NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of early and locally advanced non-metastatic triple-negative breast cancer [ID1500]

Committee Papers

ISBN: 978-1-4731-4880-2

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of early and locally advanced non-metastatic triple-negative breast cancer [ID1500]

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
   b. NCRI-ACP-RCP-RCR
4. **Evidence Review Group report** prepared by Kleijnen Systematic Reviews
5. **Evidence Review Group report – factual accuracy check**
6. **Technical engagement response from company**
7. **Technical engagement responses and statements from experts:**
   a. Prof Jean Abraham, Professor of Precision Breast Cancer Medicine/Honorary Consultant in Medical Oncology and Mr Stuart McIntosh, Clinical Reader in Surgical Oncology/Honorary Consultant Surgeon – clinical experts, nominated by the Royal College of Physicians
   b. Ms Holly Heath, Policy Manager – patient expert, nominated by Breast Cancer Now (s*ee item 3a*)
8. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews
   a. Addendum post technical engagement
   b. Addendum post pre-meeting

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 with chemotherapy for neoadjuvant and adjuvant treatment of untreated locally advanced non-metastatic triple negative breast cancer [ID1500]

Document B

Company evidence submission

November 2021

File name	Version	Contains confidential information	Date
ID1500-Pembrolizumab Early Stage TNBC_DOC-B_ V.2.0_22 09 22_REDACTED.docx	Version 2	Yes	November 2021

Contents

Tables and figures

Tables

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Abbreviations

Abbreviation	Description
AAT	Alanine aminotransferase increased
AE	Adverse event
AEOSI	Adverse events of special interest
AIC	Akaike Information Criterion
ASaT	All Subjects as Treated
AUC	Area Under the Curve
BC	Breast Cancer
BCS	Breast conserving surgery
BIC	Bayesian Information Criterion
BNF	British National Formulary
BRCA 1/2	Breast cancer 1 or 2 gene
BSA	Body Surface Area
CSR	Clinical Study Report
CI	Confidence Interval
DMC	Data monitoring committee
DM	Distant metastases
DRFS	Distant recurrence free survival
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECI	Events of clinical interest
ECOG	Eastern Co-operative Oncology Group
EF	Event free
EFS	Event free survival
eMIT	Electronic Market Information Tool
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQol 5-dimension questionnaire
EQ-5D-3L	EuroQol 5-dimension 3 level questionnaire
EQ-5D-5L	EuroQol 5-dimension 5 level questionnaire
ER	Oestrogen receptor
ERG	Evidence Review Group
ESMO	European Society of Medical Oncology
FA	Final analysis
FAS	Full Analysis Set
HCHS	Hospital and Community Health Services
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
HTA	Health technology assessment
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio

IO	Immune-oncology
ITC	Indirect treatment comparison
ITT	Intention to Treat
KM	Kaplan-Meier
LR	Locoregional recurrence
LY	Life years
LY	Life years gained
MA	Marketing Authorisation
MID	Minimally important difference
MIMS	Monthly Index of Medical Specialities
MSD	Merck Sharp & Dohme
mTNBC	Metastatic Triple Negative Breast Cancer
NAC	Neoadjuvant chemotherapy
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
pCR	Pathological Control Response
PD	Progressed Disease
PD-1	Programmed cell Death 1 (receptor)
PD-L1	Programmed Death Ligand 1
PD-L2	Programmed Death receptor Ligand-2
PH	Proportional Hazards
PLD	Patient level data
PR	Progesterone receptor
PRO	Patient Reported Outcome
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
Q3W	Once every 3 weeks
Q6W	Once every 6 weeks
QW	Every week
RCB	Residual cancer burden
RCT	Randomised controlled trial
RDI	Relative dose intensity
RWE	Real World Evidence
SAE	Serious adverse events
SAP	Statistical analysis plan
SE	Standard error
SEER	Surveillance, Epidemiology and End Results Program

SLR	Systematic Literature Review
SmPC	Summary of Product Characteristics
TA	Technology Appraisal
TIL	Tumour infiltrating lymphocytes
TNBC	Triple Negative Breast Cancer
ToT	Time on Treatment
TP	Transition probability
TSD	Technical Support Document
WTP	Willingness to pay
UK	United Kingdom

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. A summary of the decision problem for this appraisal is described in Table 1.

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	Adults with previously untreated locally advanced, nonmetastatic triple-negative breast cancer.	Adults with locally advanced, inflammatory, or early stage triple-negative breast cancer at high risk of recurrence	Wording to reflect licence wording
Intervention	Pembrolizumab in combination with standard neoadjuvant chemotherapy followed by adjuvant pembrolizumab.	Pembrolizumab in combination with standard neoadjuvant chemotherapy followed by adjuvant pembrolizumab.	N/A.
Comparator(s)	Standard neoadjuvant/adjuvant therapy without Pembrolizumab.	Carboplatin + paclitaxel follow by doxorubicin/epirubicin + cyclophosamide (neoadjuvant phase only) followed by placebo monotherapy (adjuvant phase).	To reflect KEYNOTE-522 and clinical expert opinion which notes that after neoadjuvant chemotherapy patients do not receive additional adjuvant chemotherapy in England.
Outcomes	• overall survival • pathological complete response • event-free survival • adverse effects of treatment • health-related quality of life	• overall survival • pathological complete response • event-free survival • adverse effects of treatment • health-related quality of life	N/A.

B.1.2 Description of the technology being appraised

The draft summary of product characteristics (SmPC) has been included in Appendix C; the Europe Public Assessment Report was not available at the time of the submission. The technology being appraised, pembrolizumab, is described in 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	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)	• KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. • KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC 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 first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. • 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 adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL)

	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 are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS)≥10. • KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations. • KEYTRUDA, as monotherapy for the adjuvant treatment of adults with stage III melanoma and lymph node involvement who have undergone complete resection. • KEYTRUDA, in combination with carboplatin and wither paclitaxel or nab-paclitaxel, for the first-line treatment of metastatic squamous NSCLC in adults. • KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma (NSCLC) in adults whose tumours have no EGFR or ALK positive mutations. • KEYTRUDA, as monotherapy or in combination with platinum and fluorouracil chemotherapy, for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express programmed cell death ligand-1 (PD-L1) with a combined positive score (CPS)≥1. • KEYTRUDA, in combination with axitinib, for the first-line treatment of advanced renal cell carcinoma in adults. • KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults. • KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in

	adults whose tumours express PD-L1 with a CPS ≥ 10 • KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease
Method of administration and dosage	Neo-adjuvant phase Pembrolizumab 200mg IV on day 1 of each 21 day cycle (Q3W) for 8 cycles plus • Cycles 1- 4: Carboplatin AUC 5 day Q3W (or AUC 1.5 weekly) + paclitaxel 80mg/m^2 QW • Cycles 5 to 8: Doxorubicin 60mg/m^2 Q3W or epirubicin 90mg/m^2 and cyclophosamide 600mg/m^2 Q3W Adjuvant phase Pembrolizumab 200mg Q3W for 9 cycles. Total pembrolizumab cycles across neoadjuvant + adjuvant phase = 17 Q3W infusions.
Additional tests or investigations	None
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-522 trial, the mean number of pembrolizumab administrations received was [redacted] combined across the neo-adjuvant and adjuvant phases. Therefore the average list price drug acquisition cost per treatment for pembrolizumab is [redacted] (not adjusted for relative dose intensity).
Patient access scheme (if applicable)	A patient access scheme (PAS) has been arranged with NHS England, with a simple discount in place of [redacted], therefore 200mg administration of pembrolizumab will cost £[redacted] (or £[redacted] per 100mg vial). Therefore the mean combined cost of pembrolizumab across the neo-adjuvant and adjuvant phases is [redacted] (not adjusted for relative dose intensity which is included in the cost-effectiveness analysis). [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 a lack of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2) expression. Early breast cancers are defined as those at stages 1 and 2 and locally advanced at stage 3 [3]. Approximately 15 to 20% of breast cancers diagnosed across the globe are TNBC. These 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]. TNBC is disproportionately associated with early recurrences, particularly in the first 5 years of diagnosis and the most common sites of recurrence for TNBC are distant, mainly lung, brain and liver [7].

Patients with TNBC are more likely to have grade 3 tumours and larger tumour size compared with those with other breast cancers [7]. Higher incidence of visceral metastases is observed in TNBC which can lead to a poorer prognosis [8] [9]. The five-year overall survival (OS) for patients diagnosed with TNBC in a London population was found to be between 59%-77% depending on factors such as stage and treatment received [10].

TNBC Treatment

Early stage breast cancer can be treated with surgery and/or radiotherapy, the outcomes of which can be improved with systemic anti-cancer treatment. Neoadjuvant therapy can lead to a pathological complete response (pCR), which is associated with improved OS compared to those with residual disease [11]. The most commonly used definitions of pCR are ypT0/Tis (absence of invasive cancer in the breast), ypT0/Tis ypN0 (absence of invasive cancer in the breast and axillary nodes), and ypT0 ypN0 (absence of invasive and in situ cancer in the breast and axillary nodes) [12]

The goal of neoadjuvant systemic therapy is to improve surgical outcomes: allowing for a smaller surgical resection volume, to potentially render inoperable tumors operable, and to improve the pCR rate [13-15]. A systematic literature review, which analysed 12 international trials with 11,955 breast cancer patients, found the association between pCR and long-term outcomes to be strong in people with TNBC [13].

Currently, there is a need for neoadjuvant / adjuvant therapies that improve long-term survival outcomes e.g. EFS and OS for patients with high-risk, early-stage TNBC (high risk referring to the increased risk of distant disease recurrence and death) [12]. The aim of adjuvant therapy is to prevent recurrence following resection of the tumour. However, there are limited treatment options for patients with residual TNBC. At the time that the KEYNOTE-522 study was developed, radiation therapy was the only adjuvant treatment option, if clinically indicated, for patients who received chemotherapy prior to surgery. Following the initiation of KEYNOTE-522, capecitabine results were published [16] [17].

B.1.3.2 England Clinical care pathway

In England there were 48,030 breast cancer cases registered in 2018 [18], which gives an estimated range of TNBC cases of 7,205 to 9,606 (15-20%), of which 95% [19] are early TNBC.

Since 1988, a breast screening programme has been conducted by NHS England [20] with the aim to “reduce mortality by detecting breast cancer at an early stage when there is a better chance of successful treatment” [21].

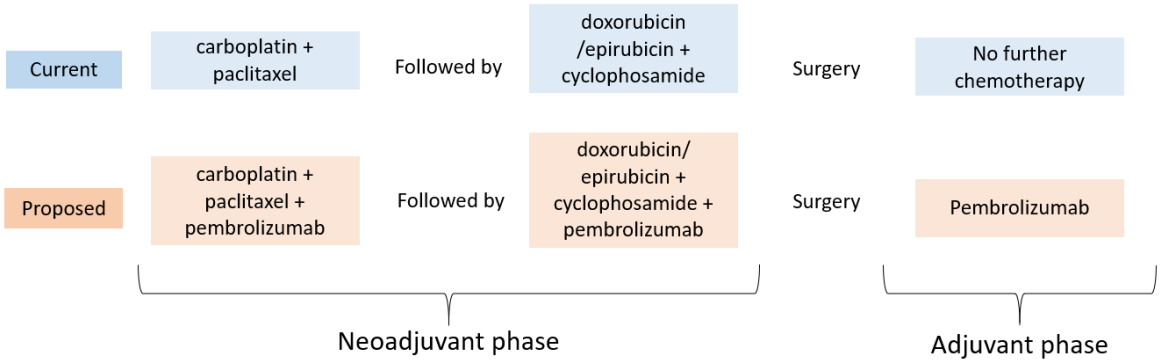
The European Society of Medical Oncology (ESMO) clinical practice guidelines recommend patients with TNBC should generally receive chemotherapy in the neoadjuvant setting with sequential anthracyclines plus taxanes with or without platinum [22].

The NICE guidelines for early and locally advanced breast cancer (NG101) recommend “people with triple-negative invasive breast cancer, consider a neoadjuvant chemotherapy regimen that contains both a platinum and an anthracycline” [23].

The results from CREATE-X trial, investigating adjuvant capecitabine for breast cancer, were published in June 2017, after the searches for NG101 was completed (30th January 2017) and the initiation of KEYNOTE-522 [17]. Local cancer guidelines do not recommend capecitabine in patients with TNBC who have had carboplatin containing chemotherapy [24]. UK clinical experts confirm that the use of adjuvant capecitabine is limited in the UK setting and that the survival benefits associated with it are small [25].

Clinical experts have informed MSD the treatments used in KEYNOTE-522 reflects the current standard of care for neoadjuvant and adjuvant treatment of TNBC where both phases are used. Figure 1 shows the current and proposed treatment pathway.

Figure 1: Current and proposed pathway for treatment of early TNBC



B.1.4 Equality considerations

MSD does not envisage any equality issues with the use of pembrolizumab in combination with chemotherapy for neoadjuvant and adjuvant treatment of untreated locally advanced non-metastatic triple negative breast cancer.

B.2 Clinical effectiveness

Key points

- TNBC is an aggressive cancer which is disproportionately associated with early recurrences, particularly in the first 5 years of diagnosis and the most common sites of recurrence for TNBC are distant, mainly lung, brain and liver
  - Recurrent disease is clinically complex to manage and is associated with poor survival outcomes
- Neo-adjuvant chemotherapy followed by surgery can improve patient survival outcomes [Event Free Survival (EFS) and Overall Survival (OS)] by preventing or delaying disease recurrence which is associated with poor long term survival outcomes.
- KEYNOTE-522 is a Phase III pivotal RCT investigating the efficacy of Pembrolizumab plus chemotherapy vs chemotherapy as neoadjuvant therapy followed by pembrolizumab vs placebo as adjuvant therapy in participants with locally advanced, inflammatory, or early-stage triple-negative breast cancer at high risk of recurrence.
  - The latest data from the IA4 database lock are used to inform the submission (23rd March 2021). The median follow up was 37.8 months.
- Study primary outcomes include pathological Complete Response (pCR) using the definition of ypT0/Tis ypN0 (assessed by the local pathologist at the time of definitive surgery) and to evaluate the EFS (by investigator) in participants with locally advanced TNBC.
  - pCR by (ypT0/Tis ypN0): 7.5 (1.6, 13.4)
  - 42-month EFS rate for Pembrolizumab compared with the placebo arm was: 83.5% (95% CI: 80.5%-86.0%) vs. 74.9% (95% CI: 69.8%-79.2%).
  - EFS HR = 0.63 (95% CI: 0.48, 0.82) representing a 37% reduction in the risk of disease progression precluding definitive surgery, recurrence, second primary malignancy, or death.
- Study secondary objectives included the assessment of OS in participants with locally advanced TNBC.
  - OS remains immature ([redacted] of information fraction accrued; final [redacted].
  - A positive trend in OS favoring the pembrolizumab arm: OS HR = 0.72 (95% CI: 0.51, 1.02)
- Pembrolizumab plus chemotherapy followed by pembrolizumab monotherapy has an acceptable tolerability profile which is consistent with the known safety profile of the therapies administered.
- HRQoL scores of patients did not decrease with the addition of pembrolizumab to chemotherapy followed by pembrolizumab monotherapy.
  - Compared to the current standard of care neoadjuvant chemotherapies, the use of an effective
  - and tolerable treatment that extends the EFS can be expected to have a positive impact on patient's HRQoL
- Pembrolizumab plus chemotherapy followed by pembrolizumab monotherapy is an innovative, effective, and well tolerated treatment option for locally advanced, inflammatory, or early stage triple-negative breast cancer at high risk of recurrence.

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. The only relevant study identified by the systematic literature review (SLR) was KEYNOTE-522.

B.2.2 List of relevant clinical effectiveness evidence

Table 3: Clinical effectiveness evidence

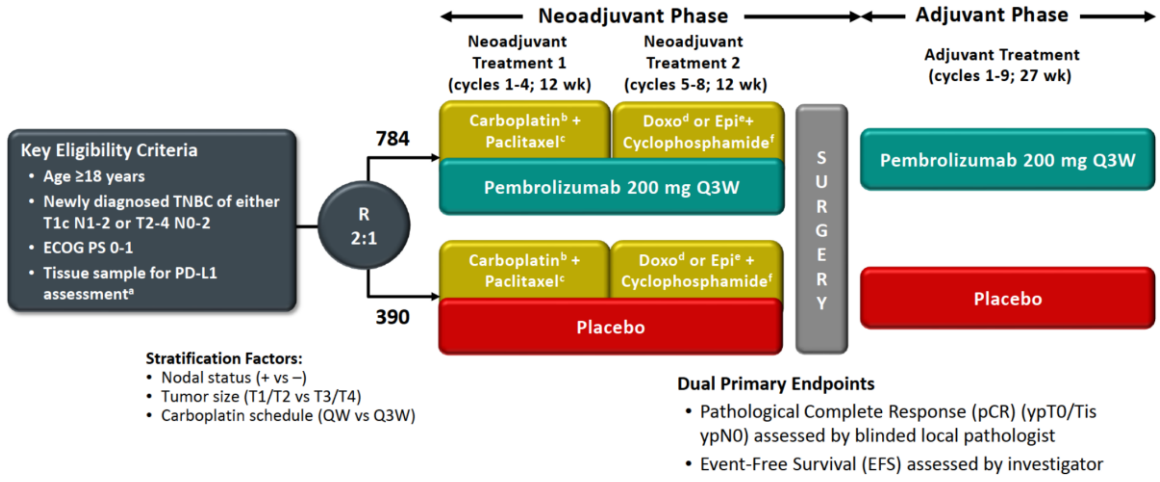
<table>
<tr><td>Study</td><td colspan="5">KEYNOTE-522: Study of Pembrolizumab (MK-3475) Plus Chemotherapy vs Placebo Plus Chemotherapy as Neoadjuvant Therapy and Pembrolizumab vs Placebo as Adjuvant Therapy in Participants With Triple Negative Breast Cancer [26]</td></tr>
<tr><td>Study design</td><td colspan="5">Phase III randomised, double blind.</td></tr>
<tr><td>Population</td><td colspan="5">Patients with untreated newly diagnosed, locally advanced, centrally confirmed TNBC and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Pembrolizumab plus chemotherapy in the neoadjuvant phase followed by monotherapy pembrolizumab in the adjuvant phase.</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Placebo plus chemotherapy in the neoadjuvant phase followed by monotherapy placebo in the adjuvant phase</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-522 is the pivotal trial in this indication</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• Pathological complete response (pCR)
• Event free survival (EFS)
• Adverse events
• Overall survival (OS)
• Health related quality of life

Bolded outcomes are included in the economic model
KEYNOTE-522 OS data is included in scenario analysis.</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">• Patient reported outcomes (PRO)
• Time on treatment

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-522 trial design [27]



[a] Must consist of at least 2 separate tumor cores from the primary tumor; [b] Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW; [c] Paclitaxel dose was 80 mg/m² QW; [d] Doxorubicin dose was 60 mg/m² Q3W; [e] Epirubicin dose was 90 mg/m² Q3W; [f] Cyclophosphamide dose was 600 mg/m² Q3W.

Eligibility criteria

Subject inclusion criteria

Male and female subjects aged 18 and older who:

- Have centrally confirmed TNBC, as defined by the most recent ASCO/CAP guidelines.
- Have previously untreated locally advanced non-metastatic (M0) TNBC defined as the following combined primary tumour (T) and regional lymph node (N) staging per AJCC staging criteria for breast cancer staging criteria as assessed by the investigator based on radiological and/or clinical assessment:
    - T1c, N1-N2
    - T2, N0-N2
    - T3, N0-N2
    - T4a-d, N0-N2
    - *These TNM statuses partly equate to stage 2A, 2B and 3A*
- Provide a core needle biopsy consisting of at least 2 separate tumor cores from the primary tumor at screening to the central laboratory.
- Have ECOG performance status of 0 or 1 performed within 10 days of treatment initiation.
- Demonstrate adequate organ function within 10 days of treatment initiation.
- Have left ventricular ejection fraction (LVEF) of ≥50% or ≥ institution lower limit of normal (LLN) as assessed by echocardiogram (ECHO) or multigated acquisition (MUGA) scan performed at screening.
- Males and female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in the protocol.

Subject exclusion criteria

Subjects were excluded from participating in the trial if they:

- Had a history of invasive malignancy ≤5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.
- Had received prior chemotherapy, targeted therapy, and radiation therapy within the past 12 months.
- Had received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137) or has previously participated in MK-3475 clinical trials.
- Were participating in or had participated in an interventional clinical trial with an investigational compound or device within 4 weeks of the first dose of treatment in this current trial.
- Had received a live vaccine within 30 days of the first dose of study treatment.
- Had an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
- Had a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
- Had a known history of Human Immunodeficiency Virus (HIV)
- Had known active Hepatitis B or Hepatitis C.
- Had a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
- Had an active infection requiring systemic therapy.
- Had significant cardiovascular disease, such as:
    - History of myocardial infarction, acute coronary syndrome or coronary angioplasty/stenting/bypass grafting within the last 6 months
    - Congestive heart failure (CHF) New York Heart Association (NYHA) Class II-IV or history of CHF NYHA class III or IV
- Had a history or current evidence of any condition, therapy, lab abnormality or other circumstance that might expose the subject to risk by participating in the trial, confound the results of the trial, or interfere with the subject's participation for the full duration of the trial.

- Had known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
- Were pregnant or breastfeeding, or expecting to conceive children within the projected duration of the trial, starting with the screening visit through 12 months after the last dose of trial treatment for subjects who have received cyclophosphamide, and for 6 months after the last dose of study medication for subjects who have not.
- Had a known hypersensitivity to the components of the study therapy or its analogues.
- Had a known history of active TB (Bacillus Tuberculosis)

Settings and locations where data were collected

The study was conducted at 177 centres in 21 countries which randomised at least one participant to receive interventional treatment. There were 54 sites within Europe and of these, six where in the United Kingdom. A total of 434 patients were enrolled in Europe of which 40 were from the UK. All treatments were administered in secondary care setting on an outpatient basis.

Trial drugs and concomitant medication

Trial drugs

All drugs are administered by intravenous infusion [9].

Table 4: Trial treatments

Treatment		Regimen	Duration of treatment	Use in study
Neoadjuvant phase				
Pembrolizumab		200mg Day 1 every 3 weeks (Q3W)	8 cycles (24 weeks)	Experimental arm only
Carboplatin + paclitaxel	Carboplatin	Day 1 every week (Q1W) area under the curve (AUC) 1.5 or Day 1 every 3 weeks (Q3W) AUC 5	12 weeks (cycle 1-4)	Experimental and comparator arm
	Paclitaxel	Day 1 Q1W 80mg/m^2		
Doxorubicin or Epirubicin + cyclophosamide	Doxorubicin	60mg/m^2 Day 1 Q3W	12 weeks (cycle 5-9)	Experimental and comparator arm
	Epirubicin	90mg/m^2 Day 1 Q3W	12 weeks (cycle 5-9)	
	Cyclophosamide	600mg/m^2 Day 1 Q3W	12 weeks (cycle 5-9)	
Placebo (normal saline or dextrose)		Day 1 Q3W	8 cycles (24 weeks)	Comparator arm only
Adjuvant phase				
Pembrolizumab		200mg Day 1 Q3W	9 cycles (27 weeks)	Experimental arm
Placebo (normal saline or dextrose)		Day 1 Q3W	9 cycles (27 weeks)	Comparator arm
Abbreviations: AUC: Area Under the Curve, Q3W: every 3 weeks, Q1W: weekly				

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 medication were to be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All prior medications received within 30 days before the screening visit, and all new concomitant medications given from the screening visit through the Adjuvant Phase safety follow-up visit were to be recorded. After the Adjuvant Phase safety follow-up visit, all

medications administered for the treatment of serious adverse events (SAEs) and events of clinical interest (ECIs) were recorded as per the study protocol.

Prohibited concomitant medications

Subjects were prohibited from receiving the following therapies from the time of screening until completion of all study therapy:

- Immunotherapy not specified in the protocol
- Chemotherapy not specified in the protocol
- Investigational agents not specified in the protocol
- Radiation therapy except as described in the protocol.
    - Post-operative radiation therapy is acceptable according to the standard of care, as applicable.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial.
- Glucocorticoids for any purpose other than to modulate symptoms from an irAE of suspected immunologic aetiology or for use as a pre-medication for chemotherapeutic agents specified in the protocol. Inhaled steroids were allowed for management of asthma. Use of prophylactic corticosteroids to avoid allergic reactions (eg, to IV contrast dye) were permitted.

The subject exclusion Criteria mentioned previously describes other prior medications prohibited for trial enrolment.

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

EFS from KEYNOTE-522 has been used in the economic model along with adverse events and health related quality of life (please refer to section B.3.2). Overall survival outcomes are explored in scenario analysis.

KEYNOTE-522 primary and secondary objectives were pre-specified and are as follows:

Primary objectives:

1. To evaluate the rate of pCR using the definition of ypT0/Tis ypN0 (i.e., no invasive residual in breast or nodes; non-invasive breast residuals allowed) as assessed by the local pathologist at the time of definitive surgery in participants with locally advanced TNBC.

2. To evaluate the EFS as assessed by investigator in participants with locally advanced TNBC.

pCR was defined as pCR rate (ypT0/Tis ypN0) is defined as the proportion of participants without residual invasive cancer on haematoxylin and eosin (H&E) evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy by AJCC staging criteria assessed by the local pathologist at the time of definitive surgery

EFS was defined as the time from randomisation to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause.

Secondary Objectives:

1. To evaluate overall survival in participants with locally advanced TNBC tumours.
2. To evaluate the rate of pCR using an alternative definition, ypT0 ypN0 (i.e. no invasive or non-invasive residual in breast or nodes) as assessed by the local pathologist at the time of definitive surgery in participants with locally advanced TNBC and in individuals with programmed death ligand 1 (PD-L1) positive tumours combined positive score (CPS) ≥1.
3. To evaluate the rate of pCR using the definition of (ypT0/Tis ypN0) (no invasive residual in breast or nodes; non-invasive breast residuals allowed) as assessed by the local pathologist at the time of definitive surgery in individuals with PD-L1 tumours CPS ≥1.
4. To evaluate the EFS as assessed by investigator in individuals with PD-L1 tumours CPS ≥1.
5. To evaluate the rate of pCR using an alternative definition, ypT0/Tis (ie, absence of invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement) as assessed by the local pathologist at the time of definitive surgery in participants with locally advanced TNBC and in individuals with PD-L1 tumours CPS ≥1.
6. To evaluate OS in individuals with PD-L1 tumours CPS ≥1.
7. To determine the safety and tolerability of pembrolizumab in combination with neoadjuvant chemotherapy and pembrolizumab as adjuvant therapy in locally advanced TNBC participants, within and across the neoadjuvant and adjuvant phases.

8. To evaluate health-related quality-of-life (HRQoL) assessments in TNBC participants and in participants with PD-L1 tumours CPS ≥1 using the European Organisation for Research and Treatment of Cancer (EORTC) QoL Core 30 (QLQC30) and EORTC Breast Cancer–Specific QoL Questionnaire (QLQ-BR23) within and across the neoadjuvant and adjuvant treatment phases.

OS is defined as the time from randomisation to death due to any cause.

pCR rate (ypT0 ypN0) is defined as the proportion of participants without residual invasive and in situ cancer on H&E evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy by AJCC staging criteria assessed by the local pathologist at the time of definitive surgery.

pCR rate (ypT0/Tis) is defined as the proportion of participants without invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement following completion of neoadjuvant systemic therapy by AJCC staging criteria assessed by the local pathologist at the time of definitive surgery.

Results of secondary objectives 2 to 6 are available in in Appendix D.1.5

Exploratory objectives

1. To evaluate the association between pCR and the ORR using RECIST 1.1 as assessed by central radiology review after Treatment 1 (neoadjuvant phase) or at the time of surgery.
2. To evaluate distant recurrence free survival (DRFS) post-surgery as assessed by investigator in participants with locally advanced TNBC and in individuals with PD-L1 tumours CPS ≥1.
3. To characterize health utilities in participants with locally advanced TNBC and in participants with PD-L1 tumors CPS ≥1 using the EuroQol-5 EQ-5D- 5L™.
4. To evaluate the rate of breast conserving surgery (BCS) at the time of definitive surgery in participants with locally advanced TNBC and in individuals with PD-L1 tumours CPS ≥1.
5. To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamics activity, and/or the mechanism of action of pembrolizumab and other treatments.
6. To evaluate the association between pCR and the ORR using MRI FTV as assessed by central radiology review after Treatment 1 (neoadjuvant phase) and at the time of surgery.

7. To evaluate Residual Cancer Burden (RCB) as assessed by the local pathologist at the time of definitive surgery in participants with locally advanced TNBC
8. To correlate extent of Tumour infiltrating lymphocytes (TILs) with pCR rate and EFS.

Results for exploratory objectives 1, 2 and 4 are available in Appendix D.1.5.

Participant baseline characteristics KEYNOTE-522

Table 5: Participant characteristics ITT

	Pembrolizumab + chemotherapy / Pembrolizumab		Placebo + chemotherapy /Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	784		390		1,174	
Sex						
Male	1	(0.1)	0	(0.0)	1	(0.1)
Female	783	(99.9)	390	(100.0)	1,173	(99.9)
Age (Years)						
< 65	700	(89.3)	342	(87.7)	1,042	(88.8)
>= 65	84	(10.7)	48	(12.3)	132	(11.2)
Mean	49.2		49.1		49.1	
SD	11.8		11.9		11.8	
Median	49.0		48.0		49.0	
Range	22 to 80		24 to 79		22 to 80	
Race						
American Indian Or Alaska Native	14	(1.8)	7	(1.8)	21	(1.8)
Asian	149	(19.0)	89	(22.8)	238	(20.3)
Black Or African American	38	(4.8)	15	(3.8)	53	(4.5)
Multiple	13	(1.7)	6	(1.5)	19	(1.6)
American Indian Or Alaska Native Black Or African American	0	(0.0)	1	(0.3)	1	(0.1)
American Indian Or Alaska Native Black Or African American White	2	(0.3)	1	(0.3)	3	(0.3)
American Indian Or Alaska Native White	7	(0.9)	2	(0.5)	9	(0.8)
Black Or African American White	3	(0.4)	2	(0.5)	5	(0.4)
White Asian	1	(0.1)	0	(0.0)	1	(0.1)
Native Hawaiian Or Other Pacific Islander	1	(0.1)	0	(0.0)	1	(0.1)
White	504	(64.3)	242	(62.1)	746	(63.5)
Missing	65	(8.3)	31	(7.9)	96	(8.2)

Geographic Region						
North America	166	(21.2)	78	(20.0)	244	(20.8)
Europe	388	(49.5)	180	(46.2)	568	(48.4)
Australia	23	(2.9)	16	(4.1)	39	(3.3)
Asia	166	(21.2)	91	(23.3)	257	(21.9)
Rest of World	41	(5.2)	25	(6.4)	66	(5.6)
ECOG PS						
0	678	(86.5)	341	(87.4)	1,019	(86.8)
1	106	(13.5)	49	(12.6)	155	(13.2)
Baseline Lactate Dehydrogenase (LDH)						
<=ULN	631	(80.5)	309	(79.2)	940	(80.1)
> ULN	149	(19.0)	80	(20.5)	229	(19.5)
Missing	4	(0.5)	1	(0.3)	5	(0.4)
Menopausal Status						
Pre-menopausal	438	(55.9)	221	(56.7)	659	(56.1)
Post-menopausal	345	(44.0)	169	(43.3)	514	(43.8)
Missing	1	(0.1)	0	(0.0)	1	(0.1)
Choice of Carboplatin (Planned)						
Carboplatin (Cb) Q3W	335	(42.7)	167	(42.8)	502	(42.8)
Carboplatin (Cb) Weekly	449	(57.3)	223	(57.2)	672	(57.2)
Primary Tumor (Planned)						
Tumor Size T1/T2	580	(74.0)	290	(74.4)	870	(74.1)
Tumor Size T3/T4	204	(26.0)	100	(25.6)	304	(25.9)
Nodal Involvement (Planned)						
Nodal Status Positive	405	(51.7)	200	(51.3)	605	(51.5)
Nodal Status Negative	379	(48.3)	190	(48.7)	569	(48.5)
Metastases						
M0	784	(100.0)	390	(100.0)	1,174	(100.0)
Overall Stage						
Stage I	0	(0.0)	1	(0.3)	1	(0.1)
Stage II	590	(75.3)	291	(74.6)	881	(75.0)
Stage III	194	(24.7)	98	(25.1)	292	(24.9)
PD-L1 CPS 1 Cutoff						
PD-L1 CPS >= 1	656	(83.7)	317	(81.3)	973	(82.9)
PD-L1 CPS < 1	128	(16.3)	69	(17.7)	197	(16.8)
Unknown	0	(0.0)	4	(1.0)	4	(0.3)
PD-L1 CPS 10 Cutoff						
PD-L1 CPS >= 10	393	(50.1)	177	(45.4)	570	(48.6)
PD-L1 CPS < 10	391	(49.9)	209	(53.6)	600	(51.1)
Unknown	0	(0.0)	4	(1.0)	4	(0.3)
PD-L1 CPS 20 Cutoff						
PD-L1 CPS >= 20	247	(31.5)	121	(31.0)	368	(31.3)
PD-L1 CPS < 20	537	(68.5)	265	(67.9)	802	(68.3)

Unknown	0	(0.0)	4	(1.0)	4	(0.3)
HER2 Status						
0-1+ by IHC	595	(75.9)	286	(73.3)	881	(75.0)
2+ by IHC (but FISH-)	188	(24.0)	104	(26.7)	292	(24.9)
Missing	1	(0.1)	0	(0.0)	1	(0.1)

Missing values in Race and Ethnicity are mainly because France is not permitted to report this information.
The missing value in Menopausal Status is from one male participant.
The missing value in HER2 Status is from the participant with missing IHC, but FISH-.
Database Cutoff Date: 23MAR2021

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Study design overview	A phase III, randomised, double-blind study to evaluate pembrolizumab plus chemotherapy vs placebo plus chemotherapy as neoadjuvant therapy and pembrolizumab vs placebo as adjuvant therapy for Triple Negative Breast Cancer.
Treatment assignment	Approximately 1150 subjects will be randomized (double-blind) in a 2:1 ratio between 2 treatment arms: 1. Pembrolizumab plus chemotherapy as neoadjuvant therapy and pembrolizumab as adjuvant therapy, or 2. Placebo plus chemotherapy as neoadjuvant therapy and placebo as adjuvant therapy. Stratification factors are as follows: Nodal status (Positive vs. Negative) Tumor size (T1/T2 vs. T3/T4) Choice of Carboplatin: Q3W vs. Weekly
Analysis populations	Efficacy: Intention-to-Treat Population [28] Safety: All Subjects as Treated (ASaT)
Primary endpoints	1. Pathological complete response (pCR) rate (ypT0/Tis ypN0) 2. Event-free survival (EFS)
Statistical methods for key efficacy analyses	Treatment comparisons of the pCR rate (ypT0/Tis ypN0) will be performed using the stratified Miettinen and Nurminen method. Treatment comparisons for time-to-event endpoints such as EFS and OS will be evaluated using a stratified log-rank test. The 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 are no Tier 1 events for this study. Point estimates and 95% confidence intervals [29] 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	Seven efficacy interim analyses (IAs) are planned. Results will be reviewed by an external DMC Efficacy Interim Analyses (IA) • IA 1 : At least 500 subjects have or would have completed surgery after ~6 months neoadjuvant treatment and enrollment is completed. It is estimated ~18 months after the first subject is randomized. Primary purpose: interim pCR(ypT0/Tis ypN0) analysis. • IA 2 : ~24 months after the first subject is randomized (The timing of IA is calendar driven). It is estimated that ~93 EFS events will have been observed and ~1000 subjects have

	or would have completed surgery after ~6 months neoadjuvant treatment. Primary purpose: interim EFS analysis and final pCR (ypT0/Tis ypN0) analysis. • IA 3: ~36 months after the first subject is randomized (The timing of IA is calendar driven). It is estimated that ~154 EFS events will have been observed. Primary purpose: interim EFS analysis. • IA 4: ~48 months after the first subject is randomized (The timing of IA is calendar driven). It is estimated that ~201 EFS events will have been observed. Primary purpose: interim EFS analysis. • IA 5: ~60 months after the first subject is randomized (The timing of IA is calendar driven). It is estimated that ~239 EFS events will have been observed. Primary purpose: interim EFS analysis. • IA 6: ~72 months after the first subject is randomized (The timing of IA is calendar driven). It is estimated that ~270 EFS events will have been observed. Primary purpose: interim EFS analysis. • IA 7: ~84 months after the first subject is randomized (The timing of IA is calendar driven). It is estimated that ~294 EFS events will have been observed. Primary purpose: interim EFS analysis. • Final analysis (FA): ~327 EFS events have been observed (event driven). It is expected to occur at ~102 months after the first subject is randomized. Primary purpose: final EFS analysis. OS will be tested only when the null hypothesis for EFS is rejected.
Multiplicity	The overall type-I error rate over the 2 primary endpoints will be strongly controlled at 2.5% (one-sided) with 0.5% allocated to the pCR (ypT0/Tis ypN0) and 2.0% allocated to the EFS hypotheses. The graphical approach of Maurer and Bretz will be applied to re-allocate alpha among hypotheses for pCR(ypT0/Tis ypN0), EFS, and OS in subjects with locally advanced TNBC. Group sequential methods will be used to allocate alpha between the interim and final analyses for pCR(ypT0/Tis ypN0), EFS and OS in subjects with locally advanced TNBC.
Sample size and power	The FA of the study is EFS event-driven and will be conducted after approximately 327 EFS events have been observed. It may occur at ~102 months after the first subject randomized. The planned sample size is approximately 1150 subjects.

