10 population. SE: Standard error, CI: Confidence Interval

B 3.4.2 Mapping

Not required since HRQoL data were collected alongside KEYNOTE-355 using the EQ-5D-3L questionnaire.

B 3.4.3 Health-related quality-of-life studies

Please refer to Appendix H for the search strategy, study identification process and list of studies identified through the HRQoL SLR including utilities from the recent TA639.

B 3.4.4 Adverse reactions

To assess the potential disutility associated with the AEs capture in the model, the disutility associated with patients experiencing Grade ≥3+ AEs was derived from KEYNOTE-355 PLD analysis ensuring a consistent source for adverse events and impact on HRQoL for pembrolizumab + taxanes. In the case of Atezolizumab, Grade ≥3+ AEs with incidence of ≥2% were sourced from key trials identified from the SLR [33].

The disutility associated with AES from the pooled utility analysis was estimated at [redacted]. The treatment specific disutilities by disease progression status were estimated at [redacted] for pembrolizumab + chemotherapy and [redacted] for chemotherapy alone. The disutility values applied within the model are dependent on the utility analysis selected.

Mean duration of for each of the AEs was estimated from KEYNOTE-355. The disutility associated with the incidence of Grade ≥3 AEs and the mean AE duration were used to estimate one-off QALY loss per patient due to AE for each treatment arm. This was [redacted] for pembrolizumab + taxanes and [redacted] for taxanes as comparator in the utility analysis by disease progression status (see section B.3.3. These QALY decrements were applied on the first cycle of the model for each comparator in the base-case.

The time to death analysis makes no further adjustments to derive an AE related disutility since it is already implicitly factored within the participant responses in the EQ-5D questionnaire. This avoiding any further assumptions on the AE incidence and duration within in each time-to-death category that would otherwise be necessary (explored in sensitivity analysis). This approach is applied in the base case to overcome limited questionnaire collection from KEYNOTE-355 at the post progression health state.

B 3.4.5 Age-related disutility

Ara and Brazier et al have suggested that utility decreases as age of the population increases, therefore age adjustments on utility estimates are incorporated in the model to account for these differences using the formula provided in the publication. Ara et al. (presented

Table 54) used a linear regression model to predict the mean utility values for individuals within the general population, conditional on age (in years), age-squared, and gender. This approach is applied based on feedback received from the ERG in a previous pembrolizumab appraisal [64-66].

Table 54: Regression coefficients used for the estimation of age-related disutility from Ara et al [64]

Parameter	Coefficient
Age (years)	-0.0002587
Age2	-0.0000332
Male	0.0212126
Intercept	0.9508566

B 3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

The time-to-death approach was selected as the primary source of utilities for the economic model since overcomes issues regarding limited data collection informing the post-progression health state utility values (Table 55).

This approach is consistent with a number of HTAs reviewed by NICE include the recent TA638 SCLC and factor in expected quality of life deterioration for aggressive cancers such as mTNBC [58-62]. Since the time-to-death approach utility is used for the base case, AE related disutilities are not included since these are intrinsically factored in the analysis and to avoid imposing any further assumptions for data analysis.

Treatment specific utilities with AEs by disease status are explored in sensitivity analysis (Table 55).

Table 55:Summary of utility values for cost-effectiveness analysis

Utilities for base case	Utility value: mean (SE)	95% CI	Reference in submission	Justification
Base case: Time to Death approach (pooled across treatment arms)				
≥ 360 days left	[redacted]	[redacted]	Section B.3.4.1 (HRQoL data from clinical trials)	Utility values from KEYNOTE-355 (IA2 Dec 2019), consistent with NICE reference case
< 360 but ≥180 days	[redacted]	[redacted]		
< 180 but ≥ 90 days	[redacted]	[redacted]		
<90 days but ≥ 30 days	[redacted]	[redacted]		
< 30 days left	[redacted]	[redacted]		
AE disutility	NA: Implicitly accounted for			
Sensitivity analysis: treatment specific with/without Grade 3+ AE for PFS				
PFS with GRADE 3+ AES			As above	As above
Pembro + chemo	[redacted]	[redacted]		
Chemo comparator	[redacted]	[redacted]		
PFS no GRADE 3+ AES				
Pembro + chemo	[redacted]	[redacted]		
Chemo comparator	[redacted]	[redacted]		
PPS utility				
Pembro + chemo	[redacted]	[redacted]		
Chemo comparator	[redacted]	[redacted]		
Alternative sensitivity analysis: Utilities by progression status (pooled)				
PFS utility pooled	[redacted]	[redacted]	As above	As above
PPS utility pooled	[redacted]	[redacted]		
AE related disutility	[redacted]			

AE adverse: event, CI: Confidence Interval, SE; Standard Error

B.3.5 Cost and healthcare resource use identification, measurement and valuation

A systematic literature review was conducted to identify relevant costs and health care resource use data to populate the economic model. No UK specific studies were identified for the population of interest. Appendix I provides the methodology, search strategy, results f the searches conducted

Public data have been used to cost resource use from an NHS+PSS perspective as per the NICE Reference Case. Costs have been inflated accordingly to the current price year using

the hospital and community health services (HCHS) index published by PSSRU for 2019 if necessary [67].

B.3.5.1 Intervention and comparators' costs and resource use

Intervention costs

Drug acquisition costs for pembrolizumab plus chemotherapy regimens used in KEYNOTE-355 were sourced from the British National Formulary (BNF), the Monthly Index of Medical Specialities (MIMs) and the electronic Market Information Tool (eMIT) (see Table 56 below). These are used to estimate the intervention cost applied in the economic model. When multiple vial/package sizes were available, the cheapest price per mg was applied as a conservative assumption.

As per the anticipated license, the model uses a 200mg fixed dose of pembrolizumab, administered as a 30-minute IV infusion every three weeks or 21 days (Q3W) in combination with a taxane (paclitaxel or nab-paclitaxel). The maximum treatment duration for pembrolizumab is for 35 infusions (or approximately 2 years), however, chemotherapy treatment could be continue beyond this point [29].

The list price of a 100mg vial is £2,630.00. Therefore, the drug cost for pembrolizumab per administration is £5,260 based on two 100mg vials using the list price. A commercial access agreement is currently in place for patients with [redacted]

The dosing schedule for the different chemotherapies used in KEYNOTE-355 alongside pembrolizumab is as follows:

- Paclitaxel: As per trial protocol, the recommended dose of paclitaxel for use in combination with pembrolizumab is 90mg/m^2 of paclitaxel, administered IV on days 1,8 and 15 of each 28 day treatment cycle (3 weeks on treatment, 1 week off treatment).
- Nab-paclitaxel: As per trial protocol, the recommended dose of nab-paclitaxel for use in combination with pembrolizumab is 100mg/m^2 of nab-paclitaxel, administered IV on days 1, 8 and 15 of each 28 day treatment cycle (3 weeks on treatment, 1 week off treatment).

Comparator costs

Drug acquisition costs for individual drugs constituting the UK SoC were taken from the BNF, MIMs or eMIT (see Table 56 below). The model applies the relevant chemotherapy

comparator cost at each cycle accordingly for each regimen separately. The model uses the taxane specific subgroup efficacy results for the comparator arm, assuming that paclitaxel and nab-paclitaxel have similar survival profile based on clinical expert opinion and AC preferences in TA639.

The cost of nab-paclitaxel in the comparator chemotherapies alone is assumed to be equal to that of paclitaxel alone since it is not approved as monotherapy for use in mTNBC patients (only used as monotherapy for those which cannot tolerate paclitaxel).

Table 56: Intervention and comparators drug acquisition costs used in the model

Drug	Vial Concentration	Cost per vial	Source
Pembrolizumab	100 mg / 4 ml	£2,630.00	MIMs UK list price (confidential PAS in place)[68]
Paclitaxel	30 mg / 8 ml	£4.69	eMIT Nov 2020[69]
	100 mg / 16.7 ml	£23.06	
	150 mg / 25 ml	£18.88	
	300 mg / 50 ml	£39.32	
Nab-paclitaxel	100 mg	£246.00	MIMS UK list price (unknown confidential PAS in place)[69]
Docetaxel	20 / 1 ml	£4.61	eMIT Nov 2020[70]
	80 / 4 ml	£12.50	
	160 / 8ml	£20.96	
Atezolizumab	840 mg / 14ml	£2,665.38	MIMs UK list price (unknown confidential PAS in place)[71]
Abbreviations: BNF: British National Formulary, MIMS: Monthly Index of Medical Specialities, eMIT: electronic Market Information Tool			

Estimating the ToT for intervention and comparators

KEYNOTE-355 patient level data were used to estimate the treatment duration for each of the comparators in the trial. Parametric curves were fitted to inform the model input and account for early treatment discontinuation of patients as per study protocol (see section 3.3.2 for more information). Further, the intervention component costs of pembrolizumab were capped at 2 years (week 104 in model), which is the maximum treatment duration for pembrolizumab as per SmPC. However, chemotherapy treatment could be continued upon progression and the costs account for this based on the ToT extrapolations.

Relative dose intensity (as reflected in the pembrolizumab arm of KEYNOTE-355) was also applied to the drug acquisition cost per infusion to account for any delays or interruptions in administration (e.g., due to AEs) in the intervention or comparators. KEYNOTE-355 data regarding dose interruption were analysed and incorporated into the model per cycle of administration across both treatment arms. Overall, in the pembrolizumab + taxane arm [redacted] of patients received pembrolizumab as planned with [redacted] planned paclitaxel and [redacted] nab-paclitaxel study treatment doses as planned. In the taxane comparator arm [redacted] received paclitaxel as planned and [redacted] received nab-paclitaxel study treatment doses as planned. Please note that costs for nab-paclitaxel monotherapy are assumed to be equal to those of paclitaxel alone (nab-paclitaxel not approved for monotherapy use in mTNBC patients).

B.3.5.2. Subsequent treatment costs

Outcomes relating to subsequent therapies have not been explicitly modelled due to complexity and increased uncertainty this would introduce to the HTA. However, the costs of subsequent treatment costs for patients experiencing disease progression is also included in the economic model. Data from CPS ≥10 score KEYNOTE-355 (all chemotherapies population) were used to explore the proportion of patients receiving subsequent therapies.

With a median follow up of [redacted] across both treatment arms showed that [redacted] of patients having experienced a progression in the pembrolizumab arm went on to receive subsequent 2L treatment versus [redacted] in the comparator chemotherapy arm with a further [redacted]% and [redacted]% receiving 3L+ respectively. A full breakdown of subsequent therapies directly derived from the trial is presented in Appendix D1.5 and Appendix M.1.1).

Only a small % of patients went on to receive subsequent IO agents for 2L + in [redacted] of Pembrolizumab + chemotherapy versus [redacted] in chemotherapy comparator arm. In the 3L setting the IO usage was [redacted] respectively. Eribulin mesylate was used as a 2L treatment by [redacted] for chemotherapy alone. Appendix M.1.1 presents the subsequent therapies including IO agents by line of therapy.

Since IO agents or eribulin mesylate have not been approved for 2L+ mTNBC treatment in the UK, these records were redistributed across all other treatments equally for the purposes of costing to better reflect the UK real world practice. Table 57 presents the subsequent treatments received by patients adapted for the UK clinical practice alongside the mean treatment duration per 2L, 3L and 4L. These estimates are derived across all chemotherapy backbones to increase the number of records for analysis.

The base-case analysis assumes an average subsequent treatment cost adapted for UK practice and derived from subsequent treatment and mean treatment duration by line of

therapy and by treatment arm from the KEYNOTE-355 data (Table 57). Alternative source of data from market research is explored in sensitivity analysis due to limited records [72]. In brief, [redacted]. Due to limited records available, KEYNOTE-355 data are used for mean treatment duration if this source is selected in the model. The posology used to estimate subsequent treatment costs was derived from public sources (Table 60).

Table 57: Subsequent treatments and mean treatment duration from KEYNOTE-355 CPS ≥ 10 score population applied in the base-case

Subsequent therapies in KEYNOTE-355*	Pembrolizumab + chemotherapy arm	Chemotherapy comparator
As 2L±	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]
Cyclophosphamide (+) doxorubicin	[redacted]	[redacted]
Carboplatin (+) gemcitabine	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Mean duration days (SE)	[redacted]	[redacted]
As 3L±	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]
Eribulin mesylate*	[redacted]	[redacted]
Capecitabine (+) vinorelbine tartrate	[redacted]	[redacted]
Cyclophosphamide (+) doxorubicin	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Mean duration days (SE)	[redacted]	[redacted]
4L±	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Nab-paclitaxel	[redacted]	[redacted]
Mean duration days (SE)	[redacted]	[redacted]

Note: ±Eribulin and IO reweighted from 2L, IOs reweighted form 3L and 4L - values presented are adjusted to reflect the UK clinical setting: for full breakdown across all therapies, please refer to Appendix M, SE: standard error

Table 58: Subsequent therapies 2L+ from market research conducted (sensitivity analysis)

2L	N = [redacted] patient records
Docetaxel	[redacted]
Gemcitabine + carboplatin[+]	[redacted]
carboplatin (+) gemcitabine (+) PARP inhibitor	[redacted]
Epirubicin	[redacted]
Capecitabine	[redacted]
Carboplatin	[redacted]
Paclitaxel	[redacted]
Docetaxel + paclitaxel	[redacted]
Vinorelbine + paclitaxel + PARP inhibitor[#]	[redacted]
3L+ therapies	**N=[redacted] patient records**
Eribulin	[redacted]
Carboplatin	[redacted]
Notes: +Also includes a record of gemcitabine + carboplatin + PARP inhibitor; #Costed as Vinorelbine + paclitaxel alone since PARP inhibitors are not approved for mTNBC (likely clinical trial record); 1 record of IO agent treatment was redistributed across all other subsequent therapies	

Table 59: Drug acquisition costs for subsequent treatments

Drug	Vial Concentration	Cost per vial	Source
Carboplatin	50 mg / 5 ml	£3.75	eMIT Nov 2020[73]
	150 mg /15 ml	£10.69	
	450 mg / 45 ml	£27.90	
	600 mg / 60 ml	£28.22	
Capecitabine	150 mg (60 tables pack)	£4.17	eMIT Nov 2020[73]
	300 mg (60 tables pack)	£7.26	
	500 mg (60 tables pack)	£25.76	
Docetaxel	20 / 1 ml	£4.61	eMIT Nov 2020[73]
	80 / 4 ml	£12.50	
	160 / 8ml	£20.96	
Eribulin	880 mg / 2 ml	£361.00	BNF UK Nov 2020 list price (unknown confidential PAS in place) [74]
	1320 mg / 3 ml	£541.50	
Gemcitabine	200 mg / 2 ml	£3.28	eMIT Nov 2020[73]
	1000 mg /10 ml	£11.85	
	2000 mg / 20 ml	£17.99	
Vinorelbine	10 mg / 1 ml	£36.71	eMIT Nov 2020[73]
	50 mg / 5ml	£133.28	
Nab-paclitaxel	100 mg	£246.00	MIMS UK Nov 2020 list price (unknown confidential PAS in place) [69]
Epirubicin	100 mg / 50 ml	£22.32	eMIT Nov 2020[73]
	10 mg /5 ml	£1.93	
	200 mg / 100 ml	£19.29	
	50 mg /25 ml	£4.84	
Doxorubicin	10 mg /5 ml	£3.30	eMIT Nov 2020 [73]
	200 mg / 100 ml	£17.21	
	50 mg /25 ml	£12.38	
Abbreviations: MIMS: Monthly Index of Medical Specialities, eMIT: electronic Market Information Tool			

Table 60: Posology and dosing frequency for subsequent treatments

Drug	Dose per administration	Frequency of administration	Source
Carboplatin	400 mg/m^2	Every 4 weeks	EMC [75]
Capecitabine	2,500 mg/m^2	Oral daily for 2 weeks with a 1 week off treatment period	EMC [76]
Docetaxel	75 mg/m^2	Every 3 weeks	EMC [73]
Eribulin	1.23 mg/m^2	Days 1 &8 of a 21 day cycle	EMC [77]
Gemcitabine	1,250mg /m^2	Days 1 &8 of a 21 day cycle	EMC [78]
Vinorelbine$^+$	30 mg/m^2	Once weekly	EMC [79]
Cyclophosphamide	600 mg/m^2	Day 1 of every 21 day cycle for 6 cycles maximum	EMC [80]
Epirubicin*	75mg/m²	Every 21 days (for 6 cycles with Cyclophosphamide)	[80, 81]
Doxorubicin	60 mg m²	Every 21 days (for 6 cycles with Cyclophosphamide)	[82, 83]

Notes: $^+$Higher dose range assumed as per SmPC section 4.2. *Lower dose assumed for metastatic setting as per NHS treatment protocol [80] . No capping was applied for cyclophosphamide or doxorubicin/epirubicin combinations in costs explicitly but total number of cycles received based on posology outlined in SmPC is lower than maximum number of cycles outlined. Abbreviations: EMC: Electronic Medicines Compendium

B.3.5.3. Administration costs

In KEYNOTE-355 pembrolizumab 200mg was administered Q3W over a 30 minute infusion for a maximum of 2 years. Paclitaxel or nab-paclitaxel were administered IV on days 1, 8 and 15 of each 28-day treatment cycle (3 weeks on treatment and 1 week off treatment) at 90 mg/m^2 or 100 mg/m^2 doses respectively [29].

Pembrolizumab is co-administered with chemotherapy every 3 or 6 weeks depending on the chemotherapy backbone selected (

Table 61). Administration costs applied in the model were dependent upon complexity and by treatment type (Table 60

Table 62 for intervention/comparators or

Table **62** for subsequent therapy administration costs) [84].

Table 61: Administration costs applied in the economic model for 1L comparators

Drug	Type of administration	NHS ref. code	Setting	Unit cost
Pembrolizumab co-administered in combination				
Pembrolizumab + paclitaxel	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	SB14Z	Outpatient	£370.68
Pembrolizumab + nab-paclitaxel				
Pembrolizumab or chemotherapies administered as monotherapies				
Pembrolizumab+ monotherapy	Deliver Simple Chemotherapy, at First Attendance	SB12Z	Outpatient	£241.06
Paclitaxel* monotherapy	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	SB14Z	Outpatient	£370.68 *
Nab-Paclitaxel monotherapy	Deliver Simple Chemotherapy, at First Attendance	SB12Z	Outpatient	£241.06
Docetaxel* monotherapy	Deliver Simple Chemotherapy, at First Attendance	SB13Z	Outpatient	£241.06 *
Additional comparators				
Atezolizumab + nab-paclitaxel combination	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	SB14Z	Outpatient	£370.68
Notes:+For pembrolizumab infusions which do not coincide with chemotherapy infusions the model applies SB12Z infusion cost. *Paclitaxel and docetaxel require pre-medications which are applied at each IV infusion; see Table 73				

Table 62: Administration costs applied for subsequent therapies

Drug	Type of administration	NHS ref. code	Unit cost	Source
Docetaxel	IV outpatient setting	SB12Z "Deliver Simple Parenteral Chemotherapy at First Attendance"	£241.06	NHS Reference costs 2018-2019[84]
Paclitaxel				
Nab-paclitaxel				
Vinorelbine				
Eribulin				
Docetaxel				
Epirubicin				
Carboplatin				
Gemcitabine				
Cyclophosphamide				
Doxorubicin				
Capecitabine	Band 6 Hospital Pharmacist time: 12 minutes preparation for each prescription	NA	£45/hr *12 min = £9.20	PSSRU 2019[67]
Abbreviations: N/A; Not applicable; NHS: National Health Service; PSSRU: Personal Social Services Research Unit.				

B.3.5.4. Health-state unit costs and resource use

A systematic literature review was conducted to identify costs and resource use in the treatment and the ongoing management of relapsed inoperable metastatic TNBC. No UK specific studies were identified. Please see Appendix I for details around methodology and study selection criteria. The most recent estimates reported in mTNBC TA639 have used as a source of health resource utilisation owing to UK specific estimates from the SLR [31]. These have been used historically across all mBC and reflect recent AC preferences. Additional regular blood tests and regular scans were introduced to supplement these based on clinical expert opinion [31, 51].

The economic model includes 3 heath defined by disease progression; PFS, PPS and Death (see section 3.2.2.). The frequency of resource use per health state is multiplied by the respective medical unit cost from published sources to estimate the total cost applied within each cycle of the economic model per health state. Table 66 includes a list of the medical resource use unit costs used within the model.

A one-off cost for patients entering the model is applied for PFS in the first model cycle to reflect the resource use for initial care regarding the disease diagnosis (

Table 63). Thereafter, ongoing disease management care costs are applied throughout the model for patients according to health state occupancy within the PFS and PPS states. The estimated monitoring and disease management costs per cycle were £74.32 the pre-progression and £69.50 at the post-progression period (

Table 64 and

Table 65). For patients experiencing a progression, an average cost related to subsequent treatments is also applied at each model cycle within the PPS health state (refer to section 3.5.2).

Table 63: Diagnosis costs for mTNBC applied as one-off at PFS

Resource	% pts using as one-off	Cost (£)	Source
Oncologist visit	100%	£143.72	NHS ref costs; 2018-2019 800 CL: WF01A Clinical Oncology (Previously Radiotherapy); Service code: 800
CT scan	50%	£103.61	NHS ref costs; 2018-2019 RD24Z Computerised Tomography Scan of Two Areas, with Contrast
MRI Scan	50%	£204.35	NHS ref costs; 2018-2019 RD05Z Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast
Full blood count	100%	£2.79	NHS ref costs; 2018-2019 DAPS05 Haematology
Total cost applied at PFS entry		£299.35	

Table 64: Resource use for ongoing disease management in the PFS health state

Resource	Frequency	Cost (£)	Reference
Health care professionals			
Oncologist visit	1 per month	£142.73	NHS ref costs; 2018-2019 800 CL: WF01A Clinical Oncology (Previously Radiotherapy); Service code: 800
GP visit	1 per month	£33.19	PSSRU 2018 Section 10.3B
Clinical nurse specialist	1 per month	£98.74	NHS ref costs; 2018-2019 N10AF Specialist Nursing, Cancer Related, Adult, Face to face
Community nurse	1 per 4 months	£39.68	NHS ref costs; 2018-2019 N02AF District Nurse, Adult, Face to face
Imaging			
CT scan*	1 every 12 weeks	£103.61	NHS ref costs; 2018-2019 RD24Z Computerised Tomography Scan of Two Areas, with Contrast
Laboratory monitoring			
Full blood count*	1 every 3 weeks	£2.79	NHS ref costs; 2018-2019 DAPS05 Haematology
Total per weekly model cycle		£74.32	
*Additional resource use assumption based on clinical expert opinion in this TA.			

Table 65: Resource costs for ongoing disease management in the PPS health state

Resource	Frequency	Cost (£)	Reference
Health care professionals			
Oncologist visit	1 per month	£142.73	NHS ref costs; 2018-2019 800 CL: WF01A Clinical Oncology (Previously Radiotherapy); Service code: 800
GP visit	1 per month	£33.19	PSSRU 2018 Section 10.3B: per 9.22 minutes consultation at GP surgery with qualifications, including direct staff costs.
Clinical nurse specialist	1 per month	£98.74	NHS ref costs; 2018-2019 N10AF Specialist Nursing, Cancer Related, Adult, Face to face
Community nurse	1 per 2 months	£39.68	NHS ref costs; 2018-2019 N02AF District Nurse, Adult, Face to face
Imaging			
CT scan*	1 every 6 months	£103.61	NHS ref costs; 2018-2019 RD24Z Computerised Tomography Scan of Two Areas, with Contrast
Total cost per weekly model cycle		69.50	
*Additional resource use assumption in this TA			

Table 66: Full list of medical resource unit costs used within the HTA submission

Resource	Cost (£)	Reference
Health care professionals		
Oncologist visit	£142.73	NHS ref costs; 2018-2019 800 CL: WF01A Clinical Oncology (Previously Radiotherapy); Service code: 800
GP visit	£33.19	PSSRU 2018 Section 10.3B
Clinical nurse specialist	£98.74	NHS ref costs; 2018-2019 N10AF Specialist Nursing, Cancer Related, Adult, Face to face
Community nurse	£39.68	NHS ref costs; 2018-2019 N02AF District Nurse, Adult, Face to face
Imaging procedures		
CT scan	£103.61	NHS ref costs; 2018-2019 RD24Z Computerised Tomography Scan of Two Areas, with Contrast
MRI	£204.35	NHS ref costs; 2018-2019 RD05Z Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast
Laboratory monitoring		
Full blood count	£2.79	NHS ref costs; 2018-2019 DAPS05 Haematology

A one-off cost is also applied at the point of death to reflect the additional costs associated with terminal and palliative care. The cost estimate has been sourced by Georgiou & Bardsley et al 2014 and is associated with the hospital care in 90 days before dying [85]. This source

of costs is in line with previous pembrolizumab submissions[86]. The estimated cost is made up of services which included emergency inpatient admissions, non-emergency inpatient admissions, outpatient attendances and accident and emergency costs (see Table 32 for the final cost estimate applied).

Table 67: Resource use and source of terminal care and end of life costs

Resource	Unit cost	Source
District nurse	£332.49	Georgiou & Bardsley et al 2014 inflated to 2019 value [85]
Nursing and residential care	£1196.04	
Hospice care – inpatient	£657.83	
Hospice care – final 3 months of life	£5382.17	
Marie Curie nursing service	£598.01	
Total cost applied	**£8166.55**	

B.3.5.5. Adverse reaction unit costs and resource use

Modelled AEs and their corresponding incidence are presented in section B.3.3.3. In brief, all grade ≥3+ AEs with incidence of ≥5% were included. AE disutilities applied in the economic model are described in section B.3.4.4.

The source of AE management costs used in TA639 (Majethia et al 2014) was not deemed robust for costing of AEs in this technology appraisal (3L metastatic breast cancer patients participating in a RCT) [31, 87]. Therefore, the resource use related to AE management is based on methodology and approaches employed in prior IO HTAs for consistency and to be reflective of AC preferences in this topic (see Table 68) [66, 88-90]. Unit costs associated with the management of AEs have been sourced from the latest NHS Reference Costs 2018/19 (presented in Table 68) [84]. A one-off cost AE management cost is applied at the first model cycle for simplicity in each of the treatment arms, presented in Table 69 (for AE incidence rates see section B.3.3.3).

Table 68: Unit costs associated with management

Grade 3+ AE	AE Cost	NHS Reference cost code	Rationale
Anaemia	£942.09	NHS ref costs; 2018-2019 weighted average of DC SA04J Iron Deficiency Anaemia with CC Score 6-9 NES SA04J Iron Deficiency Anaemia with CC Score 6-9 NEL SA04J Iron Deficiency Anaemia with CC Score 6-9	Costing per TA519[66]
Leukopenia	£66.44	As per Neutropenia	Equal to Neutropenia as inTA519[66]
Neutropenia	£66.44	NHS ref costs; 2018-2019 weighted average of NEL WJ11Z Other Disorders of Immunity NES WJ11Z Other Disorders of Immunity DC WJ11Z Other Disorders of Immunity	Costing per Approach as per TA519[66]
Thrombocytopenia	£942.09	As above for Anaemia	Equal to Anaemia - TA581 Approach[90]
ALT increased	£0.00	NA	As per TA558; Assumption of zero cost for laboratory abnormalities; (already considered under health-state management costs)
AST increased	£0.00	NA	
Neutrophil count decreased	£66.44	As per Neutropenia	Equal to Neutropenia - TA519[66]
Platelet count decreased	£66.44	As per Neutropenia	Equal to Neutropenia - TA519 & TA650
White blood cell count decreased	£66.44	As per Neutropenia	Equal to Neutropenia - TA519[66]
Diarrhoea	£1,105.89	NHS ref costs; 2018-2019NES FD10F Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 5-8 NES FD10G Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 3-4 DC FD10G Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 3-4	TA581 approach[90]
Hypothyroidism	£589.07	NHS ref costs; 2018-2019 INDEX Sheet NES Non-Elective Short Stay	Costing per TA581 approach[90]

Vomiting	£1,105.89	NHS ref costs; 2018-2019NES FD10F Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 5-8 NES FD10G Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 3-4 DC FD10G Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 3-4	Costing per TA581 approach[90]
Fatigue	£2,839.22	NHS ref costs; 2018-2019 NEL & DC Sheets code: WH52A; follow up examinations with interventions (long stay and Day case)	TA519 assumption for costing[66]
Abdominal abscess	£3,706.09	NHS ref costs; 2018-2019 NEL & DC Sheets code: YF04A to YF04C; Single abdominal abscess percutaneous drainage (NEL, NES and DC) weighted average	Assumption - this TA
Other AEs			
Pneumonitis (grade 3+)	£883.03	NHS ref costs; 2018-2019, PSSRU, BNF Aggregate cost made of: DZ69A (Bronchoscopy 19 and over) & GP Visit PSSRU & BNF cost for 4 week Fluticasone propionate Steroid cost use 50mg fluticasone (60 inhalations)	Costing per TA417 & TA553[88, 89]
Diahhroea (Grade 2+)	£1,105.89	NHS ref costs; 2018-2019NES FD10F Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 5-8 NES FD10G Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 3-4 DC FD10G Non-Malignant Gastrointestinal Tract Disorders with Single Intervention, with CC Score 3-4	Costing perTA581 approach[90]
Colitis (grade 2+)	£1,105.89	As above for Diahhroea	Assumed equal to Diahhroea 2+
Abbreviations: BNF: British National Formulary, CC: Complication Complexity, DC: day Case, NA: Not applicable, NEL; Non-elective long stay, NES: Non-elective short stay, PSSRU: Personal Social Services Research Unit			

Table 69: Total AE management costs per patient applied in the model based on KEYNOTE-355 data

Grade 3+ AE	Pembrolizumab + Taxanes	Taxane comparator	Atezolizumab + nab-paclitaxel comparator*
Weighted cost of managing AEs requiring hospitalisation	[redacted]	[redacted]	[redacted]

B.3.5.6. Miscellaneous unit costs and resource use (PD-L1 testing and pre-medication costs)

Costs associated with PD-L1 testing

PD-L1 testing costs are applied within the model depending on the comparison selected. Test costs associated with the IHC 22C3 PharmDx Assay are used. In KEYNOTE-355 38.1% of recruited patients was confirmed with CPS ≥ 10 score, which is this is also assumed to be representative of the UK population. Test costs applied also account for the patients tested for PD-L1 and which are not identified as PD-L1 positive with CPS ≥ 10. For the Atezolizumab + nab-paclitaxel, the PD-L1 SP142 unit costs are used (Table 70 below).

Table 70: PD-L1 testing cost within economic model

Drug	PD-L1 test cost as one-off*	KEYNOTE-355 patients PD-L1 positive with CPS ≥ 10 using 22C3 PharmDx Assay	Adjusted test cost per patient subsequently confirmed as PD-L1 positive	Cost per PD-L1 +ve patient with CPS ≥ 10 using the 22C3 PharmDx Assay
Pembrolizumab	£40.50*	38.1%	£40.50* 38.1%	£106.20
Atezolizumab	£121.08	As above	£121.08*38.1%	£278.49
Notes: The unit cost for PD-L1 testing used in the HTA has previously been used across all pembrolizumab HTAs including ID1140 (SCCHN) – assumed as NHS Reference costs 2018-2019; DAPS02 Histopathology and histology code [86].				

Costs of pre-medications for chemotherapy

As per the SmPC paclitaxel and docetaxel treated patients require pre-medication to reduce the impact of these chemotherapies on patients.

Table 71 includes the pre-medications necessary for each chemotherapy regimen. As per Roche submission we assume dexamethasone is administered orally rather than IV, therefore a prescription cost is applied. For chlorpheniramine and cimetidine which require IV administration, a nurse specialist cost for the time required for preparation has been applied in the economic model as per the approach followed in TA639 [31].

Table 73 presents the total pre-medication costs applied at each chemotherapy cycle.

Table 71: Pre-medication dosing for paclitaxel and docetaxel

mTNBC chemo	Pre-medication drug	Dose	Administration	Source
Paclitaxel	Dexamethasone	20 mg	Oral approx. 12 and 6 hrs or IV 30 - 60 minutes	EMC [91]
	Chlorpheniramine	10 mg	IV 30 - 60 minutes	
	Cimetidine	300 mg	IV 30 – 60 minutes	
Docetaxel	Dexamethasone	16 mg/day for 3 days	Oral 1 day prior to docetaxel commencement	EMC [92]

Table 72: Pre-medication drug acquisition costs

Pre-medication drug	Total dose per chemo administration	Drug acquisition cost	Administration	Source
Dexamethasone	2mg tablets / Packsize 50	£2.77	Oral approx. 12 and 6 hrs or IV 30 - 60 minutes	eMIT [73]
Chlorpheniramine	10 mg/ml injection, Packsize 5 x 1 ml ampoules	£22.50	IV 30 - 60 minutes prior to paclitaxel	MIMS [93]
Cimetidine	200 mg/5ml for 300ml	£34.17	IV 30 – 60 minutes	MIMS [94]

Table 73: Total pre-medication drug costs applied including administration costs

Chemotherapy	Pre-medication drug	Dose/chemo cycle	Pre-medication cost	Administration costs	Total costs	Source
Paclitaxel	Dexamethasone	20 mg	£0.55	£9.00*	£9.55	PSSRU 2019: Band 6 Pharmacist [67]
	Chlorpheniramine	10 mg	£4.50	£113	£118.35	PSSRU 2019: Band 6 Hospital nurse 1hr cost/1hr patient contact [31, 67]
	Cimetidine	300 mg	£0.85			
Total cost paclitaxel applied in model per IV infusion			**£5.91**+	**£122**+	NA	
Docetaxel	Dexamethasone	16 mg * 3 = 48 mg	£1.33	£9.00	**£10.33**	PSSRU 2019; Band 6 Pharmacist [67]
Notes: Costs are applied at each treatment cycle with chemotherapy; +**Bold** values applied within model. The model pre-medication costs are added to the paclitaxel or docetaxel drug costs and pre-medication administration costs are added to the complex IV infusion costs (SB14Z) * Band 6 Pharmacist (£45/hr) & 12min preparation.						

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1. Summary of base-case analysis inputs

The full list of variables used in the cost-effectiveness analysis is presented in Table 74 below.

Table 74:Summary of variables applied in the economic model used in base-case

Parameters	Mean / Deterministic value	Lower	Upper	Distribution used in PSA	Section in the submission document
General Information					
Model cycle length (weeks)	1	NA	NA	Not varied in PSA	See Section B.3.2
Model time horizon (years)	20	NA	NA	Not varied in PSA	
Discount rate: Costs	3.5%	NA	NA	Not varied in PSA	
Discount rate: Health outcomes	3.5%	NA	NA	Not varied in PSA	
Vial sharing	0%	NA	NA	Not varied in PSA	
Patient Information					
Patient Age	[redacted]	NA	NA	Not varied in PSA	See Section B.3.2
Proportion female	[redacted]	NA	NA	Not varied in PSA	
Average patient weight (kg)	[redacted]	[redacted]	[redacted]	Not varied in PSA	
Mean Body Surface Area (m^2)	[redacted]	[redacted]	[redacted]	Not varied in PSA	
Estimated eGFR mean	[redacted]	NA	NA	Not varied in PSA	
Utility Inputs by disease progression					
Utility Inputs by Time-to-Death (pooled)					
Utility based on time to death [0, 29] days	[redacted]	[redacted]	[redacted]	[redacted]	See Section B.3.4
Utility based on time to death [30, 89] days	[redacted]	[redacted]	[redacted]	[redacted]	
Utility based on time to death [90, 179] days	[redacted]	[redacted]	[redacted]	[redacted]	
Utility based on time to death [180, 359] days	[redacted]	[redacted]	[redacted]	[redacted]	
Utility based on time to death [≥ 360] days	[redacted]	[redacted]	[redacted]	[redacted]	
Intervention Costs (per administration)					
Drug costs (per administration for Pembrolizumab + taxanes)					
Pembrolizumab	£5,260.00	NA	NA	Not varied in SA	
Paclitaxel (no pre-medication costs)	24.62	NA	NA	Not varied in SA	

Nab-paclitaxel (with Pembro)	£430.50	NA	NA	Not varied in SA	See Section B.3.51
Drug costs (per administration for comparators)					
Paclitaxel (no pre-medication costs)	24.62	NA	NA	Not varied in SA	
Docetaxel (& pre-medication costs)	£28.67	NA	NA	Not varied in SA	
Atezolizumab	£2,665.38	NA	NA	Not varied in SA	
Nab-paclitaxel (with Atezolizumab)	£450.50	NA	NA	Not varied in SA	
Relative dose intensity (intervention)					
Pembrolizumab	[redacted]	[redacted]	[redacted]	Beta	See Section B.3.5.1
Paclitaxel (with Pembrolizumab)	[redacted]	[redacted]	[redacted]	Beta	
Nab-paclitaxel (with Pembrolizumab)	[redacted]	[redacted]	[redacted]	Beta	
Relative dose intensity (comparators)					
Paclitaxel alone	[redacted]	[redacted]	[redacted]	Beta	
Docetaxel alone (set equal to paclitaxel)	[redacted]	[redacted]	[redacted]	Beta	
Atezolizumab	[redacted]	[redacted]	[redacted]	Beta	
Nab-paclitaxel (with Atezolizumab)	[redacted]	[redacted]	[redacted]	Beta	
Subsequent therapy acquisition costs					
Pembrolizumab + taxanes	[redacted]	[redacted]	[redacted]	Gamma	See section B.3.5.2
Taxane chemotherapy comparator	[redacted]	[redacted]	[redacted]	Gamma	
Atezolizumab + nab-paclitaxel (set equal to Pembro+taxanes)	[redacted]	[redacted]	[redacted]	Gamma	
Administration costs for IV: intervention, comparators and subsequent therapies					
Deliver Simple Parenteral Chemotherapy at First Attendance	£241.06	£156.00	£344.33	Gamma	See Section B.3.5.3
Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£370.68	£214.98	£529.48	Gamma	
Pre-medication administration costs	£122.00	NA	NA	Not varied in SA	
Pre-medication acquisition costs (paclitaxel and docetaxel only)					
Paclitaxel pre-medication costs	£5.91	£3.82	£8.44	Gamma	B.3.5.6
Disease Management Costs					
PFS one off cost on 1st cycle	£299.35	£193.72	£427.59	Gamma	

PFS weekly cost in subsequent cycles	£74.32	£48.10	£106.16	Gamma	See Section B.3.5.4
PPS weekly cost in subsequent cycles	£69.50	£44.98	£99.27	Gamma	
Cost of terminal care (one-off cost)	£8,166.54	£5284.96	£11665.13	Gamma	
% AE Pembrolizumab + taxanes from KEYNOTE-355					
Anaemia	[redacted]	NA	NA	Not varied in SA	See Section B.3.3.5
Leukopenia	[redacted]	NA	NA	Not varied in SA	
Neutropenia	[redacted]	NA	NA	Not varied in SA	
Thrombocytopenia	[redacted]	NA	NA	Not varied in SA	
ALT increased	[redacted]	NA	NA	Not varied in SA	
AST increased	[redacted]	NA	NA	Not varied in SA	
Neutrophil count decreased	[redacted]	NA	NA	Not varied in SA	
Platelet count decreased	[redacted]	NA	NA	Not varied in SA	
White blood cell count decreased	[redacted]	NA	NA	Not varied in SA	
Diarrhoea	[redacted]	NA	NA	Not varied in SA	
Hypothyroidism	[redacted]	NA	NA	Not varied in SA	
Vomitting	[redacted]	NA	NA	Not varied in SA	
Fatigue	[redacted]	NA	NA	Not varied in SA	
Abdominal abscess	[redacted]	NA	NA	Not varied in SA	
Pneumonia	[redacted]	NA	NA	Not varied in SA	
Blood alkaline phosphatase increased	[redacted]	NA	NA	Not varied in SA	
Lymphocyte count decreased	[redacted]	NA	NA	Not varied in SA	
Hyperglycaemia	[redacted]	NA	NA	Not varied in SA	
Lymphopenia	[redacted]	NA	NA	Not varied in SA	
Pneumonitis	[redacted]	NA	NA	Not varied in SA	
Grade 2+ diarrhoea	[redacted]	NA	NA	Not varied in SA	
Grade 2+ colitis	[redacted]	NA	NA	Not varied in SA	
% AE Taxane chemotherapy comparator arm from KEYNOTE-355					
Anaemia	[redacted]	NA	NA	Not varied in SA	

Leukopenia	[redacted]	NA	NA	Not varied in SA	See Section B.3.4.4
Neutropenia	[redacted]	NA	NA	Not varied in SA	
Thrombocytopenia	[redacted]	NA	NA	Not varied in SA	
ALT increased	[redacted]	NA	NA	Not varied in SA	
AST increased	[redacted]	NA	NA	Not varied in SA	
Neutrophil count decreased	[redacted]	NA	NA	Not varied in SA	
Platelet count decreased	[redacted]	NA	NA	Not varied in SA	
White blood cell count decreased	[redacted]	NA	NA	Not varied in SA	
Diarrhoea	[redacted]	NA	NA	Not varied in SA	
Hypothyroidism	[redacted]	NA	NA	Not varied in SA	
Vomitting	[redacted]	NA	NA	Not varied in SA	
Fatigue	[redacted]	NA	NA	Not varied in SA	
Abdominal abscess	[redacted]	NA	NA	Not varied in SA	
Pneumonia	[redacted]	NA	NA	Not varied in SA	
Blood alkaline phosphatase increased	[redacted]	NA	NA	Not varied in SA	
Lymphocyte count decreased	[redacted]	NA	NA	Not varied in SA	
Hyperglycaemia	[redacted]	NA	NA	Not varied in SA	
Lymphopenia	[redacted]	NA	NA	Not varied in SA	
Pneumonitis	[redacted]	NA	NA	Not varied in SA	
Grade 2+ diarrhoea	[redacted]	NA	NA	Not varied in SA	
Grade 2+ colitis	[redacted]	NA	NA	Not varied in SA	
AE management costs (treatment specific)					
Pembrolizumab + taxanes	[redacted]	[redacted]	[redacted]	Gamma	See Section B.3.5.5
Taxane chemotherapy comparators	[redacted]	[redacted]	[redacted]	Gamma	
Atezolizumab + nab-paclitaxel	[redacted]	[redacted]	[redacted]	Gamma	
Survival Modelling					
Progression-Free Survival					
PFS parametric curve fitting: Pembrolizumab in combination with taxanes					
Piecewise 9 week KM + Weibull: Parameter A	[redacted]	[redacted]	[redacted]	Multivariate Normal	See section B.3.3.2

Piecewise 9 week KM + Weibull: Parameter B	[redacted]	[redacted]	[redacted]	Multivariate normal	
PFS parametric curve fitting: Taxane chemotherapy comparators					
Piecewise 9 week KM + Log-normal: Parameter A	[redacted]	[redacted]	[redacted]	Multivariate normal	See section B.3.3.2
Piecewise 9 week KM + Log-normal: Parameter B	[redacted]	[redacted]	[redacted]	Multivariate normal	
Overall Survival					
OS parametric curve fitting: Pembrolizumab in combination with taxanes					
Full Log-normal: Parameter A	[redacted]	[redacted]	[redacted]	Multivariate normal	See section B.3.3.1
Full Log-normal: Parameter B	[redacted]	[redacted]	[redacted]	Multivariate normal	
OS parametric curve fitting: Taxane chemotherapy comparators					
Full Log-logistic: Parameter A	[redacted]	[redacted]	[redacted]	Multivariate normal	See section B.3.3.1
Full Log-logistic: Parameter B	[redacted]	[redacted]	[redacted]	Multivariate normal	
Time On Treatment					
ToT parametric curve fitting: Pembrolizumab in combination with taxanes					
Full Weibull: Parameter A	[redacted]	[redacted]	[redacted]	Multivariate normal	See section B.3.3.3
Full Weibull: Parameter B	[redacted]	[redacted]	[redacted]	Multivariate normal	
ToT parametric curve fitting: Taxane chemotherapy comparators					
Full Log-logistic: Parameter A	[redacted]	[redacted]	[redacted]	Multivariate normal	See section B.3.3.3
Full Log-logistic: Parameter B	[redacted]	[redacted]	[redacted]	Multivariate normal	
PD-L1 testing by Assay					
Pembrolizumab PD-L1 positive 22C3 Dako Assay	£106.20	£68.73	£151.70	Gamma	See section B.3.5.6
Atezolizumab PD-L1 positive patient with SP142 Assay	£278.49	£180.23	£397.80	Gamma	

B.3.6.2 Assumptions

Table 75 summarises the assumptions used in the economic model.

Table 75: List of assumptions used in the economic model

Area	Assumption	Justification
Clinical efficacy for chemotherapies	Paclitaxel and nab-paclitaxel are assumed to have equivalent efficacy. KEYNOTE-355 data best reflect this in mTNBC population. Docetaxel is also assumed to have efficacy equal to the taxane arm of KEYNOTE-355.	KEYNOTE-355 chemotherapies included paclitaxel and nab-paclitaxel, however, the study was not powered to detect differences between the different chemotherapy backbones. The study provides evidence specific to the anticipated indication for both chemotherapy agents. NICE previously agreed taxanes (including docetaxel) are comparable in terms of survival outcomes. This is also supported by the clinical data from KEYNOTE-355.
PFS efficacy	Piecewise modelling applied, using KM data for the first 9 weeks for both arms, followed by Weibull for pembrolizumab +taxanes or by Log-normal for the taxane chemotherapy arm.	Based on the trial protocol of KEYNOTE-355, the first tumour assessment was performed at week 8. The 9 week timepoint was based on visual inspection of trial data and the proximity to the first tumour assessment [26].
OS efficacy	Applied a full parametric Log-normal curve on KM data for pembro +taxanes and a full Log-logistic for the taxane chemotherapy arm.	The fully parametric modelling approach, following guidance from TSD 14, was considered as the most appropriate method for modelling OS. Best fitting piece-wise models were considered implausible based on hazard function and long term OS predictions for Pembro + taxane being equal to that of standard chemotherapies from RWE. The final OS model selected for the base-case are in line with clinical expert opinion sought for long term survival estimates
Subsequent treatments	Once patients progress, they receive subsequent therapies as per KEYNOTE-355 pooled across both arms and re-weighted to remove IO agents used in 2L+.	Estimates from KN-355 subsequent treatment data appeared generalisable to the UK setting. The % of patients receiving IO in 2L+ was very limited and larger for the taxanes chemotherapy arm. Therefore it is unlikely to impact upon the C/E and estimates greatly (see section B3.5.2). Alternative sources of subsequent treatment data is also explored. Trial subsequent treatment data may be considered a conservative assumption against the Pembrolizumab+ taxanes arm since the OS benefit for the taxane comparator is partially confounded by subsequent IO usage (not available in the UK).

Area	Assumption	Justification
Safety	AE incidence rates for the CPS ≥10 score were used for the chemotherapy comparisons, assumed to be reflective of those observed in the real world practice.	Assumption based on the results of the KEYNOTE-355 trial [16, 17] (i.e. grade 3-5 AEs (incidence≥5% in one or more treatment groups, considering any grade) The same method and criteria have been applied in a number of recent NICE oncology appraisals of pembrolizumab.
HRQoL	The quality of life of patients is appropriately captured by using the analysis based on the Time-to-Death methodology. Estimates were derived from the EQ-5D-3L collected alongside the KEYNOTE-355 clinical trial.	The source of utility estimates is consistent with the NICE reference case. The Time-to-Death methodology adequately captures deterioration of HRQoL in severe cancer types like mTNBC and has been previously deemed acceptable by NICE for decision making in a number of recent TAs.
Age-related disutility	Utilities were to account for utility deceases with age using a model for disutility derived from the UK population.	Based on the Ara and Brazier study suggesting the impact of age on HRQoL[64].
Healthcare resource use costs	Resource use is assumed to be equal between pembrolizumab + taxanes and taxane comparators.	Due to paucity of data from the SLR specific to the UK, resource use was assumed to be equal per treatment arm in the pre- and post- progression health states. TA639 resource use estimates were revalidated by clinical experts and supplemented as necessary (CT scans and blood tests).These estimates are used in the base-case.
Taxane distribution with pembrolizumab & taxane arm and comparator costs	Taxane distribution (split between paclitaxel and nab-paclitaxel) in pembrolizumab in combination with taxanes is assumed to be equal to that of KEYNOTE-355. Drug acquisition costs for taxane comparators; paclitaxel or docetaxel costs are applied in the comparator trial arm.	Whilst efficacy in the comparator arm is derived from the pooled taxanes chemotherapy comparator from KEYNOTE-355, nab-paclitaxel as monotherapy is not approved for use in the UK setting. Comparator costs have been adjusted to reflect this.
Stopping rule	Pembrolizumab will be administered for a maximum of 35 cycles (~24 months). Chemotherapy treatment may be continue beyond this point if patient continues to receive benefit.	This assumption is in line with the KEYNOTE-355 clinical trial.
Vial Sharing	Full vial sharing was not assumed for patients in comparator arm	This assumption is in line with the NICE reference case.

Area	Assumption	Justification
Waning effect	No OS waning effect is applied in the base-case.	This is in line with the unique mode of action of IO agents, which are able to confer improved response to treatment over an extended period of time post treatment discontinuation. This assumption is in line with recent AC preferences formulating the base case in TA639 and all prior mBC HTAs conducted by NICE, whereby a waning effect was only explored in sensitivity analysis[31].
ITC (for comparisons versus atezolizumab + nab-paclitaxel)	The post-hoc analysis by Rugo et al is used since it reported CPS ≥ 10 score specific data from IMpassion130. Proportional hazards are then assumed to estimate the relative treatment effect for PFS and OS versus Pembrolizumab + taxanes. Evidence synthesis is conducted using the NMA framework. Pooled taxanes from KEYNOTE-355 are used in the NMA.	IMpassion130 and KEYNOTE-355 ascertain PD-L1 status using different assays. Research highlights the limited population overlap and concordance between the two assays, which impacts upon the comparability of populations. Rugo et al reports CPS ≥ 10 score specific data to adjust for key population differences. Proportional hazards were assumed due to lack of KM data which could enable time-varying hazard analysis. The use of pooled taxanes is in line with the clinical evidence from KEYNOTE-355.
Atezolizumab + nab-paclitaxel ToT	Treatment has been assumed to extend beyond 2 years for atezolizumab + nab-paclitaxel and is set equal to PFS to projections for this comparison.	IMpassion130 trial did not include an Atezolizumab maximum treatment duration. The EMA license and NICE recommendation is for treatment to progression. KEYNOTE-355 ToT data are not considered relevant for use since transferability of these across studies cannot be assessed.
Chemotherapy comparators	The base-case assumes paclitaxel is the primary taxane comparator based on TA639. Docetaxel constitutes a secondary taxane comparator. Due to limited population overlap between IMpassion130 and KEYNOTE-355, atezolizumab + nab-paclitaxel is also treated as a secondary comparator.	Until recently taxane chemotherapies were the UK SoC. Paclitaxel is preferred to docetaxel due to its more favourable safety profile. Therefore, the use of paclitaxel as the primary comparator is justified. Due to ITC uncertainties arising from the limited overlap between IMpassion130 and KEYNOTE-355 and data limitations, these comparisons are presented as secondary as they are associated with high degree of uncertainty.

B.3.7 Base-case results

The primary comparisons for the base-case constitute the chemotherapies specified in the final draft scope issued by NICE. Comparisons versus atezolizumab + nab-paclitaxel is

positioned as secondary due to data limitations introducing uncertainty in the cost-effectiveness estimates (section B 3.2.3).

B.3.7.1. Base-case incremental cost-effectiveness analysis results for Pembrolizumab versus paclitaxel (primary chemotherapy comparator)

The tables below present the results of the base-case cost-effectiveness comparisons for paclitaxel as the primary chemotherapy comparator.

The estimated mean overall survival with pembrolizumab in combination with taxanes was 3.795 life years versus 1.808 for the paclitaxel chemotherapy comparator. Patients treated with pembrolizumab + taxanes accrued [redacted] QALYs compared to [redacted] among patients in the taxane arm. Pembrolizumab in combination with taxanes was associated with a net [redacted]net QALY gain and a net life year gain of 1.987 versus the standard taxane chemotherapies. The corresponding incremental-cost-effectiveness ratio (ICER) with the current CAA in place versus paclitaxel was £29,008 per QALY. Pembrolizumab in combination with taxanes has the potential to be cost-effective compared to paclitaxel chemotherapy when considering a willingness to pay threshold of £50,000/QALY since the end-of-life criteria are applicable in this population & comparators.

Table 76: Base-case results versus paclitaxel from deterministic analysis using list prices

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Paclitaxel comparator	[redacted]	1.808	[redacted]			
Pembrolizumab + taxanes**	[redacted]	3.795	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, ** Confidential discounts in place for Atezolizumab and nab-paclitaxel with the NHS may alter the cost-effectiveness results.

Table 77: Base-case results versus paclitaxel from deterministic analysis using list prices for comparators with Pembrolizumab CAA

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Paclitaxel comparator	[redacted]	1.808	[redacted]	-	-	-
Pembrolizumab + taxanes**	[redacted]	3.795	[redacted]	[redacted]	[redacted]	£29,008
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, ** Confidential discounts in place for Atezolizumab and nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

The estimates of the clinical outcomes included in the cost-effectiveness analysis (compared with the clinical trial results) and the tabulated, disaggregated results for the base case are presented in B.3.10.1 (for up to 2 years) and Appendix J (full time horizon).

B.3.7.1. Base-case incremental cost-effectiveness analysis results for Pembrolizumab versus docetaxel (secondary chemotherapy comparator)

The tables below present the results of the base-case cost-effectiveness comparisons for docetaxel as secondary chemotherapy comparator, considering the tolerability issues associated with docetaxel for mTNBC treatment as noted in TA639 [31].

The corresponding incremental-cost-effectiveness ratio (ICER) with the current CAA in place versus docetaxel was £35,765 per QALY. Pembrolizumab in combination with taxanes has the potential to be cost-effective compared to docetaxel chemotherapy when considering a willingness to pay threshold of £50,000/QALY since the end-of-life criteria are applicable in this population & comparators.

Table 78: Base-case results versus docetaxel from deterministic analysis using list prices

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Docetaxel taxane comparator	[redacted]	1.808	[redacted]			
Pembrolizumab + taxanes**	[redacted]	3.795	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, ** Confidential discounts in place for Atezolizumab and nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

Table 79: Base-case results versus docetaxel from deterministic analysis using list prices for comparators with Pembrolizumab CAA

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Docetaxel taxane comparator	[redacted]	1.808	[redacted]			
Pembrolizumab + taxanes**	[redacted]	3.795	[redacted]	[redacted]	[redacted]	£35,765
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, ** Confidential discounts in place for Atezolizumab and nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

B.3.7.3. Base-case incremental cost-effectiveness analysis results for Pembrolizumab + taxanes versus Atezolizumab + nab-paclitaxel (secondary IO comparator for PD-L1 +ve patients)

The assumptions for this comparison use pooled taxane ITC result of OS and PFS and KEYNOTE-355 PFS estimates by investigator to better match IMpassion130 (see section 2.9.3). ToT for Atezolizumab + nab-paclitaxel was set equal to PFS projections since the SmPC does not include a treatment cap for Atezolizumab and in line with NICE's recommendations for treatment to progression. This is positioned as a secondary IO comparator considering the ITC limitations and associated uncertainty as a result of the limited population overlap.

Pembrolizumab in combination with taxanes was dominant versus Atezolizumab + nab-paclitaxel, resulting in a net LY gain of 1.519, translating to a QALY gain of [redacted].The cost effectiveness estimates for this comparator are subject to confidential commercial discounts currently in place for both atezolizumab and nab-paclitaxel.

Table 80: Base-case results versus Atezolizumab + nab-paclitaxel from deterministic analysis using LIST prices for both comparators

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Atezolizumab + nab-paclitaxel	[redacted]	2.276	[redacted]			
Pembrolizumab + taxane**	[redacted]	3.795	[redacted]	[redacted]	[redacted]	Dominant*
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years *Pembrolizumab + taxanes is less costly and QALY accruing. ** Confidential discounts in place for Atezolizumab and nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

Table 81: Base-case results versus Atezolizumab + nab-paclitaxel from deterministic analysis using list prices for comparator with Pembrolizumab CAA

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Atezolizumab + nab-paclitaxel	[redacted]	2.276	[redacted]			
Pembrolizumab + taxane	[redacted]	3.795	[redacted]	[redacted]	[redacted]	Dominant*
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years *Pembrolizumab + taxanes is less costly and QALY accruing. ** Confidential discounts in place for Atezolizumab and nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

B.3.8 Sensitivity analyses

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means and sources used to estimate the parameters are detailed in B.3.6. PSA was only conducted for chemotherapy comparators specific in the final scope. Due to uncertainty in the ITC comparisons and comparability across populations, it was not deemed methodologically relevant to conduct PSA versus Atezolizumab + nab-paclitaxel since this could inflate uncertainty further in the cost-effectiveness estimates; scenario analyses are explored instead as they can be more informative for decision making (see section B.3.8.3).

B.3.8.1. Probabilistic sensitivity analysis vs paclitaxel

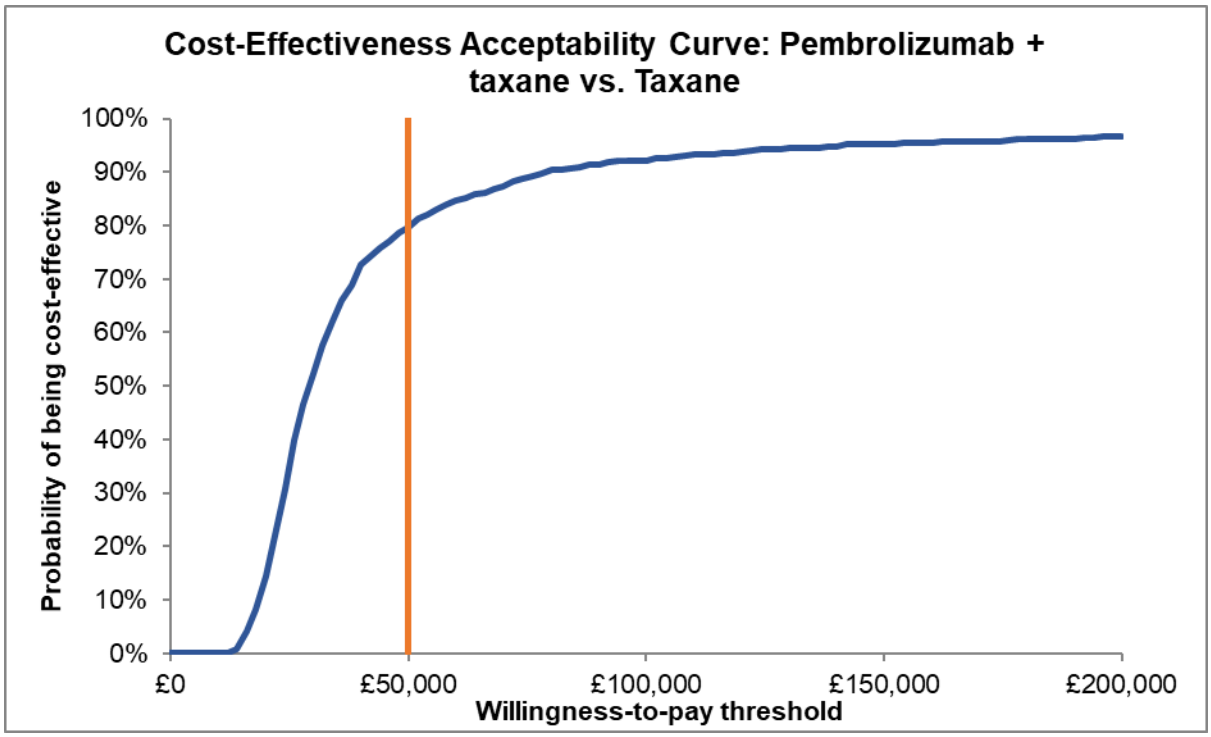
The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis versus paclitaxel are presented in Table 82. The corresponding scatterplot and cost-effectiveness acceptability curve are presented Figure 31 and Figure 32. Pembrolizumab in combination with taxanes resulted in a net of 1.965 LY and [redacted] QALY gain versus paclitaxel alone. With the current CAA discount, the cost-effectiveness acceptability curve shows that there is approximately a 79.6% of chance of pembrolizumab + taxanes being cost-effective when compared to paclitaxel chemotherapy under the End-of-Life Willingness-To-Pay (WTP) criteria.

Table 82: PSA results with Pembrolizumab CAA versus paclitaxel

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Paclitaxel comparator	[redacted]	1.828	[redacted]	-	-	-
Pembrolizumab + taxanes	[redacted]	3.793	[redacted]	[redacted]	[redacted]	£29,423
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Figure 31: Scatterplot of PSA results versus paclitaxel with Pembrolizumab CAA

Figure 32: Cost-effectiveness acceptability curve versus with Pembrolizumab CAA



B.3.8.1. Probabilistic sensitivity analysis vs docetaxel

Pembrolizumab in combination with taxanes was associated with a net LY and net QALY gain versus docetaxel as a comparator Table 83 and Figure 33 Figure 34. Overall the technology has a 71% probability of being cost-effective.

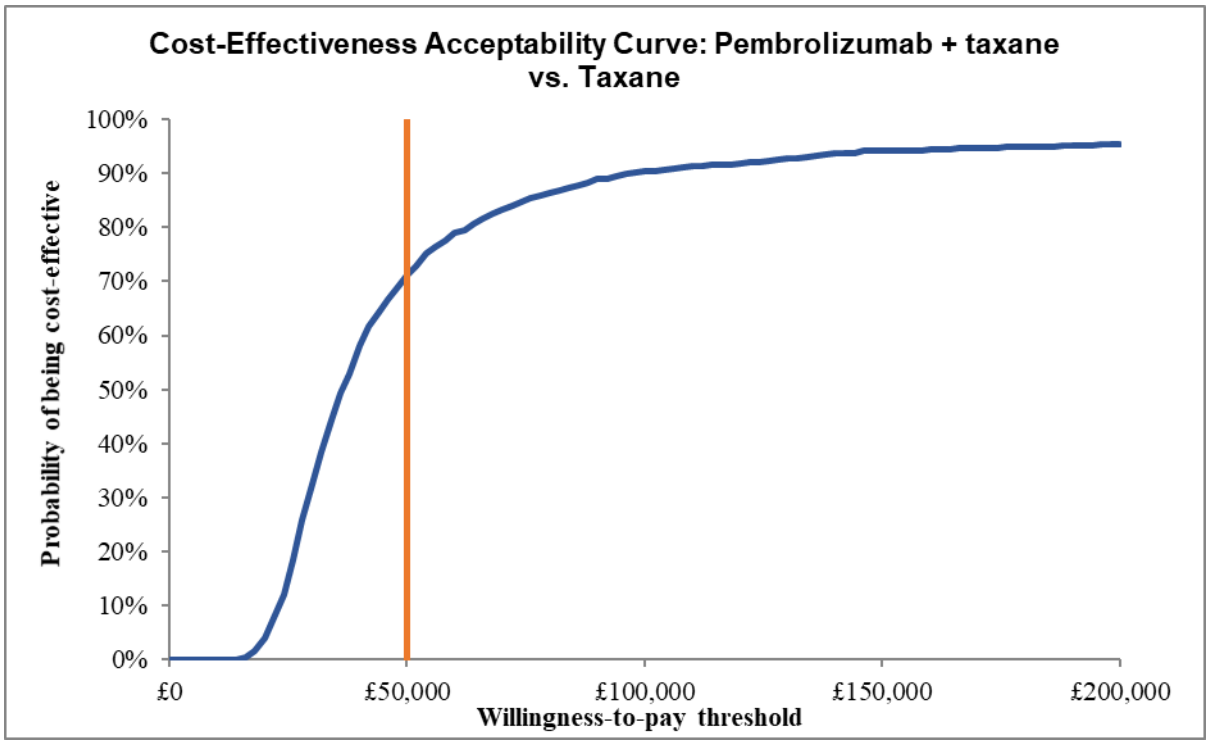
Table 83: PSA results with Pembrolizumab CAA versus docetaxel

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Docetaxel comparator	[redacted]	3.793	[redacted]	-	-	-
Pembrolizumab + taxanes	[redacted]	1.828	[redacted]	[redacted]	[redacted]	£36,485
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Figure 33: Scatterplot of PSA results versus docetaxel with Pembrolizumab CAA

[redacted]

Figure 34: Cost-effectiveness acceptability curve versus docetaxel with Pembrolizumab CAA



B.3.8.2. Deterministic sensitivity analysis vs taxanes

Deterministic sensitivity analyses were conducted for the following key variables using the 5% and 95% confidence intervals for the variables except when it is indicated otherwise:

- Baseline characteristics (i.e. age)
- Time horizon, discounting, and half-cycle correction
- Drug acquisition and administration costs
- Time on treatment estimation methods
- Resource utilisation
- Subsequent treatment cost
- Health state-based utility and time-to death-based utility
- AE costs and AE-related disutility
- Background mortality
- Parameters of the parametric curves fitted to OS, PFS and ToT.

The results of the deterministic sensitivity analyses for pairwise comparisons of pembrolizumab in combination with taxanes versus paclitaxel are presented in Figure 35 and results versus docetaxel in Figure 36 below.

The inputs that most affect the ICERs are those related to the parameters linked to OS extrapolations followed by changes in the time horizon, annual discount rate for costs and changes in utility estimates used in the model. It should be noted that the piecewise OS exponential curve for Pembrolizumab + taxane extrapolations results in implacably low survival projections versus RWE sources and can therefore be considered highly conservative (see section B.3.3.1.). Full list of inputs varied in the DSA and the impact on the base-case ICER (including results versus Atezolizumab + nab-paclitaxel) are presented in Appendix M 1.4.

Figure 35: Tornado diagram for the 20 most sensible variables versus paclitaxel with Pembrolizumab CAA

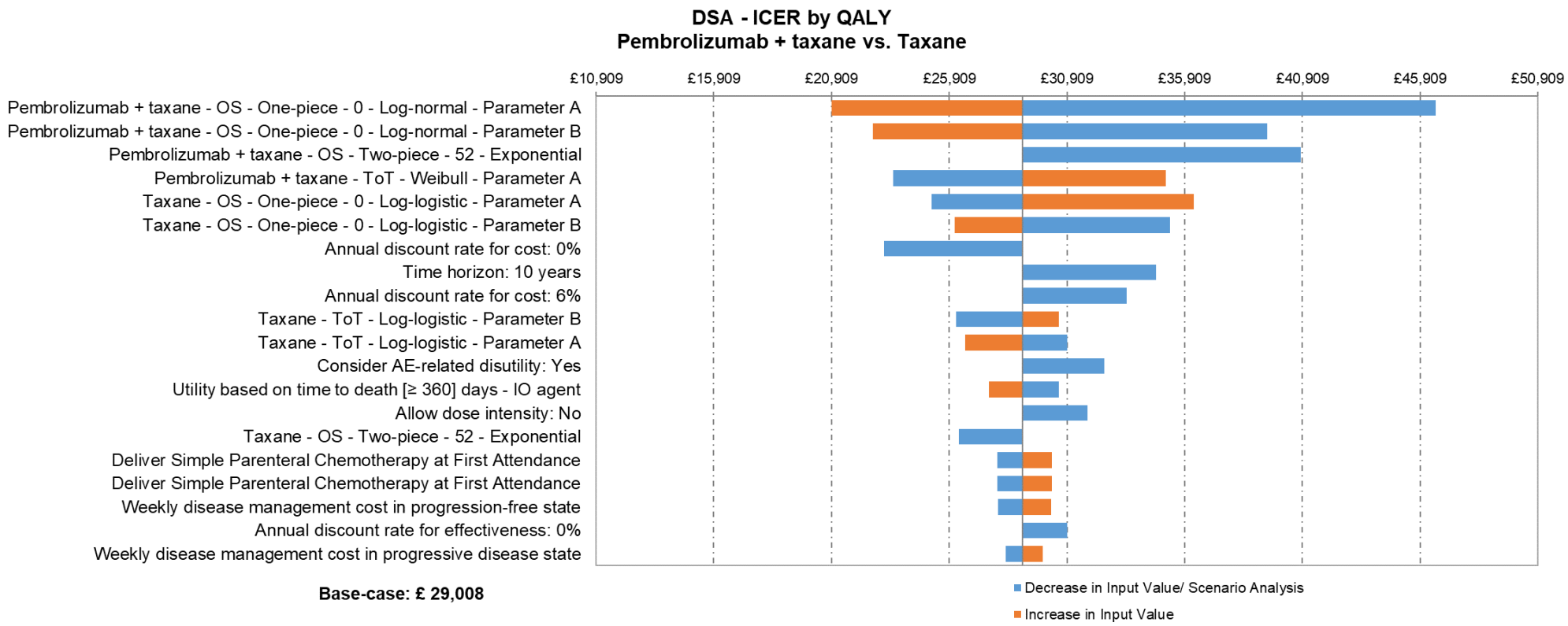
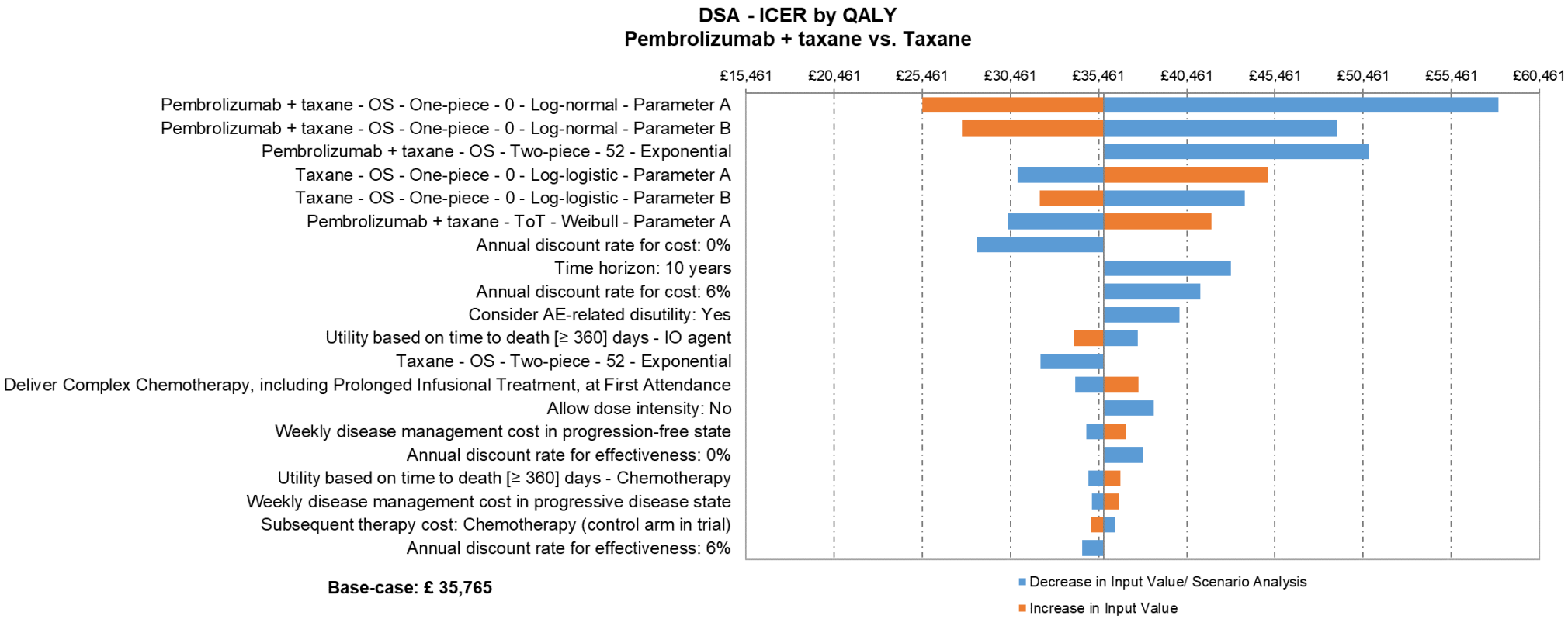


Figure 36: Tornado diagram for the 20 most sensible variables versus docetaxel with Pembrolizumab CAA



B.3.8.3. Scenario analysis vs paclitaxel primary comparator

Alternative scenario analyses were conducted to assess uncertainty regarding structural and methodological assumptions on the primary chemotherapy comparator of paclitaxel. Since docetaxel since is unlikely to be used as a chemotherapy agent in this setting scenario analyses were not conducted around this comparison.

- Base-case: assuming paclitaxel as standard chemotherapy comparator
- Scenario 1: Full log-logistic for Pembro + taxane OS (2nd best curve)
- Scenario 2: Full log-normal for Taxane OS (2nd best curve)
- Scenario 3: Piecewise model for OS for Pembro + taxanes; 52 weeks KM + exponential (model unpredicts OS survival; equal to that of long term RWE datasets; considered highly conservative)
- Scenario 4: Combined 2nd best OS curves in Pembro + Taxanes & Taxanes comparator (log-logistic and log-normal respectively: Scenarios 1 + 2 together)
- Scenario 5: PFS for Pembro + Taxanes: KM up to week 9 + Log-logistic (2nd best curve)
- Scenario 6: PFS for Taxanes: KM up to week 9 + Log-logistic (2nd best curve)
- Scenario 7: Combined 2nd best PFS curves for Pembro + Taxane and Taxane comparator (9 week KM + log-logistic and 9 week KM + Log-logistic; Scenarios 5 + 6 together)
- Scenario 8: Combined 2nd best OS & PFS curves for Pembro + taxane and taxanes (Scenarios 4 & 7 together)
- Scenario 9: Applying treatment waning using SEER dataset in the base-case (see Appendix P)
- Scenario 10: Applying treatment waning by removing OS benefit after 5 Years in the base-case
- Scenario 11: Combined 2nd best OS with 2nd best PFS curves (Scenario 8) + 5 year IO waning scenario
- Scenario 12: Half cycle correction on base-case
- Scenario 13: Removal of PD-L1 testing costs for Pembro + Taxanes
- Scenario 14: Removal of AE management costs
- Scenario 15: Using MS data for subsequent therapies
- Scenario 16: Using utilities by progression status & AEs pooled
- Scenario 17: Using utilities by progression status & AEs treatment specific
- Scenario 18: Removal of age-adjustment in utility estimates

Table 84: Scenario analyses versus Taxanes (with Pembro CAA price)

Scenario No.	Description	Pembrolizumab + taxanes			Taxanes comparator			Pembrolizumab + taxanes vs Taxanes		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base Case	Paclitaxel taxane comparator	[redacted]	3.795	[redacted]	[redacted]	1.808	[redacted]	[redacted]	[redacted]	£29,008
Scenario 1	Full log-logistic for Pembro + taxane OS (2nd best curve)	[redacted]	3.617	[redacted]	[redacted]	1.808	[redacted]	[redacted]	[redacted]	£31,422
Scenario 2	Full log-normal for Taxane OS (2nd best curve)	[redacted]	3.795	[redacted]	[redacted]	1.731	[redacted]	[redacted]	[redacted]	£28,111
Scenario 3	Piecewise model for OS for Pembro + taxanes; 52 weeks KM + exponential (model unpredicts OS survival; equal to that of long term chemotherapy RWE datasets; considered highly conservative)	[redacted]	3.145	[redacted]	[redacted]	1.808	[redacted]	[redacted]	[redacted]	£40,844
Scenario 4	Combined 2nd best OS curves in Pembro + Taxanes & Taxanes comparator (log-logistic and log-normal respectively: Scenarios 1 + 2 together)	[redacted]	3.617	[redacted]	[redacted]	1.731	[redacted]	[redacted]	[redacted]	£30,345
Scenario 5	PFS for Pembro + Taxanes: KM up to week 9 + Log-logistic (2nd best curve)	[redacted]	3.795	[redacted]	[redacted]	1.808	[redacted]	[redacted]	[redacted]	£29,079
Scenario 6	PFS for Taxanes: KM up to week 9 + Log-logistic (2nd best curve)	[redacted]	3.795	[redacted]	[redacted]	1.808	[redacted]	[redacted]	[redacted]	£29,010
Scenario 7	Combined 2nd best PFS curves for Pembro + Taxane and Taxane comparator (9 week KM + log-logistic and 9week KM + Log-logistic; Scenarios 5 + 6 together)	[redacted]	3.795	[redacted]	[redacted]	1.808	[redacted]	[redacted]	[redacted]	£29,081
Scenario 8	Combined 2nd best OS & PFS curves for Pembro + taxane and taxanes (Scenarios 4 & 7 together)	[redacted]	3.617	[redacted]	[redacted]	1.731	[redacted]	[redacted]	[redacted]	£30,418
Scenario 9	Applying treatment waning using SEER dataset in the base-case	[redacted]	4.238	[redacted]	[redacted]	2.092	[redacted]	[redacted]	[redacted]	£27,213
Scenario 10	Applying treatment waning by removing OS benefit after 5 Years in the base-case	[redacted]	3.415	[redacted]	[redacted]	1.808	[redacted]	[redacted]	[redacted]	£34,764

Scenario No.	Description	Pembrolizumab + taxanes			Taxanes comparator			Pembrolizumab + taxanes vs Taxanes		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Scenario 11	Combined 2nd best OS curves with 2nd best PFS curves (Scenario 8) + 5 year IO waning scenario	[redacted]	3.081	[redacted]	[redacted]	1.731	[redacted]	[redacted]	[redacted]	£40,560
Scenario 12	Half cycle correction on base-case	[redacted]	3.806	[redacted]	[redacted]	1.818	[redacted]	[redacted]	[redacted]	£29,242
Scenario 13	Removal of PD-L1 testing costs for Pembro + Taxanes	[redacted]	3.795	[redacted]	[redacted]	1.808	[redacted]	[redacted]	[redacted]	£28,939
Scenario 14	Removal of AE management costs	[redacted]	3.795	[redacted]	[redacted]	1.808	[redacted]	[redacted]	[redacted]	£29,083
Scenario 15	Using MS data for subsequent therapies	[redacted]	3.795	[redacted]	[redacted]	1.808	[redacted]	[redacted]	[redacted]	£29,499
Scenario 16	Using utilities by progression status & AEs pooled	[redacted]	3.795	[redacted]	[redacted]	1.808	[redacted]	[redacted]	[redacted]	£32,487
Scenario 17	Using utilities by progression status & AEs treatment specific	[redacted]	3.795	[redacted]	[redacted]	1.808	[redacted]	[redacted]	[redacted]	£32,414
Scenario 18	Removal of age-adjustment in utility estimates	[redacted]	3.795	[redacted]	[redacted]	1.808	[redacted]	[redacted]	[redacted]	£28,043

B.3.8.3. Scenario analysis vs Atezolizumab + nab-paclitaxel

Due to uncertainties in the ITC, scenario analyses were deemed more suitable versus PSA to explore uncertainty with regards to Atezolizumab + nab-paclitaxel comparisons. The following scenarios were tested upon the base-case settings (specified above):

- Scenario 1: Use KEYNOTE-355 nab-paclitaxel as common comparator for the NMA to estimate the PFS HR
- Scenario 2: Full log-logistic for Pembro + Taxane OS (2nd best curve)
- Scenario 3: Use the primary PFS endpoint from KEYNOTEN-355 blinded CIV
- Scenario 4: Set the maximum treatment duration for Atezolizumab +nab-paclitaxel = to KEYNOTE-355 nab-paclitaxel ToT parametric curve
- Scenario 5: 2nd best PFS curve used for Pembro + taxanes in comparison: 9 week KM + log-logistic
- Scenario 6: Combined 2nd best curves for PFS and OS for Pembro + Taxanes (Scenario 2 & 5)
- Scenario 7: Apply treatment waning based on SEER dataset analysis (refer to appendix P for full analysis).

Table 85: Scenario analyses versus Atezolizumab LIST Price (and Pembrolizumab CAA price)

Scenario No.	Description	Pembrolizumab + taxanes			Atezolizumab + nab-paclitaxel			Pembrolizumab + taxanes vs Atezolizumab + nab-paclitaxel		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base Case used:	KN-355 INV PFS, Pooled Taxanes, max ToT = PFS & Pembro CAA	[redacted]	3.795	[redacted]	[redacted]	2.276	[redacted]	[redacted]	[redacted]	Dominant
Scenario 1	Use KEYNOTE-355 nab-paclitaxel as common comparator for the NMA to estimate the PFS HR	[redacted]	3.795	[redacted]	[redacted]	2.849	[redacted]	[redacted]	[redacted]	Dominant
Scenario 2	Full log-logistic for Pembro + Taxane OS (2nd best curve)	[redacted]	3.617	[redacted]	[redacted]	2.175	[redacted]	[redacted]	[redacted]	Dominant
Scenario 3	Use the primary PFS endpoint from KEYNOTE-355 blinded CIV	[redacted]	3.795	[redacted]	[redacted]	2.276	[redacted]	[redacted]	[redacted]	Dominant
Scenario 4	Set the maximum treatment duration for Atezolizumab +nab-paclitaxel = to KEYNOTE-355 nab-paclitaxel ToT parametric curve	[redacted]	3.795	[redacted]	[redacted]	2.276	[redacted]	[redacted]	[redacted]	Dominant
Scenario 5	2nd best PFS curve used for Pembro + taxanes in comparison: 9 week KM + log-logistic	[redacted]	3.795	[redacted]	[redacted]	2.276	[redacted]	[redacted]	[redacted]	Dominant
Scenario 6	Combined 2nd best curves for PFS and OS for Pembro + Taxanes (Scenario 2 & 5)	[redacted]	3.175	[redacted]	[redacted]	2.027	[redacted]	[redacted]	[redacted]	Dominant
Scenario 7	Apply treatment waning based on SEER dataset analysis on Scenario 6.	[redacted]	4.102	[redacted]	[redacted]	2.397	[redacted]	[redacted]	[redacted]	Dominant

B.3.8.4. Summary of sensitivity analyses results

The probability of pembrolizumab in combination with taxanes versus paclitaxel being the most cost-effective treatment at a WTP threshold of £50,000 is 76%. The ICER generated by the PSA was consistent with that produced in the deterministic base-case for paclitaxel (£29,008 vs £29,423). The comparisons versus docetaxel indicate a 71% probability of pembrolizumab in combination with taxanes being cost-effective at a £50,000 WTP threshold.