	1. pCR (ypT0/Tis ypN0): the trial has an overall ~95% power to detect a true pCR rate difference of 15 percentage points (pembrolizumab + chemotherapy vs. placebo + chemotherapy) at alpha = 0.5% (one-sided) with ~1000 subjects who have or would have completed surgery after ~6 months neoadjuvant treatment at IA2. 2. EFS: the trial has an overall ~80% power at a one-sided 2.0% alpha level, if the true HR is 0.71. 3. OS: the trial has an overall ~79.7% power at a one-sided 2.0% alpha level, if the true HR is 0.70

The strategy for analysis of key efficacy endpoints is summarised in Table 6 while Table 7 summarises the censoring rules applied for analyses of EFS.

Table 6: Analysis strategy for key efficacy endpoints

Endpoint/Variable	Statistical Method†	Analysis Population	Missing Data Approach
Primary hypotheses			
pCR (ypT0/Tis ypN0)	Stratified M & N method‡	ITT	Subjects with relevant data missing are considered non-responders
EFS	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive and event free date
Secondary hypothesis			
OS	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date

† For stratified analyses, the stratification factors used for randomization will be used as stratification factors for analysis.

‡ Miettinen and Nurminen method with strata weighting by sample size.

Table 7: Censoring rules for primary and sensitivity analysis of EFS

Situation	Primary analysis	Sensitivity analysis 1*	Sensitivity analysis 2§
EFS event documented after ≤1 missed disease assessment, and before new anti-cancer therapy, if any	Progressed at date of documented EFS event	Progressed at date of documented EFS event	Progressed at date of documented EFS event
EFS event immediately after ≥2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Progressed at date of documented EFS event	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 EFS event, if no new anti-cancer therapy; Progressed at the date of new anti-cancer therapy, if there is new anti-cancer therapy
No EFS event; and new anti-cancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment
No EFS event; new anti- cancer treatment is initiated	Censored at last disease assessment	Censored at last disease assessment before new anti-cancer treatment	Progressed at the date of new anti-cancer therapy

* The new anti-cancer therapy in the sensitivity analysis 1 is defined as any post surgery new oncology drugs or post surgery radiation to treat metastatic disease.
§ The new anti-cancer therapy in sensitivity analysis 2 is defined as the radiation and/or oncology drugs to treat metastatic disease.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Quality assessment of KEYNOTE-522 was conducted using the Cochrane Risk of Bias tool version 2 [30]. Based upon this analysis, the study was determined to be at low risk across five out of five domains. The complete quality assessment is included in Appendix D.1.4.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 KEYNOTE-522 results

Table 8: Nomenclature used in document

	Experimental arm description	Control arm description
Full description	Pembrolizumab plus chemotherapy followed by pembrolizumab monotherapy	Placebo plus chemotherapy followed by placebo monotherapy
Shortened description	Pembrolizumab arm	Placebo arm
Neoadjuvant phase	Pembrolizumab + chemotherapy	Placebo + chemotherapy
Monotherapy phase	Pembrolizumab monotherapy	Placebo monotherapy

Interim results are presented from KEYNOTE-522, based upon the fourth interim analysis (IA4) which was calendar driven with a data cut off of 23rd March 2021.

At IA4 cut-off date, patients had a median duration of follow-up of 37.8 months (range 2.7 to 48.0), with no patients remaining on study intervention. In the neoadjuvant phase mean duration of exposure was [redacted] weeks (SD [redacted]) in the pembrolizumab arm compared with [redacted] weeks (SD [redacted]) in the placebo arm. The mean number of administrations of pembrolizumab in this phase was [redacted] and [redacted] for placebo.

For the adjuvant phase the mean duration of exposure was 22.9 weeks (SD 6.1) in the pembrolizumab arm and [redacted] weeks (SD [redacted]) in the placebo arm. The mean number of administrations in this phase for pembrolizumab was [redacted] and [redacted] for placebo.

Table 9: Summary of drug exposure - Neo-adjuvant phase

Neo-adjuvant phase	Pembrolizumab + chemotherapy	Placebo + chemotherapy	Total
Participants in population	783	389	1172
All Drugs			
Number of Weeks on Therapy n Mean SD Median Range	[redacted]	[redacted]	[redacted]
Pembrolizumab 200mg Q3W			
Number of Weeks on Therapy			

Neo-adjuvant phase	Pembrolizumab + chemotherapy	Placebo + chemotherapy	Total
n	[redacted]		[redacted]
Mean	[redacted]		[redacted]
SD	[redacted]		[redacted]
Median	[redacted]		[redacted]
Range	[redacted]		[redacted]
Number of Administrations			
n	[redacted]		[redacted]
Mean	[redacted]		[redacted]
SD	[redacted]		[redacted]
Median	[redacted]		[redacted]
Range	[redacted]		[redacted]
Placebo Q3W			
Number of Weeks on Therapy			
n		[redacted]	[redacted]
Mean		[redacted]	[redacted]
SD		[redacted]	[redacted]
Median		[redacted]	[redacted]
Range		[redacted]	[redacted]
Number of Administrations			
n		[redacted]	[redacted]
Mean		[redacted]	[redacted]
SD		[redacted]	[redacted]
Median		[redacted]	[redacted]
Range		[redacted]	[redacted]
Carboplatin Weekly			
Number of Weeks on Therapy			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Number of Administrations			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Carboplatin Q3W			
Number of Weeks on Therapy			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]

Neo-adjuvant phase	Pembrolizumab + chemotherapy	Placebo + chemotherapy	Total
Range	[redacted]	[redacted]	[redacted]
Number of Administrations			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Paclitaxel Weekly			
Number of Weeks on Therapy			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Number of Administrations			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Doxorubicin Q3W			
Number of Weeks on Therapy			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Number of Administrations			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Epirubicin Q3W			
Number of Weeks on Therapy			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Number of Administrations			
n	[redacted]	[redacted]	[redacted]

Neo-adjuvant phase	Pembrolizumab + chemotherapy	Placebo + chemotherapy	Total
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Cyclophosphamide Q3W			
Number of Weeks on Therapy			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Number of Administrations			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Participants who did not have neoadjuvant treatments but had surgery are included in ASaT population in neoadjuvant phase.			
Database Cutoff Date: 23MAR2021			

Table 10: Summary of drug exposure - Adjuvant phase

Adjuvant study phase	Pembrolizumab monotherapy	Placebo monotherapy	Total
Participants in population	588	331	919
All Drugs			
Number of Weeks on Therapy			
n	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Pembrolizumab 200mg Q3W			
Number of Weeks on Therapy			
n	[redacted]		[redacted]
Mean	[redacted]		[redacted]
SD	[redacted]		[redacted]
Median	[redacted]		[redacted]
Range	[redacted]		[redacted]

Adjuvant study phase	Pembrolizumab monotherapy	Placebo monotherapy	Total
Number of Administrations n Mean SD Median Range	[redacted]		[redacted]
Placebo Q3W Number of Weeks on Therapy n Mean SD Median Range		[redacted]	[redacted]
Number of Administrations n Mean SD Median Range		[redacted]	[redacted]
Participants who had post-surgery radiation therapy but didn't have adjuvant treatment are included in ASaT population in adjuvant phase. Database Cutoff Date: 23MAR2021			

Summary of clinical efficacy outcomes (IA4)

A summary of the clinical efficacy outcomes results from IA4 are presented in Table 11, with additional details of each endpoint provided in sections B.2.6.2 to B.2.6.4.

Table 11: Summary of clinical efficacy outcomes (IA4)

	Locally recurrent unresectable or metastatic TNBC	
Number of patients	**Pembrolizumab arm n=784**	**Placebo arm n=390**
Primary endpoints		
pCR (ypT0/Tis ypN0)		
pCR rate (95% CI)	63.0 (59.5, 66.4)	55.6 (50.6, 60.6)
	Difference: 7.5 (1.6, 13.4)	
EFS		
Median	Not reached	Not reached
EFS rate at 24 months (95% CI) [months]	87.8% (85.3, 89.9)	81.0% (76.8, 84.6)

EFS rate at 42 months(95% CI) [months]	83.5% (80.5, 86.0)	80.6% (78.1)
Secondary endpoints		
OS		
Median	Not reached	Not reached
OS rate at 24 months (95% CI) [months]	92.3% (90.2, 94.0)	91.0% (87.7, 93.5)
OS rate at 42 months(95% CI) [months]	89.2% (86.7, 91.3)	84.1% (79.5, 87.7)

B.2.6.2 Pathological Complete Response (pCR)

The definition for the primary pCR hypothesis is ypT0/Tis ypN0, meaning the absence of invasive cancer in the breast and axillary nodes. The success criterion was met at IA1 (data cut-off 24th September 2018) and continued to show a statistically significant improvement in the pembrolizumab arm at IA2 (data cut-off 24th April 2019). See Appendix D.1.5 for further information.

As prespecified in the supplementary statistical analysis plan (SAP), pCR was not formally tested at IA4 for the ITT population and data is presented for consistency.

Table 12: Analysis of pCR (ypT0/Tis ypN0) (All participants)

Treatment	N	Number of pCR	pCR Rate (%)	Difference in % vs. placebo + chemotherapy Estimate (95% CI)[a]
Pembrolizumab + chemotherapy	784	494	63.0 (59.5, 66.4)	7.5 (1.6, 13.4)
Placebo + chemotherapy	390	217	55.6 (50.6, 60.6)	

[a] Based on Miettinen & Nurminen method stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and cho ice of carboplatin (Cb) (Q3W vs. Weekly).
Database Cutoff Date: 23MAR2021

The analyses of pCR using the alternative definitions of ypT0 ypN0 and ypT0/Tis (secondary efficacy endpoints) were consistent with the primary pCR analysis (see Appendix D.1.5).

B.2.6.3 Event Free Survival (EFS)

KEYNOTE-522 met the success criterion for the primary EFS hypothesis at IA4, with a p-value that crossed the prespecified boundary for statistical significance. The addition of pembrolizumab to neoadjuvant chemotherapy (NAC) followed by adjuvant pembrolizumab resulted in a statistically significant improvement in EFS.

The EFS HR of 0.63 (95% CI: 0.48, 0.82), with a one-sided p-value of 0.0003093 that crossed the prespecified boundary for statistical significance (p=0.00516941), represents a 37% reduction in the risk of disease progression precluding definitive surgery, recurrence, second primary malignancy, or death compared with placebo + chemotherapy followed by placebo.

Table 13: Analysis of event free survival (All participants)

Treatment	N	Number of events (%)	Person-months	Event rate/100 person-months	Median EFS [months] (95% CI) [a]	EFS Rate at 42 months % (95% CI)	Vs. control Hazard Ratio (95% CI) [b]
Pembrolizumab arm	784	123 (15.7)	26,994.6	0.5	NR	83.5 (80.5, 86.0)	0.63 (0.48, 0.82)
Placebo arm	390	93 (23.8)	12,783.8	0.7	NR	74.9 (69.8, 79.2)	p-value [c] 0.0003093

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Q3W vs. Weekly).
c One-sided p-value based on log-rank test stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Cb) (Q3W vs. Weekly).
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Table 14: Summary of EFS rate over time

	Pembrolizumab arm (n=784) % (95% CI)	Placebo arm (n=390) % (95% CI)
6 months	98.3 (97.2, 99.0)	98.5 (96.6, 99.3)
12 months	93.3 (91.4, 94.9)	92.5 (89.4, 94.7)
18 months	90.0 (87.7, 91.9)	85.8 (81.9, 88.9)
24 months	87.8 (85.3, 89.9)	81.0 (76.8, 84.6)
30 months	85.8 (83.1, 88.0)	78.2 (73.7, 82.0)
36 months	84.5 (81.7, 86.9)	76.8 (72.2, 80.7)
42 months	83.5 (80.5, 86.0)	74.9 (69.8, 79.2)
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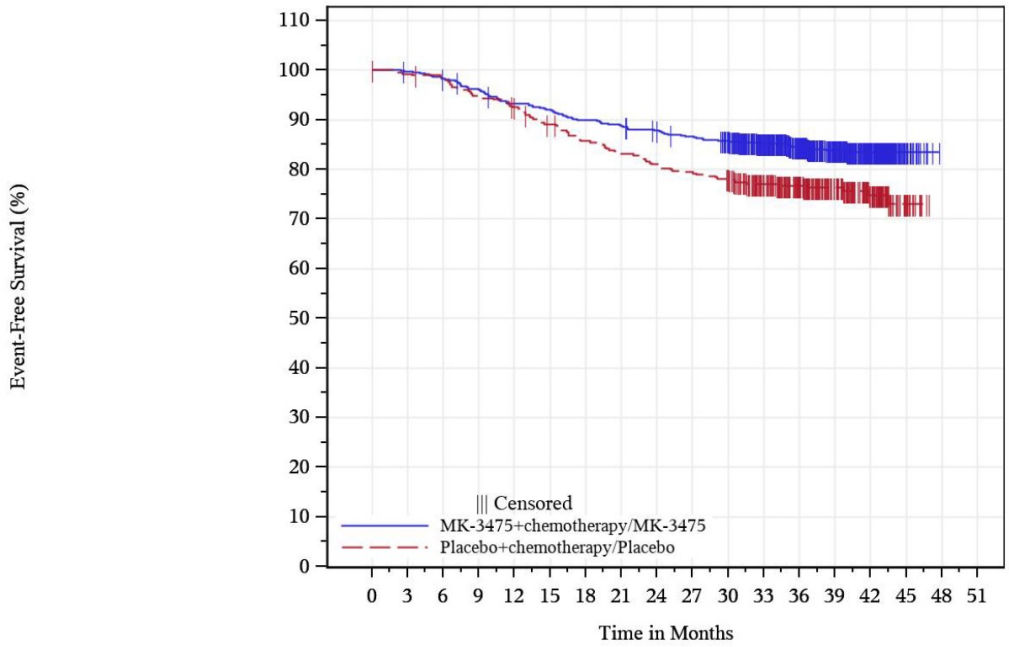
Table 15: Summary of first event in EFS analyses

Event	Pembrolizumab arm (n=784)	Placebo arm (n=390)
	n (%)	n (%)
Any EFS Event	123 (15.7)	93 (23.8)
Secondary Primary Malignancy	6 (0.8)	4 (1.0)
Local PD Precludes Surgery	3 (0.4)	4 (1.0)
Local PD Precludes Definitive Surgery	1 (0.1)	0 (0)
Distant PD	4 (0.5)	1 (0.3)
Positive Margin at Last Surgery	6 (0.8)	10 (2.6)
Local Recurrence	28 (3.6)	17 (4.4)
Distant Recurrence	60 (7.7)	51 (13.1)
Death	15 (1.9)	6 (1.5)
PD = Progressed disease Database Cutoff Date: 23MAR2021.		

Figure 2: Kaplan-Meier Estimates of Event-Free Survival (EFS) (All participants)



n at risk

MK-3475+chemotherapy/MK-3475	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Placebo+chemotherapy/Placebo	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

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B.2.6.4 Overall Survival (OS)

Overall survival is defined as the time from randomisation to death due to any cause. Given that the primary hypothesis of EFS was successful, the secondary hypothesis of OS was formally tested at the same alpha level of 2.5% according to the protocol multiplicity strategy. The analysis showed improvement in OS that favoured the pembrolizumab arm over the placebo arm at month 42. However, due to the relative early time of the analysis with respect to the OS endpoint [redacted] (information fraction of approximately [redacted]% [[redacted] of the [redacted] events needed for the final analysis]) the observed one-sided p-value did not cross the multiplicity-adjusted, one-sided prespecified p-value boundary at IA4. Therefore, the success criterion for the secondary OS hypothesis was not met.

The final analysis for the trial (for all endpoints) is due to take place in [redacted]. It is probable that the number of OS events needed to conduct statistically analysis will not have taken place since. This is because OS may be delayed for patients obtaining a pCR and subsequently remaining EFS, whilst for those who relapse, OS may in part be confounded by the availability of other anti-PD-1/anti-PD-L1 agents for treatment of metastatic disease.

[redacted]

The OS HR of 0.72 (95% CI: 0.51, 1.02), with a one-sided p-value of 0.0321377 that did not cross the prespecified boundary for statistical significance of p=[redacted], represents a 28% reduction in the risk of death compared with the placebo arm. The median OS was not reached in either arm at month 42 and will be analysed in future interim analysis as data matures.

Table 16: Analysis of OS (All participants)

Treatment	N	Number of events (%)	Person-months	Event rate/100 person-months (%)	Median OS [a] [months] (95% CI)	OS Rate at month 42 in %[†] (95% CI)	Vs. control Hazard Ratio (95% CI) [b] p-value [c]
Pembrolizumab arm	784	80 (10.2)	28,1997.7	0.3	NR	89.2 (86.7, 91.3)	0.72 (0.51, 1.02) 0.0321377
Placebo arm	390	55 (14.1)	13,908.1	0.4	NR	84.1 (79.5, 87.7)	

NR = Not reached
[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Q3W vs. Weekly).

[c] One-sided p-value based on log-rank test stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Cb) (Q3W vs. Weekly).
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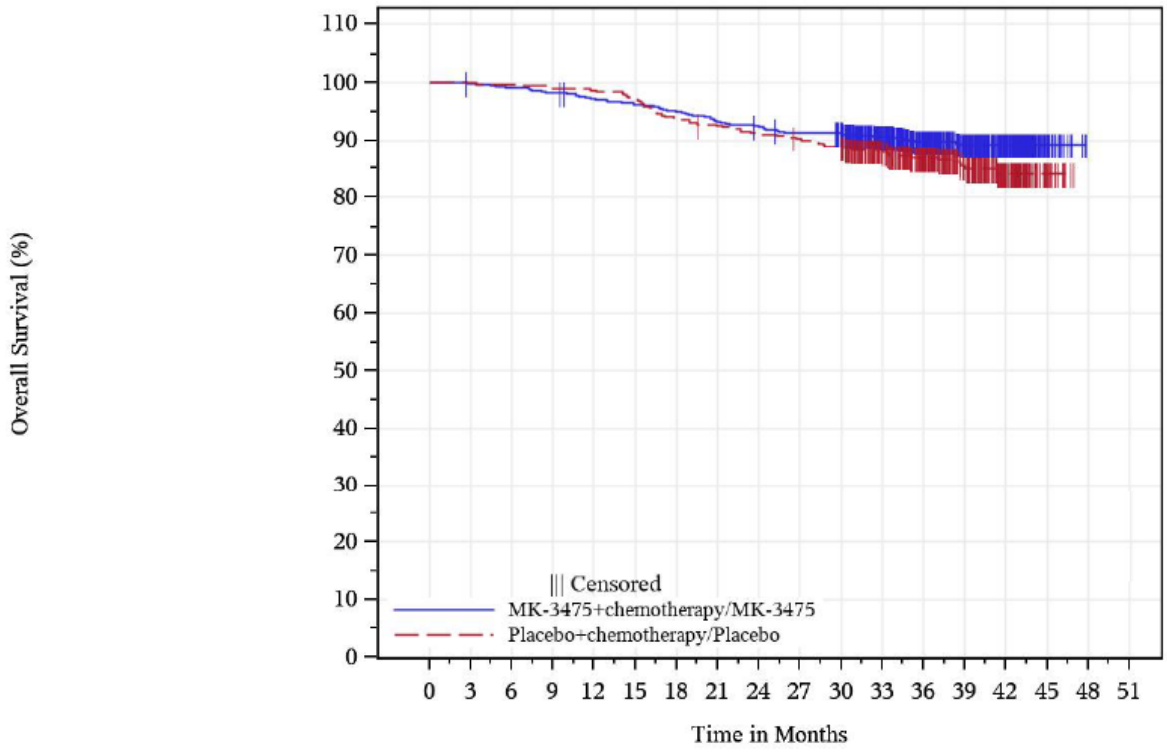
Table 17: Summary of OS rate over time (All participants)

	Pembrolizumab arm (n=784) % (95% CI)	Placebo arm (n=390) % (95% CI)
Summary of overall survival rate at time point		
12 months	97.2 (95.8, 98.1)	98.7 (96.9, 99.5)
24 months	92.3 (90.2, 94.0)	91.0 (87.7, 93.5)
36 months	89.7 (87.3, 91.7)	86.9 (83.0, 89.9)
42 months	89.2 (86.7, 91.3)	84.1 (79.5, 87.7)
Database Cutoff Date: 23MAR2021		

Figure 3: KM estimates of OS (All participants)



n at risk

MK-3475+chemotherapy/MK-3475	784	782	777	770	759	752	742	729	720	712	701	586	461	323	178	30	0	0
Placebo+chemotherapy/Placebo	390	390	389	386	385	380	366	360	354	350	343	286	223	157	89	17	0	0

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B.2.6.4 Patient reported outcomes

Three patient reported outcomes (PRO) questionnaires were used to assess patient Health Related Quality of Life (HRQoL) in the study for both the neoadjuvant and adjuvant phases: EORTC QLQ-C30 QLQ-BR23 and EQ-5D VAS. Patient-reported outcome (PRO) analyses were based on the PRO full analysis set (FAS) population, which included all randomised participants who had at least one PRO assessment available and had received at least 1 study treatment.

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).

Neoadjuvant phase

Compliance rates for EQ-5D VAS in the neoadjuvant phase were [redacted]% and [redacted]% at baseline for the pembrolizumab arm and placebo arm, respectively in the FAS population. Completion rates remained high at later weeks. At Week 21, the difference in least squares (LS) mean change from baseline in EQ-5D VAS score between the pembrolizumab arm and placebo arm was [redacted] points (95% CI: -[redacted]). This infers there was not a negative impact upon a patient's quality of life with the introduction of pembrolizumab to neoadjuvant chemotherapy.

Table 18: Analysis of change from neoadjuvant baseline in EQ-5D VAS at neoadjuvant week 21 - All participants (FAS population)

	Baseline		Neoadjuvant Week 21		Change from Baseline at Week 21	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) [a]
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]

[a] Based on cLDA model with the PRO score as the response variable, and treatment by timepoint interaction, stratification factors (Nodal status (positive vs negative), Tumour size (T1/T2 vs T3/T4), and Choice of Carboplatin (Q3W vs Weekly)) as covariates.
For Neoadjuvant Baseline and Neoadjuvant Week 21, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from Neoadjuvant Baseline, N is the number of participants in the analysis population in each treatment group.
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Figure 4: Empirical mean change from neoadjuvant baseline in EQ-5D VAS across time (Mean +/- SE) - All participants (FAS population)

[redacted],

Adjuvant phase

For the adjuvant phase the baseline compliance rates were [redacted]% and [redacted]% for the pembrolizumab arm and placebo arm, respectively. Completion rates remained high at later weeks. At Week 24 (of the adjuvant phase) the difference in LS mean change from baseline in EQ-5D VAS score between the pembrolizumab arm and placebo arm was [redacted] points (95% CI: [redacted], [redacted]). This infers there was not a negative impact upon a patient's quality of life with pembrolizumab in the adjuvant phase compared with placebo.

Table 19: Analysis of change from adjuvant baseline in EQ-5D VAS at adjuvant week 24 - all participants (FAS population)

Treatment	Baseline	Adjuvant Week 24	Change from Baseline at Week 24

	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) [a]
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise comparison					**Difference in LS Means 95% CI)**	**p-Value**
Pembrolizumab + vs. Placebo					[redacted]	[redacted]

[a] Based on cLDA model with the PRO score as the response variable, and treatment by timepoint interaction, stratification factors (Nodal status (positive vs negative), Tumour size (T1/T2 vs T3/T4), and Choice of Carboplatin (Q3W vs Weekly)) as covariates.
For Adjuvant Baseline and Adjuvant Week 24, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from Adjuvant Baseline, N is the number of participants in the analysis population in each treatment group.
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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 QLQ-BR23 are presented in section 11.2.5 of the KEYNOTE-522 Clinical Summary Report (CSR).

Figure 5: Empirical mean change from adjuvant baseline in EQ-5D VAS across time (Mean +/- SE) - All participants (FAS population)

B.2.7 Subgroup analysis

A series of analyses was pre-specified in the KEYNOTE-522 study protocol 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:

- Nodal status (positive vs. negative)
- Tumour size (T1/T2 vs. T3/T4)
- Choice of carboplatin (Q3W vs. weekly)
- PD-L1 CPS (≥1 vs <1, ≥10 vs. <10, ≥20 vs. <20)
- Overall stage (Stage II vs. stage III)
- Menopausal status (Pre vs. post)
- Age (<65 years vs. ≥ 65)

- Geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of the world)
- Ethnic origin (Hispanic vs. non-Hispanic)
- ECOG performance status (0 vs. 1)
- HER2 status by IHC (2+ but FISH vs. 0-1)
- LDH (>Upper limit of normal (ULN) vs. ≤ ULN)

The treatment difference of pembrolizumab + chemotherapy compared with placebo + chemotherapy across prespecified subgroup analysis was generally consistent with the finding in the ITT population, showing directionally favourable improvement in pCR in the pembrolizumab + chemotherapy group. The same is also true for EFS. Due to the small number of events in subgroups, the results should be interpreted with caution.

Figure 6: Forest plot of pCR (ypT0/Tis ypN0) by subgroup factors - All participants

	Pembro+ chemo #pCR/N	Pbo+chemo #pCR/N	Total #pCR/N	pCR Rate Diff (%)	95% CI
Overall	494/784	217/390	711/1174	7.5	(1.6,13.4)
Nodal status					
Positive	255/408	99/196	354/604	12.0	(3.6,20.4)
Negative	239/376	118/194	357/570	2.7	(-5.6,11.2)
Tumor size					
T1/T2	393/581	175/290	568/871	7.3	(0.6,14.1)
T3/T4	101/203	42/100	143/303	7.8	(-4.2,19.3)
Choice of Carboplatin					
Q3W	214/334	100/167	314/501	4.2	(-4.7,13.3)
Weekly	280/444	117/220	397/664	9.9	(1.9,17.8)
PD-L1 CPS 1 Cutoff					
PD-L1 CPS >= 1	436/656	187/317	623/973	7.8	(1.4,14.2)
PD-L1 CPS < 1	58/128	27/69	85/197	7.1	(-7.8,21.1)
PD-L1 CPS 10 Cutoff					
PD-L1 CPS >= 10	298/393	119/177	417/570	8.7	(0.8,16.9)
PD-L1 CPS < 10	196/391	95/209	291/600	4.3	(-4.1,12.6)
PD-L1 CPS 20 Cutoff					
PD-L1 CPS >= 20	197/247	89/121	286/368	6.8	(-2.2,16.5)
PD-L1 CPS < 20	297/537	125/265	422/802	8.2	(0.9,15.5)
Overall Stage					
Stage II	385/590	173/291	558/881	5.8	(-1.0,12.7)
Stage III	109/194	43/98	152/292	12.3	(0.2,24.1)
Menopausal status (For females only)					
Pre-menopausal	290/438	141/221	431/659	2.4	(-5.2,10.2)
Post-menopausal	204/345	76/169	280/514	14.2	(5.0,23.1)
Age Category					
< 65 years	450/700	196/342	646/1042	7.0	(0.7,13.3)
>= 65 years	44/84	21/48	65/132	8.6	(-9.1,25.7)
Geographic region					
Asia	82/136	36/80	118/216	15.3	(1.5,28.6)
Europe/Israel/North America/Australia	388/607	169/285	557/892	4.6	(-2.2,11.5)
Rest of World	24/41	12/25	36/66	10.5	(-14.0,34.1)
Ethnic origin					
Hispanic	50/86	19/39	69/125	9.4	(-9.2,27.7)
Not Hispanic	390/615	170/307	560/922	8.0	(1.3,14.8)
ECOG performance status					
0	430/678	184/341	614/1019	9.5	(3.1,15.9)
1	64/106	33/49	97/155	-7.0	(-22.2,9.7)
HER2 status					
0-1+ by IHC	384/595	155/286	539/881	10.3	(3.4,17.3)
2+ by IHC (but FISH-)	110/188	62/104	172/292	-1.1	(-12.6,10.8)
LDH					
<=ULN	398/631	174/309	572/940	6.8	(0.1,13.5)
> ULN	94/149	43/80	137/229	9.3	(-3.9,22.6)

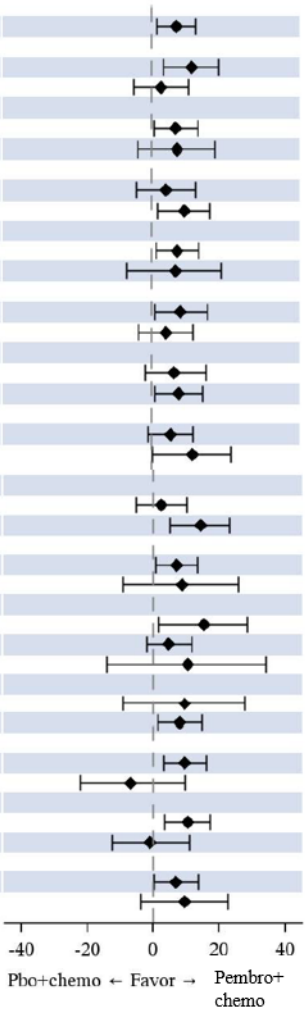
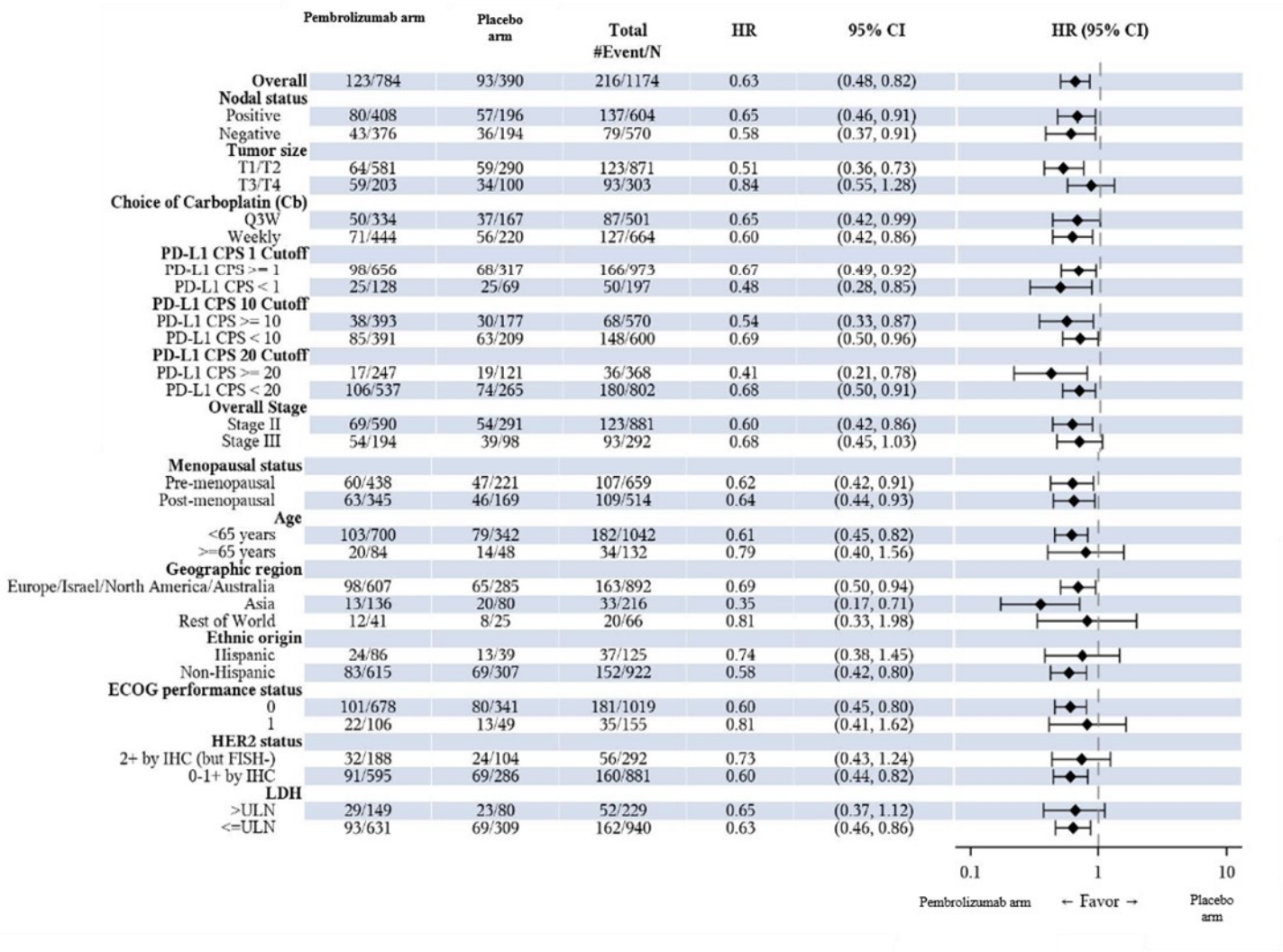


Figure 7: Forest plot of EFS by subgroup factors - All participants



B.2.8 Meta-analysis

A clinical SLR was conducted to identify any additional studies concerning the indication of interest (see appendix D). This is the only study that explores the effectiveness and safety of pembrolizumab for this indication, therefore, a meta-analysis is neither relevant nor necessary for this submission.

B.2.9 Indirect and mixed treatment comparisons

The list of comparators outlined within the final scope issued by NICE includes standard neoadjuvant/adjuvant therapy without pembrolizumab. Clinical expert advice sought confirmed that the KEYNOTE-522 study design and choice of comparators is appropriate and generalisable of the treatment pathway in the UK setting. Local cancer guidelines state capecitabine may be used in non-pCR patients who have not previously received carboplatin [24]. Also clinical experts noted that adjuvant chemotherapies (including capecitabine) post neo-adjuvant chemotherapy are not extensively used in the UK setting owning to the limited survival benefit (see section B.1.3 above).

For the purposes of this submission, the KEYNOTE-522 is used directly to model the relative treatment effect in the UK population. Please refer to appendix D for a list of studies identified from the clinical SLR.

Uncertainties in the indirect and mixed treatment comparisons

Not applicable. A head to head comparison from the Phase 3 pivotal trial RCT is used to inform the decision problem.

B.2.10 Adverse reactions

In KEYNOTE-522 safety and tolerability were assessed by clinical review of all relevant parameters including adverse events (AEs), laboratory tests, and vital signs. Safety analyses were based on the 'all subjects as treated' (ASaT) population, which included all randomised participants who received at least 1 study treatment (N=1172). Participants were included in the group corresponding to the treatment that they actually received.

After discontinuation of study treatment, each subject will be followed for 30 days for AE and events of clinical interest (ECIs). Serious AEs (SAEs) will be collected for 90 days after the end of study treatment.

The safety results of KEYNOTE-522 demonstrated pembrolizumab plus chemotherapy followed by pembrolizumab monotherapy had a manageable safety profile in participants with high-risk, early-stage TNBC. The safety profile of the pembrolizumab arm is generally consistent with the known safety profile of pembrolizumab monotherapy and a carboplatin-/anthracycline-based chemotherapy regimen. No new safety concerns were identified.

During the combined phases, the overall 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 pembrolizumab arm and the placebo arm. There was a higher overall incidence of SAEs, serious drug-related AEs, and discontinuations of any drug due to an AE in the pembrolizumab arm compared with the placebo arm, reflecting the contribution of both pembrolizumab and neoadjuvant chemotherapy.

B.2.10.1 Extent of drug exposure combined phases

Across both phases of the trial, the median duration of exposure to study intervention for all drugs was [redacted] weeks for the pembrolizumab arm (range 0.1-95.3) and [redacted] weeks for the placebo arm (range 0.1-86.1).

At the time of database cut off, in the pembrolizumab arm, [redacted] of 783 patients ([redacted] person-time) had a duration of exposure of 6 months or more compared with [redacted] of 389 ([redacted] person-time) in the placebo arm. [redacted] patients ([redacted] person-time) in the pembrolizumab arm received treatment for over 12 months compared with [redacted] ([redacted] person-time) in the placebo arm.

Drug exposures for neoadjuvant and adjuvant phase of treatment are available in Table 9 and Table 10, respectively.

Table 20: Summary of drug exposure – Combined phases (ASaT Population)

	Pembrolizumab arm (n=783)	Placebo arm (n=389)
Number of weeks on therapy		
Mean Median SD Range	[redacted]	[redacted]
Administrations		
Mean	13.2	14.4
Median	17.0	17.0
SD	5.4	4.5
Range	1.0-17.0	1.0-17.0

Table 21: Exposure by duration (ASaT Population)

	Pembrolizumab arm (n=783)		Placebo arm (n=389)	
	n	**Person-time**	**n**	**Person-time**
Treatment Duration				
> 0 m	778	[redacted]	389	[redacted]
≥ 1 m	763	[redacted]	386	[redacted]
≥ 3 m	717	[redacted]	371	[redacted]
≥ 6 m	570	[redacted]	323	[redacted]
≥ 12 m	[redacted]	[redacted]	[redacted]	[redacted]

Each participant 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.
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B.2.10.2 Summary of adverse reactions – Combined phases

Pembrolizumab + chemotherapy followed by pembrolizumab monotherapy had a manageable safety profile during the combined (neoadjuvant + adjuvant) phase.

Comparable proportion of patient in the pembrolizumab and placebo arms experienced AEs (99.2% vs. 100%), drug-related AEs (98.9% vs. 99.7%), Grade 3 to 5 AEs (82.4% vs. 78.7%), Grade 3 to 5 drug-related AEs (77.1% vs. 73.3%), deaths (0.9% vs. 0.3%), deaths due to drug-related AEs (0.5% vs. 0.3%), and any dose modification due to an AE ([redacted]) (Table 24).

There was a higher incidence (≥5 percentage points difference) of serious adverse events (SAEs, 43.6% vs. 28.5%), serious drug-related AEs (34.1% vs. 20.1%), and discontinuations of any drug due to an AE (29.9% vs. 15.4%) in the pembrolizumab arm compared with the placebo arm.

Included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non- serious adverse events and up to 90 days of the last treatment including definitive surgery and radiation therapy for the serious adverse events.

Adverse events for neoadjuvant and adjuvant phases are included in Appendix F.1.1 and F.1.2, respectively.

Table 22: Disposition of participants – study medication (ITT population)

	Pembrolizumab arm (n=784)		Placebo arm (n=390)	
	n	(%)	n	(%)
Status for Study Medication in Neoadjuvant Treatment 1				
Started	778		389	
Completed	684	(87.9)	356	(91.5)
Discontinued	94	(12.1)	33	(8.5)
Adverse Event	73	(9.4)	21	(5.4)
Clinical Progression	0	(0.0)	3	(0.8)
Physician Decision	11	(1.4)	3	(0.8)
Progressive Disease	3	(0.4)	5	(1.3)
Withdrawal By Subject	7	(0.9)	1	(0.3)
Status for Study Medication in Neoadjuvant Treatment 2				
Started	726		369	
Completed	660	(90.9)	343	(93.0)
Discontinued	66	(9.1)	26	(7.0)
Adverse Event	46	(6.3)	14	(3.8)
Clinical Progression	2	(0.3)	1	(0.3)
Physician Decision	9	(1.2)	5	(1.4)
Progressive Disease	5	(0.7)	2	(0.5)
Withdrawal By Subject	4	(0.6)	4	(1.1)
Status for Study Medication in Adjuvant Treatment				
Started	588		331	
Completed	487	(82.8)	283	(85.5)
Discontinued	101	(17.2)	48	(14.5)
Adverse Event	42	(7.1)	10	(3.0)
Physician Decision	17	(2.9)	3	(0.9)
Relapse/Recurrence	20	(3.4)	18	(5.4)
Withdrawal By Subject	22	(3.7)	17	(5.1)

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.
Participants randomized but not treated in neoadjuvant treatment 1 were due to randomization in error, or withdrawal by participant before dosing.
The study allows that participants who either completed or discontinued neoadjuvant treatment 1 can start neoadjuvant treatment 2 or go to surgery, and participants who either completed or discontinued neoadjuvant treatment 2 can go to surgery.
Database Cutoff Date: 23MAR2021

Table 23: Disposition of participants - status for trial (ITT population)

	Pembrolizumab arm (n=784)	Placebo arm (n=390)

	n	(%)	n	(%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants in population is used as the denominator for the percentage calculation. Database Cutoff Date: 23MAR2021				

Table 24: Adverse event summary - Combined phases (All participants)

	Pembrolizumab arm (n=789)		Placebo arm (n=389)	
	n	(%)	n	(%)
with one or more adverse events	777	(99.2)	389	(100)
with no adverse event	6	(0.8)	0	(0)
with drug-related [a] adverse events	774	(98.9)	388	(99.7)
with toxicity grade 3-5 adverse events	645	(82.4)	306	(78.7)
with toxicity grade 3-5 drug-related adverse events	604	(77.1)	285	(73.3)
with serious adverse events	341	(43.6)	111	(28.5)
with serious drug-related adverse events	267	(34.1)	78	(20.1)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
who died	7	(0.9)	1	(0.3)
who died due to a drug-related adverse event	4	(0.5)	1	(0.3)
discontinued any drug due to an adverse event	234	(29.9)	60	(15.4)
discontinued pembrolizumab /placebo	157	(20.1)	31	(8)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
discontinued any drug due to a drug-related adverse event	217	(27.7)	55	(14.1)
discontinued pembrolizumab /placebo	140	(17.9)	26	(6.7)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]				
discontinued any drug due to a serious adverse event	94	(12)	15	(3.9)
discontinued pembrolizumab /placebo	81	(10.3)	14	(3.6)
[redacted]				
discontinued any drug due to a serious drug-related adverse event	84	(10.7)	11	(2.8)
discontinued pembrolizumab /placebo	72	(9.2)	10	(2.6)
[redacted]				

[a] Determined by the investigator to be related to the drug.
[b] Defined as an action taken of dose reduced, drug interrupted or drug withdrawn. Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 23MAR2021

B.2.10.3 Adverse events

The most frequently reported AEs (incidence ≥30%) in either arm were nausea, alopecia, anaemia, neutropenia, fatigue, constipation, diarrhoea, vomiting, arthralgia, and ALT increased.

AEs (incidence ≥15%) with a greater risk difference for pembrolizumab arm (where the lower bound of the 95% CI for the treatment difference was >0) during the combined phases were pyrexia, hypothyroidism, diarrhoea, rash, and decreased appetite. These events were primarily Grade 1 or 2. There were no AEs (incidence ≥15%) with a greater risk difference for the placebo arm identified during the combined phases. In both treatment arms, most AEs occurred in the first 3 months of initiating study intervention; the exposure-adjusted event rate decreased at 3 to 6 months and continued to decrease beyond 12 months.

Table 25: Participants with AEs by decreasing incidence (incidence ≥10% in at least one arm; ASaT population)

	Pembrolizumab arm		Placebo arm	
	n	(%)	n	(%)

Participants in population	783		389	
with one or more adverse events	777	(99.2)	389	(100)
with no adverse events	6	(0.8)	0	(0)
Nausea	522	(66.7)	257	(66.1)
Alopecia	477	(60.9)	226	(58.1)
Anaemia	463	(59.1)	229	(58.9)
Neutropenia	376	(48)	190	(48.8)
Fatigue	365	(46.6)	168	(43.2)
Constipation	328	(41.9)	150	(38.6)
Diarrhoea	318	(40.6)	133	(34.2)
Vomiting	244	(31.2)	108	(27.8)
Headache	234	(29.9)	113	(29)
Alanine aminotransferase increased	238	(30.4)	108	(27.8)
Arthralgia	225	(28.7)	120	(30.8)
Asthenia	219	(28)	111	(28.5)
Rash	234	(29.9)	92	(23.7)
Neutrophil count decreased	191	(24.4)	113	(29)
Pyrexia	221	(28.2)	72	(18.5)
Cough	193	(24.6)	86	(22.1)
Aspartate aminotransferase increased	187	(23.9)	77	(19.8)
Neuropathy peripheral	163	(20.8)	90	(23.1)
Decreased appetite	178	(22.7)	65	(16.7)
Insomnia	161	(20.6)	74	(19)
Peripheral sensory neuropathy	156	(19.9)	72	(18.5)
Myalgia	153	(19.5)	73	(18.8)
Febrile neutropenia	151	(19.3)	66	(17)
Pruritus	147	(18.8)	56	(14.4)
Stomatitis	141	(18)	58	(14.9)
Radiation skin injury	114	(14.6)	73	(18.8)
Hot flush	117	(14.9)	69	(17.7)
Urinary tract infection	123	(15.7)	62	(15.9)
Epistaxis	117	(14.9)	63	(16.2)
Dizziness	118	(15.1)	60	(15.4)
Thrombocytopenia	110	(14)	68	(17.5)
Dysgeusia	128	(16.3)	49	(12.6)
White blood cell count decreased	113	(14.4)	56	(14.4)
Dyspepsia	111	(14.2)	56	(14.4)
Abdominal pain	112	(14.3)	49	(12.6)
Mucosal inflammation	112	(14.3)	49	(12.6)
Back pain	97	(12.4)	63	(16.2)
Upper respiratory tract infection	106	(13.5)	47	(12.1)
Dyspnoea	99	(12.6)	50	(12.9)
Leukopenia	98	(12.5)	51	(13.1)
Hypothyroidism	118	(15.1)	22	(5.7)

Pain in extremity	91	(11.6)	49	(12.6)
Erythema	81	(10.3)	36	(9.3)
Nasopharyngitis	65	(8.3)	52	(13.4)
Platelet count decreased	78	(10)	37	(9.5)
Abdominal pain upper	80	(10.2)	34	(8.7)
Hypokalaemia	88	(11.2)	24	(6.2)
Bone pain	70	(8.9)	39	(10)
Breast pain	64	(8.2)	43	(11.1)
Infusion related reaction	79	(10.1)	27	(6.9)
Gastrooesophageal reflux disease	57	(7.3)	43	(11.1)

Every participant is counted a single time for each applicable specific adverse event.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 23MAR2021

Drug related AEs

The drug-related AEs observed for participants in the pembrolizumab arm were generally consistent with the known safety profiles of pembrolizumab monotherapy and a carboplatin-/anthracycline-based chemotherapy regimen.

The overall incidences of drug-related AEs as determined by the investigator during the combined phases were similar between the pembrolizumab (98.9%) and placebo (99.7%) arms.

The incidences of the most frequently reported drug-related AEs (incidence ≥30%) during the combined phases were generally similar between the two treatment groups and included

- Pembrolizumab arm: nausea, alopecia, anaemia, neutropenia, fatigue, and diarrhoea.
- Placebo arm: nausea, alopecia, anaemia, neutropenia, and fatigue.

Table 26: Participants with drug related AEs by decreasing incidence (incidence ≥5% in one or more treatment arms; ASaT population)

	Pembrolizumab arm		Placebo arm	
	n	(%)	n	(%)
Participants in population	783		389	
with one or more adverse events	774	(98.9)	388	(99.7)
with no adverse events	9	(1.1)	1	(0.3)
Nausea	495	(63.2)	245	(63)
Alopecia	471	(60.2)	220	(56.6)

Anaemia	429	(54.8)	215	(55.3)
Neutropenia	367	(46.9)	185	(47.6)
Fatigue	330	(42.1)	151	(38.8)
Diarrhoea	238	(30.4)	98	(25.2)
Alanine aminotransferase increased	204	(26.1)	98	(25.2)
Asthenia	198	(25.3)	102	(26.2)
Neutrophil count decreased	185	(23.6)	112	(28.8)
Vomiting	200	(25.5)	86	(22.1)
Constipation	188	(24)	85	(21.9)
Rash	196	(25)	66	(17)
Neuropathy peripheral	154	(19.7)	84	(21.6)
Aspartate aminotransferase increased	157	(20.1)	63	(16.2)
Peripheral sensory neuropathy	148	(18.9)	72	(18.5)
Decreased appetite	153	(19.5)	57	(14.7)
Febrile neutropenia	144	(18.4)	65	(16.7)
Stomatitis	132	(16.9)	55	(14.1)
Arthralgia	121	(15.5)	59	(15.2)
Pyrexia	138	(17.6)	41	(10.5)
Dysgeusia	124	(15.8)	49	(12.6)
Thrombocytopenia	104	(13.3)	65	(16.7)
Myalgia	112	(14.3)	49	(12.6)
White blood cell count decreased	108	(13.8)	52	(13.4)
Pruritus	116	(14.8)	38	(9.8)
Mucosal inflammation	103	(13.2)	45	(11.6)
Headache	100	(12.8)	42	(10.8)
Leukopenia	87	(11.1)	49	(12.6)
Hypothyroidism	105	(13.4)	19	(4.9)
Epistaxis	76	(9.7)	41	(10.5)
Dyspepsia	71	(9.1)	39	(10)
Platelet count decreased	74	(9.5)	34	(8.7)
Hot flush	55	(7)	45	(11.6)
Infusion related reaction	73	(9.3)	25	(6.4)
Dizziness	61	(7.8)	29	(7.5)
Abdominal pain	65	(8.3)	22	(5.7)
Nail discolouration	48	(6.1)	31	(8)
Paraesthesia	45	(5.7)	28	(7.2)
Rash maculo-papular	50	(6.4)	23	(5.9)
Dry mouth	49	(6.3)	20	(5.1)
Dyspnoea	46	(5.9)	23	(5.9)
Dry skin	47	(6)	20	(5.1)
Cough	52	(6.6)	13	(3.3)
Gastrooesophageal reflux disease	41	(5.2)	24	(6.2)
Abdominal pain upper	39	(5)	22	(5.7)

Oedema peripheral	35	(4.5)	21	(5.4)
Dermatitis acneiform	45	(5.7)	10	(2.6)
Insomnia	42	(5.4)	13	(3.3)
Blood alkaline phosphatase increased	29	(3.7)	20	(5.1)

Every participant is counted a single time for each applicable specific adverse event.
Database Cutoff Date: 23MAR2021

Grade 3 to 5 AE's

The overall incidence of Grade 3 to 5 AEs during the combined phases was generally similar between the 2 treatment groups arms. There were no specific trends noted in the pembrolizumab arm that suggest any new safety concerns. The types and frequencies of the most common Grade 3 to 5 AEs (incidence ≥5%) during the combined phases were generally similar between the 2 treatment arms. The only risk difference of Grade 3 to 5 AEs (incidence ≥5%) during the combined phases that favoured either treatment group was ALT increased, which had a greater risk in the pembrolizumab arm (where the lower bound of the 95% CI for the treatment difference was >0).

Table 27: Participants with grade 3-5 AEs by decreasing incidence (incidence ≥5% in one or more treatment arms; ASaT population)

	Pembrolizumab arm		Placebo arm	
	n	(%)	n	(%)
Participants in population	783		389	
with one or more adverse events	645	(82.4)	306	(78.7)
with no adverse events	138	(17.6)	83	(21.3)
Neutropenia	276	(35.2)	134	(34.4)
Neutrophil count decreased	149	(19)	92	(23.7)
Anaemia	153	(19.5)	61	(15.7)
Febrile neutropenia	144	(18.4)	63	(16.2)
White blood cell count decreased	61	(7.8)	21	(5.4)
Alanine aminotransferase increased	50	(6.4)	11	(2.8)

Every participant is counted a single time for each applicable specific adverse event.
Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 23MAR2021

Drug related grade 3-5 AEs

The overall incidences of drug-related Grade 3 to 5 AEs as determined by the investigator during the combined phases were generally similar between the pembrolizumab (77.1%) and placebo arms (73.3%). The incidences of the most frequently reported drug-related Grade 3 to 5 AEs (incidence ≥5%) during the combined phases were generally similar between treatment groups.

Table 28: Participants with drug related grade 3-5 AEs by decreasing incidence (incidence ≥5% in one or more treatment arms; ASaT population)

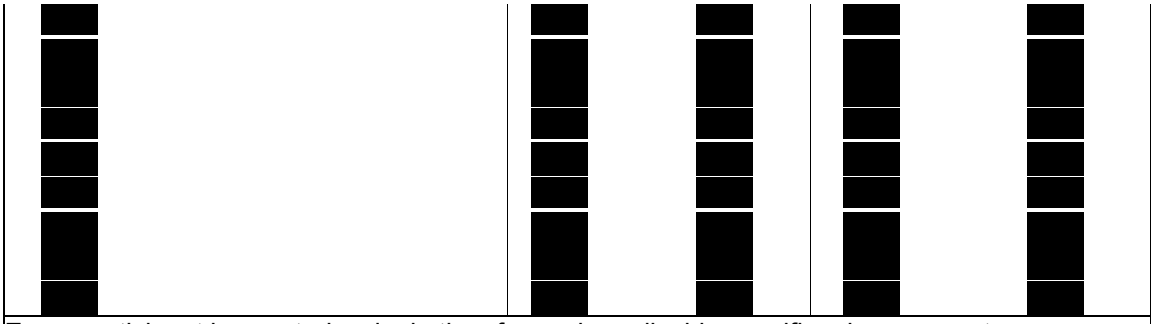
	Pembrolizumab arm		Placebo arm	
	n	(%)	n	(%)
Participants in population	783		389	
with one or more adverse events	604	(77.1)	285	(73.3)
with no adverse events	179	(22.9)	104	(26.7)
Neutropenia	270	(34.5)	130	(33.4)
Neutrophil count decreased	146	(18.6)	90	(23.1)
Febrile neutropenia	139	(17.8)	62	(15.9)
Anaemia	141	(18)	58	(14.9)
White blood cell count decreased	60	(7.7)	20	(5.1)
Alanine aminotransferase increased	43	(5.5)	9	(2.3)
Every participant is counted a single time for each applicable specific adverse event. Grades are based on NCI CTCAE version 4.0. Database Cutoff Date: 23MAR2021				

B.2.10.4 Serious Adverse events

The overall incidence of SAEs was higher in the pembrolizumab arm compared with the placebo arm. The SAEs observed for participants in the pembrolizumab arm were generally consistent with the known safety profiles of pembrolizumab monotherapy and a carboplatin-/anthracycline-based chemotherapy regimen.

Table 29: Participants with serious AEs up to 90 days after last dose by decreasing incidence (incidence ≥1% in one or more treatment arms; ASaT population)

	Pembrolizumab arm		Placebo arm	
	n	(%)	n	(%)
Participants in population	783		389	
with one or more adverse events	341	(43.6)	111	(28.5)
with no adverse events	442	(56.4)	278	(71.5)
Febrile neutropenia	118	(15.1)	47	(12.1)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



Every participant is counted a single time for each applicable specific adverse event.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 23MAR2021

Deaths due to Adverse Events

Deaths due to AEs during the combined phases occurred in 7 (0.9%) participants in the pembrolizumab arm and 1 (0.3%) participant in the placebo arm. There were 4 deaths in the pembrolizumab arm considered drug-related. Deaths due to AE in 3 participants were considered related to pembrolizumab (pneumonitis in 1 participant in the neoadjuvant phase, pulmonary embolism in 1 participant in the adjuvant phase, and autoimmune encephalitis in 1 participant in the adjuvant phase). One participant in the neoadjuvant phase experienced 3 AEs resulting in death: sepsis and multiple organ dysfunction syndrome, which were considered related to chemotherapy, and myocardial infarction, which was not considered to be drug-related. In the placebo arm, the 1 reported death due to an AE (septic shock) occurred during the neoadjuvant phase and was considered related to chemotherapy by the investigator. No new safety signals were identified upon review of these fatal events

B.2.10.5 Adverse events of special interest

The overall incidence of AEOSI during the combined phases was higher in the pembrolizumab arm (43.6%) compared with the placebo arm (21.9%).

There were 2 deaths due to an AEOSI (pneumonitis and autoimmune encephalitis) in the pembrolizumab arm, which were considered related to pembrolizumab by the investigator. The most frequently reported AEOSIs (incidence ≥5%) by category, during the combined phases were hypothyroidism, infusion reactions, severe skin reactions, and hyperthyroidism in the pembrolizumab arm and hypothyroidism and infusion reactions in the placebo arm. The

incidence of hypothyroidism in the pembrolizumab arm was higher than anticipated based on the known safety profile of pembrolizumab monotherapy and higher than the placebo arm.

Table 30: Participants with AEOSI by category (incidence >0% in one or more treatment arms; ASaT population

	Pembrolizumab arm		Placebo arm	
	n	(%)	n	(%)
Participants in population	783		389	
with one or more adverse events	341	(43.6)	85	(21.9)
with no adverse events	442	(56.4)	304	(78.1)
Infusion Reactions	141	(18)	45	(11.6)
Hypothyroidism	118	(15.1)	22	(5.7)
Severe Skin Reactions	45	(5.7)	4	(1)
Hyperthyroidism	41	(5.2)	7	(1.8)
Adrenal Insufficiency	20	(2.6)	0	(0)
Pneumonitis	17	(2.2)	6	(1.5)
Thyroiditis	16	(2)	5	(1.3)
Hypophysitis	15	(1.9)	1	(0.3)
Colitis	13	(1.7)	3	(0.8)
Hepatitis	11	(1.4)	3	(0.8)
Nephritis	7	(0.9)	0	(0)
Myocarditis	5	(0.6)	0	(0)
Pancreatitis	5	(0.6)	0	(0)
Myositis	4	(0.5)	0	(0)
Type 1 Diabetes Mellitus	4	(0.5)	0	(0)
Vasculitis	4	(0.5)	0	(0)
Encephalitis	2	(0.3)	0	(0)
Uveitis	2	(0.3)	0	(0)
Myasthenic Syndrome	1	(0.1)	0	(0)
Sarcoidosis	1	(0.1)	0	(0)

Every participant is counted a single time for each applicable specific adverse event. A participant with multiple adverse events within a bolded term is counted a single time for that bolded term.
"Infusion related reaction" includes infusion related reactions due to pembrolizumab and chemotherapy, for example, Paclitaxel.
Database Cutoff Date: 23MAR2021

B.2.11 Ongoing studies

Results provided in this submission are from the interim analysis 4 (IA4) of KEYNOTE-522, database cut off 23rd March 2021. A paper based upon IA1 and 2 data was published in 2020 [31] and a future publication is expected before [redacted]. The next database cut off (IA5) is calendar driven and will take place in [redacted].

B.2.12 Innovation

Pembrolizumab in combination with chemotherapy followed by pembrolizumab monotherapy in the adjuvant setting is an innovative treatment option in this therapy area as the first immunotherapy agent to be appraised by NICE for use in early stage locally advanced breast cancer patients which are at high risk of relapse.

The clinical data presented in section B.2 shows the addition of pembrolizumab to chemotherapy in the neoadjuvant phase statistically significantly improves the outcomes for patients in terms of pCR and EFS. A benefit in overall survival has also been observed however the number of events required for final analysis has not been reached. It has been observed that those who achieve a pCR has longer EFS and OS [13].

With its unique mode of action, pembrolizumab adjuvant systemic therapy primes the immune system to target residual micro-metastatic disease with the goal of improving event free survival and subsequently overall survival [32].

B.2.13 Interpretation of clinical effectiveness and safety evidence

The addition of pembrolizumab to chemotherapy resulted in a statistically significant and clinically meaningful improvement in pCR compared with placebo

Pembrolizumab plus chemotherapy demonstrated a statistically significant improvement in pCR after the neoadjuvant phase, defined as ypT0/Tis ypN0, compared with placebo at IA1. At IA4 7.5% (95% CI: 1.6-13.4%) more patients achieved a pCR in the pembrolizumab arm compared with the placebo arm. This was not formally tested as prespecified in the SAP. The treatment difference across prespecified subgroup analysis was generally consistent with the finding in the ITT population, showing directionally favourable improvement in pCR in the pembrolizumab arm.

Pembrolizumab plus chemotherapy followed by pembrolizumab monotherapy resulted in a statistically significant improvement in EFS compared with placebo.

The pembrolizumab arm had a higher EFS rate compared with the placebo arm at 42 months, 83.5% (95% CI: 80.5%-86.0%) vs. 74.9% (95% CI: 69.8%-79.2%). There was a 37% reduction in the risk of disease progression, a local/distant recurrence, a second primary cancer or death from any cause (HR=0.63 [95% CI, 0.48-0.82]; p=0.00031). For patients this can mean additional time where the cancer has not come back or gotten worse [33]. The treatment difference of the pembrolizumab arm compared with the placebo arm across prespecified

subgroups was generally consistent with the primary finding, showing directionally favourable improvement in EFS.

The addition of pembrolizumab to chemotherapy followed by pembrolizumab monotherapy did not result in a decrease in HRQoL

The change of EQ-5D scores between the pembrolizumab and placebo arms at week 21 (end of the neoadjuvant phase) were similar and demonstrate that the addition of pembrolizumab does not cause a greater decrease in HRQoL.

Pembrolizumab plus chemotherapy followed by pembrolizumab monotherapy has an acceptable tolerability profile which is consistent with the known safety profile of the therapies administered

The safety results of the combined (neoadjuvant + adjuvant) phases demonstrated the pembrolizumab arm had a manageable safety profile in participants. The safety profile of the pembrolizumab arm is generally consistent with the known safety profile of pembrolizumab monotherapy and a carboplatin-/anthracycline-based chemotherapy regimen. No new safety concerns were identified.

Internal validity

KEYNOTE-522 is a robust multicentre, randomised, double-blind phase III study of pembrolizumab with chemotherapy followed by pembrolizumab monotherapy versus placebo with chemotherapy followed by placebo monotherapy in patients with TNBC. The co-primary endpoints were pCR and EFS; both clinically relevant endpoints that were directly referenced in the final scope for this appraisal and decision problem.

Pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab monotherapy does not meet the end of life criteria.

B.3 Cost effectiveness

Key points

- TNBC is a very aggressive cancer with poor survival outcomes despite recent advances in management of metastatic disease.
- Locally advanced inflammatory, or early-stage triple negative breast cancer is associated with high patient burden due to increased risk of recurrence and complexities in subsequent management of systemic disease.
  - Most recurrences in this patient group happen early on and survival outcomes with subsequent treatment options remain poor even with the most recent changes in the treatment pathway.
- Neo-adjuvant chemotherapy followed by surgery can improve patient survival outcomes [Event Free Survival (EFS) and Overall Survival (OS)] by preventing or delaying disease recurrence.
- A cost-effectiveness model was developed to estimate the Incremental Cost-Effectiveness (ICER) of pembrolizumab + chemotherapy in the neoadjuvant setting followed by pembrolizumab adjuvant monotherapy post-surgical resection.
  - Similar to other neo-adjuvant and adjuvant appraisals, a 4 state Markov model was developed to of this technology.
- The economic analysis incorporates evidence from the KEYNOTE-522 Phase III pivotal RCT exploring the efficacy of Pembrolizumab for the indication of interest, and data from KEYNOTE-355, a Phase III pivotal RCT (efficacy of Pembrolizumab + chemotherapy for advanced/metastatic PD-L1+ve TNBC)
- Adding pembrolizumab to chemotherapy in the neoadjuvant setting alongside chemotherapy, followed by pembrolizumab monotherapy post-surgical resection is a highly effective and cost-effective treatment versus standard neoadjuvant chemotherapy alone:
  - ICER of £5,940 per QALY gained at the current patient access scheme (PAS)
  - 98.0% likelihood of cost-effectiveness at a willingness to pay threshold of £30,000 per QALY
- Adding pembrolizumab reduces the likelihood of recurrence, downstream costs and quality of life impacts associated with the management of advanced/metastatic disease while prolonging survival outcomes:
  - An increase of 3.07 life years over a lifetime versus the current neoadjuvant chemotherapy which translates to a net [redacted] QALY gain for a patient group at high risk of recurrence
  - Due to delay or prevention of recurrences, subsequent metastatic treatment costs may reduce by approximately [redacted] per patient.
- The ICER remained largely insensitive to the parameters and assumptions tested in extensive sensitivity and scenario analyses, with scenarios < £20,000/QALY gained.
- Key strengths of the analysis include:
  - Certainty of treatment costs with 17 cycles of pembrolizumab per trial design
  - Head-to-head data from the IA4 of KEYNOTE-552 alongside data from KEYNOTE-355 used to support the economic modeling
  - EQ-5D data collected alongside KEYNOTE-522 leveraged for economic modelling
  - Extended model validation using real world evidence sources and clinical expert opinion
- Pembrolizumab is a highly cost-effective use of the NHS resources for patients with high risk of recurrence with a very aggressive cancer, and therefore, it should be recommended for routine commissioning to address the high unmet need in this setting.

B.3.1 Published cost-effectiveness studies

A comprehensive systematic search was conducted on 16th May 2021, to identify relevant cost-effectiveness studies for the treatment of patients in neoadjuvant and adjuvant triple negative breast cancer. No cost-effectiveness studies evaluating pembrolizumab in combination with chemotherapy followed by pembrolizumab monotherapy 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

Owing to the lack of cost-effectiveness studies appraising pembrolizumab in combination with standard neoadjuvant chemotherapy followed by adjuvant pembrolizumab for the indication of interest, a *de novo* cost-effectiveness model was developed to inform the decision problem. The cost-effectiveness model was informed by the model used in TA424 pertuzumab for the neoadjuvant treatment for HER2-positive breast cancer [34] which modelled early-stage HER2-positive breast cancer differing from our population of triple-negative breast cancer. Whilst we are informed by the TA424 model, we do not replicate it, rather than a 6-state model we build a 4-state model due to the data available to us (see section B.3.2.2 below.

B.3.2.1 Patient population

The patient population included in the economic evaluation consisted of adults with locally advanced inflammatory, or early stage triple negative breast cancer at high risk of recurrence, in line with the anticipated licensed indication and the NICE final scope. Model patient characteristics were based on the KEYNOTE-522 trial (Table 31).

Table 31: Baseline characteristics of the population in the cost-effectiveness model

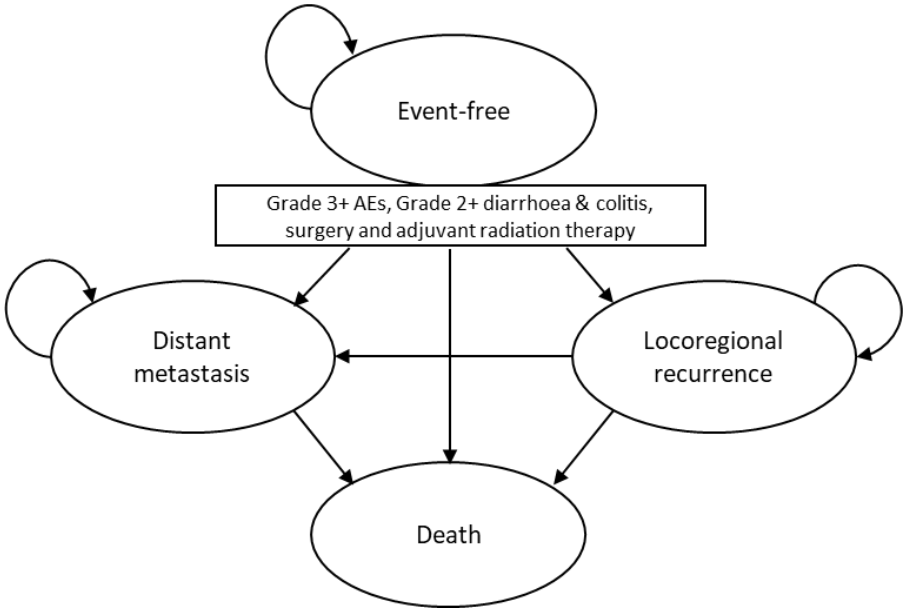
Patient characteristics	Mean value	Source
Patient age (years)	49.0	KEYNOTE-522 [35]
Age, standard deviation (years)	11.8	
Average patient weight (kg)	[redacted]	
Weight, standard deviation (kg)	[redacted]	
Average BSA (m^2)	[redacted]	
BSA, standard deviation	[redacted]	
Proportion female (assumed)*	[redacted]	
*Whilst a male subject was enrolled in the trial, a simplifying assumption was made that all patients are female.		

B.3.2.2 Model structure

Table 32 provides details of the main features of this economic analysis compared to TA424, the specific approved guidance for pertuzumab for the neoadjuvant treatment for HER2-positive breast cancer [34]. Although TA424 concerns different population, comparisons can be made with the neoadjuvant phase of KEYNOTE-522 (which includes an adjuvant phase which is also modelled).

A 4-state Markov cohort model was developed to estimate health outcomes and costs in the early-stage TNBC setting using Microsoft Excel® 2016. The state transition diagram in Figure 8 below illustrates the health states and allowable transitions in the Markov model. The model consists of four mutually exclusive health states; event-free (EF), locoregional recurrence (LR), distant metastasis (DM), and death, to track the disease course and survival of patients over time. A Markov model approach was taken because it can explicitly capture disease pathway of patients with early-stage TNBC as well as the functionality to model metastatic outcomes [36]. This model differentiates health states by type of recurrence (either LR or DM) because the primary endpoint, i.e. EFS, of the KEYNOTE-522 trial encompasses both types of recurrence events [35]. These two types of recurrences have different implications on patients' prognoses, and therefore result in different health outcomes and costs. The model developed for this submission is simpler than TA424 and structured around the KEYNOTE-522 trial co-primary endpoint, EFS, which is representative of clinical disease progression over time (pCR not explicitly modelled).