The main drivers of the economic analysis include parameters related to the extrapolation of survival endpoints, choice of parametric curves, inclusion of treatment waning and the time horizon considered in the analysis. The ICERs ranged from £20,059 to £45,909 versus paclitaxel and from £25,461 to £58,125 versus docetaxel.

Considering the current Pembrolizumab CAA, the ICERs generated are well within the NICE WTP criteria for End-of-Life treatments which are applicable to this population.

Comparison versus Atezolizumab + nab-paclitaxel are associated with a number of limitations arising from the ITC and therefore the cost-effectiveness estimates produced should be interpreted with caution. However, in a wide range of scenarios Pembrolizumab + taxanes was associated with a net overall QALY gain versus this comparator and has the potential to be cost effective at an ICER of £30,000/QALY gained.

B.3.9 Subgroup analysis

Cost-effectiveness analyses on subgroups have not been [redacted] is already a subgroup of the trial population. Based on clinical trial data from KEYNOTE-355, a request for Pembrolizumab in combination with taxanes alone is put forward for assessment.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Health economists and clinical expert option was sought to validate key aspects of the modeling methods, assumptions and inputs.

- Internal review and quality control for model inconsistencies and errors performed
- Model structure choice is appropriate reflection of the current clinical pathway
- Key model inputs including health state resource use and management of AEs
- Selection of parametric curves and extrapolation of outcomes beyond trial period (see section B.3.3 above)

Internal validation of clinical benefit

For internal validation the efficacy outcomes from KEYNOTE-355 (OS and PFS) were compared to the outcomes produced from the cost-effectiveness model. Table 86 provides a summary of the model projections compared to those from KEYNOTE-355. When overlaid on the actual clinical trial data the modelled PFS and OS curves show a very good fit (

Figure 30).

Table 86: KN-355 versus model outcomes projections

Overall survival	**Timepoint**			
	0.5	**1**	**1.5**	**2**
Observed for Pembro + Taxanes	[redacted]	[redacted]	[redacted]	[redacted]
Modelled Pembro+ taxanes	[redacted]	[redacted]	[redacted]	[redacted]
Observed for Taxanes comparator	[redacted]	[redacted]	[redacted]	[redacted]
Modelled for Taxanes comparator	[redacted]	[redacted]	[redacted]	[redacted]
Progression-Free survival				
Observed for Pembro + Taxanes	[redacted]	[redacted]	[redacted]	[redacted]
Modelled Pembro+ taxanes	[redacted]	[redacted]	[redacted]	[redacted]
Observed for Taxanes comparator	[redacted]	[redacted]	[redacted]	[redacted]
Modelled for Taxanes comparator	[redacted]	[redacted]	[redacted]	[redacted]

External validation

Long-term external OS data were sourced from the clinical literature to validate the outcomes specific to the chemotherapy SoC. A number of options are available within the model for validation within the model [14, 39, 40, 42, 43, 95]. However, the SoC OS chemotherapy arm was validated primarily using Battisti et al 2018 (a UK based study reporting) since authors report OS outcomes for advanced TNBC by DFI status (DFI $\leq$ 12 months or DFI > 12months) over an 11 year period [40]. 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 [39]. Deluche et al 2020 was not preferred for validation since it predicts a long term plateau for SoC chemotherapies which was not realistic based on clinical expert opinion [14]. Figure 37 presented the modelled SoC chemotherapy OS versus OS estimates reported in Battisti 2018 and Aly et al 2019 [39, 40] (used for model validation). As demonstrated, the model predicts accurately the short to medium term OS projections for chemotherapy, and in addition the longer term OS estimates produced up to year 12 also appear consistent versus RWE. The Pembro + taxanes OS projections are consistent clinical expert opinion elicited during this submission and in line with long term immune-therapeutic for IO agents, indicative of a long term survival for a % of patients (as observed across other tumors; see section B.3.3.1.) [48-50].

Figure 37: Modelled OS SoC outcomes versus outcomes reported in clinical literature for SoC chemotherapy

Finally, the summary model outputs of LY gained where compared where possible with TA639 outputs to the explore the consistency of results for Atezolizumab + nab-paclitaxel and taxanes between the two submissions. As seen in Table 87, the current model predicts LY gains for the taxane chemotherapy arm which are consistent to those preferred by the ERG & the AC during TA639 (1.789 vs 1.797 Lys). Although the LY gains for Atezolizumab + nab-paclitaxel are slightly lower in this submission (2.276 vs 2.433 LYs), these are close to those preferred

by the ERG and the AC in TA639 and the ERG LYs are within the range of LYs generated by this model, depending on the ITC common comparator assumptions (2.276 to 2.849).

Whilst both external validation options presented are limited by a number of methodological and data issues (population differences, lack of access to PLD to and other), triangulation of results produced indicates that the SoC OS chemotherapy projections generated by the model are plausible in the range of those deemed realistic by the AC in TA639.

Table 87: Comparison of LY gains from this submission versus TA369

Comparison (over a 15 year time horizon)	**LYs: Current submission[#]**		
Pembrolizumab + Taxanes	3.636		
Taxanes chemotherapy comparator	1.789		
Atezolizumab + nab-paclitaxel (pooled taxanes for ITC used in Company base-case)	2.276		
Atezolizumab + nab-paclitaxel (nab-paclitaxel ITC)	2.849		
TA639 extracted LY estimates[#]		**Company Submission**	**ERG preferences**
Atezolizumab + nab-paclitaxel from IMpassion-130 (Original company submission)		2.430	2.433
Paclitaxel alone – Roche ITC original analysis (Updated DBL analysis; ERG Table 33)		1.38 (1.600)	1.797
Docetaxel alone – Roche ITC original analysis (Updated DBL analysis; ERG Table 33)		1.47 (1.551)	1.797
Note: [#]TA639 used a 15Y time horizon therefore, for the purposes of comparing LY outputs the model has been run assuming a 15Y time-horizon for consistency.			

B.3.11 Interpretation and conclusions of economic evidence

A de-novo economic model was built to inform the cost-effectiveness of pembrolizumab in combination with chemotherapy in the PD-L1 positive CPS ≥ 10 score patients with locally advanced inoperable or metastatic TNBC, capturing relevant costs resource and outcomes from a UK perspective. The model adopts a simple structure which is reflective of the natural disease progression over time and consistent to that used in the most recent metastatic TNBC appraisal reviewed by NICE and other metastatic BC HTAs.

The potentially eligible population for treatment with pembrolizumab + taxanes (PD-L1 positive at CPS ≥ 10 score), determined by the IHC 22C3 PharmDx Assay. This differs to the recently approved technology of atezolizumab + nab-paclitaxel, which used the VENTANA PD-L1 SP142 assay to identify PD-L1 positive population. A recent post-hoc analysis showed that these assays identify potential distinct populations with regards to tumor biology with limited overlap. This suggests that atezolizumab + nab-paclitaxel may not be a relevant direct

comparator for this submission and cost-effectiveness estimates produced may be associated with uncertainty.

A key limitation of this technology appraisal is the lack of long term PFS and OS data beyond the trial maximum follow up period (~3 years). However, the uncertainty behind long term survival extrapolations is mitigated by exploring different methods of OS and PFS extrapolation beyond the trial period. Further, the submission leverages the most up-to-date RWE data to validate the model outputs for the SoC chemotherapy arm.

Key strengths of this appraisal include:

- the use of the most recent clinical data from KEYNOTE-355 phase III RCT to inform the submission showing a significant for PFS benefit[redacted].
- The use of KEYNOTE-355 data to estimate the cost-effectiveness versus standard of care taxane chemotherapies. An indirect comparison versus Atezolizumab + nab-paclitaxel alone was necessary despite the severe methodological limitations whilst limit the reliability of results for decision making.
- Presentation of cost-effectiveness results of pembrolizumab + taxanes versus the standard of care taxane comparators as listed in the NICE Final scope, and for the recently approved atezolizumab + nab-paclitaxel.
- Leverage of EQ-5D-3L data directly collected alongside KN-355 consistent with the NICE reference case and lack of need for using mapping to estimate utility weights consistent to the NICE reference case.
- Robust cost-effectiveness analyses results and extensive testing of uncertainty using a range of scenarios, reaching the same conclusion with regards to the cost-effectiveness of this technology.
- Review of TA639 Appraisal Committee preferences around key assumptions and application of these within the current HTA where relevant.
- Validation of model structure and inputs by clinical experts and leveraging of the most up-to-date RWE data within the submission.
- Extended internal and external validation of model outcomes versus RWE literature and TA639 outputs for consistency.

- The technology offers flexibility for clinicians to select a backbone taxane regimen to be administered alongside pembrolizumab based on clinical trial data from Keynote-355.

A high unmet medical still remains for patients with locally advanced or inoperable TNBC and therefore patients would benefit from having an additional innovative treatment option becoming available. In particular, KEYNOTE-355 potentially included more severe population based on study inclusion with regards to DFI for study inclusion. Further, patients still experience a poor prognosis with an overall survival ranging from 1.8 to 2.2 life years with the current SoC and introduction of pembrolizumab + taxanes is anticipated to improve this further.

In the base-case analysis versus paclitaxel, the estimated mean OS with pembrolizumab in combination with taxanes was 3.795 life years versus 1.808 for the taxane chemotherapy comparators, resulting in a net QALY gain of [redacted] QALYs versus [redacted] among patients treated with taxanes. Therefore, pembrolizumab in combination with taxanes provides an incremental LY gain of 1.987 and an incremental QALY gain of [redacted]versus standard taxane chemotherapies. MSD considers pembrolizumab in combination with taxanes to offer an unprecedented increase in life years and QALYs for a population experiencing very poor survival outcomes with the current standards of care.

Pembrolizumab in combination with taxanes for the treatment of locally advanced inoperable TNBC is highly cost-effective versus the paclitaxel chemotherapy with PSA ICER £29,423/QALY and a WTP of 79.6% using PAS price, at £50,000/QALY WTP Threshold. Whilst noting the limitations and uncertainty for the comparisons versus atezolizumab + nab-paclitaxel, pembrolizumab in combination with taxanes has the potential to be cost-effective across a number of plausible scenarios once confidential discounts for comparators have been included.

In conclusion, the *de novo* economic analysis brings together the best available clinical data to establish the comparative efficacy and safety of pembrolizumab + chemotherapy in the PD-L1 positive CPS ≥ 10 score patients with locally advanced inoperable or metastatic TNBC.

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B.5 Appendices

See separate document provided.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab in combination for untreated, locally recurrent inoperable or metastatic, triple negative breast cancer [ID1546] Clarification questions

February 2021

File name	Version	Contains confidential information	Date
ID1546 Pembro ERG clarification letter_MSD-Response_15-11-21_[Redacted]	V1.0	No – [Redacted]	15-11-2021

Section A: Clarification on effectiveness data

A1. **PRIORITY:** Population terms (all systematic literature reviews (SLRs)): The long search strings used to refer to the population (in all the database searches, as reproduced in the company submission (CS) and appendices D, G and H) risk missing studies where these strings were interrupted by other words, e.g. "Efficacy and safety of docetaxel combined with oxaliplatin as a neoadjuvant chemotherapy regimen for Chinese **triple-negative** local advanced **breast cancer** patients". Furthermore, the term "breast cancer" can also be found in the plural form, as in this (non-trial) paper "**Triple-negative** and HER2-positive **breast cancers** found by mammography screening show excellent prognosis." – a problem easily solved by the addition of an asterisk (*). Please comment on the potential risk of studies missed through the narrow search terms used to define the population of interest.

We thank the ERG for pointing out this way to improve the sensitivity of the search strategies. The risks of not including wild cards in the search strategy are mitigated by the use of the (exploded) MeSH term "triple negative breast neoplasms" and, as a result, the population terms used in the search strategies did identify both studies mentioned above (but both were ultimately appropriately excluded from the overall search strategies by the intervention and/or study design terms). Additionally, the database search was backstopped by searches of the US and European Clinical Trials Registry as well as the bibliographies of included studies in order to decrease the risk of missing a relevant clinical trial.

A2. Population terms in the Econlit searches (CS Appendix G, Table 31 and Appendix H table 42). After entering lengthy search strings for the specific population of interest (and having only found a handful of results), please explain why the company combined these with the single phrase "breast cancer" (without any synonyms)?

We thank the ERG for noting this way to improve the sensitivity of the search strategy. To determine whether the sensitivity of the search strategy was impacted by the population keyword used, we re-ran the Econlit search strategy on February 10, 2021 with the following terms added to line 6 of the search strategy included in the Appendix.

Table 1: Additional terms added to Econlit search strategy

"(breast and cancer).mp. or breast neoplasm*.mp. or breast carcinoma*.mp. or ductal neoplasm*.mp. or ductal carcinoma*.mp. or lobular neoplasm*.mp. or lobular carcinoma*.mp."*

The final number of publications returned by this search strategy was 3, identical to the result returned by the original search strategy (see original submission Appendix documents). This implies that no studies were missed by employing a less sensitive search strategy.

A3. Interventions, clinical SLR (CS Appendix D, Tables 1-3) Please explain the long list of comparators. In CS Document B Table 1 it is stated that the decision problem addressed in the company submission only looks at pembrolizumab, paclitaxel, docetaxel, atezolizumab and nab-paclitaxel. Please clarify why the additional comparators are included in tables 1-3.

The SLR was designed to cover all TNBC disease stages covering the neo-adjuvant, adjuvant and metastatic stage of TNBC and as such, it includes comparators that were reflective of this and may not be used in metastatic disease alone. The final list of studies relevant for the ID1546 mTNBC decision problem (that is; metastatic disease, comparators and outcomes relevant for the decision problem) were identified after the application of prespecified PICOS criteria developed for this submission (as outlined in Appendix of the original submission).

A4a. Interventions, clinical SLR (CS Appendix D, tables 1-3). Please clarify why drug terms were searched only in subject headings, titles and abstracts? These terms are also often found in other fields such as “drug name” or “name of substance”.

The drug terms were initially searched in subject headings, titles, and abstracts to balance sensitivity with specificity. We have re-run the searches using the multi-purpose .mp. suffix to search additional fields including “drug name” or “name of substance.” Thirty-seven additional records were identified but none met the PICOS inclusion criteria for this review (see table below for additional hits).

Table 2: Additional hits retrieved searching for drug names using *.mp* suffix (n=37 of which met PICOS: n=0)

#	List of additional studies
1	Impact of molecular and histological subtype of breast cancer on 18FDG-PET/CT imaging: knowledge gained from recent studies
2	PARP inhibitor and platinum agent in triple negative breast cancer: utilizing innovative trial design to bring together something "new" and something "old"
3	Whether low-dose metronomic oral cyclophosphamide improves the response to docetaxel in first-line treatment of non-triplenegative metastatic breast cancer
4	A randomized phase II trial comparing docetaxel plus cyclophosphamide with epirubicin plus cyclophosphamide f ollowed by docetaxel as neoadjuvant chemotherapy for hormone receptor-negative breast cancer. Kanagawa breast oncology group (KBOG) 1101 study.

5	Analysis of biomarkers and anthracycline benefit for hormone receptornegative breast cancer: results from a randomized phase 2 neoadjuvant study (KBOG 1101 Study)
6	Bevacizumab as first-line treatment in HER2-negative advanced breast cancer: pros and cons
7	Clinical development of talimogene laherparepvec (T-VEC): a modified herpes simplex virus type-1-derived oncolytic immunotherapy
8	Clinical experience with epothilones in patients with breast cancer.
9	Combination of Paclitaxel and MG1 oncolytic virus as a successful strategy for breast cancer treatment.
10	Comprehensive screening of target molecules by next-generation sequencing in patients with malignant solid tumors: guiding entry into phase I clinical trials
11	DETECT III und IV - Individualized CTC-based therapy of metastatic breast cancer
12	DETECT III/IV study trial-The multicenter study program in patients with HER2-negative metastatic breast cancer and circulating tumor cells
13	Do platinum salts fit all triple negative breast cancers?. [Review]
14	Efficacy of eribulin in breast cancer: a short report on the emerging new data
15	Emerging therapies for breast cancer. [Review]
16	Eribulin mesylate (eribulin) showed inhibitory effects on epithelial-mesenchymal transition (EMT) in tumors of metastatic breast cancer patients. -First preliminary report of a prospective study
17	Genetic variants in VEGF pathway genes in neoadjuvant breast cancer patients receiving bevacizumab: results from the randomized phase III GeparQuinto study
18	How high a bar to change neoadjuvant therapy for triple-negative breast cancer?.
19	Immunotherapy addition to neoadjuvant chemotherapy for early triple negative breast cancer: A systematic review and meta-analysis of randomized clinical trials. [Review]
20	Immunotherapy, an evolving approach for the management of triple negative breast cancer: Converting non-responders to responders. [Review]
21	Impact of body mass index on neoadjuvant treatment outcome: a pooled analysis of eight prospective neoadjuvant breast cancer trials
22	Multicentre, phase II study of eribulin in combination with S-1 in patients with advanced breast cancer.
23	Overall survival (OS) in KATE2, a phase II study of programmed death ligand 1 (PD-L1) inhibitor atezolizumab (atezo)1trastuzumab emtansine (T-DM1) vs placebo (pbo)1T-DM1 in previously treated HER21 advanced breast cancer (BC)
24	Over-using chemotherapy in the adjuvant setting
25	PD-1 Inhibitor promising in treatment of triple-negative breast cancer.
26	PDL1/CD274 gain/amplification as a predictive marker of checkpoint blockade inhibitor efficacy in metastatic breast cancer: exploratory analysis of the SAFIR02-IMMUNO randomized phase II trial
27	Perspectives on the mechanism of action and clinical application of eribulin for metastatic breast cancer. [Review]
28	PI3K inhibitor provides durable response in metastatic metaplastic carcinoma of the breast: A hidden gem in the BELLE-4 study.
29	Systemic treatment of metastatic breast cancer: SABCS 2018
30	Targeted and immuno-biology driven treatment strategies for triple-negative breast cancer: current knowledge and future perspectives. [Review]

31	The effect of neoadjuvant platinum-based chemotherapy in BRCA mutated triple negative breast cancers -systematic review and meta-analysis. [Review]
32	Total choline quantification measured by 1H MR spectroscopy as early predictor of response after neoadjuvant treatment for locally advanced breast cancer: The impact of immunohistochemical status.
33	Tumor-Infiltrating Lymphocytes and Breast Cancer: are Immune Checkpoint Inhibitors Ready for Prime Time in Breast Cancer?
34	Updates in Neoadjuvant Therapy for Triple Negative Breast Cancer. [Review]
35	Utilisation and outcomes of eribulin in triple-negative metastatic breast cancer (TN MBC): real-world findings
36	Whether low-dose metronomic oral cyclophosphamide improves the response to docetaxel in first-line treatment of non-triplenegative metastatic breast cancer.
37	WSG ADAPT - adjuvant dynamic marker-adjusted personalized therapy trial optimizing risk assessment and therapy response prediction in early breast cancer: study protocol for a prospective, multi-center, controlled, non-blinded, randomized, investigator initiated phase II/III trial
Meeting the prespecified PICOS criteria: n = 0	

A4b. Please clarify why some comparators (e.g. cyclophosphamide) were searched both alone and in combination with other drugs.

Please refer to response A3 above. A comprehensive list of comparators was included to meet the requirements for the metastatic indication informed from KEYNOTE-355 and [redacted] Further, some comparators were searched in combinations used in clinical practice. We acknowledge that this does not alter the sensitivity or specificity of the results when individual components of combination regimens are included in separate lines.

A5. Outcomes clinical SLR, Appendix D Tables 4 and 5. Please confirm which outcome measures were included in the SLR as these were considered necessary for inclusion in the indirect comparison (e.g. OS / PFS)

Thank you for the question. To be eligible for inclusion in the SLR, a study had to report at least one outcome of interest in the PICOS statement (Appendix D Table 4). To be eligible for consideration in the indirect comparison, a study had to report overall survival, progression-free survival, or both since these are relevant and necessary from a health economic modelling perspective and decision making.

A6. Economic SLR (CS Appendix G): Please explain why 2007 was chosen as the specific start date for the economic SLR searches?

The economic SLR searches are limited to the last 13 years (2007 to 19th November 2020) and was conducted approximately 1.5 months before the anticipated NICE submission. It is important to note that the development of novel therapies for mTNBC did not advance significantly until very recently with the introduction of IO therapies, including the recently approved by NICE TA639 [1]. With that in mind, 2007 was chosen as a start date for study eligibility within the economic SLRs. Studies published from 2007 and onwards were deemed to be reflective of the current NHS clinical practice. Older economic evaluations, costing/resource studies may not be entirely useful or generalisable with regards to informing the economic modelling and are likely to require extensive updates and clinical validation. With that in mind a decision was taken to limit the study eligibility to 2007 onwards to reflect current treatment landscape.

A7. Date of searches. Document B, section B2.2 states "The SLR was originally conducted on 27th August 2019 and an updated search was conducted on 10th August 2020". However, the searches reproduced in the appendices were run 19th November 2020. Please explain this discrepancy.

We thank the ERG for the opportunity to clarify this as this is a typographic error in our part. The original search was run on 27th August 2019 and an updated search was conducted on 10th August 2020. A final update was conducted on the 19th of November 2020 to ensure the evidence base was as up to date as possible ahead of the NICE submission. This is reflected in section 2.9.2 and section 3.1 of the submission. Section 2.2 should be updated noted that the final search was run on November 19th 2020. For simplicity we have provided the final hits generated from the November 19th 2020 search conducted ahead of the NICE submission for the clinical and economic SLRs. We also confirm that the full SLR strategy was re-run with each update, as opposed to runs being limited to the time period lapsed since the previous SLR update, to ensure no publications were missed if they had been published in the interim or not date-indexed accordingly.

A8. Please confirm if the following trials were identified by the search, and if so, why they were excluded from the review/indirect comparison: AVADO Pivot 2011; RIBBON-1 Robert 2011; CALGB40502 Rugo 2015; TURANDOT Zielinski 2016.

The above studies were identified during the SLR. However, none were included because all evaluated comparators that were not considered eligible in the pre-specified study selection criteria (ineligible comparators shown below).

Table 3: List of studies and comparators cross-checked versus original SLR results

Study	Comparator
AVADO [2]	Docetaxel+bevacizumab
CALGB40502 [3]	Ixabepilone
RIBBON-1 [4]	Chemotherapy*+bevacizumab
TURNADOT [5]	Capecitabine+bevacizumab
Chemotherapy regimen consisted of capecitabine, nab-paclitaxel, docetaxel, doxorubicin/cyclophosphamide, epirubicin/cyclophosphamide, fluorouracil/epirubicin/cyclophosphamide, or fluorouracil/doxorubicin/cyclophosphamide	

A9.**PRIORITY:** IA3 results, Page 30 CS. Please confirm when the results from IA3 will be available? Please clarify if the criterion for IA3 has been met yet (210 OS events among subjects with CPS ≥10)? If not, is it likely to be met before the first appraisal committee meeting (6/7/21)?

*****

A10. Marketing authorisation, CS page 11. Please confirm that the marketing authorisation application is limited to pembrolizumab plus chemotherapy - i.e. not pembrolizumab monotherapy and not limited to pembrolizumab plus taxane. Please also clarify if chemotherapy is limited to gemcitabine plus carboplatin, nab-paclitaxel or paclitaxel? And if KEYNOTE-355 is the only trial that supports the marketing authorisation for this indication?

The anticipated marketing authorisation is KEYTRUDA (pembrolizumab) ***** KEYNOTE-355 is the only trial to support the marketing authorisation for this indication.

A11. CHMP opinion, Appendix C. Please confirm that CHMP opinion is due prior to NICE appraisal committee meeting (6/7/21)?

The CHMP decision is currently anticipated to be delivered in ***** MSD will update NICE as soon as a date is confirmed. *****

A12. Studies of pembrolizumab in triple negative breast cancer, Appendix D. Please provide details of ongoing studies (other than KEYNOTE-355) of pembrolizumab in triple negative breast cancer (TNBC), and their expected primary completion dates.

Table 4: Phase III ongoing studies of pembrolizumab in TNBC (clinicaltrials.gov)

Trial Name	Trial title	Expected primary competition dates
KEYNOTE-522 (NCT03036488)	Study of pembrolizumab plus chemotherapy vs placebo plus chemotherapy as neoadjuvant therapy and pembrolizumab vs placebo as adjuvant therapy in TNBC	30th September 2025
KEYLYNK-009 (NCT04191135)	Study of olaparib plus pembrolizumab vs chemotherapy plus pembrolizumab after induction with first-line chemotherapy plus pembrolizumab in TNBC (Locally recurrent inoperable or metastatic)	26th January 2026
KEYNOTE-242 (NCT02954874)	Adjuvant therapy for TNBC with ≥1cm residual invasive cancer or positive lymph nodes (ypN1mi, ypN1-3) after neoadjuvant chemotherapy	31st May 2026

A13. SLR data extraction, Appendix D. Please confirm if quality assessment and data extraction was conducted by one or two researchers. Please explain the potential bias that could be introduced into the results if only one researcher was used.

Both data extraction and quality assessment were conducted in duplicate by two reviewers working independently. Any discrepancies observed between the data extracted or quality assessment decisions by the two data extractors were resolved by involving a third reviewer and coming to a consensus

A14. Quality assessment Appendix D.1.2.4., Please provide supportive evidence for the judgment of high risk of bias for "other" in both the KEYNOTE-355 and IMpassion130 trials - e.g. industry sponsored, post-hoc analyses, protocol revisions, insufficient information?

Both Impassion130 and Keynote-355 were deemed to have a high "other" risk of bias because they were industry sponsored. Although both trials were conducted prospectively, it is important to note that the data from IMpassion130 used in the indirect comparison was

derived from a post-hoc model. Although this does not bias the overall trial, this factor has been described in the indirect comparison limitations section.

A15. Overall survival (OS) CS Page 38. Please clarify the definition of “clinically meaningful” improvement in OS?

To evaluate the clinical meaningfulness of the efficacy observed in KEYNOTE-355, the Sponsor considered the totality of the evidence available. [redacted]

A16. Progression free survival (PFS) CS Page 40. Please clarify the definition of “clinically meaningful” improvement in PFS?

To evaluate the clinical meaningfulness of the efficacy observed in KEYNOTE-355, the Sponsor considered the totality of the evidence available. There was a statistically significant improvement in PFS at IA2. In addition to being statistically significant, the improvement in PFS observed in the pembrolizumab + chemotherapy group was considered clinically meaningful for the following reasons:

- The PFS HR of 0.65 (95% CI: 0.49, 0.86, p=0.0012) represents a 35% reduction in the risk of progression or death for participants with PD-L1 positive tumors (CPS ≥10).
- The median PFS was longer for participants with PD-L1 positive tumors (CPS ≥10) in the pembrolizumab + chemotherapy group compared with the placebo + chemotherapy group (9.7 months vs 5.6 months).
- Pembrolizumab + chemotherapy provided an improvement in PFS relative to what has been observed for atezolizumab + nab-paclitaxel (9.7 months [95% CI: 7.6, 11.3] vs 7.4 months [95% CI: 6.6, 9.2]) with a similar reduction in the risk of progression or death (PFS HR of 0.65 vs 0.60, respectively).
- The PFS rates by KM estimation were higher for participants with PD-L1 positive tumors (CPS ≥10) in the pembrolizumab + chemotherapy group compared with the placebo + chemotherapy group at 6 months (65.0% vs 46.9%) and 12 months (39.1% vs 23.0%).

These PFS data, when considered with [redacted] demonstrate that pembrolizumab + chemotherapy provides a substantial improvement in treatment outcomes for patients with TNBC compared with chemotherapy alone.

A17. Overall response rate (ORR) CS Page 42. Please clarify the definition of “clinically meaningful” improvement in ORR?

To evaluate the clinical meaningfulness of the efficacy observed in KEYNOTE-355, the Sponsor considered the totality of the evidence available. The improvement in ORR observed in the pembrolizumab + chemotherapy group was considered clinically meaningful for the following reasons:

- The ORR (per RECIST 1.1 by BICR) in participants with PD-L1 positive tumors (CPS ≥10) was 53.2% for the pembrolizumab + chemotherapy group versus 39.8% for the placebo + chemotherapy group, with a clinically meaningful difference of 13.6% (95% CI: 1.9, 24.8).
- The observed percentages of CR and PR in participants with PD-L1 positive tumors (CPS ≥10) were higher in the pembrolizumab + chemotherapy group compared with the placebo + chemotherapy group

Furthermore, in those who responded to pembrolizumab + chemotherapy, there was a 12 month improvement in DOR relative to the placebo + chemotherapy group (19.3 months vs 7.3 months). These ORR data, [redacted] demonstrate that pembrolizumab + chemotherapy provides a substantial improvement in treatment outcomes for patients with TNBC compared with chemotherapy alone.

A18. Adverse events Appendix F. Please clarify the definition of “serious” adverse events in the KEYNOTE-355 trial?

A serious adverse event, as defined by the protocol, is any adverse event occurring at any dose or during any use of Sponsor’s product that:

- Results in death
- Is life threatening
- Results in a persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a new cancer
- Is an overdose
- Other important medical events

A19. Life expectancy CS, Page 15. People with TNBC are said to have a poor prognosis. Please clarify the life expectancy in people who have the comparator and experimental treatments?

Clinical experts note that mTNBC being a very aggressive type of cancer. Published literature indicates that the median OS estimates with taxane chemotherapies remains

below 24 months [6-11]. Within KEYNOTE-355 ***** Impassion130 reported the median OS for atezolizumab with nab-paclitaxel for patients with PD-L1 immune cell-positive tumours was 25.0 months (95% CI 19.6 - 30.7) [12].

A20. CS, Page 27, Table 6: A higher proportion of people in the control arm of KEYNOTE-355 received nab-paclitaxel rather than paclitaxel compared to people in the experimental arm. Please comment on this difference and provide and explanation for this?

The protocol allowed for investigator's choice of chemotherapy to be used alongside pembrolizumab or placebo. The stratification between the arms was between taxanes and non-taxanes, rather than paclitaxel or nab-paclitaxel. The proportion of patients receiving taxanes is similar between the two arms, 42.7% (pembrolizumab) and 45.7% (placebo). The numbers of patients within the control arm are such that seven fewer patients in the nab-paclitaxel placebo group would make the proportion near equal.
Table 6 in the company submission reports data for a subset of the trial population (CPS≥10). For all subjects, the difference in proportion of patients receiving nab-paclitaxel between the pembrolizumab and placebo groups was 3.2%.

A21. CS, Page 37, Table 12: Please provide the estimates and 95% confidence intervals for the effect of treatment on complete response (CR) and Disease control rate (DCR).

Table 5: Analysis of Complete Response Based on BICR Assessment per RECIST 1.1. Subjects with PD-L1 CPS ≥10) (ITT population)

Treatment	N	Number of Disease Control	Complete Response Rate (%) (95% CI)	Difference in % vs. Control
Pembrolizumab + Chemotherapy	*****	*****	*****	*****
Placebo + Chemotherapy	*****	*****	*****	
Confirmed responses are included. BICR = Blinded Independent Central Review. Database Cutoff Date: 11DEC2019				

Table 6: Analysis of Disease Control Based on BICR Assessment per RECIST 1.1 Subjects with PD-L1 CPS ≥10 (ITT Population)

Treatment	N	Number of Disease Control	Disease Control Rate (%) (95% CI)	Difference in % vs. Control
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Placebo + Chemotherapy	[redacted]	[redacted]	[redacted]	

Disease Control= SD ≥ 24 Weeks+CR+PR. Confirmed responses are included.
Stable Disease (SD) includes both SD and Non-CR/Non-PD.
BICR = Blinded Independent Central Review.
Database Cutoff Date: 11DEC2019

A22. CS, Page 38: Please comment on the bias and coverage associated with the estimate of [redacted] from a conventional fixed sample analysis given the interim analyses and method used to control the family-wise type I error?

Please ensure that the KN-355 OS estimates reported in Question 22 above are redacted from the version of the ERG questions that are published in NICE website. These are Commercial In Confidence data – we have updated the CIC marking within this document. Compared to a conventional fixed sample analysis, the group sequential method applied in the analysis for OS controls family-wise type I error rate in the presence of repeated analyses. The analysis of OS IA2 carries the properties of a stratified Cox regression model: under the model assumptions, the estimate is asymptotically unbiased and the coverage for the 95% CI is 95%.

A23. CS, Page 40: Please comment on the bias and coverage associated with the estimate of PFS (HR 0.65 95% CI: 0.49, 0.86) from a conventional fixed sample analysis given the interim analysis and method used to control the family-wise type I error?

For PFS in subjects with CPS ≥10, group sequential method was not applied and the analysis at IA2 was the only analysis. The analysis of PFS at IA2 carries the properties of a stratified Cox regression model: under model assumptions, the estimate is asymptotically unbiased and the coverage for the 95% CI is 95%.

A24. CS, Page 51, Figure 7 OS: The CS states that the treatment effect is consistent across subgroups. (The ERG notes that subgroups were not adjusted for stratification

factors and interaction terms were not formally assessed.) Please comment on the following observations:

- Older patients derive more benefit than younger patients and non-hispanics or latinos derive more benefit than hispanics or latinos
- Patients treated with paclitaxel derive more benefit than patients treated with nab paclitaxel
- Patients not previously treated derive more benefit than those previously treated

There was an omission of the word 'generally' before consistent to indicate that the treatment effect was seen across most groups. The study was not designed to compare differences in treatment effect between sub-groups or powered to test treatment effect within subgroups. In addition, the numbers within some of these groups are small, especially when examining as part of another subgroups (CPS≥10) and these results should be interpreted with caution

A25. Please provide results of a re-analysis of the NMA using a random effects model incorporating reasonable prior beliefs about the between-study standard deviation such as that suggested by Turner et al. *(Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JPT. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analyses. Statistics in Medicine 2015; 34: 984-998)*. Please provide random effects estimates and the predictive distribution of the effect of treatment in a new study.

Please see below the results of the analyses requested – also incorporated in the updated model, within the "**Effectiveness**" sheet. Because only one study was available for each comparison in the network of evidence, it was not possible to estimate between-study heterogeneity based on data from trials in the network and the results of a random-effects network meta-analysis using non-informative priors for between-study heterogeneity would yield unrealistically wide credible intervals. Therefore, a fixed-effects network meta-analysis was performed. As noted in our original submission, results should be interpreted with caution as the FEM model does not account for between study heterogeneity.

We have re-run the same analysis scenarios (results provided in separate document) with informative priors based on the estimated heterogeneity for pharmacological vs. pharmacological studies (τ^2: 0.06, 95% CI: 0.05 to 0.07) as reported in *Turner RM et al 2015* [13]. In this study, τ^2 was estimated from a large number of studies appearing in the Cochrane Database of Systematic reviews.

As expected, the REM results of the NMA using a random effects model and informative priors have the same point estimate but wider credible intervals than the results of the fixed-effects NMA with non-informative priors. Therefore, the REM results also [redacted].

Because the prior for heterogeneity was derived from studies across a variety of disease areas and outcomes, it is not known whether the actual heterogeneity between studies in the evidence base is greater or less than the heterogeneity of studies used to estimate an informative prior. Additionally, informative priors can exert undue influence in sparse networks comprising few studies. Therefore, results should be interpreted with caution [14].

Table 7: Hazard ratios random-effects network meta-analysis of OS

#	Comparison	KEYNOTE-355 PD-L1 expression subgroup	IMpassion130 PD-L1 expression subgroup	HR (95% CrI)
Overall Survival				
1	Pembrolizumab + paclitaxel/nab-paclitaxel vs. atezolizumab + nab-paclitaxel **(pooled KN-355 taxanes)**	CPS ≥ 10	CPS ≥ 10	[redacted]
2	Pembrolizumab + nab-paclitaxel vs. atezolizumab + nab-paclitaxel	CPS ≥ 10	CPS ≥ 10	[redacted]

Table 8: Hazard ratios random-effects network meta-analysis of PFS

#	Comparison	KEYNOTE-355 PD-L1 expression subgroup	IMpassion130 PD-L1 expression subgroup	HR (95% CrI)
Progression-free survival (KN-355 INV-assessed PFS, IMpassion130 IA-assessed PFS)				
1	Pembrolizumab + paclitaxel/nab-paclitaxel vs. atezolizumab + nab-paclitaxel **(pooled KN-355 taxanes)**	CPS ≥ 10	CPS ≥ 10	[redacted]
2	Pembrolizumab + **nab-paclitaxel** vs. atezolizumab + **nab-paclitaxel**	CPS ≥ 10	CPS ≥ 10	[redacted]
Progression-free survival (KN-355 BICR-assessed PFS, IMpassion130 IA-assessed PFS)				
1	Pembrolizumab + paclitaxel/nab-paclitaxel vs. atezolizumab + nab-paclitaxel **(pooled KN-355 taxanes)**	CPS ≥ 10	CPS ≥ 10	[redacted]
2	Pembrolizumab + nab-paclitaxel vs. atezolizumab + nab-paclitaxel	CPS ≥ 10	CPS ≥ 10	[redacted]

Section B: Clarification on cost-effectiveness data

PRIORITY: Should the company acknowledge that changes be required within the model, please present ICERs and sensitivity analyses combining all of the changes as the ERG would take this to be the new company base case.

A number of changes were performed in the economic model based on ERG's comment on questions listed below (Life tables formula, Resource use, RDI and AE costs). Changes

within the model have been highlighted with yellow. Included below for clarity are the previous and updated ICERs versus paclitaxel with a 20 Year Time Horizon (TH) to demonstrate the limited impact in the original company base-case (Table 9).

An updated set of cost-effectiveness results using a 35 Year TH alongside the rest of the model updates implemented (Life tables formula, Resource use, RDI and AE costs, ERG feedback) is provided at the end of this document **(Section D)**. These analyses reflect the new company base case.

Table 9: Comparisons of ICERs vs paclitaxel between the original and updated model post ERG review (20 Year Time horizon)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline
Previous company base-case ICER with Pembrolizumab CAA (original submission)						
Paclitaxel comparator	[redacted]	1.808	[redacted]	-	-	-
Pembrolizumab + taxanes**	[redacted]	3.795	[redacted]	[redacted]	[redacted]	£29,008
New company base-case with Pembrolizumab CAA; after model updates (for impact of changes)						
Paclitaxel comparator	[redacted]	1.808	[redacted]			
Pembrolizumab + taxanes**	[redacted]	3.795	[redacted]	[redacted]	[redacted]	**£29,241**
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, ** Confidential discounts in place for Nab-paclitaxel within the NHS; may alter the cost-effectiveness results.						

B1. **PRIORITY:** Please clarify why a small proportion of PSA iteration are providing negative QALYs for the intervention arm compared with control (CS, Figure 31 and Figure 33).

There was a discrepancy in how the utilities values varied in the PSA were feeding into the model which has now been updated. Previously, values for the alternative approaches (i.e. utility by progression status and utility by progression status and AE) were also updated through each iteration of the PSA. We have updated formula in the trace to now ensure that these do not feed into the trace unless the dropdown selection in the "Utility" worksheet is altered. Additionally, in the PSA setup sheet (**O157:O174**) we have updated the SE to reflect the values calculated in the KEYNOTE-355 utility analysis rather than using the assumption of 20% of the mean value (see detailed response in B.11 below). In the incremental cost-effectiveness plane, there remains one iteration with negative incremental QALYs which is likely explained by the uncertainty in the parameter estimates for OS. Please see at end of this section for updated cost-effectiveness analyses.

B2. **PRIORITY:** Please clarify whether Figure 31 of the CS should be marked CIC.

We can confirm that Figures 31 and 32 of the CS "scatterplot of PSA results versus paclitaxel or docetaxel with Pembrolizumab CAA" should be marked as CIC. New versions of the submission have been shared (named as V2.0, 17th February 2021). The new CIC marking is also reflected in our updated analyses below (Section D).

B3. Please clarify how the numbers of observations for the change from baseline values in Table 21 are bigger than the number of observations in both the baseline and in Week 15. Please provide an analysis that considers only patients with complete records for both baseline and Week 15.

For clarity we include the relevant table from CS below. As stated in the 1st table footnote, the cLDA model is considering the PRO scores as the response variable, so patients with any available score at baseline or any time point up to week 15 is contributing to the analysis and is accounted for in the [redacted] patients used in the analysis population.

Table 10: (Table 21 of CS): Analysis of change from baseline in EQ-5D VAS at week 15 - CPS ≥10 (FAS population)

	Baseline		Week 15		Change from Baseline at Week 15	
Treatment	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**LS Mean (95% CI) †**
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise comparison					**Difference in LS Means 95% CI)**	**p-Value**
Pembrolizumab + chemotherapy vs. Placebo + chemotherapy					[redacted]	[redacted]

† Based on constrained Longitudinal Data Analysis (cLDA) model with the PRO scores as the response variable, and treatment by timepoint interaction, and stratum (defined by stratification factors of chemotherapy on study [taxane vs gemcitabine/carboplatin] and prior treatment with same class of chemotherapy in the (neo)adjuvant setting [yes vs no]) as covariates.

For **baseline** and **Week 15**, N is the number of **subjects in each treatment group with non-missing assessments at that specific time point**; for ***change from baseline***, N is the ***number of subjects in the analysis population in each treatment group***. Two-sided p-value.

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As the ERG correctly noted the N for change from baseline ([redacted]) does not correspond to the number of patients with a non-missing observed change from baseline at week 15. The

"change from baseline at week 15" (refers to the actual score change) values of [redacted] and [redacted] reported above are the overall number of patients used in the cLDA model and which contribute to the LS means for the change from baseline at Week 15 displayed in the last column. These values are larger than those reported in the baseline because records of patients with non-missing PRO assessments in between baseline and Week 15 are included in the cLDA model, therefore more records contributing to the change from baseline score analysis (see **Error! Reference source not found.** below reporting a PRO record breakdown by assessment timepoint).

Patients with any PRO assessment at baseline, W3, W6 or W15 are used to fit the cLDA model. Below we include a detailed count of records to offer more clarity around the estimates. This is in agreement with the prespecified statistical analysis plan (SAP) which states that; *"The PRO Full Analysis Set (FAS) population will be used for PRO analyses. The PRO FAS population consists of all randomized subjects who received at least one dose of study medication and completed at least one PRO assessment. To assess the treatment effect on the PROs, for each PRO endpoint defined, a constrained longitudinal data analysis (cLDA) model will be used as the primary analysis method, with the PRO score as the response variable. Only PRO data up to the primary analysis time point will be included in this analysis model."*

Table 11: Breakdown of records included in the cLDA CPS ≥10 model (FAS population)

INCLUDED IN cLDA CPS ≥10 FAS	Pembrolizumab + Chemotherapy CPS ≥10	Placebo + Chemotherapy CPS ≥10	TOTAL
Both baseline and Week 15 (so available CHG)	[redacted]	[redacted]	[redacted]
Baseline but no Week 15	[redacted]	[redacted]	[redacted]
Week 15 but No baseline	[redacted]	[redacted]	[redacted]
No baseline and no Week 15, but either Week 3 or 6	[redacted]	[redacted]	[redacted]
TOTAL for change on baseline scores	[redacted]	[redacted]	[redacted]

Please see below the final breakdown records included in the analyses

- [redacted] = number of subjects with non-missing assessments (i.e score) at baseline in active group ([redacted]
- [redacted] = number of subjects with non-missing assessments (i.e score) at baseline in control group ([redacted]
- [redacted] = number of subjects with non-missing assessments (i.e score) at Week 15 in active group ([redacted])
- [redacted] = number of subjects with non-missing assessments (i.e score) at Week 15 in control group ([redacted])

- [redacted] = the number of subjects in active group included in the analysis population (used to fit the cLDA model)
- [redacted] = the number of subjects in control group included in the analysis population (used to fit the cLDA model)

Liang and Zeger (2000) [15] proposed this constrained longitudinal data analysis in which the baseline value is included in the response vector together with the postbaseline values and a constraint of a common baseline mean across treatment groups is imposed on the model as a result of randomisation.

Several papers have compared cLDA with ANCOVA or LDA:

- Liu etl al (2009) [16]: In general, under similar modelling conditions, the cLDA model is more efficient than the longitudinal ANCOVA model. The longitudinal ANCOVA model underestimates the variance of the model adjusted group mean estimates by conditioning on the baseline variables while the cLDA model provides appropriate variance and confidence interval estimates. The cLDA model also provides more flexibility in handling missing data by including all observed data, which, in general, results in more power when testing treatment differences compared with the longitudinal ANCOVA model.
- Kaifeng Lu (2010) [16]: If the baseline value is subject to missingness, the constrained longitudinal data analysis is shown to be more efficient for estimating the treatment differences at postbaseline time points than the longitudinal analysis of covariance. The efficiency gain increases with the number of subjects missing baseline and the number of subjects missing all postbaseline values.
- Coffman et al (2016) [17]: Under reasonable missing data assumptions, cLDA yields efficient treatment effect estimates and robust inferential statistics. It may be regarded as the method of choice over ANCOVA and LDA.

Given the statistical advantages described in various papers (provided above), the cLDA methodology was prespecified in the statistical analysis and is considered as the most efficient method in estimating the change in EQ-VAS. An analysis considering only patients with complete records for both baseline and Week 15 has not been provided as it was not prespecified in the statistical analysis plan and is considered as less efficient, less powered and potentially biased (due to not including subjects with either missing data at baseline or missing data at all post-baseline measurements).

B4. Appendix P, Section 3:

a. Please provide details of the parameterisations used for each survival model.

Please see separate pdf document providing the information requested regarding the parameterisations for the taxanes specific subgroup included within the economic model.

b. Please provide plots of smoothed empirical hazard functions with 95% confidence intervals for each treatment group for each dataset analysed.

Displayed below are various estimates of hazards over time by treatment. The 6 parametric estimates are made by assuming the underlying true hazards follow the distributions parameterized with the ones summarized above for long-term survival extrapolations. In addition, the smooth spline estimate is made and serves as a benchmark since it does not require any parametric assumptions other than assuming the underlying true hazard being smooth over time. The shaded area represents the 95% confidence region estimated using this smooth spline approach. As a parallel to the above idea of applying KM curve, as a non-parametric benchmark for survival, to assess visually the goodness-of-fit of various parametric survival estimates for the long-term extrapolations, hazard function, rather than survival function, is applied here for the same purpose of assessment.

Figure 1: Plot of hazard function of Overall Survival assuming smooth spline or various parametric distributions used for long-term extrapolation for the group treated with Pembrolizumab + Taxanes. The shaded area refers to 95% CIs for the smooth spline estimates

Figure 2: Plot of hazard function of Overall Survival assuming smooth spline or various parametric distributions used for long-term extrapolation for the group treated with Placebo + Taxanes. The shaded area refers to 95% CIs for the smooth spline estimates

Figure 3: Plot of hazard function of BIRC-assessed Progression-free Survival assuming smooth spline or various parametric distributions used for long-term extrapolation for the group treated with Pembrolizumab + Taxanes. The shaded area refers to 95% CIs for the smooth spline estimates

Figure 4: Plot of hazard function of BIRC-assessed Progression-free Survival assuming smooth spline or various parametric distributions used for long-term extrapolation for the group treated with Placebo + Taxanes. The shaded area refers to 95% CIs for the smooth spline estimates

c. Please provide model-based plots of the absolute and relative hazards over time for each dataset analysed.

Please see above.

d. Please provide a discussion on the *expected* hazards for PFS and OS over the observed and extrapolated periods for each of the datasets analysed.

Please see separate report attached. From the OS log cumulative hazard plot there seems to be a minor inclination point at approximately 25 weeks at which time the KM curves tend to converge slightly before diverging again thereafter (see attached report: 1.1.2 – Figure 3). Based on the IA2 OS data [redacted], full piece models are justified for OS survival extrapolations, an assumption which is further supported by the shape of SoC curves reviewed from RWE literature for the chemotherapy arm extrapolations. [6-10].

For PFS and based on log cumulative hazard plot, there is a clear timepoint at the KM curves converse at around week 9, before diverging thereafter with a separation between the two curves which is maintained over time (see report 2.1.2 – Figure 3). This indicates that there is a clear timepoint at which the hazard changes, justifying the piecewise approach in PFS survival extrapolations.

e. Please provide a discussion regarding when the effect of pembrolizumab on the PFS and OS hazard functions is expected to deteriorate/wane. Please provide survival analyses with appropriate assumptions regarding the change in the hazard functions after treatment discontinuation and the impact on the ICER.

In KEYNOTE-355 treatment was administered upon disease progression or unacceptable toxicity with a maximum of 35 infusions of pembrolizumab (chemotherapy could be continued beyond this timepoint based on clinical opinion). As observed in the KN355 trial, the treatment effect of pembrolizumab + taxanes lasted beyond the study treatment and progression-free period. The sustained treatment effect is not uncommon in immune-oncology (IO) trials, therefore treatment waning was not introduced in the model base case for PFS and OS.

This assumption is consistent with the immunotherapeutic effect observed with IO agents across a number of tumours including NSCLC, Melanoma, RCC and Head & Neck, whereby due to their unique mode of action, IO agents are able to stimulate the immune system to fight cancer cells resulting in a % of patients with durable going on to achieve long term survival [18-20].

The treatment effect assumptions formulating the base-case are consistent with the AC's preferences for TA639 (and all other metastatic BC appraisals) in which it was concluded

that in the absence of clinical evidence assuming arbitrary treatment waning was not relevant. However, alternative assumptions on the impact of OS waning on the cost-effectives results have been explored in sensitivity analyses and are presented within the CS. The options available include:

- A pragmatic approach to waning effect modelling based on the SEER mTNBC patient dataset. In this analysis, the cumulative OS hazard function was used to identifying a point in time at which the OS hazard reaches a plateau. The estimated constant hazard rate estimate was applied across both arms within the economic model.
- An alternative option to arbitrarily remove the OS effect at a specific timepoint within the economic model by setting the HR =1 between the intervention and comparator, similar to the methodology used by the ERG at TA639.

The SEER approach to estimating the impact of waning implies that long-term survival trend was independent of treatment received within the dataset. However, it was explored within the CS as it is based upon actual data in absence of clinical evidence from KEYNOTE-355. Overall, waning assumptions increase the base-case ICER marginally (see analyses at end of this document).

f. The information criteria for the Gompertz distributions are difficult to interpret because they are from models with negative shape parameters, which imply that some patients are immortal. Please refit the Gompertz distributions and recalculate the information criteria with constrained parameters that result in proper survival functions.

This was briefly explored by our team which informed us that constrained parameter models did not converge – results are therefore not provided. As reported within the CS, Gompertz does lead in implausible projections and this provides further evidence as to why it should not be considered for the purposes of economic modelling.

g. Please explain why mixture models were not evaluated for the pembrolizumab arm.

Following on from our engagement with the ERG, we interpret mixture models to refer to mixture cure models. Mixture cure models were not deemed appropriate for exploration within this submission due to the limited median duration follow up of 16.8 months and the [redacted] Clinical expert opinion based on prior IO experiences suggested that a stabilisation and subsequent OS plateau could be expected to be observed from around year 3 onwards, therefore attempting to estimate a mixture cure model based on the current dataset would be premature and could inflate uncertainty. We consider the standard parametric modelling

approach to be consistent with most of the previous IO HTAs and conservative in terms of cost-effectiveness since a mixture cure model would likely result in higher incremental QALY gains therefore reduce the ICER.

h. Survival models that are members of the generalised F family or Gompertz distribution have restrictive hazard shapes. Please fit restricted cubic splines to each of the datasets analysed, comment on the relative goodness-of-fit, long-term plausibility of the models, and impact on the ICER.

The software used for survival analysis does not allow for fitting of spline models, therefore we are unable to process this request. As NICE DSU 20 states, spline models can be fitted to capture complex hazard functions [21]. A major criticism of spline models is that the whole data fitting process for extrapolations does not take into account any biological rationale around the long term shape of PFS and OS hazards. As noted on DSU TD 20, spline models should generally offer a good fit during the observed period (assuming sufficient knots have been used), however, extrapolation beyond trial period may still be limited without the introduction of external datasets. For the above reasons spline models were not deemed appropriate and therefore have not been included within the HTA submission. Instead, pricewise modelling (including a number of alternative timepoints for PFS and OS extrapolations) was deemed as more appropriate methodologically.

i. Please provide a reanalysis of the PFS data allowing for interval censoring for each of the datasets analysed.

In KEYNOTE-355 as per protocol, post baseline imaging was performed at Weeks 8 (±7 days), 16 (±7 days), and 24 (–7 days) post randomization and every 9 weeks (±7 days) thereafter during the first year followed by imaging at every 12 weeks (±7 days) after the first year [22].

Interval-censoring approach for PFS was planned in statistical analysis plan (SAP) only in case of imbalance between the treatment groups on disease assessment schedules or censoring patterns. As there was no imbalance between treatment arms on disease assessment schedules and the PFS sensitivity analyses results were consistent to the primary PFS endpoint and not borderline significant, this analysis was not performed for inclusion in the CSR.

Results of the primary PFS and sensitivity analyses with alternative censoring rules pertaining to the scheduled visits are presented below for the CPS $\geq$ 10 subgroup of KEYNOTE-355. The results remain consistent with the primary analysis suggesting no need for the interval censoring PFS analysis.

PFS sensitivity analyses:

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment in which PD was not documented and the assessment when PD is documented. For subjects who had PD, the true date of disease progression was approximated by the date of the first assessment at which PD was objectively documented based on RECIST 1.1 as assessed by a CIV. Death was always considered as a confirmed PD event. Subjects who did not experience a PFS event were censored at the last disease assessment.

In order to evaluate the robustness of the PFS endpoint based on RECIST 1.1 as assessed by a CIV, one primary and two sensitivity analyses with a different set of censoring rules were performed.

For the primary analysis, if the events (PD or death) were immediately after more than one missed disease assessment, the data are censored at the last disease assessment prior to missing visits. Also data after new anti-cancer therapy are censored at the last disease assessment prior to the initiation of new anti-cancer therapy. The censoring rules for primary analysis and sensitivity analyses are summarised in Table 12 below. If a subject met multiple criteria for censoring, the censoring criterion that occurred the earliest was applied.

The first sensitivity analysis followed the intention-to-treat principle. That is, PDs/deaths were counted as events regardless of missed study visits or initiation of new anti-cancer therapy. The second sensitivity analysis considered initiation of new anticancer treatment or discontinuation of treatment due to reasons other than complete response to be a PD event for subjects without documented PD or death. If a subject met multiple criteria for censoring, the censoring criterion that occurs earliest was applied. These analyses are provided below.

Table 12: Censoring Rules for Primary Analysis of PFS and PFS sensitivity analyses (adapted from Table 11 of SAP of KEYNOTE-355 CSR)

Situation	Primary Analysis censoring	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; and new anticancer treatment is **NOT** initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study therapy; progressed at treatment discontinuation otherwise
No PD and no death; **new anticancer** treatment is **initiated**	Censored at last disease assessment **before** new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
No PD and no death; ≥2 consecutive missed disease assessments	Censored at last disease assessment	Censored at last disease assessment prior to ≥2 consecutive missed visits	Censored at last disease Assessment
PD or death documented after ≤1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥ 2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥2 consecutive missed disease assessments	Progressed at date of documented PD or death

Table 13:(CSR Table: 14.2-15) Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Sensitivity Analysis 1)(Part 2 Subjects with PD-L1 CPS ≥10)(ITT Population)

[redacted]

Table 14: (CSR Table 14.2-16) Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Sensitivity Analysis 2) (Part 2 Subjects with PD-L1 CPS ≥10) (ITT Population)

[redacted]

Table 15: (CSR Table 14.2-18) Analysis of Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (Time to Scheduled Visit Analysis)(Part 2 Subjects with PD-L1 CPS ≥10) (ITT Population)

An additional PFS supportive analysis was performed using the time to scheduled tumour assessment visit from randomization as opposed to the actual tumour assessment time (Table 15 above). The results of all sensitivity analyses demonstrated a consistent PFS benefit with that of the primary analysis, therefore interval censoring PFS analysis was not deemed necessary.

Considering the robustness of the PFS results between the primary and sensitivity analyses presented above and the short intervals between scheduled visits, we expect the impact to the cost-effectiveness results is anticipated to be limited.

j. Section 5.1: Please provide a discussion on the relationship between the population of patients defined by the patients extracted from the SEER database and the population(s) defined by the patients in the study. Please comment on the relationship between the population hazard rates associated with each population and the assumption that these are transportable across populations

The U.S. surveillance, epidemiology, and end results (SEER) database (2000-2017) is a US based database. Geographic areas were selected for inclusion in the SEER Program based on their ability to operate and maintain a high quality population-based cancer reporting system and for their epidemiologically significant population subgroups.

Access to the data and analysis was conducted with the SEER*STAT software provided by https://seer.cancer.gov/seerstat/. We used KM method to extract monthly survival rate of stage IV TNBC patients from the database. Patient inclusion criteria are:

- Site and Morphology. Site recode ICD-O-3/WHO 2008 = ' Breast'
- cancer Stage - 6th edition. Breast - Adjusted AJCC 6th Stage (1988-2015) = 'IV'
- Extent of Disease. Breast Subtype (2010+)} = 'HR-/HER2- (Triple Negative)

From the cumulative hazard plot of the SEER OS data (Figure 5 below), the hazard rate changed over time at the beginning but stabilized and reached a constant limit (i.e. exponential distribution) in the long run. We therefore estimated the constant hazard rate from the survival data after 4 years (48 months) post diagnosis of stage IV TNBC, using a

linear regression approach based on the reported survival rate, which is then applied at each weekly model cycle *****

Figure 5: Cumulative hazard plot of the SEER OS data

*****

No detailed information on patient characteristics is available from this tool for comparison versus KEYNOTE-355 baseline characteristics. However, the SEER patient population is representative of the patients who was diagnosed with mTNBC in the United States.

Whilst management of the disease may different between geographies, TNBC is a very aggressive form of cancer with limited survival outcomes. Due to the wide geographic coverage of SEER and the limited changes in the mTNBC treatment pathway (IOs were only introduced very recently; therefore their effect on survival projections would be limited), we considered this to source to be relevant in terms of inform long term hazard projections and model adjustments.

k. Please clarify which model is used in generating the results in Figure 36.

Figure 36 of the CS presents the Tornado results of Pembrolizumab + taxanes versus docetaxel chemotherapy comparator. We would like to take the opportunity to clarify that all assumptions pertaining to comparisons versus docetaxel (such as OS, PFS and ToT extrapolations) are assumed equal to those for the comparisons of Pembrolizumab + taxanes versus paclitaxel (no docetaxel TNBC PD-L1 +ve CPS $\geq$ 10 score +ve specific available).

The model submitted to NICE can be used to run the comparisons versus docetaxel. To run these analyses please navigate into the "**Drug Cost Input**" model sheet and select in the relevant drop down menu in cell **G28** to apply the docetaxel costs. This option replaces the paclitaxel drug costs comparator (and pre-medication costs) to those of docetaxel. The One-Way Sensitivity analysis and PSA need to be rerun to extract the results versus docetaxel comparator due to the way the model is currently structured.

B5. CS, Section B3.3, page 101:

a. Please describe the process that was used to extract experts' beliefs about the proportions of patients surviving at different times in each treatment group?

b. Please clarify what information the expert(s) were given before being asked to state their 5 and 10 years expectations?

c. Please clarify how many experts were asked to state their opinions and what the point estimate represent?

A clinical and health economic advisory board was held on [redacted]). This was attended by [redacted] covering a range of geographies across the UK with experience in using IOs. The health economic related component of the advisory board was [redacted]. No information was provided to clinical experts prior to the HTA advisory board, other than publicly available references serving as pre-reads including KEYNOTE-355, IMpassion-130 and the Rugo et al 2020 [23, 24] publications.

During the advisory board, KEYNOTE-355 PFS data for the CPS $\geq$ 10 subgroup were presented alongside the PFS and OS projections reported within the TA639 CS to NICE (TA639: Tables 37, 40, 43 and 45; expert opinion estimates of PFS and OS were redacted). Publicly available information was presented for an alternative IO agent (Atezolizumab + nab-paclitaxel from TA639) to hold an informed discussion with clinical experts around the expected survivorship of patients with pembrolizumab since clinical experts remained blinded to the KEYNOTE-355 OS data.

Alongside the above information, a summary table reporting the summary study information and baseline characteristics of mTNBC RWE studies was also presented to clinical experts with the aim of facilitating discussion around the anticipated OS for the standard of care. These included Battisti et al 2018 [8], Deluche et al 2020 [6], Luhn et al 2019 [9] and Aly et al 2018 [7]. Clinical experts were aware of the RWE publications presented and were able to comment on those being more generalisable to the UK with regards to being able to inform OS projections for the standard of care chemotherapies. This information was used to validate long term projections versus external data for the taxane chemotherapy comparators and model selection within the original submission.

A qualitative process was used to elicit expert opinion ensuring everyone contributed to the discussion. Prior to being asked to provide their opinion on survival projections over time a brief discussion was held around the key differences between IMpassion-130 and KEYNOTE-355 (mainly; PD-L1 ascertainment, PFS endpoints & patient inclusion criteria amongst). OS estimates were then presented from TA639 and experts were asked to comment on expected survivorship over time based on their prior experience in using IOs to treat tumours. Drawing from prior IO experience, clinical experts noted the immunotherapeutic effect associated with IO agents and the likely timepoint this may start to be seen (36 months in Pembrolizumab + taxanes). Experts then went on to provide OS

estimates for standard of chemotherapy based on the data presented from TA639. The same process was followed for PFS estimates. However, the PFS Kaplan-Meier data from KEYNOTE-355 RCT data were presented prior to clinical experts being asked to comment on the PFS projections over time (based on TA639 survival modelling estimates).

All experts were asked to contribute their opinion, however, some declined to provide OS estimates beyond the IMpassion-130 follow up due to the absence of long term data. All experts recognised the immunotherapeutic effect associated with IO agents. Overall, [redacted] provided summary estimates for PFS and OS or commented on validity of projections noted by their colleagues during the discussion for Pembrolizumab + taxanes.
The same experts [redacted] were able to provide OS projections for the chemotherapy arm based on the RWE studies in mTNBC. Whilst experts were asked to provide estimates at different landmarks (Years; 1,2.3,10 & 20), they only provided 5 and 10 year estimate's for OS and PFS, noting that OS & PFS estimates for years 1 to 2 would be expected to be [redacted][12]. OS and PFS estimates provided by clinical experts (reported within the HTA submission) alongside RWE evidence were used in the parametric model selection process (outlined within the CS).

B6. CS, Section B3.3.1, Page 103 & Appendix P Section 4.3: Please provide a rationale for there being change-points in the marginal hazard functions (for both treatment groups) at Weeks 25, 40 and 52.

Two-phase parametric functions fit to the OS data were explored as sensitivity analysis in addition to the standard parametric distributions. We first used the cumulative hazard plots to identify potential cut point for the 2-phase models. Visual examination of the cumulative hazard plots in **Error! Reference source not found.** suggested week 25, 40 and 52 as potential turning points of the OS curves. Additionally, we used Chow tests, which is a statistical test estimating structural changes to the Kaplan Meier curve to further confirm the selection of cut-off points. With Chow test, the structural changes to the slope of the cumulative hazard curves (i.e. the hazard rate) were tested and the time point with the most pronounced change to the slope of the cumulative hazard curve was selected as the cut point. This approach was previously presented to NICE in the submission of Talimogene laherparepvec for treating metastatic melanoma [25]. The results of the Chow tests are shown in Figure 7. Optimal cut-off points were observed around week 25, 40 and 52 in the taxane subgroup. Note that cut-off points beyond week 60 were not recommended in the model, primarily due to the small number of events and heavy censoring after that.

Figure 6: ITT, Part 2, CPS≥10%, subgroup by on study chemotherapy – taxane subgroup (OS)

Figure 7: Results from the Chow Test for OS pembrolizumab + taxanes vs. chemotherapy arm ITT, Part 2, CPS≥10%, subgroup by on study chemotherapy – taxane subgroup (OS)

B7. CS, Section B3.3.1, Page 108: The CS states that "clinical experts suggested that survivorship declines rapidly after 3 years". Please confirm whether this should be interpreted as the risk of dying increases for patients surviving beyond 3 years?

Thank you for the clarification. During the clinical advisory board, clinical experts noted that TNBC is a very aggressive cancer and as such survival outcomes for metastatic TNBC are similar to those in other aggressive cancers such as lung cancer and that most patients diagnosed with metastatic disease which are subsequently treated with chemotherapy are expected to die within the first 3 years (also observed alongside a number of RWE studies). Further, most mTNBC patients treated with chemotherapy are unlikely to achieve 5-year survival and that and the survival rate with chemotherapy agents would be expected to be close to zero at 10 years.

We propose amending the above sentence to avoid misinterpretations around the long term OS hazard function for survivors beyond the 3 year timepoint, considering the clinical expert feedback received. The sentence should be amended as following: *"… clinical experts acknowledged that TNBC is a very aggressive cancer resulting in most patients dying rapidly within the first 3 years, with only a small % alive in 5 years (<10%) under optimal management and that survivorship at year 10 would be close to 0%*". This avoids imposing any further assumptions for the long term risk of death, since we would expect the small % of long survivors to have a lower risk of death of a result of mTNBC (but an increased risk of death due to all-cause mortality).

B8. Please comment on the relevance of a hazard ratio applied to a baseline lognormal model and the impact of this on the ICER for atezolizumab.

We acknowledge the methodological limitations associated with the application of a HR which has been derived under the assumption that proportionality holds and is subsequently applied upon the log normal curve in which the hazard is not assumed to be constant over time ([26]). This approach was followed due to lack of data for the population of interest from

IMpassion-130 that would enable us to explore more complex modelling for this comparison, including a varying relative treatment effect over time.

The use of a single time-invariant hazard ratio relies on the assumption that event hazards are directly proportional at all times throughout the network. However, the constant hazard ratio is also used to represent the “average” hazard ratio over time, therefore the failure of one or more of the links in an evidence chain to fully comply with the proportional hazards assumption does not necessarily indicate that a comparison between the intervention and any individual comparator may not in fact itself provide an accurate result.

B9. Please re-estimate the ICER versus atezolizumab by applying the hazard ratio calculated in A25 (predictive distribution) to a change-point survival function for pembrolizumab allowing for a deterioration/wane in the hazard function because of treatment discontinuation.

We interpret this request as being related to model functionality with regards to waning options available within the model. Please note that the current model can be used to generate analyses by applying alternative treatment waning assumptions on the selected pembrolizumab + taxane OS survival extrapolations at specific timepoints (as opposed to the alternative application of the SEER dataset for waning). This sets the OS HR = 1 between intervention and comparator at the selected timepoint.

Regarding the A25 -Random Effects Model (REM) NMA results as per ERG’s request (Table 7 Table 8 above), these have been incorporated in the updated model, within the “**Effectiveness**” sheet; **dropdown menus I19 & I20**. Both [redacted], therefore the base-case cost-effectiveness results would not impacted.

Some fundamental uncertainties exit when prior for heterogeneity is being derived from studies across a variety of disease areas and outcomes, as it is not known whether the actual heterogeneity between studies in the evidence base of interest is greater or less than the heterogeneity of studies used to estimate an informative prior. Additionally, informative priors can exert undue influence in sparse networks comprising few studies. Therefore, results should be interpreted with caution [14].

Given these limitations, we consider that using fixed effects NMA results more indicative for interpretation since the use of REM would artificially inflate uncertainty in PSA comparisons without allowing us to check the face validity of the cost-effectiveness

estimates. Considering the limitations noted above, we have not provided the cost-effectiveness results requested using the inputs from A25 (REM NMA).

B10. CS, Section 3.4.1, Page 121: Please comment on the relationship between the compliance to completing HRQL assessments and deteriorating health. Please explain how missing HRQL assessment have been handled in the analyses. Please comment on why the impact of age, gender and other factors were not assessed alongside the effect of Grade 3+ AEs.

Compliance with regards to HRQoL assessment refers to the proportion of patients who completed the PRO questionnaires among those who were expected to complete PROs at each time point excluding those missing by design (refers to death, discontinuation, translations not available, and no visit scheduled). As health deteriorates we would expect compliance rates for HRQoL completion rates to drop. Compliance rates may also be affected by the limited study follow up. The time point of 15 weeks for analysis of compliance was selected for the HRQoL assessment based on a prespecified required minimum completion rate of 60% and compliance rate of 80% to minimize the impact of missing data assumptions on PRO analysis outcomes.

We can confirm that univariate analyses were performed to explore whether the UK utility values were associated with patient baseline characteristics including; age, ECOG, baseline PD-L1 level and randomisation stratum and how other factors that could potentially be mediated by the KEYNOTE-355 interventions (such as treatment, Time-to-death category, PFS by BIRC, Grade 3-5 AE and AE Status) might be related to the utility score.

As described within the HTA submission, linear-mixed effect models were conducted for each of the above factors using the longitudinally measured UK utility value as the outcome and individual factors of interest as the single covariate. A preliminary multivariate analysis model was developed including all of the above individual baseline and time-dependent factors.

Based on the statistical significance of covariates from the preliminary multivariate model and clinical interpretations, a final multi-variate linear mixed effect was chosen including the ECOG, PFS by BIRC, Time to Death category and AE status (patients during Grade 3+ AEs). None of the other baseline characteristics tested, including: age, gender and PD-L1 status were significant.

Alternative models were considered for the purposes of the economic model including the Time to death analysis, and the utility by disease progression status (with or without the presence of Gr3+ AEs in the PFS state) as reported within the HTA submission. These models were run to derive the LS mean values that could be used in the economic model directly. The results of the final utility analyses models were provided in the original confidential Appendices submitted.

B11. CS, Section B3.6.1, Table 75 page 143: Please clarify:

a. the interpretation of the columns labelled as lower and upper.
b. the rationale for leaving some variables fixed in the PSA, such as the incidence of AEs, but changing others such as relative dose intensity.
c. whether correlations, such as the dose received of pembrolizumab and duration of survival, or in the subsequent therapy acquisition costs for the three interventions have been appropriately included.
d. The rationale for determining when a standard error of 20% of the mean was used. It is noted that this leads to an implausible low potential recommended dietary intake (RDI) estimates for pembrolizumab [redacted] When the company has decided to use a standard error of 20%, confirm that standard errors have actually been used rather than standard deviations. For example, the cost for delivering complex chemotherapy has, at face value, a wide confidence interval (mean £371, 95% CI £215 to £529) for a fairly common procedure.
e. how the uncertainty in the cost of PDL-1 testing has been derived.
f. how the lower and upper values for the parameters in the survival models have been computed; if these are univariable 95% confidence intervals, please confirm that uncertainty in the economic model covers the whole joint distribution when doing the PSA.

Please see below our response to the methodology used, with specific question points being addressed further below.

For the DSA, the focus of the analyses was around testing the 95% lower and upper values, whereas for the PSA, the uncertainty focuses around the distribution of inputs. We confirm our understanding that 20% of the mean is commonly used in the absence of Standard Error (SE) or the Standard Deviation (SD) data for the variation of costs. However, a more accurate approach was followed for the one-way sensitivity analysis as opposed to varying the mean cost by 20% directly. This was preferred to ensure the inputs varied in the DSA and the PDS were consistently evaluated.

For costs in the DSA the 95% upper and lower confidence intervals (reported in Table 75 of the CS) were derived by using the appropriate PSA distributions and assuming a SE of 20% of the mean value when SE and SD was not available from KEYNOTE-355 (like in the case of unit costs). For all clinical parameters from KEYNOTE-355 varied in the DSA, the SD has been used to estimate the associated SE, which was then used to determine the upper and lower values in Table 75 (updates of this table are included at the end of this document). The PSA Setup sheet clearly notes were the SE was assumed to be equal to 20% of the base-case value and when the SD from KEYNOTE-355 was used to derive the SE.

For example, Deliver Simple Parenteral Chemo at First Attendance = £241 and is varied in the PSA using the gamma distribution. The lower 95% CI (£156) is calculated in the PSA Setup worksheet in cell V140 (upper 95% CI is in W140 (£344)). These values then feed into the upper and lower variation in the "DSA_setup" and used in the one-way sensitivity analyses.

We consider the above methodology to be more accurate versus simply varying costs with a +/- 20%. It also ensures consistency between the inputs varied in the DSA and PSA. In addition, it can be perceived as more conservative since the upper and upper and lower estimates derived this way are wider.

Response to specific points above:

a) Lower and Upper refer to the 95% CI estimates used in the one way sensitivity analyses. See explanation above on how these were derived.
b) This approach is in line with previous oncology HTA submissions for computational purposes and due to data limitations; costs including the AE management costs and utility parameters have been varied and these would adequately quantify the impact of the AEs not being varied within the economic model.
c) Correlations specific to the doses of pembrolizumab received, duration of survival, or in the subsequent therapy have not been included in the model for computational purposes and due to complexity in implementing these. However, all key parameters are varied in the DSA and can be used to identify model drivers. Finally, the PSA explores uncertainty around the distributions of all model parameters.
d) Thank you for your comment regarding the RDI of Pembrolizumab. We would like to take the opportunity to clarify that RDI relates to Relative Dose Intensity, not recommended daily intake. Further, the upper and lower RDI values were

incorrectly calculated using the approach described above and assuming a 20% SE in the original model hence the discrepancy noted by the ERG. New RDI values have been generated for the economic model for Pembrolizumab + taxanes and taxane comparators based on the actual RDI Standard Deviation (SD) from KEYNOTE-355. These new estimates are now included in the CE model and are more consistent with the ERG's feedback. Further with regards to the unit cost associated with delivering complex chemotherapy, we can confirm that the lower value used within the company submission Table 75 of £215 is a typographical error (addressed in C6 below; the correct lower value used within the model is £239.88).

e) See response above; 20% SE was assumed for the standard error of the mean when standard error were not reported/available (in the case of costs).

f) Uncertainty in the parametric model for PFS is represented by the variance-covariance matrix of the parameter estimates. We can confirm the joint distributions are considered for the PSA.

B12. Appendix M.5, Figure 20, Page 160: There are six "lines" but only four mentioned in the key. Please clarify is discrepancy.

We thank the ERG for identifying this discrepancy. The dashed lines refer to the Kaplan Meyer data of KEYNOET-355 – applicable to Pembrolizumab + taxanes only in this instance (OS: light blue, PFS: orange). The solid lines represent extrapolations of this data based on the fitted parametric models for Pembrolizumab + taxanes and the relevant comparator, in this instance Atezolizumab + nab-paclitaxel. Green and Purple solid lines represent the modelled OS and PFS respectively for Atezolizumab + nab-paclitaxel, based on the ITC comparison results reported within the CS Section 2.9 An updated graph with corrected series labels is presented below for clarity. The model has also been amended for clarity. For Atezolizumab + nab-paclitaxel the model does not include observed KM data since these were not available from the Rugo et al 2020 publication (hence 6 curves only included in the graph output below) [23].

Figure 8: New example of graph output of modelled PFS and OS for Atezolizumab + nab-paclitaxel comparisons

B13. Please clarify why it was decided to pool the duration of AEs between treatment arms within the model when each arm has a different AE profile.

The duration of AEs between the treatment arms was pooled to increase the number of records used for the analysis considering the current KEYNOTE-355 study follow up. This decision was made to provide a more robust estimate of mean AE duration which is subsequently applied across both treatment arms of the economic mode). The impact of this assumption on the ICER is anticipated to be very limited since the cost of AEs as % of total costs is very limited _([redacted]).

B14. It is stated that the AE disutility associated with the time to death approach is intrinsically factored into the analyses. Please clarify how the pooled analyses used in the model differentiates between different AE profiles in the study arms. Further, discuss how this approach would incorporate AEs that had been initiated and resolved between rounds of EQ-5D-3L administrations.

The time-to-death utility approach was favoured for the base case as the primary source of utilities for the economic model since overcomes the limited data collection informing the post-progression health state utility values from KEYNOTE-355. The pooled utility analyses within the model do not differentiate between the different AE profiles within the model, rather, the QALY accrual is based on the proximity to death. AEs initiated and resolved between rounds of EQ-5D administration may not be reflected on patient's response, however, this is a limitation that is applicable for all ED-5D related analyses including those by disease progression status.

As noted within the company submission the time-to-death utility analysis approach used for the base case does not account for AE related disutilities to avoid imposing any further assumptions for data analysed and to ensure that the number of questionnaires that remained in each time-to-death category was not depleted. Within the submission we state that AE disutility is intrinsically factored within this method since the main factor and key driver associated with QALY gains derived would be the proximity to death. The effects of alternative utility sources (treatment pooled and treatment specific) with inclusion of AE related disutilities are provided within the submission and had a limited impact on the ICER (scenarios 16 & 17 with original ICERs [redacted]please refer to updated analyses below for new impact on ICER).

B15. Please clarify what 'treatment doses as planned' means on page 129 of the CS. Would someone who had a reduced dosage be omitted from successful planned values?

The percentage of actual vs expected number of administrations per subject was defined as the percentage of actual number of administrations per subject divided by the expected number of administrations per subject. The figures reported on page 129 of the CS have provide a summary of the % of patients receiving the actual vs. expected number of administrations regardless of the dosage itself. Therefore we can confirm that these analyses do not exclude any patients due to reduced dosage. It should also be noted that as per KEYNOTE-355 protocol reduced dose was not allowed for pembrolizumab.

B16. Table 58 (page 130 of the CS). Please clarify whether there may be more administrative censoring in the intervention arm for those in 4L+ due to spending more time in 1L.

For the purposes of this response we interpret "administrative censoring" referring to censoring due to the cut-off date as a result of the IA2 DBL for KEYNOTE-355 (19th of December 2019). We anticipate that as patients may stay longer on study medication in active arm of KEYNOTE-355, more patients with 4L+ therapy may be censored due to the cutoff date for IA2 in active treatment arm versus in the control arm. However, considering that TNBC is a very aggressive type of cancer, the impact of subsequent therapies on the ICER is expected to be limited since the majority of costs would be incurred in the 2L stage. As patients continue on subsequent lines of therapy (beyond 2L+) they would be are anticipated to spend less time on treatment as their disease worsens. Finally, this analysis does not factor in subsequent therapy competitor discounts (ie for Eribulin – TA515) and therefore the true cost to the NHS would be expected to be lower than that included in this submission.

B17. Currently the model does not allow patients to discontinue pembrolizumab within the first two years but to remain on taxane treatment. Please clarify whether this was the intention and whether this was observed in the RCT.

In KEYNOTE-355 the maximum treatment duration for pembrolizumab was for up to a maximum of 35 cycles as per KEYNOTE-355 trial protocol [22]. However, chemotherapy treatment (in this instance taxane) could be continued beyond that timepoint at investigator's discretion (section 5.8 of KEYNOTE-355 protocol) [27].

We would like to take the opportunity to clarify that the model does indeed allow for treatment discontinuation for the pembrolizumab within the first two years. The model uses the ToT data from KEYNOTE-355 to estimate accurately the time on treatment. Further, the model

applies a 2 year cap on the pembrolizumab drug costs to reflect the maximum of 35 cycles of pembrolizumab in the drug costs calculation component (no patient received ≥35 administrations). The ToT curve models time to treatment discontinuation for both components within the first 2 years, whereas from that point onwards it represents the discontinuation in represents the ToT to taxanes alone.

B18. Please clarify whether Scenario 7 in Table 86 of the CS is unfavourable to atezolizumab. If treatment is continued beyond 2 years for atezolizumab, why should atezolizumab be subject to the same waning effect as pembrolizumab where treatment was not continued beyond two years?

A number of limitations with regards to this comparison are listed in the submission which justify our approach to position this as an alternative secondary comparator for the purposes of this HTA. These arise from differences in PD-L1 ascertainment differences and lack of CPS $\geq$ 10 score data to inform the economic modelling.

The NICE AC recently concluded during TA639 (and in all other metastatic BC appraisals) that in the absence of clinical evidence from the pivotal RCTs, assuming arbitrary treatment waning was not relevant for inclusion in the base-case assumptions. For the above reasons waning was not included in the base case comparisons versus Atezolizumab to avoid any further assumptions being applied to the long term projections. Scenario 7 was only provided for completeness since similar analyses were presented for the comparisons versus taxanes.

B19. The ERG believe that there is an error in the way the probability of death per cycle has been calculated in the 'Life Table' worksheet. The ERG believe that P23:P69 should be replaced by '=1-(1-O23)^(cycle.length*days_week/days_year)'

Thank you for identifying this error in the calculation. We had interpreted qx in the ONS life tables as the 'annual rate of death'. We understand that qx is, in fact, the annual probability of death and therefore, we have updated the formula in P23:P69 as outlined above to reflect this.

B20. Please clarify how the results for pembrolizumab+taxane versus docetaxel were generated (CS, Table 79). In the model, worksheet "Model Specifications", dropdown menu in cell H51, there is not an option for choosing docetaxel as a comparator.

Please see response to Question B.4.k. The option to select docetaxel is not included in the "Model specifications" sheet. Instead to generate comparisons versus docetaxel, please navigate into the "**Drug Cost Input**" sheet, and from the dropdown menu in cell **I28**, select the option "Yes" to the scenario (applying docetaxel drug costs to paclitaxel comparator arm). This option replaces the paclitaxel drug and pre-medication costs to those of docetaxel. The base case results would be updated automatically. Any OWSA and PSA results would need to be rerun after this selection is applied in the model.

B21. CS, page 154: The company states that "*PSA was only conducted for chemotherapy comparators specific in the final scope. Due to uncertainty in the ITC comparisons and comparability across populations, it was not deemed methodologically relevant to conduct PSA versus Atezolizumab + nab-paclitaxel*." The ERG believe that the committee are likely to want to see the probabilistic results when comparing pembrolizumab and atezolizumab. Please run this comparison and provide results.

Considering the data limitations, we do not believe a PSA analysis would provide robust results for discussion. The availability of unknown competitor discounts means that PSA results become less relevant also (since the Pembro CAA is used). The assumptions formulating the comparisons versus atezolizumab + nab-paclitaxel differ to those put forward for chemotherapies. Therefore, prior to running the PSA for this comparison, base case selections should be updated to reflect those put forward in the company's base-case (please refer to original submission), such as ITC common comparator, PFS assessment type, option for ToT amongst others. PSA results can be extracted from the "PSA Results" sheet by selecting the relevant comparator.

B22. CS, Section B.3.5.2 and Model. Please clarify whether the proportion of patients who receive second line therapy in each treatment group has already taken death and treatment beyond progression into account. We note that in the model, it is possible to remain on initial treatment after progression.

The proportion of subjects who received subsequent anticancer therapies post study treatment discontinuation, is the % of patients who discontinue treatment and go on to receive a subsequent therapy. ToT data from KEYNOTE-355 were used to estimate the time on treatment for pembrolizumab + taxanes and taxanes chemotherapy comparator (chemotherapy could be continued at beyond the ~2 years at investigators discretion).

Treatment duration for each subsequent medication was defined as the number of days between the start date and the stop date of the medication, or the censoring date of overall survival if the treatment was still ongoing and the start date of the medication was not later than the censoring date of overall survival, or the database cut-off date if the treatment was still ongoing and the start date of the medication was after the censoring date of overall survival. Therefore, both treatment beyond progression and death were factored in % of patients receiving subsequent therapies.

B23. There is a disparity between the unit cost of an oncology visit which is £143.72 in the CS Table 64 and £142.58 in model worksheet 'Resource Use'. Please clarify which value is correct.

We thank the ERG for identifying this discrepancy. We note that there is a typographical error in Table 64 of the CS oncologist visit unit cost (digits reversed in CS table £143.72 versus the £142.73 in NHS-Reference costs database; see table below for clarity).

Table 16: Corrected Oncology visits unit cost within the economic model (for one-off diagnosis at PFS health state)

Currency Code	Currency Description	Service Code	Service Description	National Average Unit Cost
WF01A	Non-Admitted Face-to-Face Attendance, Follow-up	800	Clinical Oncology (Previously radiotherapy)	**£142.73**

We can confirm that the value £142.58 used to cost the oncology visits within the model in the worksheet of "**Resource Use – cell reference D19**" relates to an alternative NHS-Reference cost code and was incorrectly included in the units costs used within the model (within the one-off PFS diagnosis cost calculation only).

The model has now been updated to include the correct unit cost included in Table 65 of the CS (£142.73: "NHS ref costs; 2018-2019, CL Sheet: WF01A Clinical Oncology (Previously Radiotherapy); Service code: 800"; see table above).

B24. The ERG believes that in some parts of the model (worksheet 'Raw_Resource Use') the company has assumed a month consists of 4 weeks. If so, please provide updated analyses using a more accurate estimate.

Thank you for identifying this discrepancy. We have updated our calculations in the Raw_Resource Use worksheet to reflect the monthly frequency. Specifically, we have updated cells **E23, G23** and **G24.**

B25. There is an apparent discrepancy between the CS Table 66 (1 per 2 months) and the model worksheet 'Raw_Resource Use', cell I38 (every 3 months) for the frequency of community nurse visits in the PPS ongoing costs. Please clarify which is the correct value.

Thank you for noting this discrepancy. The model should reflect a frequency of community nurse visits of **1 per 2 months** in the PPS ongoing costs. This has been updated in cell **G38** of the 'Raw_Resource Use' worksheet.

B26. Model, worksheet 'AE costs'. The ERG believes there is an error in worksheet 'AE costs'; the values in cells T40:T42 are not influencing the total AE costs for the pembrolizumab+taxane and taxane arms. Please clarify if that is the case and if so, correct this problem.

Thank you for identifying this issue. The inputs in cells F79:F81 of the 'Raw_AE' worksheet were stored in a text format and were therefore, recognised as a 0 value in cells T40:T42 of the 'AE costs' worksheet. We have updated the format of cells **F79:F81** of the 'Raw_AE' worksheet accordingly and total AEs costs in **H44:R44** of the 'AE_cost' worksheet now incorporate the cost of all the listed AEs. Please refer to the table below which presents the updated AE management costs.

Table 17: Updated weighted AE costs applied in the economic model

Grade 3+ AE	Pembrolizumab + Taxanes	Taxane comparator	Atezolizumab + nab-paclitaxel comparator
Original CS estimates used	[redacted]	[redacted]	[redacted]
Updated estimates at ERG clarification stage	[redacted]	[redacted]	[redacted]

B27. Please clarify the rationale for assuming that patients receiving atezolizumab in combination with nab-paclitaxel incur the same costs for subsequent treatment (2nd line+) as patients who received pembrolizumab in combination with a taxane.

No access to Patient Level Data (PLD) mean that the granularity necessary for inclusion within the economic model was not available, therefore additional assumptions from

KEYNOTE-355 would had been necessary with regards to the treatment duration. Clinical experts noted that subsequent treatment data from KEYNOTE-355 (adjusted for the UK setting) adequately resented the current treatment options available within the NHS.

Based on the above limitations, a simplifying assumption was made for modelling purposes regarding the distribution of subsequent therapies with regards to Atezollizumab + nab-paclitaxel. The lack of IO agents for 2L+ subsequent therapies means that the impact on assumption on the cost-effectiveness results is likely to be very limited.

Section C: Textual clarification and additional points

Textual and editorial clarifications to the ERG's requests are included below for completeness. Please note that a new base case analysis is put forward with updated cost-effectiveness results presented below.

C1. CS, Table 9 (Document A) and Table 83 (Document B). Please clarify whether there are typos in the results for pembrolizumab + taxanes versus the secondary taxane comparator.

We thank the ERG for identifying these typographical errors (in which the some values within the table were reversed by error for the docetaxel comparison PSA results in Document A [Table A] and Document B of the submission [Table 83]). These have been corrected in the updated analyses provided in **Section D** below.

C2. Please confirm that there is typo in table 16 of the CS, and it should be 'progression-free survival' where it reads 'overall survival'.

We thank the ERG for identifying this typo. We confirm that there is a typographical error in Table 16 of the CS which should refer to "Progression-Free survival". The PFS estimates included in the table are correct, therefore an updated table version has not been provided.

C3. Please clarify whether there is a typo in the CS, page 108. Should it be 'preferred versus the log-normal'?

We thank the ERG for spotting this typographical error. We confirm that within the CS page 108, regarding the OS versus taxanes, log-logistic was selected as the most appropriate

model. Therefore the "*preferred versus the log-logistic"* should be changed to read "*preferred versus the log-normal"* for taxane chemotherapies.

C4. Please clarify whether there is a typo in table 56, and the value for PFS utility pooled should be that as in table 52.

We thank the ERG for identifying this typographical error. We confirm that there is a typo in Table 56 for PFS utility ([redacted]). The corrected value should be as per Table 52: [redacted].

C5. Please confirm that there are typos in the utility inputs within table 75 of the CS (page 143). We suspect the midpoint values have been reversed.

We thank the ERG for identifying this typographical error which was contained within the 95% Lower and Upper estimates provided in reverse for each time to death category. Additional typographical errors were identified in response to the ERG's questions (located at the 3rd decimal for some of the 95% upper and lower values). These did not affect the model since used the correct SE inputs. Please see the updated model inputs Table 18 below.

C6. CS, table 75 (page 144). Please clarify if there is a typo in the value labelled as 'lower' for the administration costs item 'Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance'.

We thank the ERG for identifying this typo. The correct 95% Lower estimate within this table should be **£239.88** (which is the value used within the original model submitted). For methodology please refer to response in B11 above. An updated version of Table 75 is provided below (Table 18) which highlights the updated parameters & settings for clarity.

Table 18:Summary of variables applied in the economic model used in base-case (updated Table 75 of original submission)

Parameters	Mean / Deterministic value	95% Lower Value	95% Upper Value	Distribution used in PSA	Submission section
General Information					
Model cycle length (weeks)	1	NA	NA	Not varied in PSA	See Section B.3.2
Model time horizon (years) – post ERG discussion	**35**	NA	NA	Not varied in PSA	
Discount rate: Costs	3.5%	NA	NA	Not varied in PSA	

Discount rate: Health outcomes	3.5%	NA	NA	Not varied in PSA	
Vial sharing	0%	NA	NA	Not varied in PSA	
Patient Information					
Patient Age	[redacted]	NA	NA	Not varied in PSA	See Section B.3.2
Proportion female	[redacted]	NA	NA	Not varied in PSA	
Average patient weight (kg)	[redacted]	[redacted]	[redacted]	Not varied in PSA	
Mean Body Surface Area (m^2)	[redacted]	[redacted]	[redacted]	Not varied in PSA	
Estimated eGFR mean	[redacted]	NA	NA	Not varied in PSA	
Utility Inputs by disease progression					
Utility Inputs by Time-to-Death (pooled); <u>no impact on model correct SEs used</u>					
Utility based on time to death [0, 29] days	[redacted]	[redacted]	[redacted]	[redacted]	See Section B.3.4
Utility based on time to death [30, 89] days	[redacted]	[redacted]	[redacted]	[redacted]	
Utility based on time to death [90, 179] days	[redacted]	[redacted]	[redacted]	[redacted]	
Utility based on time to death [180, 359] days	[redacted]	[redacted]	[redacted]	[redacted]	
Utility based on time to death [≥ 360] days	[redacted]	[redacted]	[redacted]	[redacted]	
Intervention Costs (per administration)					
Drug costs (per administration for Pembrolizumab + taxanes)					
Pembrolizumab	£5,260.00	NA	NA	Not varied in SA	See Section B.3.5.1
Paclitaxel (no pre-medication costs)	24.62	NA	NA	Not varied in SA	
Nab-paclitaxel (with Pembro)	£430.50	NA	NA	Not varied in SA	
Drug costs (per administration for comparators)					
Paclitaxel drug cost (no pre-medication costs)	24.62	NA	NA	Not varied in SA	See Section B.3.5.1
Docetaxel drug cost (& pre-medication costs)	£28.67	NA	NA	Not varied in SA	
Atezolizumab	£2,665.38	NA	NA	Not varied in SA	
Nab-paclitaxel (with Atezolizumab)	£450.50	NA	NA	Not varied in SA	
Relative dose intensity (intervention)					
Pembrolizumab	[redacted]	[redacted]	[redacted]	Beta	See Section B.3.5.1
Paclitaxel (with Pembrolizumab)	[redacted]	[redacted]	[redacted]	Beta	
Nab-paclitaxel (with Pembrolizumab)	[redacted]	[redacted]	[redacted]	Beta	
Relative dose intensity (comparators)					
Paclitaxel alone	[redacted]	[redacted]	[redacted]	Beta	
Docetaxel alone (set equal to paclitaxel)	[redacted]	[redacted]	[redacted]	Beta	

Atezolizumab	[redacted]	[redacted]	[redacted]	Beta	
Nab-paclitaxel (with Atezolizumab)	[redacted]	[redacted]	[redacted]	Beta	
Subsequent therapy acquisition costs					
Pembrolizumab + taxanes	[redacted]	[redacted]	[redacted]	Gamma	See section B.3.5.2
Taxane chemotherapy comparator	[redacted]	[redacted]	[redacted]	Gamma	
Atezolizumab + nab-paclitaxel (set equal to Pembro+taxanes)	[redacted]	[redacted]	[redacted]	Gamma	
Administration costs for IV: intervention, comparators and subsequent therapies					
Deliver Simple Parenteral Chemotherapy at First Attendance	£241.06	£156.00	£344.33	Gamma	See Section B.3.5.3
Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance **(Typographical error. No model impact, correct value used in original model)**	£370.68	**£239.88**	£529.48	Gamma	
Pre-medication administration costs	**£122.00**	**£78.95**	**£174.27**	Gamma	
Pre-medication acquisition costs (paclitaxel and docetaxel only)					
Paclitaxel pre-medication costs	£5.91	£3.82	£8.44	Gamma	B.3.5.6
Disease Management Costs					
PFS one off cost on 1st cycle	**£299.50**	**£193.72**	**£427.59**	Gamma	See Section B.3.5.4
PFS weekly cost in subsequent cycles	**£75.01**	**£48.10**	**£106.16**	Gamma	
PPS weekly cost in subsequent cycles	**£71.70**	**£44.98**	**£99.27**	Gamma	
Cost of terminal care (one-off cost)	£8,166.54	£5284.96	£11665.13	Gamma	
% AE Pembrolizumab + taxanes from KEYNOTE-355					
Anaemia	[redacted]	NA	NA	Not varied in SA	See Section B.3.3.5
Leukopenia	[redacted]	NA	NA	Not varied in SA	
Neutropenia	[redacted]	NA	NA	Not varied in SA	
Thrombocytopenia	[redacted]	NA	NA	Not varied in SA	
ALT increased	[redacted]	NA	NA	Not varied in SA	
AST increased	[redacted]	NA	NA	Not varied in SA	
Neutrophil count decreased	[redacted]	NA	NA	Not varied in SA	
Platelet count decreased	[redacted]	NA	NA	Not varied in SA	
White blood cell count decreased	[redacted]	NA	NA	Not varied in SA	
Diarrhoea	[redacted]	NA	NA	Not varied in SA	
Hypothyroidism	[redacted]	NA	NA	Not varied in SA	
Vomiting	[redacted]	NA	NA	Not varied in SA	

Fatigue	[redacted]	NA	NA	Not varied in SA	
Abdominal abscess	[redacted]	NA	NA	Not varied in SA	
Pneumonia	[redacted]	NA	NA	Not varied in SA	
Blood alkaline phosphatase increased	[redacted]	NA	NA	Not varied in SA	
Lymphocyte count decreased	[redacted]	NA	NA	Not varied in SA	
Hyperglycaemia	[redacted]	NA	NA	Not varied in SA	
Lymphopenia	[redacted]	NA	NA	Not varied in SA	
Pneumonitis	[redacted]	NA	NA	Not varied in SA	
Grade 2+ diarrhoea	[redacted]	NA	NA	Not varied in SA	
Grade 2+ colitis	[redacted]	NA	NA	Not varied in SA	
% AE Taxane chemotherapy comparator arm from KEYNOTE-355					
Anaemia	[redacted]	NA	NA	Not varied in SA	
Leukopenia	[redacted]	NA	NA	Not varied in SA	
Neutropenia	[redacted]	NA	NA	Not varied in SA	
Thrombocytopenia	[redacted]	NA	NA	Not varied in SA	
ALT increased	[redacted]	NA	NA	Not varied in SA	
AST increased	[redacted]	NA	NA	Not varied in SA	
Neutrophil count decreased	[redacted]	NA	NA	Not varied in SA	
Platelet count decreased	[redacted]	NA	NA	Not varied in SA	
White blood cell count decreased	[redacted]	NA	NA	Not varied in SA	See Section B.3.4.4
Diarrhoea	[redacted]	NA	NA	Not varied in SA	
Hypothyroidism	[redacted]	NA	NA	Not varied in SA	
Vomiting	[redacted]	NA	NA	Not varied in SA	
Fatigue	[redacted]	NA	NA	Not varied in SA	
Abdominal abscess	[redacted]	NA	NA	Not varied in SA	
Pneumonia	[redacted]	NA	NA	Not varied in SA	
Blood alkaline phosphatase increased	[redacted]	NA	NA	Not varied in SA	
Lymphocyte count decreased	[redacted]	NA	NA	Not varied in SA	
Hyperglycaemia	[redacted]	NA	NA	Not varied in SA	

Lymphopenia	[redacted]	NA	NA	Not varied in SA	
Pneumonitis	[redacted]	NA	NA	Not varied in SA	
Grade 2+ diarrhoea	[redacted]	NA	NA	Not varied in SA	
Grade 2+ colitis	[redacted]	NA	NA	Not varied in SA	
AE management costs (treatment specific)					
Pembrolizumab + taxanes	[redacted]	[redacted]	[redacted]	Gamma	See Section B.3.5.5
Taxane chemotherapy comparators	[redacted]	[redacted]	[redacted]	Gamma	
Atezolizumab + nab-paclitaxel	[redacted]	[redacted]	[redacted]	Gamma	
Survival Modelling					
Progression-Free Survival					
PFS parametric curve fitting: Pembrolizumab in combination with taxanes					
Piecewise 9 week KM + Weibull: Parameter A	[redacted]	[redacted]	[redacted]	Multivariate Normal	See section B.3.3.2
Piecewise 9 week KM + Weibull: Parameter B	[redacted]	[redacted]	[redacted]	Multivariate normal	
PFS parametric curve fitting: Taxane chemotherapy comparators					
Piecewise 9 week KM + Log-normal: Parameter A	[redacted]	[redacted]	[redacted]	Multivariate normal	See section B.3.3.2
Piecewise 9 week KM + Log-normal: Parameter B	[redacted]	[redacted]	[redacted]	Multivariate normal	
Overall Survival					
OS parametric curve fitting: Pembrolizumab in combination with taxanes					
Full Log-normal: Parameter A	[redacted]	[redacted]	[redacted]	Multivariate normal	See section B.3.3.1
Full Log-normal: Parameter B	[redacted]	[redacted]	[redacted]	Multivariate normal	
OS parametric curve fitting: Taxane chemotherapy comparators					
Full Log-logistic: Parameter A	[redacted]	[redacted]	[redacted]	Multivariate normal	See section B.3.3.1
Full Log-logistic: Parameter B	[redacted]	[redacted]	[redacted]	Multivariate normal	
Time On Treatment					
ToT parametric curve fitting: Pembrolizumab in combination with taxanes					
Full Weibull: Parameter A	[redacted]	[redacted]	[redacted]	Multivariate normal	See section B.3.3.3
Full Weibull: Parameter B	[redacted]	[redacted]	[redacted]	Multivariate normal	
ToT parametric curve fitting: Taxane chemotherapy comparators					
Full Log-logistic: Parameter A	[redacted]	[redacted]	[redacted]	Multivariate normal	See section B.3.3.3
Full Log-logistic: Parameter B	[redacted]	[redacted]	[redacted]	Multivariate normal	
PD-L1 testing by Assay					
Pembrolizumab PD-L1 positive 22C3 Dako Assay	£106.20	£68.73	£151.70	Gamma	See section B.3.5.6
Atezolizumab PD-L1 positive patient with SP142 Assay	£278.49	£180.23	£397.80	Gamma	

C7. Appendix P, section 5.1, page 44. Please clarify if there is a typo where the company, regarding incorporating SEER survival data, states that *"We applied the constant hazard rate to the OS models in both pembrolizumab and SoC arms from the start of year 5, assuming the long-term survival trend was independent of treatment received.*"

We thank the ERG for requesting further clarification on this component of the submission. We can confirm that in this scenario, the hazard rate from SEER data analysis is incorporated after 4 years (48 months). To minimise confusion we confirm that this be changed to "constant hazard rate from SEER is applied **after** 4 years" instead to minimise confusion.

Additional textual clarifications offered by the Company identified during ERG response questions:

We would like to take the opportunity to amend the following sentences in the submission documents to avoid any further confusion with regards to the SmPC. The anticipated licence for this indication will be to [redacted](although a 2 year stopping rule is applied in KEYNOTE-355 in the pembrolizumab component; refers to typographical error at page 128)

Further text clarification pertaining to Question B17:

- Page 127 of CS should be amended – edits proposed are underlined and in blue font: "*The maximum treatment duration for pembrolizumab* as per KEYNOTE-355 was *for 35 infusions (or approximately 2 years), however, chemotherapy treatment could be continued beyond this point".* This reflects the draft SmPC submitted which specifies treatment to progression or unacceptable toxicity.

- Pages 128 & 129 if CS should be amended – edits proposed are underlined and in blue font: "*Further, the intervention component costs of pembrolizumab were capped at 2 years (week 104 in model), which is the maximum treatment duration for pembrolizumab as per SmPC"*, should be changed to "*….which is the maximum treatment duration for pembrolizumab "*as per KEYNOTE-355 RCT design".

Section D: Updated cost-effectiveness results

Changes implemented to formulate the new base case: longer time horizon: 35 year time horizon (as per ERG discussion and from quick review of previous mBC HTAs) and model updates noted above: correction in Resource use estimates, AE management costs, updated life tables formula and RDI estimates.

Model version: [redacted]

D.1: Updated Base Case results

D.1.1: Base-case incremental cost-effectiveness analysis results for Pembrolizumab versus paclitaxel (primary chemotherapy comparator)

Table 19: Updated Base-case results versus paclitaxel from deterministic analysis using list prices

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Paclitaxel comparator	[redacted]	1.826	[redacted]	-		
Pembrolizumab + taxanes**	[redacted]	3.965	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, ** Confidential discounts in place for nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

Table 20: Updated Base-case results versus paclitaxel from deterministic analysis using list prices for comparators with Pembrolizumab CAA

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline
Paclitaxel comparator	[redacted]	1.826	[redacted]	-		
Pembrolizumab + taxanes**	[redacted]	3.965	[redacted]	[redacted]	[redacted]	£27,808
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, ** Confidential discounts in place for nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

D.1.2: Base-case incremental cost-effectiveness analysis results for Pembrolizumab versus docetaxel (secondary chemotherapy comparator)

Table 21: Updated Base-case results versus docetaxel from deterministic analysis using list prices

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Docetaxel comparator	[redacted]	1.826	[redacted]	-		
Pembrolizumab + taxanes**	[redacted]	3.965	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, ** Confidential discounts in place for nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

Table 22: Updated Base-case results versus docetaxel from deterministic analysis using list prices for comparators with Pembrolizumab CAA

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Docetaxel comparator	[redacted]	1.826	[redacted]	-		
Pembrolizumab + taxanes**	[redacted]	3.965	[redacted]	[redacted]	[redacted]	£34,184
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, ** Confidential discounts in place for nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

D.1.3: Base-case incremental cost-effectiveness analysis results for Pembrolizumab versus versus Atezolizumab + nab-paclitaxel (secondary IO comparator for PD-L1 +ve patients)

Table 23: Updated Base-case results versus Atezolizumab + nab-paclitaxel from deterministic analysis using LIST prices for both comparators

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Atezolizumab + nab-paclitaxel	[redacted]	2.295	[redacted]	-		
Pembrolizumab + taxane**	[redacted]	3.965	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years ** Confidential discounts in place for Atezolizumab and nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

Table 24: Updated Base-case results versus Atezolizumab + nab-paclitaxel from deterministic analysis using list prices for comparator with Pembrolizumab CAA

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Atezolizumab + nab-paclitaxel	[redacted]	2.295	[redacted]	-		
Pembrolizumab + taxane	[redacted]	3.965	[redacted]	[redacted]	[redacted]	Dominant*

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years *Pembrolizumab + taxanes is less costly and QALY accruing. ** Confidential discounts in place for Atezolizumab and nab-paclitaxel with the NHS may alter the cost-effectiveness results.

D.2: Sensitivity analyses

D.2.1: Probabilistic sensitivity analysis vs paclitaxel (with Pembrolizumab CAA)

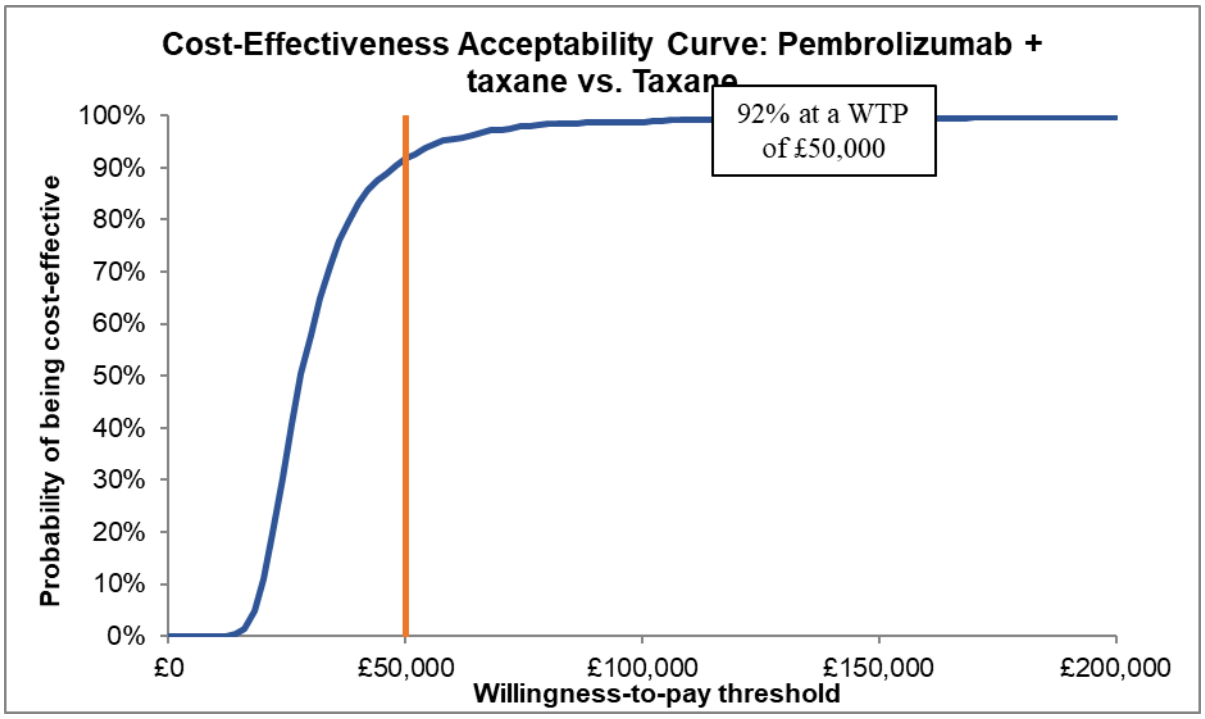
Table 25: Updated PSA results versus paclitaxel with Pembrolizumab CAA

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Paclitaxel comparator	[redacted]	1.862	[redacted]	-	-	-
Pembrolizumab + taxanes**	[redacted]	4.004	[redacted]	[redacted]	[redacted]	£27,753

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years ** Confidential discounts in place for nab-paclitaxel with the NHS may alter the cost-effectiveness results.

Figure 9: Updated Scatterplot of PSA results of Pembrolizumab + taxanes versus paclitaxel with Pembrolizumab CAA

Figure 10: Cost-effectiveness acceptability curve of Pembrolizumab + taxanes versus paclitaxel with Pembrolizumab CAA



D.2.2: Probabilistic sensitivity analysis vs docetaxel (with Pembrolizumab CAA)

**Note: To run analyses ensure Docetaxel costs are applied in the "Drug Cost Inputs" Sheet (PSA will need to run with this setting selected)*

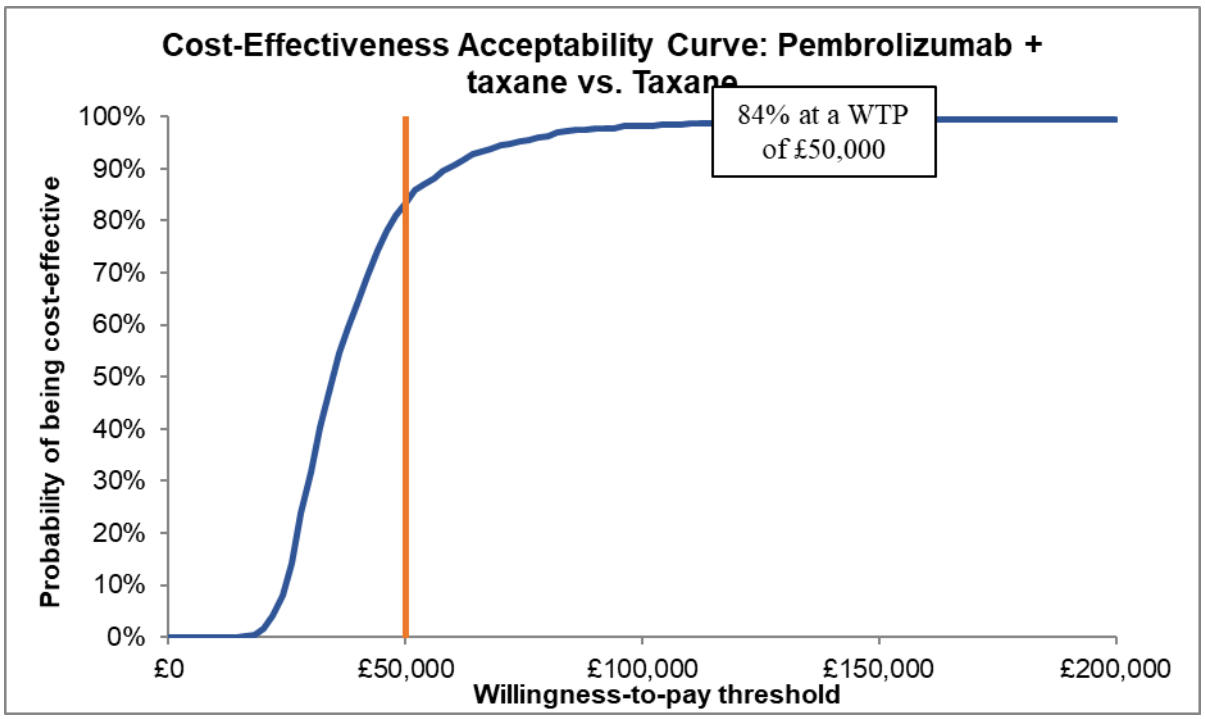
Table 26: Updated PSA results versus DOCETAXEL with Pembrolizumab CAA

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
DOCETAXEL comparator	[redacted]	1.862	[redacted]	-	-	-
Pembrolizumab + taxanes**	[redacted]	4.004	[redacted]	[redacted]	[redacted]	£34,370
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years ** Confidential discounts in place for nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

Figure 11: Updated Scatterplot of PSA results of Pembrolizumab + taxanes versus DOCETAXEL with Pembrolizumab CAA

[redacted]

Figure 12: Cost-effectiveness acceptability curve of Pembrolizumab + taxanes versus DOCETAXEL with Pembrolizumab CAA



D.2.3: Probabilistic sensitivity analysis vs Atezolizumab + nab-paclitaxel (with Pembrolizumab CAA)

The PSA results for Atezolizumab + nab-paclitaxel located in the PSA sheet do not account for assumptions and settings put forward to generate the base case results for this comparison (ITC option, PFS assessment and ToT [refer to original submission]).

PSA analyses for this comparison can be re-run by selecting the relevant base-case settings for Atezolizumab + nab-paclitaxel to ensure consistency in settings with the company base case presented above.

D.2.4: Deterministic sensitivity analysis vs taxanes (with Pembrolizumab CAA)

Figure 13: Tornado diagram for the 20 most sensible variables versus PACLITAXEL with Pembrolizumab CAA

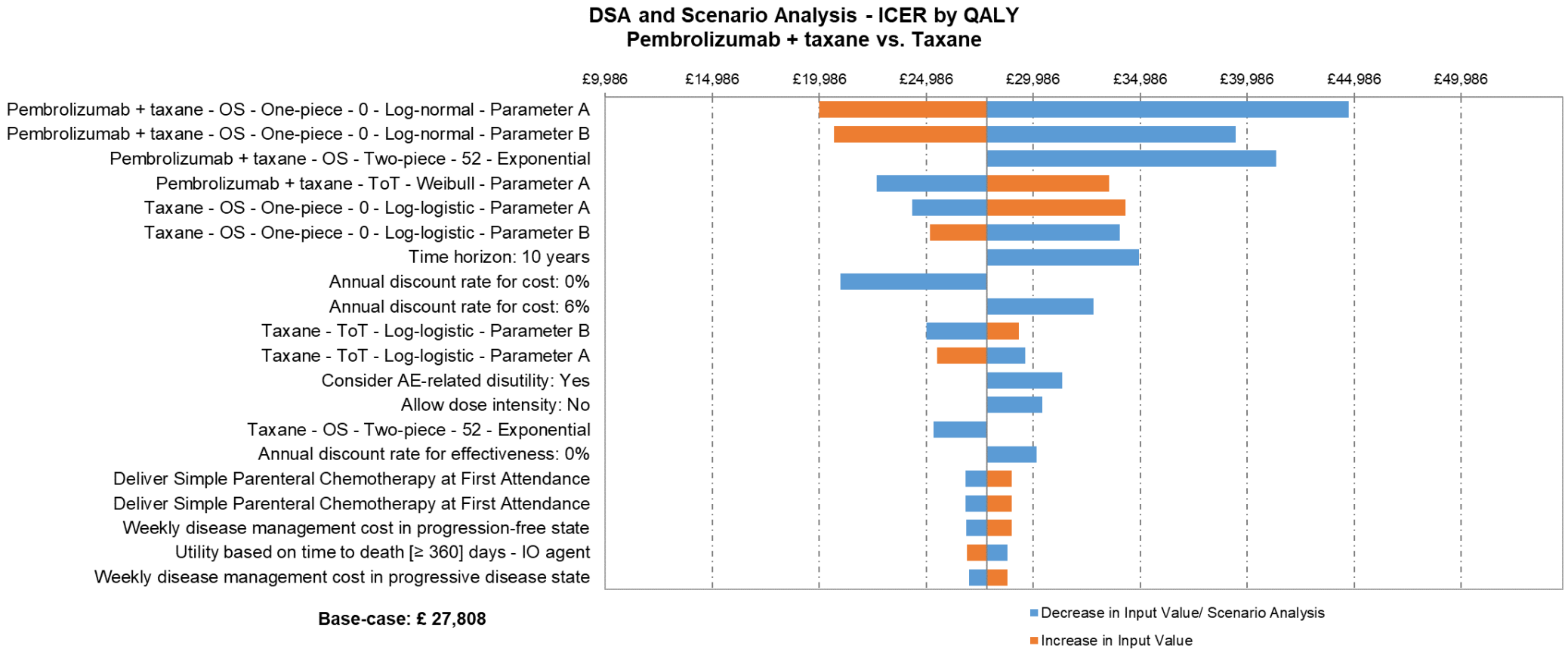
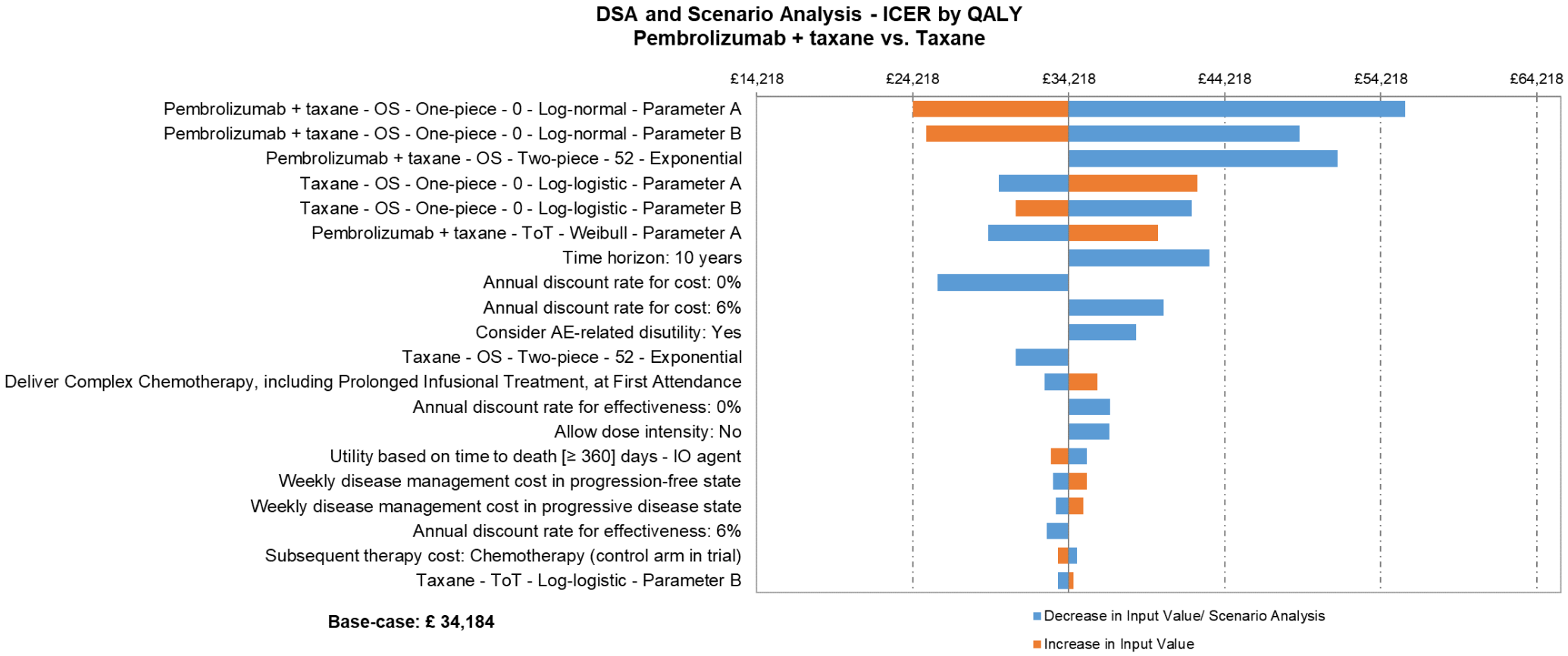


Figure 14: Tornado diagram for the 20 most sensible variables versus DOCETAXEL with Pembrolizumab CAA



**Note: To run analyses ensure Docetaxel costs are applied in the "Drug Cost Inputs" Sheet (PSA will need to run with this setting selected)*

D.2.5: Scenario analyses vs paclitaxel chemotherapy comparator (with Pembrolizumab CAA)

Table 27: Updated results of Scenario analyses versus Paclitaxel (with Pembro CAA price)

Scenario No.	Description	Pembrolizumab + taxanes			Taxanes comparator			Pembrolizumab + taxanes vs Taxanes		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Updated Base Case	**Paclitaxel taxane comparator**	[redacted]	**3.965**	[redacted]	[redacted]	**1.826**	[redacted]	[redacted]	[redacted]	**£27,808**
Scenario 1	Full log-logistic for Pembro + taxane OS (2nd best curve)	[redacted]	3.800	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£29,785
Scenario 2	Full log-normal for Taxane OS (2nd best curve)	[redacted]	3.965	[redacted]	[redacted]	1.734	[redacted]	[redacted]	[redacted]	£26,894
Scenario 3	Piecewise model for OS for Pembro + taxanes; 52 weeks KM + exponential (model unpredicts OS survival; equal to that of long term chemotherapy RWE datasets; considered highly conservative)	[redacted]	3.150	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£41,353
Scenario 4	Combined 2nd best OS curves in Pembro + Taxanes & Taxanes comparator (log-logistic and log-normal respectively: Scenarios 1 + 2 together)	[redacted]	3.800	[redacted]	[redacted]	1.734	[redacted]	[redacted]	[redacted]	£28,712
Scenario 5	PFS for Pembro + Taxanes: KM up to week 9 + Log-logistic (2nd best curve)	[redacted]	3.965	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£27,867
Scenario 6	PFS for Taxanes: KM up to week 9 + Log-logistic (2nd best curve)	[redacted]	3.965	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£27,807
Scenario 7	Combined 2nd best PFS curves for Pembro + Taxane and Taxane comparator (9 week KM + log-logistic	[redacted]	3.965	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£27,867

Scenario No.	Description	Pembrolizumab + taxanes			Taxanes comparator			Pembrolizumab + taxanes vs Taxanes		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
	and 9week KM + Log-logistic; Scenarios 5 + 6 together)									
Scenario 8	Combined 2nd best OS & PFS curves for Pembro + taxane and taxanes (Scenarios 4 & 7 together)	[redacted]	3.800	[redacted]	[redacted]	1.734	[redacted]	[redacted]	[redacted]	£28,771
Scenario 9	Applying treatment waning using SEER dataset in the base-case	[redacted]	4.443	[redacted]	[redacted]	2.150	[redacted]	[redacted]	[redacted]	£26,268
Scenario 10	Applying treatment waning by removing OS benefit after 5 Years in the base-case	[redacted]	3.493	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£34,096
Scenario 11	Combined 2nd best OS curves with 2nd best PFS curves (Scenario 8) + 5 year IO waning scenario (implausible PFS & OS intersect early on)	[redacted]	3.093	[redacted]	[redacted]	1.734	[redacted]	[redacted]	[redacted]	£40,580
Scenario 12	Half cycle correction on base-case	[redacted]	3.976	[redacted]	[redacted]	1.836	[redacted]	[redacted]	[redacted]	£28,029
Scenario 13	Removal of PD-L1 testing costs for Pembro + Taxanes	[redacted]	3.965	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£27,743
Scenario 14	Removal of AE management costs	[redacted]	3.965	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£27,744
Scenario 15	Using MS data for subsequent therapies (*selection at "Post Trt Costs" Sheet)*	[redacted]	3.965	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£28,269
Scenario 16	Using utilities by progression status & AEs pooled	[redacted]	3.965	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£31,350
Scenario 17	Using utilities by progression status & AEs treatment specific	[redacted]	3.965	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£31,320
Scenario 18	Removal of age-adjustment in utility estimates	[redacted]	3.965	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£26,653

D.2.6: Scenario analyses vs Docetaxel chemotherapy comparator (with Pembrolizumab CAA)

Table 28: Updated results of Scenario analyses versus Docetaxel (with Pembro CAA price)

Scenario No.	Description	Pembrolizumab + taxanes			Taxanes comparator			Pembrolizumab + taxanes vs Taxanes		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Updated Base Case	**Docetaxel taxane comparator**	[redacted]	**3.965**	[redacted]	[redacted]	**1.826**	[redacted]	[redacted]	[redacted]	**£34,184**
Scenario 1	Full log-logistic for Pembro + taxane OS (2nd best curve)	[redacted]	3.800	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£36,702
Scenario 2	Full log-normal for Taxane OS (2nd best curve)	[redacted]	3.965	[redacted]	[redacted]	1.734	[redacted]	[redacted]	[redacted]	£33,008
Scenario 3	Piecewise model for OS for Pembro + taxanes; 52 weeks KM + exponential (model unpredicts OS survival; equal to that of long term chemotherapy RWE datasets; considered highly conservative)	[redacted]	3.150	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£51,453
Scenario 4	Combined 2nd best OS curves in Pembro + Taxanes & Taxanes comparator (log-logistic and log-normal respectively: Scenarios 1 + 2 together)	[redacted]	3.800	[redacted]	[redacted]	1.734	[redacted]	[redacted]	[redacted]	£35,323
Scenario 5	PFS for Pembro + Taxanes: KM up to week 9 + Log-logistic (2nd best curve)	[redacted]	3.965	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£34,243
Scenario 6	PFS for Taxanes: KM up to week 9 + Log-logistic (2nd best curve)	[redacted]	3.965	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£34,183
Scenario 7	Combined 2nd best PFS curves for Pembro + Taxane and Taxane comparator (9 week KM + log-logistic	[redacted]	3.965	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£34,242

Scenario No.	Description	Pembrolizumab + taxanes			Taxanes comparator			Pembrolizumab + taxanes vs Taxanes		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
	and 9week KM + Log-logistic; Scenarios 5 + 6 together)									
Scenario 8	Combined 2nd best OS & PFS curves for Pembro + taxane and taxanes (Scenarios 4 & 7 together)	[redacted]	3.800	[redacted]	[redacted]	1.734	[redacted]	[redacted]	[redacted]	£35,383
Scenario 9	Applying treatment waning using SEER dataset in the base-case	[redacted]	4.443	[redacted]	[redacted]	2.150	[redacted]	[redacted]	[redacted]	£32,220
Scenario 10	Applying treatment waning by removing OS benefit after 5 Years in the base-case	[redacted]	3.493	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£42,201
Scenario 11	Combined 2nd best OS curves with 2nd best PFS curves (Scenario 8) + 5 year IO waning scenario (implausible PFS & OS intersect early on)	[redacted]	3.093	[redacted]	[redacted]	1.734	[redacted]	[redacted]	[redacted]	£50,442
Scenario 12	Half cycle correction on base-case	[redacted]	3.976	[redacted]	[redacted]	1.836	[redacted]	[redacted]	[redacted]	£34,495
Scenario 13	Removal of PD-L1 testing costs for Pembro + Taxanes	[redacted]	3.965	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£34,119
Scenario 14	Removal of AE management costs	[redacted]	3.965	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£34,120
Scenario 15	Using MS data for subsequent therapies (*selection at "Post Trt Costs" Sheet)*	[redacted]	3.965	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£34,645
Scenario 16	Using utilities by progression status & AEs pooled	[redacted]	3.965	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£38,538
Scenario 17	Using utilities by progression status & AEs treatment specific	[redacted]	3.965	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£38,501
Scenario 18	Removal of age-adjustment in utility estimates	[redacted]	3.965	[redacted]	[redacted]	1.826	[redacted]	[redacted]	[redacted]	£32,764

D.2.7: Scenario analyses vs Atezolizumab + nab-paclitaxel comparator (with Pembrolizumab CAA)

Table 29: Scenario analyses versus Atezolizumab + nab-paclitaxel LIST Prices (and Pembrolizumab CAA price)

Scenario No.	Description	Pembrolizumab + taxanes			Atezolizumab + nab-paclitaxel			Pembrolizumab + taxanes vs Atezolizumab + nab-paclitaxel		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Updated Base case	**KN-355 INV PFS, Pooled Taxanes, max ToT = PFS & Pembro CAA**	[redacted]	**3.965**	[redacted]	[redacted]	**2.295**	[redacted]	[redacted]	[redacted]	**Dominant**
Scenario 1	Use KEYNOTE-355 nab-paclitaxel as common comparator for the NMA to estimate the PFS HR	[redacted]	3.965	[redacted]	[redacted]	2.926	[redacted]	[redacted]	[redacted]	Dominant
Scenario 2	Full log-logistic for Pembro + Taxane OS (2nd best curve)	[redacted]	3.800	[redacted]	[redacted]	2.196	[redacted]	[redacted]	[redacted]	Dominant
Scenario 3	Use the primary PFS endpoint from KEYNOTE-355 blinded CIV	[redacted]	3.965	[redacted]	[redacted]	2.295	[redacted]	[redacted]	[redacted]	Dominant
Scenario 4	Set the maximum treatment duration for Atezolizumab +nab-paclitaxel = to KEYNOTE-355 nab-paclitaxel ToT parametric curve	[redacted]	3.965	[redacted]	[redacted]	2.295	[redacted]	[redacted]	[redacted]	Dominant
Scenario 5	2nd best PFS curve used for Pembro + taxanes in comparison: 9 week KM + log-logistic	[redacted]	3.965	[redacted]	[redacted]	2.295	[redacted]	[redacted]	[redacted]	Dominant
Scenario 6	Combined 2nd best curves for PFS and OS for Pembro + Taxanes (Scenario 2 & 5)	[redacted]	3.800	[redacted]	[redacted]	2.196	[redacted]	[redacted]	[redacted]	Dominant
Scenario 7	Apply treatment waning based on SEER dataset analysis on Scenario 6.	[redacted]	4.262	[redacted]	[redacted]	2.417	[redacted]	[redacted]	[redacted]	Dominant

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Pembrolizumab in combination for untreated, locally advanced or metastatic, triple negative breast cancer [ID1546]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Breast Cancer Now
3. Job title or position	Policy Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	Breast Cancer Care and Breast Cancer Now merged on 1 April 2019 to create one charity – Breast Cancer Now. From research to care, our charity has people affected by breast cancer at its heart – providing support for today and hope for the future. United, we'll have the ability to carry out even more world-class research, provide even more life-changing support and campaign even more effectively for better services and care.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	In the last 12 months Breast Cancer Now has received the following funding from companies listed in the appraisal matrix. Breast Cancer Now does not receive any pharmaceutical funding for our Policy, Evidence and Influencing work. Our work on access to drugs is independent of any funding we may receive from the pharmaceutical industry and is based on the evidence of the clinical effectiveness of drugs. - Roche - £44,121 – Living with Secondary Breast Cancer Service Grant (March 2020) - Pfizer - £10,000 – Helpline (May 2020) - Roche - £25,000 Helpline (May 2020) - Pfizer - £40,900 – Personalised Support Programme (November 2020) - Roche - £41,555 – Living with Secondary Breast Cancer Online Service (November 2020)

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	At Breast Cancer Now we utilise our various networks of those affected by breast cancer to gather information about patient experience. We have been unable to find patients with direct experience of this treatment.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Secondary (also known as advanced, metastatic or stage 4) breast cancer is when cancer originating in the breast has spread to other parts of the body; most commonly the lungs, brain, bones or liver. There is no cure for secondary breast cancer. Treatment aims to control and slow the spread of the cancer, relieve any symptoms, and maintain health, wellbeing and a good quality of life for as long as possible. A patient can be diagnosed with secondary breast cancer right from the start, or they can develop the condition months or years after treatment for their primary breast cancer has ended. Triple negative breast cancer is the name given to breast cancer that is: • oestrogen receptor negative (ER-) • progesterone receptor negative (PR-) • HER2 negative

	Being diagnosed with secondary breast cancer is extremely difficult to come to terms with both for patients and their family and friends. Everyone's experience of being diagnosed and living with secondary breast cancer is different. Many people will feel overwhelmed, upset and shocked or anxious, as well as angry and alone. The uncertainty of living with secondary breast cancer can be the hardest part for many people, with people telling us it has fundamentally changed their perspective on life and they feel they are living on borrowed time. These common feelings can have a huge impact on people's mental health. A diagnosis of secondary breast cancer can also affect people's relationship with those closest to them which can be particularly difficult to cope with. Triple negative breast cancer is usually more aggressive and harder to treat than other types of breast cancer, resulting in poorer in outcomes. Therefore, it can be particularly upsetting and frightening to be diagnosed with this type of breast cancer and the impact on the individual and family is high, both emotionally and physically. People living with secondary breast cancer have told us: "How confused and scared I am all the time; even when I'm happy it's always there in the back of your mind". "It is scary. I am permanently scared about my future and what my family will have to deal with without me". As well as the huge emotional toll of living with secondary breast cancer, patients often have to cope with numerous practical concerns, such as managing their day to day activities, which may include working, household and parental responsibilities as well as travelling to and from hospital appointments. People living with secondary breast cancer have shared the following: "It totally and completely affects your life after diagnosis. Endless doctors' appointments can begin to wear you down in no time at all".

	"My treatment goes on for as long as it works and this is my life now. Constant 'scanxiety', endless hospital appointments and the struggle with day to-day living that others either don't see or understand". The symptoms of secondary breast cancer can vary depending on where the cancer has spread to. For example, if it has spread to the bones the main symptoms can include pain in the bones or bone fractures. If breast cancer has spread to the lungs, someone may experience symptoms such as breathlessness or continuous pain and tightness in the chest. Also all breast cancer treatments can cause some side effects and although everyone reacts differently to drugs, for those people who experience more side effects than others, it can cause a significant impact on their day to day lives and health and wellbeing. Patients are keen to find treatments that will halt progression and extend life for as long as possible. As patients' time is limited, people tell us that quality of life is just as important to take into account as length of life, as this enables them to spend quality time with their loved ones. Therefore, the type and severity of treatment side effects are also important for patients when considering their treatment decisions.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Treatments for triple negative breast cancer have been extremely limited for a significant period of time and for many years the only treatment option for the group of patients being considered in this appraisal was chemotherapy. Clinical consensus suggested that single agent taxanes (paclitaxel or docetaxel) were the most commonly used chemotherapy as a first line treatment for patients with secondary triple negative breast cancer. Chemotherapy can result in significant side effects including increased risk of infection, sickness, hair loss and fatigue which can significantly impact on quality of life. In May 2020, we saw the welcome introduction of atezolizumab with nab-paclitaxel which now provides an important new treatment option for a specific group of patients. Evidence shows that people receiving this treatment have longer before their disease progresses whilst it may also enable them to live longer. This was a huge step forward in the treatment of triple negative breast cancer.

8. Is there an unmet need for patients with this condition?	Improvements in treatment continue to be needed for people living with incurable triple negative secondary breast cancer.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	At the time of this submission, we understand that overall survival data is not yet available. Currently the main advantage of this treatment is giving patients longer before their disease progresses. The clinical trial highlights the addition of pembrolizumab to chemotherapy improved progression free survival (PFS) by an additional 4.1 months on average when compared with chemotherapy alone for patients with a combined positive score of 10 or more. We know that patients value this extra time, as delaying disease progression means more quality time to spend with their relatives and friends. Maintaining a high quality of life for as long as possible is currently the best outcome for this patient group. Delaying progression can have a positive impact on patients' emotional wellbeing and mental health, as it may mean that the patient can continue doing the activities they enjoy. Increasing the time until a patient's disease progresses is also likely to bring some comfort to their relatives and friends, as this is the best possible outcome for an incurable disease. This is in turn could help to reduce any stress the patient is experiencing as a result of worrying about any burden on their friends and family.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	One of the main disadvantages of this treatment is the side effects associated with it. Every treatment for breast cancer has some side effects and each patient's situation will be different with side effects, affecting some patients more than others. Patients' willingness to receive treatments will vary, however, as long as all the side effects are clearly discussed with the patient, they will be able to make their own choice as to the level of risk they will be willing to take balanced against the potential benefit of that treatment option. As established in the clinical trial, the most common adverse events experienced were anaemia, neutropenia and nausea.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	This treatment looked at PD-L1 expression and results suggest patients are more likely to potentially benefit from this treatment if they have a combined positive score of ≥10 following testing with the assay. Triple negative breast cancer is more common in: - women who have inherited an altered BRCA gene (particularly BRCA1) - black women - women who have not yet reached the menopause - women under 40

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware of.
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- A diagnosis of incurable triple negative secondary breast cancer can cause considerable anxiety and fear for people and their loved ones, impacting on all aspects of their lives. The uncertainty can be the hardest part for many people. New treatments are urgently needed for this group of patients.
- In the trial, pembrolizumab in combination with chemotherapy led to a longer progression free survival when compared to placebo and chemotherapy.

- This delay in disease progression is important as it enables patients to spend quality time with their friends and families, as well as increasing the likelihood of people being able to continue with their daily activities, which can improve the emotional wellbeing of both patients and their families.
- There are side effects associated with this treatment which could negatively impact on an individual's quality of life. The benefits and risks of this treatment would need to be clearly discussed with the patient so they can make a decision that is right for them.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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

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Declared competing interests of the authors

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Aline Navega Biz and Matt Stevenson critiqued the health economic analysis submitted by the company. Emma Simpson summarised and critiqued the clinical effectiveness data reported within the company's submission. John Stevens critiqued the statistical aspects of the submission. Mark Clowes critiqued the company's search strategy. All authors were involved in drafting and commenting on the final report. Professors Coleman and Wyld acted as clinical advisors.

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Abbreviations

AEs	Adverse events
ASCO	American Society of Clinical Oncology
AWMSG	All Wales Medicines Strategy Group
BC	Breast Cancer
BICR	Blinded Independent Central Review
BRCA	BReast Cancer gene mutation
BSA	Body Surface Area
BSC	Best Supportive Care
CAA	Commercial Access Agreement
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence interval
cPAS	comparator Patient Access Scheme
CPS	Combined Proportion Score
CrI	Credible interval
CR	Complete Response
CS	Company Submission
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DoR	Duration of Response
DSA	Deterministic Sensitivity Analyses
DSU	Decision Support Unit
ECOG	Eastern Co-operative Oncology Group
ECOG PS	Eastern Co-operative Oncology Group Performance Score
eMIT	electronic Market Information Tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30
EQ-5D-3L	EuroQol 5 dimensions 3 level
ER	Oestrogen Receptor
ERG	Evidence Review Group
ESMO	European Society of Medical Oncology
FAS	Full Analysis Set
GEE	Generalised Estimating Equation
HER-2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life

IA2	Interim Analysis 2
ICER	Incremental Cost Effectiveness Ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention to Treat
IV	Intravenous
KM	Kaplan-Meier
MRU	Medical Resource Use
mTNBC	metastatic Triple Negative Breast Cancer
NCI	National Cancer Institute
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NR	Not Reported
OPA	Overall Percentage Agreement
ORR	Objective Response Rate
OS	Overall Survival
PAS	Patient Access Scheme
PD-1	Programmed cell Death 1 (receptor)
PD-L1	Programmed Death Ligand 1
PD-L2	Programmed Death receptor Ligand-2
PFS	Progression-Free Survival
PH	Proportional Hazards
PR	Progesterone Receptor
PRO	Patient-Reported Outcome
PSA	Probabilistic Sensitivity Analyses
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
RDI	Reduced Dose Intensity
RECIST	Response Evaluation Criteria in Advanced Solid Tumors
SAE	Serious adverse event
SD	Standard Deviation
SEER	Surveillance, Epidemiology and End Results
SLR	Systematic Literature Review
SMC	Scottish Medicines Consortium

SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TNBC	Triple Negative Breast Cancer
TPS	Tumour Proportion Score
TTD	Time To Treatment Discontinuation

1. Executive summary

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. The results of the ERG's exploratory analyses are presented in Section 1.7. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the view of the ERG, and do not necessarily reflect the opinion of NICE.

1.1 Overview of the ERG's key issues

Key issues identified by the ERG that impact on the incremental costs and quality-adjusted life years (QALYs) are summarised in Table 1.

Table 1: Overview of the ERG's key issues

ID1546	Summary of issue	Report sections
Issue 1	Potentially favourable extrapolation of overall survival	4.3.3 (item 1[i])
Issue 2	Uncertainty surrounding the long-term benefits of pembrolizumab plus paclitaxel/nab-paclitaxel	4.3.3 (item 1[ii])
Issue 3	Unfavourable assumption regarding treatment discontinuation for atezolizumab plus nab-paclitaxel	4.3.3 (item 1[iii])
Issue 4	Uncertainty surrounding the relative efficacy comparison of pembrolizumab plus paclitaxel/nab-paclitaxel versus atezolizumab plus nab-paclitaxel	4.3.3 (item 2)
Issue 5	Uncertainty related to the most appropriate way to estimate utility	4.3.3 (item 3)
Issue 6	Inclusion of vial sharing for IV drugs (with the exception of pembrolizumab and atezolizumab)	4.3.3 (item 4)

The key differences between the company's preferred assumptions and the ERG's preferred assumptions relate to:

(i) Choice of overall survival (OS) functions for pembrolizumab plus paclitaxel/nab-paclitaxel and taxanes. The company's model uses a lognormal distribution for pembrolizumab plus paclitaxel/nab-paclitaxel OS and a log-logistic distribution for paclitaxel/docetaxel, whilst the ERG chooses Weibull distributions for modelling OS in both treatment groups although also explores the use of an exponential distribution as an additional sensitivity analysis.

(ii) The long-term benefits duration for pembrolizumab plus paclitaxel/nab-paclitaxel. The company's base-case model assumes lifetime treatment benefits whereas the ERG preferred analysis assumes that the relative treatment effect ceases after 5 years (at which point the hazard for OS for patients who receive paclitaxel is assumed generalisable to patients who receive pembrolizumab plus paclitaxel/nab-paclitaxel). A further sensitivity analysis explores setting the hazards to the same value at 3 years.

(iii) Assumption for modelling treatment discontinuation for the atezolizumab plus nab-paclitaxel treatment group. The company's approach assumes that time-to-treatment discontinuation (TTD) for patients receiving atezolizumab plus nab-paclitaxel is equal to progression free survival (PFS), whereas in the ERG preferred analysis the TTD function for this group is modelled applying the hazard ratio (HR) for PFS generated by the company's network metanalysis (NMA) to the TTD survival function for pembrolizumab plus paclitaxel/nab-paclitaxel.

(iv) The comparative efficacy between pembrolizumab plus paclitaxel/nab-paclitaxel and atezolizumab plus nab-paclitaxel is uncertain with necessary limitations relating to the NMA and wide confidence intervals. The ERG has explored setting the efficacy of both interventions equal to that of pembrolizumab plus paclitaxel/nab-paclitaxel as an additional sensitivity analysis.

(v) The most appropriate way to estimate utility for patients with metastatic triple negative breast cancer (mTNBC) is uncertain. Both the time-to-death approach and the health state approach have limitations. As such, the ERG has provided analyses using both methods.

(vi) Vial sharing – the company assumes vial sharing is allowed for all IV drugs, except for pembrolizumab and atezolizumab, whilst the ERG assumes no vial sharing for any of the IV drugs, based on clinical opinion provided to the ERG.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life, using QALYs. An ICER is the ratio of the extra cost for every QALY gained.

Pembrolizumab plus paclitaxel/nab-paclitaxel is modelled to increase QALYs by increasing both expected overall survival and the average quality of life for patients whilst patients are alive as disease progression is also delayed.

Pembrolizumab plus paclitaxel/nab-paclitaxel is modelled to increase costs compared with taxanes primarily due to the acquisition costs of pembrolizumab. Compared to atezolizumab plus nab-paclitaxel, pembrolizumab plus paclitaxel/nab-paclitaxel is modelled to decrease costs as the acquisition cost of pembrolizumab incorporating the agreed simple discount in the patient access scheme (PAS) is lower than that of atezolizumab at list price.

The assumptions within the company's base case modelling that the ERG believes are either incorrect or uncertain that impact most on the ICER are shown in Table 1.

1.3 The decision problem: summary of the ERG's key issues

The company's submission includes one economic analysis of pembrolizumab plus paclitaxel/nab-paclitaxel for the treatment of patients with [redacted] The model compares pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel, docetaxel and atezolizumab plus nab-paclitaxel, and is informed by the KEYNOTE-355 study, external data and assumptions. The clinical evidence for paclitaxel is based on the observed data from the KEYNOTE-355 study, which administered paclitaxel three times in each four-week cycle, which may be used for certain patients as per local treatment guidelines. However, according to clinical opinion received by the ERG and in the NICE appraisal for nab-paclitaxel in this indication, this does not reflect the most common administration schedule currently used in clinical practice in the UK (which is weekly dosing). However, this potential discrepancy cannot be easily resolved and the ERG believes that this limitation does not invalidate the modelling undertaken.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The key evidence for clinical effectiveness within the CS comprises one RCT of pembrolizumab combination therapy which was relevant to the decision problem: KEYNOTE-355 (NCT02819518). which was ongoing at time of writing. At the second interim analysis [redacted], and there was a significant advantage in progression free survival (PFS) for the pembrolizumab plus chemotherapy arm over the placebo plus chemotherapy arm, hazard ratio (HR) 0.65 (95% CI: 0.49, 0.86) p=0.0012. Note: The width of the 95% confidence intervals may not reflect the nominal significance level used at the interim analysis to control the overall significance level. Hence, the apparent inconsistency with the OS result being statistically non-significant and its interval estimate not including the null value.

In the absence of head-to-head studies comparing pembrolizumab combination therapy with atezolizumab plus nab-paclitaxel, one RCT was identified by the CS for use in an indirect comparison, IMpassion130 which had necessary limitations.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

The section expands on the issues listed in Table 1. Where the change affects the comparison with paclitaxel, docetaxel and atezolizumab plus nab-paclitaxel, the summary provided is against paclitaxel for brevity.

Issue 1. Potentially favourable extrapolation of overall survival

Report section	Sections 4.3.3 and 4.4.2
Description of issue and why the ERG has identified it as important	The company has selected a lognormal distribution for pembrolizumab plus paclitaxel / nab-paclitaxel and a loglogistic distribution for paclitaxel. These distributions have a reducing hazard over time after a turning point, yet the observed underlying hazard is consistently increasing. Additionally, in the previous appraisal for atezolizumab with nab-paclitaxel in a similar population, the NICE Appraisal Committee accepted a Weibull distribution for both arms with the ERG noting that both pembrolizumab and atezolizumab are immune-oncology drugs.
What alternative approach has the ERG suggested?	The use of a Weibull distribution for both pembrolizumab plus paclitaxel / nab-paclitaxel and for paclitaxel. Exploratory analyses have also looked at using exponential distributions.
What is the expected effect on the cost-effectiveness estimates?	This change reduces the expected survival for both pembrolizumab plus paclitaxel / nab-paclitaxel and for paclitaxel, reducing the QALYs gained and increasing the ICER compared with paclitaxel.
What additional evidence or analyses might help to resolve this key issue?	Additional follow-up of patients in KEYNOTE-355 to assess changes in the hazard of death over time.

Issue 2. Uncertainty surrounding the long-term benefits of pembrolizumab plus paclitaxel/nab-paclitaxel

Report section	Sections 4.3.3 and 4.4.2
Description of issue and why the ERG has identified it as important	The company has assumed that the distributions fitted to overall survival applying throughout the time horizon despite the maximum duration for pembrolizumab treatment being two years. This creates the possibility that two patients alive at year 7 and on third-line treatment would have different hazards of death dependent on the initial treatment received.
What alternative approach has the ERG suggested?	Based on precedent set in NICE Technology Appraisal Committee C, the ERG has assumed that at 5 years (3 years after the maximum treatment duration of pembrolizumab) the hazard of death for patients initially treated with pembrolizumab plus paclitaxel / nab-paclitaxel was the same as those initially treated with paclitaxel. Exploratory analyses have also been undertaken assuming that the hazards are set equal after 3 years.
What is the expected effect on the cost-effectiveness	This change reduces the expected survival for pembrolizumab plus paclitaxel / nab-paclitaxel which reduces the QALYs gained and increases the ICER compared with paclitaxel.

estimates?	
What additional evidence or analyses might help to resolve this key issue?	Additional follow-up of patients in KEYNOTE-355 to assess changes in the hazard of death over time.

Issue 3. Unfavourable assumption regarding treatment discontinuation for atezolizumab plus nab-paclitaxel

Report section	Sections 4.3.3 and 4.4.2
Description of issue and why the ERG has identified it as important	The company has assumed that for atezolizumab plus nab-paclitaxel that TTD equals PFS due to not having the appropriate data. However, it is seen in KEYNOTE-355 that for both interventions TTD is markedly less than PFS. The assumption used for atezolizumab plus nab-paclitaxel artificially increases the acquisition costs of this intervention.
What alternative approach has the ERG suggested?	To apply the HR between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel / nab-paclitaxel for PFS to the pembrolizumab plus paclitaxel / nab-paclitaxel TTD.
What is the expected effect on the cost-effectiveness estimates?	This change reduces the expected costs associated with atezolizumab plus nab-paclitaxel which results in the ICER of pembrolizumab plus paclitaxel / nab-paclitaxel compared with atezolizumab plus nab-paclitaxel becoming less favourable.
What additional evidence or analyses might help to resolve this key issue?	The data to resolve this issue is unlikely to be available to the company or ERG. The ERG believes that the approach it has suggested is more reasonable than the assumption made by the company.

Issue 4. Uncertainty surrounding the relative efficacy comparison of pembrolizumab plus paclitaxel/nab-paclitaxel versus atezolizumab plus nab-paclitaxel

Report section	Sections 3.4, 4.3.3 and 4.4.2
Description of issue and why the ERG has identified it as important	The company has conducted an NMA to estimate the relative efficacy of atezolizumab plus nab-paclitaxel compared to pembrolizumab plus paclitaxel / nab-paclitaxel. As acknowledged by the company the NMA has limitations, but has shown favourable midpoint estimates for pembrolizumab plus paclitaxel / nab-paclitaxel but wide confidence intervals around these estimates.
What alternative approach has the ERG suggested?	The ERG has maintained the company's assumptions but has explored a scenario where the efficacy of atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel / nab-paclitaxel are assumed equal.
What is the expected effect on the cost-effectiveness estimates?	This change in the exploratory analysis results in the expected overall survival and QALYs being equal for both treatments, but also increases the costs associated with atezolizumab plus nab-paclitaxel as the HR applied to the pembrolizumab plus paclitaxel / nab-paclitaxel TTD distribution is increased to 1. The exploratory analysis essentially becomes a cost-minimisation comparison between the two treatment arms which

	may be important when the discounted price of atezolizumab is incorporated.
What additional evidence or analyses might help to resolve this key issue?	The data to resolve this issue could be generated with a head-to-head study comparing atezolizumab plus nab-paclitaxel with pembrolizumab plus paclitaxel / nab-paclitaxel.

Issue 5. Uncertainty related to the most appropriate way to estimate utility

Report section	Sections 4.3.3 and 4.4.2
Description of issue and why the ERG has identified it as important	The company has adopted two methods for estimating utility: a time-to-death approach and a health-state based approach. In its base case the company has preferred the time-to-death approach. The ERG notes that both methods have limitations and that neither approach overcomes the main limitation which is that the data collected have been heavily censored, either at the point of progression, or at treatment discontinuation.
What alternative approach has the ERG suggested?	The ERG does not have a preference for either of the methods. As such the ERG has provided exploratory analyses using both approaches, noting that the health-state approach consistently has higher ICERs than the time-to-death approach.
What is the expected effect on the cost-effectiveness estimates?	Were the Appraisal Committee to favour the health state approach, or to decide that the true ICER lay inbetween the results generated by each method then the ICER would increase.
What additional evidence or analyses might help to resolve this key issue?	The data to resolve this issue could be generated by asking patients with mTNBC to fill in a EuroQol 5 Dimensions questionnaire at regular intervals, particularly after progression.

Issue 6. Inclusion of via sharing for intravenous drugs

Report section	Sections 4.3.3 and 4.4.2
Description of issue and why the ERG has identified it as important	The company has assumed that vial sharing exists for intravenous drugs, with the exception of pembrolizumab and atezolizumab. The clinical advice to the ERG suggests that vial sharing would not happen.
What alternative approach has the ERG suggested?	Removal of assumptions related to vial sharing for all drugs.
What is the expected effect on the cost-effectiveness estimates?	This would increase the additional costs of pembrolizumab plus paclitaxel / nab-paclitaxel compared with paclitaxel and increase the ICER.
What additional evidence or analyses might help to resolve	If there is a dispute on whether there is vial sharing for the drugs appropriate to this appraisal, then the information could be generated by conducting an audit at treatment centres.

this key issue?	

1.6 Other key issues: summary of the ERG's view

None.

1.7 Summary of ERG's preferred assumptions and resulting ICER

The ERG altered the company's base case as follows: using Weibull distributions for OS, using parametric distributions for PFS without using the Kaplan-Meier, assuming that the HR between pembrolizumab plus paclitaxel / nab-paclitaxel associated with PFS also applied to TTD; assuming a loss of treatment benefit at 5 years; and removing the assumption of vial sharing for all intravenous treatments.

Within a full incremental analysis, the ERG preferred assumptions increased the deterministic ICER of pembrolizumab plus paclitaxel / nab-paclitaxel compared with docetaxel from £34,184 in the company's base case to £65,846 in the ERG's base case (£67,757 probabilistic) when a time-to-death approach for generating utilities was utilised and from £38,538 to £70,947 (£72,844 probabilistic) when a health-state approach for generating utilities was used. The two largest components relating to the increase in the ICER was using Weibull distributions for overall survival and assuming the loss of treatment benefit at 5 years. In the comparison against paclitaxel, the deterministic ICER of pembrolizumab plus paclitaxel / nab-paclitaxel increased from £27,808 in the company's base case to £53,721 in the ERG's base case (£55,074 probabilistic) when a time-to-death approach for generating utilities was utilised and from £31,350 to £57,883 (£59,208 probabilistic) when a health-state approach for generating utilities was used. In all analyses, pembrolizumab plus paclitaxel / nab-paclitaxel was assumed to dominate (lower costs and higher QALYs) atezolizumab plus nab-paclitaxel (at list price). The results of the ERG's exploratory analyses are summarised in Table 2 and

Table 3. Detailed results are provided in Table 37 to Table 44.

Table 2: Summary of ERG preferred assumptions and ICER – versus docetaxel, by modelling approach for HRQoL (deterministic)

Exploratory analysis	Time-to-death approach			Utilities by health states approach		
	Incremental QALYs	**Incremental cost**	**ICER (Change from company's base case)**	**Incremental QALYs**	**Incremental cost**	**ICER (Change from company's base case)**
Company's updated base case – using HRQoL by time-to-death	[redacted]	[redacted]	**£34,184**	[redacted]	[redacted]	**£38,538**
EA1: Use of alternative OS survival functions	[redacted]	[redacted]	£54,555 (+£20,371)	[redacted]	[redacted]	£57,348 (+£18,810)
EA2: Use of alternative PFS survival functions	[redacted]	[redacted]	£34,159 (-£25)	[redacted]	[redacted]	£39,719 (+£1,181)
EA3: Use of alternative TTD survival function for atezolizumab plus nab-paclitaxel[†]	[redacted]	[redacted]	£34,184 (£0)	[redacted]	[redacted]	£38,538 (£0)
EA4: Loss of treatment benefit after 5 years	[redacted]	[redacted]	£42,201 (+£8,017)	[redacted]	[redacted]	£46,176 (+£7,638)
EA5: Removal of vial sharing for all IV treatments	[redacted]	[redacted]	£35,126 (+£942)	[redacted]	[redacted]	£39,600 (+£1,062)
EA6: ERG's preferred analysis	[redacted]	[redacted]	**£65,846 (+£31,662)**	[redacted]	[redacted]	**£70,947 (+£32,409)**
ASA1: Use of alternative OS survival functions	[redacted]	[redacted]	£57,333 (+£23,149)	[redacted]	[redacted]	£62,431 (+£23,893)
ASA2: Assumption of lifetime treatment benefit duration	[redacted]	[redacted]	£56,112 (+£21,928)	[redacted]	[redacted]	£61,502 (+£22,964)
ASA3: Loss of treatment benefit after 3 years	[redacted]	[redacted]	£89,090 (+£54,906)	[redacted]	[redacted]	£92,370 (+£53,832)

ASA – additional sensitivity analysis; EA – exploratory analysis; ICER - incremental cost-effectiveness ratio; QALY - quality-adjusted life year
** undiscounted.*
Exploratory analysis ASA4 and ASA5 are not applicable for the pairwise comparison between pembrolizumab plus paclitaxel/nab-paclitaxel and docetaxel, and therefore does not affect the results for this comparator.

Table 3: Summary of ERG preferred assumptions and ICER – versus paclitaxel, by modelling approach for HRQoL (deterministic)

Exploratory analysis	Time-to-death approach			Utilities by health states approach		
	Incremental QALYs	**Incremental cost**	**ICER (Change from company's base case)**	**Incremental QALYs**	**Incremental cost**	**ICER (Change from company's base case)**
Company's updated base case – using HRQoL by time-to-death	[redacted]	[redacted]	**£27,808**	[redacted]	[redacted]	**£31,350**
EA1: Use of alternative OS survival functions	[redacted]	[redacted]	£44,335 (+£16,527)	[redacted]	[redacted]	£46,604 (+£15,254)
EA2: Use of alternative PFS survival functions	[redacted]	[redacted]	£27,783 (-£25)	[redacted]	[redacted]	£32,305 (+£955)
EA3: Use of alternative TTD survival function for atezolizumab plus nab-paclitaxel[†]	[redacted]	[redacted]	£27,808 (£0)	[redacted]	[redacted]	£31,350 (£0)
EA4: Loss of treatment benefit after 5 years	[redacted]	[redacted]	£34,096 (+£6,288)	[redacted]	[redacted]	£37,308 (+£5,958)
EA5: Removal of vial sharing for all IV treatments	[redacted]	[redacted]	£28,763 (+£955)	[redacted]	[redacted]	£32,426 (+£1,076)
EA6: ERG's preferred analysis	[redacted]	[redacted]	**£53,721 (+£25,913)**	[redacted]	[redacted]	**£57,883 (+£26,533)**
ASA1: Use of alternative OS survival functions	[redacted]	[redacted]	£46,527 (+£18,719)	[redacted]	[redacted]	£50,664 (+£19,314)
ASA2: Assumption of lifetime treatment benefit duration	[redacted]	[redacted]	£45,912 (+£18,104)	[redacted]	[redacted]	£50,322 (+£18,972)
ASA3: Loss of treatment benefit after 3 years	[redacted]	[redacted]	£72,375 (+£44,567)	[redacted]	[redacted]	£75,039 (+£43,689)

ASA – additional sensitivity analysis; EA – exploratory analysis; ICER - incremental cost-effectiveness ratio; QALY - quality-adjusted life year
** undiscounted.*
Exploratory analysis ASA4 and ASA5 are not applicable for the pairwise comparison between pembrolizumab plus paclitaxel/nab-paclitaxel and docetaxel, and therefore does not affect the results for this comparator.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

CS Section B.1.3.1 contains an accurate overview of the health problem.

Triple negative breast cancer (TNBC) is a subtype of breast cancer, in which cancer cells test negative for oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2. Triple negative breast cancer (TNBC) is a subtype of breast cancer, in which cancer cells test negative for oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2) expression (CS Section B.1.3.1) (NICE final scope[2]). TNBC can be aggressive, with a high incidence of visceral metastases, high risk of distant recurrence, and poor prognosis (CS Section B.1.3.1) (NICE final scope).[2-4]

TNBC is diagnosed more frequently in younger, premenopausal women, and people with pathogenic BRCA1 and BRCA2 gene mutations and people of African or Hispanic descent.[5-6] Around 15% of breast cancers are TNBC (approximately 7,500 cases a year in England and Wales).[7] TNBC accounts for approximately 25% of deaths from breast cancer.[6]

Programmed death-ligand 1 (PD-L1) is a checkpoint protein on T cells that can act to suppress the adaptive arm of the immune system effectively reducing immune protection against the cancer.[8] Infiltrating lymphocytes drive PD-L1 positivity. High expression of PD-L1 has been associated with increased tumour aggressiveness.[9]

Checkpoint inhibitor drugs are a type of immunotherapy. By blocking checkpoint proteins, they enable the T cell response to be reactivated.[10] *"Pembrolizumab releases the PD-1 pathway-mediated inhibition of the immune response and reactivates both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and anti-tumour immunity"* (CS Section B.1.2). Other checkpoint inhibitors that block PD-L1 include atezolizumab, avelumab, and durvalumab.[8]

Higher PD-L1 (Programmed Death Ligand 1) expression levels on tumour cells and greater numbers of PD-L1 positive infiltrating lymphocytes are observed in TNBC relative to other breast cancer subtypes.[11] There may be some changes with time or between lesions within an individual patient. PD-L1 testing has recently been initiated by the NHS in metastatic TNBC [11] in order to decide whether to treat with atezolizumab plus nab-paclitaxel, and PD-L1 testing has been used prior to this for other conditions.[12] PDL-1 testing is done on an archival specimen of a metastatic biopsy or, more frequently, the original primary tumour (clinical opinion) or, less commonly, on a biopsy of the metastatic recurrence if available.

The five-year overall survival (OS) for patients diagnosed with TNBC is between 59%-77% (CS Section B.1.3.1).[13] For those who go on to develop metastatic TNBC, median OS varies between 10.8 months and 16.8 months depending on current and prior treatment, Eastern Co-operative Oncology Group Performance Score (ECOG PS), disease free interval, age, and presence of visceral metastases.[14-16] The recent IMpassion130 study reported median OS in the PD-L1>1% population as 25.4 months for atezolizumab plus nab-paclitaxel treated patients, and 17.9 months for nab-paclitaxel only treated patients. [17]

CS Section B.1.3.2 describes the different assays used to detect PD-L1 expression in the KEYNOTE-355 and IMpassion130 trials (Table 4).

Table 4: PD-L1 assays (adapted from CS Table 3)

Trial	**KEYNOTE-355**	**Impassion130**
Assay	22C3 pharmDX	SP142
Manufacturer of assay	Dako	Ventana
Calculation of PD-L1 expression	$\text{CPS}=\frac{\textit{Number of PD-L1 stained cells}}{\textit{(tumour cells,lymphocytes,macrophages)}}\text{ x }100$ / $\textit{Total number of viable tumour cells}$	$\text{IC}=\frac{\textit{Tumour area that is occupied by PD-L1 staining immunce cells of any intensity}}{\textit{Total tumour area}}$
Expressed as	Whole number	Percentage (%)
Threshold in licence for PD-L1 positivity	≥10	≥1%
Unit costs per assay	£40.50	£106.20

KEYNOTE-355 used the 22C3 pharmDx assay, whereas IMpassion130 used the SP142 assay. CS Section B.2.9 states that there are differences between tests in antibodies, scoring algorithms and cut-off thresholds used to determine PD-L1 positivity.

Rugo et al 2019[18] reported the overall percentage agreement (OPA) of the VENTANA SP142 IHC assay (IC≥ 1%) with the Dako PD-L1 IHC 22C3 assay (combined proportion score [CPS] ≥1) was 69% (CS Section B.2.9). "*There was approximately 80% concordance in patients captured by immune cell 1% and above (SP142) and CPS of 10 or more, and both assays identified approximately 40% of the intention-to-treat populations that benefited from immunotherapy plus chemotherapy, these two assays should not be considered as interchangeable*."[19]

2.2 Critique of company's overview of current service provision

The proposed part of the pathway for pembrolizumab plus chemotherapy is as a first line treatment option for locally recurrent, unresectable or metastatic TNBC in patients whose tumours express PD-L1 CPS ≥10 (CS Section B.1.3.2).

The CS identifies current treatment for unresectable, locally advanced or metastatic TNBC as atezolizumab with nab-paclitaxel for patients whose tumours express PD-L1 ≥1% (CS Section B.1.3.2). NICE technology appraisal TA639[11] recommends atezolizumab with nab-paclitaxel for treating triple-negative, unresectable, locally advanced or metastatic breast cancer in adults whose tumours express PD-L1 at a level of 1% or more and who have not had previous chemotherapy for metastatic disease (final NICE scope).[2]

The CS identifies current treatment for unresectable, locally advanced or metastatic TNBC for patients with PD-L1 negative tumours, or for cases where there is no PD-L1 testing, as gemcitabine with or without carboplatin, paclitaxel or, nab-paclitaxel (CS Section B.1.3.2).

Chemotherapy is the main treatment for locally advanced or metastatic triple negative breast cancer.[2] Chemotherapy with anthracyclines (e.g. doxorubicin, epirubicin) may be used if the patient has not had prior treatment with anthracyclines in the neoadjuvant / adjuvant setting (clinical advisor opinion).[2] As most patients in the UK diagnosed with TNBC at an early stage will have been given anthracyclines, and many will have had taxanes in the adjuvant setting, it is likely that this will apply only to patients diagnosed with *de novo* metastatic disease (clinical advisor opinion). In UK practice, approximately 5–7% of breast cancers are diagnosed as stage IV, i.e., *de novo* metastatic disease.[20, 21] Some patients may not be considered fit enough for active treatment, these include patients with ECOG PS≥2 and patients with abnormal liver function tend to do poorly (clinical advice).