Figure 8: Cost-effectiveness model structure



How patients move through the different health states

Patients with locally advanced, or early-stage triple negative breast cancer at high risk of recurrence begin in the "EF" health state. At the end of each weekly cycle, patients who are in the "EF" state may stay in "EF", transition to the "LR" state, transition to the "DM" state or die. Patients who are in the "LR" state may stay in the "LR" state, transition to the "DM" state, or die at the end of each cycle, but could not transition back to the "EF" state. Similarly, patients who are in the "DM" state may stay in the "DM" state or die at the end of each cycle but could not transition back to the "EF" or "LR" state. The "death" state is an absorbing health state in which no costs or benefits are accrued.

Movement through the model is determined by transition probabilities estimated using patient-level data from KEYNOTE-522 and KEYNOTE-355 (see section B.3.3 below)

Modelling utility

Utilities were derived from the ED-5D-5L data collected alongside the KEYNOTE-522 study for the "EF" (on and off treatment), "LR" and "DM" health state and these were mapped back to the 3L tool (see section B.3.4.2). Grade 3+ AE disutility was also sourced from the KEYNOTE-522 study and considered in the economic model.

Modelling costs and resource use

Relevant drug and administration costs have been estimated using KEYNOTE-522 data. Surgery costs following the neoadjuvant phase and radiotherapy costs in the adjuvant phase were also included. Resource use was derived from the previous NICE breast cancer (BC) HTAs (TA424 and mTNBC ongoing ID1546) as well as clinical expert opinion. All costs were extracted from public sources such as the National Schedule of Reference costs, PSSRU, BNF, MIMS and eMIT. Relevant AE management costs were calculated from KEYNOTE-522 clinical data alongside the estimated costs for managing these AEs in the NHS setting and was applied as a one-off cost in the first model cycle (see section B.3.5.5).

Modelling subsequent therapies

For patients experiencing distant metastasis, the cost of first line treatment for metastatic TNBC (mTNBC) used in the UK has been included in the economic model. This was estimated using the subsequent therapy market share estimates from UK market research validated with clinical experts reflective of UK practice [25, 37]. Subsequent treatment lines (2L, 3L and 4L)

costs for mTNBC were estimated from the KEYNOTE-355 cost-effectiveness model as per ongoing ID1546 since these were representative of UK practice [38].

Table 32: Features of the economic analysis

Factor	Previous appraisals	Current appraisal	
	TA424†	Chosen values	Justification
Time horizon	50 years	51 years	Choice is in line with the NICE reference case and takes into consideration the need to model costs and benefits over a sufficiently long time horizon to characterise the full impact of the intervention [39].
Cycle length	4 weeks	7 days	Allows an accurate estimation of treatment-related costs particularly for the weekly administration of paclitaxel.
Half cycle correction	No	Yes	Consistent with the NICE reference case [39].
Treatment waning effect	Not included	Not included	Treatment waning was not incorporated in the base case. This is consistent with previous breast cancer HTAs (both early stage and metastatic stage, including the recent TA639) appraisal committee's preferences [19].
Source of utilities	Published literature	EQ-5D-5L utilities mapped to 3L collected alongside KEYNOTE-522 have been used	Consistent with the NICE reference case [39].
Source of costs	NHS reference costs, PSSRU, BNF, eMIT	NHS reference costs, PSSRU, BNF, MIMS, eMIT, published literature.	Sources of costs used are widely accepted and in-line with guidance in NICE reference case [39]. Resource use was based on TA424 and clinical input [34].

†TA424 is the appraisal for pertuzumab for the neoadjuvant treatment of HER2+ve breast cancer and is therefore not TNBC specific and only focuses on the neoadjuvant setting; hence, it is not reflective of the population for this appraisal. However, all estimates relating to healthcare resource use were used as a source and validated with clinical experts during an advisory board.

Abbreviations: NICE: National Institute for Health and Care Excellence; HTA: Health Technology Assessment; TA: Technology Appraisal; EQ-5D: EuroQol-5D; PSSRU: Personal Social Services Research Unit; BNF: British National Formulary; MIMS: Monthly Index of Medical Specialities; eMIT: Electronic Market Information Tool.

B.3.2.3 Intervention technology and comparators

The final scope intervention for this appraisal is pembrolizumab in combination with standard neoadjuvant chemotherapy followed by adjuvant pembrolizumab as a single regimen as per KEYNOTE-522. The standard neoadjuvant chemotherapy used in the KEYNOTE-522 was split into two treatments. The first treatment was carboplatin in combination with paclitaxel, followed by the second treatment of either doxorubicin or epirubicin in combination with cyclophosphamide. Following surgery, adjuvant pembrolizumab monotherapy was administered.

The pembrolizumab component 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]) in the neoadjuvant and adjuvant phases. The neoadjuvant chemotherapy component was applied as per KEYNOTE-522: carboplatin (AUC 5 Q3W or AUC 1.5 weekly on days 1, 8 and 15) and paclitaxel (80mg/m^2 weekly on days 1, 8 and 15) followed by doxorubicin (60mg/m^2 Q3W) or epirubicin (90mg/m^2 Q3W) and cyclophosphamide (600mg/m^2 Q3W).

The final scope specifies the relevant comparators as standard neoadjuvant and adjuvant therapy without pembrolizumab. The placebo arm in KEYNOTE-522 is reflective of standard chemotherapy used in the UK and this has been validated by clinical experts [25]. Capecitabine in the adjuvant setting is not an appropriate comparator for this appraisal as local cancer guidelines only recommend capecitabine adjuvant treatment in patients with TNBC who have had carboplatin containing neoadjuvant chemotherapy, however, clinical experts noted that its use is extremely limited [24].

B.3.2.3.1 Discontinuation rules

In line with the KEYNOTE-522 protocol, neoadjuvant and adjuvant therapy was continued until completion of study treatment (17 cycles of pembrolizumab/placebo), disease progression in the neoadjuvant phase or until recurrence (local or distance) after surgery, unacceptable adverse event(s) or physician's decision to withdraw treatment [40].

B.3.3 Clinical parameters and variables

The primary source of clinical data for the economic model in KEYNOTE-522, a phase III pivotal RCT to evaluate pembrolizumab in combination with chemotherapy vs. chemotherapy alone in the neoadjuvant phase followed by pembrolizumab monotherapy vs. placebo in the

adjuvant phase. Patient level data (PLD) results have been used in the model to generate the UK relevant cost-effectiveness comparisons unless otherwise stated.

KEYNOTE-522 provided efficacy, Time on Treatment (ToT), AE and utility data for the economic model. In KEYNOTE-522, patients were stratified based on their nodal status, tumour size, and carboplatin regimen, to ensure similar distribution of patient characteristics across treatment arms [35]. KEYNOTE-355 OS data from the final database lock (date: June 15, 2021) was also used to estimate the transition probability from DM to death applicable for those receiving 1L treatment for mTNBC [41]. For those who didn't receive 1L mTNBC treatment, the OS data from the a recent SEER Medicaid database publication (Aly et al 2019; no treatment subgroup) was leveraged in the economic model [42] (see Appendix M). Real world evidence (RWE) literature were used to validate EFS and OS curve extrapolations [43, 44].

Table 33: Sources of key clinical evidence used to populate the model

Clinical Evidence	Brief Description	Use in the model
KEYNOTE-522	Phase III clinical trial in early or locally advanced TNBC exploring the efficacy of pembrolizumab + chemotherapy followed by pembrolizumab monotherapy compared to chemotherapy alone.	▪ PLD for the ITT population is used to fit EFS parametric curves for economic modelling ▪ Used to estimate transition probabilities from the EF and LR states ▪ Observed ToT and relative dose intensity from PLD for the ITT population is used for the intervention and comparator agents ▪ EQ-5D-5L trial data derived from the ITT population were used for trial-based utility analysis to ensure adequate sample size ▪ Modelling of frequency of adverse events ▪ OS estimates from DM state explored in scenario analysis
KEYNOTE-355 (pembrolizumab + chemotherapy vs. chemotherapy alone 1L mTNBC)	Phase III clinical trial in recurrent inoperable or metastatic TNBC exploring the efficacy of pembrolizumab + chemotherapy (paclitaxel or nab-paclitaxel or carboplatin/gemcitabine combination) compared to chemotherapy alone.	▪ Mean OS by 1L metastatic treatments for pembrolizumab + taxanes, taxanes alone, gemcitabine + carboplatin ▪ An NMA was used to estimate OS for atezolizumab + nab-paclitaxel and carboplatin (see section B.3.3.3 below) ▪ Used to estimate transition probabilities from the DM state due to immaturity of KEYNOTE-522 OS data ▪ Key assumptions around efficacy of chemotherapy regimens (based on NMA where applicable) are outlined in section B.3.3.3 below
General population mortality	Latest estimated of general population mortality by single year of age from England	▪ 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

	have been applied from ONS	
SEER Medicaid database	External data source to estimate survival for those who did not receive 1L mTNBC treatments	▪ Mean OS for patients who did not receive 1L treatments ▪ Used to estimate transition probabilities from the DM state
Real-world evidence: Walsh 2019 [41] in Sikov 2019 (CALGB 40603) [43]	External data sources reporting long-term EFS and OS	▪ Used to validate modelled EFS and OS for the placebo arm of the KEYNOTE-522 trial
Abbreviations: DM: Distant Metastasis; EF: Event-free; EFS: Event-Free Survival; EQ-5D: EuroQol-5D; ITT: Intention To Treat; LR: Locoregional Recurrence; OS: Overall Survival; PLD: Patient Level Data; SEER: Surveillance, Epidemiology and End Results Program (USA clinical database); TNBC: Triple Negative Breast Cancer; ToT: Time on Treatment		

B.3.3.1 Modelling transitions from event-free health state

Transition probabilities starting from the EF state were estimated based on survival analyses of individual patient-level data from the KEYNOTE-522 trial. The three transition probabilities estimated from this state correspond to the three components in the EFS endpoint: EF to LR, EF to DM and EF to death. As the number of events observed in the KEYNOTE-522 trial as of the current data cutoff is low for each of these endpoints, extrapolation for each event would lead to extremely high-level of uncertainty. Therefore, the transition probability of each event occurring is estimated based on the extrapolated EFS data, along with the probabilities of experiencing LR, DM, or death as the first EFS event in each treatment arm derived from the KEYNOTE-522 clinical trial (data cutoff date: March 23, 2021).

B.3.3.1.1 Survival analysis methodology outline

The survival curve fitting was carried out in line with the NICE DSU guidelines [45]. Standard parametric models were fitted to the patient level EFS data from the pembrolizumab arm and placebo arm in the KEYNOTE-522 trial to extrapolate the endpoints from the trial over a lifetime 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 (PH) 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.

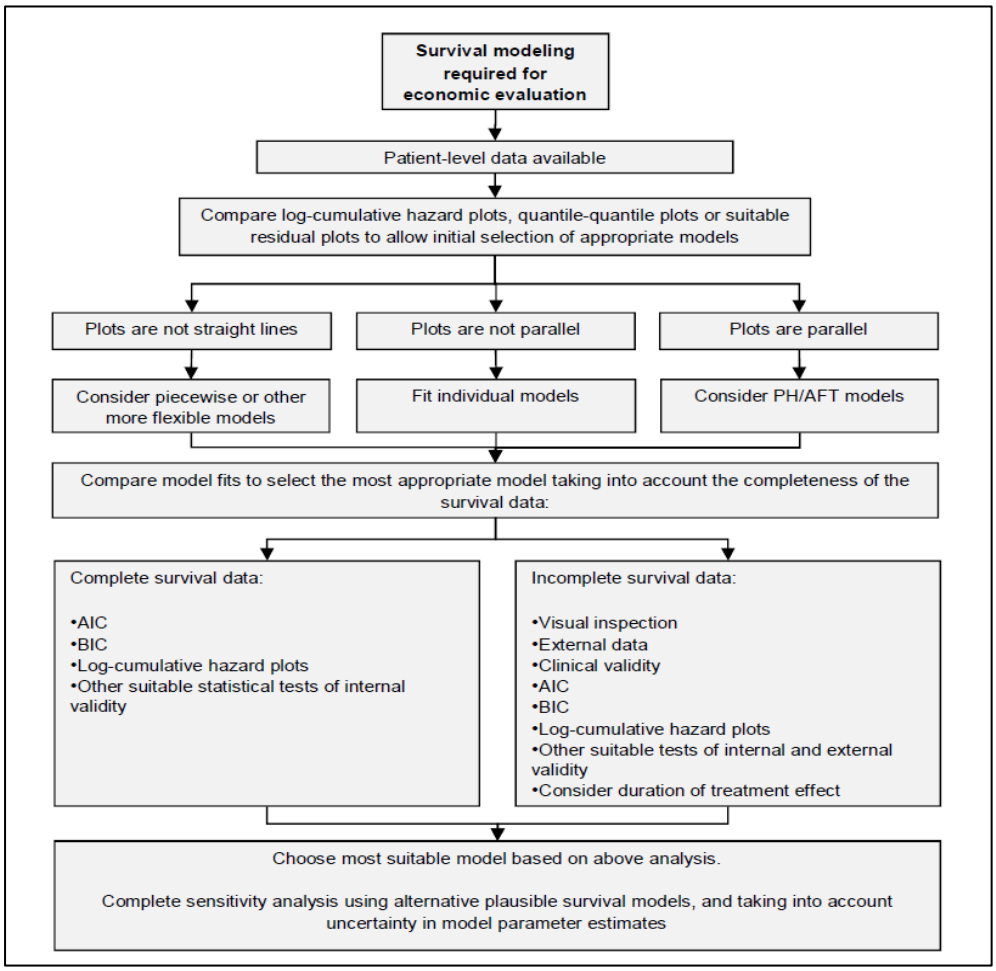
- If the PH assumption held, a comprehensive range of joint parametric survival models were to be explored. Here, data from both treatment arms were used within the same model. All standard parametric models (i.e. exponential, Weibull, Gompertz, log-logistic, log-normal and generalized gamma) were considered 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 extrapolations. 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.

The final model selection for EFS presented below took into account the model selection algorithm by NICE [45] (Figure 9). Validation of long-term extrapolation was performed by cross checking the estimates at landmark timepoints produced by each model versus estimates provided by clinical experts and those reported in the RWE clinical literature for early-stage or locally advanced treated TNBC patients [41, 42]. Appendix O provides the full survival methodology and alternative models considered for selection.

Figure 9: Survival model selection process algorithm (from NICE DSU TSD 14) [45]



B.3.3.1.2 EFS extrapolation

KEYNOTE-522 is a company sponsored phase III comparative trial for which PLD from both treatment arms are available for analysis.

Prior to model fitting, EFS cumulative and log-cumulative hazard plots were generated to assess the proportional hazards assumption (see Figure 10). From visual inspection of the log-cumulative hazard plot, the crossing the log-cumulative hazard plots of the two treatment arms suggested the implausibility of the proportional hazard assumption; therefore, separate models were used to fit the data for each arm for the projection of EFS.

Figure 10: Cumulative and log-cumulative hazard plots of EFS for pembrolizumab arm vs. placebo arm comparator based on KEYNOTE-522

Hazard plots were used to identify potential cut-off points for two-phase models. Visual examination of the cumulative hazard plot suggested week 50 as a potential turning point of the EFS curves in both treatment arms. Hazard plots also suggested week 43 and 68 as turning points for the hazard function (see Appendix O for further detail). Chow statistical tests were also used to estimate the structural changes to the Kaplan-Meier (KM) curves to further confirm the selection of cut-off points [46, 47]. With the 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-off point. The results of the Chow test suggested week 93 and 109 as potential turning points (see Appendix O for further detail).

The unique mode of action of immunotherapy (with or without chemotherapy) is not comparable to chemotherapy alone; therefore, the underlying hazard assumption for the parametric curve does not need to be the same. Furthermore, as the standard parametric distributions did not provide a good fit to the observed EFS data, two-phase parametric functions fittings were explored with three cut-off points – week 43, 50, 68 (see Appendix O for further detail). Accounting for the above considerations, the fittings with cut-off point at week 50 is used in the base-case economic model in both treatment arms because it provides

plausible visual fit and is good balance of robust KM data used directly in the first phase whilst enough data remaining can be used to fit a parametric curve in the second phase.

Statistical tests based on the AIC and BIC criterion, combined with visual inspection were used to identify the best-fitted parametric distribution from week 50 onward based on internal validity. Short term fit and long-term extrapolations are presented in Figure 11 and Figure 12 below. Differences of 5 points or greater are considered important in terms of distinguishing between models.

For the EFS of the pembrolizumab arm beyond week 50, the AIC/BIC statistics presented in Table 34 below and visual inspection both suggested that the Generalized Gamma distribution was the best fit to the data. Clinical expert opinion suggested the Gompertz distribution as a plausible extrapolation of EFS; however, this is associated with a flat tail potentially leading to overestimation of the long-term EFS (Figure 11). Clinical experts also noted Generalized Gamma as a plausible fit which is explored in the base case, followed by log-normal which is explored in scenario analysis [25]. For the EFS of the placebo arm beyond week 50, the AIC/BIC statistics (Table 34) were lowest for the Gompertz distribution with log-normal ranked the second. Again, the Gompertz distribution is associated with a flat tail potentially leading to overestimation of the long-term EFS, which suggests an implausible extrapolation (Figure 12). Clinical expert opinion and visual inspection of the curves confirmed the selection of the log-normal distribution, which is explored in the base case, followed by Generalized Gamma which is explored in scenario analysis [25].

Among the alternative parametric curves, the final choice of base case parametric survival models was a balance between the statistical fit, visual inspection, and the clinical plausibility of the extrapolated model. As a summary, the following standard parametric models were selected as the base case and plausible scenario analyses for the curves fitted to the EFS data:

- For the pembrolizumab arm:
    - Base case: KM50 + Generalized Gamma
    - Alternative: KM50 + Lognormal

- For the placebo arm:
    - Base case: KM50 + Log-normal
    - Alternative: KM50 + Generalized Gamma

Figure 11: EFS standard parametric curve fitting in the pembrolizumab arm for week 50+

Figure 12: EFS standard parametric curve fitting in the placebo arm for week 50+

Table 34: Summary of goodness of fit for EFS: pembrolizumab arm and placebo comparator arm from KEYNOTE-522 (week 50+)

Parametric distribution for EFS	Pembrolizumab arm				Placebo arm			
	AIC	BIC	AVG	Rank	AIC	BIC	AVG	Rank
Exponential	1140.24	1144.84	1142.54	4	980.85	984.75	982.80	7
Weibull	1140.71	1149.89	1145.30	6	972.61	980.39	976.50	4
Log-normal	1134.58	1143.76	1139.17	2	969.91	977.69	973.80	2
Log-logistic	1139.91	1149.09	1144.50	5	971.70	979.48	975.59	3
Gompertz	1134.88	1144.06	1139.47	3	968.49	976.27	972.38	1
Gamma	1140.95	1150.13	1145.54	7	973.15	980.94	977.05	5
Generalized Gamma	1127.35	1141.12	1134.24	1	971.87	983.54	977.71	6

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

The base case parametric curve fits for EFS compared to the KM curves are presented in Figure 13.

Figure 13: Base case standard parametric model fits to the EFS data in KEYNOTE-522

Considering the uncertainty associated with the long-term extrapolation of EFS beyond the trial period, it is important to carefully validate the EFS projections. The validation of EFS curves were conducted by 1) comparing modelled EFS vs. observed EFS in the KEYNOTE-522 trial, and 2) comparing the modelled EFS vs. external sources (see section B.3.10).

The modelled EFS at 3 years (pembrolizumab arm = [redacted]; placebo arm = [redacted]) are comparable to the observed EFS at 3 years (pembrolizumab arm = [redacted]; placebo arm = [redacted]). The modelled EFS curves match well with the observed EFS curves as shown in Figure 14 (see section B.3.10).

Figure 14: Modelled vs. observed EFS for pembrolizumab and placebo arm from KEYNOTE-522

B.3.3.1.3 Estimation of transition probabilities of the three competing events: EF→LR, EF→DM and EF→Death

The three EFS components in the KEYNOTE-522 trial – time to LR, time to DM and time to death, were analysed using Gray's method considering competing risks [48]. The three different components of EFS were defined post-hoc by grouping categories of EFS events as follows:

1. Locoregional recurrence/PD component:
    - Local progression of disease precludes surgery
    - Local progression of disease precludes definitive surgery
    - Positive margin at last surgery
    - Local recurrence
2. Distant recurrence/PD component:
    - Secondary primary malignancy
    - Distant progression of disease
    - Distant recurrence
3. Death component

To perform a competing risks analysis, time to first local recurrence/PD component is defined as the time from randomisation to the first occurrence of any of the 4 types of events as listed

above. In this definition, only the first event defining EFS is considered. If a patient had an event from another category (distant recurrence/PD or death) first, this is considered as a competing risk. Time to first distant recurrence/PD component is defined as the time from randomisation to the first occurrence of any of the 3 types of events as listed above. In this definition, only the first event defining EFS is considered. If a patient had an event from another category (local recurrence/PD or death) first, this is considered as a competing risk. Time to death component is defined as the time from randomization to death. In this definition, only the first event defining EFS is considered. If a patient had an event from another category (local or distant/recurrence/PD) first, this is considered as a competing risk.

The three time-to-EFS-component endpoints are expressed in weeks. The rules for defining participants with an event of interest, with a competing event or censored, as well as corresponding date are summarised in Table 35 (for further details see Appendix P).

Table 35: Event rules for analysis of competing risk

	Local Recurrence/PD Component	**Distant Recurrence/PD Component**	**Death Component**
Event = 0 (Censored)	If no EFS event: censored at the same time as for EFS	If no EFS event: censored at the same time as for EFS	If no EFS event: censored at the same time as for EFS
Event = 1 (Event of Interest)	If the first occurred EFS event is a local recurrence/PD (*i.e.* Local PD precludes surgery, Local PD precludes definitive surgery, Positive margin at last surgery, Local recurrence): event of interest at the same time as this first EFS event	If the first occurred EFS event is a distant recurrence/PD (*i.e.* Secondary primary malignancy, Distant PD, Distant recurrence): event of interest at the same time as this first EFS event	If the first occurred EFS event is a death: event of interest at the same time as this first EFS event
Event = 2 (Competing Event)	If the first occurred EFS event is a distant recurrence/PD (*i.e.* Secondary primary malignancy, Distant PD, Distant recurrence) or death: competing event at the same time as this first EFS event	If the first occurred EFS event is a local recurrence/PD (*i.e.* Local PD precludes surgery, Local PD precludes definitive surgery, Positive margin at last surgery, Local recurrence) or death: competing event at the same time as this first EFS event	If the first occurred EFS event is not a death): Competing event at the same time as this first EFS event
Note: Please read table from top to bottom.			

Within each cycle, the cause-specific probability of each transition (i.e. EF → LR, EF → DM and EF → death) was calculated based on the estimated probability of an EFS event, and the

probability that the EFS event being LR, DM or death (Table 36). These estimated probabilities were time-dependent and differ in Year 1 compared to Year 2+ as demonstrated by the slope changes in

and Figure 16. Specifically, the estimated probability of an EFS event is detailed in Section B.3.3.1.2. The probability of the EFS event being LR, DM or death were estimated using the KEYNOTE-522 trial, where the time to LR, time to DM and time to death were analysed using the Gray's method considering competing risks as detailed above (for further details see Appendix P).

The cost-effectiveness model further assumed that the probability of the EFS event was constrained by the all-cause natural mortality. Therefore, the transition probabilities of EF → LR, EF → DM, and EF → death were calculated as follows:

- $TP_{EF \rightarrow LR}$ = $TP_{EFS\ event}$ * probability of the first EFS event being LR
- $TP_{EF \rightarrow DM}$ = $TP_{EFS\ event}$ * probability of the first EFS event being DM
- $TP_{EF \rightarrow death}$ = max($TP_{EFS\ event}$ * probability of the first EFS event being death, probability of death among the general population – $TP_{EF \rightarrow LR}$ – $TP_{EF \rightarrow DM}$)

Table 36: Probability of the first EFS event

Treatment arm	Year 1			Year 2+		
	% LR	% DM	% Death	% LR	% DM	% Death
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B.3.3.1.4 Validation of the cumulative incidence of EF→LR, EF→DM and EF→death

The predicted cumulative incidence of EF → LR, EF → DM, and EF → death were validated with the observed cumulative incidence from the KETNOTE-522 trial.

and Figure 16, and Table 37 and Table 38 illustrate that the modelled cumulative incidence rates are comparable to the observed data.

Figure 15: Pembrolizumab arm – modelled cumulative incidence vs. observed incidence of EF → LR, EF → DM and EF → death

Abbreviations: DM, distant metastasis; EF, event-free; LR, locoregional recurrence

Figure 16: Placebo arm – modelled cumulative incidence vs. observed incidence of EF → LR, EF → DM and EF → death

Abbreviations: DM, distant metastasis; EF, event-free; LR, locoregional recurrence

Table 37: Pembrolizumab arm – modelled cumulative incidence vs. observed incidence of EF → LR, EF → DM and EF → death

Cumulative incidence	0.5-year	1.0-year	1.5-year	2.0-year	3.0-year	5.0-year
EF→ LR						
Modelled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EF→ DM						
Modelled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EF→ Death						
Modelled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DM, distant metastasis; EF, event-free; LR, locoregional recurrence

Table 38: Placebo arm – modelled cumulative incidence vs. observed incidence of EF → LR, EF → DM and EF → death

Cumulative incidence	0.5-year	1.0-year	1.5-year	2.0-year	3.0-year	5.0-year
EF→ LR						
Modelled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EF→ DM						
Modelled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EF→ Death						
Modelled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DM, distant metastasis; EF, event-free; LR, locoregional recurrence

B.3.3.2 Modelling transitions from locoregional recurrence health state

The transition probabilities of LR → DM and LR → death were estimated based on the pooled data from the two treatment arms from the KEYNOTE-522 trial which biases against pembrolizumab given the LR proportions being lower for the pembrolizumab arm than the placebo arm (Table 15). Parametric models were fitted to the time from LR to DM or death, and exponential distribution was found to be the best fit. Considering the memoryless feature of the Markov cohort model structure, constant transition probabilities from the LR state were assumed. Furthermore, exponential was also the best fit to the time from LR → DM or death so this is a reasonable assumption. The transition probabilities of LR → DM, and LR → death were calculated based on the transition probabilities of LR → DM or death, and the proportions

of DM and death respectively, which were all obtained from the KEYNOTE-522 trial (Table 39). Furthermore, the model constrained the transition probability of LR à DM or death by the all-cause natural mortality.

Therefore, the transition probabilities of LR → DM, and LR → death were calculated as follows:

- $TP_{LR \rightarrow DM} = TP_{LR \rightarrow DM \text{ or death}}$ * the proportion of patients progressed from LR to DM
- $TP_{LR \rightarrow death} = \max(TP_{LR \rightarrow DM \text{ or death}}$ * the proportion of death from LR, probability of death among the general population – $TP_{LR \rightarrow DM})$

Table 39: Exponential rate from LR to DM or death

Parameter	Value	Source
Exponential rate (weekly) from LR to DM or death	[redacted]	KEYNOTE-522 (cut-off date: 23 March, 2021)
% from LR to DM	[redacted]	
% from LR to death	[redacted]	

Abbreviations: DM, distant metastasis; LR, locoregional recurrence

B.3.3.3 Modelling transitions from distant metastasis health state

In the DM state, the model assumed that a proportion of patients would receive the 1L treatment for metastatic disease, which were obtained from the KEYNOTE-522 trial (Table 40).

Table 40: Proportion of patients who received 1L treatments

Parameter	Pembrolizumab arm	Placebo arm	Source
Proportion of patients who receive 1L	[redacted]	[redacted]	KEYNOTE-522 (Cut-off date: 23 March 2021)

The model incorporates two sources, KEYNOTE-355 and KEYNOTE-522, to estimate transition probabilities from DM to death and the treatment costs in the DM health state (see section B.3.5.2). KEYNOTE-355 data is used in the base case due to the current immaturity of the KEYNOTE-522 OS data; however, this alternative option is explored in the scenario analyses. Several assumptions had to be made around the effectiveness and time on treatment for some of the chemotherapies for which data from KEYNOTE-355 was not available and these were validated by clinical experts. Where available, hazard ratios were applied to OS and ToT. These are discussed below in B.3.3.3 (for efficacy) and B.3.5.2 (for

costs). A list of the KEYNOTE-355 data and assumptions applied in the model are provided in Table 41 below.

Data from the KEYNOTE-355 clinical trial is used in the base case with the outcomes derived based on the assumptions and inputs related to 1) rechallenge with pembrolizumab or other immune-oncology (IO) agent 2 years post initiation of neoadjuvant treatment as validated with clinical experts (this is equivalent to 1 year post completion of adjuvant treatment but has been applied as 2 years post initiation of neoadjuvant treatment in the model for simplicity) [25]; 2) PD-L1 positive rate; 3) treatment rate; and 4) treatment mix fin the metastatic setting.

The model incorporated the flexibilities of the following three scenarios for patients who received pembrolizumab in combination with chemotherapy in the neoadjuvant phase. The base case is IO-eligibility based on clinical expert input who explained their experience of rechallenge in melanoma indications and the current availability of Atezolizumab + nab-paclitaxel in the metastatic setting; the others are explored in a scenario analyses [25].

- IO-eligible: patients cannot receive pembrolizumab rechallenge or rechallenge is not applicable, patients can use other IOs in the DM setting 2 years post initiation of neoadjuvant treatment. This was assumed in the base case to reflect the current availability of atezolizumab + nab-paclitaxel in the metastatic TNBC setting. For patients who relapse within 2 years of pembrolizumab neoadjuvant treatment initiation, the IO-ineligible scenario is applied.

- Pembrolizumab rechallenge for mTNBC PD-L1 positive population: patients can receive pembrolizumab again or another IO in the DM setting 2 years post initiation of neoadjuvant treatment.

- IO ineligible: patients cannot receive any IOs, patients would receive a mix of non-IO chemotherapies

The base case treatment mix of each scenario was obtained from UK market research and clinical expert input (MSD data on file, 2021), who considered the PD-L1 testing rate, the proportion of PD-L1 positivity, and treatment mix for PD-L1 positive and PD-L1 negative/untested, respectively [25, 37]. In the base case, pembrolizumab rechallenge is not permitted to reflect the current standard of care in the UK where atezolizumab + nab-paclitaxel is the only IO therapy currently available for metastatic TNBC (Table 42). A PD-L1 positive testing rate of 38% was assumed based on KEYNOTE-355 [41] and in the base case all were

assigned to atezolizumab + nab-paclitaxel. Scenarios where pembrolizumab rechallenge is permitted were explored. In one scenario, the pembrolizumab and placebo arm assume a [redacted] split between pembrolizumab + taxanes and atezolizumab + nab-paclitaxel of those who are PD-L1 positive. This scenario should be considered conservative since it assumes that pembrolizumab+ taxanes will displace the current SoC of atezolizumab + nab-paclitaxel in 1L PD-L1 positive metastatic TNBC setting. Another scenario was explored with a [redacted] split between pembrolizumab + taxanes and atezolizumab + nab-paclitaxel of those who are PD-L1 positive. A scenario where patients cannot receive any IOs is also explored where the PD-L1 positive rate is re-weighted across all other non-IO chemotherapies. This scenario is also applied for patients who relapse within 2 years of neoadjuvant pembrolizumab treatment initiation. Market share estimates for each of the scenarios explored are included in Appendix M.

The mean OS in the DM state was estimated as a weighted average of patients who received 1L treatments based on market share estimates validated with UK clinical experts and patients who did not receive the 1L treatments (survival drawn from Aly et al 2019). The results from a metastatic TNBC NMA (see Appendix M of this submission) are used to estimate the weighted survival for those who receive 1L metastatic TNBC therapies.

More specifically, the mean OS of each 1L metastatic TNBC treatments was calculated based on the predicted OS curves from the pembrolizumab 1L mTNBC cost-effectiveness model (MSD data on file, final database lock: June 15, 2021) (Table 43) [38] alongside the NMA results if this was necessary. The predicted survival rate at each weekly interval was first obtained from the 1L mTNBC cost-effectiveness model without adjusting for natural mortality or discounting effect. The area under the OS curve (i.e., restricted mean survival time within 35 years) was then estimated using the trapezoidal rule. The same calculation was repeated for the mean TOT estimation.

The current model assumes paclitaxel and capecitabine have same OS as taxane and that carboplatin + paclitaxel has the same OS as gemcitabine + carboplatin in the 1L mTNBC cost-effectiveness model owing to the lack of comparative data from the 1L mTNBC NMA; this assumption was validated with clinical experts. The OS of carboplatin was estimated based on the HR of carboplatin versus taxanes from KEYNOTE-355. Similar assumptions were made to estimate the ToT of paclitaxel, capecitabine, and carboplatin + paclitaxel. In addition, the PFS (BICR assessed) HR was assumed as a proxy for the ToT HR. Atezolizumab + nab-paclitaxel OS was estimated based on the HR of atezolizumab + nab-paclitaxel versus

taxanes (nab-paclitaxel/paclitaxel) and this was calculated directly in the 1L mTNBC cost-effectiveness model. A similar assumption was used to estimate the atezolizumab + nab-paclitaxel ToT using the PFS by investigator assumed as a proxy for the ToT HR. Appendix M details the HRs used.

The mean OS among patients who did not receive 1L treatments were obtained from SEER Medicaid [49], and was estimated to be 21.94 weeks [42] (see Appendix M). The weighted mean OS of each arm is presented in Table 43. The transition probability of DM → death was estimated based on the constant hazard assumption.

Table 41: KEYNOTE-355 data and assumptions

Parameter	Assumption
PD-L1 positive testing rate	A PD-L1 positive testing rate of 38% was assumed based on KEYNOTE-355 [41]
Treatment mix in 1L mTNBC	The following treatments were considered in 1L mTNBC based on clinical expert opinion and KEYNOTE-355 data: • Pembrolizumab + taxanes (currently in the appraisal process) • Paclitaxel • Carboplatin • Carboplatin + paclitaxel • Gemcitabine + carboplatin • Atezolizumab + nab-paclitaxel • Capecitabine
Mean OS in the DM state	Data from KEYNOTE-355 and the 1L mTNBC cost-effectiveness model is not available for carboplatin, carboplatin + paclitaxel and capecitabine. Hence, capecitabine and paclitaxel mean OS were assumed equal to the taxanes arm mean OS and carboplatin + paclitaxel mean OS was assumed equal to the gemcitabine + carboplatin arm mean OS as validated by clinical expert opinion. An NMA was used to estimate mean OS based on HRs for atezolizumab + nab-paclitaxel (calculated in the 1L mTNBC cost-effectiveness model) and for carboplatin.
Subsequent treatment (2L+) costs	The lump sum costs of subsequent lines (2L, 3L and 4L) of treatments were obtained from the cost-effectiveness model of 1L mTNBC. Paclitaxel, carboplatin and capecitabine assumes 2L+ costs equal to the taxanes arm and carboplatin + paclitaxel assumes 2L+ costs equal to the gemcitabine + carboplatin arm of KEYNOTE-355 1L mTNBC model (MSD, data on file) [38]. Atezolizumab + nab-paclitaxel 2L+ costs are taken directly from the KEYNOTE-355 1L mTNBC model (MSD, data on file) [38]. The proportions of patients receiving each line (2L+) of treatment have been considered in the total costs (Table 57).