For patients previously treated with, or contraindicated for, anthracyclines, NICE Clinical Guideline 81[22] recommends single-agent taxane as a first-line treatment for advanced breast cancer (final NICE scope).[2] If patients may be able to tolerate additional toxicity, combination chemotherapy may be used (NICE guideline CG81).[22]

For patients relapsing within one year of taxane treatment, further taxane treatment may be suboptimal, and an alternative treatment will usually be recommended, usually carboplatin with or without gemcitabine, capecitabine, or vinorelbine (clinical advisor opinion). Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered

appropriate (NICE TA116).[23] Patients with BRCA gene mutation-positive tumours are more likely to respond to carboplatin than a taxane.[11]

2.3 Critique of company's definition of the decision problem

CS Section B.1.1 addresses the differences between the final NICE scope and the CS. A summary of the decision problem as outlined in the final scope issued by NICE, and as addressed in the CS Section B.1.1 is presented in Table 5. The ERG critiques this summary in Table 35.

Table 5: Decision problem (adapted from CS Table 1)

	Final scope issued by NICE[2]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with previously untreated locally recurrent inoperable or metastatic, triple negative breast cancer.	[redacted]	The population described by MSD reflects the draft licence indication wording.
Intervention	Pembrolizumab (with chemotherapy)	Pembrolizumab (KEYTRUDA ®) in combination with taxanes (nab-paclitaxel or paclitaxel).	To be reflective of KEYNOTE-355 clinical data and to reflect the UK standard of care.
Comparators	• Anthracycline based chemotherapy • Single agent taxane chemotherapy regimens (docetaxel or paclitaxel) For people whose tumours have PD-L1 expression ≥1% • Atezolizumab in combination with nab-paclitaxel	• Paclitaxel • Docetaxel • Atezolizumab in combination with nab-paclitaxel	To align with current standard of care in the UK
Outcomes	• overall survival (OS) • progression-free survival (PFS) • response rate (RR) • adverse effects of treatment (AEs) • health-related quality of life (HRQoL)	As scope but with the addition of • Duration of response (DoR)	Inclusion of DOR to reflect clinical trial outcomes and relevant for decision making

2.3.1 Population

The population in the final NICE scope is "*People with previously untreated locally recurrent inoperable or metastatic, triple negative breast cancer*".[2]

CS Section B.1.1 states that "*The majority of evidence presented in this submission will focus on the population of patients diagnosed with TNBC whose tumours express PD-L1 CPS ≥10*". The population differs from the scope in excluding [redacted].

[redacted]

2.3.2 Intervention

The intervention in the final NICE scope is pembrolizumab (with nab-paclitaxel, paclitaxel, or gemcitabine and carboplatin).[2] The CS, however, focussed on pembrolizumab in combination with taxanes (nab-paclitaxel or paclitaxel) stating that "*This is reflective of the KEYNOTE-355 clinical data and UK clinical experts suggesting taxane chemotherapies constitute the most relevant Standard of Care (SoC) chemotherapy options in the UK for this population (prior to IO introduction)*." The company also states that "*that the gemcitabine/carboplatin high use observed in KEYNOTE-355 would not be expected in the UK setting since it is primarily used in patients who relapse early and were previously treated with taxanes*" and cite market research data showing the limited use of gemcitabine / carboplatin in first-line mTNBC ([redacted]).

Clinical data, from the KEYNOTE-355 study, in which some patients were treated with pembrolizumab, gemcitabine and carboplatin, are included in the CS. However, the model focusses on pembrolizumab in combination with taxanes.

2.3.3 Comparators

The comparators in the final NICE scope are: anthracycline based chemotherapy; single agent taxane chemotherapy regimens (docetaxel or paclitaxel); and for people whose tumours have PD-L1 expression ≥1%, atezolizumab in combination with nab-paclitaxel.

The CS differs by:

- Excluding anthracycline based therapy – anthracycline may be given to patients diagnosed with *de novo* metastatic disease, who will not have had prior treatment with anthracyclines, which could apply to 5-7% patients (ERG section 2.2);
- Restricting the population considered for atezolizumab in combination with nab-paclitaxel treatment to those whose tumours express PD-L1 CPS ≥10 (using the Dako PD-L1 IHC 22C3 pharmDx Assay).

Although the ERG notes that the decision problem considered by the company only includes a subset of the population from the NICE scope, based on the proposed marketing authorisation indication, this deviation from the scope appears reasonable. Concentrating on taxanes and atezolizumab plus nab-paclitaxel as comparators seems reasonable for this subset of the population, however for patients diagnosed with *de novo* metastatic disease the following comparators could be considered: anthracycline based therapy; carboplatin with or without gemcitabine; capecitabine; or vinorelbine.

2.3.4 Outcomes

The outcomes from the final NICE scope are included in the CS (OS, PFS, RR, AEs, HRQoL). The CS additionally presents duration of response (DoR), that was available from the KEYNOTE-355 trial.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

3.1.1 Searches

Appendix D of the CS reports a systematic literature review (SLR) of clinical effectiveness based on literature searches of the core databases of MEDLINE, Embase and CENTRAL along with US and European trial registries and relevant congress series.

In question A7 of the clarification process [24] the company stated that initial searches were run in August 2019, with subsequent updates in August and November 2020.

In the database searches, the population (triple negative breast cancer) was defined using long search strings - some of which, when tested by the ERG, retrieved very few (if any) results. A more sensitive strategy might have been to combine the "breast cancer" and "triple negative" facets of the population where they occurred in close proximity without requiring the exact phrasing used by the company. When asked to comment on the potential risk of missing studies, the company acknowledged the limitations of their approach but argued that these were mitigated by (i) the use of the (exploded) MeSH term "triple negative breast neoplasms" and (ii) complementary search methods including checking reference lists. Furthermore, the company stressed that with regard to trials of pembrolizumab itself, "*as the manufacturer of the technology being appraised, MSD is aware of all relevant RCTs*" (clarification response, A1).[24]

Search strategies were designed to identify randomised controlled trials (RCTs) of pembrolizumab and a long list of comparators and combination therapies, not all of which were included in the final scope of the Decision Problem as stated in CS Document B table 1. The ERG queried this approach and the company responded that "*the SLR was designed to cover all TNBC disease stages covering the neo-adjuvant, adjuvant and metastatic stage of TNBC and as such, it includes comparators that were reflective of this and may not be used in metastatic disease alone. The final list of studies relevant for the ID1546 mTNBC decision problem (that is; metastatic disease, comparators and outcomes relevant for the decision problem) were identified after the application of prespecified PICOS criteria developed for this submission (as outlined in Appendix of the original submission)*" (clarification letter, A3).

The intervention terms were only searched in titles, subject headings and abstracts – an approach which was questioned by the ERG since these terms are also often found in other database field such as "drug name" or "name of substance". In response to the issues raised by the ERG, the company re-ran the searches using the multi-purpose .mp. suffix to search additional fields including "drug name" or "name

of substance", identifying an additional 37 records, however none of these met the PICOS inclusion criteria.

In spite of the concerns raised above, the ERG considers it unlikely any relevant studies eligible for inclusion have been missed, and our own informal searches did not identify any obvious omissions.

3.1.2 Inclusion criteria

The company conducted an SLR to identify clinical effectiveness and safety evidence relevant to the final NICE scope (CS Appendix D). The company undertook a broad review, designed to cover all TNBC disease stages (CS clarification response A3[24]), which was then narrowed for inclusion in the CS (CS Appendix D). Inclusion criteria for the company's original systematic review, are presented in CS Appendix D Table 4.

The SLR included populations with previously untreated locally recurrent inoperable or metastatic TNBC. For inclusion in the CS, this was narrowed to patients diagnosed with TNBC whose tumours express PD-L1 CPS ≥10.

The intervention eligible for both the SLR and CS was pembrolizumab 200 mg IV on day 1 of each 21-day cycle, plus chemotherapy. Chemotherapy regimens eligible for combination with pembrolizumab comprised: nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 every 28 days; paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 every 28 day; gemcitabine 1000 mg/m2 and carboplatin AUC 2 (AUC =area under the free carboplatin plasma concentration versus time curve, Carboplatin dose calculated using the Calvert equation [25]) on days 1 and 8 of each 21-day cycle (CS Appendix D).

Comparators in the SLR included a range of chemotherapy agents as monotherapy or combination therapy, as well as immunotherapy with atezolizumab plus nab-paclitaxel (CS Appendix D Table 4). For the CS, the comparators considered were: single agent taxane chemotherapy regimens (docetaxel or paclitaxel); or atezolizumab in combination with nab-paclitaxel for the population whose tumours express PD-L1.

The SLR sought effectiveness, adverse event and HRQoL outcomes. For the indirect comparison, a study had to report OS, PFS, or both (CS clarification response A5).[24] The CS included the outcomes from the NICE scope[2] (OS, PFS, RR, AEs, HRQoL) but additionally included DoR, that was available from the KEYNOTE-355 trial. Study design was restricted to RCTs (CS Appendix D Table 4). The ERG considers this to be generally appropriate given that RCTs represent a higher quality of evidence than other study types.

Study selection was conducted by two researchers (CS Appendix D.1.1.2), as is good practice for systematic reviews.

3.1.3 Critique of data extraction

Data extraction was conducted by two researchers (CS clarification response A13[24]), as is good practice for systematic reviews. Data in the CS were checked by the ERG against trial publications and the CSR for KEYNOTE-355[26] and were found to be accurate.

3.1.4 Quality assessment

Quality assessment was conducted by two researchers (CS clarification response A13[24]), as is good practice for systematic reviews. Quality items assessed by the company (presented in CS Appendix D.1.4) were taken from the Cochrane Risk of Bias 1.0 tool.[27] Although this is not the most up-to-date version [Cochrane RoB2.0 Higgins 2019[28]] Cochrane RoB 1.0[27] is a valid and appropriate tool for assessing quality of RCTs. The ERG has independently quality assessed KEYNOTE-355 in Table 6.

Patients were randomly assigned in a 2:1 ratio with more people in the pembrolizumab plus chemotherapy arm. Randomised sequence generation and allocation concealment were by a centralised interactive voice and web response system. This indicates a low risk of selection bias. Randomisation was stratified by: the type of on-study chemotherapy received (taxane or gemcitabine-carboplatin); PD-L1 expression at baseline (CPS≥1 or CPS<1); and previous treatment with the same class of chemotherapy in the neoadjuvant or adjuvant setting (yes or no) (CS Section B.2.3).[19] Randomisation was not stratified by PD-L1 with a CPS≥10, and so although the assessed baseline characteristics in this subgroup appeared well balanced between groups, it cannot be known if unmeasured prognostic factors were balanced with CPS≥10 introduced as a subgroup for analysis in protocol revisions after enrolment and the first interim analysis.[19] Patient baseline characteristics of the ITT population were balanced between treatment groups, and there were no unexpected imbalances in drop-outs between groups.[19]

An intention-to-treat (ITT) analysis was published for PFS results at the second interim analysis (IA2).[19] The subgroup of CPS≥10 is used in the CS, so does not include all randomised participants for the RCT, but is analysed with patients in their randomly allocated treatment arms in accordance with the ITT principle.

HRQoL analyses were based on the patient-reported outcome (PRO) full analysis set (FAS) population, defined as all randomised participants who received at least one dose of study intervention and had completed at least one PRO assessment (CS Section B.2.6.6, CS clarification response B3[24]). The safety analysis population was all randomised patients who received at least one dose of study treatment, analysed according to actual treatment received (CS Section B.2.10).

Table 6: Quality Assessment of KEYNOTE-355

Question	CS Assessment	ERG Assessment	ERG Support for judgement[19]
Sequence generation	Low risk	Low risk	Randomly assigned by a block method (block size of six)
Allocation concealment	Low risk	Low risk	Allocation by a central interactive voice response system with an integrated web-response system
Blinding of participants and personnel	Low risk	Low risk	Investigators and patients blinded
Blinding of outcome assessors	Low risk	Low risk	Blinded
Incomplete outcome data	Low risk	Low risk	Publication of IA2 PFS includes ITT analysis
Selective outcome reporting	Low risk	N/A	Study ongoing, not all outcomes complete and so could not be published (at time of writing)
Other sources of bias	High risk (Industry sponsored, CS clarification response A14[24])	High risk	Industry sponsored

N/A=not applicable. IA2=interim analysis 2

There was blinding of patients and physicians.[19] There was blinding of outcome assessors, by Blinded Independent Central Review (BICR)[19] for endpoints of objective response rate (ORR), DoR, and disease control rate (DCR), all based on RECIST version 1.1 (Response Evaluation Criteria in Advanced Solid Tumors (RECIST) version 1.1.[29] This indicates a low risk of performance bias and detection bias. [redacted]

The KEYNOTE-355 RCT is ongoing and therefore final results have not yet been collected, so it cannot be assessed if the authors measured more outcomes than they published. However, data from the clinical cut-off date (IA2: 11th December 2019) for all outcomes of relevance to this review were provided by the company in the CS and accompanying documents.

3.1.5 Study of interest identified

The CS includes one RCT of pembrolizumab which was relevant to the decision problem: KEYNOTE-355 (NCT02819518). This formed the key evidence for clinical effectiveness within the CS. [redacted] The ERG does not believe that any relevant published RCTs of pembrolizumab that could have provided effectiveness data have been missed or omitted from the CS. The trial was of good methodological quality (ERG Section 3.1.4).

At time of writing, KEYNOTE-355 was ongoing, [redacted], with final results expected in [redacted] Data from the clinical cut-off date (IA2: 11th December 2019) for outcomes of relevance to this review were provided by the company in the CS and accompanying documents.

KEYNOTE-355 had a protocol revision prior to IA2 (protocol revision October 2019) to include subjects with PD-L1 positive tumours with a higher combined positive score (CPS) cut-off of ≥10 (CPS ≥10), to identify *"an enriched population of subjects that could potentially benefit more from pembrolizumab plus chemotherapy in metastatic triple negative breast cancer"*.[19]

PFS data from the clinical cut-off date (IA2 11th December 2019) for KEYNOTE-355 have been published in an abstract[30] and a full paper in a peer-reviewed journal by Cortes et al 2020[19] which also reported safety data.

The CS identifies three other ongoing phase III studies of pembrolizumab in triple negative breast cancer (TNBC), of which one is a study in mTNBC: KEYLYNK-009 (CS clarification response A12[24]). The remaining two studies are for neoadjuvant or adjuvant therapy of mTNBC and are not relevant to the decision problem. KEYLYNK-009 (NCT04191135) is comparing olaparib plus pembrolizumab vs chemotherapy plus pembrolizumab after induction with first-line chemotherapy plus pembrolizumab in locally recurrent inoperable or metastatic TNBC (CS clarification response A12[24]), and is not due to reach primary completion date until January 2026.

3.1.6 Study design:

KEYNOTE-355 is a two-arm, multicentre international RCT (Table 7). It includes nine centres in the UK and 37 patients in the UK (CS Section B.2.3). Patients were randomised 2:1 (CS Section B.2.3)[19] to Pembrolizumab 200 mg IV infusion every 3 weeks plus chemotherapy IV infusion (one of gemcitabine plus carboplatin, nab-paclitaxel or paclitaxel); or placebo plus chemotherapy (one of gemcitabine plus carboplatin, nab-paclitaxel or paclitaxel). Doses for chemotherapy regimens were: nab-paclitaxel 100 mg/m² on days 1, 8, and 15, every 28 days; paclitaxel 90 mg/m² on days 1, 8, and 15, every 28 days; or gemcitabine 1000 mg/m² plus carboplatin area under the curve 2 on days 1 and 8, every 21 days. Treatment continued until disease progression or cessation of study treatment (CS Section B.2.3). Randomisation of patients took place from January 2017 to June 2018.[19]

Table 7: KEYNOTE-355 study characteristics (info from CS Section B.2.2 and Cortes et al 2020[19])

Study	Population	Intervention (n randomised)	Comparator (n randomised)
KEYNOTE-355 NCT02819518	Adult patients with previously untreated locally recurrent inoperable or metastatic TNBC	Pembrolizumab plus chemotherapy (one of gemcitabine plus carboplatin, nab-paclitaxel or paclitaxel) N=566	Placebo plus chemotherapy (one of gemcitabine plus carboplatin, nab-paclitaxel or paclitaxel) N=281

Primary outcomes (CS Section B.2.3) were:

- PFS defined as time from randomisation to the first documented disease progression based on RECIST 1.1 as assessed by a blinded central imaging vendor, or death due to any cause, whichever occurred first, comparing pembrolizumab with chemotherapy versus placebo with chemotherapy;
- OS of pembrolizumab with chemotherapy versus placebo with chemotherapy.

Secondary outcomes (CS Section B.2.3 and CS Section B.2.6) were:

- ORR (defined as the proportion of the participants in the analysis population who have a complete response (CR) or partial response (PR)),
- DoR and DCR (defined as the percentage of participants who have achieved CR or PR or have demonstrated stable disease for at least 24 weeks) based on RECIST 1.1 as assessed by a blinded central imaging vendor.

Other secondary outcomes (CS Section B.2.3) were:

- HRQoL assessment from baseline using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and EORTC Breast Cancer-Specific Quality of Life Questionnaire.
- Additionally, the safety and tolerability of the three pembrolizumab and chemotherapy combinations were assessed. Grades of AEs were defined according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (CS Section B.2.10).

An exploratory objective was to characterize utilities in all participants and in subgroups with PD-L1 positive tumours (CPS ≥1 and CPS ≥10) using EuroQol-5 Dimension Questionnaire (EQ-5D).

KEYNOTE-355 is ongoing and data are from the clinical cut-off date (IA2: 11th December 2019).
Three interim analyses were planned with IA2 proposed to take place after approximately 185 OS events among subjects with CPS ≥10 were observed. The family-wise type-I error rate over six primary hypotheses and two secondary hypotheses was controlled at 2.5% (one-sided) with 0.5% allocated to PFS, 1.8% allocated to OS, and 0.2% allocated to ORR hypotheses.

Key study eligibility criteria are shown in Table 8. Patients were adults (≥18 years) with previously untreated locally recurrent inoperable or metastatic TNBC. Eligibility criteria regarding ECOG PS and adequate organ function (excluded patients with moderate to severe liver dysfunction or severe renal dysfunction) meant that patients were fitter than would be seen in mTNBC in UK practice. Patients with ECOG PS≥2 and patients with abnormal liver function tend to do poorly and many will not be fit for active treatment (clinical advice).

Table 8: KEYNOTE-355 eligibility criteria (info from CS Section B.2.3)

Inclusion criteria
Adults (≥18 years) with previously untreated locally recurrent inoperable or metastatic TNBC. locally recurrent inoperable breast cancer not previously treated with chemotherapy and which cannot be treated with curative intent OR has metastatic breast cancer not previously treated with chemotherapy. centrally confirmed TNBC, as defined by the most recent American Society of Clinical Oncology/college of American Pathologists (ASCO/CAP) guidelines. completed treatment for Stage I-III breast cancer, if indicated, and ≥6 months elapsed between the completion of treatment with curative intent treated with (neo)adjuvant anthracycline, if they received systemic treatment, unless anthracycline was contraindicated or not considered the best treatment option measurable disease based on Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) recently or newly obtained core or excisional biopsy for central determination of TNBC status and PD-L1 expression, unless contraindicated. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, within 10 days prior to the start of study drug. life expectancy ≥12 weeks from randomisation. Demonstrates adequate organ function, within 10 days prior to the start of study drug. adequate method of contraception, if applicable
Exclusion criteria
participating in a clinical study currently or within 4 weeks prior to randomization. Has not recovered (e.g., to ≤ Grade 1 or to baseline) from AEs due to a previously administered therapy. neuropathy ≥ Grade 2. active autoimmune disease that has required systemic treatment in the past 2 years diagnosis of immunodeficiency or is receiving immunosuppressive therapy within 7 days prior to randomization. known additional malignancy that progressed or required active treatment within the last 5 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, and in situ cervical cancer. known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they have stable brain metastases and did not receive chemotherapy for metastatic breast cancer. history of (non-infectious) pneumonitis that required steroids or current pneumonitis. active, or a history of, interstitial lung disease. known history of active tuberculosis. active infection requiring systemic therapy. history of Class II-IV congestive heart failure or myocardial infarction within 6 months of randomization.

known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days (or longer as specified by local institutional guidelines) after the last dose of study drug.
Has received prior therapy with an anti-programmed cell death 1 (anti-PD-1), anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T cell receptor (such as cytotoxic T-lymphocyte-associated protein 4 [CTLA-4], OX-40, CD137) or has previously participated in MSD pembrolizumab (MK-3475) clinical studies.
known history of human immunodeficiency virus (HIV).
known active hepatitis B or hepatitis C.
received a live vaccine within 30 days prior to randomization.
known history of hypersensitivity or allergy to pembrolizumab and any of its components and/or to any of the study chemotherapies (e.g., nab-paclitaxel, paclitaxel, gemcitabine, or carboplatin) and any of their components.
Is receiving any medication prohibited in combination with study chemotherapies, unless medication was stopped within 7 days prior to randomization.

Concomitant medications were allowed at investigator's discretion when these were considered necessary for the patient's welfare (CS Section B.2.3). Medications not allowed during the treatment phase of the trial were antineoplastic systemic chemotherapy or biological therapy, herbal supplements, live vaccines. Glucocorticoids (except for AE of suspected immunologic aetiology, asthma, or to avoid allergic reactions), and radiation therapy was not allowed (except for after consultation with the study sponsor to a single solitary lesion or to the brain) (CS Section B.2.3).

[redacted]

Of the 566 patients randomised to Pembrolizumab plus chemotherapy, 425 had PD-L1 CPS ≥1, and of these 220 had PD-L1 CPS ≥10.[19] Of the 281 patients randomised to placebo plus chemotherapy, 211 had PD-L1 CPS ≥1, and of these 103 had PD-L1 CPS ≥10.[19]

At IA2 (11th December 2019), of 220 patients who had PD-L1 CPS ≥10, and were randomised to pembrolizumab plus chemotherapy, 219 received treatment, and 190 had discontinued treatment, 14 had completed pembrolizumab treatment (received 35 administrations of pembrolizumab and discontinued chemotherapy), and 15 patients remained on chemotherapy.[19] At the clinical cut-off date, in the placebo plus chemotherapy group, of 103 randomised who had PD-L1 CPS ≥10, 103 received

treatment, and 95 had discontinued treatment, two had completed placebo treatment, and six patients remained on chemotherapy.[19]

At IA2, in the ITT population, median duration of follow-up was 16.8 months (range 0.2 to 35.0) (CS Section B.2.6.1). Mean duration of exposure was [redacted] weeks (standard deviation (SD) [redacted] weeks) in the pembrolizumab plus chemotherapy arm, and [redacted] weeks (SD [redacted] weeks) in the placebo plus chemotherapy arm (CS Section B.2.6.1).[redacted]

The chemotherapy used was the investigator's choice (CS Section B.2.3). The proportion of patients receiving taxanes was similar between the two arms, 42.7% (pembrolizumab plus chemotherapy) and 45.7% (placebo plus chemotherapy) (CS clarification response A20[24]), with the proportion who received nab-paclitaxel lower for the pembrolizumab plus chemotherapy arm (27.7%) than for the placebo plus chemotherapy arm (35.0%).

Table 9:

[redacted] [26] **(Cortes et al 2020)**[19]

	Pembrolizumab plus Chemotherapy		Placebo plus Chemotherapy		Total	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Subjects in population	220		103		323	
Gender						
Female	220	(100.0)	103	(100.0)	323	(100.0)
Age (Years)						
< 65	[redacted]					
>= 65						
Mean						
SD						
Median	52.0		55.0			
Range						
Race						
American Indian or Alaska Native	2	(0.9)	0	(0.0)		
Asian	44	(20.0)	20	(19.4)		

Black or African American	9	(4.1)	6	(5.8)	[redacted]	[redacted]
Multiple	6	(2.7)	3	(2.9)	[redacted]	[redacted]
White	153	(69.5)	70	(68.0)	[redacted]	[redacted]
Missing	6	(2.7)	4	(3.9)	[redacted]	[redacted]
Ethnicity						
Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region						
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Australia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

North America	[redacted]					
Rest of the World						
Chemotherapy on Study						
Nab-Paclitaxel	63	(28.6)	36	(35.0)	[redacted]	
Paclitaxel	33	(15.0)	11	(10.7)		
Gemcitabine/ Carboplatin	124	(56.4)	56	(54.4)		
Chemotherapy on Study (Actual)						
Nab-Paclitaxel	61	(27.7)	36	(35.0)	97	(30.0)
Paclitaxel	33	(15.0)	11	(10.7)	44	(13.6)
Gemcitabine/ Carboplatin	125	(56.8)	56	(54.4)	181	(56.0)
Missing	1	(0.5)	0	(0.0)	1	(0.3)
Prior Treatment with Same Class Chemotherapy in the Neoadjuvant or Adjuvant Setting						
Yes	46	(20.9)	19	(18.4)	[redacted]	
No	174	(79.1)	84	(81.6)		
Prior Treatment with Same Class Chemotherapy in the Neoadjuvant or Adjuvant Setting (Actual)						
Yes	[redacted]					
No						

Missing	[redacted]					
Disease Status						
Metastatic, De Novo	68	(30.9)	35	(34.0)	[redacted]	
Metastatic, Recurrence	144	(65.5)	62	(60.2)		
Locally Recurrent Inoperable	7	(3.2)	6	(5.8)		
Missing	1	(0.5)	0	(0.0)		
ECOG PS						
0	134	(60.9)	62	(60.2)	[redacted]	
1	86	(39.1)	41	(39.8)		
HER2 Status						
0-1+ by IHC	[redacted]					
2+ by IHC						
History of Brain Metastasis						
Yes	[redacted]					
No						

Menopausal Status						
Pre-menopausal	74	(33.6)	34	(33.0)		
Post-menopausal	146	(66.4)	69	(67.0)		
Disease Free Interval						
de novo metastasis	68	(30.9)	35	(34.0)		
< 12 months	49	(22.3)	17	(16.5)		
>= 12 months	102	(46.4)	51	(49.5)		
Unknown	1	(0.5)	0	(0.0)		
Baseline Lactate Dehydrogenase (LDH)						
Normal						
> ULN and < 2 x ULN						
>= 2 x ULN						
Missing						
Sum of Target Lesion Size at Baseline (Central) (mm)						
Subjects with data						

Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Sum of Target Lesion Size at Baseline (Investigator) (mm)				
Subjects with data	[redacted]	[redacted]	[redacted]	
Mean	[redacted]	[redacted]	[redacted]	
SD				
Median				
Range	[redacted]	[redacted]	[redacted]	
Database Cut-off Date: 11DEC2019				

3.1.7 KEYNOTE-355 effectiveness

Data from KEYNOTE-355 are from IA2. Results in this section focus on the CPS≥10 subgroup of the RCT.

3.1.7.1 Overall survival

[redacted]

[redacted]

Although there isn't a standard definition of "clinically meaningful" of OS in this subset of mTNBC patients, they are considered to have poor prognosis, and so a survival advantage of three months or more is clinically relevant (clinical advice).

Table 10: OS (IA2) KEYNOTE-355 CPS ≥10 (adapted from CS tables 12 and 13 and 14) (CSR) [26]

	Pembrolizumab plus chemotherapy N=220	**Placebo plus chemotherapy N=103**
Events, n (%)	[redacted]	[redacted]
Median OS (95% CI) months	[redacted]	[redacted]
OS rate at 6 months, % (95% CI)	[redacted]	[redacted]
OS rate at 12 months, % (95% CI)	[redacted]	[redacted]
OS rate at 18 months, % (95% CI)	[redacted]	[redacted]

OS rate at 24 months, % (95% CI)	[redacted]	[redacted]

HR= hazard ratio, HR stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).
† The 95% confidence intervals may not reflect the nominal significance level used at the interim analysis to control the overall significance level.

[redacted]

The study was not powered to compare differences in treatment effects between sub-groups, especially when examining as part of another subgroups (CPS≥10), therefore subgroup results should be interpreted with caution (CS clarification response A24[24]). Within the CPS≥10 subgroup, 96 patients were treated with pembrolizumab and taxane, and 47 patients were treated with placebo plus taxane (CS Section B.2.7).

In Section B2.7 of the CS, the company evaluated the effect of treatment according to 15 univariate subgroups in participants whose tumours express PD-L1 CPS ≥ 10. The ERG notes the following when assessing whether there is a differential treatment effect according to different patient characteristics i.e., an interaction between the effect of treatment and baseline characteristics:

- RCTs should be analysed as they are randomised. Hence, given that randomisation was stratified, the effect of treatment should be assessed adjusted for strata.
- It is more efficient to assess the consistency of treatment effect according to different patient characteristics by considering interaction terms.
- Apparent interactions between treatment and patient characteristics from univariate analyses may be spurious; the effects of treatment and patient characteristics may be additive in an appropriate multivariable model.
- Continuous variables such as age should not be categorised because it is an inefficient use of information and implies that there is an abrupt change in response at the cut-off.

In the CS, the company claimed that the "*benefit of pembrolizumab + chemotherapy on PFS, OS, and ORR compared with placebo + chemotherapy in participants whose tumours express PD-L1 CPS ≥10 is consistent across subgroups".* However, in response to clarification question A24, the company stated that the treatment effect is generally consistent across subgroups "*to indicate that the treatment effect was seen across most groups*". In spite of the limitations associated with univariate subgroup analyses, the ERG notes that results of the company's univariate subgroup analyses suggest that there might be differential effects according to the following subgroups:

- Older patients derive more benefit than younger patients.
- Non- Hispanics or Latinos derive more benefit than Hispanics or Latinos.
- Patients treated with paclitaxel derive more benefit than patients treated with nab-paclitaxel.
- Patients who did not receive prior adjuvant or neoadjuvant chemotherapy derive more benefit than those who received prior adjuvant or neoadjuvant chemotherapy.
- Patients who did not receive prior adjuvant or neoadjuvant taxane treatment derive more benefit than those who received prior adjuvant or neoadjuvant taxane treatment.

3.1.7.2 Progression-free survival

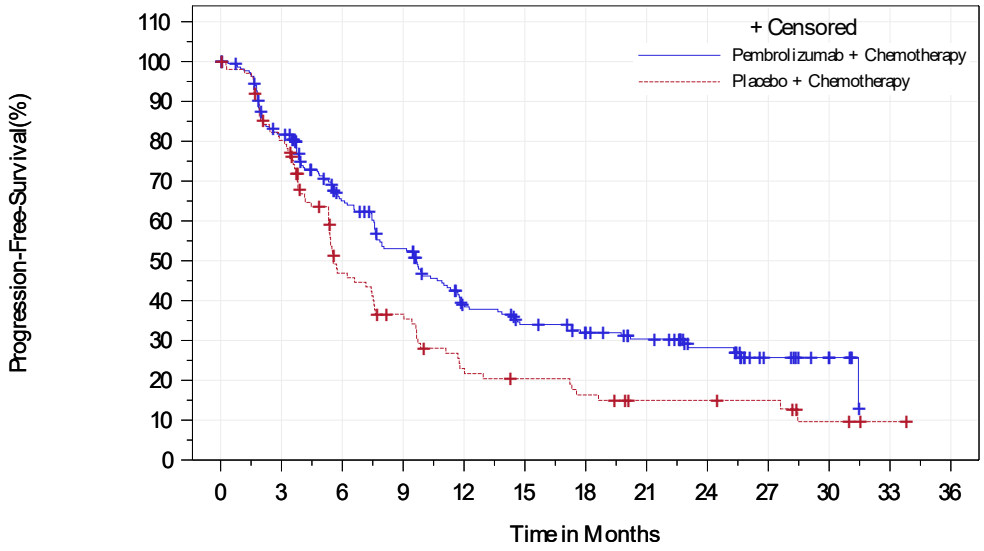
At IA2, there were 136/220 (61.8%) PFS events in the pembrolizumab plus chemotherapy arm, and 79/103 (76.7%) PFS events in the placebo plus chemotherapy arm (CS Section B.2.6.3) (Table 11). PFS Kaplan-Meier survival functions are shown in Figure 2.[19] Median PFS for the pembrolizumab plus chemotherapy arm was 9.7 months (95% CI 7.6, 11.3), and for the placebo plus chemotherapy group was 5.6 months (95% CI 5.3, 7.5) (CS Section B.2.6.3).[19] As for OS, the observed p-value for PFS did not cross the pre-specified efficacy boundary at IA2. The company presented a 95% confidence interval unadjusted for the hazard ratio (HR 0.65 (95% CI: 0.49, 0.86)). The width of the 95% confidence intervals may not reflect the nominal significance level used at the interim analysis to control the overall significance level and would likely be considerably wider if it did.

Table 11: PFS (IA2) – CPS ≥10 (ITT population) (adapted from CS tables 12 and 15 and 16 and Cortes et al 2020[19])(CSR)[26]

PFS (BICR per RECIST 1.1)	Pembrolizumab plus chemotherapy N=220	Placebo plus chemotherapy N=103
Events, n (%)	136 (61.8)	79 (76.7)
Median PFS (95% CI) months	9.7 (7.6, 11.3)	5.6 (5.3, 7.5)
	HR: 0.65 (95% CI 0.49, 0.86); p=0.0012[†]	
PFS rate at 3 months, % (95% CI)	81.8 (76.0, 86.4)	80.2 (71.0, 86.8)
PFS rate at 6 months, % (95% CI)	65.0 (58.1, 71.2)	46.9 (36.5, 56.6)
PFS rate at 9 months, % (95% CI)	53.0 (45.8, 59.8)	36.6 (26.9, 46.4)
PFS rate at 12 months, % (95% CI)	39.1 (32.0, 46.0)	23.0 (14.7, 32.3)

BICR=Blinded Independent Central Review. HR= hazard ratio, HR stratified by chemotherapy on study (taxane vs gemcitabine/carboplatin) and prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no)
[†] The 95% confidence intervals may not reflect the nominal significance level used at the interim analysis to control the overall significance level.

Figure 2: PFS Kaplan-Meier survival functions based on BICR assessment per RECIST 1.1 - CPS ≥10 (copied from CS Figure 4)



Number of subjects at risk

Pembrolizumab + Chemotherapy	220	173	122	96	63	52	44	37	25	12	5	0	0
Placebo + Chemotherapy	103	80	41	30	18	15	12	8	8	7	3	1	0

Database Cutoff Date:11DEC2019

[redacted]Within the CPS≥10 subgroup, n=96 patients were treated with pembrolizumab and taxane, and n=47 were treated with placebo plus taxane (CS Section B.2.7). [redacted] (CS Section B.2.7). [redacted]

Although there isn't a standard definition of "clinically meaningful" PFS in this subset of mTNBC patients, they are considered to have poor prognosis, and so a survival advantage of three months or more is clinically relevant (clinical advice).

3.1.7.3 Response rate

At IA2 (as shown in Table 12), the ORR was 117/220 (53.2%, (95% CI 46.4, 59.9)) for the pembrolizumab plus chemotherapy arm versus 41/103 (39.8%, (95% CI 30.3, 49.9)) for the placebo plus chemotherapy arm, between group difference 13.6% (95% CI 1.9, 24.8) (CS Section B.2.6.4). At IA2, the observed DCR was 143/220 (65.0% (95% CI 58.3, 71.3)) for in the pembrolizumab plus chemotherapy arm, and 56/103 (54.4% (95% CI 44.3, 64.2)) in the placebo plus chemotherapy arm (CS Section B.2.6.4) with a difference between the arms of 10.8 (95% CI -0.7, 22,3).

[redacted]

.

Table 12: ORR (BICR per RECIST 1.1 (IA2) CPS ≥10 (adapted from CS tables 12 and 17 and 18, and CS clarification response A21[24])(CSR)[26]

	Pembrolizumab plus chemotherapy N=220	**Placebo plus chemotherapy N=103**
Objective Response number	117	41
Confirmed ORR % (95% CI)	53.2 (46.4, 59.9)	39.8 (30.3, 49.9)
Difference in % vs control (95% CI)	13.6 (1.9, 24.8) [redacted]	
% of patients who achieved a CR (95% CI)	[redacted]	[redacted]
Disease control rate [CR+PR+stable disease] (95% CI)	65.0 (58.3, 71.3) [redacted]	54.4 (44.3, 64.2)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Duration of response Median (range) months	[redacted]	[redacted]

† indicates that the patient was administratively censored (at time of last disease assessment) without progression or death.

[redacted]

Clinical advice to the ERG considered this difference in ORR to be clinically relevant.

3.1.7.4 HRQoL

HRQoL analyses were based on PRO full analysis set (FAS) population, defined as all randomised participants who received at least one dose of study intervention and had completed at least one PRO assessment (CS Section B.2.6.6). Completion rates decreased over time point, as more patients discontinued the study, probably also reflecting lower completion rates as health deteriorates (CS Section B.2.6.6 and CS clarification response B10[24]).

From baseline to week 15 in the CPS ≥10 subgroup (see Table 13), there was some worsening of HRQoL indicated by decreasing EQ-5D VAS in both treatment groups (CS Section B.2.6.6). [redacted]

Table 13: KEYNOTE-355 EQ-5D VAS CPS ≥10 (copied from CS Table 21)

	Baseline		Week 15		Change from Baseline at Week 15	
Treatment	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**LS Mean (95% CI) †**
Pembrolizumab plus chemotherapy	[redacted]					
Placebo plus chemotherapy						
Pairwise comparison					**Difference in LS Means 95% CI)**	**p-Value**
Pembrolizumab plus chemotherapy vs. Placebo plus chemotherapy						

† Based on cLDA model with the PRO scores as the response variable, and treatment by timepoint interaction, and stratum (defined by stratification factors of chemotherapy on study [taxane vs gemcitabine/carboplatin] and prior treatment with same class of chemotherapy in the (neo)adjuvant setting [yes vs no]) as covariates.
For baseline and Week 15, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group. Two-sided p-value.
Database Cut-off Date: 11DEC2019

[redacted]

[redacted]

3.1.7.5 Adverse events

The safety population of the CPS≥10 comprised 219 people in the pembrolizumab plus chemotherapy group, and 103 people in the placebo plus chemotherapy group (CS Section B.2.10). Non-serious adverse events up to 30 days after last dose and serious adverse events up to 90 days after last dose are included. Median time on treatment in the pembrolizumab plus chemotherapy treated group was [redacted], and in the placebo plus chemotherapy treated group was [redacted] (CS Section B.2.10).

Serious AEs were defined as any adverse event occurring at any dose or during any use of company's product that meets one of the following criteria: results in death; life threatening; results in a persistent or significant disability/incapacity; a congenital anomaly/birth defect; a new cancer; an overdose; other important medical event (CS clarification response A18[24]). SAEs were experienced by [redacted] in the pembrolizumab plus chemotherapy group, and [redacted] in the placebo plus chemotherapy group (CS Section B.2.10) (see

Table 14).

[redacted]

Grades of AEs were defined according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (CS Section B.2.10).

[redacted]

AEs of any grade were experienced by 216 patients (98.6%) in the pembrolizumab plus chemotherapy group, and 100 patients (97.1%) in the placebo plus chemotherapy group (CS Section B.2.10). The most frequently reported AEs were [redacted] (CS Section B.2.10).

AEs graded 3 or above were experienced by [redacted] in the pembrolizumab plus chemotherapy group, and [redacted] in the placebo plus chemotherapy group (CS Section B.2.10).

[redacted]

[redacted]

Table 14: KEYNOTE-355 CPS≥10 subgroup AEs and all safety population AEs (adapted from CS Tables 28 and 32 and Section B.2.10.4 and CS Appendix F)(CSR)[26]

Event	**CPS≥10 Pembrolizumab plus chemotherapy (n=219)**	**CPS≥10 Placebo plus chemotherapy (n=103)**	[redacted]	[redacted]
Weeks on therapy Mean	[redacted]	[redacted]	[redacted]	[redacted]
Weeks on therapy SD	[redacted]	[redacted]	[redacted]	[redacted]
Weeks on therapy Median	[redacted]	[redacted]	[redacted]	[redacted]
Weeks on therapy Range	[redacted]	[redacted]	[redacted]	[redacted]
Any grade AE n (%)	216 (98.6)	100 (97.1)	[redacted]	[redacted]
Any grade AE drug-related n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Grade ≥ 3	[redacted]	[redacted]	[redacted]	[redacted]
Grade ≥ 3 drug-related	[redacted]	[redacted]	[redacted]	[redacted]

Event	**CPS≥10 Pembrolizumab plus chemotherapy (n=219)**	**CPS≥10 Placebo plus chemotherapy (n=103)**	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs drug-related	[redacted]	[redacted]	[redacted]	[redacted]
Death from AE	[redacted]	[redacted]	[redacted]	[redacted]
Death from AE drug-related			[redacted]	[redacted]
AE leading to discontinuation of any drug	[redacted]	[redacted]	[redacted]	[redacted]

3.2 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

To be considered for inclusion in the indirect comparison, a study had to report overall survival, progression-free survival, or both (CS clarification response A5[24]). The company's SLR identified seven RCTs in the relevant population (CS Section B.2.2), including the KEYNOTE-355 RCT. Of the other six identified studies, one was included in the indirect comparison, the IMpassion130[31] RCT (CS Appendix D.1.1.3). The remaining five studies were excluded as one of two arms having a "*NICE non-eligible comparator*" (CS Appendix D.1.1.3): E2100[32]; JapicCTI-090921[33]; MERiDiAN[34]; TNT[35]; tenacity.[15] Additionally, four studies considered by NICE TA639[11] were excluded for having a NICE non-eligible comparator (CS clarification response A8[24]): AVADO[36]; RIBBON-1[37]; CALGB40502[38]; TURANDOT.[39] None of these references provided data for a CPS≥10 subgroup.[15, 32-39]

Only the subgroups of CPS≥10 patients were used in the CS indirect comparison. Neither the KEYNOTE-355 nor the IMpassion130 trial had originally been designed to assess the subgroup CPS≥10. KEYNOTE-355 had a protocol revision to investigate CPS≥10, and PFS data for this subgroup have been published from IA2.[19] A subgroup of CPS≥10 from IMpassion130 was investigated in a post-hoc analysis in the publication by Rugo 2020.[40]

Both IMpassion130 and KEYNOTE-355 trials had randomisation stratified by PD-L1 ≥1% (not by CPS ≥10). The assay for assessing PD-L1 expression differed between trials. IMpassion130 used PD-L1 SP142 immunohistochemical assay (Ventana Medical Systems)[31]. KEYNOTE-355 used PD-L1 IHC 22C3 pharmDx test (Agilent Technologies, Carpinteria, CA, USA)[19] (CS Section B.2.9.1). Rugo 2020 [40] used a Dako 22C3 assay to identify the CPS≥10 subgroup from IMpassion130. This was based on a subset of the IMpassion130 study with available samples. [40]

IMpassion130 (NCT02425891)[31] was a phase 3, multicentre, double-blind, placebo-controlled RCT comparing atezolizumab 840mg by intravenous infusion on days 1 and 15 of a 4-week cycle plus nab-paclitaxel intravenously on days 1, 8 and 15 at a dose of 100mg/m^2, with placebo plus nab-paclitaxel at the same doses.[31] The population was locally advanced or metastatic TNBC.[31] Atezolizumab plus nab-paclitaxel is recommended by NICE for treatment in this population, whereas the comparator of nab-paclitaxel is not.[11] Randomisation was stratified by: PD-L1+ disease (≥1%); liver metastases (yes or no); and taxane treatment in the neoadjuvant or adjuvant settings (yes or no).[31] There were nine treatment centres in the UK, which recruited 46 patients.[11]

The eligible population for IMpassion130 was people aged 18 years and over with previously untreated locally advanced or metastatic TNBC, with ECOG PS 0 or 1 and adequate organ and haematological function.[31] IMpassion130 excluded patients with radiotherapy and previous curative chemotherapy within 12 months before randomisation,[31] whereas KEYNOTE-355 included patients with ≥6 months elapsed between the completion of treatment for stage I-III with curative intent (CS Section B.2.9.1). Clinical advice to the ERG suggested that patients relapsing between 6 and 12 months of adjuvant chemotherapy would not be good candidates for retreatment with a taxane, so pembrolizumab plus gemcitabine and carboplatin would be preferred to atezolizumab plus nab-paclitaxel. However, the company has not made a case for pembrolizumab plus gemcitabine and carboplatin within its submission. There could, however, be implications for the NMA if the treatment effect of taxanes was modified by time since relapse and this may produce results unfavourable to pembrolizumab plus paclitaxel / nab-paclitaxel as these included patients who had relapsed before 12 months.

Outcomes included in the indirect comparison were OS, and PFS which was assessed, in IMpassion130 by investigators per RECIST 1.1.[31] RECIST 1.1 was also used in KEYNOTE-355[19] (CS Section B.2).

The final OS analysis of IMpassion130 has been published as an abstract[17] and data from the second interim overall survival analysis (data cut-off the 2nd of January, 2019) have been published as a full paper in a peer-reviewed journal , including effectiveness and safety outcomes.[31] PROs have also been published.[41]

IMpassion130 was at low risk of bias (see Table 15). The use of a post-hoc subgroup in the indirect comparison, for which randomisation was not stratified, conveys the risk of treatment groups not being balanced for unmeasured covariates (CS Section B.2.9.1). Samples from the IMpassion130 trial that had additional Dako 22C3 IHC assay testing were derived from n = 614 (68%) of the ITT population, and it was unclear if testers were blinded. [40]

Table 15: Quality Assessment of IMpassion130

Question	CS Assessment (CS Appendix D.1.2.4)	ERG Assessment	ERG Support for judgement[31]
Sequence generation	Low risk	Low risk	Randomly assigned with permuted block method (with a block size of four)
Allocation concealment	Low risk	Low risk	Allocation by a central interactive voice–web response system
Blinding of participants and personnel	Low risk	Low risk	Investigators and patients blinded
Blinding of outcome assessors	Low risk	Low risk	Effectiveness data assessed by blinded investigators
Incomplete outcome data	Low risk	Low risk	Reported ITT analyses
Selective outcome reporting	Low risk	Low risk	All outcomes from protocol published
Other sources of bias	High risk	High risk	Industry sponsored

Baseline characteristics were similar across trials for both the ITT and PD-L1≥1 populations (CS Section B.2.9.1).[19, 31] However, the IMpassion130 PD-L1≥1 population, compared with the KEYNOTE-355 CPS≥10 population, had a higher proportion of brain metastases (7.0% vs 3.4%), and lower proportion of metastatic disease (87.0% vs 95.7%).[19, 31]

In the IMpassion130 PD-L1≥1 subgroup (see Table 16), median OS was 25.4 months (95% CI 19.6, 30.7) in the atezolizumab plus nab-paclitaxel group, and 17.9 months (95% CI 13.6, 20.3) in the placebo

plus nab-paclitaxel group.[17] In the PD-L1≥1 subgroup, median PFS was 7.5 months (95% CI 6.7–9.2) in the atezolizumab plus nab-paclitaxel group, and 5.3 months (95% CI 3.8–5.6) in the placebo plus nab-paclitaxel group.[31]

In the IMpassion130 CPS≥10 subgroup, median OS was 22 months (95% CI not reported) in the atezolizumab plus nab-paclitaxel group, and 18.7 months (NR) in the placebo plus nab-paclitaxel group. [40] In the CPS≥10 subgroup, median PFS was 7.5 months (95% CI not reported) in the atezolizumab plus nab-paclitaxel group, and 5.5 months (95% CI NR) in the placebo plus nab-paclitaxel group.[40]

Table 16: IMpassion130 results

	ITT atezolizumab plus nab-paclitaxel	**ITT placebo plus nab-paclitaxel**	**PD-L1≥1 subgroup atezolizumab plus nab-paclitaxel**	**PD-L1≥1 subgroup placebo plus nab-paclitaxel**	**CPS≥10 subgroup atezolizumab plus nab-paclitaxel**	**CPS≥10 subgroup placebo plus nab-paclitaxel**
n	**N=451**	**N=451**	**N=185**	**N=184**	**n=325 total across both groups**	
OS Events, n (%)	322 (71%)	344 (76)	120 (65)	139 (76)	NR	NR
OS months Median (95% CI)	21.0 (19.0, 23.4)	18.7 (16.9, 20.8)	25.4 (19.6, 30.7)	17.9 (13.6, 20.3	22 (NR)	18.7 (NR)
	stratified HR 0.87 (0.75, 1.02); p=0.0770		stratified HR 0.67 (0.53, 0.86) *		0.77 (0.57, 1.03)	
PFS events, n (%)	379 (84%)	404 (90%)	NR	NR	NR	NR
PFS months Median (95% CI)	7.2 months (95% CI 5.6–7.4)	5.5 months (5.3–5·6)	7.5 months (95% CI 6.7–9.2)	5.3 months (3.8–5.6)	7.5 (NR)	5.5 (NR)
	stratified HR 0·80 (95% CI 0·69–0·92), p=0·0021		stratified HR 0·63 (95% CI 0·50–0·80), p<0·0001		0.71 (0.56, 0.91)	

**(significance Not formally tested per prespecified testing hierarchy) (Emens et al 2020) [17]; Stratification factors: prior taxane use, liver metastases, PD-L1 status. NR=not reported. HR=hazard ratio. OS ITT and PD-L1≥1 subgroup data from final OS analysis, median follow-up 18.8 months (IQR, 8.9-34.7 months) (Emens et al 2020) [17]. OS PD-L1≥1 data, and all PFS data, from second interim analysis (data cut-off Jan 2, 2019), median follow-up 18.5 months (IQR 9.6–22.8) in the atezolizumab group and 17.5 months (8.4–22.4) in the placebo group (Schmid 2020) [31]. CPS≥10 data from Rugo 2020 [40].*

In the ITT population of IMpassion 130, grade 3 or 4 AEs were experienced by 224 (49%) in the atezolizumab plus nab-paclitaxel group, and 187 (43%) in the placebo plus nab-paclitaxel group.[31] The most common grade 3 or 4 AEs were neutropenia (8% both treatment groups), peripheral neuropathy (6% in the atezolizumab plus nab-paclitaxel group, 3% in the placebo plus nab-paclitaxel group), decreased neutrophil count (5% and 4%, respectively), and fatigue (4% and 3%, respectively).[31] Deaths deemed treatment-related occurred in two (<1%) patients in the atezolizumab plus nab-paclitaxel group

(one autoimmune hepatitis related to atezolizumab, and one septic shock related to nab-paclitaxel); and one (<1%) patient in the placebo plus nab-paclitaxel group (hepatic failure).[31]

3.3 Critique of the indirect comparison and/or multiple treatment comparison

The company identified two studies that satisfied the inclusion/exclusion criteria for a network meta-analysis: KEYNOTE-355 and IMpassion130. KEYNOTE-355 compared pembrolizumab plus chemotherapy against placebo plus chemotherapy. IMpassion130 compared atezolizumab plus nab-paclitaxel against placebo plus nab-paclitaxel. An indirect treatment comparison between pembrolizumab plus chemotherapy and atezolizumab plus nab-paclitaxel can be made assuming that placebo plus chemotherapy and placebo plus nab-paclitaxel are common comparators.

The company identified (CS, Section B2.9.2) various differences between the IMpassion130 and KEYNOTE-355 studies that affected the comparison, including that: patient characteristics for IMpassion130 was only reported in the PD-L1≥1% group and the KEYNOTE-355 included treatment with both paclitaxel and nab-paclitaxel whereas IMpassion130 only included nab-paclitaxel.

A Kaplan-Meier survival function was not available for IMpassion130 for participants whose tumours express PD-L1 CPS ≥10. Hence, it was not possible to reconstruct the patient-level data and estimate time-varying treatment effects in the target population.

A network meta-analysis (NMA) was conducted with respect to hazard ratios (HR). A HR provides an estimate of the average treatment effect of the duration of a study ignoring any treatment by time interaction and, as the company recognised, may not reflect the underlying ratio of hazard over the lifetime of patients.

The company initially used a fixed effect model to estimate treatment effects, although it recognised that a random effects model is more realistic. In response to clarification question A25, and in the absence of being able to elicit a prior distribution for the between-study standard deviation, the company reanalysed the data using a random effects model and a prior distribution for the between-study standard deviation taken from Turner *et al*.[42]

The company used a Bayesian approach to estimate parameters. A fundamental feature of the Bayesian approach is the ability to incorporate external information, including about the parameter representing between-study heterogeneity. Table 17 and Table 18 show that while the point estimates are unaffected, there is greater uncertainty about the overall population treatment effect using a random effects model. Furthermore, the predictive distribution about the effect in a new study would exhibit greater uncertainty. Within the company's base case model, the HR used for OS ([redacted]) was taken from a fixed

effects model assuming that paclitaxel and nab-paclitaxel have the same efficacy when added to pembrolizumab. A similar approach was taken for PFS with the blinded independent central review value used ([redacted]).

Table 17: OS hazard ratios

#	Comparison	KEYNOTE-355 PD-L1 expression subgroup	IMpassion130 PD-L1 expression subgroup	HR (95% CrI) Random Effects	HR (95% CrI Fixed effect
Overall Survival					
1	Pembrolizumab plus paclitaxel/nab-paclitaxel vs. atezolizumab plus nab-paclitaxel **(pooled KN-355 taxanes)**	CPS ≥ 10	CPS ≥ 10	[redacted]	[redacted]
2	Pembrolizumab **plus nab-paclitaxel** vs. atezolizumab plus nab-paclitaxel	CPS ≥ 10	CPS ≥ 10	[redacted]	[redacted]

Table 18: PFS hazard ratios

#	Comparison	KEYNOTE-355 PD-L1 expression subgroup	IMpassion130 PD-L1 expression subgroup	HR (95% CrI) Random Effects	HR (95% CrI Fixed Effect
Progression-free survival (KN-355 INV-assessed PFS, IMpassion130 IA-assessed PFS)					
1	Pembrolizumab plus paclitaxel/nab-paclitaxel vs. atezolizumab plus nab-paclitaxel **(pooled KN-355 taxanes)**	CPS ≥ 10	CPS ≥ 10	[redacted]	[redacted]
2	Pembrolizumab **plus nab-paclitaxel** vs. atezolizumab plus nab-paclitaxel	CPS ≥ 10	CPS ≥ 10	[redacted]	[redacted]
Progression-free survival (KN-355 BICR-assessed PFS, IMpassion130 IA-assessed PFS)					
1	Pembrolizumab plus paclitaxel/nab-paclitaxel vs. atezolizumab plus nab-paclitaxel **(pooled KN-355 taxanes)**	CPS ≥ 10	CPS ≥ 10	[redacted]	[redacted]
2	Pembrolizumab **plus nab-paclitaxel** vs. atezolizumab plus nab-paclitaxel	CPS ≥ 10	CPS ≥ 10	[redacted]	[redacted]

3.4 Additional work on clinical effectiveness undertaken by the ERG

No additional work was undertaken by the ERG.

3.5 Conclusions of the clinical effectiveness section

The ERG does not believe that any relevant published RCTs of pembrolizumab that could have provided effectiveness data have been missed or omitted from the CS. The key evidence of the clinical effectiveness and safety of pembrolizumab in mTNBC was taken from KEYNOTE-355.

KEYNOTE-355 was of good methodological quality. However, the trial was designed as a group sequential design and it did not reach the success criteria defined to control the family-wise type I error, and the trial is ongoing (at time of writing). The company presented 95% confidence intervals that may be consistent with the nominal significance level may not have the specified coverage; hence, results should be treated with caution. Furthermore, the restriction of data to a subgroup not stratified by randomisation gives the potential for bias, and also limits the availability of data available for indirect comparison.

The baseline demographics of the KEYNOTE-355 RCT were broadly representative of the mTNBC UK population; however, eligibility criteria regarding ECOG PS and adequate organ function meant that patients were fitter than would be seen in routine UK practice. It is likely the less fit patients could only be considered for agents like capecitabine or supportive care only.

At IA2 (11th December 2019), for the CPS≥10 subgroup, [redacted]

At IA2, for the CPS≥10 subgroup, there was a significant advantage in PFS for the pembrolizumab plus chemotherapy arm over the placebo plus chemotherapy arm, HR 0.65 (0.49, 0.86) p=0.0012. However, the ERG could not ascertain coverage provided by the confidence interval was consistent with the nominal significance level used in the interim analysis. Median PFS for the pembrolizumab plus

chemotherapy arm was 9.7 months (95% CI 7.6, 11.3), and for the placebo plus chemotherapy group was 5.6 months (95% CI 5.3, 7.5).

AEs graded as 3 or greater were experienced by [redacted] in the pembrolizumab plus chemotherapy group, and [redacted] in the placebo plus chemotherapy group (CS Section B.2.10).

[redacted]

No head-to-head trials of pembrolizumab plus chemotherapy with atezolizumab plus nab-paclitaxel were identified. One RCT was identified by the CS for use in an indirect comparison, IMpassion130.

The company's original NMA under-estimated uncertainty associated with the population HR by ignoring plausible variability between studies. In the presence of unexplained heterogeneity between studies uncertainty should be based on the predictive distribution of the HR in a new study rather than the mean of the random effect distribution. The predictive distribution should be used to represent uncertainty in an economic model. In this case, while the central estimates will be the same in each model, uncertainty will be greater than originally estimated.

The company's NMA was of HRs. A HR can be interpreted as an average treatment effect over the duration of a study ignoring any potential treatment by time interaction. Using HRs to generate survival functions and estimate population mean benefit may be misleading if survival functions are not based on proportional hazard models.

4 COST EFFECTIVENESS

This chapter presents a summary and critique of the company's health economic analyses of pembrolizumab in combination with paclitaxel/nab-paclitaxel for the first-line treatment of locally recurrent, unresectable or mTNBC with PD-L1 CPS≥ 10. Section 4.1 presents a critique of the company's review of existing health economic analyses. Section 4.2 summarises the methods and results of the company's model. Sections 4.3 and 4.4 present the critique of the model and additional exploratory analyses undertaken by the ERG, respectively. Section 4.5 presents a discussion and critique of the available economic evidence.

4.1 Company's review of published cost-effectiveness studies

The company undertook a systematic review to identify relevant cost-effectiveness studies from published literature and from previous NICE technology appraisals.

4.1.1 Company's search objective and methods

Appendices G and H of the CS include an SLR of economic evidence including studies of cost and resource use and an SLR of HRQoL studies, respectively. Searches, conducted on 19th November 2020, covered MEDLINE, Embase, Econlit and Cochrane as well as recent conference proceedings.

For the economic review, searches were limited to results since 2007 – a start date which the company justified in their clarification response as follows: "*It is important to note that the development of novel therapies for mTNBC did not advance significantly until very recently with the introduction of IO therapies, including the recently approved by NICE TA639… studies published from 2007 and onwards were deemed to be reflective of the current NHS clinical practice. Older economic evaluations, costing/resource studies may not be entirely useful or generalizable with regards to informing the economic modelling and are likely to require extensive updates and clinical validation*." (clarification response A1[24]).

The population terms used for the database searches of MEDLINE and Embase were the same as those used for the clinical SLR – as noted above, the ERG does not consider long strings to be optimal for retrieval purposes; however, any risk of missing studies is likely to be mitigated by the other search methods used. In the case of the Econlit search, the ERG noted an unusual approach (CS Appendix G, Table 31) whereby after entering these lengthy strings for the specific population of interest (and having only found a handful of results), the company combined these with the single phrase "breast cancer" (without any synonyms). The company re-ran a corrected version of the Econlit search strategy on February 10th, 2021 but found no additional studies (clarification response A2[24]).

It was not possible for the ERG to re-run every SLR with corrections to assess the implications downstream. However, our own informal searches did not identify any eligible studies missed by the company's searches.

4.1.2 Eligibility criteria for the company's review of published economic evaluations

The inclusion and exclusion criteria used by the company are presented in Appendix G, Table 28 of the CS. The ERG considers the inclusion criteria to be appropriate to capture recent and relevant published evidence.

4.1.3 Findings of the cost effectiveness review

Details on the review process are provided in Appendix G of the CS. Thirty citations, representing 27 unique studies were identified that were deemed relevant to the decision problem. These consisted of 13 economic evaluations, and 14 studies informing resource use and costs (12 observational cohort studies, a cost-of-illness study and a systematic literature review). However, none of these included as an option pembrolizumab in combination with chemotherapy for patients with inoperable or metastatic TNBC as first line therapy. Table 33 and Table 35 in Appendix G of the CS summarise the evidence found in the 13 economic evaluations identified. All were cost-utility analyses reporting incremental cost per QALY gained; no analysis of the modelling methods used within these studies was provided by the company.

4.1.4 Conclusions of the cost effectiveness review

As the company's searches did not identify any relevant studies including pembrolizumab in combination with chemotherapy for patients with inoperable or metastatic TNBC as first line therapy, they developed a *de novo* health economic model.

4.2 Description of company's health economic analysis

This section provides a detailed description of the methods and results of the company's health economic analysis. Following the clarification process, the company submitted a revised version of the economic model which included updated estimates of the cost-effectiveness of pembrolizumab plus paclitaxel/nab-paclitaxel. The changes included extending the time horizon to 35 years and the correction of minor errors identified by the ERG related to disease management costs, AE costs, and the lower and upper values used in the probabilistic sensitivity analyses (PSA) and univariate sensitivity analyses. For brevity, this report will only refer to the model (and results) received after clarification.

4.2.1 Model scope

As part of its submission to NICE,[43] the company submitted a fully executable health economic model programmed in Microsoft Excel®. The scope of the company's model is summarised in Table 19.

Table 19: Summary of company's model scope

Population	[redacted]
Time horizon	35 years (lifetime)
Intervention	Pembrolizumab in combination with taxane-based chemotherapy (paclitaxel/nab-paclitaxel)
Comparators	• Paclitaxel* • Atezolizumab in combination with nab-paclitaxel • Docetaxel
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% for health outcomes and costs
Price year	2018/19

CPS – combined positive score; PD-L1 - programmed death-ligand 1; PSS - Personal Social Services; QALY - quality-adjusted life year.
** The ERG notes that the company uses interchangeably 'paclitaxel' and 'taxanes' when refers to the primary comparator in the CS and model. In the report, the ERG adopted 'paclitaxel' for when it refers to the primary comparator.*

The company's base case analysis assess the incremental cost-effectiveness of pembrolizumab in combination with paclitaxel/nab-paclitaxel versus paclitaxel alone, with their efficacy outcomes based on data from KEYNOTE-355 trial.[26] The company also presents secondary cost-effectiveness analyses comparing pembrolizumab plus paclitaxel/nab-paclitaxel to: (i) atezolizumab in combination with nab-paclitaxel, based on the company's NMA for the metastatic PD-L1 CPS≥10 TNBC population; and (ii) docetaxel, based on the assumption of efficacy equivalence to paclitaxel.[43]

The analyses adopt the perspective of the National Health Service (NHS) and Personal Social Services (PSS) over a 35-year (lifetime) horizon. Resource Unit costs are valued at 2018/19 prices. Health outcomes and costs are discounted at a rate of 3.5% per annum. Cost-effectiveness is expressed in terms of the incremental cost per quality-adjusted life year (QALY) gained.

Population

The population within the company's base case analysis is adults with PD-L1 positive (CPS≥10) untreated locally recurrent inoperable or metastatic TNBC, reflecting a subgroup of the KEYNOTE-355 study.[26] Additional key characteristics are defined by the inclusion criteria applied in the study: ECOG PS 0 or 1; ≥6 months between the completion of treatment with curative intent and first documented local or distant disease recurrence; adequate organ function and measurable disease based on RECIST 1.1; life expectancy ≥12 weeks; and completion of treatment for stage I-III breast cancer, if indicated.

The company reports the anticipated wording of the marketing authorisation as being related to "[redacted][43] Following the clarification process, the company clarified that [redacted] and a decision from the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) is anticipated to be delivered in [redacted] (clarification response question A10 and A11).[24]

The population included in the company's economic analysis is generally in line with the final NICE scope.[2] However, the definition of the population is [redacted], in order to reflect the anticipated marketing authorisation wording.[43]

Interventions and comparators

The intervention included in the company's model is pembrolizumab in combination with either paclitaxel or nab-paclitaxel (pembrolizumab plus paclitaxel/nab-paclitaxel therapy). This is generally in line with the final NICE scope[2] and the anticipated marketing authorisation, although the economic analyses submitted restricts the chemotherapy component in combination with pembrolizumab to paclitaxel and nab-paclitaxel and excludes pembrolizumab in combination with gemcitabine and carboplatin. The company states that this is "*to be reflective of KEYNOTE-355 clinical data and to reflect the UK standard of care*" (CS, Table 1).[43]

Pembrolizumab is assumed to be given intravenously at a fixed dose of 200mg once every 3 weeks (Q3W) until treatment discontinuation, for a maximum of 35 doses (approximately 2 years of treatment). Paclitaxel and nab-paclitaxel are assumed to be given intravenously at a dose of 90mg/m^2 and 100mg/m^2, respectively, based on the mean body surface area (BSA) of patients in KEYNOTE-

355;[26] these are assumed to be administered on days 1, 8 and 15 of every 28-day cycle until treatment discontinuation.[43]

The comparator evaluated within the company's primary base case analysis is paclitaxel. The ERG notes that the company uses 'paclitaxel' and 'taxanes' interchangeably when referring to the primary comparator in the model. For this comparator, the company uses efficacy results from the taxanes treatment arm in KEYNOTE-355, assuming that paclitaxel and nab-paclitaxel have the same efficacy, whilst drug acquisition costs are based solely on paclitaxel, since the use of nab-paclitaxel monotherapy is not approved in the UK for TNBC (CS, pages 128-129).[43] For consistency, from this point on in the report, the ERG adopts the term 'paclitaxel' when referring to the company's primary comparator. In the comparator group, paclitaxel is administered in monotherapy and assumed to be given intravenously at a dose of 90mg/m^2 on days 1, 8 and 15 of every 28-day cycle, based on the mean BSA of patients in KEYNOTE-355 until treatment discontinuation.[26] The ERG notes, however, that the typical frequency of the paclitaxel administration in the UK is on a weekly basis (clinical opinion and previous NICE appraisal for atezolizumab plus nab-paclitaxel[11]). Whilst the administration schedule for paclitaxel as a comparator should reflect its routine use in the UK which would be associated with additional cost it is probable that additional use of paclitaxel would provide better OS and PFS outcomes, but the magnitude of this benefit is unknown. As such, the ERG believes it is reasonable to use the treatment schedules within the clinical study.

Within the secondary cost-effectiveness analyses, the comparators presented are:

(i) atezolizumab plus nab-paclitaxel, administered as an IV until treatment discontinuation, where atezolizumab is given at a fixed dose of 840mg once every 2 weeks (Q2W) and nab-paclitaxel is assumed to be administered at a dose of 100mg/m^2, based on the mean BSA of patients in KEYNOTE-355,[26] on days 1, 8 and 15 of every 28-day cycle until treatment discontinuation; and

(ii) docetaxel, which is assumed to be administered as an IV at a dose of 100mg/m^2 once every 3 weeks (Q3W) based on the mean BSA of patients in KEYNOTE-355.[43]

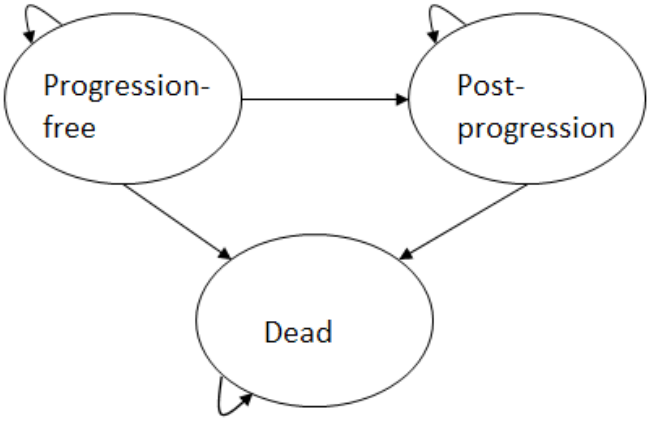
The final NICE scope[2] also include anthracycline based chemotherapy as a comparator; this regimen is not included in the company's economic analyses, as the company states, due to a lack of relevant evidence and previous agreement in TA639[44] that its use is very limited in this population (CS, page 98).[43]

4.2.2 Model structure and logic

The general structure of the company's economic model is described on pages 93-96 of the CS[43] as a partitioned survival model based on three health states: (1) progression-free and alive; (2) post- disease progression and alive, and (3) dead (see Figure 3).

The ERG notes that this partition influences only the costs of the treatment options in the base-case analysis as health-related quality of life (HRQoL) outcomes are modelled using a time-to-death approach rather than based on patient's modelled health state. However, the structure of the model allows the use of utilities by progression status which is explored by the company in a scenario analysis. The ERG also comments that the model was relatively cumbersome and had a file size approaching 82 Megabytes, which is excessive for a partitioned survival model.

Figure 3: Company's model structure (drawn by the ERG)



The model logic operates as follows. In the company's primary base case analysis, patients enter the model in the progression-free state and receive first-line treatment with either pembrolizumab plus paclitaxel/nab-paclitaxel or paclitaxel alone. The allocation of patients amongst the health states are determined by two chosen distributions, one for survival (OS), and one for progression-free survival (PFS). At any time *t*, the probability of being alive and progression-free is given by the probability of PFS, the probability of being alive following disease progression is calculated as the probability of survival minus the probability of PFS, and the probability of being dead is the complement of the probability of survival. A partition survival approach does not explicitly model transitions between health states. Time on first-line treatment is estimated from the selected time to treatment discontinuation (TTD) survival function.

The cumulative probabilities of OS, PFS and TTD in each time interval are modelled using treatment group-specific approaches with parametric distributions fitted to time-to-event data for patients from the PD-L1 CPS ≥10 subgroup in KEYNOTE-355 trial.[26] The survivor functions and the evidence

sources to derive these functions are summarised in Table 20, with further detail provided in Section 4.2.4. Within each treatment group, the model applies three structural constraints: that (i) TTD and (ii) (ii) PFS must be less than or equal to OS, and (iii) that the PFS and OS risks for women with TNBC must be at least as high as the mortality risk of the age- and sex-matched general population of the UK.[43]

HRQoL is assumed to be independent of treatment received and determined by the patient's time to death, based on five categorical groups (<30 days; ≥30 to 90 days; ≥90 to 180 days; ≥180 to 360 days, and ≥360 days) with utility declining as patients approach death. Health utilities used in the model are based on the results of a linear mixed-effect model with fixed effects, fitted to EQ-5D data collected from the CPS ≥ 10 population in KEYNOTE-355.[26] Health utilities are adjusted by age.[45] The model does not explicitly include any QALY loss associated with Grade 3-5 AEs for pembrolizumab plus paclitaxel/nab-paclitaxel or paclitaxel.

The model includes costs associated with: (i) drug acquisition; (ii) drug administration; (iii) disease management; (iv) second and further-line (2L+) treatment; (v) management of AEs; (vi) end-of-life (terminal care) costs and (vii) costs related to PD-L1 testing. These are detailed in section 4.2.4.4.

The incremental health gains, costs and cost-effectiveness of pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel are modelled in a pairwise fashion over a time horizon of 35 years using 1-week cycles. Half-cycle correction is applied to account for the timing of events.

Secondary analyses are presented in the CS for comparisons against docetaxel and against atezolizumab plus nab-paclitaxel. For these analyses, the structure of the model remains the same as in the primary base case as do the majority of the parameter values (See Section 4.2.3).

4.2.3 Key assumptions employed in the company's model

The company's model employs the following key assumptions for its base cases:

- OS, PFS and TTD for pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel are modelled using the observed time-to-event data from the subgroup of patients with PD-L1 CPS ≥10 in pembrolizumab plus taxane and taxane arms from KEYNOTE-355.[26]
- The model includes a general population mortality constraint to ensure that the risk of death for patients with PD-L1 positive TNBC is never lower than for the age-gender matched general population; additional constraints are included to ensure that there can never be more people in the progression-free health state than are alive, and that there are never more people on treatment than are alive;

- OS and PFS for atezolizumab plus nab-paclitaxel are modelled using HRs from the company's NMA (see Section 3.4), applied to the OS and PFS distributions chosen for the pembrolizumab plus paclitaxel/nab-paclitaxel treatment group assuming proportional hazards hold;
- The distributions used for OS, PFS and TTD for patients receiving paclitaxel are assumed to be generalisable to the docetaxel group;
- Time on treatment for a patient is estimated from time to treatment discontinuation functions for each treatment evaluated;
- Patients receiving pembrolizumab plus paclitaxel/nab-paclitaxel, paclitaxel or docetaxel are assumed to remain on treatment until discontinuation, at which point all first-line treatment is stopped. The exception is for pembrolizumab treatment, which has a maximum of 35 doses (approximately 2 years); patients who receive 35 doses are assumed to continue receiving either paclitaxel or nab-paclitaxel as monotherapy indefinitely until discontinuation;
- Patients receiving atezolizumab plus nab-paclitaxel are assumed to remain on treatment until they progress or die, at which point treatment is stopped;
- HRQoL is modelled according to the patients' time to death with utility declining as a patient approaches death; utilities are assumed to be independent of treatment;
- No utility decrements related to AEs are applied in the company's base-case analysis, which uses the time-to-death approach; these are assumed to be already captured on the mean utility values generated from EQ-5D data collected from patients event-free and on treatment in KEYNOTE-355.[26]
- Drug acquisition and administration costs of the intervention and comparators are modelled using the TTD survival functions;
- The proportion of patients receiving second, third and fourth line of treatment and mean duration of each therapy following pembrolizumab plus paclitaxel/nab-paclitaxel or paclitaxel therapies are based on data from KEYNOTE-355;[26] the cost of subsequent lines of treatment after pembrolizumab in combination with paclitaxel/nab-paclitaxel is assumed generalisable for patients receiving atezolizumab plus nab-paclitaxel, whilst the costs after paclitaxel is assumed generalisable for patients who received docetaxel.
- The frequency of follow-up and monitoring interventions (clinical visits, image and blood tests) are assumed independent of treatment, but to decrease with disease progression;
- A cost associated with terminal care was assumed in the model which was the same for all treatments evaluated and based on data from literature.
- Costs of PD-L1 testing are assumed to be based on the prevalence of CPS≥10 of patients in KEYNOTE-355;[26] the company's model assumes all patients receiving pembrolizumab plus paclitaxel/nab-paclitaxel are tested using the IHC 22C3 pharmDx Assay, whilst patients receiving atezolizumab plus nab-paclitaxel are tested using the PD-L1 SP142 test. Patients

receiving taxanes (paclitaxel or docetaxel treatment groups) are assumed not to receive PD-L1 testing.

- The costs of only Grade 3-5 AEs occurring in ≥5% of patients in one or both treatment groups of KEYNOTE-355[26] are included in the company's model for pembrolizumab plus paclitaxel/nab-paclitaxel therapy and paclitaxel treatment groups. The AE profile for docetaxel is assumed to be the same as for paclitaxel. Only Grade 3-5 AEs occurring in ≥2% of patients in the atezolizumab plus nab-paclitaxel trial arm in IMpassion130[46] are included in the model for this treatment group.

4.2.4 Evidence used to inform the company's model parameters

Table 20 summarises the evidence sources used to inform the model's parameters in the company's base case analyses. These are discussed in detail in the subsequent sections.

Table 20: Summary of evidence used to inform the company's base case analyses

Parameter group	Source
Patient characteristics (age, BSA, weight, proportion of females)	Based on characteristics of trial participants with PD-L1 CPS≥10 enrolled at Part 2 of KEYNOTE-355[26]
PFS – pembrolizumab plus paclitaxel/nab-paclitaxel therapy	Observed intervention group† KM survival function for first 9 weeks followed by Weibull model fitted to post-9-week data from KEYNOTE-355.[26] Modelled PFS is constrained by modelled OS.
PFS – paclitaxel	Observed comparator group‡ KM survival function for first 9 weeks followed by lognormal distribution fitted to post-9-week data from KEYNOTE-355[26] Modelled PFS is constrained by modelled OS.
PFS – docetaxel	Assumed to be the same as paclitaxel
PFS – atezolizumab plus nab-paclitaxel	The HR for PFS for atezolizumab plus nab-paclitaxel estimated from the company's NMA is applied to the PFS survival function for pembrolizumab plus paclitaxel/nab-paclitaxel group.
OS – pembrolizumab plus paclitaxel/nab-paclitaxel therapy	A lognormal distribution fitted to observed intervention group† OS data from KEYNOTE-355.[26] Modelled OS is constrained by general population mortality risk.
OS – paclitaxel	A log-logistic distribution fitted to observed comparator‡ group OS data from KEYNOTE-355.[26] Modelled OS is constrained by general population mortality risk.
OS – docetaxel	Assumed to be the same as paclitaxel
OS - atezolizumab plus nab-paclitaxel	The HR for OS for atezolizumab plus nab-paclitaxel estimated from the company's NMA is applied to the OS survival function for pembrolizumab plus paclitaxel/nab-paclitaxel group.
Mortality - general population	Derived from interim life tables for England 2017-2019[47]
TTD - pembrolizumab plus paclitaxel/nab-paclitaxel therapy	A Weibull model fitted to observed intervention group† TTD data from KEYNOTE-355[26] (truncated at 2 years). Modelled TTD is constrained by modelled OS.
TTD - paclitaxel	A log-logistic model fitted to observed comparator‡ group TTD data from KEYNOTE-355.[26] Modelled TTD is constrained by modelled OS.
TTD - docetaxel	Assumed to be the same as paclitaxel
TTD - atezolizumab plus nab-paclitaxel	TTD is assumed to be the same as PFS

Parameter group	Source
HRQoL	EQ-5D-3L data collected in KEYNOTE-355.[26] Data analysed according to time to death (<30 days; ≥30 to 90 days; ≥90 to 180 days; ≥180 to 360 days, and ≥360 days).
QALY loss resulting from AEs	Not explicitly included in the company's base case; the company assumed that the utility values from KEYNOTE-355 captured the effects of AEs on HRQoL.[43]
Probability of receiving subsequent therapy (2L+)	Based on KEYNOTE-355[26] for pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel treatment groups; atezolizumab plus nab-paclitaxel is assumed to be the same as pembrolizumab plus paclitaxel/nab-paclitaxel, and docetaxel assumed to be the same as paclitaxel.
Mean duration of subsequent therapies (2L+)	Based on the KEYNOTE-355 study[26]
Drug acquisition costs	Commercial Medicines Unit (CMU) Electronic Market Information Tool (eMIT), British National Formulary (BNF) and Monthly Index of Medical Specialities (MIMS).[48-50]
Drug administration costs	NHS Reference Costs 2018/19[51]
RDI	Based on KEYNOTE-355 trial[26]
Disease management costs	Based on NICE TA639,[44] NHS Reference Costs 2018/19,[51] PSSRU 2019,[52] clinical expert opinion and assumptions
Costs associated with AEs	AE frequencies for pembrolizumab plus paclitaxel/nab-paclitaxel therapy and paclitaxel treatment groups based on Grade ≥3+ AEs with incidence of ≥5% from KEYNOTE-355 (PD-L1 CPS≥10 analysis).[26] AE frequencies for docetaxel were assumed to be equal to the paclitaxel treatment group. AE frequencies for atezolizumab plus nab-paclitaxel based on grade ≥3+ AEs with incidence of ≥2% from IMpassion130.[46] Unit costs based on previous NICE TAs,[12, 53-55 56 57] NHS Reference Costs 2018/19[51] PSSRU 2019[10], BNF[49, 52] and assumptions.
PD-L1 testing costs	PD-L1 CPS≥10 prevalence from KEYNOTE-355;[26] unit costs from NICE TA639[44] and NHS Reference Costs 2018/19.[51]
End of life care costs	Based on a previous NICE appraisal (TA553),[54] which was based on data in Georghiou & Bardsley (2014)[58] inflated to 2019 costs using the HCHS pay & prices and the NHSCII indices.[52]

AE - adverse event; BSA - body surface area; EQ-5D-3L - EuroQol EQ-5D 3-level; HCHS - hospital & community health services; HR - hazard ratio; HRQoL - health-related quality of life; NHSCII - NHS cost Inflation Index; NMA - network meta-analysis; OS - overall survival; PD-L1 - programmed death-ligand 1; PFS - progression-free survival; QALY - quality-adjusted life year; TTD - time to treatment discontinuation

†*Intervention group corresponds to the pembrolizumab plus taxanes arm (paclitaxel and nab-paclitaxel) in KEYNOTE-355 trial.*

‡*Comparator group corresponds to the taxanes arm (paclitaxel and nab-paclitaxel) in KEYNOTE-355 trial.*

4.2.4.1 Initial patient characteristics at model entry

The model assumes that all patients that enter the model are female and at an initial age of [redacted] years, with a mean weight of [redacted] and BSA of [redacted]; these characteristics reflect the population of patients with PD-L1 CPS ≥10 in the KEYNOTE-355 study.[43]

4.2.4.2 Time-to-event parameters

The key features of the company's survival analysis approach and its application within the health economic model are summarised in Box 1. The approach used for each individual endpoint and each

arm is described in further detail in the subsequent sections. Time-to-event outcomes for the pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel groups are based on data for pembrolizumab plus taxanes and taxanes treatment arms from KEYNOTE-355.[26] For atezolizumab plus nab-paclitaxel, OS and PFS are based on the company's NMA using data from KEYNOTE-355 and IMpassion130 and the respective distributions for pembrolizumab plus paclitaxel / nab-paclitaxel. TTD for atezolizumab plus nab-paclitaxel was assumed equal to its PFS distribution. The ERG notes minor discrepancies between the CS and the model regarding some goodness-of-fit values however, this does not impact on the choice of the selected distributions or the cost-effectiveness results.

Box 1: Summary of company's approach to modelling OS, PFS and TTD in the model

Company's selected models:

- **Pembrolizumab plus paclitaxel/nab-paclitaxel group**
  - OS: Lognormal distribution
  - PFS: Piecewise KM survival function for the first 9 weeks + Weibull distribution
  - TTD: Weibull distribution
- **Paclitaxel group**
  - OS: Log-logistic distribution
  - PFS: Piecewise KM survival function for the first 9 weeks + lognormal distribution
  - TTD: Log-logistic distribution
- **Docetaxel group (assumed the same efficacy outcomes as paclitaxel)**
  - OS: Log-logistic distribution
  - PFS: Piecewise KM survival function for the first 9 weeks + lognormal distribution
  - TTD: Log-logistic distribution
- **Atezolizumab plus nab-paclitaxel group**
  - OS: HR derived from the company's NMA for OS applied to pembrolizumab plus paclitaxel/nab-paclitaxel OS model
  - PFS: HR derived from the company's NMA for PFS applied to pembrolizumab plus paclitaxel/nab-paclitaxel PFS model
  - TTD: assumed the same as PFS

OS - overall survival; PFS - progression-free survival; TTD - time to treatment discontinuation; NMA - network meta-analysis; HR - hazard ratio

4.2.4.2.1 Overall survival (OS)

OS is modelled using available individual patient data (IPD) for the subgroup of patients with PD-L1 CPS≥10 receiving pembrolizumab plus taxane and taxane treatments in KEYNOTE-355[26] (pembrolizumab plus taxanes N=220; taxane N= 103).

The company considered five distributions that are members of the generalized F family of distributions (i.e., exponential, Weibull, log-logistic, lognormal and generalized gamma distributions) and the Gompertz distribution. These models are associated with fairly restrictive hazard shapes and none may provide a reasonable representation of the underlying hazard function over the lifetime of patients.

The CS[43] states that the candidate models were assessed for inclusion in the base case analysis through consideration of: relative goodness-of-fit statistics (the Akaike Information Criterion [AIC] and the Bayesian Information Criterion [BIC]); visual inspection of the fitted distributions to the observed data; examination of the Schoenfeld residual and the log-cumulative hazard functions, internal and external validity and clinical plausibility (CS, page 101).

The AIC and BIC statistics for the candidate models for OS in each treatment group are presented in Table 21. Kaplan-Meier survival functions and modelled OS survival functions for the pembrolizumab plus paclitaxel/nab-paclitaxel and the paclitaxel groups are presented in Figure 4 and Figure 5, respectively. The ERG has a preference to using BIC rather than AIC, and these sometimes result in a different ordering of the models.

Table 21: AIC and BIC statistics for company's parametric models for OS, from data for pembrolizumab plus taxane and taxane treatment arms of KEYNOTE-355 (adapted from Table 44 of the CS)

Parametric distribution	Pembrolizumab plus taxane			Taxane		
	AIC	BIC	Sum	AIC	BIC	Sum
Exponential	537.61	**540.17**	1077.78	398.39	400.24	798.63
Log-logistic	536.47	541.60	1078.06	**394.60**	**398.30**	**792.91**
Lognormal	**535.93**	541.06	**1076.98**	394.81	398.51	793.33
Generalised Gamma	539.08	544.21	1083.29	397.05	400.75	797.79
Gompertz	537.87	545.57	1083.44	396.04	401.59	797.63
Weibull	537.61	542.74	1080.35	394.66	398.36	793.03

AIC - Akaike Information Criteria, BIC - Bayesian Information Criteria.
Note – Models chosen by the company are shaded; lowest values are presented in bold

The ERG noted that the Gompertz distribution was fitted with unconstrained parameters. In response to clarification question B4f, the company stated that unconstrained parameter models did not converge and "*should not be considered for the purposes of economic modelling*."

Figure 4: OS survival functions using company's parametric modelling, pembrolizumab plus paclitaxel/nab-paclitaxel therapy group

Figure 5: OS survival functions using company's parametric modelling, paclitaxel therapy group

The CS[43] states that lognormal and log-logistic distributions were selected for inclusion for pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel, respectively, for the base-case analysis based on consideration of: relative goodness-of-fit statistics (the AIC and BIC criteria combined); visual inspection of the fitted distributions; examination of hazard and validation by real-world evidence (RWE) data. The piecewise models were ruled out for being considered less plausible based on validation exercises using RWE data for both treatment arms, and after examination of the cumulative hazard functions and the Chow test results; [redacted] (CS, page 104 and clarification response, question B4[d]).[24, 43]

In response to clarification question B4b, the company provided plots of smoothed empirical hazard functions with 95% confidence intervals for each treatment group. This is replicated in Figure 6 for the pembrolizumab plus taxanes group. The empirical hazard function for the pembrolizumab plus taxanes group suggests a small linear increase in the risk of death over the first 150 weeks. The empirical hazard function for the placebo plus taxanes group (replicated in Figure 7) also suggests a linear increase in the risk of death over the first 150 weeks with the rate of change being greater than in the pembrolizumab plus taxanes group.

Figure 6: Plot of hazard function of Overall Survival assuming smooth spline or various parametric distributions used for long-term extrapolation for the group treated with pembrolizumab plus taxanes

The shaded area represents the 95% CI for the smooth spline estimate.

Figure 7: Plot of hazard function of Overall Survival assuming smooth spline or various parametric distributions used for long-term extrapolation for the group treated with placebo plus taxanes

The shaded area represents the 95% CI for the smooth spline estimate.

The ERG asked what was believed *a priori* to be the risk of death (i.e., shape of the hazard function) over the lifetime of patients included in KEYNOTE-355 (Clarification question B4d), although no specific response was provided. However, in the CS (Section B3.3.1) and in response to clarification question B4g, the company discusses the unique mode of action of immunotherapies and the potential for long-term survivors but considered the use of standard parametric models "*to be consistent with most of the previous IO HTAs and conservative in terms of cost-effectiveness*".

In the CS, the company suggested that the empirical evidence suggested a change in the shape of the cumulative hazard functions at weeks 25, 40 and 52. The ERG suggests that the smoothed empirical hazard functions do not support this assertion. In response to clarification question B6, which asked for a rationale for there being change-points in the marginal hazard functions (for both treatment groups) at Weeks 25, 40 and 52, the company discussed the use of cumulative hazard functions and Chow tests but did not offer a clinical rationale for the change-points. The ERG believes that a change in the shape of the hazard function for the pembrolizumab plus taxanes group is more likely to occur after two years corresponding to the discontinuation of pembrolizumab as specified in the KEYNOTE-355 protocol subject to re-treatment under specific clinical criteria (CS Section B3.3.3).

In the CS, the company referred to the unique mode of action of a combination of immunotherapy combined with taxanes and the presence of long-term survivors. In response to clarification question B4g, the company wrote that it did not consider using mixture models because of the lack of sample data with which to estimate parameters. The ERG believes that the approach taken to model OS, while consistent with NICE TSD 14, conflates the issues of structural and parameter uncertainty. Essentially, if there is reason to believe that a particular model represents the underlying data generating process then external evidence should be used to estimate parameters.

In response to clarification question B4h, the company did not provide results using restricted cubic splines because "*the software used for survival analysis does not allow for fitting of spline models*" and "*extrapolation beyond trial period may still be limited without the introduction of external datasets*". The ERG does not consider the availability of software to be an acceptable justification for not providing results of the analysis requested. Furthermore, the ERG believes that the use of external evidence to mitigate data gaps is a useful addition to represent the underlying data generating process.

The best fitting model to the sample data based on BIC for the Pembrolizumab plus taxanes group was an exponential distribution, although there is little to distinguish between exponential, Weibull, lognormal and log-logistic distributions. However, the smoothed empirical hazard function does not support a unimodal, increasing then decreasing hazard function. The ERG suggests that a Weibull distribution is likely to be the most appropriate model over the observed period although has explored the use of an exponential model in scenario analyses.

The best fitting model to the sample data based on BIC for the placebo plus taxanes group was a log-logistic distribution, although there was weak evidence to distinguish between any of the models. However, the smoothed empirical hazard function does not support a unimodal, increasing then decreasing hazard function. The ERG suggests that of the models evaluated and the empirical hazard function, a Weibull distribution is likely to be the most appropriate model. The ERG as explored the use of an exponential model in scenario analyses. The ERG notes that alternative models could provide a better representation of the data generation process over the observed and unobserved periods. However, the company did not provide any information on the expected shape of the hazard function in the unobserved period (clarification question B4d); did not explore the use of mixture models because of insufficient sample data and did not consider incorporating external information (clarification question B4g); and did not explore the use of restricted cubic spline models as requested by the ERG (clarification question B4h).

The process used to extract experts' beliefs about the proportions of patients surviving at different times in each treatment group is described in response to clarification question B5 and in Section 3.3.1 of the

CS. The ERG believes that many aspects of the process are consistent with what would be expected if a formal elicitation of experts' beliefs of uncertain quantities as probability distributions was performed but with some limitations:

- Four out of eight UK medical oncologists declined to provide estimates of the proportion of patients surviving "*beyond the IMpassion130 follow up due to the absence of long-term data*". Experts may have been forthcoming if questioned as part of a facilitated elicitation process during which they express their uncertainty as a probability distribution.
- Of the four experts who did express their beliefs, they did so as a point estimate, although it is not clear what the value represents. For example, if elicitation was performed using the bisection method then the point estimate would represent the median of a beta distribution.
- It is not clear what the 5- and 10-year quantities in Tables 45 and 46 of the CS represent. A formal elicitation of experts' beliefs could use behavioural aggregation in which experts discuss their opinions and provide a final estimate (with uncertainty) representing the beliefs of a rationale impartial observer. Alternatively, mathematical aggregation (with uncertainty) could be used.
- Uncertainty associated with the experts' opinions could be consistent with uncertainty about survival functions based on the sample data. It is not necessary that a fitted survival function should coincide with the experts' best estimates.

In the company's base case OS for the pembrolizumab plus taxanes group was modelled using a lognormal distribution and the survival function for the atezolizumab plus nab-paclitaxel group was estimated by applying the hazard ratio from the fixed effect NMA. The ERG notes the following issues:

- The company's fixed effect NMA underrepresented uncertainty by ignoring reasonable prior beliefs about the extent of heterogeneity in relative treatment effects between studies and the recommendation that uncertainty should be represented in economic models using the predictive distribution for the effect of treatment in a new study.
- The use of a hazard ratio assumes that hazards are proportional, which is unlikely in practice, and will generate a biased estimate of population mean benefit, which could be favourable or unfavourable to the intervention. The CS states that due to data limitations the model uses an assumption that PH holds for this population; and that the treatment effect estimates and cost-effectiveness results for atezolizumab plus nab-paclitaxel may be associated with high uncertainty (CS, page 117).[43]
- A lognormal distribution is not a proportional hazards models so that applying a hazard ratio to the survival function is technically incorrect. Within the clarification process the company acknowledged the methodological limitations associated with applying a HR to a lognormal distribution. The ERG believes that any inaccuracy introduced by this limitation will be relatively small compared with other uncertainties in the decision problem.

The fitted OS model for the paclitaxel treatment group is assumed generalisable for the docetaxel treatment group, based on an assumption of clinical equivalence between taxane treatments from the appraisal committee in TA639. The ERG notes that final appraisal determination document (FAD) for TA639 documents the clinical experts' opinion that considered nab-paclitaxel was broadly equivalent to the taxanes currently in routine use in the UK, rather than explicitly comparing docetaxel and paclitaxel. The committee's clinical experts also highlighted that paclitaxel *"has more favourable toxicity profile than docetaxel so people are able tolerate treatment, and maintain a treatment response, for longer"*.[44]

The model also includes a structural constrain to ensure that the risk of death for women with PD-L1 positive TNBC is never lower than the mortality risk of the age- and sex-matched general population of England.[47] The Kaplan-Meier survival functions and modelled OS survival functions are presented in Figure 8.

Figure 8: OS survival functions for all treatment options included in company's base case analysis (generated by the ERG from the company's model)†

† Note - the modelled OS survival function for docetaxel is assumed identical to the OS survival function for paclitaxel. The hazards are constrained to be at least as great as general population mortality

Alternative OS models were assessed in the company's sensitivity analyses, such as: use of the log-logistic distribution and piecewise exponential distributions with a knot at 52 weeks for pembrolizumab plus paclitaxel/nab-paclitaxel; the lognormal distribution for paclitaxel; the log-logistic distribution for pembrolizumab plus paclitaxel/nab-paclitaxel and lognormal distribution for paclitaxel simultaneously; and the log-logistic distribution for pembrolizumab plus paclitaxel/nab-paclitaxel in the analysis against atezolizumab plus nab-paclitaxel.

4.2.4.2.2 Progression-free survival (PFS)

As with the OS analysis, the analysis of PFS was informed by IPD for those patients in the PD-L1 CPS≥10 subgroup receiving pembrolizumab plus taxane or taxane in KEYNOTE-355[26] (pembrolizumab plus taxanes N=220; taxane N= 103). PFS was defined as the time from the date of randomisation until the date of the first documented disease progression per RECIST 1.1 based on a blinded central imaging vendor (CIV) or death from any cause, whichever occurred first.[43] The company fitted the same range of standard parametric survival models (exponential, Weibull, Gompertz, log-logistic, lognormal, and generalised gamma) and piecewise models to PFS data independently for each treatment group. During the clarification process (clarification response, question B4[i]) the company stated that it had conducted analysis to evaluate the potential impact of disease progression happening earlier than the scheduled visit and that these "*sensitivity analyses demonstrated a consistent PFS benefit with that of the primary analysis, therefore interval censoring PFS analysis was not deemed necessary.*"[24]

The company's model adopts a piecewise approach for PFS in the pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel treatment groups. The decision to adopt this approach was taken on the basis of a decrease in the proportion without a PFS event is observed between weeks 8 and 9 in both treatment arms of KEYNOTE-355,[26] driven by the trial protocol where the first radiological tumour response assessment was performed in week 8 (±1week).[29] Within the base case analysis, PFS is modelled using the observed KM survival function up to 9 weeks, and using a Weibull and a lognormal distributions fitted to the post-9 week data from KEYNOTE-355 thereafter for pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel, respectively. The decision to use a 9-week knot was made based on the visual inspection of the KM survival functions, the results of Chow tests and examination of the log-cumulative hazard functions for PFS.[43]

Figure 9 and Figure 10 present comparisons of the model-predicted survival probabilities for PFS and observed KM survival functions for pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel, respectively. The AIC and BIC statistics for the candidate PFS piecewise models (9-week cut-point) are presented in Table 22.

Table 22: AIC and BIC statistics for company's piecewise parametric models for PFS (week 9 cut-point), from data for pembrolizumab plus taxane and taxane treatment arms of KEYNOTE-355 (adapted from Table 47 of the CS)

Parametric distribution	Pembrolizumab plus taxane			Taxane		
	AIC	BIC	Sum	AIC	BIC	Sum
Exponential	421.54	423.91	845.46	255.08	256.69	511.77
Log-logistic	**418.19**	422.93	841.13	247.33	250.56	497.89
Lognormal	421.78	426.52	848.29	247.07	**250.29**	**497.36**
Generalised Gamma	420.68	427.79	848.46	**245.92**	250.75	496.67
Gompertz	417.67	**422.41**	**840.07**	247.59	250.81	498.40
Weibull	418.78	423.52	842.30	255.05	258.27	513.31

AIC - Akaike Information Criteria, BIC - Bayesian Information Criteria.
Note – Models chosen by the company are shaded; lowest values are presented in bold

Figure 9: PFS survival functions using company's piecewise parametric modelling approach, pembrolizumab plus paclitaxel/nab-paclitaxel therapy group

† Note that the KM was used for the initial 9 weeks.

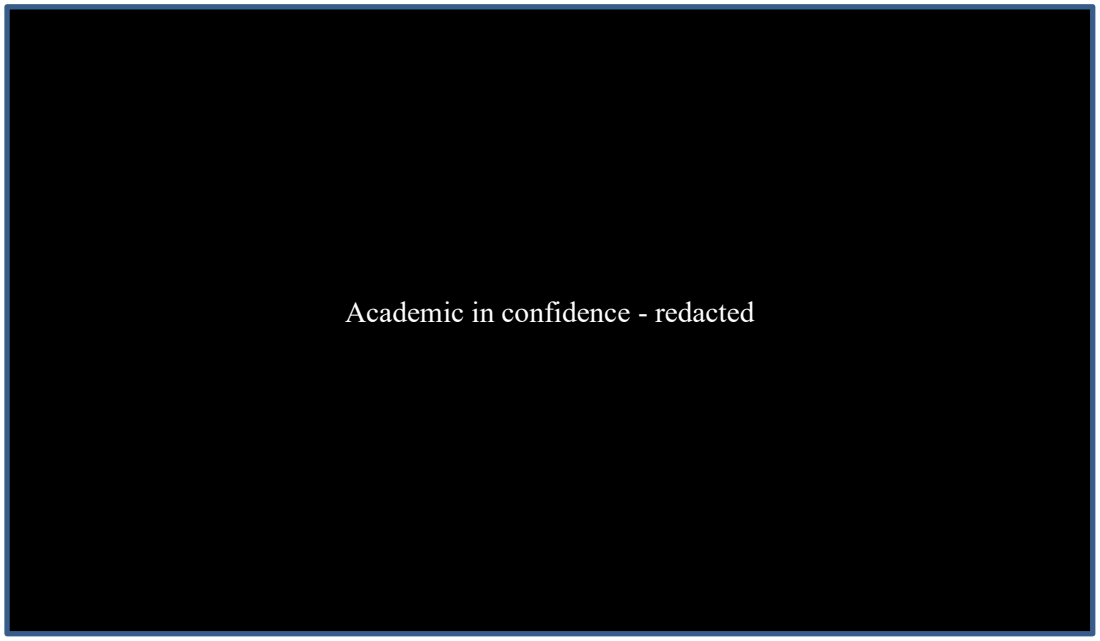
Figure 10: PFS survival functions using company's piecewise parametric modelling, paclitaxel therapy group

† Note that the KM was used for the initial 9 weeks

The distribution with the lowest AIC and BIC for pembrolizumab plus paclitaxel/nab-paclitaxel was the Gompertz; however, it was excluded based on visual fit which led to an overestimation of the long-term PFS. The company chose the Weibull distribution (third best fit) rather than the log-logistic distribution (second-best fit) although the difference in BIC is small enough to not warrant a distinction. However, in CS appendix P,[43] the company appears to recommend the selection of the log-logistic for the base-case analysis and the lognormal as an alternative for scenario analysis. For paclitaxel, the company chose the second-best fit model based on the combined AIC/BIC statistics (lognormal, lower BIC) which predicted lower long-term PFS estimates than the generalised gamma, which had a similar BIC value.

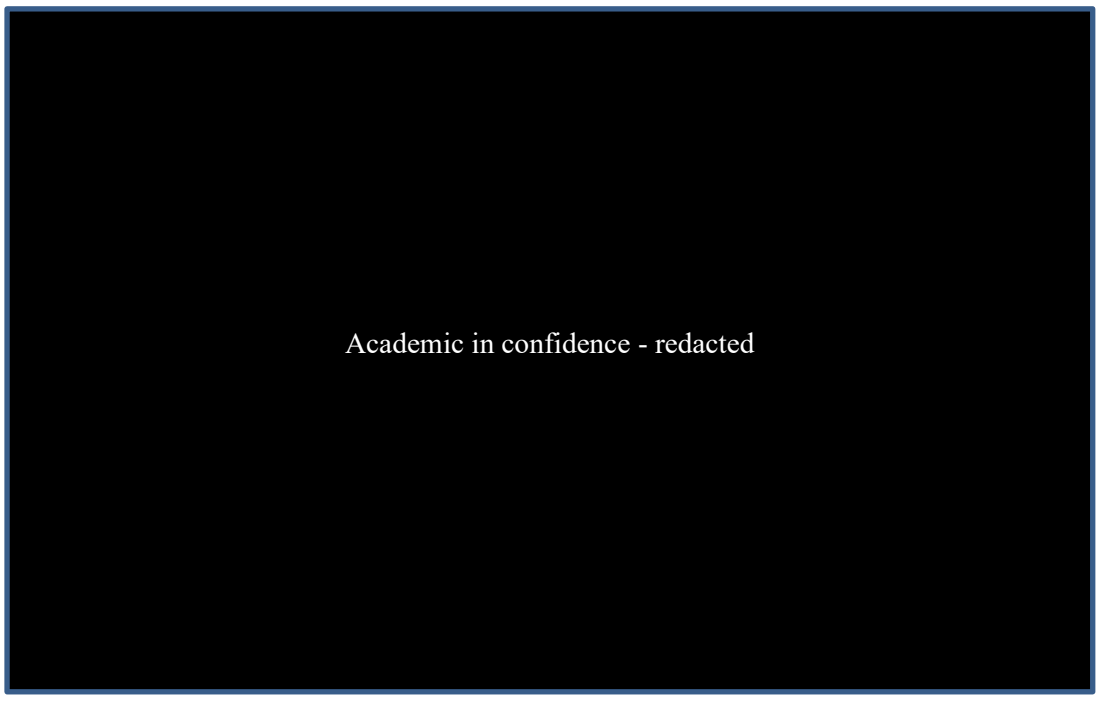
In response to clarification question B4b, the company provided plots of smoothed empirical hazard functions with 95% confidence intervals for each treatment group (Figure 11 for pembrolizumab plus taxanes and Figure 12 for placebo plus taxanes).

Figure 11: Plot of hazard function of BIRC-assessed Progression-free Survival assuming smooth spline or various parametric distributions used for long-term extrapolation for the group treated with pembrolizumab plus taxanes



The shaded area represents the 95% CI for the smooth spline estimate.

Figure 12: Plot of hazard function of BIRC-assessed Progression-free Survival assuming smooth spline or various parametric distributions used for long-term extrapolation for the group treated with placebo plus taxanes



The shaded area represents the 95% CI for the smooth spline estimate.

The empirical hazard function for the pembrolizumab plus taxanes group suggests a non-linear monotonically decrease in the risk of progression or death over the first 150 weeks. The empirical hazard function for the placebo plus taxanes group suggests an increase in the risk of progression or death over the first approximately 18 weeks followed by a monotonically decrease in the risk of progression or death thereafter.

The company asserted that the change in the empirical hazard function for the placebo plus taxanes group occurs at week 9, although the empirical hazard function is still increasing between weeks 9 and 18. In the opinion of the ERG, the company suggests that the change in the shape of the hazard function provides a justification for a piecewise approach to modelling the hazard function. In fact, the empirical hazard function is consistent with a lognormal and log-logistic distribution.

The first post-randomisation imaging assessment was performed at Week 8 (±7 days). Hence, the Kaplan-Meier survival function showed a decline in the proportion of patients not experiencing a PFS event at around Week 9. The company modelled the data using a hybrid model based on the Kaplan-Meier survival function up to Week 9 and a parametric survival fitted to the sample data after Week 9. The ERG has a preference for modelling time-to-progression using accounting for interval censoring in which the time to progression is not known precisely but is known to fall in a particular interval specific to each patient. In response to clarification question B4i the company wrote that an "*interval-censoring approach for PFS was planned in statistical analysis plan (SAP) only in case of imbalance between the treatment groups on disease assessment schedules or censoring patterns. As there was no imbalance between treatment arms on disease assessment schedules and the PFS sensitivity analyses results were consistent to the primary PFS endpoint and not borderline significant, this analysis was not performed for inclusion in the CSR.*" In the company's response, it provided results of three sensitivity analyses but none according to a proper interval-censored analysis. The ERG does not accept the company's rationale for not doing a proper interval censored analysis. Furthermore, it is the opinion of the ERG that the assuming disease progression occurs at the date of documented progression overestimates time-to-progression (and, as a consequence, QALYs when using a methodology that attaches utility to the progression-free and the progressed health states) and underestimates uncertainty. However, this limitation is unlikely to be a key driver of the incremental cost-effectiveness ratio (ICER).

Ignoring the Gompertz distribution, which is fitted without parameters constrained to be positive and the issue of interval censoring, the best fitting model to the sample data, assuming the KM survivor function is used for the first 9 weeks, based on BIC for the pembrolizumab plus taxanes group was a log-logistic distribution, although there is little to distinguish between exponential, Weibull, lognormal and log-logistic distributions. However, the smoothed empirical hazard function does not support a

unimodal, increasing then decreasing hazard function or a constant hazard; there seems to be an inconsistency in the exponential BIC presented in Table 47 of the CS and the empirical hazard function presented in response to clarification question B4b. The ERG suggests that a Weibull distribution, for the entire time horizon, is likely to be the most appropriate model, of those evaluated, over the observed period.

Ignoring the Gompertz distribution, which is fitted without parameters constrained to be positive and the issue of interval censoring, the best fitting model to the sample data based on BIC for the placebo plus taxanes group was a lognormal distribution, although there is little to distinguish between lognormal, log-logistic and generalised gamma distributions. The smoothed empirical hazard function supports a unimodal, increasing then decreasing hazard function. The ERG suggests that any of these distributions is likely to be the most appropriate model over the observed period. In the CS (Section B3.3.2) the company dismisses the log-logistic distribution on the basis that the long-term mean proportion of patients who are event free exceeds the mean proportion of patients still alive. The inconsistency arises as a consequence of modelling the data independently. The ERG does not believe that the discrepancy implies that a log-logistic distribution is not plausible, rather that the joint distribution of model parameters needs to be constrained to avoid the inconsistency, that is effectively modelling PFS and OS bivariately.

Analogously to the approach used for OS, the fitted PFS model for the paclitaxel treatment group is assumed generalisable for the docetaxel treatment group. The PFS for the atezolizumab plus nab-paclitaxel group is modelled by applying the inverse of the HR derived from the NMA for atezolizumab plus nab-paclitaxel versus pembrolizumab plus paclitaxel/nab-paclitaxel (HR=[redacted], 95% CrI [redacted]) to the fitted Weibull distribution used after 9 weeks for the pembrolizumab plus paclitaxel/nab-paclitaxel group. The ERG notes that the same reservations noted by the company about the uncertainty associated with the results of the NMA for OS also apply to PFS.

A constraint is applied to the model to ensure that PFS must be less than or equal to OS at any given time *t*. The Kaplan-Meier survival functions and modelled PFS survival functions are presented in Figure 13.

Figure 13: PFS survival functions for all treatment options included in company's base case analyses, week 9 cut-point (generated by the ERG from the company's model)†

† Note - the modelled PFS survival function for docetaxel is assumed identical to the PFS survival function for paclitaxel

Alternative scenarios were assessed in the company's sensitivity analyses, such as the use of: the piecewise log-logistic with cut-off point of 9 weeks for pembrolizumab plus paclitaxel/nab-paclitaxel and for paclitaxel, both separately and simultaneously; the piecewise log-logistic with cut-off point of 9 weeks for pembrolizumab plus paclitaxel/nab-paclitaxel in the analysis against atezolizumab plus nab-paclitaxel; and the use of nab-paclitaxel as common comparator in the NMA to estimate the PFS HR applied to generate the PFS probabilities for atezolizumab plus nab-paclitaxel.

4.2.4.2.3 Time to treatment discontinuation (TTD)

TTD was modelled using different approaches depending on the treatment group under consideration. For pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel, the company fitted standard parametric models (exponential, Weibull, lognormal, log logistic, Gompertz and generalised gamma distributions) independently to the observed TTD data for patients with CPS≥10 in the pembrolizumab plus taxanes and taxanes treatment arms in KEYNOTE-355. The CS notes that "*at the IA2 cut-off date, patients had a median duration of follow-up of 16.8 months (range 0.2 to 35.0), with 8.7% of patients in the pembrolizumab in combination with chemotherapy group and 6.0% in the control group remaining on assigned treatment"* (CS, page 34), although this relates to the ITT population, and not specific to patients with CPS≥10.[43]

The AIC and BIC data for the candidate TTD models provided within the CS are presented in Table 23. The Weibull distribution was selected for use for pembrolizumab plus paclitaxel/nab-paclitaxel whilst the log-logistic was assigned for paclitaxel in the base case analyses, based on the values of BIC and AIC combined and visual inspection (CS, pages 115 to 117). Comparisons of the fitting parametric models to the observed TTD KM data for pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel are shown in

Figure **14** and Figure 15, respectively.

Table 23: AIC and BIC statistics for company's parametric models for TTD (from data for pembrolizumab plus taxane and taxane treatment arms of KEYNOTE-355, adapted from Table 50 of the CS)

Parametric distribution	Pembrolizumab plus taxane			Taxane		
	AIC	BIC	SUM	AIC	BIC	SUM
Exponential	856.43	858.99	1715.42	398.08	399.93	798.01
Log-logistic	852.07	857.18	1709.26	**392.02**	**395.73**	**787.75**
Lognormal	850.10	855.21	1705.31	398.42	402.12	800.54
Generalised Gamma	852.62	857.73	1710.35	399.08	402.78	801.87
Gompertz	849.75	857.41	1707.17	398.19	403.74	801.94
Weibull	**849.47**	**854.57**	**1704.04**	399.91	403.61	803.51

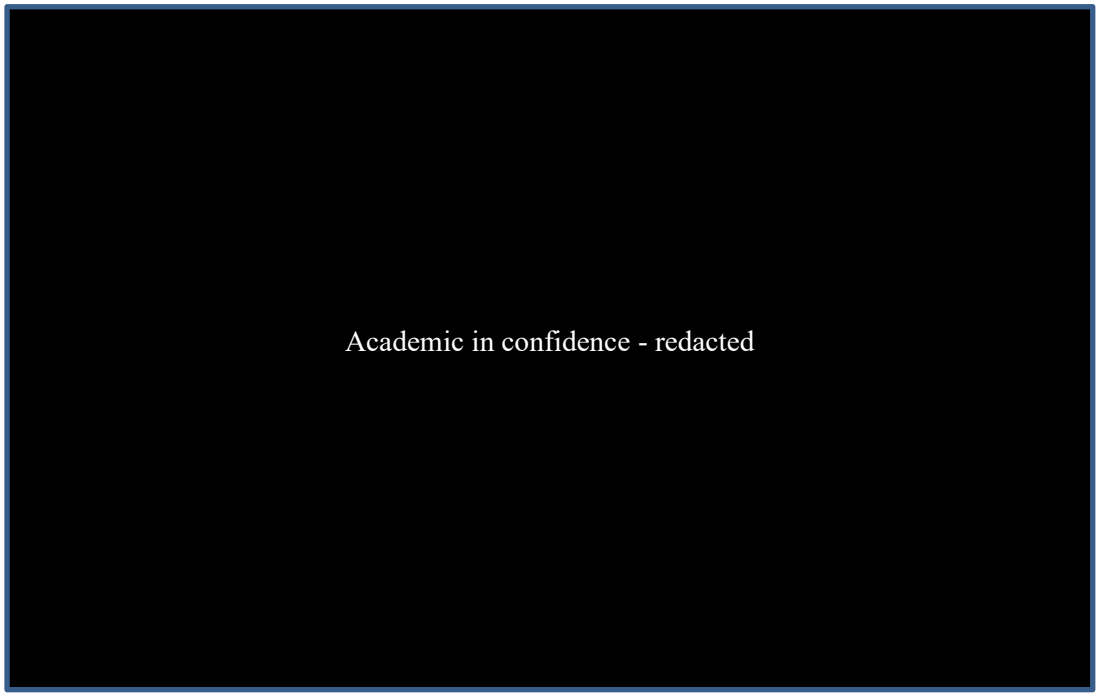
AIC - Akaike Information Criteria, BIC - Bayesian Information Criteria.
Note – Models chosen by the company are shaded; lowest values are presented in bold

Figure 14: TTD survival functions using company's parametric modelling pembrolizumab plus paclitaxel/nab-paclitaxel therapy group

Figure 15: TTD survival functions using company's parametric modelling, paclitaxel therapy group

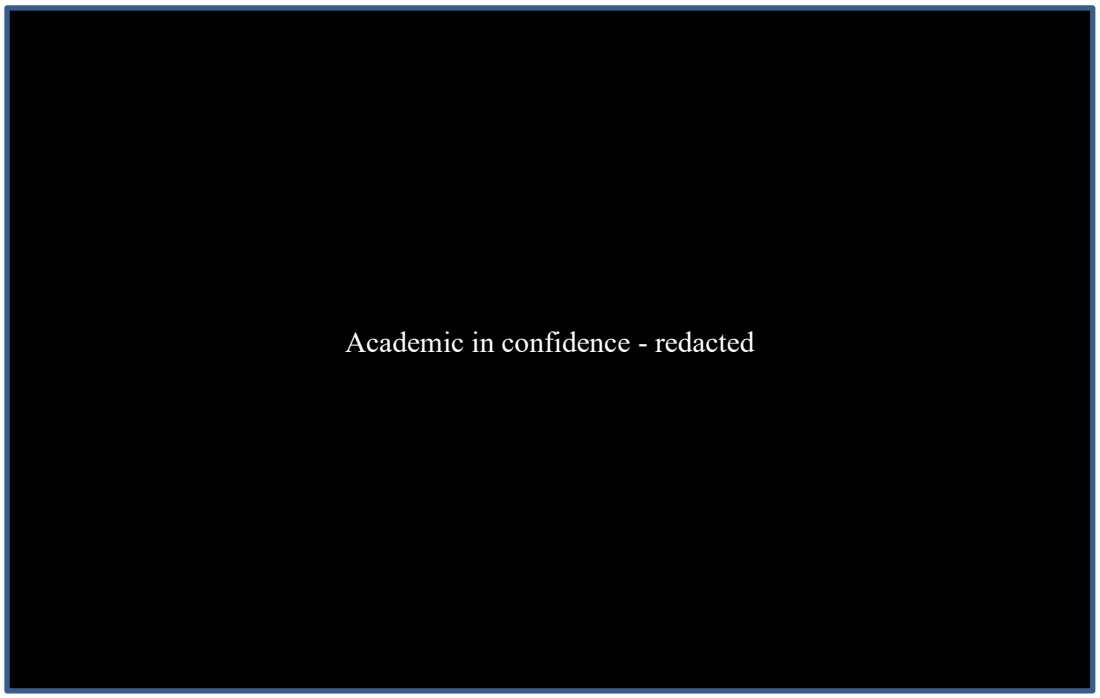
The empirical hazard function for treatment discontinuation is shown in Figure 16 for the pembrolizumab plus taxanes group and Figure 17 for the placebo plus taxanes group.

Figure 16: Plot of hazard function of treatment discontinuation assuming smooth spline or various parametric distributions used for long-term extrapolation for the group treated with pembrolizumab plus taxanes



The shaded area represents the 95% CI for the smooth spline estimate.

Figure 17: Plot of hazard function of treatment discontinuation assuming smooth spline or various parametric distributions used for long-term extrapolation for the group treated with placebo plus taxanes



The shaded area represents the 95% CI for the smooth spline estimate.

The best fitting model to the sample data based on BIC for the pembrolizumab plus taxanes group was a Weibull distribution. Although there was weak evidence to distinguish between any of the models, the Weibull distribution appeared to be most consistent with the empirical smoothed hazard function. The best fitting model to the sample data based on BIC for the placebo plus taxanes group was a log-logistic distribution, which appeared to be most consistent with the empirical smoothed hazard function. The ERG noted that these distributions assume that after 2 years when both study arms would be on taxanes alone that the risk of discontinuation would be increasing in those assigned to the pembrolizumab plus taxanes arm but decreasing in the placebo plus taxanes arm. This is not intuitive, but is unlikely to significantly impact on the ICER.

The TTD distribution for the atezolizumab plus nab-paclitaxel group is assumed to equal the PFS distribution for atezolizumab plus nab-paclitaxel. The fitted TTD model for the paclitaxel treatment group is assumed generalisable to the docetaxel treatment group.

The ERG notes that the sampled TTD is assumed to apply to all components of treatment, therefore, all treatments are stopped at the same time. The exception to this is for the pembrolizumab treatment which is stopped at 2 years to reflect the maximum treatment duration; after that period, patients continue to receive either paclitaxel or nab-paclitaxel until discontinuation or pre-progression death. The model also applies a structural constraint to prohibit TTD exceeding OS at any given time t. The ERG notes, however, that a constraint to ensure that TTD does not exceed PFS is not included in the base case analyses. This leads to the assumption that patients can receive first-line treatment after disease progression. In the CS it is stated that "*Administration of pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator [29]"* and that *"Taxane chemotherapy treatment could be continued as per clinician's choice upon cessation of pembrolizumab".* As treatment beyond progression was permitted in KEYNOTE-355 and the impact on the ICER of curtailing first-line treatment on progression was small, the ERG did not change this assumption.

Figure 18 summarises the TTD functions included in the company's base case analyses. The ERG believes that the Weibull distribution for pembrolizumab plus paclitaxel/nab-paclitaxel and log-logistic distribution for paclitaxel, as selected by the company, appear to provide a good fit to the data but notes that the company does not explore any alternative functions in scenario analyses for pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel. In addition, the assumption that atezolizumab plus nab-paclitaxel discontinue treatment only upon disease progression results in much longer TTD than for other treatments, resulting in higher acquisition costs. This is deemed unfavourable to atezolizumab plus nab-paclitaxel considering that the PFS for atezolizumab plus nab-paclitaxel is lower than for pembrolizumab plus paclitaxel/nab-paclitaxel (Figure 13). A sensitivity analysis was undertaken by the

company where the TTD function for atezolizumab plus nab-paclitaxel was set equal to the Weibull distribution fitted to data for pembrolizumab plus nab-paclitaxel from KEYNOTE-355. This is described by the company as equivalent to *"set a maximum treatment duration period for atezolizumab plus nab-paclitaxel"* (CS, page 164).[43]

Figure 18: TTD survival functions for all treatment options included in company's base case analyses, week 9 cut-point (includes PFS constraint, generated by the ERG from the company's model) †*

Notes: † - the modelled TTD survival function for docetaxel is assumed identical to the TTD survival function for paclitaxel

** - the modelled TTD survival function for atezolizumab plus nab-paclitaxel is assumed identical to the PFS survival function*

4.2.4.3 Health-related quality of life

HRQoL data used in the company's model are based on EQ-5D data collected in KEYNOTE-355.[26] Within the study, the questionnaire was administered at baseline, every 3 weeks for the first 3 treatment cycles (weeks 1, 4 and 7), then every 9 weeks until week 52; and thereafter every 12 weeks until treatment progression whilst patients were on treatment (maximum of 2 years); in the case of treatment discontinuation, the questionnaire was also applied at the treatment discontinuation and 30-day post-treatment safety follow-up visits.[29, 43]

The ERG notes that the company's submission is unclear regarding which HRQoL instrument was used. Section B.3.4 and Appendix O of the company's submission report the EQ-5D-3L instrument as being the method used to determine health utilities in the company's model. However, on the clinical section of the CS and on the KEYNOTE-355 CSR, the only results presented are for the EQ-5D VAS.[26, 43] The study CSR also describes the EQ-5D applied in the trial as having five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), but the number of levels used (three or five) is omitted.[26] The ERG believes it is likely that the EQ-5D-3L questionnaire was the instrument used in the company's analyses.

The company fitted a linear mixed-effect model with fixed effects to the available EQ-5D data from the full analysis set (FAS) for the pooled pembrolizumab plus chemotherapy and chemotherapy treatment arms for the CPS ≥ 10 population in part 2 of KEYNOTE-355[26] (IA2 data-cut, change from baseline to week 15, pembrolizumab plus chemotherapy [redacted] and chemotherapy [redacted]). The ERG notes that the distribution of EQ-5D-3L data does not follow standard parametric distribution: there is an upper bound of one at full health, data are left bounded at the worst health state, there are gaps between values and the data tend to be multimodal. Linear models implicitly appeal to the Central Limit Theorem but can result in implausible predictions and are likely to be statistically inefficient. Alternative models that appropriately represent the underlying data generation process have been proposed.[59] The ERG is unable to comment on the difference that a more representative modelling approach may have on the estimates. Furthermore, the company assumed that utility for patients receiving gemcitabine and carboplatin is equal to the utility of patients receiving taxanes. The final multi-variate model used treatment group and the following factors as covariates: ECOG, PFS by BICR, AE status and each time-to-death category, whilst accounting for repeated measures in the same patient (clarification response, question B10).[24] Utility values in the base-case analysis were estimated for the pooled treatment arms by proximity to death, based on five categorical groups (<30 days; ≥30 to 90 days; ≥90 to 180 days;

≥180 to 360 days, and ≥360 days). The utilities for each time-to-death category are assumed to be independent of initial treatment.

Within the model, the proportion of patients in the time-to-death categories at each time *t* were calculated as follows:

- < 30 days from death: calculated as the probability of dying during the interval *t*+0 cycles and *t*+4 cycles;
- ≥30 days to 90 days from death: calculated as the probability of dying during the interval *t*+5 cycles and *t*+12 cycles;
- ≥90 days to 180 days from death: calculated as the probability of dying during the interval *t*+13 cycles and *t*+25 cycles;
- ≥180 to 360 days from death: calculated as the probability of dying during the interval *t*+26 cycles and *t*+51 cycles;
- ≥360 days from death: calculated as the 1 minus of the sum of the probabilities of being in the other four states.

The ERG notes that the description of the time-to-death categories do not align with the implementation in the model. In the model, the five categories are: <4 weeks (28 days); ≥4 to 12 weeks (28 to 84 days); ≥12 to 25 weeks (84 to 175 days); ≥25 to 51 weeks (175 to 357 days), and ≥51 weeks (357 days). The ERG notes, however, that this is unlikely to noticeably affect the ICER and fitted in with the weekly time cycle in the model.

The use of a time-to-death approach for modelling HRQoL is justified by the company on the basis of it would overcome *"the problem of limited questionnaire availability to inform the PPS health state utility estimates"*, which is a consequence of the EQ-5D questionnaire collection not being collected after treatment discontinuation or beyond 30-days after disease progression. The lack of data for patients in the progressive state for longer periods is a limitation of the study and the estimates of utility data for post-progression health state *"may not be representative of the patient's quality of life in the whole post progression state"* (CS, page 120).

The company applied UK tariffs to the EQ-5D scores using Dolan (1997).[60] The estimates for utility data applied in the company's model are summarised in Table 24.

Table 24: Mean EQ-5D utilities used in the company's base case analyses (adapted from CS Table 54)[43]

Time to death category	Utility value (all treatment groups)*	SE
≥360 days from death	[redacted]	[redacted]
≥180 to 360 days	[redacted]	[redacted]
≥90 days to 180 days	[redacted]	[redacted]
≥30 days to 90 days	[redacted]	[redacted]
< 30 days	[redacted]	[redacted]

SE – standard error
** Age adjustment not included, estimates for patients aged 53 years old.*

Health utilities are adjusted by age using absolute utility decrements for each age compared to the utility at the start age (53 years), based on UK general population values reported by Ara and Brazier.[45] The company assumes that the effects of AEs on HRQoL would have been captured in the EQ-5D data collected from patients in KEYNOTE-355 (CS, Table 54 and page 124); therefore, its base-case analysis do not include any QALY losses associated with Grade 3-5 AEs. The use of utility values by progression status with QALY losses due to AE (pooled and by treatment arm) and the removal of the health utilities age-adjustment are explored in the company's scenario analyses for the comparison of pembrolizumab plus paclitaxel/nab-paclitaxel to paclitaxel (see CS, Pages 161-163).[43] The utility values were similar for each study arm and in the analyses independent of arm, the utility values were [redacted] for progression-free survival, and [redacted] for progressed disease, with a utility loss of [redacted] related to AEs.

4.2.4.4 Resource costs

The model includes costs associated with: (i) drug acquisition; (ii) drug administration; (iii) disease management; (iv) second and further-line (2L+) treatment; (v) management of AEs; (vi) end-of-life (terminal care) costs and (vii) costs related to PD-L1 testing. Table 25 summarises the costs in the company's base case analyses; the derivation of these values is described in the subsequent sections.

Table 25: Costs parameters for each comparator used in the model

Cost parameter	Pembrolizumab plus paclitaxel/ nab-paclitaxel	Paclitaxel	Docetaxel	Atezolizumab plus nab-paclitaxel
Drug costs (weekly cycle, at intended dose)	[redacted]	£30.52	£28.67	£3,095.88† / £430.50‡
RDI	[redacted]	[redacted]	[redacted]	[redacted]
Drug costs (weekly cycle, including RDI)	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs (per week cycle)	£413.51† / £241.06§ / £329.39‡	£492.68**	£250.06**	£370.68† / £241.06‡

Cost parameter	Pembrolizumab plus paclitaxel/ nab-paclitaxel	Paclitaxel	Docetaxel	Atezolizumab plus nab-paclitaxel
Subsequent lines (2L+) treatment costs (once-only)	[redacted]	[redacted]	[redacted]	[redacted]
Disease management – progression-free (once-only)	£299.50	£299.50	£299.50	£299.50
Disease management – progression-free (weekly)	£75.01	£75.01	£75.01	£75.01
Disease management – progressed disease (weekly)	£71.70	£71.70	£71.70	£71.70
Terminal care (once-only)	£8,166.55	£8,166.55	£8,166.55	£8,166.55
AEs	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS≥10 testing*	£106.20	£0.00	£0.00	£278.49

2L+ – second and beyond lines of treatment; AE – Adverse event; RDI – relative dose intensity; PD-L1 – Programmed Death Ligand 1; CPS – Combined Positive Score.
**The unit assay cost divided by the proportion of patients tested with PD-L1 CPS≥ 10.*
⁂ includes premedication costs;
† week when pembrolizumab is administered in combination with paclitaxel or nab-paclitaxel or atezolizumab with nab-paclitaxel in the same week;
§ weeks when only pembrolizumab is administered;
‡ weeks when only the taxane regimens (paclitaxel and/or nab-paclitaxel) are administered.

(i) Drug acquisition costs

Drug acquisition costs are modelled as a function of the planned treatment schedule, relative dose intensity (RDI), the observed mean BSA observed in KEYNOTE-355 where dosages are weight-based, the chosen TTD survival function and relevant unit costs. The model includes vial sharing for all IV drugs except for pembrolizumab and atezolizumab, although no evidence was provided that this occurs in practice. The treatment options included in the first-line setting are summarised in Table 26. In the model, acquisition costs for combination therapies are calculated separately for each regimen component as the treatment schedules differ between components.

The list price for pembrolizumab is £2,630.00 per vial of 100mg. The company has proposed a PAS which takes the form of a simple price discount of [redacted]; including this discount results in a cost per vial of [redacted]. In line with the draft SmPC, pembrolizumab is assumed to be given at a fixed dose of 200mg per day on the first day of every 21-day cycle (Q3W). Treatment with pembrolizumab is assumed to have a maximum duration of 35 administrations (approximately 2 years).

Paclitaxel is assumed to be given as three doses of 90mg/m^2 on days 1, 8 and 15 of every 28-day cycle, for both monotherapy (as a comparator) and in combination with pembrolizumab (part of the intervention). The ERG comments that the frequency of paclitaxel monotherapy does not reflect

standard UK practice which is weekly doses (see Section 4.2.1). The list price per vial of 30mg of paclitaxel is £4.69. The costs for paclitaxel also include premedication drugs, which are 20mg of dexamethasone, 10mg of chlorpheniramine and 300mg of cimetidine being administered on the same days as paclitaxel.[61] Nab-paclitaxel as part of a combination regime with either pembrolizumab or atezolizumab is assumed to be given as doses of 100mg/m^2 on days 1, 8 and 15 of every 28-day cycle. The list price per vial of 100mg of nab-paclitaxel is £246.00. Docetaxel is assumed to be given at a dose of 100mg/m^2 on the first day of every 21-day cycle. The list price per vial of 80mg of docetaxel is £12.50. The costs for docetaxel also include 16mg of dexamethasone as a premedication drug, being administered for three days before the administration of docetaxel.[62] Atezolizumab is assumed to be given at a fixed dose of 840mg every two weeks;[63] the list price for vial of 840mg of atezolizumab is £2,665.38. Unit costs were taken from the Commercial Medicines Unit (CMU) Electronic Market Information Tool (eMIT) and the Monthly Index of Medical Specialities (MIMS).[48, 50] Comparator PAS (cPAS) discounts are also available for atezolizumab, nab-paclitaxel, docetaxel, eribulin, carboplatin, capecitabine, vinorelbine and doxorubicin; the impact of these cPASs on the ICER of pembrolizumab plus paclitaxel/nab-paclitaxel is presented in a separate confidential appendix to this ERG report.

The company has used the distribution of patients using paclitaxel and nab-paclitaxel observed in the pembrolizumab plus taxanes treatment arm in KEYNOTE-355[26] (35.1% receive paclitaxel and 64.9% receive nab-paclitaxel) to estimate the costs of the pembrolizumab plus paclitaxel/nab-paclitaxel intervention. All treatment regimens are assumed to be administered indefinitely until treatment discontinuation or death, with exception of pembrolizumab, which has a stopping rule of 35 administrations (approximately 2 years) in place, and atezolizumab plus nab-paclitaxel, which is assumed to be given until progression or death.

Table 26: Dosing, treatment schedules and drug cost per cycle for first-line treatments included in the company's model

Regimen	Regiment component	Adm route	Dosing schedule	RDI	% treatment allocation	Drug costs per admin*	NHS reference code	Administration costs per drug admin
Pembrolizumab plus paclitaxel/ nab-paclitaxel	Pembrolizumab	IV	200mg once every 3 weeks (Q3W), maximum of 35 doses (~2years)	[redacted]	100%	[redacted]	SB14Z (in combination)/ SB12Z (alone)	£370.68 (in combination) ‡ § /£241.06 (alone) ⸸
	Paclitaxel	IV	90mg/m^2 on days 1, 8 and 15 of every 28-day cycle	[redacted]	35.1%	£30.52⁂	SB14Z (paclitaxel); premedication costs from PSSRU[52] and TA639[44]	£492.68⁂§
	Nab-paclitaxel	IV	100mg/m^2 on days 1, 8 and 15 of every 28-day cycle	[redacted]	64.9%	£430.50	SB14Z (in combination)/ SB12Z (alone)	£370.68 (in combination) ‡ § / £241.06 (alone)⸸
Paclitaxel	Paclitaxel	IV	90mg/m^2 on days 1, 8 and 15 of every 28-day cycle	[redacted]	100%	£30.52⁂	SB14Z (paclitaxel); premedication costs from PSSRU[52] and TA639[44]	£492.68⁂
Docetaxel	Docetaxel	IV	100mg/m^2 once every 3 weeks (Q3W)	[redacted]	100%	£28.67	SB12Z (docetaxel); premedication costs from PSSRU[52] and TA639[44]	£250.06†
Atezolizumab plus nab-paclitaxel	Atezolizumab	IV	840mg once every 2 weeks (Q2W)	[redacted]	100%	£2,665.38	SB14Z (in combination)/ SB12Z (alone)	£370.68 (in combination)‡ / £241.06 (alone)⸸
	Nab-paclitaxel	IV	100mg/m^2 on days 1, 8 and 15 of every 28-day cycle	[redacted]	100%	£430.50	SB14Z (in combination)/ SB12Z (alone)	£370.68 (in combination)‡ / £241.06 (alone)⸸

Adm – administration; RDI -

** These values do not include application of RDI; ‡ when administered in combination with the other drugs of the regimen in the same week. ⸸ when administered without the other drugs of the regimen in the week.*

⁂*Pre-medication costs for paclitaxel include dexamethasone 20mg orally 6-12 hrs prior to paclitaxel, chlorpheniramide 10 mg as IV infusion 30-60 mins prior to paclitaxel and cimetidine 300mg as an IV infusion 30-60 mins prior to paclitaxel.*

† Pre-medication costs for docetaxel include dexamethasone given as oral tablets 16mg/day for 3 days, one day prior to docetaxel administration.

§ The company uses a separate calculation of administration costs for each treatment arm. However, in the pembrolizumab plus paclitaxel/nab-paclitaxel treatment group, on the weeks when the drugs are administered in combination, or on the weeks when paclitaxel/nab-paclitaxel are administered alone, the company applies a weighted administration cost based on the observed distribution of the taxane therapy treatments in pembrolizumab+taxanes arm from KEYNOTE-355.

(ii) Drug administration costs

Administration costs are modelled as a function of the TTD for each treatment and were based on NHS Reference Costs 2018/19 and PSSRU 2019 (see Table 26) together with additional assumptions.[43] Administration costs for combination therapies are calculated separately for each regimen component, considering that the treatment schedule can differ between the components. When two components were scheduled to be administered in the same week, only the higher cost was applied. For the pembrolizumab plus paclitaxel/nab-paclitaxel regimen, the company calculated a weighted average for the administration costs of paclitaxel and nab-paclitaxel, using the observed distribution of treatments in KEYNOTE-355[26] (35.1% received paclitaxel and 64.9% received nab-paclitaxel). The administration cost for premedication drugs were assumed to be subject to: (i) a prescription fee (dexamethasone), obtained by multiplying the average time spent per patient for dispensing treatment by the hourly cost of a pharmacist; or (ii) a preparation cost (chlorpheniramine and cimetidine), obtained by multiplying the average time of contact per patient by the hourly cost of a hospital nurse.[52] These administration costs are added to the administration costs for the treatment regimens that contain paclitaxel or docetaxel.

(iii) Disease management costs

Health care resource use related to the disease management include the costs associated with medical visits (GPs, nurses and oncologists), blood tests and imaging (computerised tomography [CT] and magnetic resonance image [MRI]). The model includes three different sets of costs. Costs associated with (i) the disease diagnosis are applied once only in the first cycle of the model to patients in PFS state, (ii) ongoing follow-up and monitoring of patients in the progression-free state and (iii) ongoing follow-up and monitoring costs of patients in the post-progression state. The last two sets of costs are applied in all cycles; weekly costs of disease ongoing management are assumed to decrease after disease progression (see Table 27). Disease management costs are assumed independent of treatment and were based on NICE TA639;[44] NHS Reference Costs 2018/19;[51] PSSRU 2019,[52] clinical expert opinion and assumptions.

Table 27: Type of resources, frequencies and unit costs for disease management costs used in the model for all treatment groups, (adapted from the company's CS and model)

Resource	% patients receiving the procedure (one-off cost)	Weekly frequency (ongoing management costs)		Unit costs	Total costs		
	PF health state	PF health state	PP health state		PF (one-off)	PF (weekly)	PP (weekly)
Oncologist visits (initial visit)	100%	–	–	£142.73	£142.73	–	–
Oncologist visits (ongoing monitoring)	–	0.23	0.23	£142.73	–	£32.83	£32.83
GP visits	–	0.23	0.23	£33.19	–	£7.63	£7.63
Specialist clinical nurse visits	–	0.23	0.23	£98.74	–	£22.71	£22.71
Community nurse visits	–	0.06	0.11	£39.68	–	£2.28	£4.56
CT scan	50%	0.08	0.04	£103.61	£51.81	£8.63	£3.97
MRI Scan	50%	–	–	£204.35	£102.17	–	–
Full blood count	100%	0.33	–	£2.79	£2.79	£0.93	–
Total costs					**£299.50**	**£75.01**	**£71.70**

CT – computerised tomography; GP – general practitioner; MRI – magnetic resonance image; PF – progression-free; PP – post-progression.

(iv) Subsequent treatment costs (2L+)

The model includes the costs of subsequent treatment (second, third and fourth-lines, referred to hereafter as 2L+) following pembrolizumab plus paclitaxel/nab-paclitaxel or paclitaxel as first-line therapies. These costs are applied as a fixed sum at the point of progression, and are based on the subsequent therapies received, the mean duration of use observed at IA2 of KEYNOTE-355,[26] (see Table 28) and the costs associated with each treatment. Unit drug acquisition and administration costs were taken from eMIT, BNF, MIMS and NHS Reference Costs 2018/19.[48-51] The model includes vial sharing for all IV drugs but does not include drug wastage for oral drugs (capecitabine). The cost of subsequent lines of treatment after pembrolizumab plus paclitaxel/nab-paclitaxel is assumed generalisable for patients receiving atezolizumab plus nab-paclitaxel, whilst the costs after paclitaxel is assumed generalisable for patients who received docetaxel.

The ERG notes that these estimates include the list price for drugs, which would overestimate costs where PAS are agreed. The estimates employed by the company may also underestimate of the costs of subsequent treatments for patients receiving pembrolizumab plus paclitaxel/nab-paclitaxel as first-line therapy, since patients in this treatment group receiving later lines of therapy may be administrative censored more frequently than patients in the comparators treatment groups.[24] However, the ERG conducted sensitivity analyses that showed that the ICER was not noticeably sensitive to assumptions related to the costs of subsequent treatments.

Table 28: Proportion of patients and costs for post-progression treatment used in the model (subsequent lines – 2L+, adapted from CS, table 58 and model)

Subsequent lines of therapies and regimens	Patients receiving treatment (%)		Total weighted drug costs (per regimen)†	
	Pembrolizumab plus paclitaxel/nab-paclitaxel	Paclitaxel	Pembrolizumab plus paclitaxel/nab-paclitaxel	Paclitaxel
Second-line therapies				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide plus doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin plus gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Weighted total costs – 2L			[redacted]	[redacted]
Third-line therapies				
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin mesylate	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine plus vinorelbine tartrate	[redacted]	[redacted]	[redacted]	[redacted]
Cyclophosphamide plus doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Weighted total costs – 3L			[redacted]	[redacted]
Fourth-line therapies				
Vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Nab-paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Weighted total costs – 4L			[redacted]	[redacted]
Overall proportion of patients receiving 2L treatment*	[redacted]	[redacted]	[redacted]	[redacted]
Overall proportion of patients receiving 3L treatment*	[redacted]	[redacted]	[redacted]	[redacted]
Overall proportion of patients receiving 4L treatment*	[redacted]	[redacted]	[redacted]	[redacted]
Total costs 2L+ weighted by patients receiving each treatment line and treatment line component			[redacted]	[redacted]

2L – second-line treatment; 2L+ – second-line treatment and beyond; 3L – third -line treatment; 4L – fourth-line treatment.
**The proportion of patients who discontinue the first line of treatment who receive this line of treatment.*

† *Weighted drug costs consider both drug acquisition and administration costs and the mean duration of treatment. Treatment duration is dependent on study arm and line of treatment: (i) 3.83 months and 3.49 months for second-line treatment for patients receiving first-line pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel, respectively; (ii) 2.84 months and 2.67 months for patients receiving third-line who received first-line pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel, respectively; and (iii) 2.51 and 3.37 months for patients receiving fourth-line treatment after first-line pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel, respectively.*

(v) AE management costs

Costs related to the management of treatment-specific AEs are included in the model, being applied once only, during the first model cycle. These costs are calculated using the weighted average of the incidence of each Grade 3-5 AE in each treatment arm and the corresponding unit cost (see Table 29). AE incidence rates for pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel therapy groups are based on grade 3-5 AEs occurring in ≥5% of patients in one or both treatment groups of KEYNOTE-355[26] and AEs considered of clinical interest, whilst for atezolizumab plus nab-paclitaxel they are based on grade 3-5 AEs occurring in ≥2% of patients in this study arm of the IMpassion130 study, which may be unfavourable to atezolizumab plus nab-paclitaxel.[46] Unit costs were taken from NHS Reference Costs,[51] previous NICE STA submissions,[53, 56] and assumptions. Mean duration of each AE were estimated from the treatment arms pooled data from KEYNOTE-355 ([redacted]).[26] AEs costs are estimated to be [redacted] for the pembrolizumab plus paclitaxel/nab-paclitaxel group, [redacted] for the paclitaxel therapy group and [redacted] for the atezolizumab plus nab-paclitaxel. AE costs for the docetaxel therapy group are assumed to be the same as those for the paclitaxel therapy group.

Table 29: Incidence rates and unit costs for Grade 3-5 AEs used in the model

Adverse event	Frequency of AEs			Unit cost	Total costs		
	Pembrolizumab plus paclitaxel/ nab-paclitaxel	Paclitaxel	Atezolizumab plus nab-paclitaxel		Pembrolizumab plus paclitaxel/ nab-paclitaxel	Paclitaxel	Atezolizumab plus nab-paclitaxel
Anaemia	[redacted]	[redacted]	3.1%	£942.09	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	-	£66.44	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	8.4%	£66.44	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	-	£0.00	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	2.0%	£0.00	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	4.9%	£66.44	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	-	£66.44	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	1.8%	£1,105.89	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	-	£589.07	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	0.9%	£1,105.89	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	3.8%	£2,839.22	[redacted]	[redacted]	[redacted]
Abdominal abscess	[redacted]	[redacted]	-	£3,706.09	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	2.2%	£2,326.11	[redacted]	[redacted]	[redacted]
Blood alkaline phosphatase increased	[redacted]	[redacted]	-	£66.44	[redacted]	[redacted]	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]	-	£66.44	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	-	£1,058.71	[redacted]	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]	-	£942.09	[redacted]	[redacted]	[redacted]
Pneumonitis	[redacted]	[redacted]	-	£883.03	[redacted]	[redacted]	[redacted]
Grade 2+ diarrhoea	[redacted]	[redacted]	-	£1,105.89	[redacted]	[redacted]	[redacted]
Grade 2+ colitis	[redacted]	[redacted]	-	£1,105.89	[redacted]	[redacted]	[redacted]
Total	-	-	-	-	[redacted]	[redacted]	[redacted]

Source – CS[43] and company's model

(vi) End-of-life (terminal) costs

The model includes terminal care costs of £8,167. The ERG believes this value is based on the estimate for terminal care costs used in a previous NICE appraisal (TA553, pembrolizumab for adjuvant treatment of resected melanoma with high risk of recurrence),[54] which was based on Georghiou & Bardsley,[58] and inflated to 2019 using the hospital & community health services (HCHS) pay & prices and the NHS cost Inflation Index (NHSCII) indices.[52] The ERG notes that this approach may lead to a slight inaccurate in the estimates of costs, but that these would not noticeably impact on the ICERs. The costs associated with end-of-life care are applied at the patient's point of death.

(vii) PD-L1 testing costs

The costs of PD-L1 testing are included in the company's economic analysis for the pembrolizumab plus paclitaxel/nab-paclitaxel and atezolizumab plus nab-paclitaxel treatment groups. The model estimates the testing costs based on the prevalence of PD-L1 CPS≥10 of 38.1% observed in KEYNOTE-355[26] and assumes that patients receiving pembrolizumab will be tested using the IHC 22C3 pharmDx Assay, whilst patients receiving atezolizumab will be tested using the PD-L1 SP142 test. Unit costs were taken from NHS Reference Costs and NICE TA639.[44, 51] PD-L1 testing costs were estimated to be £106.20 for the pembrolizumab plus paclitaxel/nab-paclitaxel therapy group and £278.49 for the atezolizumab plus nab-paclitaxel group; these costs are applied once only, during the first model cycle.

The ERG believes that the costs of testing for those treated with atezolizumab plus nab-paclitaxel is overestimated as it is presumed that the cost of the PD-L1 SP142 test will have already been incurred in determining whether a patient was PD-L1 ≥1% and would not need to be rerun, thus the cost of testing associated with atezolizumab plus nab-paclitaxel in the context of treating those with a PD-L1 CPS≥10 could be zero. The testing costs associated with pembrolizumab plus paclitaxel / nab-paclitaxel may also be overestimated as it is uncertain whether the information from the PD-L1 SP142 test would be used to either treat a proportion of patients directly with pembrolizumab plus paclitaxel / nab-paclitaxel if the PD-L1 SP142 score were sufficiently high, or used to filter the number of patients who would go on to receive the IHC 22C3 pharmDx Assay, by not testing those in whom the clinicians believed there was minimal chance of the patient having a PD-L1 CPS≥10. Both of these options would reduce the costs of testing in the pembrolizumab plus paclitaxel / nab-paclitaxel arm. Sensitivity analyses conducted by the ERG show that the ICERs were not particularly sensitive to the assumed values related to the costs of tests as these were small relative to the acquisition costs of pembrolizumab and atezolizumab. For simplicity, the ERG left the costs of testing as those within the company's base case noting the slight bias, of unknown magnitude, in the results for pembrolizumab plus paclitaxel / nab-paclitaxel.

4.2.5 Model evaluation methods

The CS[43] presents the results of the base case analyses in terms of the ICERs using pairwise comparisons for pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel (primary comparator), and docetaxel and atezolizumab plus nab-paclitaxel (secondary comparators). The company's base case results were generated using the deterministic version of the model. The results of the PSA, based on 1,000 Monte Carlo simulations, are also presented for the comparisons against paclitaxel and docetaxel. Following the clarification process, the ERG requested the company to present the results for the PSA for the comparison against atezolizumab plus nab-paclitaxel (clarification response, question B21).[24] However, the company has not provided these, on the justification that this analysis would not provide robust results for discussion due to the data limitations and different assumptions relating to the comparisons versus atezolizumab plus nab-paclitaxel in relation to those applied to chemotherapy regimens.

The distributions used for the PSA undertaken by the company are presented in Table 30. The company used what it believed was the most appropriate of the following methods to generating sample values in the PSA: standard deviation (SDs), 95% confidence intervals and variance-covariance matrix of the parameter estimates from data from the KEYNOTE-355 trial; standard errors obtained from the company's NMA; or assumed standard errors which were 20% of the mean. The results of the PSA are additionally presented as a cost-effectiveness plane and as cost-effectiveness acceptability curves (CEACs) for pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel and versus docetaxel.

Table 30: Summary of distributions used in company's PSA

Parameter group	Distribution applied in PSA	ERG comment
Patient characteristics (start age, probability female, BSA, weight)	Fixed (start age, probability female)/Normal (BSA, weight)	The ERG notes that they are listed in the CS as being fixed; however, scrutiny of the model showed that uncertainty is modelled for BSA and weight.
Parameters for OS survival function	Multivariate normal	-
Parameters for PFS survival function	Multivariate normal	No uncertainty included prior to 9-week cut-point
Parameters for TTD survival function	Multivariate normal	-
HR for OS for atezolizumab plus nab-paclitaxel	Lognormal	-
HR for PFS for atezolizumab plus nab-paclitaxel	Lognormal	
Health utilities	Beta	Following the clarification process (question B1),[24] the company has amended the analysis to model uncertainty around the time-to-death utility estimates using the SEs generated by the analysis based on data from the KEYNOTE-355 trial.[26]

Drug acquisition costs	Fixed (except premedication costs - gamma)	No uncertainty included in the distribution of patients receiving paclitaxel or nab-paclitaxel in the pembrolizumab plus paclitaxel/nab-paclitaxel treatment group. For the costs of premedication associated with paclitaxel and docetaxel treatments the SE was arbitrarily assumed to be equal to 20% of mean.
Drug administration costs	Gamma	Following the clarification process (question B1),[24] the company has amended the analysis to assess uncertainty using gamma distributions for all administration costs, where the SE are arbitrarily assumed to be equal to 20% of mean.
RDI	Beta	-
PD-L1 testing costs	Gamma	-
Post-progression treatment costs (subsequent therapy)	Gamma	SE arbitrarily assumed to be equal to 20% of mean.
Health state costs	Gamma	Gamma distribution applied to aggregate costs by health state; SE arbitrarily assumed to be equal to 20% of mean.
AE frequencies	Fixed	These parameters are subject to uncertainty. However, uncertainty is modelled in AE costs.
AE duration	Fixed	These parameters are subject to uncertainty. However, uncertainty is modelled in AE costs.
AE costs	Gamma	Gamma distribution applied to aggregate AE costs; SE arbitrarily assumed to be equal to 20% of mean.
End of life costs	Gamma	-

AE – adverse event; BSA – body surface area; ERG – Evidence Review Group; HR – hazard ratio; ICER – incremental cost-effectiveness ratio OS – overall survival; PD-L1 - programmed death-ligand 1; PFS – progression-free survival; PSA – probabilistic sensitivity analysis; RDI – relative dose intensity.

Deterministic sensitivity analyses (DSAs) are presented for pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel and versus docetaxel using tornado plots. These analyses varying parameters according to their 95% CIs where available, or 95% CIs assuming a standard error of 20% of the mean. The CS also reports a number of scenario analyses undertaken to explore the impact of: using a limited set of alternative parametric distributions for OS and PFS and cut-points for each of the treatment groups, and combining the alternative parametric functions used; applying alternative assumptions regarding the loss of OS treatment effect for pembrolizumab combination therapy (treatment waning); removing the half-cycle correction; removing PD-L1 testing; removing AE costs; using alternative assumptions and approach regarding HRQoL; the exclusion of age-adjustment of utilities; and applying an alternative assumption regarding TTD for atezolizumab plus nab-paclitaxel.

4.2.6 Company's model validation and verification

The CS (pages 167-169)[43] describes the company's model validation activities, which involved checking for errors and inconsistencies, the model structure choice, key model inputs, the selection of the parametric models by health economists and clinical experts, but no details were provided about these activities. Following the clarification process, the company updated the model to remove a small number of errors identified by the ERG.[24] The company states an additional validation exercise was conducted, comparing model predictions against efficacy outcomes from the KEYNOTE-355 study and from other literature sources (in the case of outcomes specific to the chemotherapy SoC). The summary model aggregated outputs (LYs) for atezolizumab plus nab-paclitaxel and taxanes were compared with those from TA639 to explore consistency between the submissions.

4.2.7 Company's cost-effectiveness results

The probabilistic and deterministic results presented in this section are based on the updated version of the company's model submitted in response to the clarification process.[24] The results presented in this section include the existing CAA discount for pembrolizumab whilst excluding price discounts available for any other drugs used as comparators or in subsequent treatments. The results with cPAS discounts incorporated into the analysis are provided in a confidential appendix to this ERG report.

The ERG notes that the updated results for the comparison of pembrolizumab plus paclitaxel/nab-paclitaxel against atezolizumab plus nab-paclitaxel reported in the company's clarification response do not match with those presented in the company's model. The ERG replicated the amendments described by the company in their clarification response and reached the same results presented in the updated model for all comparisons. For this reason, in Table 33 the ERG presents the results from the updated model. The results based on the probabilistic version of the model were also generated by the ERG from the company's updated model, since these are not reported.

Central estimates of cost-effectiveness

The CS[43] presents pairwise ICERs for pembrolizumab plus paclitaxel/nab-paclitaxel versus each of the comparators (paclitaxel, docetaxel and atezolizumab plus nab-paclitaxel).

Table 31 presents the central estimates of cost-effectiveness generated using the company's model for the comparison of pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel (primary base case analysis). The probabilistic version of the model suggests that pembrolizumab combination therapy is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient; the corresponding ICER is £27,753 per QALY gained. The deterministic version of the model produces a slightly lower ICER of £27,808 per QALY gained with the model appearing relatively linear.

Table 31: Company's results - Base Case Analysis, pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel

Options	LYGs*	QALYs	Cost	Inc. LYGs*	Inc QALYs	Inc Costs	ICER
Probabilistic model							
Paclitaxel	2.06	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.98	[redacted]	[redacted]	2.92	[redacted]	[redacted]	**£27,753**
Deterministic model							
Paclitaxel	2.00	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.89	[redacted]	[redacted]	2.89	[redacted]	[redacted]	**£27,808**

Inc – incremental; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** Undiscounted*

Table 32 and Table 33 present the central estimates of cost-effectiveness generated using the company's model for the comparison of pembrolizumab plus paclitaxel/nab-paclitaxel versus docetaxel and versus atezolizumab plus nab-paclitaxel, respectively (secondary base case analyses). The analysis against atezolizumab plus nab-paclitaxel suggests that atezolizumab plus nab-paclitaxel is dominated by pembrolizumab plus paclitaxel/nab-paclitaxel, whilst the analysis against docetaxel suggests that pembrolizumab combination therapy is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient; the corresponding ICER is £34,370 per QALY gained (probabilistic model). The deterministic version of the model produces a slightly lower ICER of £34,184 per QALY gained.

Table 32: Company's results - Base Case Analysis, pembrolizumab plus paclitaxel/nab-paclitaxel versus docetaxel

Options	LYGs*	QALYs	Cost	Inc. LYGs*	Inc QALYs	Inc Costs	ICER
Probabilistic model							
Docetaxel	2.06	[redacted]	[redacted]				
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.98	[redacted]	[redacted]	2.92	[redacted]	[redacted]	**£34,370**
Deterministic model							
Docetaxel	2.00	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.89	[redacted]	[redacted]	2.89	[redacted]	[redacted]	**£34,184**

Inc – incremental; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** Undiscounted*

Table 33: Company's results - Base Case Analysis, pembrolizumab plus paclitaxel/nab-paclitaxel versus atezolizumab plus nab-paclitaxel

Options	LYGs*	QALYs	Cost	Inc. LYGs*	Inc QALYs	Inc Costs	ICER
Probabilistic model							
Atezolizumab plus nab-paclitaxel	2.80	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.98	[redacted]	[redacted]	2.18	[redacted]	[redacted]	**Dominating**
Deterministic model							
Atezolizumab plus nab-paclitaxel	2.56	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.89	[redacted]	[redacted]	2.33	[redacted]	[redacted]	**Dominating**

Inc – incremental; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** Undiscounted*

The ERG considers it more appropriate to include all options within a fully incremental analysis. Table 34 presents the results of a fully incremental analysis of all options included in both all primary and secondary base case analyses, using the deterministic version of the model.

Table 34: Company's results - Base Case Analyses, fully incremental analysis of pembrolizumab plus paclitaxel/nab-paclitaxel and all comparators (primary and secondary), deterministic model

Options	LYGs	QALYs	Cost	Inc. LYGs*	Inc QALYs	Inc Costs	ICER
Docetaxel	2.00	[redacted]	[redacted]	-	-	-	-
Paclitaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.89	[redacted]	[redacted]	2.89	[redacted]	[redacted]	**£34,184**
Atezolizumab plus nab-paclitaxel	2.56	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**

Inc – incremental; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** Undiscounted*

This analysis suggests that paclitaxel (the KEYNOTE-355 primary comparator) is dominated by docetaxel, and also that atezolizumab plus nab-paclitaxel is dominated by pembrolizumab plus paclitaxel/nab-paclitaxel. The ICER for pembrolizumab plus paclitaxel/nab-paclitaxel versus docetaxel is £34,184 per QALY gained, the ICER for pembrolizumab plus paclitaxel/nab-paclitaxel compared with paclitaxel is £27,808 per QALY gained, which is pertinent should a patient not be able to receive docetaxel.

4.2.8 Company's PSA

The company presented the updated scatterplots and CEACs for pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel and versus docetaxel in its clarification response (section D, pages 57-59).[24] Assuming willingness-to-pay (WTP) thresholds of £30,000 and £50,000 per QALY gained, the company's model suggests that the probability that pembrolizumab plus paclitaxel/nab-paclitaxel generates more net benefit than paclitaxel is 52.3%, and 79.6% respectively Figure 19), and the same probabilities are suggested for the comparison of pembrolizumab plus paclitaxel/nab-paclitaxel versus docetaxel (Figure 20). The company does not present in either the CS or clarification response the CEACs for the comparison of pembrolizumab plus paclitaxel/nab-paclitaxel versus the atezolizumab plus nab-paclitaxel since it declined to run PSA for this comparison. The ERG has generated it from the company's model (Figure 21) after fixing a perceived error in how the estimates of net benefit for atezolizumab plus nab-paclitaxel were generated. The ERG notes that fixing this error, which involved the formulae in column CB of the 'PSA Setup' worksheet being changed so that these refer to column AAZ instead of column AZ when calculating net monetary benefit. At WTP thresholds of £30,000 and £50,000 per QALY gained, the probabilities that pembrolizumab plus paclitaxel/nab-paclitaxel generates more net benefit than atezolizumab plus nab-paclitaxel is 100%, and 99.9% respectively.

Figure 19: Company's base case cost-effectiveness acceptability curve, pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel (adapted from the company's model)

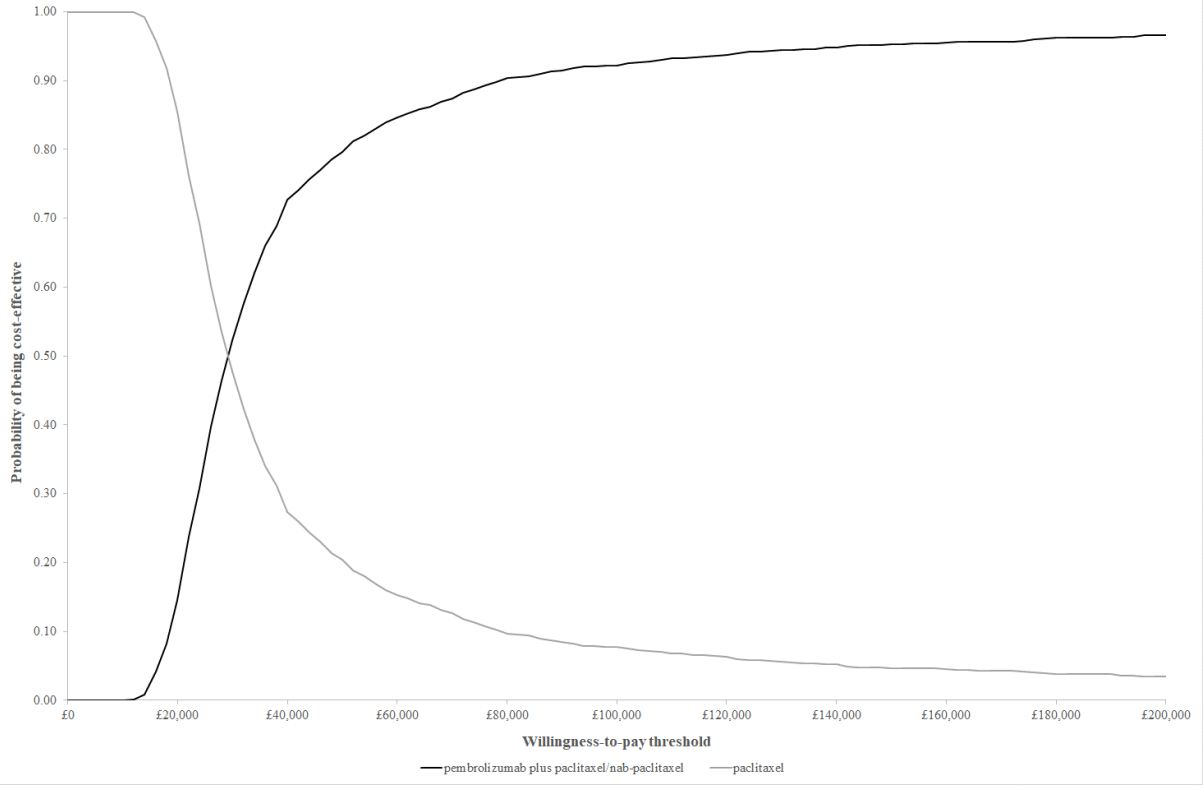


Figure 20: Company's base case cost-effectiveness acceptability curve, pembrolizumab plus paclitaxel/nab-paclitaxel versus docetaxel (adapted from the company's model)

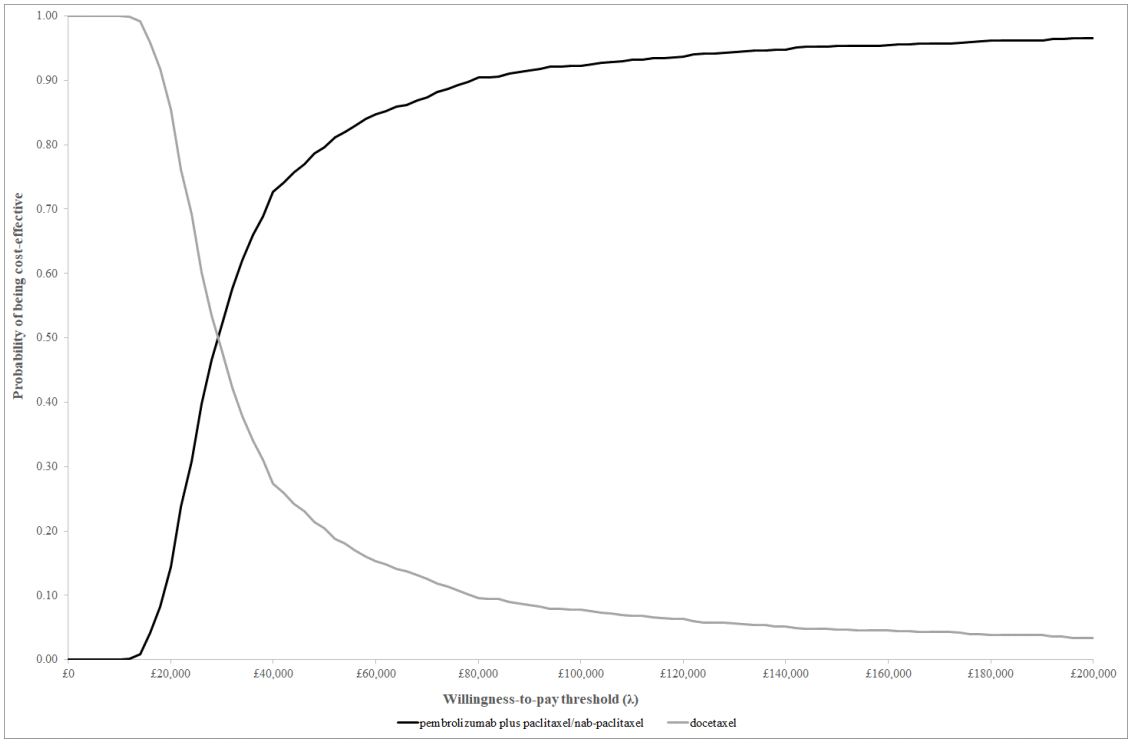


Figure 21: Company's base case cost-effectiveness acceptability curve, pembrolizumab plus paclitaxel/nab-paclitaxel versus atezolizumab plus nab-paclitaxel (generated by the ERG from the company's model)

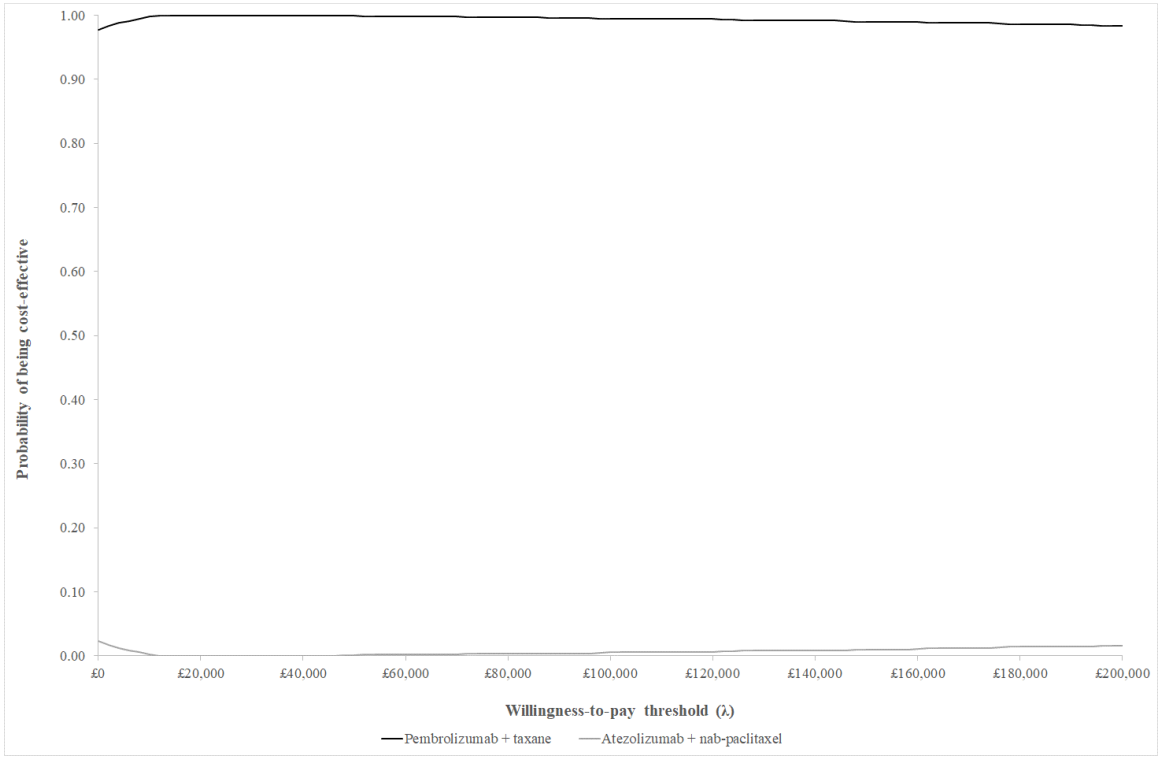


Figure 22, Figure 23 and Figure 24 present the company's base case model traces for pembrolizumab plus paclitaxel/nab-paclitaxel, paclitaxel and atezolizumab plus nab-paclitaxel, respectively.