Table 42: KEYNOTE-355 – Market shares of 1L metastatic TNBC treatment by neoadjuvant treatment arm used in base case based on UK market research and clinical expert input

Treatment mix among patients who received 1L	Pembrolizumab + chemotherapy		Chemotherapy
	IO-eligible (Pembro ineligible)	IO-ineligible	IO-eligible (Pembro ineligible)
Pembrolizumab + taxanes (paclitaxel or nab-paclitaxel)	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]
Carboplatin (or containing regimens)	[redacted]	[redacted]	[redacted]
Carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]
Gemcitabine + carboplatin	[redacted]	[redacted]	[redacted]
Atezolizumab + Nab-paclitaxel*	[redacted]	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]	[redacted]

IO-eligible is applied in the base case where treatment with atezolizumab + nab-paclitaxel is permitted in the metastatic setting 2 years post neoadjuvant treatment initiation for the pembrolizumab arm. For patients who relapse within 2 years of neoadjuvant pembrolizumab treatment, the IO-ineligible scenario is applied. Additional scenarios presented in Appendix M. *Assumes PD-L1 SP132 positive as per Impassion130 study.

Table 43: KEYNOTE-355 – Mean OS by 1L metastatic TNBC treatment

Treatment mix among patients who received 1L	Mean OS (weeks)	Comments
Pembrolizumab + taxanes (paclitaxel or nab-paclitaxel)	[redacted]	Taken directly from KEYNOTE-355 1L mTNBC model
Paclitaxel*	[redacted]	Taken directly from KEYNOTE-355 1L mTNBC model for taxanes pooled arm in line with previous NICE assumptions
Carboplatin (or containing regimens)†	[redacted]	Applied OS HR of carboplatin versus taxanes (paclitaxel/nab-paclitaxel)
Carboplatin + paclitaxel^	[redacted]	Assumed equal to gemcitabine + carboplatin arm of KEYNOTE-355 1L mTNBC model
Gemcitabine + carboplatin	[redacted]	Taken directly from KEYNOTE-355 1L mTNBC model
Atezolizumab + Nab-paclitaxel	[redacted]	Applied OS HR of atezolizumab + nab-paclitaxel versus taxanes (paclitaxel/nab-paclitaxel) from KEYNOTE-355 1L mTNBC model

Capecitabine*	[redacted]	Assumed equal to taxanes arm of KEYNOTE-355 1L mTNBC model
†Mean OS estimated from NMA. ^Mean OS assumed equal to gemcitabine + carboplatin. *Mean OS assumed equal to taxanes. See Appendix M for further detail. Abbreviations: 1L, first-line; IO, immune-oncology. See Appendix M for further details.		

Table 44: KEYNOTE-355 – Transition probabilities of DM à death for the pembrolizumab and placebo arms

Treatment arm	Eligibility for IOs in the DM state	Weighted mean OS (weeks)	DM → death: Exponential rate (weekly) based on weighted mean OS
Pembrolizumab	IO-eligible*	[redacted]	[redacted]
Pembrolizumab	Pembrolizumab rechallenge-eligible	[redacted]	[redacted]
Pembrolizumab	IO ineligible	[redacted]	[redacted]
Placebo	-	[redacted]	[redacted]
*IO-eligible assumed in base case. Abbreviations: DM, distant metastasis; IO, immune-oncology; OS, overall survival			

A scenario analysis was conducted with the KEYNOTE-522 OS data. The mean OS was calculated from KEYNOTE-522, which was estimated among all patients who had documented distant recurrence/progression. As the mean OS was estimated among all patients regardless of whether they have received treatments or not, the transition probabilities of DM → death were estimated based on the mean OS by assuming a constant hazard (Table 45). The mean OS is estimated from the point of arrival in the DM state.

The treatment mix observed in the KEYNOTE-522 trial was not applicable to the UK setting (see Appendix M); therefore, the treatment mix and market shares used were obtained from UK market research and validated with clinical experts as presented in Table 42 above. These were used for the calculation of treatment costs (see Section B.3.5.2).

Table 45: KEYNOTE-522 – Transition probabilities of DM → death for the pembrolizumab and placebo arms

Treatment arm	Mean OS (weeks)	DM → death: Exponential rate (weekly) based on mean OS	Source
Pembrolizumab arm	[redacted]	[redacted]	KEYNOTE-522 (Cut-off date: 23 March 2021)
Placebo arm	[redacted]	[redacted]	
Abbreviations: DM, distant metastasis; OS, overall survival. Note: Mean OS is estimated from the point of arrival at the DM state.			

B.3.3.3.1 Validation of OS based on KEYNOTE-355

The predicted OS was validated against internal and external sources (see section B.3.10). The model validated the predicted OS based on KEYNOTE-355 with the observed OS from the KEYNOTE-522 trial. The modelled OS at 3 years (pembrolizumab arm = [redacted]; placebo arm = [redacted]) are comparable to the observed OS at 3 years (pembrolizumab arm = [redacted]; placebo arm = [redacted]). The modelled OS curves match well with the observed OS curves as shown in Figure 17 (see section B.3.10).

Figure 17: Modelled vs. observed OS for pembrolizumab and placebo arm from KEYNOTE-355

B.3.3.4 Overview of health state transitions considered in the economic model

As a summary, an overview of the approaches used to estimate transitions between health states is provided below. The scenario and sensitivity analyses, used to explore the uncertainty in these parameter estimations, are also outlined. The results are presented in Section B.3.8.

Table 46: Summary of health state transitions considered in the model

Transition(s)	Estimation approach	Data source(s)	Scenario or one-way sensitivity analyses performed
EF → LR EF → DM EF → Death†	**Time dependent transition probabilities were estimated based on 1) extrapolated EFS and 2) proportion of LR, DM and death as the first EFS event.** ▪ Using PLD from KEYNOTE-522, EFS was extrapolated based on parametric functions for each arm o Pembrolizumab arm: KM50 + Generalized Gamma o Placebo arm: KM50 + Log-normal ▪ No remission assumption was applied in the base-case ▪ No treatment waning effect was considered in the base-case ▪ Probability of experiencing LR, DM or death per cycle were estimated from EFS ▪ The probability of patients experiencing LR, DM and death as the first EFS event in Year 1 and Year 2+ respectively, were obtained from the KEYNOTE-522 clinical trial ▪ The transition probabilities of EF → LR, EF → DM and EF → death were then calculated based on the probability of experiencing event (LR, DM or death) and the proportions of each event, accounting for competing risks	▪ Treatment specific PLD from KEYNOTE-522. ▪ Life tables for England & Wales (2018-2020) [50] – *for transitions to death*	▪ Alternative parametric distributions fitted to EFS for each treatment arm of KEYNOTE-522: o Pembrolizumab arm: KM50 + Log-normal o Placebo arm: KM50 + Generalized Gamma ▪ The probability of patients experiencing LR, DM and death as the first EFS event in Year 1 and Year 2+ varied by 95% confidence interval.
LR → DM LR → Death†	**Transition probabilities starting from LR were assumed to be equivalent between arms, and constant across all cycles** ▪ The transition probabilities of LR → DM or death were obtained from the KEYNOTE-522 clinical trial by pooling data from the two treatment arms ▪ The proportions of patients experiencing DM and death respectively, were obtained from the KEYNOTE-522 clinical trial ▪ The transition probabilities of LR à DM, and LR → death were calculated based on the probability of experiencing either event (DM or death) and the proportions of each event	▪ Treatment specific PLD from KEYNOTE-522. ▪ Life tables for England & Wales (2018-2020) [50] – *for transitions to death*	▪ The proportions of patients experiencing DM and death varied by 95% confidence interval.
DM → Death†	**Transition probability from DM → death was estimated based on the treatment rate, the expected mix of 1L treatments in the DM state, the efficacy of these 1L treatments in**	▪ Treatment specific PLD from KEYNOTE-355 for patients who receive 1L	▪ Using KEYNOTE-522 to estimate mean OS of all patients following distant metastasis.

	terms of mean OS, and mean OS for those who did not receive 1L treatments ▪ KEYNOTE-355 was selected as the base-case source to estimate mean OS of all patients following distant metastasis given the immaturity of KEYNOTE-522 OS data ▪ The transition probability was derived based on assumptions and inputs related to 1) rechallenge other IO agent; 2) PD-L1 positive rate; 3) treatment rate; 4) treatment mix in the metastatic setting; and 5) mean OS of patients who received each 1L treatment and who did not receive 1L treatments	mTNBC treatments. ▪ SEER Medicaid database [42] for patients who do not receive 1L mTNBC treatments. ▪ Life tables for England & Wales (2018-2020) [50] – *for transitions to death*	▪ Exponential rate of DM varied by 95% confidence interval.
† Transition probabilities to death were constrained to be at least as high as all-cause mortality, as estimated from national life tables given the age of the cohort at each cycle. Abbreviations: EF: event-free; EFS: event-free survival; DM: distant metastasis; IO: Immune-oncology; KM: Kaplan-Meier; LR: locoregional recurrence; N/A: Not applicable; PLD: patient-level data.			

B.3.3.5 Adverse events within the 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-522 study. The model considers all-cause Grade 3+ AEs (incidence rate ≥ 5%). Additional AEs deemed as clinically relevant for inclusion in the economic modelling included:

- Diarrhoea (of Grade 2+)
- Colitis (of Grade 2+)

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 hospitalization 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 47: Incidence and duration of modelled AEs from KEYNOTE-522

All-cause Grade 3+ AEs	Grade	Pembrolizumab arm	Placebo arm	Mean AE duration (days)[#]
Neutropenia	3+	35.2%	34.4%	[redacted] days
Neutrophil count decreased	3+	19.0%	23.7%	
Anaemia	3+	19.5%	15.7%	
Febrile neutropenia	3+	18.4%	16.2%	
White blood cell count decreased	3+	7.8%	5.4%	
Alanine aminotransferase increased	3+	6.4%	2.8%	
Diarrhoea (prior IO HTAs)	2+	[redacted]	[redacted]	
Colitis (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-522 trial using the EuroQoL EQ-5D-5L. The NICE guidelines stipulate that the EQ-5D is the preferred instrument measuring changes in the HRQoL alongside clinical trial and that data collected directly from patients alongside a clinical study should be used to estimate utility weights to populate the economic model [39].

In KEYNOTE-522, the EQ-5D-5L questionnaire was administered as follows. In the neoadjuvant phase, the questionnaire was administered on day 1 of cycle 1 of treatment 1 (carboplatin + paclitaxel with or without pembrolizumab) and on day 1 of cycles 1 and 4 of treatment 2 (doxorubicin/epirubicin + cyclophosphamide with or without pembrolizumab). In the adjuvant phase, the questionnaire was administered on day 1 of cycles 1, 5 and 9. Assessments were also conducted at the early discontinuation visits and for long-term follow-up visits every 12 months for 2 years or until PD, whichever is earlier [40].

As the EQ-5D-5L system was used, the data was mapped back to the 3L tool using the crosswalk method developed by van Hout et al. [51] as per the NICE position statement for reference case analyses [52]. The EQ-5D-3L value set was then used to derive utility values for the economic model. The 5L value set was explored in scenario analyses.

Analysis of the EQ-5D scores reported below was based on the full analysis set (FAS) population using the IA4 data-cut of KEYNOTE-522 which took place on the 23rd of March

2021. UK preference-based scores were used for all patients analysed from the KEYNOTE-522 clinical trial with the UK scoring functions being developed based on the time trade-off technique by Dolan et al 1997 [53].

EQ-5D utility values collected in the relevant patient population to the decision problem are preferred for decision-making [39]. Base-case utility values for the event-free, locoregional recurrence and distant metastasis states were derived through repeated measures regression analyses of patient-level EQ-5D data from the KEYNOTE-522 trial. At each visit where health state was assessed, the corresponding EQ-5D score was used to characterise utility. Within the event-free health state, EQ-5D utility values were also derived by treatment status using the same regression analyses with the "on-treatment" period defined as the period between the start of neoadjuvant therapy to the end of the whole treatment course. Visits with missing EQ-5D scores were excluded.

Since patients could have multiple EQ-5D score measurements within each health state or treatment status category, linear mixed-effect models with fixed effects including treatment and one of the following factors: health state, treatment status, AE status; were applied to the 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 from the respective models:

1. By health state and by treatment arm
2. By treatment status within event-free state and by treatment arm
3. By AE status within event-free on treatment period and by treatment arm

At the baseline assessment, the difference in utility between the two arms is not statistically significant or clinically meaningful. EQ-5D utility values were estimated based on health status (and treatment status within event-free state) with further adjustments for the measurement of EQ-5D during a grade 3+ AE incidence rate ≥ 5%. Using both analyses (by health state and treatment status within event-free state), no statistically significant or clinically meaningful differences were identified in the utility values between treatment arm. This means, the coefficients for the placebo arm versus the pembrolizumab arm were not statistically significant and the associated decrement was < 0.08 which is defined as the minimally important difference (MID) in EQ-5D scores for cancers [54].

The presence of Grade 3+ AEs was associated with a statistically significant coefficient in the event-free on treatment period; therefore, utilities for the event-free health state with or without Grade 3+ AEs have also been estimated and introduced into the model.

A summary of compliance rates is reported below along with the estimated utilities generated are presented in Table 48, Table 49 and Table 50. Appendix N provides the full methodology, results, and compliance rates at each assessment time point.

B.3.4.1.1 Utility analyses results from KEYNOTE-522

Compliance to HRQoL assessments was very good with [redacted]% and [redacted]% completing the questionnaires at neoadjuvant baseline for the pembrolizumab arm and placebo arm respectively. Compliance rates slowly decreased over time with [redacted]% and [redacted]% at adjuvant baseline for the pembrolizumab arm and placebo arm respectively. The lowest reported compliance was at week 24 of the adjuvant phase with [redacted]% and [redacted]% for the pembrolizumab arm and placebo arm respectively.

Table 48: Estimated utilities by health state (pooled treatment arms)

Coefficient	Pooled Value (N=1126 patients[#])	SE	95% CI
Event-free	[redacted]	[redacted]	[redacted]
Local recurrence	[redacted]	[redacted]	[redacted]
Distant metastasis	[redacted]	[redacted]	[redacted]

EQ-5D score during baseline is not included. [#]Number of records analysed per category is provided in Appendix N. Abbreviations: SE, standard error; CI, confidence interval.

Table 49: Estimated utilities in event-free state by treatment status (pooled treatment arms)

Coefficient	Pooled Value (N=1126 patients[#])	SE	95% CI
Event-free, on treatment	[redacted]	[redacted]	[redacted]
Event-free, off treatment	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]		

EQ-5D score during baseline is not included. [#]Number of records analysed per category is provided in Appendix N. Abbreviations: SE, standard error; CI, confidence interval.

Table 50: Estimated utilities by AE status (event-free, on treatment period)

Coefficient	Pembrolizumab arm (N=749 patients[#])			Placebo arm (N=377 patients[#])			Pooled (N=1126 patients[#])		
	Value	SE	95% CI	Value	SE	95% CI	Value	SE	95% CI
Event-free, on treatment without Grade 3+ AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Event-free, on treatment during Grade 3+ AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility applied in event-free state (calculated)	[redacted]			[redacted]			[redacted]		

EQ-5D score during baseline is not included. [#]Number of records analysed per category is provided in Appendix N. Abbreviations: AE, adverse event; CI, confidence interval; SE, standard error.

B.3.4.2 Mapping

As the EQ-5D-5L system was used, the data was mapped back to the EQ-5D-3L tool using the crosswalk method developed by van Hout et al. [51] as per the NICE position statement for reference case analyses [52]. The 3L value set was then used to derive utility values for the economic model.

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 identifies through the HRQoL SLR.

B.3.4.4 Adverse reactions

To assess the potential disutility associated with AEs captured in the model, the disutility associated with patients experiencing Grade 3+ AEs was derived from KEYNOTE-522 PLD analysis ensuring a consistent source for adverse events and impact on HRQoL from treatment.

The disutility associated with AEs from the pooled utility analysis was estimated at [redacted]. The treatment specific disutilities in the event-free state on treatment period was estimated as [redacted] for the pembrolizumab arm and [redacted] for the placebo arm. The pooled disutility associated with AEs are applied in the base case. The grade 3+ AE disutility were also applied to the grade 2+ AEs included in the model (see section B.3.3.5).

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 into the model to account for these differences using the formula provided in the publication. Ara et al. (presented Table 51) 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 [55-57].

Table 51: Regression coefficients used for the estimation of age-related disutility from Ara et al [55]

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 model permits different options for 1) the source to model utility for each arm, 2) the utility estimation approach, and 3) the utility algorithm. A summary of the utility values used for cost-effectiveness analysis is provided in Table 52.

The utility input of "EF on treatment" was applied to the time to end of adjuvant treatment curve (see section B.3.5.1) to estimate the QALY gains when patients remain in the EF state and receive treatments, and the time to end of adjuvant treatment curve was constrained to be lower than the EFS curve. The utility input of "EF off treatment" was applied to the difference between EFS and time to end of adjuvant treatment to estimate the QALY gains when patients remain the EF state and do not receive treatments, which were constrained to be no less than zero.

The QALY gains in each health state were calculated as follows:

- $QALY_{EF\ on\ treatment}$ = $Utility_{EF\ on\ treatment}$ * minimum (time to end of adjuvant treatment, EFS)
- AE-related QALY decrement = one-time grade 3+ AE utility decrement

- $QALY_{EF\ off\ treatment}$ = Utility $_{EF\ off\ treatment}$ * max (EFS – time to end of adjuvant treatment, 0)
- $QALY_{LR}$ = Utility $_{LR}$ * time spent in the LR state
- $QALY_{DM}$ = Utility $_{DM}$ * time spent in the DM state

Table 52: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Base case: Pooled utility by health state, treatment status, and AE status				
Event-free, on treatment	[redacted]	[redacted]	Section B.3.4.1 (HRQoL data from clinical trials)	Utility values from KEYNOTE-522 5L crosswalk to 3L (IA4 March 2021), consistent with the NICE reference case [39]
Event free, off treatment	[redacted]	[redacted]		
Grade 3+ AE utility decrement	[redacted]			
Locoregional recurrence	[redacted]	[redacted]		
Distant metastasis	[redacted]	[redacted]		
Scenario analysis: Utility by treatment arm by health state, treatment status, and AE status				
Pembrolizumab arm				
Event-free on treatment	[redacted]	[redacted]	Section B.3.4.1 (HRQoL data from clinical trials)	Scenario analysis
Event free off treatment	[redacted]	[redacted]		
Grade 3+ AE utility decrement	[redacted]			
Locoregional recurrence	[redacted]	[redacted]		
Distant metastasis	[redacted]	[redacted]		

Placebo arm				
Event-free on treatment	[redacted]	[redacted]	Section B.3.4.1 (HRQoL data from clinical trials)	Scenario analysis
Event free off treatment	[redacted]	[redacted]		
Grade 3+ AE utility decrement	[redacted]			
Locoregional recurrence	[redacted]	[redacted]		
Distant metastasis	[redacted]	[redacted]		
Scenario analysis: Pooled utility by health state, treatment status, and AE status using 5L value set				
Event-free on treatment	[redacted]	[redacted]	Section B.3.4.1 (HRQoL data from clinical trials)	Scenario analysis
Event free off treatment	[redacted]	[redacted]		
Grade 3+ AE utility decrement	[redacted]			
Locoregional recurrence	[redacted]	[redacted]		
Distant metastasis	[redacted]	[redacted]		
Abbreviations: AE, adverse event; HRQoL, health-related quality of life				

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 and results for the searches conducted.

Public data sources have been used to cost resource use from an NHS and 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 where necessary [58].

B.3.5.1 Intervention and comparators' costs and resource use

Intervention costs

Drug acquisition costs for pembrolizumab plus chemotherapy in the neoadjuvant phase followed by pembrolizumab monotherapy in the adjuvant phase used in KEYNOTE-522 were sourced from the British National Formulary [59], the Monthly Index of Medical Specialities [60] and the electronic Market Information Tool (eMIT) (see Table 53 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 applies 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 chemotherapy (carboplatin + paclitaxel, followed by doxorubicin/epirubicin + cyclophosphamide) in the neoadjuvant phase and pembrolizumab monotherapy in the adjuvant phase. As per the clinical trial, pembrolizumab in combination with chemotherapy is administered for 8 cycles in the neoadjuvant phase and pembrolizumab monotherapy is administered for 9 cycles in the adjuvant phase [40].

The list price of a 100mg vial is £2,630.00; therefore, the drug cost for pembrolizumab per administration is £5,260.00 based on two 100mg vials using the list price. A patient access scheme (PAS) is currently in place as stated in Table 2 in section B.1.2.

The detailed dosing schedule, relative dose intensity and treatment allocation are presented in Table 54. The dosing schedule of KEYNOTE-522 is as follows:

Treatment 1 – cycles 1-4 (neo-adjuvant)

- Carboplatin: As per the trial protocol, the recommended dose of carboplatin in combination with pembrolizumab (and paclitaxel) in the neoadjuvant phase is AUC 5 administered IV Q3W on day 1 of cycles 1-4 OR AUC 1.5 administered IV weekly on day 1, 8 and 15 of cycles 1-4.

- Paclitaxel: As per the trial protocol, the recommended dose of paclitaxel in combination with pembrolizumab (and carboplatin) in the neoadjuvant phase is 80mg/m^2 administered IV weekly on days 1, 8 and 15 of cycles 1-4.

- Pembrolizumab: As per the trial protocol, the recommended dose of pembrolizumab (in combination with carboplatin and paclitaxel) in the neoadjuvant phase is 200mg administered IV Q3W on day 1 of cycles 1-4.

Treatment 2 – cycles 5-8 (neo-adjuvant)

- Doxorubicin: As per the trial protocol following treatment 1 above, the recommended dose of doxorubicin in combination with pembrolizumab (and cyclophosphamide) in the neoadjuvant phase is 60mg/m^2 administered IV Q3W on day 1 of cycles 5-8.

- Epirubicin: As per the trial protocol following treatment 1 above, the recommended dose of epirubicin in combination with pembrolizumab (and cyclophosphamide) in the neoadjuvant phase is 90mg/m^2 administered IV Q3W on day 1 of cycles 5-8.

- Cyclophosphamide: As per the trial protocol following treatment 1 above, the recommended dose of cyclophosphamide in combination with pembrolizumab (and either doxorubicin or epirubicin) in the neoadjuvant phase is 600mg/m^2 administered IV Q3W on day 1 of cycles 5-8.

- Pembrolizumab: As per the trial protocol, the recommended dose of pembrolizumab (in combination with doxorubicin and epirubicin) in the neoadjuvant phase is 200mg administered IV Q3W on day 1 of cycles 5-8.

Adjuvant phase – cycles 1-9

- Pembrolizumab: As per the trial protocol, the recommended dose of pembrolizumab monotherapy in the adjuvant phase is 200mg administered IV Q3W on day 1 of cycles 1-9.

Comparator costs

Drug acquisition costs for individual drugs constituting the UK SoC were taken from the BNF, MIMS or eMIT (see Table 53 below). The model applies the relevant chemotherapy comparator costs at each cycle accordingly for each regimen separately. The detailed dosing schedule, relative dose intensity and treatment allocation are presented in Table 54.

Table 53: Intervention and comparator drug acquisition costs used in the model

Drug	Vial concentration	Cost per vial	Source
Pembrolizumab	100mg/4ml	£2,630.00	MIMS UK list price (confidential PAS in place) [60]
Carboplatin	50mg / 5ml	£3.18	eMIT September 2021 [61]
	150mg / 15ml	£6.08	
	450mg / 45ml	£13.51	
Paclitaxel	30mg / 5ml	£4.15	eMIT September 2021 [61]
	100mg / 16.7ml	£8.06	
	150mg / 25ml	£10.15	
	300mg / 50ml	£15.97	
Doxorubicin	10mg / 5ml	£2.83	eMIT September 2021 [61]
	50mg / 25ml	£7.09	
	200mg / 100ml	£20.02	
Epirubicin	10mg / 5ml	£5.06	eMIT September 2021 [61]
	50mg / 25ml	£23.23	
	200mg / 100ml	£35.42	
Cyclophosphamide	500mg / vial	£8.23	eMIT September 2021 [61]
	1000mg / vial	£13.55	
	2000mg / vial	£27.50	

Table 54: Dosing schedule, relative dose intensity and treatment allocation of intervention and comparators used in the model

Treatment arm	Component	Dosing schedule	Relative dose intensity (%)	Treatment allocation
Pembrolizumab (*neoadjuvant)*	Pembrolizumab (200mg Q3W)	200mg Q3W on day 1 of cycles 1-8	[redacted]	[redacted]
	Carboplatin (AUC 5, Q3W)	AUC 5 (max 750mg) Q3W on day 1 of cycles 1-4	[redacted]	[redacted]
	Carboplatin (AUC 1.5, weekly)	AUC 1.5 (max 225mg) weekly on days 1, 8, 15 of cycles 1-4	[redacted]	[redacted]
	Paclitaxel	80mg/m^2 weekly on days 1, 8, 15 of cycles 1-4	[redacted]	[redacted]
	Cyclophosphamide	600mg/m^2 Q3W on day 1 of cycles 5-8	[redacted]	[redacted]
	Doxorubicin	60mg/m^2 Q3W on day 1 of cycles 5-8	[redacted]	[redacted]
	Epirubicin	90mg/m^2 Q3W on day 1 of cycles 5-8	[redacted]	[redacted]
Pembrolizumab *(adjuvant)*	Pembrolizumab (200mg Q3W)	200mg Q3W on day 1 of cycles 1-9	[redacted]	[redacted]
Placebo (*neoadjuvant*)	Carboplatin (AUC 5, Q3W)	AUC 5 (max 750mg) Q3W on	[redacted]	[redacted]

		day 1 of cycles 1-4		
	Carboplatin (AUC 1.5, weekly)	AUC 1.5 (max 225mg) weekly on days 1, 8, 15 of cycles 1-4	[redacted]	[redacted]
	Paclitaxel	80mg/m^2 weekly on days 1, 8, 15 of cycles 1-4	[redacted]	[redacted]
	Cyclophosphamide	600mg/m^2 Q3W on day 1 of cycles 5-8	[redacted]	[redacted]
	Doxorubicin	60mg/m^2 Q3W on day 1 of cycles 5-8	[redacted]	[redacted]
	Epirubicin	90mg/m^2 Q3W on day 1 of cycles 5-8	[redacted]	[redacted]

B.3.5.1.1 Estimating the ToT for intervention and comparators

KEYNOTE-522 patient level data were used to estimate the treatment duration for each of the comparators in the trial. In the trial, patients received pembrolizumab or placebo treatment for up to a maximum of 17 cycles across both the neoadjuvant and adjuvant phase as per the trial protocol. Based on this maximum treatment duration, there was sufficient follow-up data from the trial to directly observe time on treatment without the need for extrapolation. Kaplan-Meier analysis was conducted for time to end of neoadjuvant treatment, time to end of surgery, and time to end of treatment course.

The proportion of patients on neoadjuvant treatment is determined directly from the time to end of neoadjuvant treatment K-M curve (Figure 18). The proportion of patients on adjuvant treatment is derived using the survival function from the time to end of treatment course (Figure 19) and subtracting from this the survival function for the time to end of surgery (Figure 20) at each time point. These K-M curves were fitted to inform the model input and account for early treatment discontinuation of patients as per the study protocol.

Relative dose intensity (as reflected in the pembrolizumab arm of KEYNOTE-522) 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 comparator. KEYNOTE-522 data regarding dose

interruption were analysed and incorporated into the model per cycle of administration across both treatment arms. The relative dose intensities for each component of the intervention and comparator arms are reported in Table 54. In the neoadjuvant phase, [redacted] of patients received pembrolizumab as planned whilst in the adjuvant phase [redacted] of patients received pembrolizumab as planned.

Figure 18: Observed Kaplan-Meier curve for time to end of neoadjuvant treatment in KEYNOTE-522

Figure 19: Observed Kaplan-Meier curve for time to end of treatment course in KEYNOTE-522

Figure 20: Observed Kaplan-Meier curve for time to end of surgery in KEYNOTE-522

B.3.5.2 Subsequent treatment costs

Drug acquisition and administration costs associated with metastatic TNBC therapies were applied as one-time costs upon entry into the DM state. As detailed in section B.3.3.3, a proportion of patients who entered the DM state were assumed to receive an active 1L treatment for the metastatic disease. As described in section B.3.3.3, KEYNOTE-355 was considered to estimate the 1L treatment costs in the DM state in the base-case and KEYNOTE-522 was considered in the scenario analysis. Patients who receive 1L treatments were also assumed to receive subsequent lines (2L, 3L and 4L) of treatments for the metastatic disease and a lump sum of subsequent lines treatment costs following each 1L treatment were obtained from the 1L mTNBC cost-effectiveness model and the proportions of patients receiving 2L, 3L and 4L respectively have

been considered in the subsequent treatment costs [38]. Section B.3.3.3 presents the proportion of patients receiving 1L treatments in Table 40, and the market shares of treatment mix from KEYNOTE-355 in Table 42.

The total costs for each 1L metastatic treatment regimen were calculated as a function of the weekly drug acquisition costs (Table 55) and mean treatment duration (Table 56) and administration costs (Table 60). Dosing schedule and relative dose intensity were obtained from the cost-effectiveness model of 1L mTNBC (MSD, data on file) [38]. The relative dose intensity (RDI) for carboplatin, carboplatin + paclitaxel and capecitabine was not available from the 1L metastatic TNBC cost-effectiveness model; therefore, assumptions were made: RDI for carboplatin and the carboplatin component of carboplatin + paclitaxel was taken from the carboplatin component of gemcitabine + carboplatin and the RDI for capecitabine and the paclitaxel component of carboplatin + paclitaxel was assumed equal to paclitaxel monotherapy (Table 56).

The lump sum costs of subsequent lines (2L, 3L and 4L) of treatments were also obtained from the cost-effectiveness model of 1L mTNBC. Paclitaxel, carboplatin and capecitabine assumes 2L+ costs equal to the taxanes arm and carboplatin + paclitaxel assumes 2L+ costs equal to the gemcitabine + carboplatin arm of KEYNOTE-355 1L mTNBC model (MSD, data on file) [38]. The proportions of patients receiving each line (2L+) of treatment have been considered in the total costs (Table 57).

Table 55: Subsequent treatment drug acquisition costs used in the model

Drug	Vial concentration	Cost per vial	Source
Pembrolizumab	100mg/4ml	£2,630.00	MIMS UK list price (confidential PAS in place) [60]
Paclitaxel	30mg / 5ml	£4.15	eMIT September 2021 [61]
	100mg / 16.7ml	£8.06	
	150mg / 25ml	£10.15	
	300mg / 50ml	£15.97	
Nab-paclitaxel	100mg	£246.00	MIMS UK list price (unknown

			confidential PAS in place) [62]
Carboplatin	50mg / 5ml	£3.18	eMIT September 2021 [61]
	150mg / 15ml	£6.08	
	450mg / 45ml	£13.51	
Gemcitabine	200mg / 2ml	£3.18	eMIT September 2021 [61]
	1000mg / 10ml	£10.06	
	2000mg / 20ml	£17.78	
Atezolizumab	840 mg / 14ml	£2,665.38	MIMS UK list price (unknown confidential PAS in place) [63]
Capecitabine	150mg (60 tablets pack)	£4.43	eMIT September 2021 [61]
	300mg (60 tablets pack)	£7.77	
	500mg (120 tablets pack)	£26.30	

Table 56: Dosing schedule, dose intensity and mean treatment duration of 1L metastatic treatment from KEYNOTE-355

1L mTNBC treatment regimen	Component	Dosing schedule	Relative dose intensity (RDI) (%)	Mean treatment duration (week)
Pembrolizumab + taxanes (paclitaxel/nab-paclitaxel)	Pembrolizumab†	200mg Q3W	[redacted]	[redacted]

	Paclitaxel	90mg/m^2 on days 1, 8, 15 of every 28-day cycle	[redacted]	[redacted]
	Nab-paclitaxel	100mg/m^2 on days 1, 8, 15 of every 28-day cycle	[redacted]	[redacted]
Paclitaxel	Paclitaxel	90mg/m^2 on days 1, 8, 15 of every 28-day cycle	[redacted]	[redacted]
Carboplatin	Carboplatin^	AUC 2 on days 1 and 8 of every 21-day cycle	[redacted]	[redacted]
Carboplatin + paclitaxel†	Carboplatin^	AUC 2 on days 1 and 8 of every 21-day cycle	[redacted]	[redacted]
	Paclitaxel*	90mg/m^2 on days 1, 8, 15 of every 28-day cycle	[redacted]	[redacted]
Gemcitabine + carboplatin	Gemcitabine	1000mg/m^2 on days 1 and 8 of every 21-day cycle	[redacted]	[redacted]
	Carboplatin	AUC 2 on days 1 and 8 of every 21-day cycle	[redacted]	[redacted]
Atezolizumab + nab-paclitaxel	Atezolizumab	840mg Q2W	[redacted]	[redacted]
	Nab-paclitaxel	100mg/m^2 on days 1, 8, 15 of	[redacted]	[redacted]

		every 28-day cycle		
Capecitabine	Capecitabine*	1250mg/m^2 twice daily days 1-14 of every 21-day cycle	[redacted]	[redacted]
Data taken from KEYNOTE-355 1L mTNBC cost-effectiveness model [38]. †RDI for pembrolizumab component of pembrolizumab + taxanes is a weighted average of pembrolizumab + paclitaxel/nab-paclitaxel. ^RDI assumed equal to carboplatin component of gemcitabine + carboplatin. *RDI assumed equal to paclitaxel.				

Table 57: Lump sum costs for subsequent lines of treatments in mTNBC, by 1L mTNBC treatment

1L mTNBC treatment regimen	Subsequent treatment (2L+) costs (£)	Source
Pembrolizumab + taxanes (paclitaxel/nab-paclitaxel)	[redacted]	KEYNOTE-355 1L mTNBC CEM [38]
Paclitaxel	[redacted]	KEYNOTE-355 1L mTNBC CEM [38] (taxanes pooled arm)
Carboplatin*	[redacted]	Assumed same as taxanes from KEYNOTE-355 1L mTNBC CEM [38]
Carboplatin + paclitaxel^	[redacted]	Assumed same as gemcitabine + carboplatin from KEYNOTE-355 1L mTNBC CEM [38]
Gemcitabine + carboplatin	[redacted]	KEYNOTE-355 1L mTNBC CEM [38]
Atezolizumab + nab-paclitaxel	[redacted]	KEYNOTE-355 1L mTNBC CEM [38]
Capecitabine*	[redacted]	Assumed same as taxanes from KEYNOTE-355 1L mTNBC CEM [38]
*Subsequent treatment (2L+) costs duration assumed equal to taxanes. ^Subsequent treatment (2L+) costs assumed equal to Gemcitabine + Carboplatin.		

The weighted average cost for each treatment arm was calculated as a function of the proportion of patients who receive 1L treatments (Table 40) and the weighted average costs of patients who receive 1L treatments. The weighted average costs of patients who received 1L treatments were calculated based on the total treatment costs by 1L mTNBC treatment and the market shares of each 1L metastatic treatment for KEYNOTE-355 in the base case (Table 42). As a result, the weighted average costs of each arm are presented in Table 58.

Table 58: Total treatment costs in the DM setting by treatment arm

Weighted average costs	Pembrolizumab arm	Placebo arm
Total metastatic treatment costs	[redacted]	[redacted]
Note: Total metastatic treatment costs may be overestimated as subsequent treatments may have confidential discounts in place which are unknown to the public.		