Figure 22: Company's base case survival curves for pembrolizumab plus paclitaxel/nab-paclitaxel (model traces)

HR - hazard ratio; KM – Kaplan-Meier; KM9W – observed KM for nine weeks; OS - overall survival; PFS - progression-free survival; TTD - time to treatment discontinuation.

Figure 23: Company's base case survival curves for paclitaxel (model traces)

HR - hazard ratio; KM – Kaplan-Meier; KM9W – observed KM for nine weeks; OS - overall survival; PFS - progression-free survival; TTD - time to treatment discontinuation.

Figure 24: Company's base case survival curves for atezolizumab plus nab-paclitaxel (model traces)

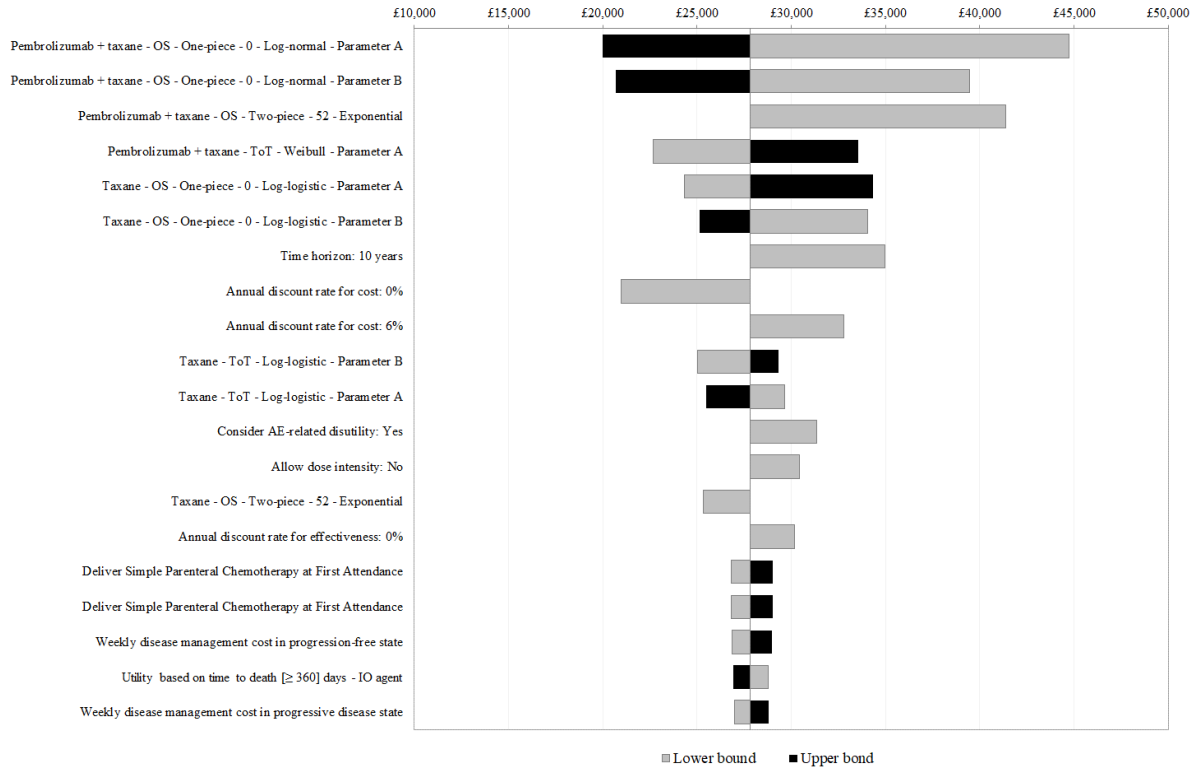
HR - hazard ratio; OS - overall survival; PFS - progression-free survival; TTD - time to treatment discontinuation.

4.2.9 Company's DSA

Following the clarification process, the company presented revised results for the deterministic univariate sensitivity analyses.[24]

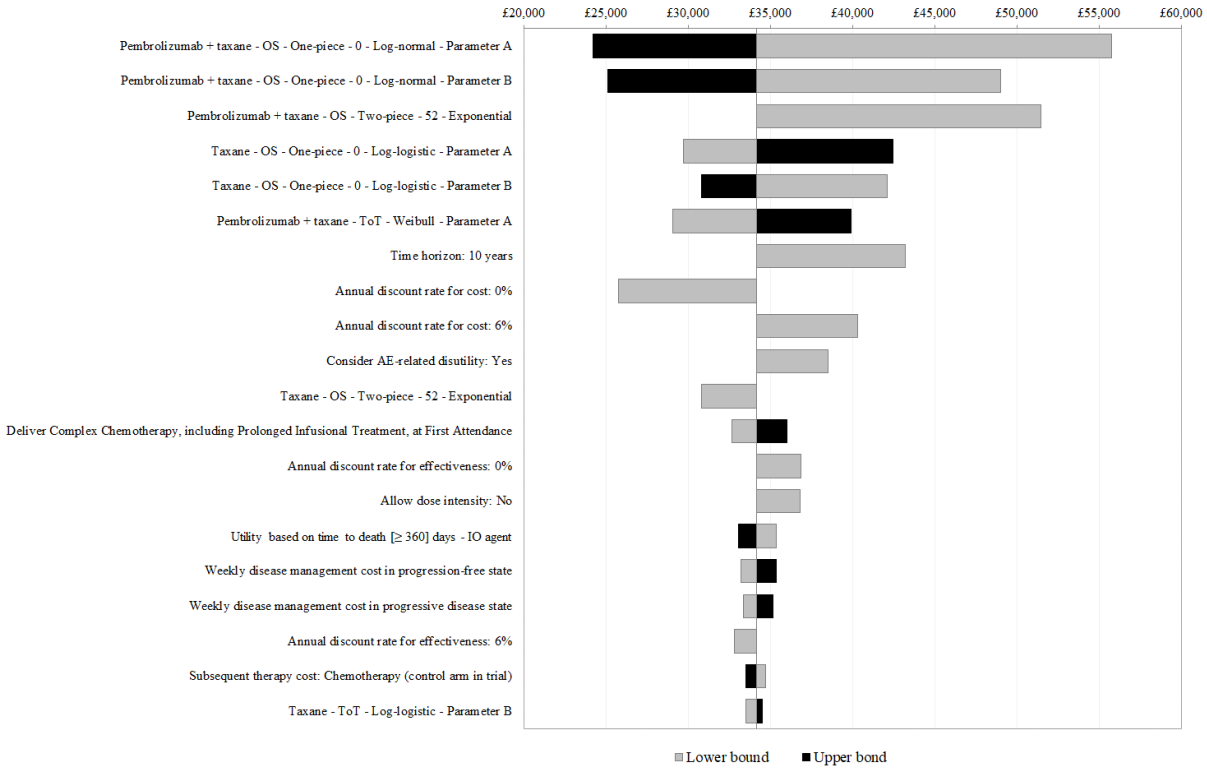
Figure 25 presents the results of the company's DSAs in the form of a tornado diagram for pembrolizumab plus paclitaxel/nab-paclitaxel therapy group versus paclitaxel. Based on these analyses, the company's base case ICER is estimated to range from £19,986 to £44,750 per QALY gained. The most influential model parameters relate to modelling OS.

Figure 25: Company's updated results, deterministic sensitivity analyses, pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel (adapted from the company's model)



The company has also presented updated results for the company's DSAs for pembrolizumab plus paclitaxel/nab-paclitaxel versus docetaxel (Figure 26). Based on these analyses, the company's base case ICER is estimated to range from £24,218 to £55,767 per QALY gained. As with the comparison with paclitaxel, the most influential parameters were those related to OS.

Figure 26: Company's updated results, deterministic sensitivity analyses, pembrolizumab plus paclitaxel/nab-paclitaxel versus docetaxel (adapted from the company's model)



The ERG notes that the company has not presented results for the deterministic univariate sensitivity analyses for the comparison against atezolizumab plus nab-paclitaxel following the clarification process.

Company's scenario analyses

Updated results for scenario analyses for pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel, docetaxel, and atezolizumab plus nab-paclitaxel are provided from pages 62 to 66 of the clarification response.[24]

The scenarios for the comparisons against paclitaxel and docetaxel involved: using alternative survivor functions for modelling PFS and OS for pembrolizumab plus paclitaxel/nab-paclitaxel or the comparator separately and in combination; removing half-cycle correction; removal of PD-L1 testing costs; removal of costs related to AE management; using alternative data for subsequent therapy costs; using alternative approach for modelling HRQoL (based on disease status, and the inclusion of AE disutilities); and removal of age-adjustment to estimate the utility values. The company has also presented two scenarios where it explored the loss of treatment benefit for pembrolizumab plus paclitaxel/nab-paclitaxel: (i) based on external data from the US Surveillance, Epidemiology and End Results (SEER) Program after 4 years and (ii) removing OS benefit after 5 years; which correspond to

applying treatment waning at 2 and 3 years after maximum treatment duration with pembrolizumab, respectively. As part of their clarification response (question B4[e]),[24] the company justifies its base case assumption of a lifetime benefit for pembrolizumab citing that a sustained treatment effect is not uncommon in immune-oncology (IO) studies given the agents' mode of action, and from previous NICE technology appraisals committee preferences.

For the comparison against atezolizumab plus nab-paclitaxel, the company presented a reduced number of scenarios which involved: using an alternative survivor function for modelling PFS and OS for pembrolizumab plus paclitaxel/nab-paclitaxel, separately and in combination; using alternative endpoint from KEYNOTE-355 for PFS; using nab-paclitaxel as the common comparator in the NMA to estimate the PFS HR; and applying treatment waning based on SEER data. An additional sensitivity analysis was undertaken by the company where the TTD survival function for atezolizumab plus nab-paclitaxel was set equal to the Weibull distribution fitted to TTD data for pembrolizumab plus nab-paclitaxel from KEYNOTE-355. This is described by the company as equivalent to *"set a maximum treatment duration period for atezolizumab plus nab-paclitaxel"* (CS, page 164).[43]

Generally, most of the analyses produced ICERs that were similar to the company's base case scenarios. However, scenarios that use an alternative distribution for OS for pembrolizumab plus paclitaxel/nab-paclitaxel (using a piecewise exponential model with knot at 52 weeks, which was considered '*highly conservative*' by the company), and a combination of the second-best fits for OS and PFS for pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel, and the loss of treatment effect at 5 years (considered implausible by the company) result in ICERs above £40,000 per QALY gained.

A scenario analysis assuming a loss of comparative benefit at 5 years leads to an increase in the ICER to £34,096 per QALY gained. An alternative analysis using the SEER data to assume exponential distributions from year five onwards had a neglectable impact on the ICER. Using utility values based on disease progression status led to moderate increases in the ICER.

The analyses for pembrolizumab plus paclitaxel/nab-paclitaxel versus docetaxel suggest that the same scenarios have a similar (limited) impact on the ICER as for the comparison with paclitaxel, although these reach slightly higher values (above £50,000 per QALY gained) for the analyses that uses a piecewise exponential model with knot at 52 weeks for pembrolizumab plus paclitaxel/nab-paclitaxel OS and that combines the second-best fits for OS and PFS for pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel with the loss of treatment effect at 5 years. The scenarios explored for the atezolizumab plus nab-paclitaxel comparator suggest that this comparator at list price is always dominated by pembrolizumab plus paclitaxel/nab-paclitaxel. However, whilst the scenario that use nab-paclitaxel as the common comparator in the NMA to estimate the PFS HR has the most impact on costs,

favouring pembrolizumab plus paclitaxel/nab-paclitaxel even further, applying a maximum treatment duration of 2 years for atezolizumab plus nab-paclitaxel has a significant impact on the TTD survival function (see

Figure 27 in section 4.3.3), and would generate a reduction in the total costs for atezolizumab plus nab-paclitaxel of approximately [redacted].

Company's subgroup analyses

The company didn't present subgroup analysis; although the ERG comments that the base case analyses presented in the company's submission already relate to the subgroup of patients from the KEYNOTE-355 study[43] being those patients with PD-L1 CPS≥10.

4.3 Critical appraisal of the company's health economic analysis

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying health economic model upon which this was based. These included:

- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Double-programming of the deterministic version of the company's model to fully assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any apparent errors in the implementation of the model.
- Examination of the correspondence between the description of the model reported in the CS[43] and the company's executable model.
- Replication of the base case results, PSA, DSAs and scenario analyses presented within the CS.[43]
- Where possible, checking of parameter values used in the company's model against their original data sources.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

4.3.1 Model verification

The ERG rebuilt the deterministic version of the company's base case model in order to verify its implementation. The ERG's results are almost identical to those generated using the company's original submitted model. During the process of rebuilding the original version of the model, the ERG has identified a few programming errors which were resolved by the company during the clarification process.[24] The ERG believes the company's updated version of the model to be generally well programmed and free from major errors, and that the model structure and parameter values used are appropriate for the decision problem.

4.3.2 Adherence of the company's model to the NICE Reference Case

The company's economic analysis of pembrolizumab plus paclitaxel/nab-paclitaxel therapy for untreated TNBC is generally in line with the NICE Reference Case.

Table 35: Adherence of the company's economic analyses to the NICE Reference Case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The company's economic analysis is generally in line with the final NICE scope;[2] except that the population within the company's base case is narrower than specified within the scope (restricted to those [redacted]), in order to reflect *"the draft licence indication wording"*.[43] As noted in Section 2.3.1, the company has not yet been granted an EU marketing authorisation for pembrolizumab in this indication.
Comparator(s)	As listed in the scope developed by NICE	The NICE scope[2] specifies three comparators: (1) Anthracycline based chemotherapy (2) Single agent taxane chemotherapy regimens (docetaxel or paclitaxel) (3) Atezolizumab in combination with nab-paclitaxel (for people whose tumours have PD-L1 expression ≥1%) The company's analysis does not include anthracycline based chemotherapy regimens based on the view that its use in a mTNBC population is currently limited in UK practice and also that the available data were limited. The company's base case focusses on paclitaxel as the key comparator; nevertheless, the company present the analyses of pembrolizumab plus paclitaxel/nab-paclitaxel versus docetaxel and versus atezolizumab plus nab-paclitaxel as secondary base case analyses. The frequency of paclitaxel administration reflects its use in the KEYNOTE-355 study (days 1, 8 and 15 of every 28-day cycle) and does not reflect its routine use in the UK (weekly doses). Given the uncertainty in the magnitude of any OS or PFS gains associated with additional paclitaxel use the approach adopted by the company appears reasonable.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health gains accrued by patients are valued in terms of QALYs gained. Health impacts on caregivers were not included in the analysis.
Perspective on costs	NHS and PSS	The analysis adopts an NHS and PSS perspective.

Element	Reference case	ERG comments
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The results of the analyses are presented in terms of the incremental cost per QALY gained for pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel (and versus docetaxel and versus atezolizumab plus nab-paclitaxel in secondary analyses, as pairwise comparisons). A full incremental analysis was not presented.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 35-year time horizon. Approximately 98.3% of patients have died in the pembrolizumab plus paclitaxel/nab-paclitaxel group, 99.8% in the paclitaxel and docetaxel groups and 99.9% in the atezolizumab plus nab-paclitaxel group by the end of the modelled time horizon.
Synthesis of evidence on health effects	Based on systematic review	Time-to-event outcomes (TTD, PFS and OS), HRQoL estimates and AE frequencies for patients receiving pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel are based on data from the subgroup of patients with PD-L1 CPS>=10 from KEYNOTE-355 study.[26] Health outcomes for patients who receive atezolizumab plus nab-paclitaxel are based on the results of a fixed-effects NMA using data from patients with PD-L1 CPS≥10 in KEYNOTE-355[26] and IMPassion130[40] studies. Health outcomes (except drug acquisition costs) for patients who receive docetaxel are based on the assumption of clinical equivalency between docetaxel and paclitaxel.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health gains are valued in terms of QALYs and were directly reported by patients. Whilst there is ambiguity in the CS regarding the specific EQ-5D instrument collected in the KEYNOTE-355 study, it is likely that HRQoL estimates used in the model were based on EQ-5D-3L data. A linear mixed-effects regression model was fitted to the EQ-5D-3L data with fixed effects for treatment and the following factors: ECOG, PFS by BICR, AE status and time-to-death category. Preference-based utilities were valued using the UK tariff. The ERG notes that alternative models that appropriately represent the underlying data generation process have been proposed as option to linear models, which can result in implausible predictions and are likely to be statistically inefficient. However, the impact that a more representative modelling approach may have on the estimates is currently unknown.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	

Element	Reference case	ERG comments
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains, although the company makes the claim that NICE's 'End of Life' criteria are met, implicitly suggesting a higher QALY weighting.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource costs include those relevant to the NHS and PSS. Unit costs were valued at 2018/19 prices with drug costs set at 2020 prices.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects are discounted at a rate of 3.5% per annum.

AE – adverse event; CPS – combined positive score; EQ-5D - EuroQol EQ-5D; HRQoL - health-related quality of life; NMA - network meta-analysis; OS - overall survival; PD-L1 - programmed death-ligand 1; PFS - progression-free survival; PSS - Personal Social Services; QALY - quality-adjusted life year; TTD - time to treatment discontinuation.

4.3.3 Main issues identified within the critical appraisal

Box 2 summarises the main issues identified within the ERG's critical appraisal of the company's revised economic analyses. These issues are discussed in further detail in the subsequent sections. Limitations identified by the ERG, or parameter estimates that are debatable, that have only a minor impact on the central estimate of the ICER have been omitted from our list. Examples include: the fact that the KM survival function for PFS was used for the first 9 weeks without consideration of the uncertainty, that the distribution of patients receiving paclitaxel or nab-paclitaxel in combination with pembrolizumab was assumed fixed, the underestimation of uncertainty in the NMA, and potential overestimation of testing relating to atezolizumab plus nab-paclitaxel.

Box 2: Main issues identified within the critical appraisal undertaken by the ERG

(1) Uncertainty surrounding long-term extrapolations

(i) Potentially favourable extrapolation of time to event data

(ii) Assumption of lifetime benefit for pembrolizumab plus paclitaxel/nab-paclitaxel versus taxane therapies and atezolizumab plus nab-paclitaxel

(iii) Using PFS as a proxy for TTD for atezolizumab plus nab-paclitaxel is likely to be unfavorable to atezolizumab plus nab-paclitaxel

(2) Limitations regarding the comparison of pembrolizumab plus paclitaxel / nab-paclitaxel and atezolizumab plus nab-paclitaxel

(3) Limitations regarding the company's approach to modelling HRQoL

(i) The time-to-death approach for modelling HRQoL

(ii) Limitations regarding the non-inclusion of the impact of AEs on HRQoL

(4) Issues relating to vial sharing

(1) Uncertainty surrounding long-term extrapolations

(i) Potentially favourable extrapolation of time to event data

As detailed in Section 4.2.4.2 the ERG did not deem that the distributions chosen to represent OS by the company (lognormal for pembrolizumab in combination with paclitaxel / nab-paclitaxel and log-logistic for taxanes) were the most appropriate of those considered as the hazard was consistently increasing over time. As such, the ERG has assumed two Weibull distributions in its base case, noting that such a distribution was also accepted by the committee in the STA of atezolizumab plus nab-

paclitaxel.[11]. For PFS the ERG has used the distributions selected by the company but preferred to use these for the entire time horizon rather than using a piecewise approach using the KM for the initial 9 weeks. The selection of TTD distribution for atezolizumab + nab-paclitaxel is discussed in sub-section (iii).

Acknowledging uncertainty, the ERG has also conducted scenario analyses using an exponential distribution for OS for each study arm.

(ii) Assumption of a lifetime benefit for pembrolizumab plus paclitaxel/nab-paclitaxel versus taxane therapies and atezolizumab plus nab-paclitaxel

The company's base case assumes an indefinite treatment benefit of pembrolizumab combination therapy on OS compared to paclitaxel, despite the short follow-up duration of IA2 of KEYNOTE-355 and that no patient receives treatment with pembrolizumab for more than 2 years (although they may continue receiving taxane treatment). The ERG believes that whether the effects of pembrolizumab on the survival of patients with mTNBC are maintained, and if so, for how long, after treatment discontinuation are uncertain but note that the proportions of patients receiving second-line treatment after discontinuation (see Table 28) [redacted] The ERG believes that this assumption is likely to be favourable to pembrolizumab plus paclitaxel/nab-paclitaxel and deemed it unlikely that there would be a significant difference in prognosis between two patients who have progressed on first-line treatment and are receiving capecitabine. The ERG would prefer the same hazard to be applied to both arms after a specified period of time.

One of the authors of this report is a member of NICE Technology Appraisal Committee C where, from multiple appraisals, a precedent for immuno-oncology drugs with a maximum duration of two-years has been developed. This precedent is to apply a loss of benefit at 5 years (that is, three years after maximum treatment duration) by setting the hazard in the intervention arm to that of the control arm. The ERG has preferred to use this assumption in its base case and evaluate a full lifetime benefit in a scenario analysis along with a scenario analysis looking at a loss of benefit at 3 years (one year after maximum treatment duration). The ERG notes that this differs from the assumption preferred by the NICE Technology Appraisal Committee A in TA639[11] which accepted a lifetime relative benefit on OS despite the committee considerations saying that "*the treatment effect was unlikely to last more than 5 years after treatment had stopped. It concluded that although it was biologically plausible for the treatment effect to continue after stopping treatment, the length of any continued effect was uncertain*." However, unlike pembrolizumab, atezolizumab + nab-paclitaxel was not subject to a fixed duration of treatment. The ERG does not believe it plausible that many years after cessation of pembrolizumab

treatment, and after the use of subsequent treatments, that there would still be a relative survival benefit to patients who had initially received pembrolizumab compared with those who had received taxane treatment.

(iii) Using PFS as a proxy for TTD for atezolizumab plus nab-paclitaxel is likely to be unfavourable to atezolizumab plus nab-paclitaxel

In the model base case, the company assumed that TTD for atezolizumab plus nab-paclitaxel is the same as PFS, which was estimated by applying a HR to the PFS survival model for pembrolizumab plus paclitaxel/nab-paclitaxel.

Figure 18 in Section 4.2.4.2.3 shows the TTD survival functions used in the model for all treatment options. It can be seen that the probability of remaining on treatment after a year is significantly higher for atezolizumab plus nab-paclitaxel than for other treatment groups. This assumption, together with the absence of a maximum treatment duration rule leads to significant higher acquisition costs for atezolizumab plus nab-paclitaxel in comparison to pembrolizumab plus paclitaxel/nab-paclitaxel.

Figure 27 replicates the TTD survival models used in the company's base-case for pembrolizumab plus paclitaxel/nab-paclitaxel and atezolizumab plus nab-paclitaxel (red and yellow lines, respectively). It also includes two alternative scenarios for modelling TTD survival for atezolizumab plus nab-paclitaxel: (i) assumed to equal the TTD survival function for pembrolizumab plus nab-paclitaxel (blue dashed line), to which the company refers to being equivalent to assuming a maximum treatment duration; and (ii) assuming the HR for PFS is generalisable to TTD, and applying it to the pembrolizumab plus paclitaxel/nab-paclitaxel TTD survival function (Weibull distribution, grey dashed line, scenario generated by the ERG). The figure shows that the probability of remaining on treatment for atezolizumab plus nab-paclitaxel is significantly lower using any of the alternative scenarios than the original approach employed by the company. The ERG believes that it is reasonable to assume that there would be correlation between the ratio of PFS and TTD for pembrolizumab plus paclitaxel/nab-paclitaxel and the corresponding ratio for atezolizumab plus nab-paclitaxel.

Figure 27: TTD survival functions for all treatment options and alternative assumption for atezolizumab plus nab-paclitaxel (generated by the ERG from the company's model) †

† Functions constrained to not be higher than the base case OS function

(2) Limitations regarding the comparison of pembrolizumab plus paclitaxel / nab-paclitaxel and atezolizumab plus nab-paclitaxel

The company has provided as part of its clarification response the results of a random effects model with prior distribution for the between-study standard deviation which shows greater uncertainty in the relative treatment effect, although point estimates are the ICER. As the company did not conduct PSA for the comparison of pembrolizumab plus paclitaxel / nab-paclitaxel with atezolizumab with nab-paclitaxel, it maintained using a fixed-effect model within its base case. The ERG has used the values from the random effects NMA although this will only impact on the probabilistic ICER.

The HRs for OS and PFS were taken from the comparison that uses the pooled taxanes as the common comparator in the NMA, which assumes that paclitaxel and nab-paclitaxel have the same efficacy when added to pembrolizumab. Given the data available to the company and the fact that pembrolizumab is used with both paclitaxel and nab-paclitaxel whereas atezolizumab is only used with nab-paclitaxel this approach appears reasonable but does introduce additional uncertainty. Given the wide confidence intervals associated with the comparison of pembrolizumab plus paclitaxel / nab-paclitaxel with

atezolizumab with nab-paclitaxel and the limitations in the comparator of the NMA the ERG has explored the impact of assuming clinical equivalence between pembrolizumab plus paclitaxel/nab-paclitaxel and atezolizumab plus nab-paclitaxel (HRs=1.0).

(3) Limitations regarding the company's approach to modelling HRQoL

(i) The time-to-death approach for modelling HRQoL

There is considerable uncertainty related to whether using a time-to-death-based approach for estimating utility is preferential to a health state-based approach that has been historically more widely used. The ERG comments that neither approach overcomes the main limitation which is that the data collected have been heavily censored, either at the point of progression, or at treatment discontinuation.

The time-to-death approach has the potential limitation that any extension of life would be at a relatively high utility, for example should a patient survive for two additional years on Treatment A compared with Treatment B and both produced a survival gain of over a year, then the extension of life would be at the utility for those with a life expectancy longer than one year ([redacted]). However, the health-state approach has the limitation that all patients within the state are assumed to have the same utility despite being a heterogeneous mix, that there may be few utility values recorded for people in the progressed disease state, and that (to the ERG) it appears intuitive that utility would decline as a patient neared death with clinical input to the ERG suggesting there is a marked decrease in utility in the month before death. The company provided analyses using both methods – the ERG notes that the health-state utilities taken from KEYNOTE-355 ([redacted] for progression-free survival and [redacted] for progressed disease) are similar to those apparently accepted by the appraisal committee for the appraisal of atezolizumab plus nab-paclitaxel (0.73 for progression-free survival and 0.65 for progressed disease). The use of a health-state method (including losses in utility associated with AEs) increased the company's deterministic base case ICER from £27,808 to £31,350.

(ii) Limitations regarding the non-inclusion of the impact of AEs on HRQoL

The time-to-death approach for HRQoL employed in the base-case analysis of pembrolizumab plus paclitaxel/nab-paclitaxel versus taxane therapies or atezolizumab plus nab-paclitaxel does not include the impact of AEs on patients' quality of life. In its submission, the company states that in the time to death approach, the associated AE disutility is intrinsically factored into the analyses.[43] In the clarification process (clarification response, question B14)[24], the company states that *"the base case does not account for AE related disutilities to avoid imposing any further assumptions for data analysed and to ensure that the number of questionnaires that remained in each time-to-death category was not depleted"* and that *"AEs initiated and resolved between rounds of EQ-5D administration may not be reflected on patient's response, however, this is a limitation that is applicable for all EQ-5D related analyses including those by disease progression status."* The ERG believes that the impact of Grade 3-

5 AEs on patients HRQoL should be modelled separately in order to explicitly capture events that resolved in between administrations of the EQ-5D.

(4) Issues relating to vial sharing not being allowed and drug wastage

The company allows vial sharing for all IV drugs within its base case analysis except for atezolizumab and pembrolizumab, however, the ERG notes that no evidence was provided that this occurs in practice. As such, the ERG believes that the default should be no vial sharing which increases the ICER moderately.

4.4 Exploratory analyses undertaken by the ERG

This section presents the methods and results of the ERG's exploratory analyses undertaken using the company's model.

4.4.1 Overview of ERG's exploratory analyses

The ERG has defined two base cases based on the different approaches for modelling HRQoL: (a) one using the time-to-death approach (equivalent to the company's base-case) and (b) one using a health state approach with the incorporations of QALY losses associated with AEs (equivalent to the company's scenario analysis 16) which also aligns with previous appraisals in this area. Two base-cases are provided to reflect the uncertainty in the most appropriate method as both have advantages and limitations.

The ERG undertook exploratory analyses to address the key points identified within the critical appraisal (Section 4.3.3). These included using alternative survival functions for OS, PFS for all interventions and a different TTD distribution for atezolizumab plus nab-paclitaxel, including the loss of treatment benefit for of immune-oncology treatments after 5 years and removing the assumption of vial sharing for the remaining IV drugs. The exploratory analyses were combined to form the ERG's preferred base case analysis.

The ERG also undertook additional sensitivity analyses using the ERG's preferred base case model to explore the impact of alternative extrapolations of OS, alternative estimations of the duration of benefit of immune-oncology treatments, and the TTD associated with atezolizumab plus nab-paclitaxel. The key features of the ERG's exploratory analyses are summarised in Table 36. Technical details regarding the implementation of these analyses in the company's model are presented in Appendix 1.

Table 36: Summary of ERG's exploratory analyses

		Company base-case	EA 1	EA 2	EA 3	EA4	EA 5	EA 6 - ERG preferred	ASA 1	ASA 2	ASA 3	ASA 4	ASA 5
OS	**Pembro+**	Lognormal	Weibull	Log normal	Log normal	Log normal	Log normal	Weibull	Exponential	Weibull	Weibull	Weibull	Weibull
	Taxanes	Log-logistic	Weibull	Log-logistic	Log-logistic	Log-logistic	Log-logistic	Weibull	Exponential	Weibull	Weibull	Weibull	Weibull
PFS	**Pembro+**	KM 9W + Weibull	KM 9W + Weibull	Weibull	KM 9W + Weibull	KM 9W + Weibull	KM 9W + Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull
	Taxanes	KM 9W + Lognormal	KM 9W + Lognormal	Log normal	KM 9W + Lognormal	KM 9W + Lognormal	KM 9W + Lognormal	Log normal	Lognormal	Log normal	Log normal	Log normal	Log normal
TTD	**Pembro+**	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull
	Taxanes	Log-logistic	Log-logistic	Log-logistic	Log-logistic	Log-logistic	Log-logistic	Log-logistic	Log-logistic	Log-logistic	Log-logistic	Log-logistic	Log-logistic
	Atezolizumab+	TTD assumed equal to PFS	TTD assumed equal to PFS	TTD assumed equal to PFS	PFS HR applied to pembro+ TTD model	TTD assumed equal to PFS	TTD assumed equal to PFS	PFS HR applied to pembro+ TTD model	PFS HR applied to pembro+ TTD model	PFS HR applied to pembro+ TTD model	PFS HR applied to pembro+ TTD model	assumed equal to pembro plus nab-paclitaxel TTD	PFS HR applied to pembro+ TTD model
Treatment benefit duration for pembrolizumab		Lifetime	Lifetime	Lifetime	Lifetime	5 years	Lifetime	5 years	5 years	Lifetime	3 years	5 years	5 years
Vial sharing*		✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✗	✗
Random effects		✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical efficacy equivalence assumed between atezolizumab and pembrolizumab		✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✓

Atezolizumab+ - atezolizumab plus nab-paclitaxel; ASA – additional sensitivity analysis; EA – exploratory analysis; HR – hazard ratio; pembro+ – pembrolizumab plus paclitaxel/nab-paclitaxel; PFS – progression-free survival; OS – overall survival; TTD – time to treatment discontinuation.
**for all IV drugs except for pembrolizumab and atezolizumab*

4.4.2 ERG's exploratory analyses - methods

In all exploratory and additional sensitivity analyses, the ERG has used the estimates generated by the company from the random effects model, as part of their clarification response (see Section 3.4 and Table 17). This change does not have an impact on results from the deterministic version of the model but can be observed on the probabilistic results of the ERG preferred analysis.

ERG exploratory analysis 1: Use of alternative OS survival functions

Based on the examination of the smoothed empirical hazard function, the ERG assessed the impact on the ICER of using the Weibull survival OS functions for pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel instead of, respectively, the lognormal and log-logistic distributions for OS.

ERG exploratory analysis 2: Use of alternative PFS survival functions

The ERG assessed the impact on the ICER of using the parametric functions fitted to the entire PFS data instead of the piecewise approach that used the observed KM survival function up to 9 weeks. The distributions remain the originally used: Weibull survival function for pembrolizumab plus paclitaxel/nab-paclitaxel and the lognormal for paclitaxel.

ERG exploratory analysis 3: Use of alternative TTD survival function for atezolizumab plus nab-paclitaxel

Within this analysis, the TTD function for atezolizumab plus nab-paclitaxel is modelled applying the HR for PFS generated by the company's NMA directly to the TTD survival function for pembrolizumab plus paclitaxel/nab-paclitaxel which assumes correlation between the paired TTD and PFS function. This contrasts with the company's approach which assumes that TTD is equal to PFS for patients receiving atezolizumab plus nab-paclitaxel. The ERG notes that its assumption is associated with uncertainty and it is not known whether this favours or disfavours pembrolizumab treatment but believes this is more reasonable than the assumption made by the company.

ERG exploratory analysis 4: Alternative assumption of treatment effect duration

The ERG notes that the company's assumption of a lifetime relative treatment benefit of pembrolizumab plus paclitaxel/nab-paclitaxel is likely to be optimistic. Within this analysis, the ERG assumes that the relative treatment effect ceases after 5 years (at which point the hazard for OS from paclitaxel is assumed generalisable to pembrolizumab plus paclitaxel/nab-paclitaxel) as has been often assumed by NICE Technology Appraisal Committee C. This will be unfavourable to atezolizumab plus nab-paclitaxel as atezolizumab treatment is not curtailed at 2 years, however, the number of patients remaining on atezolizumab in the ERG-preferred TTD function for atezolizumab is small (2.6% at 2 years) so when combined with exploratory analysis 3 the inaccuracy is anticipated to be small.

ERG exploratory analysis 5: No vial sharing considered

Clinical opinion provided to the ERG suggests vial sharing is unlikely for drugs which are low-cost (e.g., paclitaxel) or not frequently used (e.g., nab-paclitaxel). In this analysis, the ERG explored the impact of assuming no vial sharing for any IV drugs.

ERG exploratory analysis 6: ERG's preferred base case

The ERG's preferred base case includes ERG exploratory analysis 1 to 5.

ERG additional sensitivity analysis 1: Use of alternative models for OS

Within this analysis, the ERG assessed the impact on the ICER of using the exponential survival OS functions for pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel.

ERG additional sensitivity analysis 2: Alternative assumption of treatment effect duration

In this analysis, the ERG explores the impact of restoring the assumption of a lifetime relative treatment benefit of pembrolizumab plus paclitaxel/nab-paclitaxel.

ERG additional sensitivity analysis 3: Alternative assumption of treatment effect duration

Within this analysis, the ERG assumes that the relative treatment effect ceases after 3 years.

ERG additional sensitivity analysis 4: Use of alternative TTD model for atezolizumab plus nab-paclitaxel

Within this analysis, the TTD function for atezolizumab plus nab-paclitaxel is assumed to be the same as the TTD survival function for pembrolizumab plus nab-paclitaxel.

ERG additional sensitivity analysis 5: Assumption of equivalent clinical efficacy between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel/nab-paclitaxel

Within this analysis, the ERG assumes that there is no relative difference on treatment effect between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel/nab-paclitaxel (HRs are assumed to be =1.0). The ERG notes that the comparative efficacy between the two immunotherapy treatment strategies is associated with uncertainty. Setting the efficacy of both interventions equal to that of pembrolizumab plus paclitaxel/nab-paclitaxel has been explored, as this position was not ruled out in the NMA and these results may be informative to the Appraisal Committee. In this analysis only the treatment costs differ between the interventions.

4.4.3 ERG's exploratory analyses - results

The results of the ERG's preferred analyses are presented separately dependent on the approach adopted for modelling HRQoL (time-to-death or by disease progression state). All exploratory analyses use the list price for interventions with the exception for pembrolizumab.

4.4.3.1 – Time-to-death approach for modelling HRQoL (Exploratory analyses a)

Table 37 presents the results of the ERG exploratory analyses that used the time-to-death approach for modelling HRQoL as fully incremental analyses. Individual changes are applied relative to the company's base case in ERG exploratory analysis 1a to 5a; all individual changes are combined in ERG exploratory analysis 6a.

As shown in the table, paclitaxel and atezolizumab plus nab-paclitaxel are dominated in all analyses; using the company's deterministic model the ICER for pembrolizumab plus paclitaxel/nab-paclitaxel therapy versus docetaxel is estimated to be £34,184 per QALY gained. Using alternative PFS survival functions and removing vial sharing do not have a substantial impact on the ICER (ERG exploratory analyses 2a and 5a). However, using alternative OS survival functions (Weibull for pembrolizumab plus paclitaxel/nab-paclitaxel and for paclitaxel) and removing treatment benefit at 5 years are key drivers of the ICER. Under the ERG's preferred scenario, the ICER for pembrolizumab plus paclitaxel/nab-paclitaxel therapy versus docetaxel is estimated to be £65,846 (deterministic) and £67,757 (probabilistic) per QALY gained.

Table 37: 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)
Company's base case a – using HRQoL by time-to-death							
Docetaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.89	[redacted]	[redacted]	2.89	[redacted]	[redacted]	**£34,184**
Atezolizumab plus nab-paclitaxel	2.56	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 1a – Using Weibull distributions for OS							
Docetaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.97	[redacted]	[redacted]	1.42	[redacted]	[redacted]	**£54,555**
Atezolizumab plus nab-paclitaxel	1.99	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 2a - Using the parametric distributions for PFS without using the KM							
Docetaxel	2.00	[redacted]	[redacted]	-	-	[redacted]	-

Paclitaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.89	[redacted]	[redacted]	2.89	[redacted]	[redacted]	**£34,159**
Atezolizumab plus nab-paclitaxel	2.56	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 3a – Assuming that the HR between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel / nab-paclitaxel associated with PFS also applied to TTD							
Docetaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.89	[redacted]	[redacted]	2.89	[redacted]	[redacted]	**£34,184**
Atezolizumab plus nab-paclitaxel	2.56	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 4a – Loss of treatment benefit after 5 years							
Docetaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.10	[redacted]	[redacted]	2.09	[redacted]	[redacted]	**£42,201**
Atezolizumab plus nab-paclitaxel	2.33	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 5a – Removal of vial sharing for IV treatments†							
Docetaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.89	[redacted]	[redacted]	2.89	[redacted]	[redacted]	**£35,126**
Atezolizumab plus nab-paclitaxel	2.56	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 6a - ERG preferred analysis – time-to-death approach (deterministic)							
Docetaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.71	[redacted]	[redacted]	1.16	[redacted]	[redacted]	**£65,846**
Atezolizumab plus nab-paclitaxel	1.93	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 6a - ERG preferred analysis – time-to-death approach (probabilistic)							
Docetaxel	1.57	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	1.57	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.70	[redacted]	[redacted]	1.13	[redacted]	[redacted]	**£67,757**
Atezolizumab plus nab-paclitaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**

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 which were already assumed not to share vials.*

Considering that paclitaxel was considered the main comparator in TA639,[11] and was defined as the principal comparator in this appraisal, the results of the pairwise comparison of pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel are presented in Table 38. However, clinical advice to the ERG suggests that the majority of patients are treated with docetaxel rather than paclitaxel. The ERG has therefore provided both full incremental analyses and a pairwise comparison with paclitaxel to provide all potentially relevant ICERs to the appraisal committee.

Using Weibull distributions for OS survival functions increases the ICER in the company's base case from £27,808 to £44,335 per QALY gained, whilst removing treatment benefit for pembrolizumab plus paclitaxel/nab-paclitaxel at 5 years increases it to £34,096 per QALY gained. The ICER for the ERG's preferred probabilistic analysis for pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel is estimated to be £55,074 per QALY gained, (deterministic value £53,721). Exploratory analysis 2a, 3a and 5a do not have a substantial impact on the ICER.

Table 38: 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)
Company's base case a – using HRQoL by time-to-death							
Paclitaxel	2.00	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.89	[redacted]	[redacted]	2.89	[redacted]	[redacted]	**£27,808**
ERG exploratory analysis 1a – Using Weibull distributions for OS							
Paclitaxel	1.55	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.97	[redacted]	[redacted]	1.42	[redacted]	[redacted]	**£44,335**
ERG exploratory analysis 2a - Using the parametric distributions for PFS without using the KM							
Paclitaxel	2.00	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.89	[redacted]	[redacted]	2.89	[redacted]	[redacted]	**£27,783**
ERG exploratory analysis 4a – Loss of treatment benefit after 5 years							
Paclitaxel	2.00	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.10	[redacted]	[redacted]	2.09	[redacted]	[redacted]	**£34,096**
ERG exploratory analysis 5a – Removal of vial sharing for IV treatments†							
Paclitaxel	2.00	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.89	[redacted]	[redacted]	2.89	[redacted]	[redacted]	**£28,763**
ERG exploratory analysis 6a - ERG preferred analysis – time-to-death approach (deterministic)							
Paclitaxel	1.55	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.71	[redacted]	[redacted]	1.16	[redacted]	[redacted]	**£53,721**
ERG exploratory analysis 6a - ERG preferred analysis – time-to-death approach (probabilistic)							
Paclitaxel	1.57	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.70	[redacted]	[redacted]	1.13	[redacted]	[redacted]	**£55,074**

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 which were already assumed not to share vials.*
Exploratory analysis 3a is not applicable for the pairwise comparison between pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel, and therefore does not affect the results for this comparator.

Table 39 and Table 40 present the results of the ERG's additional sensitivity analyses for pembrolizumab plus paclitaxel/nab-paclitaxel versus all the comparators (full incremental analyses) and against paclitaxel, respectively. As shown in the full incremental analyses, paclitaxel and atezolizumab plus nab-paclitaxel are dominated in all analyses; changing the assumption around the TTD model used for atezolizumab plus nab-paclitaxel increases its total costs but it does not materially affect the ICER. Using exponential OS survival models reduces the deterministic ICERs for pembrolizumab plus paclitaxel/nab-paclitaxel therapy: from £65,846 to £57,333 per QALY gained versus docetaxel and from £53,721 to £46,527 against paclitaxel. Restoring the assumption of lifetime treatment benefit from pembrolizumab plus paclitaxel/nab-paclitaxel reduces the ICER to £56,112 per QALY gained against docetaxel and to £45,912 per QALY gained against paclitaxel. Conversely, reducing the benefit to no effect after 3 years increases the ICER to £89,090 per QALY gained against docetaxel and to £72,375 per QALY gained against paclitaxel.

Table 39: Results of ERG additional sensitivity 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)
ERG preferred analysis – time-to-death approach (deterministic)							
Docetaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.71	[redacted]	[redacted]	1.16	[redacted]	[redacted]	**£65,846**
Atezolizumab plus nab-paclitaxel	1.93	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 1a – Using exponential distributions for OS							
Docetaxel	1.73	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	1.73	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.12	[redacted]	[redacted]	1.38	[redacted]	[redacted]	**£57,333**
Atezolizumab plus nab-paclitaxel	2.07	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 2a – Assumption of lifetime treatment benefit duration							
Docetaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.97	[redacted]	[redacted]	1.42	[redacted]	[redacted]	**£56,112**
Atezolizumab plus nab-paclitaxel	1.99	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 3a – Loss of treatment benefit after 3 years							
Docetaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.38	[redacted]	[redacted]	0.82	[redacted]	[redacted]	**£89,090**
Atezolizumab plus nab-paclitaxel	1.78	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 4a – TTD for atezolizumab plus nab-paclitaxel assumed equal to pembrolizumab plus paclitaxel / nab-paclitaxel							
Docetaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.71	[redacted]	[redacted]	1.16	[redacted]	[redacted]	**£65,846**
Atezolizumab plus nab-paclitaxel	1.93	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 5a – assumption of the same clinical efficacy between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel / nab-paclitaxel							
Docetaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.71	[redacted]	[redacted]	1.16	[redacted]	[redacted]	**£65,846**
Atezolizumab plus nab-paclitaxel	2.71	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
** undiscounted.*

Table 40: Results of ERG additional sensitivity 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)
ERG preferred analysis – time-to-death approach (deterministic)							
Paclitaxel	1.55	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.71			1.16			**£53,721**
ERG additional sensitivity analysis 1a – Using exponential distributions for OS							
Paclitaxel	1.73	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.12			1.38			**£46,527**
ERG additional sensitivity analysis 2a – Assumption of lifetime treatment benefit duration							
Paclitaxel	1.55	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.97			1.42			**£45,912**
ERG additional sensitivity analysis 3a – Loss of treatment benefit after 3 years							
Paclitaxel	1.55	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.38			0.82			**£72,375**

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
** undiscounted;*
Exploratory analyses 4a and 5a are not applicable for the pairwise comparison between pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel, and therefore do not affect the results for this comparator.

4.4.3.2 – Approach for modelling HRQoL by health states (Exploratory analyses b)

Table 41 presents the results of the ERG exploratory analyses that used health states to estimate HRQoL, including additional disutility from AEs, as fully incremental analyses. Individual changes are applied relative to the company's base case where this approach has been included (equivalent to the company's scenario analysis 16); all individual changes from exploratory analysis 1b to 5b are combined in ERG preferred analysis (exploratory analysis 6b).

Paclitaxel and atezolizumab plus nab-paclitaxel are dominated in all analyses. Under the company's deterministic model, the ICER for pembrolizumab plus paclitaxel/nab-paclitaxel therapy versus docetaxel is estimated to be £38,538 per QALY gained. Using Weibull OS survival functions for pembrolizumab plus paclitaxel/nab-paclitaxel and for paclitaxel increases this ICER to £57,348, whilst removing treatment benefit at 5 years increases the ICER to £46,176 per QALY gained. Using different PFS survival functions without cut-off points and removing vial sharing for taxanes do not have a substantial impact on the ICER. In the ERG's preferred scenario, the ICER for pembrolizumab plus paclitaxel/nab-paclitaxel therapy versus docetaxel is estimated to be £70,947 (deterministic) and £72,844 (probabilistic) per QALY gained.

Table 41: Results of the ERG exploratory analyses, pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel, docetaxel and atezolizumab plus nab-paclitaxel, utilities by health states approach for modelling HRQoL

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's base case b – HRQoL by health state							
Docetaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.89	[redacted]	[redacted]	2.89	[redacted]	[redacted]	**£38,538**
Atezolizumab plus nab-paclitaxel	2.56	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 1b – Using Weibull distributions for OS							
Docetaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.97	[redacted]	[redacted]	1.42	[redacted]	[redacted]	**£57,348**
Atezolizumab plus nab-paclitaxel	1.99	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 2b - Using the parametric distributions for PFS without using the KM							
Docetaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.89	[redacted]	[redacted]	2.89	[redacted]	[redacted]	**£39,719**
Atezolizumab plus nab-paclitaxel	2.56	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 3b - Assuming that the HR between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel / nab-paclitaxel associated with PFS also applied to TTD							
Docetaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.89	[redacted]	[redacted]	2.89	[redacted]	[redacted]	**£38,538**
Atezolizumab plus nab-paclitaxel	2.56	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 4b – Loss of treatment benefit after 5 years							
Docetaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.10	[redacted]	[redacted]	2.09	[redacted]	[redacted]	**£46,176**
Atezolizumab plus nab-paclitaxel	2.33	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 5b – Removal of vial sharing for IV treatments†							
Docetaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.89	[redacted]	[redacted]	2.89	[redacted]	[redacted]	**£39,600**
Atezolizumab plus nab-paclitaxel	2.56	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 6b - ERG preferred analysis – HRQoL by health state (deterministic)							
Docetaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**

Pembrolizumab plus paclitaxel/nab-paclitaxel	2.71	[redacted]	[redacted]	1.16	[redacted]	[redacted]	**£70,947**
Atezolizumab plus nab-paclitaxel	1.93	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 6b - ERG preferred analysis – HRQoL by health state (probabilistic)							
Docetaxel	1.57	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	1.57	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.70	[redacted]	[redacted]	1.13	[redacted]	[redacted]	**£72,844**
Atezolizumab plus nab-paclitaxel	2.00	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**

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 which were already assumed not to share vials.*

Table 42 presents the results of the pairwise comparison of pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel. Using Weibull distributions for OS survival functions for pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel increases the ICER from £31,350 to £46,604 per QALY gained, whilst removing treatment benefit for pembrolizumab plus paclitaxel/nab-paclitaxel at 5 years increases it to £37,308 per QALY gained. The analyses suggest that the other alternative approaches do not have individually a substantial impact on the ICER. The ICER for the ERG's preferred probabilistic analysis for pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel is estimated to be £59,208 per QALY gained (£57,883 deterministic).

Table 42: Results of the ERG exploratory analyses, pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel, utilities by health states approach for modelling HRQoL

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's base case + HRQoL by health state							
Paclitaxel	2.00	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.89	[redacted]	[redacted]	2.89	[redacted]	[redacted]	**£31,350**
ERG exploratory analysis 1b – Using Weibull distributions for OS							
Paclitaxel	1.55	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.97	[redacted]	[redacted]	1.42	[redacted]	[redacted]	**£46,604**
ERG exploratory analysis 2b - Using the parametric distributions for PFS without using the KM							
Paclitaxel	2.00	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.89	[redacted]	[redacted]	2.89	[redacted]	[redacted]	**£32,305**
ERG exploratory analysis 4b – Loss of treatment benefit after 5 years							
Paclitaxel	2.00	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.10	[redacted]	[redacted]	2.09	[redacted]	[redacted]	**£37,308**
ERG exploratory analysis 5b – Removal of vial sharing for IV treatments†							
Paclitaxel	2.00	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.89	[redacted]	[redacted]	2.89	[redacted]	[redacted]	**£32,426**
ERG exploratory analysis 6b - ERG preferred analysis – HRQoL by health state (deterministic)							
Paclitaxel	1.55	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.71	[redacted]	[redacted]	1.16	[redacted]	[redacted]	**£57,883**
ERG exploratory analysis 6b - ERG preferred analysis – HRQoL by health state (probabilistic)							
Paclitaxel	1.57	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.70	[redacted]	[redacted]	1.13	[redacted]	[redacted]	**£59,208**

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 which were already assumed not to share vials. Exploratory analysis 3b is not applicable for the pairwise comparison between pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel, and therefore does not affect the results for this comparator.*

Table 43 and Table 44 present the results of the ERG's additional sensitivity analyses for pembrolizumab plus paclitaxel/nab-paclitaxel (full incremental analyses with all comparators and against paclitaxel, respectively). As for the sensitivity analyses using the time-to-death approach for generating utilities, paclitaxel and atezolizumab plus nab-paclitaxel are dominated and changing the assumption around the TTD model used for atezolizumab plus nab-paclitaxel increases its total costs but does not materially affect the ICER. Using exponential OS survival functions lead to reductions in the ICERs for pembrolizumab plus paclitaxel/nab-paclitaxel: to £62,431 per QALY gained in the comparison against docetaxel and to £50,664 per QALY gained against paclitaxel. Restoring the assumption of lifetime treatment benefit reduces the ICERs: to £61,502 per QALY gained against docetaxel and to £50,322 per QALY gained against paclitaxel. Conversely, reducing the benefit to no

effect after 3 years increases the ICER to £92,370 per QALY gained against docetaxel and to £75,039 per QALY gained against paclitaxel.

Table 43: Results of ERG additional sensitivity analyses, pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel, docetaxel and atezolizumab plus nab-paclitaxel, utilities by health states approach for modelling HRQoL

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
ERG preferred analysis – HRQoL by health state (deterministic)							
Docetaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.71	[redacted]	[redacted]	1.16	[redacted]	[redacted]	**£70,947**
Atezolizumab plus nab-paclitaxel	1.93	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 1b – Using exponential distributions for OS							
Docetaxel	1.73	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	1.73	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.12	[redacted]	[redacted]	1.38	[redacted]	[redacted]	**£62,431**
Atezolizumab plus nab-paclitaxel	2.07	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 2b – Assumption of lifetime treatment benefit duration							
Docetaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.97	[redacted]	[redacted]	1.42	[redacted]	[redacted]	**£61,502**
Atezolizumab plus nab-paclitaxel	1.99	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 3b – Loss of treatment benefit after 3 years							
Docetaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Paclitaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.38	[redacted]	[redacted]	0.82	[redacted]	[redacted]	[redacted]
Atezolizumab plus nab-paclitaxel	1.78	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
ERG additional sensitivity analysis 4b - TTD for atezolizumab plus nab-paclitaxel assumed equal to pembrolizumab plus paclitaxel / nab-paclitaxel							
Docetaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.71	[redacted]	[redacted]	1.16	[redacted]	[redacted]	**£70,947**
Atezolizumab plus nab-paclitaxel	1.93	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 5b – assumption of the same clinical efficacy between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel / nab-paclitaxel							
Docetaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	1.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.71	[redacted]	[redacted]	1.16	[redacted]	[redacted]	**£70,947**

Atezolizumab plus nab-paclitaxel	2.71	[redacted]	[redacted]	-	[redacted]	[redacted]	**£10,046,096**

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
** undiscounted.*

Table 44: Results of ERG additional sensitivity analyses, pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel, utilities by health states approach for modelling HRQoL

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
ERG preferred analysis – HRQoL by health state (deterministic)							
Paclitaxel	1.55	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.71	[redacted]	[redacted]	1.16	[redacted]	[redacted]	**£57,883**
ERG additional sensitivity analysis 1b – Using exponential distributions for OS							
Paclitaxel	1.73	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.12	[redacted]	[redacted]	1.38	[redacted]	[redacted]	**£50,664**
ERG additional sensitivity analysis 2b – Assumption of lifetime treatment benefit duration							
Paclitaxel	1.55	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.97	[redacted]	[redacted]	1.42	[redacted]	[redacted]	**£50,322**
ERG additional sensitivity analysis 3b – Treatment benefit loss after 3 years							
Paclitaxel	1.55	[redacted]	[redacted]	-	-	[redacted]	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	2.38	[redacted]	[redacted]	0.82	[redacted]	[redacted]	**£75,039**

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
** undiscounted;*
Exploratory analyses 4b and 5b are not applicable for the pairwise comparison between pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel, and therefore do not affect the results for this comparator.

4.5 Discussion

The model submitted by the company was implemented to a good standard although was associated with a large file size. The ERG, however, preferred alternative assumptions to those used by the company which markedly increased the ICER, primarily due to the different distributions used for OS and curtailing the benefit of pembrolizumab plus paclitaxel / nab-paclitaxel at 5 years. The deterministic ICER of pembrolizumab plus paclitaxel / nab-paclitaxel compared with docetaxel increased from £34,184 in the company's base case to £65,846 in the ERG's base case (£67,757 probabilistic) when a time-to-death approach for generating utilities was utilised and from £38,538 to £70,947 (£72,844 probabilistic) when a health-state approach for generating utilities was used.

The deterministic ICER of pembrolizumab plus paclitaxel / nab-paclitaxel versus paclitaxel increased from £27,808 in the company's base case to £53,721 in the ERG's base case (£55,074 probabilistic)

when a time-to-death approach for generating utilities was utilised and from £31,350 to £57,883 (£59,208 probabilistic) when a health-state approach for generating utilities was used.

The ICER for pembrolizumab plus paclitaxel / nab-paclitaxel compared with atezolizumab plus nab-paclitaxel was relatively insensitive to the changes made by the ERG, however, this was primarily due to the fact that, as instructed by NICE, the list price of atezolizumab was used in the analyses. A confidential appendix contains the results of these analyses incorporating cPAS.

5 END OF LIFE

On page 90 of the CS, the company puts forward the case that pembrolizumab plus a taxane meets the NICE End of Life criteria. These criteria are:

- 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 offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The company's base case probabilistic analysis estimates that for patients receiving a taxane alone that the mean life years per patient is 2.06 years (24.7 months), whereas for patients receiving pembrolizumab plus a taxane this value is 4.98 years (an extension of life approaching 3 years). Whilst the criterion related to the extension of life appears to be met when comparing pembrolizumab plus a taxane with a taxane alone, the short life criterion may not be met.

However, the CS did not discuss whether pembrolizumab plus a taxane met the End of Life criteria when the comparator was atezolizumab plus nab-paclitaxel. For atezolizumab plus nab-paclitaxel, the company's base case deterministic analysis estimated 2.56 life years (30.7 months) gained. If correct, this would mean that the short life expectancy criterion would appear not to be met when atezolizumab plus nab-paclitaxel could be used.

The exploratory analyses conducted by the ERG supported the company's view that the extension to life criterion was met (1.13 years against taxanes and 0.71 years against atezolizumab plus nab-paclitaxel). These analyses reduced the expected life year for patients receiving paclitaxel or docetaxel to 1.57 years, and to 2.00 years for patients receiving atezolizumab plus nab-paclitaxel, suggesting that the short life expectancy criterion would be met when taxanes was the comparator, and that this was debatable when atezolizumab plus nab-paclitaxel was the comparator.

6 OVERALL CONCLUSIONS

The key evidence of the clinical effectiveness and safety of pembrolizumab in mTNBC was taken from a subgroup (CPS≥10) of the ongoing KEYNOTE-355 RCT. In the absence of head-to-head evidence comparing pembrolizumab combination therapy and atezolizumab plus nab-paclitaxel, one RCT was identified by the CS for use in an indirect comparison, IMpassion130.

The baseline demographics of the KEYNOTE-355 RCT were broadly representative of the mTNBC UK population, however eligibility criteria regarding ECOG PS and adequate organ function meant that patients were fitter than would be seen in UK practice. Restricting the population to those sufficiently fit for active treatment, CPS≥10, and de novo metastatic or relapse > 6 months after adjuvant treatment, probably comprises 15-20% of mTNBC patients (clinical advice).

OS data were immature; [redacted]. There was a significant advantage in PFS for the pembrolizumab plus chemotherapy arm over the placebo plus chemotherapy arm, HR 0.65 (0.49, 0.86) p=0.0012. [redacted]

The model submitted by the company was implemented to a good standard, although the ERG preferred alternative assumptions to those used by the company. Incorporating the assumptions preferred by the ERG increased the deterministic ICER of pembrolizumab plus paclitaxel / nab-paclitaxel compared with docetaxel from £34,184 in the company's base case to £65,846 in the ERG's base case (£67,757 probabilistic) when a time-to-death approach for generating utilities was utilised and to £70,947 (£72,844 probabilistic) when a health-state approach for generating utilities was used. The ICER of pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel increased from £27,808 in the company's base case to £53,721 in the ERG's base case (£55,074 probabilistic) when a time-to-death approach for generating utilities was utilised and from £31,350 to £57,883 (£59,208 probabilistic) when a health-state approach for generating utilities was used.

The model estimated that pembrolizumab plus paclitaxel / nab-paclitaxel dominated atezolizumab plus nab-paclitaxel, although these results do not incorporate the agreed PAS discount for atezolizumab. A confidential appendix contains the results when cPAS are incorporated.

7 REFERENCES

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8 APPENDICES

Appendix 1: Technical appendix detailing methods for implementing the ERG's exploratory analyses

For the base-case analyses using time-to-death approach for modelling HRQoL (base-case a), apply each of the following steps described below from the company's updated model. To change the analysis to the HRQoL by health states approach, go to worksheet "Model Specifications", click on the dropdown menu cell H130 and choose the option "Utility by progression and AE status". Do not change the options for the source of utility values.

Before running all analyses, go to worksheet 'Effectiveness", click on the dropdown menu on cells I19:J19 and choose the option "Random effects". This change will only apply for the probabilistic results in the ERG-preferred analysis.

Exploratory analysis 1 – Use of alternative OS survival functions

Go to worksheet "Model Specifications", click on dropdown menu on cells I98 and I103 and choose the option "Weibull" in both of them.

Exploratory analysis 2 – Use of alternative PFS survival functions

Go to worksheet "Model Specifications", click on dropdown menu on cells H78 and H83 and choose the option "One-piece" in both of them. Make sure that the dropdown menu on cell I78 has the option "Weibull" selected, and on cell I83 the option 'log-normal' is selected.

Exploratory analysis 3 – Use of alternative TTD survival function for atezolizumab plus nab-paclitaxel

Replace the formula in worksheet "Calculation_Treatment Costs" cell EV27 with formula '=AE27^hr_pfs_tx11'. Drag the formula down to the bottom of the array.

Exploratory analysis 4 – Loss of treatment benefit after 5 years

Go to worksheet "Model Specifications", click on dropdown menu on cells G90:H90 and choose the option "Applying treatment waning for IO + chemotherapy arms". Make sure the value in cell G92 says '5 years'.

Exploratory analysis 5 – Removal of vial sharing

Go to worksheet "Model Specifications", click on dropdown menu on cells H142 and choose the option "No".

Exploratory analyses 6 - ERG-preferred analysis (deterministic)

Apply all changes from ERG exploratory analyses 1-5, as described above.

Additional sensitivity analysis and subgroup analysis should start from these versions of the model.

Additional sensitivity analysis 1 – Use of alternative OS survival functions
Go to worksheet "Model Specifications", click on dropdown menu on cells I98 and I103 and choose the option "Exponential" in both of them.

Additional sensitivity analysis 2 – Assumption of lifetime treatment benefit
Go to worksheet "Model Specifications", click on dropdown menu on cells G90:H90 and choose the option "Not applying treatment waning or RWE data".

Additional sensitivity analysis 3 – Assumption of lifetime treatment benefit
Go to worksheet "Model Specifications", click on dropdown menu on cells G90:H90 and choose the option "Applying treatment waning for IO + chemotherapy arms". Change the value in cell G92 to '3 years'.

Additional sensitivity analysis 4 – Use of alternative TTD survival function for atezolizumab plus nab-paclitaxel
Replace the formula in worksheet "Calculation_Treatment Costs" cell EV27 with formula '=BX27'. Drag the formula down to the bottom of the array.

Additional sensitivity analysis 5 – Assumption of equivalent clinical efficacy between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel/nab-paclitaxel
Go to worksheets "Calculation_PFS_HR" and "Calculation_OS_HR" and replace the formulas in cells O9 with the value '1.0'.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Pembrolizumab in combination for untreated, locally recurrent inoperable or metastatic, triple negative breast cancer [ID1546]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 31 March 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 : Paclitaxel administration in UK

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 13, section 1.3 The clinical evidence for paclitaxel is based on the observed data from the KEYNOTE-355 study, which administered paclitaxel three times in each four-week cycle, which does not reflect current clinical practice in the UK of weekly dosing	The clinical evidence for paclitaxel is based on the observed data from the KEYNOTE-355 study, which administered paclitaxel three times in each four-week cycle, *which is used for certain patients, as per local treatment guidelines*.	Weekly paclitaxel is included on publicly available chemotherapy protocols as an option for those with metastatic/advanced breast cancer (1, 2). The Royal Surrey protocol states weekly paclitaxel are an option for those who have had no previous chemotherapy for early breast cancer or had relapsed >12 months after chemotherapy for early BC (3). Further, from a cost-effectiveness perspective, weekly paclitaxel as alluded to by the ERG, offers a more robust approach to the estimated resources associated with paclitaxel administration.	The ERG does not believe this is a matter of factual inaccuracy. Clinical opinion received by the ERG and the previous NICE appraisal for atezolizumab plus nab-paclitaxel state that the typical frequency of the paclitaxel administration in the UK is on a weekly basis. However, the ERG agrees that the weekly regimen may be one option of treatment available, and has amended the wording to: "The clinical evidence for paclitaxel is based on the observed data from the KEYNOTE-355 study, which administered paclitaxel three times in each four-week cycle, which may be used for certain patients as per local treatment guidelines. However, according to clinical opinion received by the ERG and in the NICE appraisal for nab-paclitaxel in this indication, this does not reflect the most common administration schedule currently used in clinical practice in the UK

			(which is weekly dosing). However, this potential discrepancy cannot be easily resolved and the ERG believes that this limitation does not invalidate the modelling undertaken.”

Issue 2 : Clinical evidence from KEYNOTE-355

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 25, second bullet point Restricting the population considered for atezolizumab in combination with nab-paclitaxel treatment to those whose tumours express PD L1 CPS ≥10… This is a subset of patients with PD-L1 expression ≥1%.	Remove “**This is a subset of patients with PD-L1 expression ≥1%”.** Please also introduce Figure 13 of the company submission within the ERG report which demonstrates the differences and population overlaps between SP142 PD-L1 ≥1% IC and 22C3 Dako CPS ≥10 PD-L1 +ve populations.	Patients whose tumour expresses PD-L1 with a CPS ≥10 are not a subset of those who express PD-L1 ≥1% IC, since this implies that the CPS ≥10 population is contained exclusively within the PD-L1 ≥1% IC population. As the Rugo posters demonstrate there is overlap, some patients will have CPS ≥10 and ≤1% due to the different assays and scoring methods utilised in KEYNOTE-355 and Impassion130. The proposed changes will aid the AC in its review of the evidence.	We have removed the erroneous sentence. The ERG believes that inclusion of Figure 13 is not needed in the ERG report but can be raised, if necessary, by the company at the Appraisal Committee.
Within the ERG report, it is noted that the company presented a “naïve analysis unadjusted for the interim analyses for	We propose that the ERG add some additional text to specify that multiplicity was accounted for within the interim	The proposed changes add more context with regards to the interim OS data included within the submission, removing any potential	The ERG accepts that its wording was not precise and that it should not have written that the company presented a naïve analysis. However, 95%

OS". References to this are found on pages 13 and 38. We understand that the ERG may have misunderstood the "unadjusted" 95% CI as not appropriately taking into account multiplicity which is due to the interim database locks taking place. If that is the case, then we would like to take the opportunity to offer further clarification and to confirm that multiplicity was adequately accounted for within these interim analyses by adequately controlling for using group sequential method to control the family-wise type I error (from this approach, the one-sided nominal alpha-level of 0.00472 was used to compare the IA2 p-value of 0.0066). Please refer to the original CSR provided for further detail.	database locks taking place in KEYNOTE-355.	misinterpretation around the issue of multiplicity.	confidence intervals for hazard ratios presented by the company in the submission do not include the null value and yet the corresponding test statistic is described in the submission as being not statistically significant which is an apparent inconsistency. The ERG believes that the apparent inconsistency has arisen because the width of the confidence intervals presented in the submission do not correspond to the nominal significance level used in the interim analysis. The company has not provided any information in the submission or in its description of the problem that explains the apparent inconsistency. The text has been changed to remove all mention of "naïve".

Issue 3 : Potentially favourable extrapolations for OS selected by the company

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG notes within its report that the company has potentially selected optimistic extrapolations with regards to OS for the economic modelling. Within the ERG's preferred base case	To reflect upon the ERG's model selection process whilst also providing more context with regards to the justification of the Weibull function, we ask the following amendments are	The proposed amendments ensure consistency with the NICE DSU TS14 methods with regards	Our main argument for model choice was based on the comparison of the empirical hazard functions. The ERG did not adopt the company's

assumptions, the Weibull is noted as more appropriate with regards to long term extrapolations for OS and is subsequently used for both pembrolizumab + taxanes and the paclitaxel comparator. Additional exploratory analyses are conducted using the exponential function. We noted that within TA639, the Weibull was the Company's preferred parametric model which was accepted by the AC. However, we consider that the ERG's justification to use Weibull solely on the basis of previous AC's preferences on OS extrapolation for Atezolizumab + nab-paclitaxel as unjustified. Parametric model fitting is dependent upon the underling clinical data from the pivotal study itself in consideration. Further, the ERG's preference above does not take into account the number of differences reported in terms of the patient population between IMpassion-130 and KEYNOTE-355. Therefore, the use of Weibull distribution on this basis is not adequately justified by the ERG. This is further supported by virtual inspection of the survival curves versus the KM data. The Weibull distribution for pembrolizumab + taxanes arm offers the worst fit since it overpredicts for most of	implemented in the relevant pages of the for transparency. "*The ERG's choice of Weibull distribution was based upon previous OS extrapolations of Atezolizumab + nab-paclitaxel as reported in TA639 alone; rather than consideration of the model selection process as outlined within the NICE DSU TSD 14"* In addition, we ask we ask that the ERG provide further justification with regards to their preference for BIC alone for the model selection. This should be added on pages 65, 69 and 76 where the ERG states quotes the BIC statistic alone for model section. Since this approach constitutes a deviation from the from the NICE DSU TSD14, the additional context would offer more clarity and enable us to assess the validity of this approach (4).	to the model selection process of the survival data (4). Further, the proposed amendments ensure that key caveats with regards to the ERG's preferred base-case assumptions are clearly reported for the AC to consider when interpreting the cost-effectiveness results. This will also ensure a more balanced view of the robustness of these assumptions to inform the base-case.	preferred distribution because, as stated in the ERG report, "*the smoothed empirical hazard function does not support a unimodal, increasing then decreasing hazard function.*" The ERG have a preference for using BIC to compare models based on goodness-of-fit but not in using goodness-of-fit measures alone to decide which is the preferred model. Various authors have considered the relative merits of different criterion for assessing model choice but there is no overall agreement on which to use in all circumstances. TSD14 does not state a preference for the use of AIC or BIC (or their sum). Furthermore, goodness-of-fit criterion do not tell which model is true and different ordering of models may reflect high model uncertainty. The ERG does not consider it reasonable to make arm-based comparisons with external data (i.e. SEER) or to compare point estimates of the proportion of patients surviving at different times without

the observed period versus the company's preferred model for a period of time, followed by an underprediction at the end of follow up. The smoothed hazard plots demonstrate that the long-term hazard function of the Weibull distribution is above the empirical hazard function and ever increasing during the study follow up for both pembrolizumab + taxanes and the taxanes comparator arm. This highlights the conservatism of this selection and is in contrast to the ERG's comment in page 69 of the ERG report noting that the Weibull was the "likely most appropriate distribution". Whilst the ERG chose an alternative extrapolation curve (exponential), this is based upon constant hazards which is an overly simplistic assumption. This means that the project OS estimates for both treatment arms during the study follow up, fall outside the predicted 95% KM-CIs or in the case of pembrolizumab + taxanes (please refer to figures 18 and 19 of the report). In addition, from a quick validation of the anticipated survival outcomes on the taxane comparator arm, the Weibull model results in an almost 0% survival, when the latest RWE evidence from			considering uncertainty and acknowledging the mix of patient characteristics. Therefore, no amendments have been made to the text.

SEER, suggest this to be in the range of ~7.2%. The evidence above highlights in its totality that the Weibull function is not appropriate for extrapolation of neither for Pembrolizumab + taxanes and nor for the taxanes comparator arm. We ask that the ERG's preferred approaches to the model selection process are further justified within the ERG report noting that Weibull is considered a very pessimistic choice for OS modelling based on the reasons outlined above. Further, we ask that the ERG outline the caveats with regards to their preferred alternative choice of parametric curves for OS (exponential), as reported within the company's submission . References of the above are included within the ERG report on the following pages: 11, 14, 17, 69, 114 and 121. Within page 65, the ERG states that the BIC was used as a justification for the selection of the Weibull survival function. However, the ERG does not provide further adequate justification as to why the Bayesian Information Criterion [BIC] alone should be preferred as the only goodness of fit statistic alone to assess			

the relative goodness of fit to the observed data. Therefore, we consider the ERG's preference to the use of BIC alone as unjustified and in deviation to the NICE DSU Document 14 algorithm for model selection (as opposed to with consideration of the of the Akaike Information Criterion [AIC]) (4). When both AIC and BIC are considered (as per the company's preferred methodology which is consistent to the NICE DSU TSU 14), there is almost a 3.37 point difference between Weibull and log-normal models for Pembrolizumab + taxanes. This approach demonstrates that the log-normal is the most optimal model for OS extrapolation. We ask that the ERG revise their preferred model selection process to align to the NICE DSU 14 methodology to ensure a fair and consistent application of the methods for this technology appraisal and accordingly, the CE estimates presented for consideration to the AC(4). References of this approach are within the ERG report on the following pages: 65, 69 and 76 (alongside the pages			

noted above which discuss the OS selection process).			
In a number of instances within the ERG report, it is noted that the smoothed empirical hazard function can be used to assess changes of hazard over time: *"In the CS, the company suggested that the empirical evidence suggested a change in the shape of the cumulative hazard functions at weeks 25, 40 and 52. The ERG suggests that the smoothed empirical hazard functions do not support this assertion."* We wanted to offer some additional clarity that the smoothed empirical hazard function was not used to determine the likely time points at which the hazard function might change. As noted within the submission, the likely time points at which hazard may change (week 24, 40 and 52) was based upon cumulative hazard functions and Chow tests. Further, these change points are likely to be purely data driven. Upon review of the RWE evidence for the current SoC alongside model projections based upon different cut-off points, full piece OS models were selected for the base case.	Please amend the wording in page 68 and 69 to add clarity upon the methods used within the submission and to avoid subsequent misinterpretation by the AC. By definition the smoothed empirical hazard functions cannot be used to identify change points because these points have been "smoothed". Further, there is no evidence or clinical rationale at this stage to suggest that a change in hazard for Pembrolizumab + taxanes is likely to occur after 2 years.	The proposed amendment adds clarity with regards to the methods followed to justify the full piece OS model section process.	The ERG did not claim that the company used smoothed empirical hazard functions to determine the likely time points at which the hazard function might change, only that the plots did not support there being changes in the underlying hazard function. We disagree that smoothed hazard plots would mask changes in hazard functions if these changes were sufficiently large. Therefore, no amendments have been made to the text.

References to this are included in page 68, 69.			

Issue 4 : Long term treatment effect for Pembrolizumab and survival extrapolation considerations

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG has assumed that the treatment effect of pembrolizumab + taxanes at year 5 in the ERG base case ICERs. As noted by the ERG, this was based upon the precedent set in NICE Technology Appraisal Committee C. Exploratory analyses were undertaken assuming that the hazards are set equal after 3 years as well as using a lifetime effect (which is the company's preferred assumption for the base-case). The ERG provides a rationale for the application a 5-year treatment cap based on Appraisal Committee C preferences and prior precedent. This is inconsistent with all previous Brest Cancer submissions, including the recent TA639 whereby the Appraisal Committee A acknowledged that incorporating inappropriate arbitrary treatment waning effect into the base case was not appropriate (5).	Please insert additional text on the relevant ERG report pages to add more context by re-iterating that the ERGs preferred base-case deviates from the assumptions preferred by the Appraisal Committee - A in the recent TA639 (and all prior BC HTAs) which was in favour of a life time OS effect due to lack of relevant evidence to do otherwise (6). Please amend the wording on the relevant ERG pages by removing references to the Appraisal Committee C preferences with regards to life time treatment effect and instead introduce the preferences of Appraisal Committee A with regards to OS effect. Further, please add a note explaining that the ERG's preferred base-case should be considered as extremely pessimistic since the	The proposed amendments offer clarity with regards to the assumptions used in the ERG's preferred base-case versus those recently deemed preferable by the Appraisal Committee A within TA639 (as well as those within previous breast cancer submissions)(5). The proposed changes will also demonstrate that the impact on the cost-effectiveness estimates, is unlikely to be as extreme as the scenarios which assume waning at 3 or 5 years. This will offer a more balanced view on the impact of long-term effect on the C/E estimates for Pembrolizumab + taxanes in the NHS setting.	This is not a matter of factual inaccuracy. The ERG believes that the duration of relative treatment benefit for patients receiving pembrolizumab combination therapy is uncertain. In the opinion of the ERG, assuming a lifetime treatment effect for pembrolizumab represents a highly optimistic assumption, given the maximum treatment duration of approximately 2 years (35 doses). No evidence was submitted in the CS to support the assumption that the treatment effect for pembrolizumab persists beyond the observed period of the KEYNOTE-355 trial, which has a short median follow-up duration of 16.8 months (range 0. to 35.0) at the IA2 cut-off date (11Dec2019). In TA639 (Atezolizumab with nab-paclitaxel for treating PD-L1-positive, triple-negative, advanced breast cancer), the ERG report shows a similar discussion around this issue: limiting the duration of the treatment effect for atezolizumab plus nab-paclitaxel has been explored by the ERG (at 3 and 5 years), with the precedent of TA520 being mentioned (atezolizumab for treating locally advanced or metastatic NSCLC after chemotherapy, where the committee considered that *"the treatment effect was unlikely to last more than 5 years after*

The long term immunotherapeutic effect and the unique mode of action of IO agents which has been observed across different tumors with IO agents, whereby a % of patients are seen to experience durable responses (5). Our approach to model a life-time treatment effect with regards to OS, is consistent with the recent TA639 Appraisal Committee's preferences as well as with all prior Breast Cancer HTAs that have been reviewed by Appraisal Committee A. Assuming a HR=1 at any timepoint is completely arbitrary and lacks scientific rationale. This option was only included within the model as scenario analysis for consistency because it was explored previously as scenario analysis. Considering the limitations noted above as well as factoring in the Appraisal Committee's comments in TA639, we sought a pragmatic approach to estimate the impact of waning by conducting a SEER dataset analysis, which resulted in waning adjustments being made from Year 4 onwards. This	assumptions formulating it are contrast to those preferred by the AC A in TA639 (and all previous BC HTAs). To reflect the lack of relevant evidence with regards to treatment waning, please also present a scenario analyses using the SEER dataset to inform treatment waning, since this is based upon actual RWE data. This option demonstrates the impact of alternative assumptions, considering the lack of relevant evidence as noted by the AC previously in TA639, since an arbitrary assumption of OS HR=1 is not methodologically robust.		*treatment had stopped. It concluded that although it was biologically plausible for the treatment effect to continue after stopping treatment, the length of any continued effect was uncertain.").* The company argues that in the final appraisal document for TA639, (https://www.nice.org.uk/guidance/ta639/documents/final-appraisal-determination-document) the Committee *"concluded that incorporating an arbitrary treatment waning effect was not appropriate".* However, it should be noted that in TA639: (i) the time horizon used in the model was shorter than in the current appraisal (15 years versus 35 years), (ii) the committee also noted that in previous NICE appraisals limited treatment effect duration had been explored whilst a treatment stopping rule were also applied in the analyses, which was not the case of atezolizumab for TNBC (but it is the case for pembrolizumab in this appraisal), and (iii) even not agreeing with the inclusion of the assumption of a limited treatment effect, the appraisal committee acknowledged its duration is an area of uncertainty. The ERG agrees that the exact period of time to which the treatment benefit on PFS and OS is lost is unknown, although cites the precedent regularly used in NICE Technology Appraisal C and believes that it is unlikely that pembrolizumab would deliver a relative treatment benefit many years in the future. Sensitivity analyses have been conducted using alternative values for the time point at which the hazard for patients who had

demonstrates that when a more pragmatic approach to waning is used (as opposed to simple set up of HR =1.0), the impact on the C/E results is not as extreme as implicated by a cap of the effect at year 3 or at year 5. Due to the issues noted above, we ask that you provide additional context around the ERG's base case, noting that it deviates from the TA639 Appraisal Committee's preference with regards to the modelling of the OS, by arbitrarily introducing 5-year treatment waning against TA639 base-case assumptions. Further, this base case should be positioned as extremely pessimistic considering the arbitrary HR change implied. These changes will ensure a more balanced view on the potential impact of waning in the C/E results. References of the above are included within the ERG report on the following pages: 14, 115 and 121.			initially received pembrolizumab treatment is assumed equal to that of patients who had received taxanes. The ERG also notes that, as mentioned in TA639, many previous appraisals of immunotherapies (not only for breast cancer), the long-term benefit of new technologies on PFS and OS have been considered subject to uncertainty by the ERGs and the appraisal committees. Additional text has been added to state that this contrasts with the assumption made by Committee A in a previous appraisal.
On pages 76 of the ERG report, it is noted that the two-piece PFS models preferred in the company's	Within the ERG report, in page 72, the ERG re-iterates the company's approach accurately.	The proposed textual amendments add clarity to the process followed by the	The ERG has removed the word 'wrongly' from the text.

base-case may not be appropriate and that it was *"wrongly suggested by the company as these were not supported by the shape of the hazard function".* We wanted to add more clarity to the ERG that we did not use the smoothed hazard functions to identify potential turning points for PFS. Instead, this was based upon review of the log-cumulative hazard plots for IRC PFS. Clear inclination points can be seen where the PFS curves converge early on. The cutoff point of week 9 was specified based on a protocol-driven drop of PFS between weeks 8 and 9. This turning point is clearly shown in the KM curve and has strong clinical rationale as the first radiological tumor response assessment in KN355 was performed in week 8 (+/-1 week). Finally, two-piece models provide a much better fit against the observed data versus full piece models. On page 77, the ERG notes a minor inconsistency between the exponential BIC presented in Table 47 of the submission and the empirical hazard function in	Please update the wording in the relevant pages by removing the word *"wrongly"* to reflect that the two-piece PFS fitting provided is considered to be relevant for consideration, when considering the log-cumulative hazard plots of KEYNOTE-355. As noted previously, the two piece models improve fit to the observed data and is reflective of the methods outlined in the NICE DSU TSU 14(4).	company and provide further justification as why the two-piece PFS modelling may be more appropriate for cost-effectiveness modelling.	

response to the clarification question 4b. We have reviewed these table again and no inconsistencies have been identified. We welcome any further ERG input on this.			
On page 70 the ERG described the formal expert elicitation process conducted by the company during the submission stage. Further information was provided at the clarification response of question B6. We would like to take the opportunity to clarify that point survival estimates and ranges were derived, which are included within the main submission. Tables 45 and 46 represent expert opinion on the probability of mTNBC patients surviving up to that specific timepoint when treated with Pembrolizumab + taxanes or standard of care chemotherapies alone. The ranges of anticipated OS were provided and rationale on the choice of OS parametric survival curves was provided within the submission alongside an assessment of the most recent RWE evidence. Therefore, we disagree with the ERG's statement that "the fitted survival function should coincide with point estimates".	We ask that the ERG amends the relevant text to reflect upon the actual methods and processes used by the company within the main submission noting the assessment of RWE evidence in parallel with uncertainty around the clinical expert estimates provided. These changes will remove any ambiguity around the elicitation process.	These amendments offer a more balanced overview of the robust elicitation process followed by the company and offer further justification with regards to the OS modelling proposed in the base-case.	The ERG did not say that the fitted survival function should coincide with point estimates, rather, "It is not necessary that a fitted survival function should coincide with the experts' best estimates." Therefore, no amendments have been made to the text.

Issue 5 : Treatment discontinuation assumptions for Atezolizumab + nab-paclitaxel perceived as unfavourable

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG stated that the assumptions for Time to Treatment Discontinuation (TTD) pertaining to the Atezolizumab + nab-paclitaxel were overly unfavorable to Atezolizumab + nab-paclitaxel. Within the CS we noted the data limitations for this comparison, including the lack of relevant TTD data for modelling from the Impassion-130 CPS $\geq$ 10 score population. For this reason and based upon the Atezolizumab SmPC, we assumed a TTD equal to PFS since in IMpassion-130, atezolizumab treatment could continue beyond 2 years (in contrast to KEYNOTE-355 pembrolizumab component). An alternative scenario analysis was conducted that assumed Atezolumab + nab-paclitaxel TTD being equal to that of Pembrolizumab + taxanes, despite the fact that TTD data may not be deemed generalizable considering differences in RCT design and in patient population as well as the lack of further evidence to assess the validity of this assumption.	As we note in our original submission, the cost-effectiveness comparisons versus Atezolizumab + nab-paclitaxel are subject to a number of limitations which is why this was positioned as a secondary alternative comparator. Please update all relevant sections noting the limitations associated with the ERG's preferred assumptions with regards to the TTD of Atezolizumab + nab-paclitaxel, as well as the potential bias against Pembrolizumab + taxanes in the cost component of this comparison. We suggest the following wording to capture the limitations outlined: *"The application of a PFS HR on the TTD data is likely to bias against Pembrolizumab + taxanes when the totality of the evidence is being considered (RCT design and patient population), alongside the estimates of TTD reported within TA639.Therefore,*	The proposed amendments ensure the likely direction of bias which is against Pembrolizumab with regards to the cost-effectiveness results is clearly communicated to the AC. Therefore, additional context will eliminate the likelihood of misinterpreting the cost-effectiveness results for this comparison.	The ERG agrees that the lack of Time to Treatment Discontinuation (TTD) data from Impassion-130 CPS $\geq$ 10 score population limits the approach used for modelling treatment costs for Atezolizumab plus nab-paclitaxel. However, the assumption made by the company that patients receiving this treatment would only discontinue it upon disease progression or death, is considered to be highly favourable to pembrolizumab. Figure 18 in the ERG Report shows the TTD survival functions used in the model for all treatment options, where it can be seen that the probability of remaining on treatment for atezolizumab plus nab-paclitaxel after a year is significantly higher than for other treatment groups. This assumption together with the absence of a maximum

However, the ERG preferred an alternative method, whereby the PFS HR was applied on the TTD data of Pembrolizumab + taxanes. No formal evidence was provided to support the correlations between PFS and TTD. Further, due to lack of TTD data specific to the CPS 10 population from IMpassion-130, it is unclear whether further adjustments would be necessary. It is also worth noting that the ERG's preferred approach now introduces bias against Pembrolizumab + taxanes for the following reasons outlined below. This process artificially decreases the drug cost component of Atezolizumab + nab-paclitaxel, in contract to the Impassion-130 trial design, whereby Atezolizumab could be continued beyond 2 years. In addition, the inclusion of paclitaxel within KEYNOTE-355 as opposed to Impassion-130 (which only included nab-paclitaxel), would in reality be expected to result in lower TTD for Pembrolizumab + taxanes versus the anticipated TTD for Atezolizumab + nab-paclitaxel (since nab-paclitaxel is better tolerated than paclitaxel itself). Considering the methodological limitations of the ERG's alternative	*the cost-effectiveness results should be interpreted with caution"*		treatment duration rule leads to significant higher acquisition costs for the atezolizumab plus nab-paclitaxel treatment group. In the ERG preferred analysis, the TTD function for atezolizumab plus nab-paclitaxel is modelled by assuming there would be correlation between the ratios of PFS and TTD for pembrolizumab plus paclitaxel/nab-paclitaxel and atezolizumab plus nab-paclitaxel, and therefore, the HR for PFS generated by the company's NMA, based on data from KEYNOTE-355 and IMPassion-130, could be assumed generalisable to TTD. The ERG believes this its proposed approach is less biased than the company's assumption. Additional text has been added on p121 to state that it is not known whether this favours or disfavours pembrolizumab.

approach to TTD modelling for Atezolizumab + nab-paclitaxel, as well as the potential disadvantage against pembrolizumab + taxanes, we ask that the ERG communicates these limitations and the likely direction of bias (against pembrolizumab + taxanes) when it refers to cost-effectiveness results pertaining to this comparison References of the above are included within the ERG report on the following pages: 11, 12, 116 (& Figure 27) and 121.			

Issue 6 : Indirect treatment comparison clarifications.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG notes the uncertainty associated with regards to the ITC estimates surrounding the relative efficacy versus Atezolizumab + nab-paclitaxel (noted as issue 4). On page 50, the ERG also notes that NMA results using Random Effects models (REM) at the clarification stage and that these were considered to be "more realistic". We disagree that our original fixed effects NMA under-represented uncertainty (pages 50 & 70 of the ERG report) and that the REM was a	We propose that the ERG note the additional limitations associated with the REM NMA by introducing the following text in the relevant pages: *"In the absence of a sufficient number of studies relevant for the decision problem to inform study heterogeneity, this was based upon prior for heterogeneity derived from studies across a variety of disease areas and outcomes. Therefore, it is not known whether the actual heterogeneity between studies in the evidence base is greater or less than the heterogeneity of*	The proposed amendments add clarity around our justification not to use the REM in any of our analyses, whilst we provided it to the ERG for consideration. Pertaining to ASA5, highlighting the caveats and conflicting inconsistencies will increase transparency when these analyses may be reviewed by the AC . These clarifications will eliminate the likelihood of misinterpreting the of the cost-effectiveness results for	An informative prior distribution for the between-study standard deviation is *meant* to exert influence in sparse networks comprising few studies, otherwise it is not informative. The point of the work by Turner at al 2015 was to provide prior distributions to use in Bayesian meta-analyses such as this. The alternative of using a fixed effect model implies that it is

"more realistic model" (page 50 of the ERG report). As we already explained at the clarification stage, the absence of relevant studies to inform the REM meant that prior distribution for the between-study standard deviation were taken Turner at al 2015 as per the ERG's request (page 50). Since prior heterogeneity was derived from studies across a variety of disease areas and outcomes, as it is not known whether the actual heterogeneity between studies in the evidence base of interest is greater or less than the heterogeneity of studies used to estimate an informative prior. Additionally, as noted in our B.9 clarification response, informative priors can exert undue influence in sparse networks comprising few studies. Considering the above, the REM results should be interpreted with caution and therefore the FEM model still remains relevant for consideration. Therefore, we ask that the ERG reflect upon this across the relevant pages. References of the above are included within the ERG report on the following pages: 11, 15, 50, 53, 70, 117, 121,	*studies used to estimate an informative prior, and REM results may artificially inflate uncertainty when used in the PSA"* Further, please add more context around the potential limitations of the ASA 5 so that these are clearly communicated to the AC.	these comparisons and their impact on the cost-effectiveness results.	believed that the between-study standard deviation is zero with probability one. We fundamentally disagree that incorporating external information about the true value of the between-study standard deviation could result in an artificial inflation of uncertainty. Incorporating external information is fundamental to Bayesian statistics and Bayesian meta-analyses. The alternative of ignoring potential heterogeneity has the effect of artificially understating uncertainty. The additional exploratory analysis ASA5 conducted by the ERG, as detailed in the report, "*assumes that there is no relative difference on treatment effect between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel/nab-paclitaxel (HRs are assumed to be =1.0)."* Therefore, both HRs (for PFS and OS) were set to

Further, on page 117 it is noted that the company did not conduct a PSA using the REM. This was fully justified considering the limitations associated with the REM methodology (as outlined above) which could result in artificial inflation of uncertainty. We ask that the ERG provides an additional clarification point at the end of the relevant sentences to reflect this. As noted by the ERG, an exploratory analysis (ASA5) was conducted whereby the OS HR for Pembrolizumab + taxanes vs Atezolizumab + nab-paclitaxel is set to 1.0. We would like to take the opportunity to state that we do not agree with an overly simplistic assumption pertaining to the efficacy of atezolizumab + nab-paclitaxel being equal to that pembrolizumab plus paclitaxel / nab-paclitaxel as noted in ASA 5. Despite the limitations of the NMA, the availability of CPS $\geq$ 10 score data from IMpassion-130 means that the NMA itself could be conducted and should be considered across all scenarios presented by the ERG. Assuming otherwise even in exploratory scenarios, suggests the assumption of transferability of the KEYNOTE-355 directly to the Impassion-130 population, which is inappropriate			one, not only for OS. Since the start point of this analysis is the ERG preferred analysis (EA6), which includes modelling the TTD function for atezolizumab plus nab-paclitaxel by applying the HR for PFS to the TTD survival function for pembrolizumab plus paclitaxel/nab-paclitaxel, in ASA5 the TTD function for atezolizumab plus nab-paclitaxel is consequently the same as the TTD function for pembrolizumab plus paclitaxel/nab-paclitaxel. Additional sensitivity analyses were undertaken using the ERG's preferred models to explore the impact of further assumptions that might be relevant for the committee, including alternative assumptions around the duration of the clinical benefit of pembrolizumab (lifetime or 3 years), alternative models for OS and assuming clinical efficacy between the two treatment strategies which include immunotherapies: atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel/nab-paclitaxel.

considering the differences across RCTs and in patient populations. We would also like to point out a further inconsistency in the assumptions formulating ASA5 whereby, OS equivalence is assumed (NMA HR is not applied) whilst at the same time applying the HR PFS on the TTD as part of the assumptions underpinning ASA5. It should be noted that the application of a PFS HR onto the TTD data from Pembrolizumab + taxanes may be inappropriate. Considering methodological limitations and the inability to validate the assumptions put forward to combine this analysis, we ask that the ERG provide additional context with regards to the limitations of the ASA5 within the EG report. References of the above are included within the ERG report on the following pages: 15, 120 and 122.			However, in order to improve clarity, the text in page 122 has been amended to include: *"The ERG notes that the comparative efficacy between the two immunotherapy treatment strategies is associated with uncertainty. Setting the efficacy of both interventions equal to that of pembrolizumab plus paclitaxel/nab-paclitaxel has been explored, as this position was not ruled out in the NMA and these results may be informative to the Appraisal Committee. In this analysis only the treatment costs differ between the interventions."*

Issue 7 : Appropriate methods in utility estimation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG acknowledges the limitations associated with both utility methods. Within our submission, we outlined our preference to the Time to Death Utilities approach being used in the base-case. We did also provide a scenario analysis	We suggest the ERG consider amending the following statement from: "*No utility decrements …. and on treatment in KEYNOTE-355"* to:	The company suggests amending the wording around this statement to add clarity that AE related disutilities were indeed explored by	The section where the forementioned text belongs to relates to the assumptions employed in the company's base-case analysis. However, in order to improve clarity, the

using utilities derived by heath state. As we note in our submission, the TTD utilities did not include AE related disutility estimates to avoid over imposing additional assumptions on the data analysed, ensuring sufficient sample of questionnaires was retained to inform each time to death category. However, AE disutilities are intrinsically factored into the utility scores generated since some of the patients completing the EQ-5D could be experiencing AEs, therefore this method avoids the double counting of the AE disutility. Whilst the ERG offers a balanced view with regards to the utility analyses we ask that further minor clarifications are included in page 61 to specify explicitly that AE related disutilities are not included in the base-case since it uses the time to death approach for the reasons stated above and that a scenario analysis presented by the company (based on utility score per disease progression status) does factor the impact of AEs, although this may result in double counting of the disutilitues associated with AEs References of the above are included within the ERG report on the following pages: 61.	*"No utility decrements related to AEs are applied in the model;* ***using the Time to Death approach to avoid double counting;*** *…."*. Please also add the following statement at the end of the bullet point: "***Alternative methods explore the impact of AE related disutilities (using utilities by disease progression status), although this may result in double counting of disutilities associated with AEs"***	the Company as a scenario analysis.	text has been amended by the ERG to *"No utility decrements related to AEs are applied in the company's base-case analysis, which uses the time-to-death approach; these are assumed to be already captured on the mean utility values generated from EQ-5D data collected from patients event-free and on treatment in KEYNOTE-355.*[26]" Scenario analyses presented by the company are mentioned in pages 107-109 of the ERG report.

Issue 8 : Vial sharing inclusion for IV drugs

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states that vial sharing was not captured in the base-case and that "vial sharing is allowed for all IV drugs" or "model includes vial sharing for all IV drugs". This is factually partially incorrect, since the model intrinsically does not account for vial sharing for the Pembrolizumab and Atezolizumab comparators within the model, due to their flat dosing in terms of posology, therefore vial sharing is only assumed for the rest of the IV comparator drugs. Refences of this issue are included in the following pages of the ERG report: 11, 12, 16 (Issue 6 summary table), 17, 19, 87, 92, 114, 118, 119, 120, 122 to 125, 129, 131.	We propose the following amendments where references of this are being made throughout the ERG report (including tables and text) to add more clarity around this issue: *"The modelled base case did not include vial sharing for pembrolizumab or atezolizumab, however, vial sharing was assumed by the manufacturer for other IV chemotherapy drugs."* Or "Vial sharing is assumed by the manufacturer for all IV drugs with the exception of pembrolizumab and atezolizumab." We also propose the re-editing of Issue 6 table on page 16 to better reflect the above changes.	The company asks the ERG to reconsider amending the wording around this statement to add clarity around the assumptions of this since the impact of vial sharing may otherwise be misinterpreted by the AC, although we do acknowledge that the ERG correctly states the limited impact of this in the cost-effectiveness results.	The ERG agrees with the company and has amended the text in the report in line with the suggestion.

Issue 9 : Full incremental analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
As noted within our submission and in TA639, docetaxel not a relevant comparator since it is being used primarily at earlier stages of Breast Cancer and is also associated with a less favourable AE profile versus that of paclitaxel. The ERG acknowledges that paclitaxel was considered as the most relevant taxane comparator within TA639 as per AC preferences and clinical expert opinion (based on the points notes above; page 124). However, a full incremental analysis is presented by the ERG which can be misleading since paclitaxel and docetaxel cannot be assumed as fully interchangeable within this population. Refences of this issue are included in the following pages of the ERG report: 17, 101, 112, 125 and 132. Further, on page 124 the ERG report states: "*However, clinical advice to the ERG suggests that the majority of patients are treated with docetaxel rather than paclitaxel so the appropriateness of these results is unclear."*	Where references to a fully incremental analysis are being made, additional text should be added for context and to reflect the limitations of the fully incremental analyses in conjunction with discussion around the relevance of docetaxel being an appropriate comparator for this setting and the likelihood that the dominance versus paclitaxel is driven by the cost-effectiveness model itself and assumptions around the clinical equivalence between taxanes, which implies that the dominance may be artificial to some extent.. We propose the following wording to reflect this: *"Due to its more favourable AE profile, paclitaxel is considered the most relevant primary taxane comparator (as per TA639). Since docetaxel is used primarily in earlier* Breast Cancer (e*BC) it was not considered an appropriate comparator by the AC during TA639. This means that a fully incremental analysis may not be relevant for the purposes of decision making since it is caveated by a number of limitations."*	The proposed amendments eliminate the likelihood of misinterpretation of the cost-effectiveness analyses results and also add clarity to the ERG clinical expert statement around the appropriateness of paclitaxel as a comparator. As per clinical expert opinion sought by MSD in the submission development process, paclitaxel was confirmed to be the main taxane comparator. This is consistent withTA639 clinical expert opinion which noted that paclitaxel has a more favourable profile versus that of docetaxel and it would likely constitute the main taxane comparator. Further, docetaxel is used more frequently in eBC disease stages alongside other chemotherapeutic agents and therefore, it is unlikely to be used again in patients which have progressed following on treatment with docetaxel, concluding that paclitaxel was the most relevant taxane comparator.	This is not a matter of factual inaccuracy. Full incremental analyses are considered best-practice when there is more than one comparator being evaluated against a new technology. Nonetheless, the ERG also presents results separately for the pairwise comparison between pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel for all analysis to allow the committee to see the ICERs should paclitaxel be the most relevant comparator. We have amended the text on p124 to state the reasons why we have provided both full incremental analyses and pairwise analyses against paclitaxel which allows the committee to have ICERs for whichever is the chosen comparator.

We do not agree with the statement above as it is written currently. This is because it lacks the context from TA639 Appraisal Committee preferences around the primary taxane comparator (being that of paclitaxel). Further, clinical expert advice sought by MSD during the submission development process confirmed that paclitaxel was the primary taxane comparator used in the clinical settings. The company also wishes to offer more clarity to the ERG, that the results of the fully incremental analysis (QALY equivalence for paclitaxel and docetaxel) are likely to be driven by the cost-effectiveness model itself and assumptions around the equivalence between docetaxel and paclitaxel. Considering that docetaxel has a worse AE profile versus that of paclitaxel, it is unlikely that patients would receive the same LYs and QALY benefit as with paclitaxel, therefore, the dominance element is purely driven by this simplifying (but necessary) assumption. This means that a fully incremental analysis is not appropriate for presentation within the ERG report.	Further, we propose that the ERG amend the statement related to the clinical expert opinion sought (on page 124) to: *"However, clinical advice to the ERG suggests that the majority of patients are treated with docetaxel rather than paclitaxel –* ***this is in contract to the AC preferences and clinical expert opinion during TA639, which concluded that paclitaxel was the most relevant comparator."***	Due to the reasons noted above and based on prior AC preferences, we positioned docetaxel as an secondary alternative taxane comparator because it was included within the final scope. This means that references to fully incremental analyses may not be appropriate and instead, the results focus should be on pairwise cost-effectiveness as per our original submission.	

Issue 10 : Application of end-of-life criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The ERG states that the company's base case probabilistic analysis estimates for patients receiving a taxane alone the mean undiscounted life years per patient is 2.06 years (24.7 months) and therefore the short life expectancy criterion may not be met. However, this value is marginally above the 24-month restriction and our base case deterministic analysis estimate meets this criterion and additional evidence provided within the original submission demonstrates the poor survival with current SoC chemotherapies, which was also the conclusion of the Appraisal Committee during TA639. Our base case deterministic analysis estimates for patients receiving a taxane alone the mean life years per patient is 1.83 (22.0 months) which meets the short life expectancy criterion. The ERG also state that company's base case deterministic analysis estimates 2.56 life years (30.7 months) for atezolizumab plus nab-paclitaxel and therefore the short	We ask that the ERG report the discounted LY gained for all comparators using the recommended discount rate of 3.5%. Further, we ask that the ERG provide additional textual clarification pertaining to the additional clinical and RWE evidence provided within the HTA submission, which demonstrate that End of Life criteria are being met, as per the AC's conclusions during TA639. Upon considering the discounted LYs, our base case probabilistic analysis demonstrated that the mean life years per patient is 1.862 (22.3 months) for patients receiving a taxane alone therefore meeting the short life expectancy criterion. We propose that the following wording on Page 136 to reflect this: *"The company's base case probabilistic analysis estimates that for patients receiving a taxane alone that the mean life years per patient is* ***1.86 years (22.3 months)****, whereas for patient receiving pembrolizumab*	The guide to the methods of technology appraisal explicitly state that the same annual discount rate should be applied for both costs and health effects which is currently at 3.5%. The ERG provide undiscounted results for life years gained which is inconsistent with this recommendation. Furthermore, the other results reported (costs and QALYs) are discounted; hence, providing undiscounted results for life years gained is inconsistent. Additionally, Table 40 in the original submission supports that pembrolizumab in combination with taxanes meets the NICE end-of-life criteria. Based on the clinical trial data from [redacted] The estimated OS extension is greater	This is not a matter of factual inaccuracy. One of the authors is a member of a NICE Technology Appraisal Committee who states that it is routine practice for the NICE Committees to use undiscounted LYs when evaluating the End of Life Criteria. The ERG believes that this point can be raised by the company at the committee meeting in case of disagreement. No amendments have been made to the report.

life expectancy criterion would not be met in this scenario. We would like to highlight that the ERG reports undiscounted life years gained rather than discounted life years gained which is inconsistent with the recommendations in the guide to the methods of technology appraisal and the other results reported. Further, median OS from the KEYNOTE-355 SOC arm and RWE OS evidence provided within the original submission are not reported for consideration within the ERG report. This additional evidence provides further support that the current taxanes SoC is associated with short survival which is < 2 years. This assessment is consistent with the Appraisal Committee's conclusion for End of Life being met during TA639.	*plus a taxane this value is* ***4.004 years (an extension of life of over 2 years) with the recommended discount rate of 3.5%. Therefore, the NICE End of Life criteria appears to be met since the taxane SoC is associated with <2 years survival." This is also supported by median OS estimates from the SoC arm from KEYNOTE-355 as well as RWE estimates of OS provided by the company within the main submission. The assessment of short life expectancy under the current SoC is consistent with the Appraisal Committee's conclusions during TA639.***	than the minimum 3-month extension to life as observed directly from the RCT. Based in the RWE literature available, current chemotherapies are associated with median OS survival below 24 months. This means that the short life expectancy criterion is met. The conclusions of this assessment are in agreement to the Appraisal Committee's conclusions in TA639. Data pertaining to the end-of-life criteria are paramount for decision making purposes and the proposed changes would eliminate ambiguity around these criteria being met for the purposes of decision making.	

Issue 11 : Presentation of Atezolizumab + nab-paclitaxel ICERs

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
The footnote associated with EA3 is missing from tables 2 and 3 of the executive summary. As noted within the main submission cost effectiveness pairwise comparisons versus paclitaxel in Tables 38 and Tables 42, the ERG exploratory analysis 3 (EA3: TTD adjusted with the PFS HR), does not affect the CE results. This footnote should be added in all of the CE result stables to offer additional clarity when interpreting the CE results. This is reflected within the following pages of the ERG report: 18, 19, 120 (table 36), 124, 129.The ERG present results of the additional sensitivity analysis (ASA4 and ASA5) pertaining to Atezolizumab plus nab-paclitaxel in tables where this is not the comparator stated in the table heading. Specifically: Table 2 page 18, Table 3 page 19, Table 40 page 128, Table 44 page 134. The presentation of the additional sensitivity analysis in these tables is redundant as the results are the same as the base case results since these additional sensitivity analyses	We suggest that the additional sensitivity analysis (ASA4 and ASA5) for atezolizumab plus nab-paclitaxel results are removed where this comparator is not the one being presented as per the table heading. Please add the relevant footnote noting that EA3 only affects the comparisons versus Atezolizumab + nab-paclitaxel per se, as noted in footnotes of the Tables 38 and 42 of the ERG report. Since this formulates the ERG's preferred base-case it should be clear that the CE results versus the primary chemotherapy comparator (paclitaxel), are not impacted by this. The above change should be implemented in each of the tables presenting results of the EA3 on pages; 18,19, 124 and 129.	The cost-effectiveness results tables are currently very crowded. The proposed amendments will aid the AC to interpret the CE results. We suggest that these are removed for clarity since presentation of these results have no effect as they do not change the ICER of the comparator in question.	We have removed the analyses which do not impact on the results and highlighted these in a footnote.

are not relevant for the stated comparator.			

Issue 12 : Incorrect cost-effectiveness results for ASA3b

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG Response</th></tr>
<tr>
<td>In Table 43 on page 133, there is an incorrect ICER result for the ERG's additional sensitivity analysis 3b – loss of treatment benefit after 3 years</td>
<td>The changes to be made to that section of the table have been noted in red
<table>
<tr><th>Option</th><th>LYGs*</th><th>QALYs</th><th>Costs</th><th>Inc. LYGs*</th><th>Inc. QALYs</th><th>Inc. costs</th><th>ICER (per QALY gained)</th></tr>
<tr><td colspan="8">ERG additional sensitivity analysis 3b – Loss of treatment benefit after 3 years</td></tr>
<tr><td>Docetaxel</td><td>1.55</td><td>****</td><td>[redacted]</td><td>-</td><td>-</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Paclitaxel</td><td>1.55</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>-</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Pembrolizumab plus paclitaxel/nab-paclitaxel</td><td>2.38</td><td>[redacted]</td><td>[redacted]</td><td>0.82</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Atezolizumab plus nab-paclitaxel</td><td>1.78</td><td>[redacted]</td><td>[redacted]</td><td>-</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>The company notes this typographical error resulting in an incorrect ICER result and requests amendment for factual accuracy.</td>
<td>The ERG apologises for the typo. It has been corrected in Table 43 and also in Table 2 and the text in page 133.</td>
</tr>
</table>

Missing or Incorrect marking

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG Response
Page 24, 1st paragraph.	The CS explains this difference as being due to the population	The CS explains this difference [redacted]	The ERG has added the AiC marking as

	addressed in the CS reflecting the draft licence indication wording	*Makes reference to draft licence wording which is not yet in the public domain.*	suggested by the company.

Further Textual clarifications or other minor amendments

Location of textual clarification	Description of typographical error	Suggested amendment	ERG Response
Page 41, figure 2	PFS Kaplan-Meier survival functions based on BICR assessment per RECIST 1.1 - **CPS ≥1**	Should be CPS ≥10. *PFS Kaplan-Meier survival functions based on BICR assessment per RECIST 1.1 - CPS ≥10*	This was a typo and it has been amended by the ERG as suggested by the company.
Page 22 (last paragraph)	gemcitabine, capecitabine, or **vinorlebine**	Spelling error of Vinorelbine	This typo has been fixed by the ERG. A similar misspelling has also been fixed in page 26 of the ERG report.
Page 57 – paclitaxel and taxanes being used interchangeably within the original submission and the model. Please see more	NA: This is the case because we wanted to highlight that the paclitaxel standard of care comparator arm leveraged the efficacy data from both nab-paclitaxel and paclitaxel (taxanes). When paclitaxel (or docetaxel) was explicitly used was to note the differences in the cost-component of the SOC arm.	NA: We hope this provides more clarity to the ERG.	No action required.
Page 62 - OS – paclitaxel	Lognormal is stated as the distribution fitted to observed comparator‡ group OS data. This is incorrect.	Log-logistic was used for the Taxane OS comparator arm.	This was a typo and it has been fixed by the ERG.

Page 117 (second paragraph)	the comparison that uses the **polled** taxanes	Spelling error of pooled	This was a typo and it has been fixed by the ERG.

References

1. Networks. NWCSC. Chemotherapy protocol - Weekly paclitaxel 2016 [30th March 2021]. Available from: https://www.healthierlsc.co.uk/application/files/4215/1810/1055/Paclitaxel_weekly_breast_v16.pdf.
2. Trust. TCCCNF. Systemic Anti Cancer Treatment Protocol - Paclitaxel Weekly Advanced Breast Cancer 2018 [30th March 2021]. Available from: https://www.clatterbridgecc.nhs.uk/application/files/3315/3555/1546/Paclitaxel_Weekly_Advanced_Breast_Cancer_Protocol_V1.0.pdf.
3. Trust. RSNF. Chemotherapy Policies and Protocols [30th March 2021]. Available from: https://www.royalsurrey.nhs.uk/chemotherapy-policies-and-protocols?smbfolder=525.
4. Latimer N. TSD 14: SURVIVAL ANALYSIS FOR ECONOMIC EVALUATIONS ALONGSIDE CLINICAL TRIALS - EXTRAPOLATION WITH PATIENT-LEVEL DATA 2013.
5. NICE. Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer Technology appraisal guidance [TA639] Appraisal consultation committee papers 2020 [30th March 2021]. Available from: https://www.nice.org.uk/guidance/ta639/evidence/appraisal-consultation-committee-papers-pdf-8776324045.
6. NICE. Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer Technology appraisal guidance [TA639] Final appraisal determination committee papers 2020 [30th March 2021]. Available from: https://www.nice.org.uk/guidance/ta639/evidence/final-appraisal-determination-committee-papers-pdf-8776324046.

Technical engagement response form

Pembrolizumab in combination for untreated, locally recurrent inoperable or metastatic, triple negative breast cancer [ID1546]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Friday 10 December 2021.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

About you

Table 1 About you

Your name	[redacted]
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**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Potentially favourable extrapolation of overall survival	Yes	The ERG disagrees with the parametric curves selected by the company to model overall survival (OS) and suggests that Weibull may be more appropriate , with exponential tested in exploratory sensitivity analysis. **MSD would like to take this opportunity to present the final analysis (FA) data set from KEYNOTE-355. We report the FA OS data from the study and have updated the survival analyses in the model. Repeating the curve/extrapolation approach with the FA OS data indicates that the most appropriate extrapolations/parameterisations are log-normal for the pembrolizumab + taxanes arm and log-logistic for the taxanes arm. This is consistent with the extrapolations used to model OS in the original submission. Additional plausible scenarios exploring the impact of survival extrapolations on the ICER are also presented for consideration by the Appraisal Committee (AC).** **Updated clinical evidence:** The data submitted in the original dossier in January 2021 had a data cutoff of 11th of December 2019. The final analysis (FA) for KEYNOTE-355, with a data cutoff of 15th of June 2021 is provided in the Appendix. The median follow up with the FA data set is [redacted]) months for the pembrolizumab and placebo arm, respectively. Median follow-up was defined as time from randomisation to the date of death or the database cutoff if the subject was alive.

These data support the continued Progression Free Survival (PFS) and Overall Survival (OS) benefit of pembrolizumab in combination with taxanes. The FA HR for PFS at was [redacted] The HR OS was 0.54 (95% CI: 0.36, 0.82). These results suggest a consistent clinically meaningful and statistically significant benefit for pembrolizumab + taxanes versus taxanes alone in this population for both PFS and OS endpoints.

Updated survival analysis + parametric extrapolations:

The survival analyses and parametric curve selection for OS and PFS was updated using the FA dataset from KEYNOTE-355. The NICE TSD DSU14 was used to guide selection of the most appropriate parametric models for survival extrapolations. The process included; assessment of goodness of fit statistics (AIC/BIC), clinical plausibility of long term extrapolations, and validity of long term projections.

Visual inspection and assessment based on the AIC/BIC goodness of fit statistics (Table 1) supports the selection of one-piece log-normal model for pembro + taxanes (2nd best model), followed by one-piece log-logistic (3rd best). The exponential model is not appropriate. The AIC/BIC statistic is 0.01 smaller compared with the preferred log-normal (a non-meaningful difference). The exponential function itself is simplistic and underpinned by a strong assumption of constant hazard which is not observed in the trial data.

For taxanes alone, log-logistic remained the best fitting model followed by log-normal (2nd best). Clinical experts suggested that the hazard of OS for both pembro + taxanes and taxanes alone is likely to decrease after 3 years. This trend has been observed at the latest KM curves as well as the cumulative hazard plot from the final analysis. Therefore, the models for both treatments capture the change of hazard over time which is reflective of the clinical expert opinion received by UK healthcare professionals.

Consistency in parametric survival selections:

The OS parametric curve selection with the additional follow up period time remains consistent with those selected based using the IA2 database lock which was included in the original submission. The additional data at follow up clearly demonstrate the robustness of the original curves selected to inform the base-case.

Table 1: AIC/BIC statistics – goodness of it on the observed data

	Pembrolizumab + taxanes	Taxanes comparator

Parametric distribution for OS	AIC	BIC	AVRG	Rank	AIC	BIC	AVRG	Rank
Exponential	759.61	762.18	760.89	1	440.33	442.18	441.25	4
Weibull	759.80	764.93	762.36	5	441.05	444.75	442.90	6
Log-normal	**758.34**	**763.47**	**760.90**	**2**	436.06	439.76	437.91	2
Log-logistic	758.45	763.58	761.02	3	**435.79**	**439.49**	**437.64**	**1**
Gompertz	761.17	766.30	763.74	6	442.26	445.96	444.11	7
Gamma*	759.31	764.44	761.88	4	439.97	443.67	441.82	5
Generalized Gamma	759.91	767.60	763.76	7	437.97	443.53	440.75	3

Abbreviations: AIC: Akaike Information Criteria, BIC: Bayesian Information Criteria; AVRG: Average, Ranking is based on the average AIC/BIC statistic. *Gamma not included in the model functionality due to the limitations outlined in the clarification questions. Note: green indicates MSD's base case curve selections, blue indicates alternative plausible curve selections and red indicates ERG curve selections.

Updated hazard plots do not support the Weibull or exponential models:

In page 70 of the ERG report it is stated that *"The empirical hazard function for the placebo plus taxanes group (replicated in Figure 7) also suggests a linear increase in the risk of death over the first 150 weeks with the rate of change being greater than in the pembrolizumab plus taxanes group."* Updated smooth hazard plots are presented below using the latest clinical data, for pembrolizumab + taxanes (Figure 1) and for taxane chemotherapies (Figure 2). Whilst a minor increasing trend was observed in an earlier DBL (IA2) as noted by the ERG, this is no longer the case for pembrolizumab + taxanes where it appears that the smooth hazard (shows the evolution of hazard over time) has now stabilised (although we caution against overinterpretation of these graphs). For taxanes alone, the smoothed hazard plot decreases from week 100 onwards.

Figure 1: Hazard plot of OS for pembrolizumab + taxanes from KEYNOTE-355

Figure 2: Hazard plot of OS for taxanes arm in KEYNOTE-355

Weibull or exponential survival extrapolations, additional limitations of these curves

The justification to select Weibull in the ERGs preferred base case is that it was an appraisal committee's preference for the OS extrapolation of Atezolizumab + nab-paclitaxel. This is not sufficient to justify choice of the Weibull curve. As outlined in NICE DSU TSD14 model selection is dependent upon an algorithm applied to specific clinical data from the pivotal study itself, visual inspection and plausibility of long-term projections based on clinical expert opinion in consideration and not based upon prior precedence.

The choice of the Weibull curve is inconsistent with the NICE DSU TSD14 model selection process:

- It does not take into account the number of differences reported in terms of the patient population between IMpassion-130 and KEYNOTE-355.

- Visual inspection of the survival curves versus the KM data demonstrates that the Weibull distribution continues to have the worst fit on the pembrolizumab + taxanes arm since it overpredicts for part of the observed period versus the company's preferred model. This overprediction is even more pronounced the in the taxanes treatment arm. The poor fit of Weibull versus the observed data is clearly apparent when comparing the AIC/BIC statistics (Table 1).

- The Weibull model ranks 5th for pembrolizumab + taxanes and 6th for taxanes alone based on AIC/BIC goodness-of-fit statistics. The smoothed hazard plots demonstrate that the long-term hazard function of the Weibull distribution is monotonically increasing and sits above the empirical hazard function during the study follow up for both pembrolizumab + taxanes and the taxanes comparator arm. This highlights the conservatism of this selection and is in contrast to the ERG's comment in page 69 of the ERG report noting that the Weibull was the "likely most appropriate distribution over the observed period".

		A quick validation of the anticipated survival outcomes on the taxane comparator arm shows that using Weibull results in a 0.60% survival at year 8, when the RWE evidence suggests this to be in the range of 3.49%. It should also be noted that Weibull predicts worse long-term survival than exponential for taxanes alone (see Figure 3 and Figure 4 below). This evidence demonstrates that the Weibull function is not appropriate for extrapolation of neither for pembrolizumab + taxanes and nor for the taxanes comparator arm. Therefore, based on this evidence, the choice of the Weibull distribution is not justified by either the clinical data or the by long term external data sources and it does not lead in clinically plausible long-term projections. Therefore, it should not be a preferred base case. The ERG choses the exponential model as an alternative extrapolation curve for OS. This is based upon constant hazards which is an overly simplistic assumption. The exponential curve does not fit the data well particularly for modelling OS in the taxanes arm whereby extrapolated OS falls outside the 95% KM- CIs for part of the observed period early on, which is also supported by the smooth hazard functions. It also results in pessimistic projections for the taxanes comparators arm versus RWE evidence although not as extensively as with Weibull (see Figure 4 below). MSD does not believe that the exponential can be used to inform decision making, however, we do explore its impact in alternative analyses presented below (Table 2). **Figure 3: ERG preferred (EA6) modelled OS vs. observed OS – pembrolizumab + taxanes and taxanes arm Weibull distribution**  Figure 3 above demonstrates the poor fit of the modelled taxanes OS with Weibull distribution to the observed OS from KEYNOTE-355 and the RWE validation sources. **Figure 4: ERG alternative (ASA1) modelled OS vs. observed OS – pembrolizumab + taxanes and taxanes arm exponential distribution** 

		Figure 4 above demonstrates the poor fit of the modelled taxanes OS with exponential distribution to the observed OS and the RWE validation sources; however, this fits better than the Weibull distribution both for the part of observed OS from KEYNOTE-355 and at later timepoints using external data sources. **Figure 5: Company preferred modelled OS vs. observed OS – pembrolizumab + taxanes log-normal distribution and taxanes arm log-logistic distribution**  Figure 5 above demonstrates the good fit of the modelled taxanes OS with log-logistic distribution to the observed OS and the external RWE validation sources as per our preferred base case which is supported by the latest survival analysis. **Impact of alternative plausible extrapolations of OS vs ERG's preferred analyses** The ERG preferred base-case (EA6) uses Weibull whereas the additional sensitivity analysis 1 (ASA1) uses exponential for OS extrapolation across both treatment arms. MSD does not consider the ERG's preferred survival extrapolations to be sufficiently justified. This is particularly the case for Weibull whereby the ERG argue that the hazard monotonically increases over time based on the plots presented above (1). MSD recognises that the ERG's ASA1 (using exponential across both arms) may be relevant for discussion despite the very strong over-simplistic assumption of constant hazards for pembrolizumab + taxanes and the continued discrepancy in the long-term survival projections for the taxanes arm compared with RWE studies. The impact of applying exponential is presented in additional scenarios below alongside some alternative, clinically plausible scenarios. Please note that the incorporation of the latest clinical data (plus the updated NMA results) from KEYNOTE-355 into the economic model has led to increase in the original base case versus paclitaxel from £27,808/QALY to £34,887/QALY. We have also presented the updated C/E results for all the scenarios included within the original submission – see Appendix 4 below. These results demonstrate that when plausible OS extrapolation scenarios

are considered the ICER ranges from £31,605 to £50,828 per QALY (*note the highest ICER in this range includes a model that underpredicts OS survival for pembrolizumab + taxanes; equal to that of long-term chemotherapy RWE datasets; considered highly conservative)*. An alternative scenario is presented by MSD using the combined alternative 3rd best OS curve for pembrolizumab + taxanes and 2nd best OS curve for taxanes which represents a more appropriate alternative curve selection where the resultant ICER estimate was £33,731. The analyses run by MSD in totality quantify the impact of alternative OS extrapolations on the ICER where all ICERs generated using clinically plausible approaches remain below £50,000 per QALY gained.

Table 2: Impact of alternative extrapolations on the ICERs presented

Scenarios (versus paclitaxel)	ICER per QALY
Original ICER versus paclitaxel (using IA2 dataset): Uses log-normal (Pembrolizumab + taxanes) vs log-logistic (Taxanes)	£27,808
Updated ICER versus paclitaxel (using FA dataset): Uses log-normal (Pembrolizumab + taxanes) vs log-logistic (Taxanes)	£34,887
Scenario A: Recreation of ASA1 with exponential distribution OS for both arms, PFS 2-piece company preferred optimised extrapolations, lifetime benefit	£43,738
Scenario B: Recreation of ASA1 with exponential distribution OS for both arms, PFS full-piece company preferred optimised extrapolations, lifetime benefit	£43,710
Scenario C: Combined 3rd best OS curve for Pembro + Taxanes (log-logistic) & 2nd best OS curve for Taxanes comparator (log-normal)	£33,731

To conclude, from the updated clinical data there is no evidence to support the use of Weibull or exponential for OS extrapolations. Having explored alternative scenarios MSD is confident that when plausible curves are selected for OS extrapolations, the ICER versus taxanes remains within the threshold considered cost-effective by NICE for approval under the End of Life (EoL) criteria. Appendix 4 below presents additional scenarios around the updated base case with additional OS extrapolations for discussion.

Issue 2: Uncertainty surrounding the long-term benefits of pembrolizumab plus paclitaxel/nab-paclitaxel	Yes	The ERG disagrees with regards to the longevity of the treatment effect for pembrolizumab + taxanes and instead imposes a 5-year treatment effect cap in its preferred base-case. **Based on updated clinical trial data from KEYNOTE-355 there is no evidence of treatment waning. MSD disagrees with the application of treatment waning and considers the 'prior precedent' justification to be a weak, in the absence of any data indicating there is a loss of treatment effect.** With the latest DBL from KEYNOTE-355 (median follow up of 23.2 (range: 0.8- 52.6) and 16.1 (range: 0.3-53.1) months for the pembrolizumab and placebo arm, respectively), the clinical benefit remains consistent for both PFS and OS. The FA HR for PFS was [redacted] The FA HR OS was [redacted] Whilst KEYNOTE-355 included a maximum treatment with Pembrolizumab for 35 cycles (or ~ 2 years), 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 been observed consistently across a number of tumours whereby a small subset of patients experiences long term survival benefit, which clinical experts expect to observe in mTNBC also (2). Therefore, there is no evidence to point towards a waning assumption being relevant for inclusion in the ERG's base-case. We are aware that Appraisal Committee A discussed the impact of waning in the recent TA639 (Atezolizumab + nab-paclitaxel). However, it concluded that whilst waning assumptions are an area of uncertainty, incorporation of an arbitrary treatment waning was inappropriate (3). The AC-A remained consistent with its preferred assumptions around treatment duration from previous breast cancer submissions do not consider any waning of treatment effect for inclusion in the base-case. The long-term immunotherapeutic effect and the unique mode of action of IO agents which has been observed across different tumours with IO agents, whereby clinical expert opinion suggests [redacted] of patients will survive at 10 years with pembrolizumab + taxanes, these are expected to be long-term survivors (3). Our approach to model a life-time treatment effect with regards to OS, is consistent with the recent TA639 Appraisal Committee's preferences as well as with all prior breast cancer HTAs that have been reviewed by Appraisal Committee A.

Regardless of the limitations highlighted above, arising from the lack of clinical data to justify such assumptions proposed by the ERG, MSD explored the impact of waning as a scenario analysis within the original submission. In brief, a pragmatic approach was used to estimate the impact of waning by conducting a SEER dataset analysis, which resulted in gradual waning adjustments being made from year 4 onwards. Please note that within the original submission we have explained the methodology around the SEER analyses and the justification for the 4-year timepoint is data driven based on the SEER data which do not fully reflect recent changes in the metastatic treatment pathway. Based on the KEYNOTE-355 maximum follow up (53 months), we consider the application of gradual waning at 4 years a conservative assumption which potentially biases against pembrolizumab + taxanes, in reality if any waning takes place this would have limited impact on the ICER.

Alternative methodology to incorporate waning is applied by setting the OS hazard rate of pembrolizumab + taxanes equal to the OS hazard rate of the taxanes arm after year 5. It should be noted that this scenario is artificial and not based upon clinical evidence; it is highly unlikely for all OS benefit to be lost at year 5 in the real-world setting.

The more appropriate approach for treatment waning using SEER shows a limited impact on the ICER compared with the more abrupt scenario of waning at specific timepoint. **Plausible OS extrapolations alongside scenarios caping the long-term benefit for pembro + taxanes still result in estimated ICERs under the EoL threshold – see Table 3 below. The treatment waning approach using the SEER data shows a limited impact on the ICER compared with the scenario of waning at specific timepoint (year 5 explored).**

Table 3: Impact of waning on the ICERs presented

Scenarios	**ICER / QALY vs paclitaxel**
Company original base-case no waning	£27,808
Original company base-case + 5 years waning	£34,096

<table>
<tr><td></td><td></td><td><table>
<tr><td>Updated company base-case (PFS for taxanes arm and ToT for pembrolizumab + taxanes arm changed) + 5 years waning</td><td>£39,531</td></tr>
<tr><td>Updated company base-case (PFS for taxanes arm and ToT for pembrolizumab + taxanes arm changed) + SEER waning for all arms at year 4</td><td>£31,605</td></tr>
<tr><td>Scenario A: 3rd best parametric selection for Pembro + taxanes OS (log-logistic) + 5 years waning</td><td>£40,596</td></tr>
<tr><td>Scenario B: 3rd best parametric selection for Pembro + taxanes OS (log-logistic) + SEER waning</td><td>£32,388</td></tr>
<tr><td>Scenario C: 2nd best parametric selection for Taxane OS (log-normal) + 5 years waning</td><td>£44,714</td></tr>
<tr><td>Scenario D: 2nd best parametric selection for Taxane OS (log-normal) + SEER waning</td><td>£32,531</td></tr>
<tr><td colspan="2">Note: Please see Appendix 4 for scenario analysis against the secondary comparator atezolizumab + nab-paclitaxel including waning scenarios.</td></tr>
</table></td></tr>
<tr><td>Issue 3: Unfavourable assumption regarding treatment discontinuation for atezolizumab plus nab-paclitaxel</td><td>No</td><td>The ERG disagrees with regards to assumptions pertaining to the time to treatment discontinuation (TTD) for atezolizumab + nab-paclitaxel, noting that these bias against pembrolizumab + taxanes.

MSD’s original base-case assumptions assume that the TTD for atezolizumab + nab-paclitaxel is equal to PFS for atezolizumab + nab-paclitaxel due to lack of specific data for the subgroup of interest, Impassion-130 CPS ≥ 10 score population. For this reason this comparator is positioned as secondary within the submission. The ERG proposes the PFS HR for pembrolizumab + taxanes is applied to atezolizumab + nab-paclitaxel TTD.

In the original submission we noted the data limitations pertaining to the comparison versus Atezolizumab + nab-paclitaxel, including the lack of relevant TTD data for modelling from the Impassion-130 CPS ≥ 10 score population. For this reason and based upon the Atezolizumab SmPC, we assumed a TTD equal to the PFS projections since in IMpassion-130, atezolizumab treatment could continue beyond 2 years, in contrast to KEYNOTE-355 RCT whereby pembrolizumab is capped at 35 cycles.

An alternative scenario analysis was conducted that assumed Atezolizumab + nab-paclitaxel TTD being equal to that of Pembrolizumab + taxanes. We now revise the base case to use this assumption, despite the fact that TTD data may not be generalisable considering differences in RCT design and in patient population as well as the lack of further evidence to assess the validity of this assumption.</td></tr>
</table>

		The ERG's preferred assumptions around TTD for Atezolizumab + nab-paclitaxel, are very likely introducing bias against Pembrolizumab + taxanes since this results in an artificial decrease of the drug cost component of Atezolizumab + nab-paclitaxel, in contrast to the Impassion-130 trial design and the inclusion of nab-paclitaxel alone in Impassion-130 could in reality be expected to result in higher TTD for Atezolizumab + nab-paclitaxel (since nab-paclitaxel is better tolerated than paclitaxel itself). Further evidence to the ERG's conservatism around the TTD for Atezolizumab + nab-paclitaxel can be sourced from the TA639 Company submission documents (Table 48 for Atezolizumab and Table 49 for nab-paclitaxel). 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 new 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 model a lower TTD for atezolizumab + nab-paclitaxel. **MSD disagrees with the ERG's alternative preferred assumption for this comparison to apply the HR of PFS from the NMA to the TTD model of Pembrolizumab + Taxanes from KEYNOTE-355. The ERG's preferred approach is very likely to bias against Pembrolizumab + taxanes and no formal evidence has been presented to justify this. MSD previously formulated a base-case with TTD for Atezolizumab + nab-paclitaxel being equal to projected PFS for Atezolizumab + nab-paclitaxel; however, we now revise this base case TTD for Atezolizumab + nab-paclitaxel being equal to TTD for Pembrolizumab + Taxanes. We cannot justify using TTD for a treatment with a stopping rule (pembrolizumab + taxanes) applied to a treatment without a stopping rule (atezolizumab + nab-paclitaxel); however, with no other data source the atezolizumab + nab-paclitaxel TTD estimates are more closely aligned with those reported in TA639.** MSD has updated base-case assumption using the TTD for Atezolizumab + nab-paclitaxel equal to that of Pembrolizumab + taxanes based on the above evidence (see Appendix 4). The results (using list prices for comparators) show that pembrolizumab + taxanes remains dominant. This evidence suggests that the ERG's preferred assumption which applies the PFS HR onto the Pembrolizumab + taxanes TTD biases against Pembrolizumab + taxanes, therefore disadvantaging Pembrolizumab in this comparison it should not be considered further**. Instead, we have demonstrated that**

		our updated approach is more robust given the current limitations and we ask that the AC considers this as more relevant for discussion in the ACM.
Issue 4: Uncertainty surrounding the relative efficacy comparison of pembrolizumab plus paclitaxel/nab-paclitaxel versus atezolizumab plus nab-paclitaxel	Yes	The ERG notes the uncertainty associated with regards to the ITC estimates surrounding the relative efficacy versus Atezolizumab + nab-paclitaxel. Whilst the ERG retained the NMA to inform the relative efficacy of Pembrolizumab + taxanes versus Atezolizumab + nab-paclitaxel, a scenario analysis explores the impact on the C/E results by assuming no difference between the two agents based on the wide 95% Credible Intervals generated from the NMA which crossing the line of no difference. **MSD raised at multiple occasions during the HTA process some key differences between the two studies (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 (CPS10 score ≥ 10) Considering these limitations, we positioned Atezolizumab +nab-paclitaxel as a secondary alternative IO comparator. Despite the ITC limitations MSD believes that the most appropriate way to infer the C/E estimate for this secondary IO comparator is by incorporating the NMA into the economic model. This is necessary to generate the relative treatment effect for the PD-L1+ve CPS10 score ≥ 10 population, all relevant evidence needs to be considered.** Considering the availability of the final DBL from KEYNOTE-355, an update of the original NMA was conducted and is presented below in Appendix 2. The updated NMA results remain consistent with the earlier NMA results presented in the main submission and continue [redacted] pembrolizumab + taxanes versus Atezo + nab-paclitaxel for both OS 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]. MSD understands there may be some uncertainty around the HR point estimates but welcomes the ERG's position to maintain the NMA results in the base-case for the comparisons of interest. However, MSD disagrees with the scenarios exploring equivalence between the two agents for decision making and in particular that of ASA5. This is an overly simplistic assumption pertaining to the efficacy of atezolizumab + nab-paclitaxel being equal to that pembrolizumab plus paclitaxel / nab-paclitaxel. Despite the limitations of the NMA, the availability of CPS ≥ 10 score data from IMpassion-130 means that the NMA itself can be conducted as outlined in the NICE DSU methods and should therefore be considered across

		all scenarios presented by the ERG pertaining to this comparison. Assuming otherwise even in exploratory analysis, suggests the assumption of transferability of the KEYNOTE-355 directly to the Impassion-130 population. This is inappropriate considering the differences in the clinical trial designs and the patient populations in the two studies. We would also like to take the opportunity to point out a further inconsistency with the assumptions formulating the ERG's ASA5 which explored the equivalence between two agents, whereby, OS equivalence is assumed (NMA HR is not applied) but at the same time the NMA is considered robust enough to inform adjustments on TTD on Atezolizumab + nab-paclitaxel by applying the PFS HR on the TTD data from Pembrolizumab + taxanes. **Whilst the ITC has some limitations, the updated NMA results remain consistent to those presented in the original submission. This increases the confidence around the point estimates generated from the NMA for Pembro + taxanes versus Atezolizumab + nab-paclitaxel which is positioned as a secondary alternative IO comparator within the submission. MSD therefore believes that the NMA remains relevant for informing the relative treatment effects for this comparison.**
Issue 5: Uncertainty related to the most appropriate way to estimate utility	No	The ERG comments that there is uncertainty related to whether using a time-to-death-based approach for estimating utility is preferential to a health state-based approach; however, it states that neither approach overcomes the main limitation of the data collected being heavily censored either at the point of progression or at treatment discontinuation. **MSD does not have a preference for the utility estimation approach; however, we believe the time-to-death approach is the most appropriate based on the severity of this disease and other reasons outlined below.** As discussed in our submission, the time-to-death-based approach was used in the base-case to overcome the issue of limited questionnaire availability to inform the post-progression health state utility. This method also captures the expected deterioration in patient's quality of life as they reach the terminal phase of their disease. Furthermore, it has been deemed acceptable for decision making by NICE previously for several recent HTA submissions including NSCLC, SCLC, RCC and Melanoma (4-8); hence, is used in the base-case as it was considered more robust for decision making purposes.

		A scenario analysis using utilities derived based on disease progression status is also explored to reflect the alternative approach. This has limited impact on the ICER with an increase of £718 on the base case (£34,887 base-case using time-to-death-based approach versus £35,605 using utilities by progression status & AEs). **Based on the limitations of both approaches, we advocate for the use of the time-to-death-based utility estimation approach based on the aggressiveness of TNBC and the use and acceptance of this approach for other recent HTA submissions.**
Issue 6: Inclusion of vial sharing for IV drugs (with the exception of pembrolizumab and atezolizumab)	No	The ERG has removed vial sharing assumptions for chemotherapies other than Pembrolizumab and Atezolizumab. **MSD understands that in order to maximise value in the clinical care setting, vial sharing is routine for chemotherapies which are not flat dosed (nab-paclitaxel, paclitaxel and subsequent chemotherapies). Particularly as several of these standard chemotherapies are used for the treatment of other cancers. Vial sharing has not been assumed for pembrolizumab and atezolizumab which use flat dosing therefore the impact of this assumption is likely to be very limited as demonstrated by the ERG.** With the revised base-case ICER based using the final DBL, the impact of assuming no vial sharing (with the exception of pembrolizumab and atezolizumab) increases the ICER by £1,350 (base-case ICER £34,887 with vial sharing vs. £36,237 without vial sharing). As presented above and noted by the ERG, the limited impact on the ICER is due to the fact that the economic analysis already does not assume vial sharing for Pembrolizumab and Atezolizumab, which constitute the key drug cost elements in the economic evaluation. Considering that some scheduled appointments may overlap in the real-world setting with use of standard chemotherapies for other cancers, some vial sharing for chemotherapies that do not require flat dosing may still take place potentially to limit wastage, which means that the true ICER is likely to lie between the estimates presented with and without vial sharing.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Fully incremental analysis	Section 4.4, page 129	No	As noted within our submission and in TA639, **docetaxel is not a relevant comparator** since it is being used primarily at earlier stages of breast cancer and is also associated with a less favourable AE profile versus that of paclitaxel. The ERG acknowledges that paclitaxel was considered as the most relevant taxane comparator within TA639 as per AC preferences and clinical expert opinion (based on the points notes above; page 129). However, a full incremental analysis is presented by the ERG which is misleading as paclitaxel and docetaxel cannot be assumed as fully interchangeable within this population. As per clinical expert opinion sought by MSD in the submission development process, paclitaxel was confirmed to be the main taxane comparator. This is consistent with TA639 clinical expert opinion which noted that paclitaxel has a more favourable profile versus that of docetaxel and it would likely constitute the main

			taxane comparator. Further, docetaxel is used more frequently in eBC disease stages alongside other chemotherapeutic agents and therefore, it is unlikely to be used again in patients which have progressed following on treatment with docetaxel, concluding that paclitaxel was the most relevant taxane comparator. Due to the reasons noted above and based on prior AC preferences, we positioned docetaxel as a secondary alternative taxane comparator because it was included within the final scope. **This means that references to fully incremental analyses may not be appropriate and instead, the results focus should be on pairwise cost-effectiveness as per our original submission.**

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)

N/A. Updated ICER based on final DBL	MSD's original base-case used data from interim analysis 2 (IA2).	MSD has updated the base-case to use final analysis (FA) data. Curve selections have been optimised using new data (see issue 1 above).	Original ICER (with IA2) = £27,808 New ICER (with FA, optimised curve selections) = £34,887 See Appendix 4 for full breakdown of results and sensitivity analysis.
Issue 3: Unfavourable assumption regarding treatment discontinuation for atezolizumab plus nab-paclitaxel	MSD's original base-case assumptions assume that the TTD for Atezolizumab + nab-paclitaxel is equal to the PFS due to lack of data specific for the subgroup of interest, Impassion-130 CPS ≥ 10 score population, for this reason this comparator is positioned as secondary within the submission.	MSD has updated to base-case assumption using the TTD for Atezolizumab + nab-paclitaxel equal to that of Pembrolizumab + taxanes based on the TTD estimates from TA639.	Original ICER (with FA DBL, comparators at list price = Dominant Original incremental costs (with FA DBL, comparators at list price) = [redacted] New ICER (with FA DBL, comparators at list price) = Dominant New incremental costs (with FA DBL, comparators at list price) = [redacted] See Appendix 4 for full breakdown of results and sensitivity analysis.

Sensitivity analyses around revised base case

Please see Appendix 4 for sensitivity analyses around revised base case.

Appendix 1. KEYNOTE-355 final DBL results for PFS and OS estimates for pembrolizumab + taxanes versus placebo + taxanes

Table 1: Analysis of OS (CPS ≥10 and taxane population)

Treatment	N	Number of events (%)	Vs. control Hazard Ratio (95% CI)†
Pembrolizumab + taxane	96	61 (63.5)	0.54 (0.36, 0.82)
Placebo + taxane	47	39 (83.0)	

† 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 2: Analysis of PFS based on BCIV per RECISTS 1.1 (CPS ≥10 and taxane population)

Treatment	N	Number of events (%)	Vs. control Hazard Ratio (95% CI)†
Pembrolizumab + taxane	96	[redacted]	[redacted]
Placebo + taxane	47	[redacted]	

† 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

Figure 2: KM estimates of OS (CPS ≥10 and taxane population)

Figure 3: KM estimates of PFS based on BICR assessment per RECIST 1.1 (CPS ≥10 and taxane population)

Appendix 2. Updated NMA results for Pembrolizumab + taxanes versus Atezolizumab + nab-paclitaxel

Overall survival

The results of the base case fixed-effects constant HR NMA are shown in
Table 3. Pembrolizumab + taxanes was associated with a [redacted] versus atezolizumab + nab-paclitaxel (HR of [redacted]). Using nab-paclitaxel alone as a common comparator from KEYNOTE-355 also generated a [redacted] in favour Pembrolizumab + nab-paclitaxel versus atezolizumab + nab-paclitaxel of [redacted]). The confidence intervals associated with this analyses are wider due to the smaller sample size used from KEYNOTE-355.

Table 3: Hazard ratios fixed-effects constant HR network meta-analysis of OS

Comparison	KEYNOTE-355 PD-L1 expression subgroup	IMpassion130-PD-L1 expression subgroup	HR (95% CI)
Base-case – taxanes pooled			
Pembrolizumab + paclitaxel/nab-paclitaxel vs. atezolizumab + nab-paclitaxel	CPS ≥ 10	CPS ≥ 10	[redacted]
Sensitivity analysis – nab-paclitaxel common comparator from KEYNOTE-355			
Pembrolizumab + nab-paclitaxel vs. atezolizumab + nab-paclitaxel	CPS ≥ 10	CPS ≥ 10	[redacted]

Progression Free Survival

The results of the base case fixed-effects constant HR NMA are shown in Table 4. Pembrolizumab + taxanes was associated with a numerical PFS benefit versus atezolizumab + nab-paclitaxel [redacted]). The same was seen in the comparison using nab-paclitaxel alone as a common comparator ([redacted] The results remained consistent when BICR PFS data from KEYNOTE-355 were used in the ITC, suggesting a numerical PFS benefit in favour of Pembrolizumab. To be consistent across study PFS assessment atezolizumab comparisons use the pooled taxanes PFS HRs within the model.

Table 4: Hazard ratios fixed-effect network constant HR meta-analysis of PFS

Comparison	KEYNOTE-355 PD-L1 expression subgroup	IMpassion130-PD-L1 expression subgroup	HR (95% CI)
Base-case – using KN-355 INV-assessed PFS & taxanes pooled; for secondary IO comparator			
Pembrolizumab + paclitaxel/nab-paclitaxel vs. atezolizumab + nab-paclitaxel	CPS ≥ 10	CPS ≥ 10	[redacted]
Sensitivity analysis – using KN-355 INV-assessed PFS & nab-paclitaxel as common comparator from KEYNOTE-355			
Pembrolizumab + nab-paclitaxel vs. atezolizumab + nab-paclitaxel	CPS ≥ 10	CPS ≥ 10	[redacted]
Scenario analyses – using KN-355 BICR-assessed PFS from KEYNOTE-355			
Pembrolizumab + paclitaxel/nab-paclitaxel vs. atezolizumab + nab-paclitaxel	CPS ≥ 10	CPS ≥ 10	[redacted]
Pembrolizumab + nab-paclitaxel vs. atezolizumab + nab-paclitaxel	CPS ≥ 10	CPS ≥ 10	[redacted]
INV: investigator/local radiology assessed PFS in KN-355. IMpassion130 IA-only reports investigator assessed PFS results; see Appendix D1.2.1 & Figure 8 for PFS effect sizes used in the NMA.			

In all of the analyses presented the NMA results suggested that Pembrolizumab in combination with taxanes is associated with [redacted] PFS and [redacted]. In particular for the OS, the estimates used form KEYNOTE-355 are based on the final dataset (date: 15th June 2021), therefore they reduce the uncertainty around the point estimates produced by the ITC by leveraging upon the most up to date information from KEYNOTE-355 .

Appendix 3. Impact of final DBL on original cost-effectiveness analysis presented (original survival curve selections unchanged)

Base case analysis – original survival curve selection

Original curve selections

Table 5: Original curve selections

Intervention	OS	PFS	ToT
Pembrolizumab + taxanes	Log-normal	KM 9+ Weibull	Weibull
Taxanes	Log-logistic	KM 9+ Log-normal	Log-logistic

Base-case incremental cost-effectiveness analysis results for pembrolizumab + taxanes versus paclitaxel (primary chemotherapy comparator)

Table 6: Updated base-case results versus paclitaxel from deterministic analysis using list prices

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Paclitaxel comparator	[redacted]	2.012	[redacted]	-	-	-
Pembrolizumab + taxanes**	[redacted]	3.715	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, ** Confidential discounts in place for nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

Table 7: Updated base-case results versus paclitaxel from deterministic analysis using list prices for comparators with pembrolizumab PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Paclitaxel comparator	[redacted]	2.012	[redacted]	-	-	-
Pembrolizumab + taxanes**	[redacted]	3.715	[redacted]	[redacted]	[redacted]	£35,148
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, ** Confidential discounts in place for nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

Base-case incremental cost-effectiveness analysis results for pembrolizumab + taxanes versus docetaxel (secondary chemotherapy comparator)

Table 8: Updated base-case results versus docetaxel from deterministic analysis using list prices

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Docetaxel comparator	[redacted]	2.012	[redacted]	-	-	-
Pembrolizumab + taxanes**	[redacted]	3.715	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, ** Confidential discounts in place for nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

Table 9: Updated base-case results versus docetaxel from deterministic analysis using list prices for comparators with pembrolizumab PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Docetaxel comparator	[redacted]	2.012	[redacted]	-	-	-
Pembrolizumab + taxanes**	[redacted]	3.715	[redacted]	[redacted]	[redacted]	£42,676
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, ** Confidential discounts in place for nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

Base-case incremental cost-effectiveness analysis results for Pembrolizumab versus Atezolizumab + nab-paclitaxel (secondary IO comparator for PD-L1 +ve patients)

Table 10: Updated base-case results versus Atezolizumab + nab-paclitaxel from deterministic analysis using LIST prices for both comparators

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Atezolizumab + nab-paclitaxel	[redacted]	2.172	[redacted]	-	-	-
Pembrolizumab + taxane**	[redacted]	3.715	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. ** Confidential discounts in place for Atezolizumab and nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

Table 11: Updated base-case results versus Atezolizumab + nab-paclitaxel from deterministic analysis using list prices for comparator with pembrolizumab PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Atezolizumab + nab-paclitaxel	[redacted]	2.172	[redacted]	-	-	-
Pembrolizumab + taxane	[redacted]	3.715	[redacted]	[redacted]	[redacted]	Dominant*
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years *Pembrolizumab + taxanes is less costly and QALY accruing. ** Confidential discounts in place for Atezolizumab and nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

Appendix 4. Cost-effectiveness analysis – optimised survival curve selection based on final DBL

Base case analysis - optimised curve selection based on final database lock

Optimised curve selections based on final database lock

Table 12: Optimised curve selections based on final database lock

Intervention	OS	PFS	ToT
Pembrolizumab + taxanes	Log-normal	KM 9+ Weibull	Log-normal
Taxanes	Log-logistic	KM 9+ Log-logistic	Log-logistic

Base-case incremental cost-effectiveness analysis results for pembrolizumab versus paclitaxel (primary chemotherapy comparator)

Table 13: Updated base-case results versus paclitaxel from deterministic analysis using list prices and updated optimized curves

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Paclitaxel comparator	[redacted]	2.012	[redacted]	-		
Pembrolizumab + taxanes**	[redacted]	3.715	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, ** Confidential discounts in place for nab-paclitaxel with the NHS may alter the cost-effectiveness results.

Table 14: Updated base-case results versus paclitaxel from deterministic analysis using list prices and updated optimized curves with pembrolizumab PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Paclitaxel comparator	[redacted]	2.012	[redacted]	-		
Pembrolizumab + taxanes**	[redacted]	3.715	[redacted]	[redacted]	[redacted]	£34,887

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, ** Confidential discounts in place for nab-paclitaxel with the NHS may alter the cost-effectiveness results.

Base-case incremental cost-effectiveness analysis results for pembrolizumab versus docetaxel (secondary chemotherapy comparator)

Table 15: Updated Base-case results versus docetaxel from deterministic analysis using list prices and updated optimized curves

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Docetaxel comparator	[redacted]	2.012	[redacted]	-	-	-
Pembrolizumab + taxanes**	[redacted]	3.715	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, ** Confidential discounts in place for nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

Table 16: Updated Base-case results versus docetaxel from deterministic analysis using list prices and updated optimized curves for comparators with pembrolizumab PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Docetaxel comparator	[redacted]	2.012	[redacted]	-	-	-
Pembrolizumab + taxanes**	[redacted]	3.715	[redacted]	[redacted]	[redacted]	£42,415
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years, ** Confidential discounts in place for nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

Base-case incremental cost-effectiveness analysis results for pembrolizumab versus Atezolizumab + nab-paclitaxel (secondary IO comparator for PD-L1 +ve patients)

Table 17: Updated Base-case results versus Atezolizumab + nab-paclitaxel from deterministic analysis using LIST prices and updated optimized curves for both comparators

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Atezolizumab + nab-paclitaxel	[redacted]	2.172	[redacted]	-	-	-
Pembrolizumab + taxane**	[redacted]	3.715	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. ** Confidential discounts in place for Atezolizumab and nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

Table 18: Updated base-case results versus Atezolizumab + nab-paclitaxel from deterministic analysis using list prices and updated optimized curves for comparator with pembrolizumab PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Atezolizumab + nab-paclitaxel	[redacted]	2.172	[redacted]	-	-	-
Pembrolizumab + taxane	[redacted]	3.715	[redacted]	[redacted]	[redacted]	Dominant*
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years *Pembrolizumab + taxanes is less costly and QALY accruing. ** Confidential discounts in place for Atezolizumab and nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis vs paclitaxel (with pembrolizumab PAS)

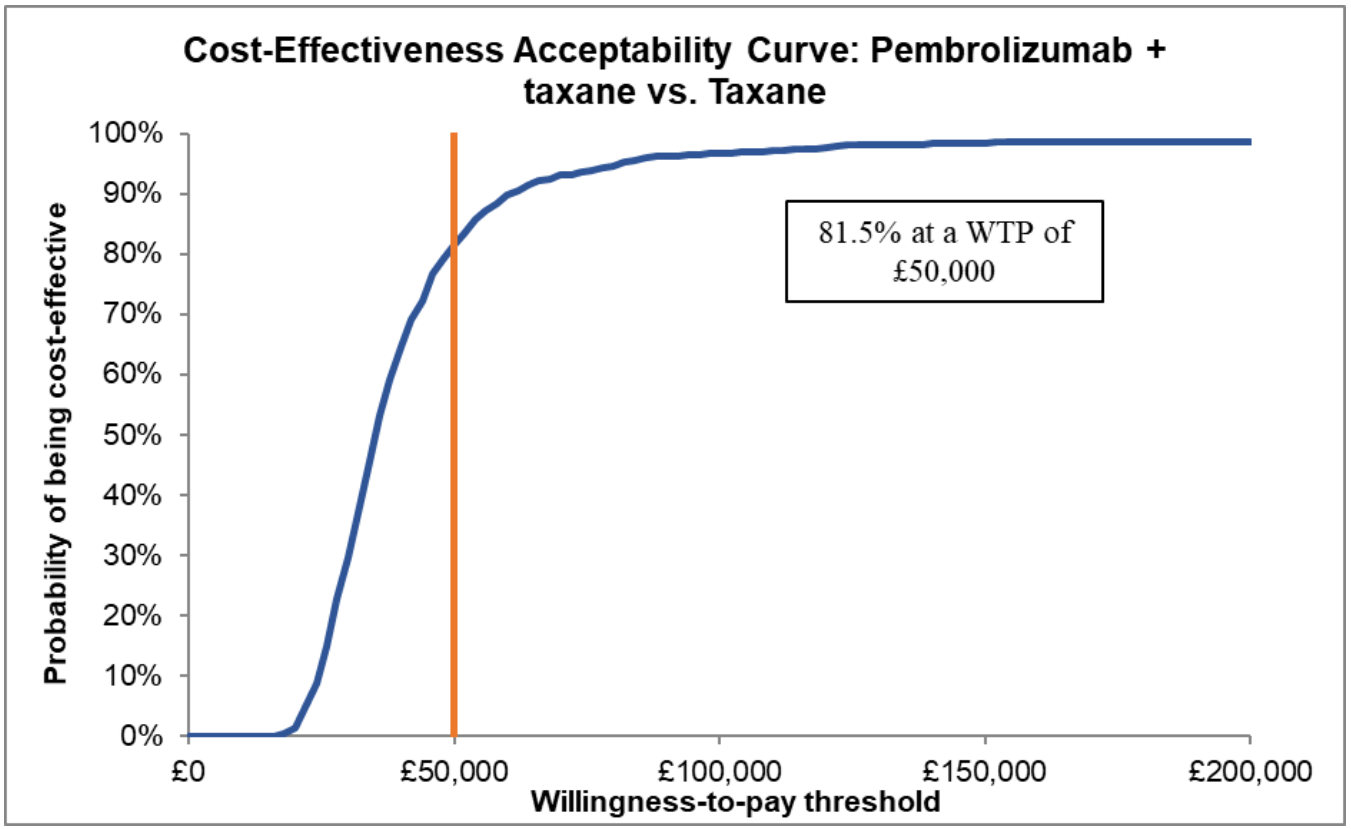
Table 19: Updated PSA results versus paclitaxel with pembrolizumab PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Paclitaxel comparator	[redacted]	2.039	[redacted]	-	-	-
Pembrolizumab + taxanes**	[redacted]	3.730	[redacted]	[redacted]	[redacted]	£35,105

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years ** Confidential discounts in place for nab-paclitaxel with the NHS may alter the cost-effectiveness results.

Figure 4: Updated Scatterplot of PSA results of pembrolizumab + taxanes versus paclitaxel with pembrolizumab PAS

Figure 5: Cost-effectiveness acceptability curve of pembrolizumab + taxanes versus paclitaxel with pembrolizumab PAS



Probabilistic sensitivity analysis vs docetaxel (with pembrolizumab PAS)

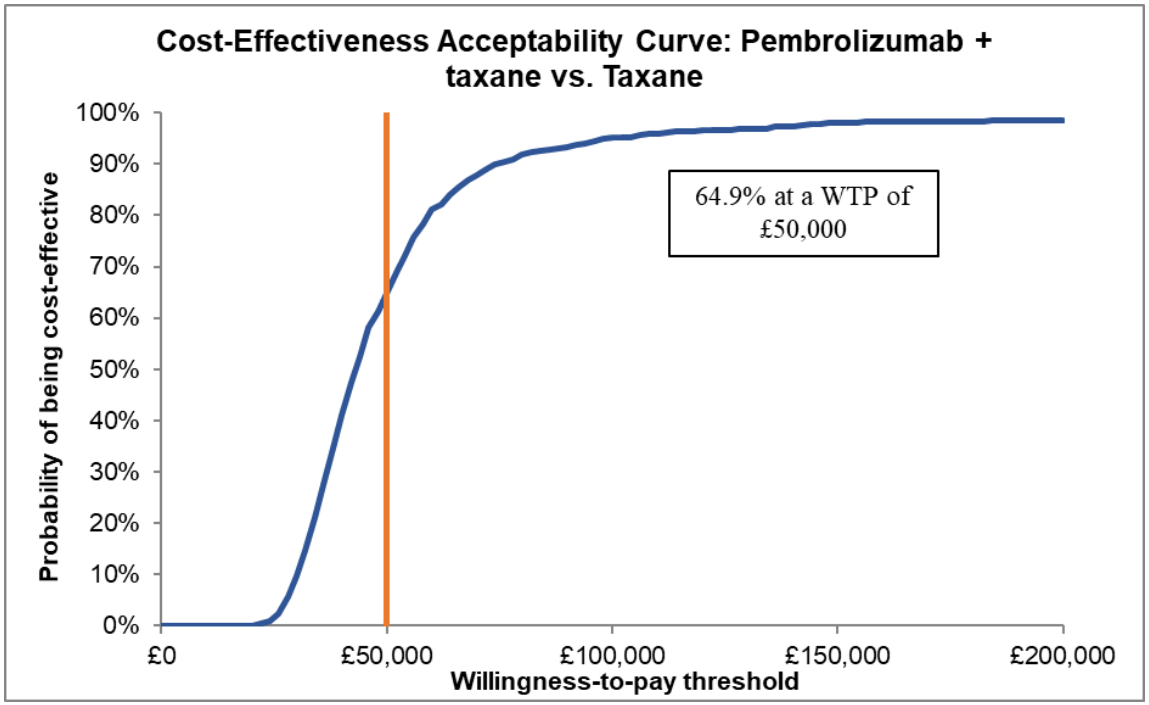
**Note: To run analyses ensure docetaxel costs are applied in the "Drug Cost Inputs" Sheet (PSA will need to run with this setting selected)*

Table 20: Updated PSA results versus docetaxel with pembrolizumab PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
DOCETAXEL comparator	[redacted]	2.039	[redacted]	-	-	-
Pembrolizumab + taxanes**	[redacted]	3.730	[redacted]	[redacted]	[redacted]	£42,904
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years ** Confidential discounts in place for nab-paclitaxel with the NHS may alter the cost-effectiveness results.						

Figure 6: Updated Scatterplot of PSA results of pembrolizumab + taxanes versus DOCETAXEL with pembrolizumab PAS

Figure 7: Cost-effectiveness acceptability curve of pembrolizumab + taxanes versus DOCETAXEL with pembrolizumab PAS



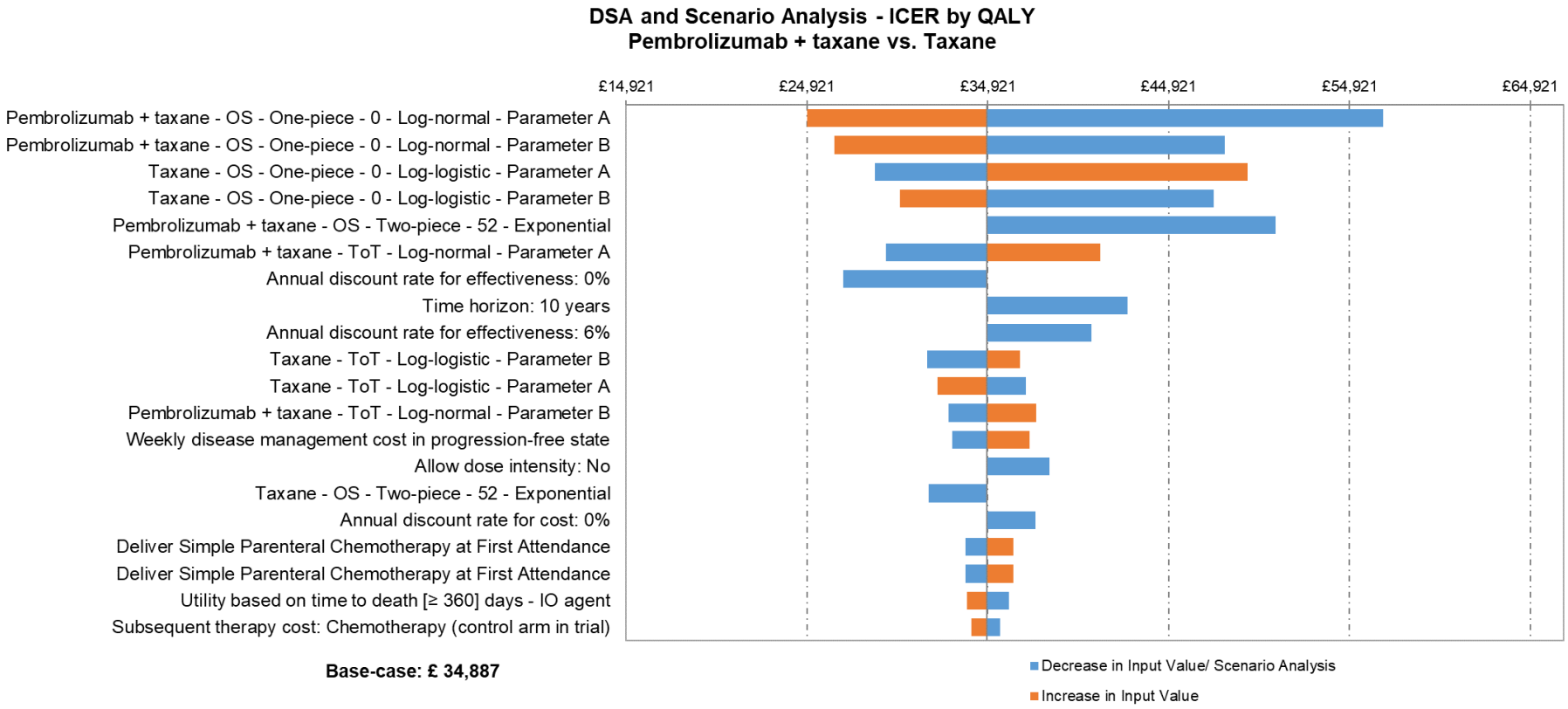
Probabilistic sensitivity analysis vs Atezolizumab + nab-paclitaxel (with pembrolizumab PAS)

It is not methodologically relevant to conduct PSA versus atezolizumab + nab-paclitaxel dur to the uncertainty in the ITC comparisons and comparability across populations (see original submission). Hence, scenario analyses are explored instead as they can be more informative for decision making.