B.3.5.3 Administration costs

In KEYNOTE-522, pembrolizumab 200mg was administered Q3W over a 30-minute infusion in the neoadjuvant phase (cycles 1-8) and the adjuvant phase (cycles 1-9). In the neoadjuvant phase, pembrolizumab was administered with carboplatin (AUC5 Q3W or AUC1.5 weekly) and paclitaxel (80mg/m^2 weekly) in cycles 1-4 followed by doxorubicin (60mg/m^2 Q3W) or epirubicin (90mg/m^2 Q3W) and cyclophosphamide (600mg/m^2 Q3W) in cycles 5-8. Pembrolizumab is administered as monotherapy in the adjuvant phase [40]. Administration costs applied in the model were dependent on complexity and treatment type (Table 59 for intervention/comparators and Table 60 for subsequent therapy administration costs) [64].

Table 59: Administration costs applied in the economic model for intervention and comparators

Drug	Type of administration	NHS reference code	Setting	Unit cost
Neoadjuvant phase				

Pembrolizumab	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	SB14Z	Outpatient	£352.24
Carboplatin	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	SB14Z	Outpatient	£352.24
Paclitaxel	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	SB14Z	Outpatient	£352.24
Cyclophosphamide	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	SB14Z	Outpatient	£352.24
Doxorubicin	Deliver Subsequent Elements of a Chemotherapy Cycle	SB15Z	Outpatient	£253.77
Epirubicin	Deliver Subsequent Elements of a Chemotherapy Cycle	SB15Z	Outpatient	£253.77
Adjuvant phase				
Pembrolizumab*	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	SB14Z	Outpatient	£352.24
*Application of complex infusion unit cost in adjuvant phase only can be considered a conservative assumption for Pembrolizumab monotherapy due to the 30 minute IV infusion required.				

Table 60: Administration costs applied for subsequent therapies 1L mTNBC

Drug	Type of administration	NHS reference code	Setting	Unit cost
Pembrolizumab + taxanes	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	SB14Z	Outpatient	£352.24
Paclitaxel	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	SB14Z	Outpatient	£352.24
Carboplatin	Deliver Simple Chemotherapy, at First Attendance	SB12Z	Outpatient	£221.35
Carboplatin + paclitaxel	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	SB14Z	Outpatient	£352.24
Gemcitabine + carboplatin	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	SB14Z	Outpatient	£352.24
Atezolizumab + Nab-paclitaxel	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	SB14Z	Outpatient	£352.24
Capecitabine	Oral. PSSRU 2020: Band 6 - Hospital-based scientific and professional staff including Pharmacists at entry level (£50/hr) & 12min prep time as in TA639. Cost applied as daily in the economic model.	NA	Outpatient	£10.00

Please refer to section B.2.3 for a trial schema and Appendix M for details on the neoadjuvant administration schedule applied in the economic model as per KEYNOTE-522.

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 TNBC. Though the target population in this submission is patients with early-stage TNBC, published literature on cost and healthcare resource use often focuses on TNBC irrespective of disease stage. Thus, the SLR was designed to capture relevant information for TNBC patients of any disease stage to ensure studies reporting data from a broader population relevant to the decision problem were not excluded. Despite this, no UK specific studies were identified. Please see Appendix I for details around methodology and study selection criteria. The estimates reported in TA424 (Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer) have been used as a source of health care resource utilisation owing to the lack of UK specific estimated from the SLR [34]. Although this is a different target population, this reflects appraisal committee preferences for early-stage breast cancer and were validated by clinical expert opinion. Additional one-off healthcare resource use was introduced to reflect resource utilisation whilst on treatment to supplement these based on clinical expert opinion [25].

Recurring disease management costs were applied to the event-free, locoregional recurrence and distant metastasis stated. The event-free state was split into 4 stages: year 1-3, year 4-5, year 6-10, year 11+ to reflect the decreased resource use with the length of time spent in the event-free state. Disease management costs are assumed to be zero for patients who remain in the event-free state for more than 10 years. 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. Additional health care resource use for the first year in the event-free state is also applied to reflect the resource use whilst on treatment which is split by treatment arm. Table 61 includes a list of the disease management resource use costs used within the model, Table 62 reports the frequency of recurring resource use and weekly cost applied in the model and

Table 63 reports the additional resource use and weekly cost applied in the model whilst on treatment.

Table 61: Disease management resource use costs

Resource	Cost (£)	Reference
Health care professionals		
Oncologist visit	£151.03	NHS reference costs 2019-20: 800CL WF01A Clinical Oncology (Previously Radiotherapy), Service code: 800
GP visit	£39.23	PSSRU 2020 Section 10.3B: per 9.22 minutes consultation at GP surgery with qualifications, including direct staff costs.
Clinical nurse specialist	£91.24	NHS reference costs 2019-2020: N10AF Specialist Nursing, Cancer Related, Adult, Face to face
Community nurse	£41.04	NHS reference costs 2019-2020: N02AF District Nurse, Adult, Face to face
Imaging		
Mammogram	£12.25	TA424 (2016) - NHS BSP (inflated to 2020)
CT scan	£118.64	NHS reference costs 2019-2020: RD24Z Computerised Tomography Scan of Two Areas, with Contrast
MRI scan	£202.52	NHS reference costs 2019-2020: RD05Z Magnetic Resonance Imaging Scan of Two or Three Areas, with Contrast
Laboratory monitoring		
Full blood count	£2.58	NHS reference costs 2019-2020: DAPS05 Haematology

Table 62: Frequency of recurring disease management resource use by health state and weekly cost applied in the model

Disease state	Oncologist visit (annual)	GP visit (annual)	Mammogram (annual)	CT scan (annual)	Clinical nurse specialist (annual)	Community nurse (annual)	FBC (annual)	MRI scan (annual)	Cost per week (£)	Source
Event-free (Year 1-3)	2	2	1	-	-	-	-	-	£7.55	TA424 (2016) Table 90, validated with clinical experts
Event-free (Year 4-5)	1	1	1	-	-	-	-	-	£3.89	TA424 (2016) Table 90, validated with clinical experts
Event-free (Year 6-10)	-	1	-	-	-	-	-	-	£0.75	TA424 (2016) Table 90, validated with clinical experts
Locoregional recurrence	2	-	1	2	-	-	-	1	£14.50	TA569 (2018) Table 42 after discussion with clinical experts, for all patients
Distant metastasis	12	1	-	4	12	3	17	-	£69.00	ID1546 (2020) Table 65 and TA639 Table 64, validated with clinical experts - reduced GP visit to 1 annual visit as followed up with oncologist monthly

Table 63: Additional disease management costs for the event free state (whilst on treatment)

Disease state	Oncologist visit (annual)	Clinical nurse specialist (annual)	FBC (annual)	Cost per week (£)	Source
Event-free (Year 0-1) – *pembrolizumab arm*	17	17	25	£81.99	Assumption from clinical expert opinion
Event-free (Year 0-1) – *placebo arm*	8	8	16	£38.06	As above adjusted for chemo arm

A one-off cost is applied for the locoregional recurrence and distant metastasis states in the first model cycle to reflect the resource use for initial care regarding disease diagnosis (Table 64). Thereafter, ongoing disease management costs are applied throughout the model for patients according to their respective health states.

Table 64: One-off costs for locoregional recurrence and distant metastasis states

Disease state	Oncologist visit	CT scan	Clinical nurse specialist	FBC	MRI scan	Total cost (£)	Source
Locoregional recurrence	1	1	-	1	1	£474.76	Assumed equal to DM state
Distant metastasis	1	1	-	1	1	£474.76	NICE ID1546 Table 64 and TA639 Table 63

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 hospital care in the 90 days before dying [65]. The source of costs is in line with previous pembrolizumab submissions [66]. The estimated cost is made up of services with include emergency inpatient admissions, non-emergency inpatient admissions, outpatient attendances and accident and emergency costs (see Table 65 for the final cost estimate applied).

Table 65: Resource use and source of terminal care and end of life costs

Resource	Unit cost	Source
District nurse	£339.84	Georgiou & Bardsley et al 2014 inflated to 2020 value [65].
Nursing and residential care	£122.47	
Hospice care – inpatient	£672.36	
Hospice care – final 3 months of life	£5,501.12	
Marie Curie nursing service	£611.23	
Total cost applied	**£8,347.03**	

B.3.5.5 Adverse reaction unit costs and resource use

Modelled AEs and their corresponding incidence are presented in section B.3.3.5. 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 resource use related to AE management is based on methodology and approaches employed in prior IO HTAs for consistency and to reflective of AC preferences in this topic [57, 67-69]. Unit costs associated with the management of AEs have been sourced from the latest NHS Reference Costs 2019/20 [64]. A one-off AE management cost is applied at the first model cycle for simplicity in each of the treatment arms, presented in Table 66.

Table 66: Unit costs associated with AE management

Grade 3+ AE	AE cost	NHS reference cost code	Rationale
Neutropenia	£635.68	NHS ref costs; 2019-2020 weighted average of NEL WJ11Z Other Disorders of Immunity; NES WJ11Z Other Disorders of Immunity; DC WJ11Z Other Disorders of Immunity	Costing as per TA519 approach [57]
Neutrophil count decreased	£635.68	As per Neutropenia	Equal to Neutropenia as in TA519 [57]
Anaemia	£762.54	NHS ref costs; 2019-2020 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 as per TA519 approach [57]
Febrile neutropenia	£3,580.80	NHS ref costs; 2019-2020 weighted average of DC SA35A Agranulocytosis with CC Score 13+; NES SA35A Agranulocytosis with CC Score 13+; NEL SA35A Agranulocytosis with CC Score 13+	Costing as per TA737 approach [68]

White blood cell count decreased	£635.68	As per Neutropenia	Equal to Neutropenia as in TA519 [57]
AAT increased	£0.00	N/A	Costing as per TA684 (previously TA558); Assumption of zero cost for laboratory abnormalities; (already considered under health-state management costs) [69]
Other AEs			
Diarrhoea (Grade 2+)	£2,166.42	NHS ref costs; 2019-2020 NES 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 as per TA581 approach [67]
Colitis (Grade 2+)	£2,166.42	As per Diarrhoea (Grade 2+)	Equal to Diarrhoea (Grade 2+) as in TA581 [67]
Abbreviations: AAT: Alanine aminotransferase increased; AE: Adverse event; N/A: Not applicable.			

B.3.5.6 Miscellaneous unit costs and resource use

B.3.5.6.1 Surgery costs

Surgery costs were applied within the model as a one-time cost and were calculated based on the unit costs of surgery and the proportion of patients receiving surgery in each arm as presented in Table 67. A weighted average of the unit costs for breast surgery was estimated from the NHS reference costs [64]. The healthcare resource group (HRG) codes chosen were validated by clinical experts [25]. The proportion of patients receiving surgery was obtained from the KEYNOTE-522 trial for each treatment arm.

Table 67: Surgery costs

Resource use	Weighted average cost (£)	% patients received surgery		Source
		Pembrolizumab arm	Placebo arm	
Surgery	£5,823.04	98.0%	97.7%	Weighted average by activity of codes JA30Z, JA31Z, JA34Z, JA35Z, JA38A, JA38B, JA38C, JA39Z from NHS reference costs [64]

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 parameters used in the base-case cost-effectiveness analysis is presented in Table 68 below.

Table 68: Summary of base-case analysis inputs

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.3.2.2
Model time horizon (years)	51.0	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 characteristics					
Patient age (years)	49.0	NA	NA	Not varied in PSA	See Section B.3.2.1
Proportion female	[redacted]	NA	NA	Not varied in PSA	
Average patient weight (kg)	[redacted]	[redacted]	[redacted]	[redacted]	
Average Body Surface Area (m^2)	[redacted]	[redacted]	[redacted]	[redacted]	
Utility Inputs by health state, treatment status and AE status					
Event-free, on treatment	[redacted]	[redacted]	[redacted]	[redacted]	See Section B.3.4.6
Event-free, off treatment	[redacted]	[redacted]	[redacted]	[redacted]	
Grade 3+ AE utility decrement	[redacted]	[redacted]	[redacted]	[redacted]	
Locoregional recurrence	[redacted]	[redacted]	[redacted]	[redacted]	
Distant metastasis	[redacted]	[redacted]	[redacted]	[redacted]	
Intervention and comparator drug acquisition costs					
Drug costs (per unit) for intervention arm					
Pembrolizumab 100mg/4ml	£2,630.00	NA	NA	Not varied in PSA	See Section B.3.5.1
Carboplatin 50mg/ml	£3.18	NA	NA	Not varied in PSA	

Paclitaxel 30mg/5ml	£4.15	NA	NA	Not varied in PSA	
Doxorubicin 10mg/5ml	£2.83	NA	NA	Not varied in PSA	
Epirubicin 200mg/100ml	£35.42	NA	NA	Not varied in PSA	
Cyclophosphamide 1000mg/vial	£13.55	NA	NA	Not varied in PSA	
Drug costs (per administration) for comparator arm					
Carboplatin 50mg/ml	£3.18	NA	NA	Not varied in PSA	See Section B.3.5.1
Paclitaxel 30mg/5ml	£4.15	NA	NA	Not varied in PSA	
Doxorubicin 10mg/5ml	£2.83	NA	NA	Not varied in PSA	
Epirubicin 200mg/100ml	£35.42	NA	NA	Not varied in PSA	
Cyclophosphamide 1000mg/vial	£13.55	NA	NA	Not varied in PSA	
Relative dose intensity for intervention arm					
Pembrolizumab (neoadjuvant)	[redacted]	NA	NA	Not varied in PSA	See Section B.3.5.1
Carboplatin (AUC 5, Q3W)	[redacted]	NA	NA	Not varied in PSA	
Carboplatin (AUC 1.5, weekly)	[redacted]	NA	NA	Not varied in PSA	
Paclitaxel	[redacted]	NA	NA	Not varied in PSA	
Cyclophosphamide	[redacted]	NA	NA	Not varied in PSA	
Doxorubicin	[redacted]	NA	NA	Not varied in PSA	
Epirubicin	[redacted]	NA	NA	Not varied in PSA	
Pembrolizumab (adjuvant)	[redacted]	NA	NA	Not varied in PSA	
Relative dose intensity for comparator arm					
Carboplatin (AUC 5, Q3W)	[redacted]	NA	NA	Not varied in PSA	See Section B.3.5.1
Carboplatin (AUC 1.5, weekly)	[redacted]	NA	NA	Not varied in PSA	
Paclitaxel	[redacted]	NA	NA	Not varied in PSA	
Cyclophosphamide	[redacted]	NA	NA	Not varied in PSA	
Doxorubicin	[redacted]	NA	NA	Not varied in PSA	
Epirubicin	[redacted]	NA	NA	Not varied in PSA	
Subsequent treatment drug acquisition costs					

Pembrolizumab	£2,630.00	NA	NA	Not varied in PSA	See Section B.3.5.2
Paclitaxel	£4.15	NA	NA	Not varied in PSA	
Nab-paclitaxel*	£246.00	NA	NA	Not varied in PSA	
Carboplatin	£3.18	NA	NA	Not varied in PSA	
Gemcitabine	£10.06	NA	NA	Not varied in PSA	
Atezolizumab*	£2,665.38	NA	NA	Not varied in PSA	
Capecitabine	£26.30	NA	NA	Not varied in PSA	
*Unknown confidential PAS in place					
Administration costs					
Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	£352.24	£227.95	£503.14	Gamma	See Section B.3.5.3
Deliver Subsequent Elements of a Chemotherapy Cycle	£253.77	£164.22	£362.48	Gamma	
Deliver Simple Chemotherapy, at First Attendance	£221.35	£143.24	£316.17	Gamma	
Oral administration costs (per 28 days of capecitabine administration)	£0.36	£0.23	£0.51	Gamma	
Disease management costs					
Recurring disease management costs (cost per week)					
Event-free (Year 1-3)	£7.55	£4.89	£10.79	Gamma	See Section B.3.5.4
Event-free (Year 4-5)	£3.89	£2.52	£5.56	Gamma	
Event-free (Year 6-10)	£0.75	£0.49	£1.08	Gamma	
Locoregional recurrence	£14.50	£9.38	£20.71	Gamma	
Distant metastasis	£69.00	£44.65	£98.56	Gamma	
Event-free (Year 0-1) – *pembrolizumab arm*	£81.99	£53.06	£117.12	Gamma	
Event-free (Year 0-1) – *placebo arm*	£38.06	£24.63	£54.37	Gamma	
One-off disease management costs					
Locoregional recurrence	£474.76	£307.24	£678.15	Gamma	See Section B.3.5.4
Distant metastasis	£474.76	£307.24	£678.15	Gamma	
Cost of terminal care	£8,347.03	£1,669.41	£5,401.76	Gamma	

Surgery					
% patients received surgery – *pembrolizumab arm*	0.9800	[redacted]	[redacted]	Beta	See Section B.3.5.6.1
% patients received surgery – *placebo arm*	0.9770	[redacted]	[redacted]	Beta	
Surgery costs	£5,823.04	£3,768.36	£8,317.65	Gamma	
Incidence of AEs for pembrolizumab arm from KEYNOTE-522					
Neutropenia	35.2%	NA	NA	Not varied in PSA	See Section B.3.3.5
Neutrophil count decreased	19.0%	NA	NA	Not varied in PSA	
Anaemia	19.5%	NA	NA	Not varied in PSA	
Febrile neutropenia	18.4%	NA	NA	Not varied in PSA	
White blood cell count decreased	7.8%	NA	NA	Not varied in PSA	
Alanine aminotransferase increased	6.4%	NA	NA	Not varied in PSA	
Grade 2+ Diarrhoea	[redacted]	NA	NA	Not varied in PSA	
Grade 2+ Colitis	[redacted]	NA	NA	Not varied in PSA	
Incidence of AEs for placebo arm from KEYNOTE-522					
Neutropenia	34.4%	NA	NA	Not varied in PSA	See Section B.3.3.5
Neutrophil count decreased	23.7%	NA	NA	Not varied in PSA	
Anaemia	15.7%	NA	NA	Not varied in PSA	
Febrile neutropenia	16.2%	NA	NA	Not varied in PSA	
White blood cell count decreased	5.4%	NA	NA	Not varied in PSA	
Alanine aminotransferase increased	2.8%	NA	NA	Not varied in PSA	
Grade 2+ Diarrhoea	[redacted]	NA	NA	Not varied in PSA	
Grade 2+ Colitis	[redacted]	NA	NA	Not varied in PSA	
AE management costs					
Pembrolizumab arm	£1,528.81	£989.37	£2,183.76	Gamma	See Section B.3.5.5
Placebo arm	£1,302.78	£843.09	£1,860.89	Gamma	
Transition probability modelling					
From event-free state					

EFS parametric curve fitting					
EFS - Pembrolizumab + chemotherapy - Piecewise - 50 - Generalized Gamma - A	[redacted]	[redacted]	[redacted]	Multivariate normal	See Section B.3.3.1
EFS - Pembrolizumab + chemotherapy - Piecewise - 50 - Generalized Gamma - B	[redacted]	[redacted]	[redacted]	Multivariate normal	
EFS - Pembrolizumab + chemotherapy - Piecewise - 50 - Generalized Gamma - C	[redacted]	[redacted]	[redacted]	Multivariate normal	
EFS - Chemotherapy - Piecewise - 50 - Log-normal - A	[redacted]	[redacted]	[redacted]	Multivariate normal	
EFS - Chemotherapy - Piecewise - 50 - Log-normal - B	[redacted]	[redacted]	[redacted]	Multivariate normal	
Probability of the first EFS event					
% LR among first EFS event (Year 1) - Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	Beta	See Section B.3.3.1
% LR among first EFS event (Year 1) - Chemotherapy	[redacted]	[redacted]	[redacted]	Beta	
% DM among first EFS event (Year 1) - Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	Beta	
% DM among first EFS event (Year 1) - Chemotherapy	[redacted]	[redacted]	[redacted]	Beta	
% LR among first EFS event (Year 2+) - Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	Beta	
% LR among first EFS event (Year 2+) - Chemotherapy	[redacted]	[redacted]	[redacted]	Beta	
% DM among first EFS event (Year 2+) - Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	Beta	

% DM among first EFS event (Year 2+) - Chemotherapy	[redacted]	[redacted]	[redacted]	Beta	
From locoregional recurrence state					
Exponential rate of LR to DM or death	[redacted]	[redacted]	[redacted]	Normal	See Section B.3.3.2
% transition from LR to DM	[redacted]	[redacted]	[redacted]	Beta	
From distant metastasis state using KEYNOTE-355 data					
Exponential rate of DM (IO-eligible) to death – *pembrolizumab arm*	[redacted]	[redacted]	[redacted]	Normal	See Section B.3.3.3
Exponential rate of DM to death – *placebo arm*	[redacted]	[redacted]	[redacted]	Normal	

B.3.6.2 Assumptions

Table 69 summarises the assumptions used in the economic model

Table 69: List of parameters and assumptions used in the economic model

Parameter	Assumption	Justification
EFS efficacy	Piecewise modelling applied using KM data for the first 50 weeks for both arms, followed by Generalized Gamma for pembrolizumab arm and Log-normal for placebo arm.	The 50-week timepoint was based on visual inspection of the cumulative hazard plot and provides a good balance of robust KM data to be used directly in the first phase and enough remaining data to be used to fit a parametric curve in the second phase.
Transition probabilities from EF	Time dependent transition probabilities were estimated based on extrapolated EFS and proportion of LR, DM and death as the first EFS event.	Time dependent transition probabilities were used to reflect to reflect the time dependent hazard rate of EFS observed in the KEYNOTE-522 trial.
Transition probabilities from LR	Transition probabilities starting from LR were assumed to be equivalent between arms and constant across all cycles.	Pooled data from KEYNOTE-522 was used as the transition from LR onwards is assumed to be equivalent for the pembrolizumab arm and placebo arm as similar time to DM/death from LR is observed between treatment arms; however, this is a conservative assumption and biases against the pembrolizumab arm.
Transition probabilities from DM → death	Transition probability from DM à death was based on the treatment rate, the expected mix of 1L treatments in the DM state and the efficacy of these 1L treatments in terms of mean OS from KEYNOTE-355.	KEYNOTE-355 was selected as the base-case source due to the immaturity of KEYNOTE-522 OS data. KEYNOTE-522 OS data was explored in a scenario analysis but used treatment mix and market shares used obtained from UK market research and validated with clinical experts as the trial data was not reflective of the UK setting.

Subsequent treatments	Once patients progress to DM, they receive subsequent therapies. The proportion receiving subsequent therapies in each treatment arm is based on KEYNOTE-522. The 1L treatment regimens is based on KEYNOTE-355 and clinical expert input with mean OS, treatment duration and 2L+ costs sourced from KEYNOTE-355 and market share estimates from UK market research validated by clinical expert opinion.	Subsequent therapies used in KEYNOTE-522 were not generalisable to the UK setting. UK market research identified 1L mTNBC treatment regimens with market shares which were validated with clinical experts. Hence, the KEYNOTE-355 cost-effectiveness model was used to source efficacy, treatment rates and 2L+ costs for these regimens. KEYNOTE-522 efficacy (OS) data was also explored in a scenario analysis as mentioned above.
Safety	AE incidence rates were sourced from KEYNOTE-522 assumed to be reflective of those observed in real world practice.	Assumption based on the results of the KEYNOTE-522 trial [35] (i.e. grade 3-5 (incidence≥5% in one or more treatment groups, considering any grade) in addition to grade 2+ diarrhoea and colitis 5 (incidence≥0% in one or more treatment groups, considering any grade). The same method and criteria have been applied in several recent NICE oncology appraisals of pembrolizumab.
HRQoL	The quality of life of patients is appropriately captured by using pooled utility estimates by health state, treatment status and AE status. Estimates were derived from the EQ-5D-5L collected alongside the KEYNOTE-522 clinical trial. This was mapped back to the 3L tool using the crosswalk method.	The source of utility estimates is consistent with the NICE reference case. The use of the crosswalk algorithm developed by van Hout et al. [51] is in line with the NICE position statement for reference case analyses [52].
AE disutility	The disutility associated with patients experiencing grade 3+ AEs was derived from KEYNOTE-522 and was also applied to grade 2+ AEs included in the economic model	Use of KEYNOTE-522 ensures a consistent source for adverse events and impact on HRQoL from treatment.
Age-related disutility	Utility decreases with age were accounted for using a model for disutility from the UK population.	Based on the Ara and Brazier study suggesting the impact of age on HRQoL and in line with methodology used in previous appraisals [55-57].
Time on treatment	Time on treatment was estimated directly from KEYNOTE-522 using KM analysis for time to end of neoadjuvant treatment, time to end of surgery and time to end of treatment course.	KM curves directly from the trial were fitted to inform the model input and account for early treatment discontinuation of patients as per the study protocol.
Healthcare resource use costs	Resource use is assumed to be equal between treatment arms with the exception of the time on	Due to the lack of data from the SLR specific to the UK, resource use was assumed to be equal per treatment arm following the time

	treatment to reflect the more frequent resource use with pembrolizumab in the adjuvant setting.	on treatment. Resource use estimates from TA424, TA569 and ID1546 were validated with clinical experts and updated as necessary [34, 70, 71].
Vial sharing	No vial sharing was assumed.	This assumption is in line with the NICE reference case.

B.3.7 Base-case results

The comparison for the base case reflects the UK standard of care chemotherapies in line the final scope issued by NICE.

B.3.7.1 Base-case incremental cost-effectiveness analysis results

The tables below present the results of the base case cost-effectiveness comparison.

The estimated mean overall survival for the pembrolizumab arm was 16.89 life years versus 13.82 for the placebo arm. Patients treated in the pembrolizumab arm accrued [redacted] QALYs compared to [redacted] among patients in the placebo arm. The pembrolizumab arm was associated with a net [redacted] QALY gain and a net life year gain of 3.07 versus the placebo arm. The corresponding incremental cost-effectiveness ratio (ICER) with the current PAS in place was £5,940 per QALY. The pembrolizumab regimen is cost-effective versus the current standard of care when considering the willingness-to-pay (WTP) threshold of £30,000/QALY.

Table 70: Base-case results using list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Placebo arm	[redacted]	13.82	[redacted]	-	-	-
Pembrolizumab arm	[redacted]	16.89	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 71: Base-case results using pembrolizumab PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Placebo arm	[redacted]	13.82	[redacted]	-	-	-
Pembrolizumab arm	[redacted]	16.89	[redacted]	[redacted]	[redacted]	£5,940
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

The estimates the tabulated, disaggregated results for the base case are presented in Appendix J. The disaggregated results show that the majority of QALY gain comes from patients remaining in the event-free state for longer in the pembrolizumab arm and accruing fewer metastatic treatment costs as fewer patients reach the distant metastasis state.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken with 1,000 simulations. The mean values, distributions around the means and sources used to estimate the parameters are detailed in section B.3.6.1.

The incremental cost-effectiveness results from the PSA are presented in Table 72. The corresponding scatterplot and cost-effectiveness acceptability curve (CEAC) are presented in Figure 21 and Figure 22 respectively. The PSA results show that the pembrolizumab arm was associated with a net [redacted] QALY gain and a net life year gain of 2.93 versus the placebo arm. The corresponding incremental cost-effectiveness ratio (ICER) with the current PAS in place was £6,128 per QALY. With the current PAS discount, the CEAC shows that there is an 98.0% chance of the pembrolizumab regimen being cost-effective when compared with the current standard of care under the WTP threshold.

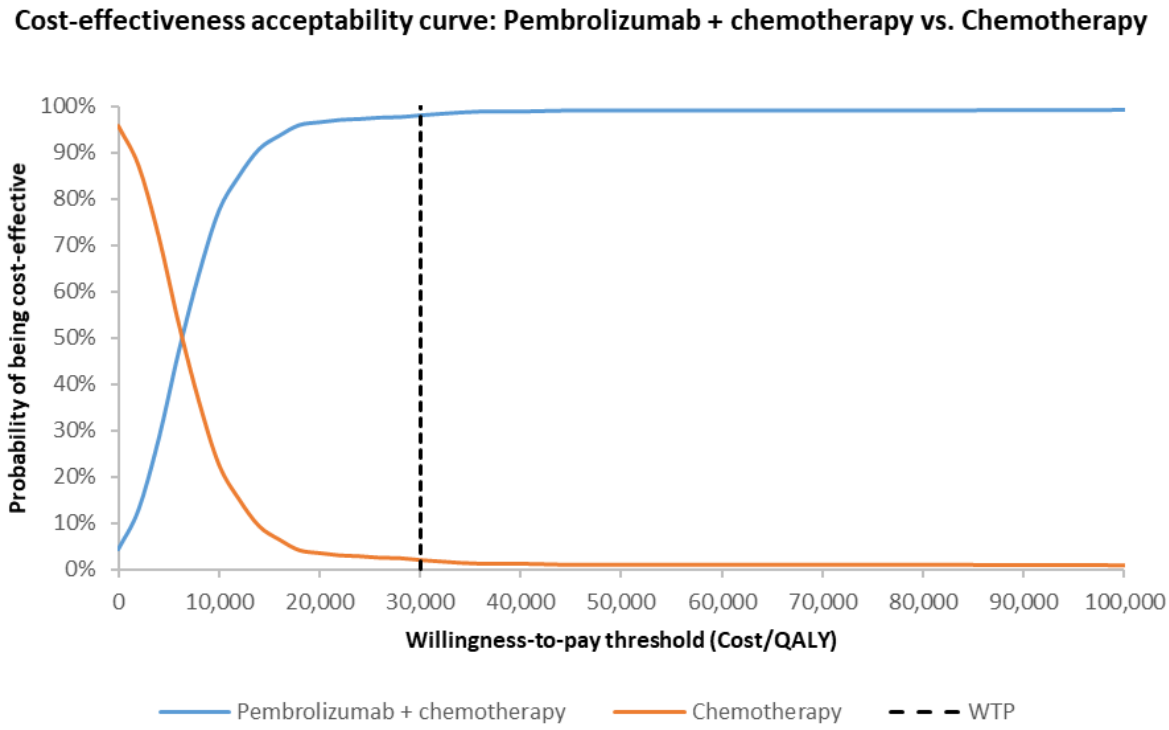
Table 72: Base-case results from PSA using pembrolizumab PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Placebo arm	[redacted]	13.79	[redacted]	-	-	
Pembrolizumab arm	[redacted]	16.72	[redacted]	[redacted]	[redacted]	£6,128
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Figure 21: Scatterplot of PSA results with pembrolizumab PAS price

[redacted]

Figure 22: Cost-effectiveness acceptability curve (CEAC) with pembrolizumab PAS price



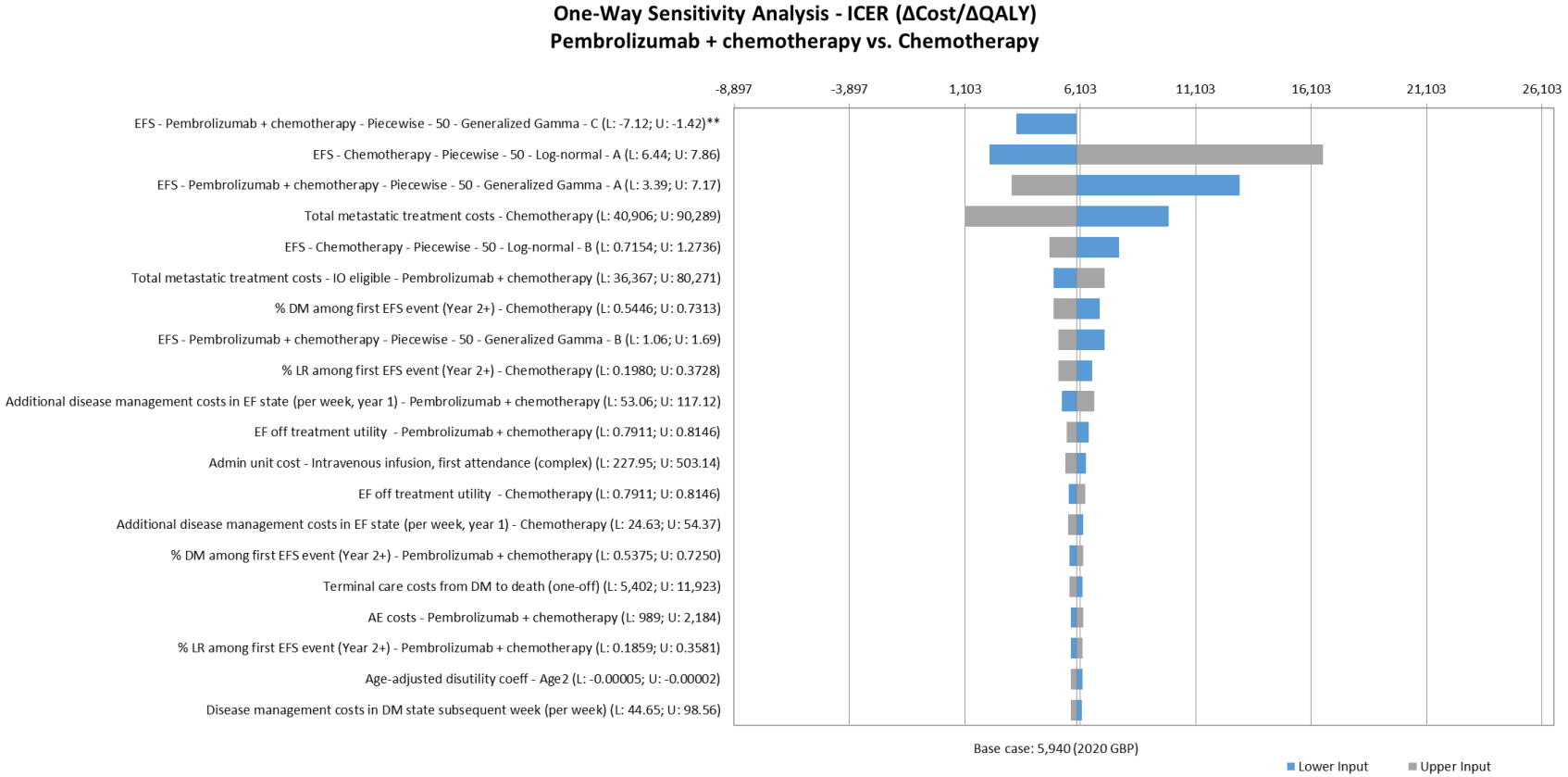
B.3.8.2 Deterministic sensitivity analysis

Extensive sensitivity analyses were conducted to explore the uncertainty associated with the estimates of cost-effectiveness. Deterministic sensitivity analyses (DSA) were conducted for the following key parameters using the 95% confidence intervals where applicable:

- Baseline characteristics (i.e. weight, BSA)
- Parameters of the parametric curves fitted to EFS
- Exponential rate of LR to DM or death and DM to death
- % transition from LR to DM
- % experiencing LR or DM among first EFS event
- % received surgery and surgery costs
- Pooled utility by health state, treatment status and AE status
- AE and age-related disutility
- Administration, AE disease management, subsequent treatment and terminal care costs

The results of the deterministic sensitivity analysis are presented in Figure 23 below. The inputs that have most impact on the ICERs are those related to parameters linked to EFS extrapolations followed by metastatic treatment costs. The full list of inputs varied in the DSA and the impact on the base-case ICER are presented in Appendix M1.4.

Figure 23: Tornado diagram for the 20 most sensitive parameters with pembrolizumab PAS price



**Upper limit parameter pembrolizumab arm is dominated i.e. more costly and less effective; therefore an ICER statistic cannot be presented for the tornado diagram

B.3.8.3 Scenario analysis

Alternative scenario analyses were conducted to assess the uncertainty regarding structural and methodological assumptions in the economic model. The parameters explored are listed below:

- Scenario 0: current base case
- Scenario 1: EFS function - Pembrolizumab + chemotherapy - Piecewise - Week 50 - Log-normal; second best option of pembrolizumab arm curve by clinical experts)
- Scenario 2: EFS function - Chemotherapy - Piecewise - Week 50 - Generalized Gamma; second best option of placebo arm curve by clinical experts
- Scenario 3: EFS function - Pembrolizumab + chemotherapy - Piecewise - Week 50 - Log-normal and Chemotherapy - Piecewise - Week 50 – Generalized Gamma; combined second best option of pembrolizumab arm and placebo arm curves by clinical experts
- Scenario 4: Time horizon (20 years)
- Scenario 5: Allow vial sharing
- Scenario 6: Utility by treatment arm
- Scenario 7: Utility algorithm (UK 5L)
- Scenario 8: TOT measure - Pembrolizumab + chemotherapy - KM lower 95% CI
- Scenario 9: TOT measure - Pembrolizumab + chemotherapy - KM upper 95% CI
- Scenario 10: TOT measure - Chemotherapy - KM lower 95% CI
- Scenario 11: TOT measure - Chemotherapy - KM upper 95% CI
- Scenario 12: Annual discount rate - costs (1.5%)
- Scenario 13: Annual discount rate - effects (1.5%)
- Scenario 14: Annual discount rate – costs and effects (1.5%)
- Scenario 15: Remission after 8 years (note: remission assumes the probability of EFS event for both treatment arms = 0, only transition applied is background mortality; based on clinical expert opinion)
- Scenario 16: Remission after 10 years (note: remission assumes the probability of EFS event for both treatment arms = 0, only transition applied is background mortality; based on clinical expert opinion)
- Scenario 17: KEYNOTE-522 OS data used to model DM → death
- Scenario 18: Pembrolizumab 400mg Q6W dosing applied across for neoadjuvant and adjuvant setting
- Scenario 19: Pembrolizumab rechallenge scenario with atezolizumab 50:50 split for both treatment arms*
- Scenario 20: Pembrolizumab rechallenge scenario with atezolizumab 17:83 split for both treatment arms*

**Scenarios have been run manually*

Table 73: Scenario analyses with pembrolizumab PAS price

Scenario No.	Description	Pembrolizumab arm		Placebo arm		Pembrolizumab vs. placebo arm		
		Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
0	Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,940
1	EFS function - Pembrolizumab + chemotherapy - Piecewise - Week 50 - Log-normal (second best option of pembrolizumab arm curve by clinical experts)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,444
2	EFS function - Chemotherapy - Piecewise - Week 50 - Generalized Gamma (second best option of placebo arm curve by clinical experts)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,768
3	EFS function - Pembrolizumab + chemotherapy - Piecewise - Week 50 - Log-normal and Chemotherapy - Piecewise - Week 50 – Generalized Gamma (combined second best option of pembrolizumab arm and placebo arm curves by clinical experts)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£19,206
4	Time horizon (20 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,023
5	Allow vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,177
6	Utility by treatment arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,180
7	Utility algorithm (UK 5L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,535
8	TOT measure - Pembrolizumab + chemotherapy - KM lower 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,490
9	TOT measure - Pembrolizumab + chemotherapy - KM upper 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,427
10	TOT measure - Chemotherapy - KM lower 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,994
11	TOT measure - Chemotherapy - KM upper 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,888
12	Annual discount rate - costs (1.5%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,789
13	Annual discount rate - effects (1.5%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,081

Scenario No.	Description	Pembrolizumab arm		Placebo arm		Pembrolizumab vs. placebo arm		
		Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
14	Annual discount rate – costs and effects (1.5%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£3,290
15	Remission after 8 years (note: remission assumes the probability of EFS event for both treatment arms = 0, only transition applied is background mortality; based on clinical expert opinion)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,791
16	Remission after 10 years (note: remission assumes the probability of EFS event for both treatment arms = 0, only transition applied is background mortality; based on clinical expert opinion)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,268
17	KEYNOTE-522 OS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,938
18	Pembrolizumab 400mg Q6W dosing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,380
19	Pembrolizumab rechallenge scenario with atezolizumab 50:50 split for both treatment arms*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£8,471
20	Pembrolizumab rechallenge scenario with atezolizumab 17:83 split for both treatment arms*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,792

*Scenarios run manually

B.3.8.4 Summary of sensitivity analyses results

The probability of the pembrolizumab regimen versus the current standard of care being the most cost-effective treatment at a WTP threshold of £30,000/QALY is 98.0%. The ICER generated by the PSA was consistent with that produced in the deterministic base-case (£6,128 per QALY gained vs. £5,940 per QALY gained).

The main drivers of the economic analysis include parameters related to EFS extrapolations, choice of parametric curves and remission assumptions. The ICERs ranged from £3,290 per QALY gained to £19,206 per QALY gained.

Considering the current pembrolizumab PAS, the ICERs generated are well within the NICE WTP threshold.

B.3.9 Subgroup analysis

Subgroup analysis was not performed as it is not relevant for this indication.

B.3.10 Validation

B.3.10.1 Validation of cost-effectiveness analysis

Clinical expert opinion was sought to validate key aspects of the modelling methods, assumptions and inputs listed below:

- 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 healthcare resource use
- Selection of parametric curves and extrapolation of outcomes beyond the trial period (see section B.3.3 above)

B.3.10.1.1 Internal validation of clinical benefit

KEYNOTE-522 EFS

For internal validation, the efficacy outcomes from KEYNOTE-522 (EFS) were compared to the outcomes produced from the economic model. Table 74 provides a summary of the model

projections for EFS from KEYNOTE-522 for the pembrolizumab arm and Table 75 for the placebo arm. The modelled EFS curves match well with the observed EFS curves (Figure 24).

Table 74: Modelled EFS vs. observed EFS for the pembrolizumab arm

Pembrolizumab arm	6 months	1 year	18 months	2 years	3 years	5 years	8 years	10 years	20 years
Modelled EFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed EFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EFS, event-free survival

Table 75: Modelled EFS vs. observed EFS for the placebo arm

Placebo arm	6 months	1 year	18 months	2 years	3 years	5 years	8 years	10 years	20 years
Modelled EFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed EFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EFS, event-free survival

Figure 24: Modelled EFS vs. observed EFS for the pembrolizumab arm and placebo arm

Abbreviations: EFS, event-free survival; KM, Kaplan-Meier

KEYNOTE-355 OS

For internal validation, the efficacy outcomes KEYNOTE-355 (OS) were compared to the outcomes produced from the economic model. Table 76 provides a summary of the model projections for OS from KEYNOTE-355 for the pembrolizumab arm and Table 77 for the placebo arm. The modelled OS curves match well with the observed OS curves (Figure 25).

Table 76: Modelled OS (KN-355) vs. observed OS (KN-522) for the pembrolizumab arm

Pembrolizumab arm	6 months	1 year	18 months	2 years	3 years	5 years	8 years	10 years	20 years
Modelled OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS, overall survival

Table 77: Modelled OS (KN-355) vs. observed OS (KN-522) for the placebo arm

Placebo arm	6 months	1 year	18 months	2 years	3 years	5 years	8 years	10 years	20 years
Modelled OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Observed OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS, overall survival

Figure 25: Modelled OS (KN-355) vs. observed OS (KN-522) for the pembrolizumab arm and placebo arm

Abbreviations: KM, Kaplan-Meier; OS, overall survival

B.3.10.1.2 External validation

KEYNOTE-522 EFS

A targeted literature review to identify studies that report long-term EFS in patients with early-stage TNBC following neoadjuvant chemotherapy (NACT). Two external sources were

identified, Walsh 2019 [68] and Sikov 2019 (CALGB 40603) [43]. Clinical experts did not identify any further relevant sources for model validation purposes and noted that both studies could be sources of validation for the placebo modelled EFS.

Walsh 2019 [68] was a retrospective study of outcomes in a cohort who were diagnosed with TNBC at Galway University Hospital between January 2000 and December 2015, with a median follow-up of 30 months. Sikov 2019 [43] was a randomized, open-label phase II trial of 443 patients with stage II to III TNBC which was designed to examine the impact of adding carboplatin and/or bevacizumab to conventional NACT. The base case model projection of long-term EFS of the placebo arm was compared with the disease-free survival (DFS) following NACT in the Walsh 2019 study and the EFS following neoadjuvant carboplatin-based chemotherapy in the Sikov 2019 study, respectively. As presented in Figure 26, the projected placebo arm EFS curve matched well with the DFS curve from Walsh 2019 and the EFS curve from Sikov 2019 are reasonably close to the projected EFS curve of the chemotherapy arm confirming the plausibility of the EFS projections. Clinical experts also validated these sources of long-term EFS. Clinical expert opinion of the curves confirmed the selection of the log-normal distribution, which is explored in the base case, followed by Generalized Gamma which is explored in scenario analysis to model the placebo arm [25].

As there are currently no clinical or real-world long-term EFS data for early-stage TNBC patients who have received pembrolizumab, the plausibility of the projected long-term EFS of the pembrolizumab arm was validated with a group of clinical experts in this therapeutic area [25]. They suggested that the Gompertz distribution as a plausible extrapolation of EFS; however, this is associated with a flat tail which is observed early on, potentially leading to overestimation of the long-term EFS (see Figure 11 in section B.3.3.1 above). Clinical experts also noted Generalized Gamma as a plausible fit which is explored in the base case, followed by log-normal which is explored in scenario analysis [25].

Figure 26: External validation of EFS extrapolation

Abbreviations: DFS, disease-free survival; EFS, event-free survival; KM, Kaplan-Meier

KEYNOTE-355 OS

External studies were sought from the clinical literature to validate the modelled OS of the chemotherapy arm (process described above). Of the studies identified, both Walsh 2019 [68] and Sikov 2019 (CALGB 40603) [43]. Clinical experts did not identify any further relevant sources for model validation purposes and noted that both studies could be sources of validation for the chemotherapy modelled OS. As reported above, Walsh et al is a retrospective study which run in Ireland between 2000 and 20015 (n=333). The study was run from 2000 to 2015 and therefore its generalisability may be limited due to advances in early diagnosis and management over this time. Clinical experts noted that the generalisability of the results may be further limited by the fact that older patient cohort was included in Walsh et al 2019 which reports breast cancer specific survival. These elements may be reflected in the projected estimates versus the modelled chemotherapy OS. Sikov et al is a Phase II study which took place in the US between the years of 2009 and 2014 (n=443).

The OS trajectories from Walsh and Sikov align visually very well and their OS estimates overlap visually with the lower 95% CI of the chemotherapy OS observed in KEYNOTE-522 study. When validating the predicted chemotherapy OS curve (base case derived using data from KEYNOTE-355 data) versus versus Walsh 2019 [68] and Sikov 2019 (CALGB 40603) [43], the modelled OS sits within the 95% CI OS from KEYNOTE-522 (Figure 27). This means that the model produces robust estimates of OS for the chemotherapy arm.

The use of KEYNOTE-522 OS resulted in a slightly improved visual alignment of modelled chemotherapy OS versus external sources. However, OS data form from KEYNOTE-522 remain immature and subsequent treatment data from they study may need some further

adjustments to be fully reflective of the UK setting. Therefore, further external validation of OS using KEYNOTE-522 data is presented in Appendix M.

As there is no clinical or real-world long-term OS available for early-stage TNBC patients who receive pembrolizumab currently, the plausibility of projected long-term OS of the pembrolizumab arm was validated with clinical experts in this therapeutic area [25].

Figure 27: External validation of modelled OS

Abbreviations: OS, overall survival

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 standard neoadjuvant chemotherapy followed by adjuvant pembrolizumab for patients [redacted], 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 other early-stage breast cancer appraisals reviewed by NICE.

Key strengths of this appraisal include:

- The use of the most recent clinical data from KEYNOTE-522 phase III RCT to inform the submission showing a statistically significant and clinically meaningful improvement in EFS.

- The use of KEYNOTE-522 and KEYNOTE-355 data to estimate the cost-effectiveness versus standard of care.

- Presentation of cost-effectiveness results of pembrolizumab in combination with chemotherapy followed by pembrolizumab monotherapy versus the standard of care neoadjuvant chemotherapy regimen as listed in the NICE final scope.

- Leverage of EQ-5D-5L data directly collected alongside KEYNOTE-522 consistent with the NICE reference case and the use of mapping to estimate utility weights consistent with the NICE position statement.

- Robust cost-effectiveness analyses results and extensive testing of uncertainty using a range of scenarios confirming the conclusion regarding the cost-effectiveness of this technology.

- Validation of model structure and inputs by clinical experts and leveraging the most up-to-date RWE data within the submission.

- Extended internal and external validation of model outcomes versus RWE literature.

A limitation of this technology appraisal is the lack of long-term EFS and OS data beyond the trial maximum follow up period. However, the uncertainty behind long term survival extrapolations is mitigated by exploring different methods of EFS extrapolation beyond the trial period. Due to the immaturity of the OS data in KEYNOTE-522, OS data from KEYNOTE-355 for metastatic TNBC was used to inform the transition from distant metastasis to death. Furthermore, the submission leverages the most up-to-date RWE data to validate the model outputs for the standard of care arm.

In the base-case analysis, the estimated OS with the pembrolizumab regimen was 16.89 years versus 13.82 for the standard of care placebo arm, resulting in an incremental LY gain of 3.07 for the pembrolizumab regimen versus the standard of care placebo arm. The estimated QALY gain for patients treated with the pembrolizumab regimen is [redacted] QALYs versus [redacted] among patients treated with standard chemotherapy, resulting in an incremental QALY gain of [redacted]. MSD considers pembrolizumab in combination with chemotherapy followed by

pembrolizumab monotherapy to offer an unprecedented increase in life years and QALYs for a population experiencing poor survival outcomes with the current standard of care in an aggressive cancer. The demonstrated improvement in EFS provides life extension for patients at an early stage of the TNBC pathway. A high unmet medical need remains for patients with early-stage TNBC and therefore patients would benefit from having an additional innovative treatment option becoming available.

Pembrolizumab in combination with chemotherapy followed by pembrolizumab monotherapy for the treatment of early-stage TNBC is highly cost-effective versus the current standard of care chemotherapy with an ICER of £5,940 per QALY gained and a 98.0% chance of cost-effectiveness with the WTP threshold of £30,000/QALY using the pembrolizumab PAS price and therefore a candidate for baseline commissioning.

In conclusion, the *de novo* economic analysis brings together the best available clinical data to establish the comparative efficacy and safety of pembrolizumab in combination with chemotherapy followed by pembrolizumab monotherapy in patients with early-stage TNBC.

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B.5 Appendices

See separate document provided

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of untreated locally advanced non-metastatic triple negative breast cancer [ID1500]

Clarification questions

April 2022

File name	Version	Contains confidential information	Date
ID1500 Pembrolizumab TNBC ERG clarification	0.2	Yes	04.04.22

Section A: Clarification on effectiveness data

Literature searches

A1. Please provide full details of the searches of conference proceedings referred to in Appendix D.1.1.1 of the company submission (CS), including the specific resources searched, URL links, date searched, the search strategies or search terms used, and results.

Hand searches were performed on July 27, 2021, for conference proceedings from the American Society of Clinical Oncology (2020-2021; https://meetinglibrary.asco.org/), European Society of Medical Oncology (2020; https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020), and Antonio Breast Cancer Symposium (2020; https://www.abstractsonline.com/pp8/#!/9223) using the search terms "triple-negative breast cancer," "triple negative breast cancer," or "TNBC." Three abstracts met the inclusion criteria and were included in the SLR.

A2. Please provide full details of the searches of trials registries referred to in Appendix D.1.1.1 of the CS, including the search strategies or search terms used, date searched, and results.

ClinicalTrials.gov (https://clinicaltrials.gov/) was searched on July 27, 2021, for trials relevant to triple-negative breast cancer with participants age-restricted to "18+" and study type restricted to "interventional." There were 116 hits, but none met the inclusion criteria. Clinicaltrialsregister.edu (https://www.clinicaltrialsregister.eu/) was also searched, and while there were 69 hits, none met the inclusion criteria.

A3. Please provide full details of the grey literature searches of health technology assessment organisations, economic specific resources and the Northern Light Life Sciences Conference Abstracts database referred to in Appendices G.1.2, H.1.1, and I.1.1 of the CS, including the specific resources searched, the search strategies or search terms used, date searched, and results.

In parallel with the database searches, the following grey literature sources were searched using key population and disease search terms, such as "triple-negative breast cancer", "triple negative breast cancer", or "TNBC", to identify relevant

studies: The Agency for Healthcare Research and Quality (AHRQ); the National Institute of Health Research Health Technology Assessment (NIHR HTA); the Health Technology Assessment database of the International Network of Agencies for Health Technology Assessment (INAHTA); the Scottish Medicines Consortium (SMC); the All Wales Medicines Strategy Group (AWMSG); the Canadian Agency for Drugs and Technologies in Health (CADTH); the French National Authority for Health (Haute Autorité de Santé; HAS); the Institute for Quality and Efficiency in Healthcare (IQWIG); the Institute for Clinical and Economic Review (ICER); the National Institute for Health and Clinical Excellence (NICE); the University of Sheffield School of Health and Related Research health utilities database (ScHARRHUD); and the Health Economics Research Centre mapping algorithm database. No materials met the inclusion criteria. Across these resources, inconsistent formatting and search functionality often precluded the determination of the magnitude of the available materials. Thus, in accordance with historical precedent, detailed records of grey literature searches were not recorded in a manner analogous to that of the traditional database searches of Embase, MEDLINE, and CENTRAL.

Decision problem

A4. Priority question. The decision problem defined the population of interest as "adults *with locally advanced*, inflammatory, or early-stage triple-negative b*reast cancer at high risk of recurrence*". This definition is narrower than the population defined in the final scope issued by the National Institute for Health and Care Excellence (NICE), i.e. "adults with previously untreated locally advanced, nonmetastatic triple-negative breast cancer".

a. **Please discuss how the narrower population and comparator reflect the population defined in the NICE final scope.**

MSD's response to the draft scope consultation included the anticipated marketing authorisation. This was marked as commercial in confidence and as such NICE were not able to make this wording public. The CHMP have adopted a positive opinion for the indication which has been published on the EMA website, therefore it does not need to be redacted [1]. The final label wording is, 'KEYTRUDA, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults wit***h locally***

advanced, or early stage triple negative breast cancer at high risk of recurrence'

b. Please provide a definition of "high risk of recurrence", i.e. the classification used, including supporting references.

The Food and Drug Administration refers to high risk patients as those 'with early-stage breast cancer who continue to have a high risk of distant disease recurrence and death despite use of optimal modern local and systemic adjuvant therapy.' [2] Also 'patients may be classified as high risk for recurrence on the basis of conventional histologic features or by appropriately validated genomic measures, but in general should have a 5-year EFS of less than 75 percent'.

Within KEYNOTE-522, 'high-risk TNBC' is synonymous with 'locally advanced TNBC', the latter defined as T1c, N1-N2; T2-T4d, N0-N2 (thus, Stage II-III) per the American Joint Committee on Cancer (AJCC) staging criteria for breast cancer.

c. Please discuss the implications of any difference between the definition as applied in the KEYNOTE-522 trial and NHS clinical practice.

MSD understands the definition applied in the KEYNOTE-522 resonates with NHS clinical practice.

A5 Priority question. The market indication for this appraisal has not been included in Table 2 of the CS. Please confirm the wording of the market indication and how this relates to the population addressed in the decision problem.

The approved indication which the CHMP have adopted a positive opinion for is 'KEYTRUDA, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early stage triple negative breast cancer at high risk of recurrence' [1].

Systematic literature review (SLR)

A5. Priority question. Given the approximate 20 interventions listed in the Table 4 of Appendix D.1.1.2, the total number of included trials (N=8) looks small. Furthermore, the eligibility criteria for the SLR were vague.

a. **Participants in the I-Spy2 trial received standard neoadjuvant chemotherapy: 80 mg/m^2 intravenous paclitaxel, followed by doxorubicin plus intravenous cyclophosphamide, which is in line with the eligibility criteria. Please explain why it was excluded.**

To facilitate an understanding of the relative treatment effect of interventions of interest, studies must have included at least two treatment arms of interest to be eligible for inclusion in the SLR of clinical evidence. Patients with TNBC enrolled in ISPY-2 were treated with paclitaxel with or without pembrolizumab followed by doxorubicin plus cyclophosphamide. As one of the treatment arms—pembrolizumab plus paclitaxel followed by doxorubicin plus cyclophosphamide—was not listed in the PICOS criteria, this trial was excluded from the SLR.

b. **As per Table 56 of the Appendix, the PROCEED Trial (KCSG BR 11-01) was excluded from the SLR based on outcomes when in fact Park et al. 2019 reported OS, PFS, QoL and AEs. Please explain why it was excluded.**

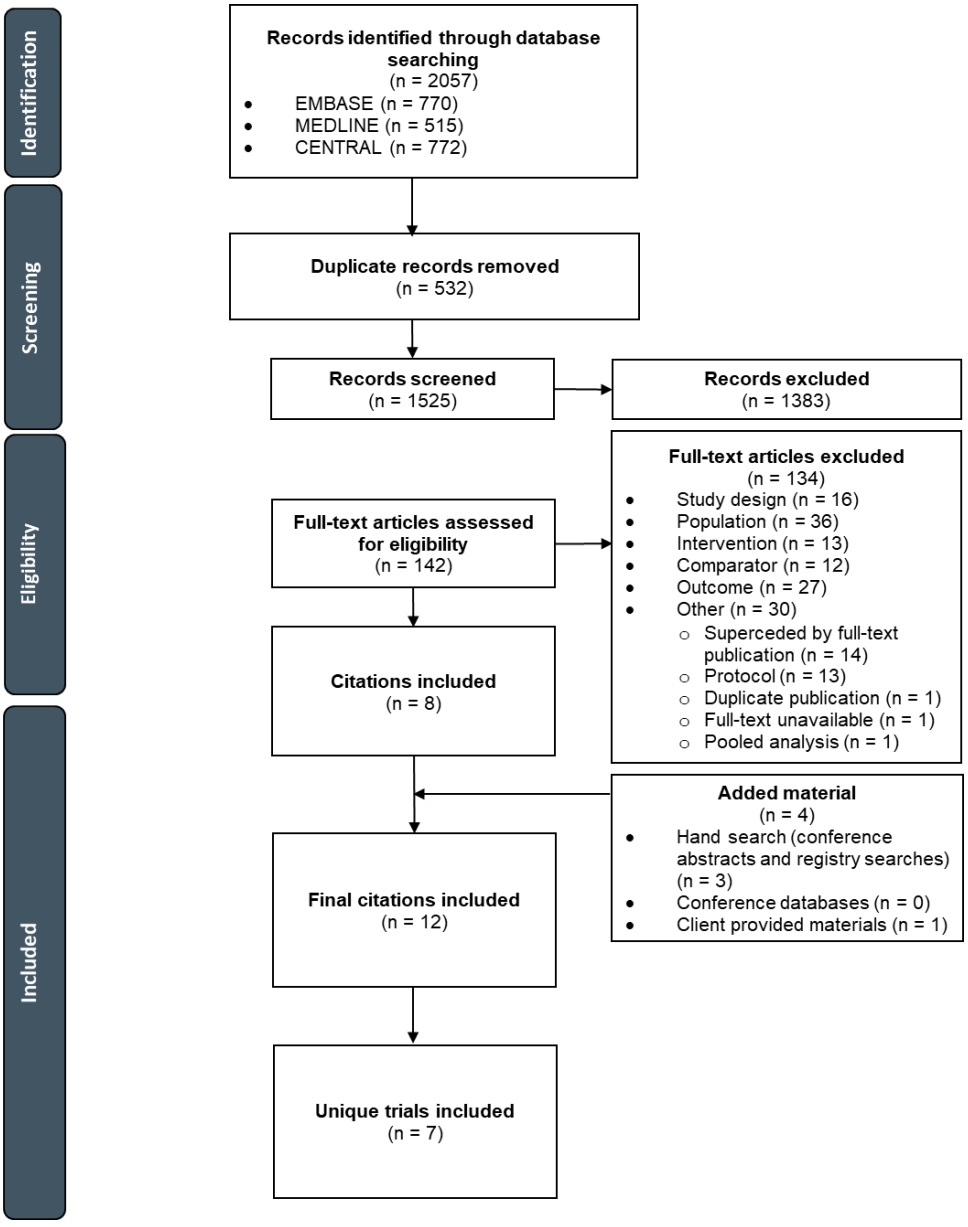
The PROCEED trial (KCSG BR 11-01) enrolled patients with HER2-negative metastatic breast cancer. While subgroup results for patients with TNBC were reported for overall survival and progression-free survival in Park et al. 2019, these outcomes were not of interest to the SLR on HRQoL, and subgroup results for these patients were not reported for HRQoL measurements. Thus, this trial was excluded from the SLR of HRQoL studies.

c. **Table 8 of the Appendix lists 30 studies excluded for 'other' reasons. It is unclear what those reasons are. Please provide a detailed breakdown.**

The PRISMA diagram has been updated (**Error! Reference source not found.**) and excluded publications table of the SLR of clinical evidence to include specific reasons for exclusion with "Other." Fourteen citations were excluded because full-

text publications superseded them, 13 citations were excluded because they were study protocols, one citation was excluded as a duplicate, one citation was excluded because the full-text was unavailable, and one citation was excluded because it was a pooled analysis and not of interest to the SLR of clinical evidence.

Figure 1: Updated PRISMA diagram



d. Several phase III trials were excluded based on 'inappropriate study design'. However Table 4 of the appendix lists phase III studies as eligible, e.g. Impassion130 Trial or NCT01287624. Please explain.

Additional notes are provided in Table 26 (appendix), for those references excluded due to ‘study design’ reasons such as non-randomized study design or prognostic/predictive/genomic/correlative study design.

A6. Please provide further details on how the data extraction and quality assessment processes were carried out, e.g.

a. How many reviewers were involved at each stage and how were discrepancies resolved?

Two reviewers, working independently, extracted data and performed the quality assessment. Following reconciliation between the two reviewers, a third reviewer was included to reach a consensus for any remaining discrepancies.

b. Please provide a detailed breakdown for all signalling questions for the risk of bias (ROB)-2 tool.

Please see below a table showing a detailed breakdown of all signalling questions for the risk of bias (ROB)-2 tool.

Trial ID	1.1	1.2	1.3	2.1	2.2	2.3	2.4	2.5	2.6	2.7	3.1	3.2	3.3	3.4	4.1	4.2	4.3	4.4	4.5	5.1	5.2	5.3
ETNA	Y	PY	PN	Y	Y	PN	NA	NA	Y	NA	Y	NA	NA	NA	PN	PN	Y	PN	NA	Y	PN	PN
GeparSepto	Y	PY	N	Y	Y	PN	NA	NA	Y	NA	Y	NA	NA	NA	PN	PN	N	NA	NA	Y	PN	PN
IMpassion031	Y	PY	PN	N	NI	N	NA	NA	Y	NA	Y	NA	NA	NA	PN	PN	N	NA	NA	Y	PN	PN
KEYNOTE-522	Y	PY	N	N	N	NA	NA	NA	Y	NA	Y	NA	NA	NA	PN	PN	N	NA	NA	Y	PN	PN
NATT	Y	NI	N	Y	Y	N	NA	NA	Y	NA	Y	NA	NA	NA	NI	PN	Y	PN	NA	Y	PN	PN
NCI 10013	Y	NI	NI	Y	Y	PN	NA	NA	Y	NA	Y	NA	NA	NA	NI	PN	Y	PN	NA	PY	PN	PN

Trial

A7. Priority question. The CS states that the KEYNOTE-522 trial recruited [redacted] participants from six United Kingdom (UK) study sites.

a. **Please discuss the generalisability of the study baseline demographic and disease characteristics to the clinical practice population in England and Wales.**

While there is little published data on the demographics of UK patients with early stage triple negative breast cancer, we have not identified any characteristics of subjects in the trial that are not generalisable to patients in the UK.

A study on patients in the North East London Cancer Network with TNBC (any stage) between 2005 and 2007, reported 82.8% were 69 years and under [3]. The proportion of patients under the age of 65 in KEYNOTE-522 was slightly higher, 88.8%, but this is to be expected as the trial recruited only patients with early-stage non-metastatic disease. Jack et al (2013) reported just over one in five patients were within the black ethnicity group, which is in line with the UK KEYNOTE-522 participants. Stage at diagnosis for breast cancer data, published by the National Disease Registration Service (NDRS), is reported for all subtypes combined in England [4]. Of the 19,633 patients diagnosed with stage II and III breast cancers, 81.4% were the former, which is in line with KEYNOTE-522 ITT population and UK, 75.0%. and 80.0%, respectively. No major differences are noted between the key baseline demographic and disease characteristics in the UK versus KEYNOTE-522 ITT population, therefore we consider that the trial population is generalisable to that of UK patients.

b. **Please provide the baseline characteristics of these patients by study arm, if possible, in comparison with the trial intention-to-treat (ITT) population's baseline characteristics.**

Table 1: Baseline characteristics of UK participants

	Pembrolizumab + chemotherapy/ Pembrolizumab		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	*****	*****	*****	*****	*****	*****

Sex [redacted]						
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (Years) [redacted]						
< 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>= 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race [redacted]						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black Or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity [redacted]						
Not Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region [redacted]						
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS [redacted]						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Lactate Dehydrogenase (LDH)						
<=ULN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> ULN	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Menopausal Status [redacted]						
Pre-menopausal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-menopausal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Choice of Carboplatin (Actual) [redacted]						
Q3W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weekly	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Choice of Carboplatin (Planned) [redacted]						
Carboplatin (Cb) Q3W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin (Cb) Weekly	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary Tumor (Actual) [redacted]						
T1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary Tumor (Planned) [redacted]						
Tumor Size T1/T2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tumor Size T3/T4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nodal Involvement (Actual)						
N0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
N2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nodal Involvement (Planned) [redacted]						
Nodal Status Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Nodal Status Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastases [redacted]						
M0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall Stage [redacted]						
Stage II	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stage III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS 1 Cutoff [redacted]						
PD-L1 CPS >= 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS < 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS 10 Cutoff [redacted]						
PD-L1 CPS >= 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS < 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS 20 Cutoff [redacted]						
PD-L1 CPS >= 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS < 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HER2 Status						
0-1+ by IHC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2+ by IHC (but FISH-)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Database Cutoff Date: 23MAR2021						

c. **Please discuss the representativeness of the control arm to England and Wales and if the trial comparator is consistent with clinical practice.**

Clinical experts have informed MSD the treatments used in KEYNOTE-522 reflects the current standard of care for neoadjuvant and adjuvant treatment of TNBC where both phases are used. The NICE guidelines for early and locally advanced breast cancer (NG101) recommend “people with triple-negative invasive breast cancer, consider a neoadjuvant chemotherapy regimen that contains both a platinum and an anthracycline”. [5]. Local NHS cancer guidelines list carboplatin + paclitaxel followed by doxorubicin/epirubicin plus cyclophosamide (or order of chemotherapies is switched) for neoadjuvant treatment of TNBC patients [6-8].

d. **Results by breast cancer gene (BRCA1) mutation are missing. Please clarify whether patients would be offered pembrolizumab regardless of the BRCA mutation.**

Determination of BRCA status was not required for KEYNOTE-522. Of the 54 (4.6%) participants with a BRCA1/2 mutation detected, 40 participants were in the pembrolizumab + NAC / pembrolizumab group and 14 participants were in the placebo + NAC / placebo group (as a reminder, randomisation ratio was 2:1). The

number of participants with known BRCA status is too small to provide a meaningful assessment for pCR, EFS, or OS.

Patients received pembrolizumab regardless of BRCA mutation results in KEYNOTE-522.

A8. Priority question. Subgroup analyses results indicate some potential differences between geographical regions and Eastern Co-operative Oncology Group (ECOG) statuses.

a. Please provide all results sub-grouped for 1) Europe versus rest of world and 2) UK versus rest of world.

Results for event free survival for Europe and the Rest of the World are provided in Table 2. It should be noted that KEYNOTE-522 was not powered to find differences between these groups.

Table 2: Event Free Survival for geographical subgroups

	Pembrolizumab + chemotherapy / Pembrolizumab			Placebo + chemotherapy / Placebo			Pembrolizumab + chemotherapy / Pembrolizumab vs. Placebo + chemotherapy / Placebo
	N[b]	Subjects with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Subjects with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]
Geographic Location							
Europe[e]	*****	*****	*****	*****	*****	*****	*****
Rest of World	*****	*****	*****	*****	*****	*****	*****

Database Cutoff Date: 23MAR2021
b: Number of subjects: intention-to-treat population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
e: Europe is defined as: France, Germany, Ireland, Italy, Poland, Portugal, Russia, Spain, Sweden, Turkey and the United Kingdom

b. As per Figure 6 of the CS, higher percentage of patients in the placebo–chemotherapy group with ECOG status 1 achieved pathological complete response (pCR) compared with pembrolizumab–chemotherapy (67.3% vs 60.3%). Please discuss any implications for the clinical decision making.

A comparison of baseline characteristics Table 3 for all participants in KEYNOTE-522 with an ECOG PS of 1 demonstrated that, compared with the placebo + NAC / placebo group, participants in the pembrolizumab + NAC / pembrolizumab subgroup were older (median age of 53.5 years vs 47.0 years) and included greater proportions (≥5 percentage points) of the following parameters: participants who were post-menopausal, participants with PD-L1 positive tumors (CPS cutoff of 10), and participants with a primary tumor size of T3/T4, respectively.

A comparison of baseline characteristics for all participants in KEYNOTE-522 treated with pembrolizumab + NAC / pembrolizumab demonstrated that, compared with the ECOG PS of 0 subgroup, participants with an ECOG PS of 1 were older (median age of 53.5 years vs 48.5 years) and included higher proportions (≥5 percentage points) of the following participants aged 65 or older, participants who were post-menopausal, participants treated with Q3Weekly carboplatin, participants with a primary tumor size T3/T4, participants with a nodal status of positive, and overall disease stage III (Table 4).

As noted above, there were differences observed in baseline characteristics between treatment groups for participants with an ECOG PS of 1 (n=155), including menopausal status, primary tumor size, and PD-L1 expression (CPS cutoff of 10). These differences may have had an impact on the efficacy results. Therefore, ad-hoc exploratory analyses of EFS and OS adjusting for these baseline factors were performed. A Cox regression model with covariates of treatment, and baseline factors of menopausal status, primary tumor size, and a PD-L1 CPS cutoff of 10 were conducted. The EFS HR (95% CI) was [redacted] and the OS HR (95% CI) was [redacted]), respectively. Ad-hoc exploratory analyses of pCR using logistic regression with and without adjusting for baseline factors mentioned above were performed. The odds ratios (95% CI) were [redacted]) and 0[redacted] for with and without adjusting for baseline, respectively.

It should also be noted that the number of patients with ECOG PS of 1 is relatively small (106 participants in pembrolizumab + NAC / pembrolizumab group and 49 participants in placebo + NAC / placebo group) and the study was not powered to detect statistically significant differences across subgroups, therefore, caution should

be taken in interpreting efficacy differences between these two groups and clinical decision making should not be impacted by these results.