Deterministic sensitivity analysis

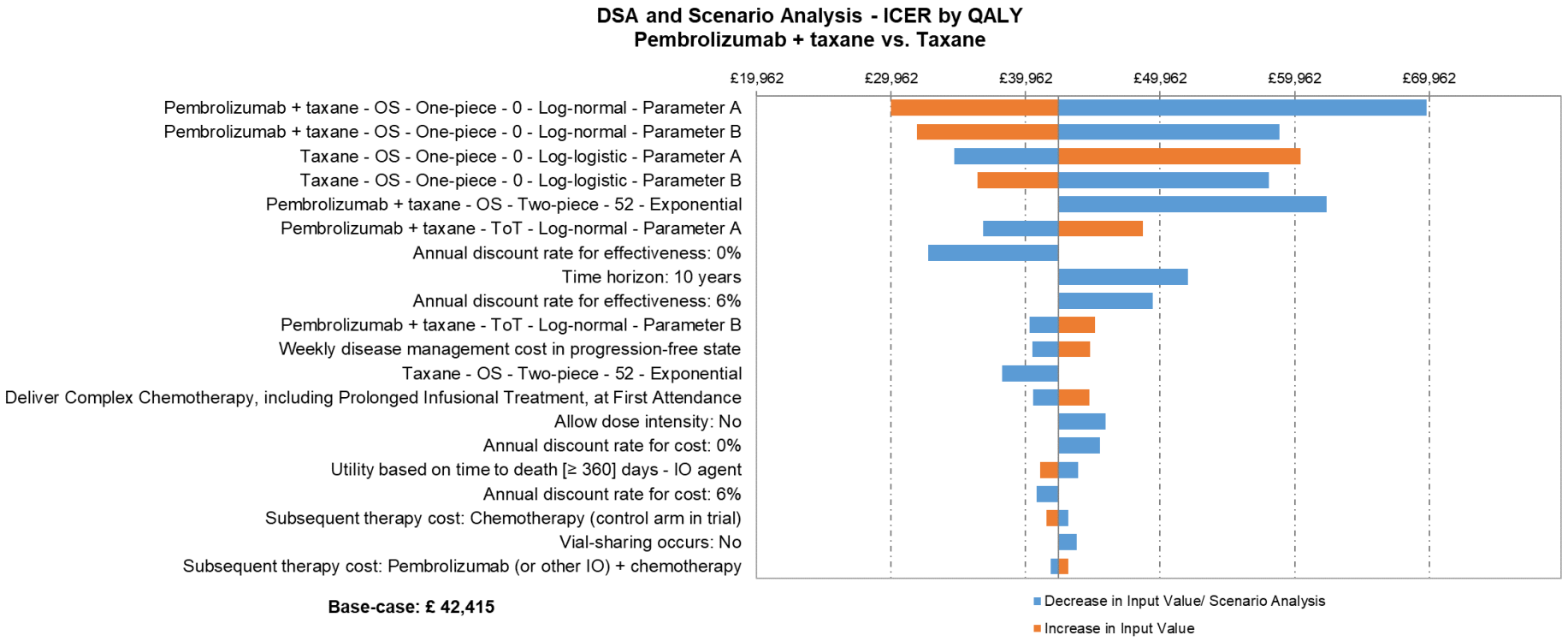
Deterministic sensitivity analysis vs paclitaxel (with pembrolizumab PAS)

Figure 8: Tornado diagram for the 20 most sensible variables versus paclitaxel with pembrolizumab PAS



Deterministic sensitivity analysis vs docetaxel (with pembrolizumab PAS)

Figure 9: Tornado diagram for the 20 most sensible variables versus docetaxel with pembrolizumab PAS



**Note: To run analyses ensure Docetaxel costs are applied in the "Drug Cost Inputs" Sheet (DSA will need to run with this setting selected)*

Scenario analysis

Scenario analyses vs paclitaxel chemotherapy comparator (with pembrolizumab PAS)

Table 21: Updated results of scenario analyses versus paclitaxel (with pembrolizumab PAS price)

Scenario No.	Description	Pembrolizumab + taxanes			Taxanes comparator			Pembrolizumab + taxanes vs Taxanes		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Updated Base Case	**Paclitaxel taxane comparator**	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£34,887
Scenario 1	Full log-logistic for pembrolizumab + taxane OS (3rd best curve) *Note: 2nd best curve now exponential; however, this is implausible due to taxane OS initially higher*	[redacted]	3.737	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£34,597
Scenario 2	Full log-normal for Taxane OS (2nd best curve)	[redacted]	3.715	[redacted]	[redacted]	1.955	[redacted]	[redacted]	[redacted]	£34,004
Scenario 3	Piecewise model for OS for Pembro + taxanes; 52 weeks KM + exponential (model unpredicts OS survival; equal to that of long term chemotherapy RWE datasets; considered highly conservative)	[redacted]	3.101	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£50,828
Scenario 4	Combined 3rd best OS curve for Pembro + Taxanes (log-logistic) & 2nd best OS curve for Taxanes comparator (log-normal): Scenarios 1 & 2 combined	[redacted]	3.737	[redacted]	[redacted]	1.955	[redacted]	[redacted]	[redacted]	£33,731
Scenario 5	PFS for Pembro + Taxanes: KM up to week 9 + Log-logistic (2nd best curve)	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£34,911
Scenario 6	PFS for Taxanes: KM up to week 9 + Generalised Gamma (2nd best curve)	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£34,863

Scenario No.	Description	Pembrolizumab + taxanes			Taxanes comparator			Pembrolizumab + taxanes vs Taxanes		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
	Note: previous 2nd best log-logistic is now base case									
Scenario 7	Combined 2nd best PFS curves for Pembro + Taxane (9 week KM+ log-logistic) and Taxane comparator (9 week KM+ generalised gamma): Scenarios 5 & 6 combined	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£34,887
Scenario 8	Combined 2nd best OS & PFS curves for Pembro + taxane and taxanes (Scenarios 4 & 7 together)	[redacted]	3.737	[redacted]	[redacted]	1.955	[redacted]	[redacted]	[redacted]	£33,736
Scenario 9	Applying treatment waning using SEER dataset in the base-case	[redacted]	4.286	[redacted]	[redacted]	2.368	[redacted]	[redacted]	[redacted]	£31,605
Scenario 10	Applying treatment waning by removing OS benefit after 5 Years in the base-case	[redacted]	3.481	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£39,531
Scenario 11	Combined 2nd best OS curves with 2nd best PFS curves (Scenario 8) + 5 year IO waning scenario	[redacted]	3.191	[redacted]	[redacted]	1.955	[redacted]	[redacted]	[redacted]	£45,734
Scenario 12	No half cycle correction on base-case	[redacted]	3.726	[redacted]	[redacted]	2.022	[redacted]	[redacted]	[redacted]	£35,158
Scenario 13	Removal of PD-L1 testing costs for Pembro + Taxanes	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£34,803
Scenario 14	Removal of AE management costs	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£34,580
Scenario 15	Using MS data for subsequent therapies (*selection at "Post Trt Costs" Sheet)*	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£35,381
Scenario 16	Using utilities by progression status & AEs pooled	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£35,605

Scenario No.	Description	Pembrolizumab + taxanes			Taxanes comparator			Pembrolizumab + taxanes vs Taxanes		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Scenario 17	Using utilities by progression status & AEs treatment specific	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£35,411
Scenario 18	Removal of age-adjustment in utility estimates	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£33,546

Scenario analyses vs docetaxel chemotherapy comparator (with pembrolizumab PAS)

Table 22: Updated results of Scenario analyses versus docetaxel (with pembrolizumab PAS price)

Scenario No.	Description	Pembrolizumab + taxanes			Taxanes comparator			Pembrolizumab + taxanes vs Taxanes		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Updated Base Case	**Docetaxel taxane comparator**	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£42,415
Scenario 1	Full log-logistic for pembrolizumab + taxane OS (3rd best curve) *Note: 2nd best curve now exponential; however, this is implausible due to taxane OS initially higher*	[redacted]	3.737	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£42,052
Scenario 2	Full log-normal for Taxane OS (2nd best curve)	[redacted]	3.715	[redacted]	[redacted]	1.955	[redacted]	[redacted]	[redacted]	£41,310
Scenario 3	Piecewise model for OS for Pembro + taxanes; 52 weeks KM + exponential (model unpredicts OS survival; equal to that of long term chemotherapy RWE datasets; considered highly conservative)	[redacted]	3.101	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£62,358

Scenario No.	Description	Pembrolizumab + taxanes			Taxanes comparator			Pembrolizumab + taxanes vs Taxanes		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Scenario 4	Combined 3rd best OS curve for Pembro + Taxanes (log-logistic) & 2nd best OS curve for Taxanes comparator (log-normal): Scenarios 1 & 2 combined	[redacted]	3.737	[redacted]	[redacted]	1.955	[redacted]	[redacted]	[redacted]	£40,968
Scenario 5	PFS for Pembro + Taxanes: KM up to week 9 + Log-logistic (2nd best curve)	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£42,439
Scenario 6	PFS for Taxanes: KM up to week 9 + Generalised Gamma (2nd best curve) *Note: previous 2nd best log-logistic is now base case*	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£42,391
Scenario 7	Combined 2nd best PFS curves for Pembro + Taxane (9 week KM+ log-logistic) and Taxane comparator (9 week KM+ generalised gamma): Scenarios 5 & 6 combined	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£42,415
Scenario 8	Combined 2nd best OS & PFS curves for Pembro + taxane and taxanes (Scenarios 4 & 7 together)	[redacted]	3.737	[redacted]	[redacted]	1.955	[redacted]	[redacted]	[redacted]	£40,973
Scenario 9	Applying treatment waning using SEER dataset in the base-case	[redacted]	4.286	[redacted]	[redacted]	2.368	[redacted]	[redacted]	[redacted]	£38,310
Scenario 10	Applying treatment waning by removing OS benefit after 5 Years in the base-case	[redacted]	3.481	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£48,221
Scenario 11	Combined 2nd best OS curves with 2nd best PFS curves (Scenario 8) + 5 year IO waning scenario	[redacted]	3.191	[redacted]	[redacted]	1.955	[redacted]	[redacted]	[redacted]	£55,991
Scenario 12	No half cycle correction on base-case	[redacted]	3.726	[redacted]	[redacted]	2.022	[redacted]	[redacted]	[redacted]	£42,791

Scenario No.	Description	Pembrolizumab + taxanes			Taxanes comparator			Pembrolizumab + taxanes vs Taxanes		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Scenario 13	Removal of PD-L1 testing costs for Pembro + Taxanes	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£42,331
Scenario 14	Removal of AE management costs	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£42,108
Scenario 15	Using MS data for subsequent therapies (*selection at "Post Trt Costs" Sheet)*	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£42,909
Scenario 16	Using utilities by progression status & AEs pooled	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£43,289
Scenario 17	Using utilities by progression status & AEs treatment specific	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£43,052
Scenario 18	Removal of age-adjustment in utility estimates	[redacted]	3.715	[redacted]	[redacted]	2.012	[redacted]	[redacted]	[redacted]	£40,785

Scenario analyses vs Atezolizumab + nab-paclitaxel comparator (with pembrolizumab PAS)

Table 23: Scenario analyses versus Atezolizumab + nab-paclitaxel LIST Prices (and pembrolizumab PAS price)

Scenario No.	Description	Pembrolizumab + taxanes			Atezolizumab + nab-paclitaxel			Pembrolizumab + taxanes vs Atezolizumab + nab-paclitaxel		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Updated Base case	**KN-355 INV PFS, Pooled Taxanes, atezo + nab ToT = pembro + nab ToT & pembrolizumab PAS**	[redacted]	3.715	[redacted]	[redacted]	2.172	[redacted]	[redacted]	[redacted]	Dominant
Scenario 1	Use KEYNOTE-355 nab-paclitaxel as common comparator for the NMA to estimate the PFS HR	[redacted]	3.715	[redacted]	[redacted]	2.210	[redacted]	[redacted]	[redacted]	Dominant
Scenario 2	Full log-logistic for pembrolizumab + taxane OS (3rd best curve) *Note: 2nd best curve now exponential; however, this is implausible due to taxane OS initially higher*	[redacted]	3.737	[redacted]	[redacted]	2.172	[redacted]	[redacted]	[redacted]	Dominant
Scenario 3	Use the primary PFS endpoint from KEYNOTE-355 blinded CIV	[redacted]	3.715	[redacted]	[redacted]	2.172	[redacted]	[redacted]	[redacted]	Dominant
Scenario 4 (revised with updated base case)	Set the maximum treatment duration for Atezolizumab +nab-paclitaxel = PFS	[redacted]	3.715	[redacted]	[redacted]	2.172	[redacted]	[redacted]	[redacted]	Dominant

Scenario No.	Description	Pembrolizumab + taxanes			Atezolizumab + nab-paclitaxel			Pembrolizumab + taxanes vs Atezolizumab + nab-paclitaxel		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Scenario 5	2nd best PFS curve used for Pembro + taxanes in comparison: 9 week KM + log-logistic	[redacted]	3.715	[redacted]	[redacted]	2.172	[redacted]	[redacted]	[redacted]	Dominant
Scenario 6	Combined 2nd best curves for PFS and OS for Pembro + Taxanes (Scenario 2 & 5)	[redacted]	3.737	[redacted]	[redacted]	2.172	[redacted]	[redacted]	[redacted]	Dominant
Scenario 7	Apply treatment waning based on SEER dataset analysis on Scenario 6.	[redacted]	4.286	[redacted]	[redacted]	2.420	[redacted]	[redacted]	[redacted]	Dominant

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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 company's technical engagement response

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Declared competing interests of the authors
None of the authors has any conflicts of interest to declare.

1 Introduction

In December 2021, the company submitted its technical engagement (TE) response for the appraisal of pembrolizumab in combination with paclitaxel/nab-paclitaxel for untreated, locally recurrent inoperable or metastatic, triple negative breast cancer (TNBC) in December 2021.[1] The company's response was structured around the six key issues raised within the Evidence Review Group (ERG) report, together with one additional issue raised by the company. The company's TE response includes a written technical engagement response document, together with updated version of the executable model.

This document provides a commentary on the company's TE response and should be read in conjunction with the ERG report.[2] Section 2 provides a summary of the company's changes in the updated model and provides information relating to the new analyses of time-to-event data from KEYNOTE-355. Section 3 provides a fuller description of the company's response and the ERG's critique of these points. Section 4 presents the results of the company's updated base case and scenario analyses and additional analyses undertaken by the ERG. Overall conclusions are presented in Section 5.

All results presented in this document include the Patient Access Scheme (PAS) discount for pembrolizumab, but exclude confidential comparator PAS discounts. Results which include confidential comparator PAS discounts are presented in a separate confidential addendum.

2 Summary of the company's response to technical engagement

The company submission (CS[3]) was submitted in January 2021; subsequently, further data relating to the pivotal study, KEYNOTE-355, have become available. In the TE response, the company presents additional clinical effectiveness evidence from the final analysis (FA) dataset (data cut-off 15th of June 2021), replacing the data from the interim IA2 data cut-off from the 11th of December 2019 presented in the CS. The reported median follow-up for this final analysis is [redacted] for the pembrolizumab and placebo arm respectively.[1]

In addition to the more mature data-cut, the company's updated model includes a number of further amendments related to some of the key issues raised by the ERG. Furthermore, the model includes a number of additional modifications, most of which relate to updating drugs prices, updating the assumed unit costs for resource use and fixing minor errors in formulae. These changes are not mentioned by the company in the TE response but have been identified by the ERG within the verification of the new version of the submitted model. The ERG comments that most of the amendments relate to the availability of more recent data from KEYNOTE-355 or relevant cost databases. However, it is not clear the reason for revising some input values such as the dose strength for eribulin and epirubicin, although the ERG believes the impact on the results of such changes are minor and have maintained the values used by the company in its revised base case.

Table 1 summarises the company's original base case model, the ERG's preferred analysis at the time of the ERG report and the company's updated base case model as presented in the TE response. A more detailed discussion of each issue including an ERG critique and, where appropriate, changes to the ERG base case is provided in Section 3, although a summary of the more mature data from KEYNOTE-355 is provided in Section 2.1.

Table 1: Summary of company's original base case (CS),ERG preferred analysis (ERG report) and company's updated base-case (TE response)

Aspect of model	Company's original base case	ERG preferred analysis	Company's updated base case model	Did the assumption change between the original and updated base case?
Amendments relating to updated survival data from KEYNOTE-355 and parametric functions for OS, PFS and TTD (Issue 1)				
PFS distributions	KM 9W+ Weibull (pembro + taxanes) and KM 9W+ log-normal (taxanes)	Weibull (pembro+ taxanes) and log-normal (taxanes)	KM 9W+ Weibull (pembro + taxanes) and KM 9W+ log-logistic (taxanes)	Yes
OS distributions	Log-normal (pembro + taxanes) and log-logistic (taxanes)	Weibull (pembro+ taxanes) and Weibull (taxanes)	Log-normal (pembro + taxanes) and log-logistic (taxanes)	No
TTD distributions	Weibull (pembro + taxanes) and log-logistic (taxanes)	Weibull (pembro + taxanes) and log-logistic (taxanes)	Log-normal (pembro + taxanes) and log-logistic (taxanes)	Yes
Amendments relating to key issues presented in ERG Report				
Issue 2: Uncertainty surrounding the long-term benefits of pembrolizumab plus paclitaxel/nab-paclitaxel	No loss of treatment benefit applied.	Loss of treatment benefit applied at 5 years (No loss of benefit and loss at 3 years explored in ASA 2 and 3)	No loss of treatment benefit applied. Alternative approaches (5 years and SEER-based approach) presented as additional scenario analyses.	No
Issue 3: Unfavourable assumption regarding treatment discontinuation for atezolizumab plus nab-paclitaxel	$TTD_{Atezo} = PFS_{Atezo}$	$TTD_{Atezo} = HR_{PFS}$ applied to TTD_{Pembro} (Alternative approach $TTD_{Atezo} = TTD_{Pembro}$ explored in ASA 4)	$TTD_{Atezo} = TTD_{Pembro}$	Yes
Issue 4: Uncertainty surrounding the relative efficacy comparison of pembrolizumab plus paclitaxel/nab-paclitaxel versus atezolizumab plus nab-paclitaxel	Company base case uses the estimates from ITC analyses using *fixed* effect models: OS HR= [redacted] PFS HR= [redacted]	The ERG preferred-analyses include the estimates from ITC analyses using *random* effect models provided by the company in the clarification response: OS HR= [redacted] PFS HR= [redacted]	Company presents the results of the updated ITC analyses using *fixed* effect models: OS HR = [redacted]PFS HR = [redacted]	No

Aspect of model	Company's original base case	ERG preferred analysis	Company's updated base case model	Did the assumption change between the original and updated base case?
Issue 5: Uncertainty related to the most appropriate way to estimate utility	Only results for time-to-death approach presented by the company as part of base case.	Results of both approaches presented by the ERG	Only results for time-to-death approach presented as part of base case. Additional scenario analyses using utilities by progression status presented in Appendix.	No
Issue 6: Inclusion of vial sharing for IV drugs (with the exception of pembrolizumab and atezolizumab)	Vial sharing included.	No vial sharing. Impact of vial sharing presented in TE response.	Vial sharing included. Impact of vial sharing removal presented in TE response.	No
Other amendments detailed in the company's Technical Engagement response				
Additional issue 1: Fully incremental analysis	Fully incremental analysis not presented; however, pairwise comparisons against paclitaxel, docetaxel and atezolizumab plus nab-paclitaxel were presented	Fully incremental analysis presented by the ERG. In addition, pairwise comparisons against paclitaxel and docetaxel were also presented.	Not included. Pairwise comparisons against paclitaxel presented in base case, but results of comparisons against docetaxel and atezolizumab plus nab-paclitaxel presented in Appendix.	No
Other amendments included in company's updated model				
Price year for drugs in 2L and subsequent treatments	2020	2020	2021	Yes
Price year for unit costs for resource use and CPI index	2018/2019	2018/2019	2019/2020	Yes
Data cut used for other inputs from KEYNOTE-355 (RDI, AE frequencies, utility estimates)	IA2	IA2	FA	Yes
Changes in drug dose strength for eribulin and epirubicin	Not Applicable	No	Yes	Yes

ASA - ERG additional sensitivity analysis; Atezo – atezolizumab plus nab-paclitaxel; FA - final analysis; IA2 - interim analysis 2; Pembro – pembrolizumab plus paclitaxel/nab-paclitaxel; PFS - progression-free survival, OS - overall survival; EA - ERG exploratory analysis;

† The ERG notes that the HR PFS estimate in the company's TE response contains a typographical error, where the estimate reported corresponds to the investigator-assessed (INV) PFS instead of the blinded independent central review (BIRC) assessed PFS.

As shown in Table 1, the more mature data from the extended follow-up of approximately 18 months resulted in the company choosing different distributions for progression-free survival (PFS) and time to treatment discontinuation (TTD). In addition, the company has amended estimates of drug acquisition and administration costs, subsequent treatment costs, health state costs and adverse events probabilities.

The company's TE response includes updated incremental cost-effectiveness ratios (ICERs), reported in terms of cost per quality-adjusted life year (QALY) gained, which changed due to the extended data collection period and due to changes in assumptions made within the company's base case. The company's revised base case had a deterministic ICER of £34,887 compared with paclitaxel, which was increased to £35,105 in probabilistic sensitivity analyses (PSA). The company also presents results for comparisons against docetaxel, atezolizumab plus nab-paclitaxel for the updated base case and a number of additional scenarios; for brevity, these additional scenarios are not presented in this document.

2.1 Additional data from KEYNOTE-355

The company's TE response[1] reports new overall survival (OS) data from the KEYNOTE-355 study, a two-arm, multicentre international randomised controlled trial (RCT) which compares pembrolizumab 200 mg IV infusion every 3 weeks plus chemotherapy IV infusion to placebo plus chemotherapy.

As in the CS, time-to-event outcomes for the pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel groups are modelled using available individual patient data (IPD) for the subgroup of patients with PD-L1 CPS≥10, but now use the FA data-cut from KEYNOTE-355. The same candidate models (i.e., exponential, Weibull, log-logistic, log-normal, Gompertz and generalized gamma distributions) were assessed for inclusion in the base case analysis through consideration of: relative goodness-of-fit statistics (the Akaike Information Criterion [AIC] and the Bayesian Information Criterion [BIC]); visual inspection of the fitted distributions to the observed data; examination of the smooth hazard functions, and the clinical plausibility of the projections.

Kaplan-Meier (KM) survival functions and modelled OS survival functions for the pembrolizumab plus paclitaxel/nab-paclitaxel and the paclitaxel groups are presented in Figure 1 and Figure 2, respectively. The company's TE response does not present the data for the updated PFS or TTD models, but the ERG was able to reconstruct these from the information provided in the submitted model. KM functions and modelled PFS functions are presented for the pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel groups in Figure 3 and Figure 4, respectively, whilst Figure 5 and Figure 6 show the KM functions and modelled TTD functions, respectively. The KMs and modelled OS, PFS and TTD survival functions chosen by the company for its updated base case are presented in Figure 7, Figure 8 and Figure 9, respectively.

Figure 1: OS survival functions using company's updated parametric modelling from FA data cut, pembrolizumab plus paclitaxel/nab-paclitaxel therapy group (redrawn by the ERG, includes general population mortality constraint)*

**Taxanes: paclitaxel/nab-paclitaxel*

Figure 2: OS survival functions using company's updated parametric modelling from FA data cut, paclitaxel therapy group redrawn by the ERG, includes general population mortality constraint)*

**Taxanes: paclitaxel/nab-paclitaxel*

Figure 3: PFS survival functions using company's piecewise parametric modelling with week 9 cut-point from FA data cut, pembrolizumab plus paclitaxel/nab-paclitaxel therapy group (redrawn by the ERG, does not include OS constraint)*

**Taxanes: paclitaxel/nab-paclitaxel*

Figure 4: PFS survival functions using company's piecewise parametric modelling with week 9 cut-point from FA data cut, paclitaxel therapy group (redrawn by the ERG, does not include OS constraint)*

**Taxanes: paclitaxel/nab-paclitaxel*

Figure 5: TTD survival functions using company's parametric modelling from FA data cut, pembrolizumab plus paclitaxel/nab-paclitaxel therapy group (redrawn by the ERG, does not include PFS constraint)*

**Taxanes: paclitaxel/nab-paclitaxel*

Figure 6: TTD survival functions using company's parametric modelling from FA data cut, paclitaxel therapy group (redrawn by the ERG, does not include PFS constraint)*

**Taxanes: paclitaxel/nab-paclitaxel*

Figure 7: OS survival functions for all treatment options included in company's base case analysis (generated by the ERG from the company's model)†

**Taxanes: paclitaxel/nab-paclitaxel*
† Includes constraints for general population mortality and the error in the estimate for OS HR spotted by the ERG (See Section 3.8)

Figure 8: PFS survival functions for all treatment options included in company's base case analyses, week 9 cut-point (generated by the ERG from the company's model) †

**Taxanes: paclitaxel/nab-paclitaxel*
† Includes constraints for OS

Figure 9: TTD survival functions for all treatment options included in company's base case analyses (generated by the ERG from the company's model) †

**Taxanes: paclitaxel/nab-paclitaxel*
† Includes constraints for PFS, the atezolizumab model includes the company's modelling approach of assuming TTD for atezolizumab plus nab-paclitaxel equals to TTD for pembrolizumab plus nab-paclitaxel.

Based on the additional data provided from the pivotal trial, the company maintained its original choices regarding the survival models of: log-normal and log-logistic distributions for OS for both pembrolizumab plus paclitaxel/nab-paclitaxel and taxanes (paclitaxel/docetaxel) respectively; a Weibull distribution for PFS for pembrolizumab plus paclitaxel/nab-paclitaxel and a log-logistic distribution for TTD for taxanes. For PFS for taxanes, the company selected a log-logistic distribution instead of the log-normal distribution used in the CS and for TTD for pembrolizumab plus paclitaxel/nab-paclitaxel, the log-normal distribution was chosen instead of the Weibull distribution

used in the CS. Estimates of relative goodness-of-fit (AIC and BIC) to the more mature observed data in relation to PFS or TTD were not provided by the company within the company's TE response, but these appear to be able to be retrieved from the updated version of the model. The company did not provide justification for the changes in its model choices. The ERG notes that the model results are not overly sensitive to the choice of distributions used to estimate PFS; however, changing the TTD distributions to the best-fitting model (using BIC) to the observed data increased the company's base case ICER by more than £1000.

3 ERG critique of the company's TE response

This ERG addendum is also structured around the six key issues in the initial ERG report which are detailed in Sections 3.1 to 3.6, plus the additional comment raised by the company (discussed in Section 3.7). Each section summarises the issue as reported by the ERG, new data presented by the company (if any), the view put forward by the company, and any new ICERs generated when using the company's preferred assumptions. Each section also includes the ERG's opinion on the new data / assumptions; the impact of these assumptions on the ICER is presented in Section 4 alongside the company's preferred ICER and the range of ICERs preferred by the ERG.

3.1 Key Issue 1: Potentially favourable extrapolation of overall survival

In the CS, the company modelled OS using a log-normal distribution for pembrolizumab plus paclitaxel/nab-paclitaxel and a log-logistic distribution for paclitaxel. These distributions have an increasing hazard before reaching a turning point and then having a decreasing hazard over time. However, the observed underlying hazard (based on the data available at the time of the CS) was consistently increasing and was thus inconsistent with the distributions selected by the company. The ERG noted that in the appraisal of atezolizumab with nab-paclitaxel in a similar population (NICE TA639[4]), the Appraisal Committee accepted a Weibull distribution for both arms, which was consistent with the observed hazard. The ERG believed, based on the data available at the time of writing the ERG report, that the Weibull distribution was likely to be the most appropriate model, but stated that additional follow-up of patients in KEYNOTE-355 to assess changes in the hazard of death over time would be beneficial. Such data have become available and new analyses have been presented in the company's TE response.

The hazard plot for death for pembrolizumab plus taxanes based on the latest data-cut (FA) is shown in Figure 10, whilst the corresponding plot for taxanes alone is provided in Figure 11. These have noticeably different smoothed hazards over time, with pembrolizumab plus taxanes suggesting a marginally monotonically increasing hazard over time, whereas for taxanes alone there now appears to be a turning point in the hazard ([redacted]).

Figure 10: The hazard plot for death for pembrolizumab plus taxanes (reproduced from Figure 1 of the company's TE response)

Figure 11: The hazard plot for death for taxanes (reproduced from Figure 2 of the company's TE response)

The company also provides estimates of relative goodness-of-fit (AIC and BIC) to the observed data which are shown in Table 2. The ERG notes however that differences in AIC or BIC of less than 3 are not considered to be significant.[5] As such, using BIC, the majority of distributions fit the observed data well – all but the Gompertz and generalized gamma models for pembrolizumab + taxanes, and all but the gamma, the Weibull and the Gompertz models for taxanes lie within 3 points of the best-fitting distribution.

Table 2: Summary of goodness of fit (AIC / BIC values) for OS when fitting distributions to KEYNOTE-355 data (FA data-cut)

Parametric distribution for OS	Pembrolizumab + taxanes				Taxanes comparator			
	AIC	BIC	AVRG	Rank	AIC	BIC	AVRG	Rank
Exponential	759.61	762.18	760.89	1	440.33	442.18	441.25	4
Weibull	759.80	764.93	762.36	5	441.05	444.75	442.90	6
Log-normal	758.34	763.47	760.90	2	436.06	439.76	437.91	2
Log-logistic	758.45	763.58	761.02	3	435.79	439.49	437.64	1
Gompertz	761.17	766.30	763.74	6	442.26	445.96	444.11	7
Gamma*	759.31	764.44	761.88	4	439.97	443.67	441.82	5
Generalized Gamma	759.91	767.60	763.76	7	437.97	443.53	440.75	3

AIC - Akaike Information Criteria; BIC - Bayesian Information Criteria; AVRG – average ranking is based on the average AIC/BIC statistic
**Gamma not included in the model functionality due to the limitations outlined in the clarification questions.*

The company has maintained the distributions used in its original base case, which is using the log-normal distribution for pembrolizumab plus paclitaxel/nab-paclitaxel and the log-logistic distribution for paclitaxel. The ERG agrees that these appear plausible, but prefers an alternative distribution for the pembrolizumab plus paclitaxel/nab-paclitaxel arm. Based on the smoothed hazard shown in Figure 10

the ERG prefers an exponential distribution for pembrolizumab plus paclitaxel/nab-paclitaxel rather than the log-normal distribution. Whilst the difference in BIC between the exponential and the log-normal distributions does not show a meaningful difference in fitting the observed data, the smoothed hazard shows no turning point, whereas the best-fitting log-normal distribution had reached its turning point within the first year. In scenario analyses, the use of Weibull and log-normal distributions has been explored for the pembrolizumab plus paclitaxel/nab-paclitaxel treatment group as these have different long-term changes in the hazard function.

The company states that '*from the updated clinical data there is no evidence to support the use of Weibull or exponential for OS extrapolations.*' It describes the exponential model as '*based upon constant hazards which is an overly simplistic assumption*' but does not comment on the restrictive assumptions related to its chosen distributions. The company also states that '*The exponential curve does not fit the data well particularly for modelling OS in the taxanes arm whereby extrapolated OS falls outside the 95% KM- CIs for part of the observed period early on, which is also supported by the smooth hazard functions.*' Following similar logic used by the ERG in selecting the best distribution for pembrolizumab plus paclitaxel/nab-paclitaxel, the ERG agrees that the exponential distribution, despite generating a BIC value within 3 units of the best fitting distribution, does not capture the apparent turning point in the observed data for taxanes and has not been selected for the ERG's base case, but the use of this distribution has been explored in scenario analyses within this document (see Section 4).

The company's TE response states that it '*does not believe that the exponential can be used to inform decision making, however, we do explore its impact in alternative analyses*.' This scenario analysis, which assumed the exponential distribution for both arms, increased the company's deterministic ICER from £34,887 to £43,788.

The ERG has run additional analyses using an exponential distribution for pembrolizumab plus paclitaxel/nab-paclitaxel and a log-logistic distribution for paclitaxel. The ERG is comfortable using distributions with noticeably different characteristics for the underlying hazard (the exponential distribution assumes a constant hazard whereas the log-logistic distribution has an increasing hazard before reaching a turning point and then having a perpetually decreasing hazard) due to the different modes of action of the interventions, with the company citing the '*unique*' mode of action of pembrolizumab. The different characteristics of the exponential and log-logistic distributions could result in the hazard of death being lower in the model for paclitaxel than for pembrolizumab plus paclitaxel/nab-paclitaxel if patients lived for a sufficiently long-time, however, in the ERG-preferred approach to modelling the benefits of pembrolizumab following cessation of treatment (see Key Issue 2) prevents this from happening.

3.2 Key Issue 2: Uncertainty surrounding the long-term benefits of pembrolizumab plus paclitaxel/nab-paclitaxel

The company assumed that the distributions fitted to OS apply throughout the modelling time horizon despite the maximum duration for pembrolizumab treatment being two years. The ERG highlighted that this creates the possibility that two patients alive at year 7 and on third-line treatment would have different hazards of death dependent on the initial treatment received. The ERG does not believe that this is plausible and instead chose to explore the impact of an assumption regularly used in NICE Technology Appraisal Committee C [an author is a member of this Appraisal Committee], when assessing immuno-oncology drugs with a maximum treatment period of two years, which is that the hazard of death is assumed equal in the two arms at five years.

The company does not agree with this approach and comments in its TE response that '*based on updated clinical trial data from KEYNOTE-355 there is no evidence of treatment waning. MSD disagrees with the application of treatment waning and considers the 'prior precedent' justification to be a weak, in the absence of any data indicating there is a loss of treatment effect.*' The company further states that due to '*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.*' Additionally, the company states that '*there is no evidence to point towards a waning assumption being relevant for inclusion in the ERG's base-case. We are aware that Appraisal Committee A discussed the impact of waning in the recent TA639 (Atezolizumab + nab-paclitaxel). However, it concluded that whilst waning assumptions are an area of uncertainty, incorporation of an arbitrary treatment waning was inappropriate (3). The AC-A remained consistent with its preferred assumptions around treatment duration from previous breast cancer submissions do not consider any waning of treatment effect for inclusion in the base-case.*' The company concludes that '*it is highly unlikely for all OS benefit to be lost at year 5 in the real-world setting*'. The company performed scenario analyses to explore the impact on the ICER of changing assumptions related to treatment waning, which involved gradual waning adjustments using data from the Surveillance, Epidemiology, and End-Results Program in the USA and the approach originally proposed by the ERG which is to use the hazard of death for taxanes for patients who received pembrolizumab plus paclitaxel/nab-paclitaxel treatment five years after treatment initiation. These resulted in the company's base case deterministic ICER changing from £34,887 to a range of £31,605 to £44,714 dependent on the assumptions made.

The ERG notes the arguments put forward by the company, but remarks that:

- In TA639, there was no stopping rule at two years applied to atezolizumab as it is currently proposed for pembrolizumab, so the discussion of waning had more emphasis on whether the treatment would lose efficacy over time rather than longer-term residual benefit

- The additional data collected in KEYNOTE-355 are consistent with the ERG approach that there would be no waning in treatment efficacy over the initial five-year period (that is, three years after maximum treatment duration). No data are available from KEYNOTE-355 beyond [redacted]
- Most importantly, 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. From interrogation of the company's updated model it appears that the hazard of death in the pembrolizumab plus paclitaxel/nab-paclitaxel treatment arm is higher than in the taxanes arm at approximately [redacted] years.

For these reasons, the ERG maintains the five-year relative OS benefit for pembrolizumab plus paclitaxel/nab-paclitaxel compared with taxanes, as has been regularly used in Appraisal Committee C appraisals, within its base case.

3.3 Key Issue 3: Unfavourable assumption regarding treatment discontinuation for atezolizumab plus nab-paclitaxel

Owing to the absence of appropriate data available from the IMpassion130 study[6], the company's original model assumed that the TTD for atezolizumab plus nab-paclitaxel was equal to PFS for this regimen. The ERG noted that the data provided in the CS shows that TTD in KEYNOTE-355 is markedly less than PFS for both pembrolizumab plus taxanes and for taxanes. Therefore, the assumption employed by the company for atezolizumab plus nab-paclitaxel artificially increases the acquisition costs for this comparator. The exploratory analyses undertaken by the ERG assumed that the Hazard Ratio (HR) for PFS for atezolizumab plus nab-paclitaxel versus pembrolizumab plus paclitaxel/nab-paclitaxel would also be generalisable to TTD. The ERG believes that this approach is more reasonable than that used in the CS, and it was included as part of the ERG preferred analysis.

In its TE response[1], the company has suggested that the approach included in the ERG preferred analysis is '*very likely*' to bias against pembrolizumab plus paclitaxel / nab-paclitaxel as nab-paclitaxel is better tolerated than paclitaxel, and also based on comparisons to the IMpassion130 study. The company compared the TTD for atezolizumab plus nab-paclitaxel generated by the ERG's preferred approach with data provided in the CS for the atezolizumab plus nab-paclitaxel appraisal (TA639) and concluded that the ERG's approach generated lower values than the data reported in the TA639.

The company has revised its assumption such that the TTD for atezolizumab plus nab-paclitaxel is set equal to the TTD to that of pembrolizumab plus nab-paclitaxel. This assumes a HR between the TTD of pembrolizumab plus nab-paclitaxel and atezolizumab plus nab-paclitaxel of 1, in contrast to the ERG's approach which assumes that the HR for PFS was generalisable to TTD. The approach selected by the company had also been explored by the ERG as part of an additional sensitivity analysis (ASA 4); The company states that the TTD distribution produced using its revised assumptions are '*more closely aligned with those reported in TA639*'. The ERG comments that its intended approach wasn't implemented correctly in the ERG report; the ERG intended comparing pembrolizumab plus paclitaxel/nab-paclitaxel with atezolizumab plus nab-paclitaxel, but used pembrolizumab plus nab-paclitaxel alone in error. This error has been amended in this document, with this change being favourable to pembrolizumab plus paclitaxel/nab-paclitaxel.

The results generated by the company indicate that pembrolizumab plus paclitaxel/nab-paclitaxel dominates atezolizumab plus nab-paclitaxel, although this comparison was generated using the list price of atezolizumab but using the PAS price for pembrolizumab, as directed by NICE. The ERG reports ICERs taking the PAS for atezolizumab into account in a confidential appendix.

The ERG highlights that there is no reason to expect that the TTD results generated from an indirect comparison for atezolizumab plus nab-paclitaxel applying the HR to the pembrolizumab plus paclitaxel/nab-paclitaxel arm of KEYNOTE-355 should match the results from IMpassion130. An indirect treatment comparison generates a relative measure of treatment effect, whereas the absolute effect depends on the baseline to which the hazards are applied. Therefore, comparisons with the results from IMpassion130 may be meaningless if populations differ between studies. The ERG notes that the company's TE response states that '*on multiple occasions*' it had raised '*key differences between the two studies (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 (CPS10 score ≥ 10)*'; these statements also question the validity of attempting to match to the results from Impassion130.

Figure 12 presents the TTD survival models using data from the FA of KEYNOTE-355. The red line shows the company's updated base-case used for pembrolizumab plus paclitaxel/nab-paclitaxel (assuming a lognormal distribution) whilst the grey line shows the ERG-preferred analysis (assuming a log-logistic distribution). The figure also includes alternative scenarios for modelling TTD survival for atezolizumab plus nab-paclitaxel: (i) assumed equal to the TTD survival function for pembrolizumab plus nab-paclitaxel (company's updated base-case, blue line, using an exponential distribution) and (ii) assuming the HR between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel/nab-paclitaxel for PFS applies to the pembrolizumab plus paclitaxel/nab-paclitaxel ERG-preferred TTD survival function for pembrolizumab plus paclitaxel/nab-paclitaxel (orange line).

Whilst the ERG's approach has the key limitation in that it is not known whether the HR between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel/nab-paclitaxel for PFS is generalisable to TTD, the ERG believes that this is still a better approach than arbitrarily assuming an HR of 1 by setting the TTD for atezolizumab plus nab-paclitaxel equal to the TTD for pembrolizumab plus nab-paclitaxel.

Figure 12: TTD survival functions for pembrolizumab plus paclitaxel/nab-paclitaxel and alternative assumption for atezolizumab plus nab-paclitaxel (generated by the ERG from the company's updated model) †

† Functions constrained to not be higher than the base case OS function

3.4 Key Issue 4: Uncertainty surrounding the relative efficacy comparison of pembrolizumab plus paclitaxel/nab-paclitaxel versus atezolizumab plus nab-paclitaxel

In the CS, the company conducted a network meta-analysis (NMA) to estimate the relative efficacy of atezolizumab plus nab-paclitaxel compared to pembrolizumab plus paclitaxel/nab-paclitaxel. As acknowledged by the company, the NMA has limitations, but showed favourable midpoint estimates for pembrolizumab plus paclitaxel/nab-paclitaxel with wide credible intervals around these estimates. These credible intervals (CrI) included unity, indicating the possibility that there may be no difference in efficacy between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel/nab-paclitaxel.

The company has updated its NMA results, using a fixed effects model only, in Appendix 2 of its TE response.[1] The conclusions remain largely unchanged in that there is [redacted] for pembrolizumab plus paclitaxel/nab-paclitaxel compared with atezolizumab plus nab-paclitaxel but with wide CrIs (and that pembrolizumab plus paclitaxel/nab-paclitaxel dominates atezolizumab plus nab-paclitaxel). The HRs are [redacted] when using pooled taxanes as the common comparator and [redacted] when nab-paclitaxel alone was used.

The ERG comments that given the heterogeneity in the studies that a random effects model would be preferable, which is unlikely to influence the point estimate materially, but would increase the width of the CrIs. Estimates generated by the company from the random effects model were provided as part of their clarification response; an indication of the likely impact of using these different approaches on the PFS and OS HR estimates is presented in Table 17 of the ERG report. In all exploratory and additional sensitivity analyses presented in the original ERG report, the ERG has used the estimates from the random effects model, which does not have an impact on results from the deterministic version of the model but can be observed on the probabilistic results of the ERG preferred analysis (Tables 37, 38, 41 and 42). The company has not provided updated estimates of the HRs using random effect models in its TE response. As such, the ERG can only run PSA using the fixed effects model; this may be favourable to pembrolizumab plus paclitaxel/nab-paclitaxel, as in the ERG report the PSA using a fixed effects model had a similar ICER to the deterministic estimate, whereas the PSA using a random effects model increased the ICER.

The company believes that using the results from the NMA is better than assuming equivalence of efficacy between pembrolizumab plus paclitaxel/nab-paclitaxel and atezolizumab plus nab-paclitaxel. The ERG has used the NMA data as part of the ERG preferred analysis (as preferred by the company) but has explored the assumption of equal efficacy as part of an additional sensitivity analysis (ASA 5), in case the Appraisal Committee wishes to explore this scenario. The new data do not change the ERG's view on this matter and an exploratory analysis where atezolizumab plus nab-paclitaxel has the same efficacy as pembrolizumab plus paclitaxel/nab-paclitaxel has been run in case this could inform the Appraisal Committee's decision.

3.5 Key Issue 5: Uncertainty related to the most appropriate way to estimate utility

The company adopted two methods for estimating utility: a time-to-death approach and a health-state based approach. In its base case the company has preferred the time-to-death approach. The ERG notes that both methods have limitations and that neither approach overcomes the main limitation which is that the data collected have been heavily censored, either at the point of progression, or at treatment discontinuation. The ERG had no preference for either approach and presented ICERs using both

approaches and noted that were the Appraisal Committee to favour the health state approach, or to decide that the true ICER lay in between the results generated by each method then the ICER would increase.

In its response to technical engagement, the company stated that '*MSD does not have a preference for the utility estimation approach; however, we believe the time-to-death approach is the most appropriate based on the severity of this disease and other reasons outlined below'*. These reasons included that '*the time-to-death-based approach was used in the base-case to overcome the issue of limited questionnaire availability to inform the post-progression health state utility. This method also captures the expected deterioration in patient's quality of life as they reach the terminal phase of their disease.*' The company also reference several recent HTA submissions that used a time-to-death approach. Sensitivity analyses performed by the company indicated that the deterministic ICERs generated by the two methods were relatively similar (£34,887 using the time-to-death approach and £35,605 using utilities based on progression status and adverse events). The company state that '*based on the limitations of both approaches, we advocate for the use of the time-to-death-based utility estimation approach based on the aggressiveness of TNBC and the use and acceptance of this approach for other recent HTA submissions.*'

The ERG maintains its view that it has no preference for either method and that both approaches have limitations relating to the level of censoring post-progression. The company did not report how many recent HTA submissions estimated utility based on health state approach and thus the relative frequency of the time-to-death approach is unknown. The ERG has provided the ICERs generated using both methods so that these data are available should the Appraisal Committee prefer one method.

3.6 Key Issue 6: Inclusion of vial sharing for intravenous (IV) drugs (with the exception of pembrolizumab and atezolizumab)

In its TE response and revised base case, the company has assumed that vial sharing exists for IV drugs, with the exception of pembrolizumab and atezolizumab. The company notes that several of the IV drugs assumed to be vial-shared are used for the treatment of other cancers and state that '*Considering that some scheduled appointments may overlap in the real-world setting with use of standard chemotherapies for other cancers, some vial sharing for chemotherapies that do not require flat dosing may still take place potentially to limit wastage, which means that the true ICER is likely to lie between the estimates presented with and without vial sharing.*' When vial-sharing is not assumed the deterministic ICER increases from the company base case of £34,887 to £36,237.

Clinical advice to the ERG suggested that vial sharing would not happen in practice. Based on this clinical advice, the ERG maintains that the ICER without vial-sharing is more appropriate than the

ICER with vial sharing, although this would overestimate the ICER if vial sharing does occur in a proportion of centres. An audit related to vial sharing at treatment centres would allow a more accurate estimate of the ICER to be generated.

3.7 Additional issue raised by the company: Inclusion of docetaxel as a comparator

The company's TE response states that '*As noted within our submission and in TA639, docetaxel is not a relevant comparator since it is being used primarily at earlier stages of breast cancer and is also associated with a less favourable adverse event profile versus that of paclitaxel.*' The company also states that docetaxel is used more frequently in early breast cancer and it is '*it is unlikely to be used again in patients which have progressed following on treatment with docetaxel*'.

However, as the final NICE scope included docetaxel as a comparator, the company provided secondary analyses for pembrolizumab plus paclitaxel/nab-paclitaxel against docetaxel with the assumption that docetaxel had equivalent efficacy to paclitaxel. This assumption resulted in docetaxel having the same clinical outcomes as paclitaxel but at a lower cost, as acquisition costs were £20.75 and £28.05 respectively and administration costs (per weekly cycle) were £231.35 and £451.24 respectively with docetaxel administered once every 3 weeks whereas paclitaxel was administered three times every 28 days in KEYNOTE-355. The ERG notes that the KEYNOTE-355 schedule was used rather than weekly doses (as is believed to be the typical frequency in the UK) in order to align drug costs and clinical outcomes for paclitaxel. The lower costs, but equal effectiveness, of docetaxel compared with paclitaxel means that docetaxel dominates paclitaxel, thus in a full incremental analysis the ICER comparing pembrolizumab plus paclitaxel/nab-paclitaxel against docetaxel is relevant, particularly as docetaxel was explicitly listed as a comparator in the NICE scope.

The ERG presented full incremental analyses, but noting the company's concerns with using docetaxel as a comparator, it also provided supplementary tables comparing pembrolizumab plus paclitaxel/nab-paclitaxel against paclitaxel only (Tables 38, 40, 42 and 44 of the ERG report). The ICERs for pembrolizumab plus paclitaxel/nab-paclitaxel compared with both docetaxel and paclitaxel for all ERG exploratory and additional sensitivity analyses are provided in the Section 1.7 (Summary of ERG's preferred assumptions and resulting ICER) and Section 6 (Overall Conclusions) of the ERG report. This dual approach provides the Appraisal Committee with relevant information regardless of whether it believes that docetaxel is an appropriate comparator. As such, the same approach has been undertaken within this document.

The ERG comments that any additional adverse events (AEs) associated with docetaxel compared with paclitaxel have not been incorporated in the analyses, due to the assumption made by the company of equal health impact, which means that the ICER of pembrolizumab plus paclitaxel/nab-paclitaxel

compared to docetaxel may be unfavourable to pembrolizumab plus paclitaxel/nab-paclitaxel. The ERG expects that this impact would not be substantial although this could only be corroborated or disproved by the company including the impact of adverse events for each of these regimens within the model.

3.8 Additional issues from the ERG assessment of the new model version

During the verification of the company's new model, the ERG identified one programming error, where the updated HR for OS for atezolizumab plus nab-paclitaxel is not applied, with the original value in the CS being used instead. This error has been fixed by the ERG in all exploratory and additional sensitivity analyses presented in Section 4.2; the ERG notes that this change has an impact only on results for atezolizumab plus nab-paclitaxel and that the change in the incremental costs and QALYs are moderate.

The ERG explored the impact on the ICER of selecting the distributions for TTD that had the lowest BIC values. These were the log-logistic for pembrolizumab plus paclitaxel/nab-paclitaxel and the log-normal distribution for taxanes.

4 Additional analyses undertaken by the company and the ERG

4.1 Results of the analyses presented by the company

This section presents the central estimates of costs effectiveness using the probabilistic and deterministic versions of the updated version of the company's model submitted at the TE response, as replicated by the ERG based on the analyses described by the company. As mentioned in Section 2, for brevity the scenario analyses are not presented here (see Appendix 4 of the company's TE response).[1]

Table 3 presents the central estimates of cost-effectiveness generated using the company's updated model for the pairwise comparison of pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel, whilst Table 4 and Table 5 present the estimates of cost-effectiveness for the comparisons against docetaxel and atezolizumab plus nab-paclitaxel, respectively.

Table 3: Company's updated results - Base Case Analysis, pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel

Options	LYGs*	QALYs	Cost	Inc. LYGs*	Inc QALYs	Inc Costs	ICER
Probabilistic model							
Paclitaxel	2.31	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.54	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£35,105**
Deterministic model							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£34,887**

Inc – incremental; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** Undiscounted*

Table 4: Company's results - Base Case Analysis, pembrolizumab plus paclitaxel/nab-paclitaxel versus docetaxel

Options	LYGs*	QALYs	Cost	Inc. LYGs*	Inc QALYs	Inc Costs	ICER
Probabilistic model							
Docetaxel	2.31	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.54	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£42,904**
Deterministic model							
Docetaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£42,415**

Inc – incremental; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** Undiscounted*

Table 5: Company's results - Base Case Analysis, pembrolizumab plus paclitaxel/nab-paclitaxel versus atezolizumab plus nab-paclitaxel†

Options	LYGs*	QALYs	Cost	Inc. LYGs*	Inc QALYs	Inc Costs	ICER
Probabilistic model							
Atezolizumab plus nab-paclitaxel	2.53	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.54	[redacted]	[redacted]	2.02	[redacted]	[redacted]	**Dominating**
Deterministic model							
Atezolizumab plus nab-paclitaxel	2.40	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.10	[redacted]	[redacted]	**Dominating**

Inc – incremental; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** Undiscounted*
† The result presented here does not include fixing the error identified by the ERG in the estimate used for the HR for OS for atezolizumab plus nab-paclitaxel.

The probabilistic version of the model suggests that pembrolizumab combination therapy, when compared to paclitaxel, is expected to generate an additional [redacted] QALYs at an additional cost of [redacted] per patient; the corresponding ICER is £35,105 per QALY gained. The deterministic version of the model produces a slightly lower ICER of £34,887 per QALY gained with the model appearing relatively linear. In comparison against docetaxel, pembrolizumab combination therapy is expected to generate the same amount of additional QALYs, but at a higher additional cost of [redacted] per patient; the corresponding ICER is £42,904 per QALY gained in the probabilistic version of the model, whilst the deterministic version generates an ICER of £42,415. The analysis against atezolizumab plus nab-paclitaxel suggests that atezolizumab plus nab-paclitaxel is dominated by pembrolizumab plus paclitaxel/nab-paclitaxel, by generating fewer QALYs at a higher cost.

4.2 Description of additional exploratory analyses undertaken by the ERG

In all exploratory and additional sensitivity analyses, the ERG has used the company's updated version of the model, although this contains the HR estimates generated by the company from a fixed effects model rather than a random effects model as would be preferred by the ERG. The ERG has also amended the value of the HR for OS for atezolizumab plus nab-paclitaxel to correct an error in the company's model (see Section 3.8) and additionally has changed the assumption that the TTD for atezolizumab plus nab-paclitaxel is set equal to the TTD to that of pembrolizumab plus paclitaxel/nab-paclitaxel rather than being equal to the TTD for pembrolizumab plus nab-paclitaxel. The exploratory analyses are linked to the key issues identified in the ERG report; further analyses, denoted additional

sensitivity analyses, are also provided which explore additional assumptions that the ERG believes are plausible or that the Appraisal Committee may want to consider. All exploratory analyses except for exploratory analysis 1 and exploratory analysis 6 are maintained from the ERG report; the assumptions within exploratory analyses 1 has changed due to the availability of more mature data whereas exploratory analysis 6 has been introduced following changes made by the company in estimating TTD.

ERG exploratory analysis 1: Use of alternative OS survival functions

The ERG assessed the impact on the ICER of using the exponential survival function for OS for pembrolizumab plus paclitaxel/nab-paclitaxel instead of the log-normal model. The distribution of choice for the taxanes treatment group for OS remained the log-logistic.

ERG exploratory analysis 2: Use of alternative PFS survival functions

The ERG explored using parametric functions fitted to the entire PFS dataset rather than the company's piecewise approach that used the observed KM survival function up to 9 weeks, whilst the distributions remain the same as those originally used by the company. Goodness-of-fit statistics were not provided by the company in relation to PFS with the more mature data, the ERG has maintained the distributions from the ERG report noting that the model is not overly sensitive to the choice of distributions used to estimate PFS.

ERG exploratory analysis 3: Use of alternative TTD survival function for atezolizumab plus nab-paclitaxel

The ERG assumed that the TTD function for atezolizumab plus nab-paclitaxel can be estimated by applying the HR for PFS generated by the company's NMA to the TTD survival function for pembrolizumab plus paclitaxel/nab-paclitaxel.

ERG exploratory analysis 4: Alternative assumption of treatment effect duration

The ERG explored the impact of assuming that the hazard of death for pembrolizumab plus paclitaxel/nab-paclitaxel became equal to that of taxanes 5 years after initiation of pembrolizumab plus paclitaxel/nab-paclitaxel treatment.

ERG exploratory analysis 5: No vial sharing considered

In this analysis, the ERG explored the impact of assuming no vial sharing for any IV drugs.

ERG exploratory analysis 6: Alternative distributions used for TTD

In this analysis, the ERG used a log-logistic distribution for pembrolizumab plus paclitaxel/nab-paclitaxel and a log-normal distribution for taxanes as these appeared to be the best fitting distributions based on BIC.

ERG exploratory analysis 7: ERG's updated preferred base case

The ERG's preferred base case includes ERG exploratory analysis 1 to 6.

ERG additional sensitivity analysis 1: Use of alternative models for OS

Within this analysis, the ERG assessed the impact on the ICER of using the Weibull or the log-normal distributions for pembrolizumab plus paclitaxel/nab-paclitaxel, and the exponential survival OS function for paclitaxel rather than the exponential and the log-logistic used in the ERG's base case. The Weibull and the log-normal distributions were chosen for pembrolizumab plus paclitaxel/nab-paclitaxel as these have opposite longer-term hazards, with the Weibull distribution having a hazard that perpetually increases, whilst the log-normal distribution has a hazard that perpetually decreases after the turning point. Analyses ASA1a to ASA1e present all the possible combinations of these distributions.

ERG additional sensitivity analysis 2: Alternative assumption of treatment effect duration

In this analysis, the ERG explores the impact of restoring the assumption of a lifetime relative treatment benefit of pembrolizumab plus paclitaxel/nab-paclitaxel. However, as stated in Section 3.2, the ERG does not believe that this is a plausible assumption given [redacted].

ERG additional sensitivity analysis 3: Alternative assumption of treatment effect duration

Within this analysis, the ERG assumes that the hazard of death for pembrolizumab plus paclitaxel/nab-paclitaxel became equal to that of taxanes 3 years after initiation of pembrolizumab plus paclitaxel/nab-paclitaxel treatment.

ERG additional sensitivity analysis 4: Use of alternative TTD model for atezolizumab plus nab-paclitaxel

Within this analysis, the ERG assesses the impact of assuming the TTD function for atezolizumab plus nab-paclitaxel is the same as the TTD survival function for pembrolizumab plus paclitaxel/nab-paclitaxel (as included in the company's updated base case).

ERG additional sensitivity analysis 5: Assumption of equivalent clinical efficacy between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel/nab-paclitaxel

Within this analysis, the ERG assumes that there is no relative difference in treatment effect between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel/nab-paclitaxel (HRs are assumed to be equal to 1 for all clinical outcomes and only the treatment costs differ between the interventions).

4.3 Results of exploratory analyses undertaken by the ERG

Time-to-death approach for modelling HRQoL (Exploratory analyses a)

Table 6 and Table 7 present the results of the ERG exploratory analyses that used the time-to-death approach for modelling HRQoL versus all the comparators (full incremental analyses) and against paclitaxel, respectively.

The largest change in the ICER is generated when assuming that an exponential distribution is appropriate for OS for pembrolizumab plus paclitaxel/nab-paclitaxel rather than a log-normal distribution. This is because the hazard of death is higher when an exponential distribution is used after approximately [redacted] than when the log-normal distribution is used (see Figure 10). However, when this is combined with the ERG's preference to set the HR to 1, 5 years after the initiation of pembrolizumab plus paclitaxel/nab-paclitaxel treatment, the ICER is reduced as the hazard of death in the longer-term would not be greater for those treated with pembrolizumab plus paclitaxel/nab-paclitaxel compared with taxanes. These interpretations also apply to when HRQoL is estimated using a health-state approach.

The ERG preferred ICERs are lower than in the ERG report as the underlying distribution for OS for taxanes has changed from a Weibull distribution, which has a perpetually increasing hazard, to a log-logistic distribution, where the hazard perpetually decreases after the turning point. Together with the ERG's assumption that patients in the pembrolizumab plus paclitaxel/nab-paclitaxel arm would have the same hazard of death as those in the taxanes arm 5 years after treatment initiation, these result in the additional survivors due to pembrolizumab plus paclitaxel/nab-paclitaxel treatment generating more QALYs than had previously been the case, increasing the QALYs gained, and reducing the ICER. This interpretation also applies to when HRQoL is estimated using a health-state approach.

Table 6: 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)
Company's updated base case a – using HRQoL by time-to-death							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£42,415**
Atezolizumab plus nab-paclitaxel	2.40	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Company's updated base case a + fixing error in the atezolizumab plus nab-paclitaxel HR for OS and in TTD approach for atezolizumab plus nab-paclitaxel (assumed equal to pembrolizumab plus paclitaxel / nab-paclitaxel)							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£42,415**
Atezolizumab plus nab-paclitaxel	2.86	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 1a – Using an exponential distribution for OS for pembrolizumab plus paclitaxel/nab-paclitaxel							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.51	[redacted]	[redacted]	1.25	[redacted]	[redacted]	**£60,625**
Atezolizumab plus nab-paclitaxel	2.47	[redacted]	£106,768	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 2a - Using the parametric distributions for PFS without using the KM							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£42,376**
Atezolizumab plus nab-paclitaxel	2.86	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 3a – Assuming that the HR between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel/nab-paclitaxel associated with PFS also applied to TTD							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£42,415**
Atezolizumab plus nab-paclitaxel	2.86	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 4a – Hazard of death for pembrolizumab plus paclitaxel/nab-paclitaxel set equal to taxanes hazard 5 years after treatment initiation							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.12	[redacted]	[redacted]	1.87	[redacted]	[redacted]	**£48,221**
Atezolizumab plus nab-paclitaxel	2.69	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
ERG exploratory analysis 5a – Removal of vial sharing for IV treatments†							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£43,761**
Atezolizumab plus nab-paclitaxel	2.86	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 6a – Using alternative TTD functions for pembrolizumab plus paclitaxel/nab-paclitaxel (log-logistic) and taxanes (log- normal)							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£43,944**
Atezolizumab plus nab-paclitaxel	2.86	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 7a - ERG preferred analysis – time-to-death approach (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**
Atezolizumab plus nab-paclitaxel	2.60	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 7a - ERG preferred analysis – time-to-death approach (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]	**£54,893**
Atezolizumab plus nab-paclitaxel	2.73	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**

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 which were already assumed not to share vials.*

Table 7: 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)
Company's updated base case a – using HRQoL by time-to-death							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£34,887**
ERG exploratory analysis 1a – Using an exponential distribution for OS for pembrolizumab plus paclitaxel/nab-paclitaxel							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.51	[redacted]	[redacted]	1.25	[redacted]	[redacted]	**£49,426**
ERG exploratory analysis 2a - Using the parametric distributions for PFS without using the KM							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£34,847**
ERG exploratory analysis 4a – Hazard of death for pembrolizumab plus paclitaxel/nab-paclitaxel set equal to taxanes hazard 5 years after treatment initiation							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.12	[redacted]	[redacted]	1.87	[redacted]	[redacted]	**£39,531**
ERG exploratory analysis 5a – Removal of vial sharing for IV treatments†							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£36,237**
ERG exploratory analysis 6a – Using alternative TTD functions for pembrolizumab plus paclitaxel/nab-paclitaxel (log-logistic) and taxanes (log- normal)							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£35,955**
ERG exploratory analysis 7a - ERG preferred analysis – time-to-death approach (deterministic)							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.99	[redacted]	[redacted]	1.73	[redacted]	[redacted]	**£44,930**
ERG exploratory analysis 7a - ERG preferred analysis – time-to-death approach (probabilistic)							
Paclitaxel	2.31	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.02	[redacted]	[redacted]	1.72	[redacted]	[redacted]	**£44,637**

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 which were already assumed not to share vials.*
The company's updated fixed case with the errors fixed and exploratory analysis 3a are not applicable for the pairwise comparison between pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel, and therefore does not affect the results for this comparator.

Table 8 and Table 9 present the results of the ERG's additional sensitivity analyses for pembrolizumab plus paclitaxel/nab-paclitaxel versus all the comparators (full incremental analyses) and against paclitaxel, respectively.

The most noticeable changes in the ICER are when an exponential distribution is used to model OS for taxanes. This is because the additional survivors associated with pembrolizumab plus paclitaxel/nab-paclitaxel treatment live less long and generate fewer QALYs, reducing the incremental QALYs gained and increasing the ICER. The ICER is highest when a Weibull distribution is used for pembrolizumab plus paclitaxel/nab-paclitaxel in addition to an exponential distribution for taxanes. These interpretations also apply to when HRQoL is estimated using a health-state approach.

Table 8: Results of ERG additional sensitivity 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)
ERG preferred analysis – time-to-death approach (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**
Atezolizumab plus nab-paclitaxel	2.60	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 1a (i) – Using alternative distributions for OS (OS pembro = log-normal, OS taxanes = log-logistic)							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.12	[redacted]	[redacted]	1.87	[redacted]	[redacted]	**£51,640**
Atezolizumab plus nab-paclitaxel	2.69	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 1a (ii) – Using alternative distributions for OS (OS pembro = Weibull, OS taxanes = log-logistic)							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.82	[redacted]	[redacted]	1.56	[redacted]	[redacted]	**£58,844**
Atezolizumab plus nab-paclitaxel	2.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 1a (iii) – Using alternative distributions for OS (OS pembro = exponential, OS taxanes = exponential)							
Docetaxel	1.94	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	1.94	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.13	[redacted]	[redacted]	1.19	[redacted]	[redacted]	**£69,932**
Atezolizumab plus nab-paclitaxel	2.32	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 1a (iv) – Using alternative distributions for OS (OS pembro = log-normal, OS taxanes = exponential)							
Docetaxel	1.94	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	1.94	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.19	[redacted]	[redacted]	1.25	[redacted]	[redacted]	**£67,084**

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Atezolizumab plus nab-paclitaxel	2.38	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 1a (v) – Using alternative distributions for OS (OS pembro = Weibull, OS taxanes = exponential)							
Docetaxel	1.94	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	1.94	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.08	[redacted]	[redacted]	1.14	[redacted]	[redacted]	**£72,114**
Atezolizumab plus nab-paclitaxel	2.33	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 2a – Assumption of lifetime treatment benefit duration							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.51	[redacted]	[redacted]	1.25	[redacted]	[redacted]	**£65,045**
Atezolizumab plus nab-paclitaxel	2.47	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 3a – Hazard of death for pembrolizumab plus paclitaxel/nab-paclitaxel set equal to taxanes hazard 3 years after treatment initiation							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.68	[redacted]	[redacted]	1.42	[redacted]	[redacted]	**£64,125**
Atezolizumab plus nab-paclitaxel	2.43	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 4a – TTD for atezolizumab plus nab-paclitaxel assumed equal to pembrolizumab plus paclitaxel / nab-paclitaxel							
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**
Atezolizumab plus nab-paclitaxel	2.60	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 5a – assumption of the same clinical efficacy between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel / nab-paclitaxel							
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**
Atezolizumab plus nab-paclitaxel	3.99	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
** undiscounted.*

Table 9: Results of ERG additional sensitivity 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)
ERG preferred analysis – time-to-death approach (deterministic)							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.99	[redacted]	[redacted]	1.73	[redacted]	[redacted]	**£44,930**
ERG additional sensitivity analysis 1a (i) – Using alternative distributions for OS (OS pembro = log-normal, OS taxanes = log-logistic)							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.12	[redacted]	[redacted]	1.87	[redacted]	[redacted]	**£42,422**
ERG additional sensitivity analysis 1a (ii) – Using alternative distributions for OS (OS pembro = Weibull, OS taxanes = log-logistic)							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.82	[redacted]	[redacted]	1.56	[redacted]	[redacted]	**£48,208**
ERG additional sensitivity analysis 1a (iii) – Using alternative distributions for OS (OS pembro = exponential, OS taxanes = exponential)							
Paclitaxel	1.94	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.13	[redacted]	[redacted]	1.19	[redacted]	[redacted]	**£57,075**
ERG additional sensitivity analysis 1a (iv) – Using alternative distributions for OS (OS pembro = log-normal, OS taxanes = exponential)							
Paclitaxel	1.94	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.19	[redacted]	[redacted]	1.25	[redacted]	[redacted]	**£54,801**
ERG additional sensitivity analysis 1a (v) – Using alternative distributions for OS (OS pembro = Weibull, OS taxanes = exponential)							
Paclitaxel	1.94	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.08	[redacted]	[redacted]	1.14	[redacted]	[redacted]	**£58,832**
ERG additional sensitivity analysis 2a – Assumption of lifetime treatment benefit duration							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.51	[redacted]	[redacted]	1.25	[redacted]	[redacted]	**£53,168**
ERG additional sensitivity analysis 3a – Hazard of death for pembrolizumab plus paclitaxel/nab-paclitaxel set equal to taxanes hazard 3 years after treatment initiation							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.68	[redacted]	[redacted]	1.42	[redacted]	[redacted]	**£52,445**

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
** undiscounted;*
Exploratory analyses 4a and 5a are not applicable for the pairwise comparison between pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel, and therefore do not affect the results for this comparator.

Approach for modelling HRQoL by health states (Exploratory analyses b)

Table 10 and Table 11 present the results of the ERG exploratory analyses that used health states to estimate HRQoL, including additional disutility from AEs, versus all the comparators (full incremental analyses) and against paclitaxel, respectively.

Table 10: Results of the ERG exploratory analyses, pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel, docetaxel and atezolizumab plus nab-paclitaxel, utilities by health states approach for modelling HRQoL

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's updated base case b (HRQoL by health state)							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£43,289**
Atezolizumab plus nab-paclitaxel	2.40	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Company's updated base case b + fixing error in the atezolizumab plus nab-paclitaxel HR for OS and in TTD approach for atezolizumab plus nab-paclitaxel (assumed equal to pembrolizumab plus paclitaxel / nab-paclitaxel)							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£43,289**
Atezolizumab plus nab-paclitaxel	2.86	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 1b – Using an exponential distribution for OS for pembrolizumab plus paclitaxel/nab-paclitaxel							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.51	[redacted]	[redacted]	1.25	[redacted]	[redacted]	**£59,045**
Atezolizumab plus nab-paclitaxel	2.47	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 2b - Using the parametric distributions for PFS without using the KM							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£45,150**
Atezolizumab plus nab-paclitaxel	2.86	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 3b - Assuming that the HR between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel/nab-paclitaxel associated with PFS also applied to TTD							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£43,289**

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Atezolizumab plus nab-paclitaxel	2.86	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 4b – Hazard of death for pembrolizumab plus paclitaxel/nab-paclitaxel set equal to taxanes hazard 5 years after treatment initiation							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.12	[redacted]	[redacted]	1.87	[redacted]	[redacted]	**£47,881**
Atezolizumab plus nab-paclitaxel	2.69	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 5b – Removal of vial sharing for IV treatments†							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**-**
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£44,662**
Atezolizumab plus nab-paclitaxel	2.86	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 6b – Using alternative TTD functions for pembrolizumab plus paclitaxel/nab-paclitaxel (log-logistic) and taxanes (log- normal)							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£44,849**
Atezolizumab plus nab-paclitaxel	2.86	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 7b - ERG preferred analysis – HRQoL by health state (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]	**£56,659**
Atezolizumab plus nab-paclitaxel	2.60	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 7b - ERG preferred analysis – HRQoL by health state (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]	**£56,678**
Atezolizumab plus nab-paclitaxel	2.73	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**

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 which were already assumed not to share vials.*

Table 11: Results of the ERG exploratory analyses, pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel, utilities by health states approach for modelling HRQoL

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company's updated base case (HRQoL by health state)							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£35,605**
ERG exploratory analysis 1a – Using an exponential distribution for OS for pembrolizumab plus paclitaxel/nab-paclitaxel							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.51	[redacted]	[redacted]	1.25	[redacted]	[redacted]	**£48,138**
ERG exploratory analysis 2b - Using the parametric distributions for PFS without using the KM							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£37,129**
ERG exploratory analysis 4b – Hazard of death for pembrolizumab plus paclitaxel/nab-paclitaxel set equal to taxanes hazard 5 years after treatment initiation							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.12	[redacted]	[redacted]	1.87	[redacted]	[redacted]	**£39,251**
ERG exploratory analysis 5b – Removal of vial sharing for IV treatments†							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£36,983**
ERG exploratory analysis 6b – Using alternative TTD functions for pembrolizumab plus paclitaxel/nab-paclitaxel (log-logistic) and taxanes (log- normal)							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.50	[redacted]	[redacted]	2.24	[redacted]	[redacted]	**£36,696**
ERG exploratory analysis 7b - ERG preferred analysis – HRQoL by health state (deterministic)							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.99	[redacted]	[redacted]	1.73	[redacted]	[redacted]	**£46,478**
ERG exploratory analysis 7b - ERG preferred analysis – HRQoL by health state (probabilistic)							
Paclitaxel	2.31	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.02	[redacted]	[redacted]	1.72	[redacted]	[redacted]	**£46,088**

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 which were already assumed not to share vials. The company's updated base case with the errors fixed and exploratory analysis 3b are not applicable for the pairwise comparison between pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel, and therefore does not affect the results for this comparator.*

Table 12 and Table 13 present the results of the ERG's additional sensitivity analyses using health states to estimate HRQoL, including additional disutility due to AEs, for pembrolizumab plus paclitaxel/nab-paclitaxel versus all the comparators (full incremental analyses) and against paclitaxel, respectively.

Table 12: Results of ERG additional sensitivity analyses, pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel, docetaxel and atezolizumab plus nab-paclitaxel, utilities by health states approach for modelling HRQoL

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
ERG preferred analysis – HRQoL by health state (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]	**£56,659**
Atezolizumab plus nab-paclitaxel	2.60	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 1b (i) – Using alternative distributions for OS (OS pembro = log-normal, OS taxanes = log-logistic)							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.12	[redacted]	[redacted]	1.87	[redacted]	[redacted]	**£53,811**
Atezolizumab plus nab-paclitaxel	2.69	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 1b (ii) – Using alternative distributions for OS (OS pembro = Weibull, OS taxanes = log-logistic)							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.82	[redacted]	[redacted]	1.56	[redacted]	[redacted]	**£59,869**
Atezolizumab plus nab-paclitaxel	2.55	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 1b (iii) – Using alternative distributions for OS (OS pembro = exponential, OS taxanes = exponential)							
Docetaxel	1.94	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	1.94	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.13	[redacted]	[redacted]	1.19	[redacted]	[redacted]	**£68,824**
Atezolizumab plus nab-paclitaxel	2.32	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 1b (iv)– Using alternative distributions for OS (OS pembro = log-normal, OS taxanes = exponential)							
Docetaxel	1.94	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	1.94	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.19	[redacted]	[redacted]	1.25	[redacted]	[redacted]	**£66,268**
Atezolizumab plus nab-paclitaxel	2.38	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
ERG additional sensitivity analysis 1b (v)– Using alternative distributions for OS (OS pembro = Weibull, OS taxanes = exponential)							
Docetaxel	1.94	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	1.94	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.08	[redacted]	[redacted]	1.14	[redacted]	[redacted]	**£70,420**
Atezolizumab plus nab-paclitaxel	2.33	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 2b – Assumption of lifetime treatment benefit duration							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.51	[redacted]	[redacted]	1.25	[redacted]	[redacted]	**£64,906**
Atezolizumab plus nab-paclitaxel	2.47	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 3b – Hazard of death for pembrolizumab plus paclitaxel/nab-paclitaxel set equal to taxanes hazard 3 years after treatment initiation							
Docetaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	-
Paclitaxel	2.26	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.68	[redacted]	[redacted]	1.42	[redacted]	[redacted]	**£64,347**
Atezolizumab plus nab-paclitaxel	2.43	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 4b - TTD for atezolizumab plus nab-paclitaxel assumed equal to pembrolizumab plus paclitaxel / nab-paclitaxel							
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]	**£56,659**
Atezolizumab plus nab-paclitaxel	2.60	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG additional sensitivity analysis 5b – assumption of the same clinical efficacy between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel / nab-paclitaxel							
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]	**£56,659**
Atezolizumab plus nab-paclitaxel	3.99	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
** undiscounted.*

Table 13: Results of ERG additional sensitivity analyses, pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel, utilities by health states approach for modelling HRQoL

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
ERG preferred analysis – HRQoL by health state (deterministic)							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.99	[redacted]	[redacted]	1.73	[redacted]	[redacted]	**£46,478**
ERG additional sensitivity analysis 1a (i) – Using alternative distributions for OS (OS pembro = log-normal, OS taxanes = log-logistic)							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	4.12	[redacted]	[redacted]	1.87	[redacted]	[redacted]	**£44,206**
ERG additional sensitivity analysis 1b (ii) – Using alternative distributions for OS (OS pembro = Weibull, OS taxanes = log-logistic)							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.82	[redacted]	[redacted]	1.56	[redacted]	[redacted]	**£49,048**
ERG additional sensitivity analysis 1b (iii) – Using alternative distributions for OS (OS pembro = exponential, OS taxanes = exponential)							
Paclitaxel	1.94	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.13	[redacted]	[redacted]	1.19	[redacted]	[redacted]	**£56,171**
ERG additional sensitivity analysis 1b (iv) – Using alternative distributions for OS (OS pembro = log-normal, OS taxanes = exponential)							
Paclitaxel	1.94	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.19	[redacted]	[redacted]	1.25	[redacted]	[redacted]	**£54,133**
ERG additional sensitivity analysis 1b (v) – Using alternative distributions for OS (OS pembro = Weibull, OS taxanes = exponential)							
Paclitaxel	1.94	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.08	[redacted]	[redacted]	1.14	[redacted]	[redacted]	**£57,450**
ERG additional sensitivity analysis 2b – Assumption of lifetime treatment benefit duration							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.51	[redacted]	[redacted]	1.25	[redacted]	[redacted]	**£53,054**
ERG additional sensitivity analysis 3b – Hazard of death for pembrolizumab plus paclitaxel/nab-paclitaxel set equal to taxanes hazard 3 years after treatment initiation							
Paclitaxel	2.26	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.68	[redacted]	[redacted]	1.42	[redacted]	[redacted]	**£52,626**

Inc. - incremental; ICER - incremental cost-effectiveness ratio; LYG - life year gained; QALY - quality-adjusted life year
** undiscounted;*
Exploratory analyses 4b and 5b are not applicable for the pairwise comparison between pembrolizumab plus paclitaxel/nab-paclitaxel and paclitaxel, and therefore do not affect the results for this comparator.

5 End-of-Life criteria

In the CS the company puts forward the case that pembrolizumab plus a taxane meets the NICE End of Life criteria. These criteria are:

- 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 offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The company's base case probabilistic analysis estimates that for patients receiving a taxane alone that the mean life years gained per patient is 2.31 years (27.7 months), which is also the value in the ERG's preferred analysis. For patients who could receive atezolizumab plus nab-paclitaxel, the company estimated a probabilistic average survival of 2.53 years whilst the ERG estimated 2.73 years. These values cast doubt over whether the short life criterion is met. In order to inform the Appraisal Committee's decision, the ERG generated two additional graphs which show the Kaplan-Meier survival functions and modelled OS survival functions for all treatment options in the company's updated base-case (including fixing the issue related to the OS HR for atezolizumab) and the ERG-preferred analysis (Figure 13 and Figure 14, respectively).

Figure 13: OS survival functions for all treatment options included in company's base case plus correction of errors analysis (generated by the ERG)*†

[redacted]

**Taxanes: paclitaxel/nab-paclitaxel*
† Note - the modelled OS survival function for docetaxel is assumed identical to the OS survival function for paclitaxel. The hazards are constrained to be at least as great as general population mortality The company's base-case plus correction of errors includes fixing the issue related to the OS HR for atezolizumab plus nab-nab-paclitaxel (See Section 3.8)

Figure 14: OS survival functions for all treatment options, ERG-preferred analysis (generated by the ERG) *†

[redacted]

**Taxanes: paclitaxel/nab-paclitaxel*
† Note - the modelled OS survival function for docetaxel is assumed identical to the OS survival function for paclitaxel. The hazards are constrained to be at least as great as general population mortality

The company's base-case estimates that approximately [redacted] of patients receiving pembrolizumab plus paclitaxel/nab-paclitaxel, [redacted] receiving atezolizumab plus nab-paclitaxel, and [redacted] receiving

paclitaxel or docetaxel will still be alive at 2 years. The corresponding values for the ERG-preferred analysis are [redacted], [redacted], and [redacted] respectively.

The estimated mean life years gained for patients receiving pembrolizumab plus paclitaxel/nab-paclitaxel is 4.54 years in the company's base case and 4.02 years in the ERG's preferred analyses. Under all scenarios it is expected that the use of pembrolizumab plus paclitaxel/nab-paclitaxel would result in a life extension of greater than three months indicating that the criterion related to the extension of life appears to be met. The ERG comments that that life years gained presented in the company's response to technical engagement are discounted life years which explains any potential discrepancy.

6 Overall conclusions

The model submitted by the company was implemented to a good standard, although the ERG preferred alternative assumptions to those used by the company. Incorporating the assumptions preferred by the ERG increased the deterministic ICER of pembrolizumab plus paclitaxel / nab-paclitaxel compared with docetaxel from £42,415 in the company's base case to £54,771 in the ERG's base case (£54,893 probabilistic) when a time-to-death approach for generating utilities was utilised and from £43,289 to £56,659 (£56,678 probabilistic) when a health-state approach for generating utilities was used. The ICER of pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel increased from £34,887 in the company's base case to £44,930 in the ERG's preferred analysis (£44,637 probabilistic) when a time-to-death approach for generating utilities was utilised and from £35,605 to £46,478 (£46,088 probabilistic) when a health-state approach for generating utilities was used.

Additional sensitivity analyses conducted by the ERG suggests that the deterministic ICER of pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel could range from £51,640 to £72,114 when compared with docetaxel and from £42,422 to £58,832 when compared with paclitaxel (time-to-death approach for generating utilities), whilst when using a health-state approach for generating utilities these could range from £53,811 to £70,420 (versus docetaxel) and from £44,206 to £57,450 (versus paclitaxel).

The model estimated that pembrolizumab plus paclitaxel / nab-paclitaxel dominated atezolizumab plus nab-paclitaxel, although these results do not incorporate the agreed PAS discount for atezolizumab. A confidential appendix contains the results when PASs for other interventions are incorporated.

7 References

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

Confidential Appendix: Corrected results from ERG technical engagement response for atezolizumab plus nab-paclitaxel at list price for all drugs except pembrolizumab

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1. Introduction

Shortly before the NICE Appraisal Committee the ERG identified a limitation in the way in which the long-term overall survival of atezolizumab plus nab-paclitaxel was modelled. In the company's model, a hazard ratio (HR) was applied to the pembrolizumab plus paclitaxel/nab-paclitaxel arm to estimate the overall survival for patients treated with atezolizumab plus nab-paclitaxel. This HR is applied throughout the model's time horizon.

In analyses where the HR for pembrolizumab plus paclitaxel/nab-paclitaxel compared with taxanes was set to 1 at 5 years, this resulted in the risk of death being greater for atezolizumab plus nab-paclitaxel compared with taxanes, which did not appear plausible. The ERG adjusted its preferred analyses by assuming that at 5 years the hazard of death for atezolizumab plus nab-paclitaxel was equal to that for taxanes (and therefore equal to that for pembrolizumab plus paclitaxel/nab-paclitaxel).

This change impacted on the life years gained (LYG), quality-adjusted life years (QALYs), and costs associated with atezolizumab plus nab-paclitaxel treatment in some analyses.

For the analysis using the list price of atezolizumab, the conclusion that atezolizumab plus nab-paclitaxel was dominated by pembrolizumab plus paclitaxel/nab-paclitaxel was maintained. The ERG has provided the new values associated with its two preferred base cases (7a and 7b in the Technical Engagement response document) in Table 1, which is a full incremental analysis and in Table 2, which compares pembrolizumab plus paclitaxel/nab-paclitaxel with only atezolizumab plus nab-paclitaxel.

Results incorporating the confidential discount of atezolizumab are provided in a separate document.

2. Results without cPAS

Table 1: Results from the ERG preferred analysis – time-to-death and by health state approaches for modelling HRQoL, pembrolizumab plus paclitaxel/nab-paclitaxel versus paclitaxel, docetaxel and atezolizumab plus nab-paclitaxel (deterministic)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
ERG exploratory analysis 7a - ERG preferred analysis – time-to-death approach (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**
Atezolizumab plus nab-paclitaxel	2.87	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**
ERG exploratory analysis 7b - ERG preferred analysis – HRQoL by health state (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]	**£56,659**
Atezolizumab plus nab-paclitaxel	2.87	[redacted]	[redacted]	-	[redacted]	[redacted]	**Dominated**

Inc – incremental; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** Undiscounted*

Table 2: Results from the ERG preferred analysis – time-to-death and by health state approaches for modelling HRQoL, pembrolizumab plus paclitaxel/nab-paclitaxel versus atezolizumab plus nab-paclitaxel (deterministic)

Options	LYGs*	QALYs	Cost	Inc. LYGs*	Inc QALYs	Inc Costs	ICER
ERG exploratory analysis 7a - ERG preferred analysis – time-to-death approach (deterministic)							
Atezolizumab plus nab-pacliaxel	2.87	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.99	[redacted]	[redacted]	1.11	[redacted]	[redacted]	**Dominates**
ERG exploratory analysis 7b - ERG preferred analysis – HRQoL by health state (deterministic)							
Atezolizumab plus nab-pacliaxel	2.87	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus paclitaxel/nab-paclitaxel	3.99	[redacted]	[redacted]	1.11	[redacted]	[redacted]	**Dominates**

Inc – incremental; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio
** Undiscounted*