Table 3: Participant characteristics with ECOG=1

	Pembrolizumab + NAC / pembrolizumab	Percentage	Placebo + NAC / Placebo	Percentage
Participants with ECOG = 1	106		49	
Age				
Median age (range)	[redacted]		[redacted]	
<65	[redacted]	[redacted]	[redacted]	[redacted]
>=65	[redacted]	[redacted]	[redacted]	[redacted]
Race				
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Black of 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				
North America	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]
Australia	[redacted]	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Lactate Dehydrogenase (LDH)				
<=ULN	[redacted]	[redacted]	[redacted]	[redacted]
>ULN	[redacted]	[redacted]	[redacted]	[redacted]
Menopausal status				
Pre-menopausal	[redacted]	[redacted]	[redacted]	[redacted]
Post-menopausal	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Choice of carboplatin (Actual)				
Q3W	[redacted]	[redacted]	[redacted]	[redacted]

Weekly	[redacted]	[redacted]	[redacted]	[redacted]
Primary Tumour (Planned)				
Tumour size T1/T2	[redacted]	[redacted]	[redacted]	[redacted]
Tumour size T3/T4	[redacted]	[redacted]	[redacted]	[redacted]
Nodal Involvement (Planned)				
Nodal status positive	[redacted]	[redacted]	[redacted]	[redacted]
Nodal status negative	[redacted]	[redacted]	[redacted]	[redacted]
Overall stage				
Stage II	[redacted]	[redacted]	[redacted]	[redacted]
Stage III	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS 10 Cutoff				
PD-L1 CPS ≥10	[redacted]	[redacted]	[redacted]	[redacted]
PS-L1 CPS <10	[redacted]	[redacted]	[redacted]	[redacted]
Database cutoff 23 March 2021				

Table 4: Participant characteristics who received pembrolizumab by ECOG status

	ECOG 0	Percentage	ECOG 1	Percentage
In pembro + NAC/pembro arm	678		106	
Age				
Median age (range)	[redacted]		[redacted]	
<65	[redacted]	[redacted]	[redacted]	[redacted]
>=65	[redacted]	[redacted]	[redacted]	[redacted]
Race				
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Black of African American	[redacted]	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[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				
North America	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]
Australia	[redacted]	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Lactate Dehydrogenase (LDH)				
<=ULN	[redacted]	[redacted]	[redacted]	[redacted]
>ULN	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Menopausal status				
Pre-menopausal	[redacted]	[redacted]	[redacted]	[redacted]
Post-menopausal	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Choice of carboplatin (Actual)				
Q3W	[redacted]	[redacted]	[redacted]	[redacted]
Weekly	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Primary Tumour (Planned)				
Tumour size T1/T2	[redacted]	[redacted]	[redacted]	[redacted]
Tumour size T3/T4	[redacted]	[redacted]	[redacted]	[redacted]
Nodal Involvement (Planned)				
Nodal status positive	[redacted]	[redacted]	[redacted]	[redacted]
Nodal status negative	[redacted]	[redacted]	[redacted]	[redacted]
Overall stage				
Stage II	[redacted]	[redacted]	[redacted]	[redacted]
Stage III	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS 10 Cutoff				
PD-L1 CPS ≥10	[redacted]	[redacted]	[redacted]	[redacted]
PS-L1 CPS <10	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]

Database cutoff 23 March 2021

c. **Please provide separate results by treatment arm for patients with ECOG = 0 and for those with ECOG = 1.**

Please see response to A8b. As noted above these results should be interpreted with caution. Figures 6 and 7 in the company submission are forest plots for pCR and EFS, respectively, which show results for patients ECOG with 0 and 1 status.

A9. Priority question. In the KEYNOTE-522 trial only a proportion of randomised patients proceed to adjuvant therapy.

a. **Please explain why only a proportion of randomised patients proceed to adjuvant therapy? Is this determined by performance of surgery; i.e. only those patients who undergo surgery proceed to adjuvant therapy?**

About 98% of patients in both treatment arms underwent surgery; therefore, performance of surgery did not differentially impact start of adjuvant therapy. The primary reason for which randomized patients in either treatment arm did not proceed to adjuvant therapy was discontinuation due to adverse events Table 5). The higher incidence of discontinuation in the neoadjuvant phase in the pembrolizumab + NAC group was driven primarily by a higher discontinuation rate due to adverse events (14.3%) compared with the placebo + NAC group (5.1%) (Table 5). Per protocol, if a participant discontinued either pembrolizumab or placebo during the neoadjuvant phase due to toxicity related to pembrolizumab/placebo, the participant was not permitted to receive it in the adjuvant phase of the study. For all other reasons for discontinuation, proportions were similar between groups (Table 5).

Despite fewer participants starting adjuvant treatment, KEYNOTE-522 demonstrated that the complete regimen of pembrolizumab + NAC followed by pembrolizumab monotherapy after surgery in the adjuvant phase resulted in a statistically significant and clinically meaningful improvement in both pCR and EFS in the ITT population.

Table 5: Reasons for discontinuation from all treatments for participants who did not start adjuvant phase - All participants (ITT Population)

	Pembrolizumab + NAC / Pembrolizumab	Percentage	Placebo + NAC / Placebo	Percentage
Participants randomized	784		390	
Untreated participants	1	0.1%	1	0.3%
Treated participants	783	99.9%	389	99.7%
Participants who started adjuvant phase	588	75.0%	331	84.9%
Participants who did not start adjuvant phase	195	24.9%	58	14.9%
Discontinued in neoadjuvant phase	190	24.2%	58	14.9%
Adverse events	112	14.3%	20	5.1%
Clinical progression [a]	2	0.3%	3	0.8%
Physician decision	32	4.1%	15	3.8%
Progressive disease	8	1.0%	7	1.8%
Relapse/recurrence	7	0.9%	3	0.8%
Withdrawal by subject	29	3.7%	10	2.6%
Had surgery, but did not receive study medication	5	0.6%	0	0.0%
Still on treatment in neoadjuvant phase	0	0.0%	0	0.0%
Participants with surgery	768	98.0%	381	97.7%

Participants who did receive study medication but had surgery were included in subjects treated.
[a] Clinical progression" is disease progression determined by the Investigator. "Progressive disease" is disease progression determined by imaging using RECIST 1.1 criteria.
Database cutoff date: 23 March 2021

b. Please compare the proportion who receive surgery/adjuvant therapy in the trial to NHS clinical practice.

Publicly available data to ascertain the proportion of TNBC patients who receive surgery/adjuvant therapy is not available. Therefore, information from the most recent national report of the Scotland Breast Cancer Quality Performance Indicators (QPI) is used. QPI 11 states measure the percentage of 'Patients with invasive breast cancer who have a ≥5% overall survival benefit of chemotherapy treatment predicted at 10 years that undergo adjuvant chemotherapy'[9]. For patient diagnosed between January 2015 and December 2017 this proportion was 80%. However, the denominator for the QPI included patients with all subtypes of breast cancer, while it did not include those who had neoadjuvant therapy and did not include English hospitals.

c. Please discuss the implications of any difference.

The figure of 20% of patients in Scotland not receiving adjuvant chemotherapy is in between the figures seen in KEYNOTE-522 in the pembrolizumab and placebo arms for patients who did not start adjuvant therapy, 24.9% and 14.9%, respectively. The licensed indication includes pembrolizumab as a backbone immunotherapy agent across both the neoadjuvant and adjuvant study phase. Therefore, the data from KEYNOTE-522 data are reflective of the trial design itself and relevant for decision making. In the NHS practice, the proportion of patients not receiving adjuvant therapy could potentially be attributed to the patient choice itself alongside clinical reasons presented in the table above.

A10. Compared to the comparator arm, more than double the number of patients on the pembrolizumab arm discontinued study treatment in both the neoadjuvant phase and adjuvant phase of the KEYNOTE-522 trial.

a. Please detail and discuss study discontinuation due to adverse events (AEs).

As noted by the agency, in KEYNOTE-522, there was a higher incidence of participants who discontinued all treatment due to AEs in the pembrolizumab + NAC / pembrolizumab treatment group vs the placebo + NAC / placebo group during both the neoadjuvant (14.3% vs. 5.1%, respectively) and adjuvant (5.4% vs. 2.6%, respectively) phases. However, due to the relatively small numbers of participants in these subgroups, results need to be interpreted with caution.

Overall, treatment discontinuation rates in KEYNOTE-522 were consistent with the add-on study design of neoadjuvant and adjuvant pembrolizumab added to standard-of care NAC. The safety profile of pembrolizumab + NAC / pembrolizumab were attributable to the safety profiles of the individual treatment components, namely NAC and pembrolizumab. Addition of pembrolizumab did not negatively impact the administration of NAC and no new safety concerns were identified for treatment with pembrolizumab + NAC / pembrolizumab.

In the neoadjuvant phase, the higher incidence of AEs resulting in discontinuation in the pembrolizumab + NAC treatment group compared with the placebo + NAC group (14.3% vs. 5.1%, respectively) were primarily driven by events occurring in <1% of participants. Only 3 AEs leading to discontinuation in the pembrolizumab + NAC

treatment group occurred at an incidence ≥1% (ALT increased [2.0%], AST increased [1.3%], and febrile neutropenia [1.0%]).

In the adjuvant phase, the slightly higher incidence of AEs resulting in discontinuation in the pembrolizumab + NAC / pembrolizumab treatment group compared with the placebo + NAC / placebo group (5.4% vs. 2.6%, respectively) were again primarily driven by events occurring in <1% of participants. No AE leading to discontinuation in the pembrolizumab + NAC / pembrolizumab treatment group occurred at an incidence ≥1%.

In summary, although the incidence of study treatment discontinuation due to an AE was higher in the pembrolizumab +NAC / pembrolizumab group compared with the placebo + NAC / placebo group in both the neoadjuvant and adjuvant phases, there were no specific trends noted in the pembrolizumab +NAC / pembrolizumab group that suggested any new safety concerns.

b. Please discuss the criteria used to characterise a “clinically important protocol deviation”.

There was a standard process to determine what protocol deviations are clinically important. Clinically important protocol deviations are those that may compromise critical data analyses, especially those pertaining to (1) primary efficacy and/or primary safety endpoints, or (2) the participant’s safety. These are evaluated by the clinical team with consultation from other functional areas as necessary.

c. Please clarify if the greater number of protocol deviations with study intervention observed on the pembrolizumab arm was due to AEs.

The protocol deviations mentioned here are not due to AEs. Information on protocol deviations in the pembrolizumab and placebo arms can be found in Table 10-2 Summary of Important Protocol Deviations Considered to be Clinically Important All Participants (ITT Population) in the Clinical Study Report (provided as part of the company submission). Eleven patients and one in the pembrolizumab and placebo arm, respectively, had a Study Intervention deviation. Protocol deviations in the Study Intervention category are defined as when “Participant was dispensed study intervention other than what was assigned in the allocation schedule, i.e. incorrect medication or potential cross-treatment”. This definition does not include AEs.

d. Please clarify if cross treatment was introduced in the KEYNOTE-522 trial as a protocol deviation.

Universal unblinding upon disease progression/recurrence and cross treatment on study (for example, a subject in the placebo + NAC / placebo group was switched to the pembro + NAC / pembro group after disease progression/recurrence) was not allowed per protocol; however, off-study treatment with an immune-oncology agent after discontinuation of study treatment due to disease progression/recurrence was at physician's discretion. If this occurred, it was not considered to be a clinically important protocol deviation.

A11. Please provide more details on the processes used to implement randomisation and allocation concealment in the KEYNOTE-522 trial. Please clarify whether the pathologists interpreting surgical specimens for assessment of pCR were blinded.

Treatment allocation/randomisation occurred centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). Subjects were assigned randomly in a 2:1 ratio to pembrolizumab and placebo, respectively, after stratification. The choice of QW carboplatin or Q3W carboplatin should have been determined prior to randomisation, and carboplatin schedule was a stratification factor.

All pathologists reviewing and interpreting surgical specimens for assessment of pCR were required to be blinded to treatment assignment

A12. The comparator treatment in the adjuvant phase did not include an active treatment, and only placebo was given. The rationale given for this is that this reflects current UK practice, where no active treatments are given after definitive surgery. However, it is also stated that recent evidence (that came to light after initiation of KEYNOTE-522) has shown that capecitabine in the adjuvant phase may improve disease survival and recurrence-free survival.

a. Please explain how including capecitabine as an active comparator in the adjuvant phase might have changed findings in the trial (the intervention would have been capecitabine + pembrolizumab).

In 2017, as a result of data from the CREATE-X study (N=910), the NCCN guidelines were updated to include adjuvant capecitabine as an option for patients with TNBC

who do not achieve pCR after neoadjuvant chemotherapy [10]. Following discussions with the US FDA who discouraged inclusion of adjuvant capecitabine, MSD decided not to allow adjuvant capecitabine in the KEYNOTE-522 so as not to confound the final results; however, an amendment was instituted to preserve the power of the study by adjusting the control EFS rate and drop-out rate after surgery to account for the potential impact of off study use of adjuvant capecitabine.

Optional use of adjuvant capecitabine in patients who do not achieve pCR after neoadjuvant therapy may confound the EFS endpoint, due to the potential for imbalanced capecitabine use between the two treatment arms. In the control arm, more patients are expected to not achieve pCR, and thus opt for adjuvant capecitabine. In this case, depending on the number of patients who receive adjuvant capecitabine in the control arm, the control EFS rate for patients with poor prognosis may increase to a maximum of about 74%, as observed in the CREATE-X study, thus confounding the EFS results.

b. Please explain how this might be accounted for in any sensitivity analyses.

Off-study adjuvant capecitabine use in KEYNOTE-522 was balanced between the 2 treatments, with 31 (4.0%) participants and 13 (3.3%) participants who received adjuvant capecitabine in the pembrolizumab + NAC / pembrolizumab group and the placebo + NAC / placebo group, respectively. As note, the randomization ratio was 2 to 1.

Prespecified sensitivity analysis 1 considered the impact of post-surgery new anticancer therapy, for example, the use of adjuvant capecitabine. Sensitivity analysis 1 was the same as the primary analysis, except that any events after 2 consecutive missed disease assessments or after initiation of post-surgery new anticancer therapy, were censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessments and initiation of post-surgery new anticancer therapy, and if no events before new anticancer therapy, participants were censored at last disease assessment before initiation of post-surgery new anticancer treatment. The EFS HR in sensitivity analysis 1 was 0.64 (95% CI: 0.48, 0.84) see Table 6. The treatment effect of pembrolizumab + NAC / pembrolizumab on EFS in this sensitivity analysis was consistent with the primary analysis with HR of 0.63 (95% CI: 0.48, 0.82).

Table 6: Analysis of Event-Free Survival (EFS) (Sensitivity Analysis) ITT

	Pembrolizumab + chemotherapy / Pembrolizumab (N=784)	Placebo + chemotherapy / Placebo (N=390)	Total (N=1174)
Number of Events (%)	112 (14.3)	84 (21.5)	196 (16.7)
Number of Censored (%)	672 (85.7)	306 (78.5)	978 (83.3)
Kaplan-Meier Estimates (Months)[a]			
Median (95% CI)	[redacted]	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]	[redacted]
Person-Months	[redacted]	[redacted]	[redacted]
Event Rate / 100 Person-Months	[redacted]	[redacted]	[redacted]
EFS Rate at 6 Months (%) (95% CI)	[redacted]	[redacted]	[redacted]
EFS Rate at 12 Months (%) (95% CI)	[redacted]	[redacted]	[redacted]
EFS Rate at 18 Months (%) (95% CI)	[redacted]	[redacted]	[redacted]
EFS Rate at 24 Months (%) (95% CI)	[redacted]	[redacted]	[redacted]
EFS Rate at 30 Months (%) (95% CI)	[redacted]	[redacted]	[redacted]
EFS Rate at 36 Months (%) (95% CI)	[redacted]	[redacted]	[redacted]
EFS Rate at 42 Months (%) (95% CI)	[redacted]	[redacted]	[redacted]
vs Placebo + chemotherapy / Placebo			
Hazard Ratio (95% CI)[b]	[redacted]		
p-value[c]	[redacted]		

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Cb) (Q3W vs. Weekly).
[c] One-sided p-value based on log-rank test stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4) and choice of carboplatin (Cb) (Q3W vs. Weekly).
Database Cutoff Date: 23MAR2021

A13. The KEYNOTE-522 trial protocol stated that "all treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator".

a. Please discuss the protocol-specified concomitant medications

Supportive care for the chemotherapeutic agents administered in KEYNOTE-522 could be found in the local product label for each agent. Corticosteroids (such as prednisone), insulin replacement therapy, hormonal replacements, beta blockers,

thyroid replacement hormones and other medications were included in the toxicity management guidelines of immune related adverse events.

b. Please discuss if non-protocol specified concomitant medications were used during the trial.

As detailed in B.2.3 of the company submission the protocol specific prohibited concomitant medications. Glucocorticoids were administered to some patients, but in line with the protocol to manage immune-related adverse events, as a pre-medication for chemotherapy or for the management of asthma. *****.

c. Please supply a table of the most frequently used concomitant medications during the trial, by arm.

Please see Table 25 in the appendices for this information (incidence of ≥ 5% % in One or More Treatment Groups).

A14. The CS stated that the definition for the primary outcome of pCR is ypT0/Tis ypN0 (p17). On page 14 of the CS this is defined as absence of invasive cancer in the breast. However, it is also stated on the same page that other commonly used definitions of pCR are ypT0/Tis (absence of invasive cancer in the breast) and ypT0 ypN0 (absence of invasive and in situ cancer in the breast and axillary nodes)

a. Please clarify the definition for the primary outcome pCR.

The definition for the primary outcome of pCR is ypT0/Tis yp N0, meaning the absence of invasive cancer in the breast or all resected lymph nodes. Non-invasive breast residuals were allowed.

b. Please discuss why the definition indicative of more complete recovery (absence of invasive and in situ cancer in the breast and axillary nodes) was not used as the primary outcome pCR.

FDA guidance recognises ypT0/Tis ypN0 as an acceptable definition of pCR, and so that was selected as the definition used for pCR as the primary outcome. The alternative definition, ypT0 ypN0, was used as the definition for the secondary outcome analysis.

A15. The CS provides details of the numbers of participants in KEYNOTE-522 with stage 1, 2 and stage 3 disease, but not the four detailed TNM gradings mentioned in the inclusion criteria (p19 of the CS): T1c, N1-N2; T2, N0-N2; T3, N0-N2; and T4a-d, N0-N2.

a. Please provide more details on the numbers with TNM stages T1c, N1-N2; T2, N0-N2; T3, N0-N2; and T4a-d, N0-N2.

Table 7: Additional participant characteristics (ITT)

	Pembrolizumab + chemotherapy / Pembrolizumab		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	784		390		1,174	
Tumor Stage and Nodal Involvement Grading						
T1b, N1	[redacted]		[redacted]		[redacted]	
T1c, N1-N2	[redacted]		[redacted]		[redacted]	
T1c, N3	[redacted]		[redacted]		[redacted]	
T2, N0-N2	[redacted]		[redacted]		[redacted]	
T2, N3	[redacted]		[redacted]		[redacted]	
T3, N0-N2	[redacted]		[redacted]		[redacted]	
T4, N0-N2	[redacted]		[redacted]		[redacted]	
T4a-d, N0-N2	[redacted]		[redacted]		[redacted]	

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The one patient with Stage I disease was considered a protocol deviation, as the inclusion criteria only allowed enrollment of patients with Stage II or III disease

b. Please provide TNM grading data on the UK population of patients with triple negative breast cancer, to allow evaluation of whether the proportions of participants at different stages in the trial are similar to those in the UK population.

Data for TNM grading for TNBC patients is not available from publicly available data. Information published by the cancer registry is reported as stage 1, 2, 3 and 4.

A16. Main results are given for IA4, which were collected in March 2021. According to the CS, the next database cut off (IA5) will take place in [redacted].

Please confirm when data from IA5 can be made available.

As dual-primary endpoints pCR (at IA1) and EFS (at IA4) achieved statistical significance, the study continues to follow OS in a blinded manner. Per the protocol, the next interim analysis (IA5) will occur ~60 months after the first participant was randomized, 1 year after IA4. If OS achieves statistical significance, the external

DMC will inform MSD and updated efficacy results may be available in *****. If OS doesn't achieve statistical significance, the study will continue in a blinded manner.

A17. For the comparator treatment in the second part of the neoadjuvant phase, a choice is made between doxorubicin and epirubicin.

a. Please explain why this choice was made, who in the study was responsible for making the choice, and upon which criteria the choice was made.

Doxorubicin and epirubicin are commonly used neoadjuvant anthracycline regimens for TNBC. The choice of treatment was made by the investigator at the initiation of the second phase of neoadjuvant treatment and was largely dependent on local/ institutional guidance and guidelines.

b. Please provide a comparison with NHS clinical practice and the implications of any difference.

The combination of doxorubicin or epirubicin plus cyclophosamide is available in NHS clinical practice [7, 8].

c. Please provide a sub-group analysis of results by doxorubicin / epirubicin use.

Results for event free survival for chemotherapy received in the neoadjuvant phaser are provided in Table 8. It should be noted that KEYNOTE-522 was not powered to find differences between these groups.

Table 8: Event free survival for chemotherapy received in neoadjuvant phase

	Pembrolizumab + chemotherapy / Pembrolizumab			Placebo + chemotherapy / Placebo			Pembrolizumab + chemotherapy / Pembrolizumab vs. Placebo + chemotherapy / Placebo
	N[b]	Subjects with Event n (%)	Median Time[c] in Months [95 %-CI]	N[b]	Subjects with Event n (%)	Median Time[c] in Months [95 %-CI]	Hazard Ratio [95 %-CI][d]
Actual Chemotherapy Group							
Doxorubicin	488	*****	*****	247	*****	*****	*****
Epirubicin	238	*****	*****	122	*****	*****	*****

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b: Number of subjects: intention-to-treat population
c: From product-limit (Kaplan-Meier) method for censored data
d: Based on Cox regression model with treatment as a covariate using Wald confidence interval
Only participants who received at least one dose of doxorubicin or epirubicin as part of the neoadjuvant therapy are included in the subgroup analysis of actual chemotherapy group

A18. The short duration of follow-up precludes the assessment of mature survival data and the long-term safety profile. Please discuss these limitations and consequences for clinical decision making.

At IA4 with median follow up at IA4 was over three years (39.1 months) [11], the EFS HR of 0.63 (95% CI: 0.48, 0.82), with a one-sided *p*-value of 0.0003093 that crossed the prespecified boundary for statistical significance (0.00516941), represents a 37% reduction in the risk of disease progression precluding definitive surgery, recurrence, second primary malignancy, or death compared with placebo + NAC / placebo [11]. The information fraction of EFS was approximately 66% [216 of the 327 events needed for the final analysis. As note, EFS is an endpoint listed on the FDA surrogate table for breast cancer [12].

By the time of the IA4 Last Patient Last Visit (LPLV) there had been one year since the last exposure which occurred on 11th February 2020.

Clinical experts advised MSD the pCR and EFS outcomes from KEYNOTE-522 were good and acknowledged they hoped to use the pembrolizumab combination in the future based upon the trial results [13]. They also suggested that OS events are driven by a reduction in distant recurrences, which equates to a survival benefit in the TNBC setting based on the reduction in distant recurrences observed to date with pembrolizumab in KEYNOTE-522 and therefore, an OS benefit is expected in future analyses [13].

A19. Section 10.2 of the KEYNOTE-522 CSR states that “Protocol deviations (important and not important) associated with COVID-19 were reported for 285 participants.”

a. Please explain how ‘important’ and ‘not important’ protocol deviations were classified.

Protocol deviations were classified as ‘“important or ‘not important’ by a standard method assessing the potential impact of the protocol deviation on endpoints and safety.”

b. Please discuss how COVID-19 may have affected the KEYNOTE-522 trial.

Part of KEYNOTE-522 was conducted during the COVID-19 pandemic. MSD continued to follow its Standard Operating Procedures (SOPs) for study conduct, monitoring, and oversight during the pandemic. Exceptions and deviations from SOPs were documented. Study sites were advised to follow local and national guidance regarding the pandemic and to share any mitigation plans for study participant management with the Institutional Review Board/Ethics Review Committee and the sponsor. Study sites were also advised to remain in contact with study participants to monitor for safety concerns and to keep participants informed of changes to the study and other study activities.

There were no changes in the planned analyses of the study due to the COVID-19 pandemic.

A20. Section 10.1.2 of the KEYNOTE-522 CSR states that, "[redacted]" Please discuss the potential effects of premature unblinding during the trial on outcomes measurement.

*****Sponsor-approved non-emergency unblinding requests for participants who had disease progression / recurrence, knowing their study treatment would guide future treatment plans *****Inadvertent unblinding of investigator site and/or Sponsor personnel *****Emergency unblinding *****

A summary of participants with or without an EFS event for participants with premature unblinding is provided in Table 9. ***** out of ***** participants with premature unblinding already had an EFS event occurred on or prior to the date of unblinding, therefore, unblinding had no impact on the EFS data of those participants. The number of participants with premature unblinding either with an EFS event occurred after the date of unblinding, or without EFS event occurred is small *****) and generally consistent between the pembrolizumab + NAC / pembrolizumab group and the placebo + NAC / placebo group. There is no evidence to show the premature unblinding of participants without an EFS event at the time of unblinding had an impact on interpretation of the EFS results.

Table 9: Summary of participants with or without an EFS event. All participants with premature unblinding

	Pembrolizumab + chemotherapy / Pembrolizumab		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)

Participants in population	784		390		1,174	
Scenarios						
An EFS event occurred on or prior to the date of unblinding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
An EFS event occurred after the date of unblinding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No EFS event occurred	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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A21. The KEYNOTE-522 study inclusion criteria specified that patients would have "ECOG performance status of 0 or 1 performed within 10 days of treatment initiation." Please confirm if patients with previously untreated locally advanced, nonmetastatic triple-negative breast cancer in real-world practice with an ECOG PS ≥2 would not be expected to receive Pembrolizumab. If so, please provide supporting documents for UK clinical practice.

In previous approvals of immunotherapies in oncology a criterion is included on Blueteq forms for only patients who have an ECOG PS of 0 or 1, for example PEMB1 on the baseline funded drugs list [14].

Indirect treatment comparison

A22. According to Section B.2.9 of the CS, "clinical expert advice sought confirmed that the KEYNOTE-522 study design and choice of comparators is appropriate and generalisable of the treatment pathway in the UK setting".

Please provide supporting references and please provide a report describing the clinical expert advice solicitation.

The report from the advisory board is provided as a separate confidential reference for consideration.

Section B: Clarification on cost-effectiveness data

Patient population

B1. The patient population included in the economic evaluation consisted of adults with locally advanced inflammatory, or early stage triple negative breast cancer at high risk of recurrence. Please clarify how the company determined the high risk of

recurrence. The NICE final scope does not exclude patients with low risk of recurrence.[1]

Please see the explanation provided in response to question A4.

Intervention technology and comparators

B2. For adjuvant treatment after surgery, NG101 recommends offering a regimen that contains both a taxane and an anthracycline. Although the CS does elaborate on why capecitabine is not included, there is no justification for the exclusion of taxanes and anthracyclines.[2] Please justify the comparison to only placebo instead of taxane and an anthracycline as adjuvant treatment.

A taxane and anthracycline regimen for the treatment of early-stage breast cancer is generally given either before or after surgery with curative intent, but not both before and after surgery as neoadjuvant and adjuvant chemotherapy treatment, respectively. For chemotherapy, neoadjuvant vs adjuvant administration of a taxane and anthracycline regimen is considered equivalent in terms of distant recurrence, breast cancer mortality or death from any cause for breast cancer patients [15]. The adjuvant guidelines within NG101 do not make a recommendation of what a clinician should do if a patient has already received a taxane and anthracycline in the neoadjuvant setting. As mentioned above and per common clinical practice, such a patient would not be also treated with the same adjuvant chemotherapy regimen. Furthermore, use of anthracycline is limited by a maximum exposure dose due to cardiotoxicity and adjuvant administration of a neoadjuvant chemotherapy regimen that did not result in a pathological complete response (pCR) is not recommended. A relevant clinical practice example comes from the HER2+ breast cancer space, as women who received a neoadjuvant anthracycline + taxane regimen are not treated with the same chemotherapy agents in the adjuvant setting; however, anti-HER2 treatment is given both before and after surgery independent of the surgical outcome (pCR vs not) [16].

UK Clinical experts have informed MSD that the treatments used in KEYNOTE-522 reflect the current standard of care for neoadjuvant and adjuvant treatment of TNBC where a taxane and anthracycline regimen given either before or after surgery with curative intent. From the perspective of the clinical evidence base, the early breast

cancer systematic literature review conducted to support this submission did not identify any relevant publications that explored the effectiveness and safety of adjuvant taxane and/or anthracycline after administration of a neoadjuvant chemotherapy regimen (see Appendix D1.2.1).

Since no relevant publications were retrieved, it was not possible to incorporate neoadjuvant chemotherapy followed by an anthracycline/taxane adjuvant treatment option via an indirect treatment comparison within the model.

Model structure

B3. PRIORITY QUESTION: The Markov model structure was based on a previous appraisal for pertuzumab for neoadjuvant treatment of HER2+ breast cancer patients. However, as described in Section B.3.2.2., "The model developed for this submission is simpler than TA424 and structured around the KEYNOTE-522 trial co-primary endpoint, EFS, which is representative of clinical disease progression over time (pCR not explicitly modelled)." This does not explain why remission of locoregional recurrence and differentiating between no progression and progressed metastatic disease is not relevant to this submission, as it concerns a comparable disease course. Assuming patients will remain in the locoregional recurrence state and cannot experience remission does not reflect clinical practice. Differentiating between not-progressed and progressed metastatic patients is essential to correctly reflect clinical disease progression and cost-effectiveness, since mortality, costs, and quality of life differ considerably between pre-progression and post-progression metastatic patients.

a. **Please justify why it is acceptable to leave out these two health states in the base case analysis.**

As a reminder, TA424 recommends the use of pertuzumab as a neoadjuvant therapy of HER2 positive breast cancer [17]. MSD consider that the EAG enquires about the following health states of "Remission" and "Distant metastasis progressed disease" which are included in the TA424 model but are not included in the model submitted as part of this submission. Please note that we are limited in the extent to which we can comment on another manufacturer's submission and this can only be based

upon available public materials. We would like to take the opportunity to comment on the model development process used to inform this submission and the key differences of the current model versus that of TA424. As stated in the submission section B.3.2.2, TA424 was used to inform in part the model development process. Due to less clinical data being available for metastatic TNBC setting (as opposed to HER2 positive breast cancer which has seen very radical changes in the treatment pathway over the last 10 years) we opted to develop a 4-state Markov model. However, the current model is able to accurately capture costs and outcomes of the disease evolution over time. We offer the justification for our model structure selection below.

TA424 model and patient propagation:

In TA424 the manufacturer developed a 6-state Markov model (including a death state) which is reflective of the disease evolution, data availability and trial design used to inform that submission. In brief, the following health states were included;

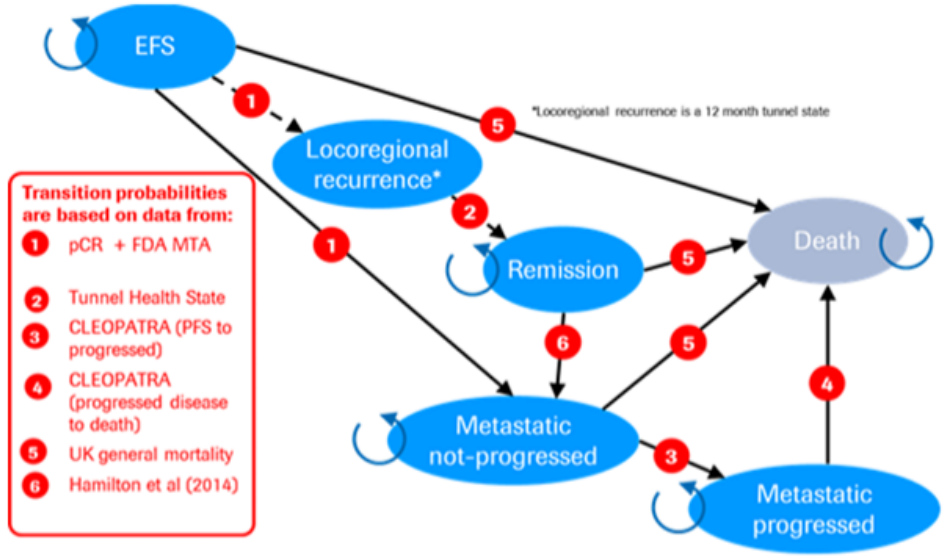
- Event Free health state; EFS
- Locoregional recurrence: LRR
- Remission state: REM
- Metastatic not-progressed: Met-no-prog (1st Line metastatic treatment)
- Metastatic progressed: Met-prog (2nd Line metastatic treatment)
- Death

A model schema from TA424 is included below (Figure 2). As noted within the TA424 documents, the model captures two distinct pathways: locoregional disease; and metastatic disease.

Patients enter at EFS and can experience a worsening condition which results in them transitioning from EFS→LRR, EFS→Met-no-prog or EFS→Death. The manufacturer also states that the LRR state is modelled using a series of tunnel states (N.B. A 12 month tunnel states as stated in page 249 of submission documents versus schema below which states a 12 month tunnel state although this

does not have any major implications). Patients could not transition to Death from LRR during this 12 month period (see ERG report page 82). Once in LRR, patients could experience 12 months of further treatment with pertuzumab as adjuvant therapy and accrue relevant costs and QALYs (see issued FAD §5.1). After completion of further treatment, LRR-modelled patients were **assumed to be in remission** and transitioned to the REM health state. If disease recurrence occurred within that health state, patients transited to the "Met no-prog" or Death health states. Only patients in "Met-no-progr" could transition to the "Met-prog" state.

Figure 2:Model structure used in TA424



Model structure in current ID1500 submission:

Within the current appraisal, a 4-state Markov model is used to model costs and outcomes. The model consists of four mutually exclusive health states; event-free (EF), locoregional recurrence (LR), distant metastasis (DM), and death, to track the disease course and survival of patients over time. The Markov framework was used because it can explicitly capture the disease pathway of patients with early-stage TNBC as well as including the functionality to model metastatic outcomes [18]. This model differentiates health states by type of recurrence (either LR or DM) because the primary endpoint, i.e. EFS, of the KEYNOTE-522 trial encompasses both types of recurrence events [19]. These two types of recurrences have different implications on patients' prognoses, and therefore result in different health outcomes and costs.

Patients enter the model in the “EF” health state. At the end of each weekly cycle, patients who are in the “EF” state may stay in “EF”, transition to the “LR” state, transition to the “DM” state, or die. Patients who are in the “LR” state may stay in the “LR” state, transition to the “DM” state, or die at the end of each cycle, but could not transition back to the “EF” state. Similarly, patients who are in the “DM” state may stay in the “DM” state or die at the end of each cycle but could not transition back to the “EF” or “LR” state. The “death” state is an absorbing health state in which no costs or benefits are accrued.

Key differences concerning the locoregional recurrence part of the TA424 model versus the model used in this submission include the lack of a “Remission” health state and lack of tunnel states to model a 12-month locoregional recurrence period before entering the “Remission” health state. The deviations noted above are based on clinical data from KEYNOTE-522 but also from the trial design itself. The NeoSphere trial which informed TA424 explored pathological Complete Response (pCR) as a primary clinical outcome. In contrast, KEYNOTE-522 included both pCR and Event free Survival as co-primary endpoints. Event free survival from KEYNOTE-522 could be used to directly inform transition probabilities without the need to intrinsically assume the fixed duration of time in which patients would remain within the LR state before moving into a “Remission” health state downstream.

In contrast to TA424, subsequent retreatment with therapy at locoregional relapse was not allowed in KEYNOTE-522 based on trial design (all patients were eligible for adjuvant therapy across both arms; pembrolizumab monotherapy or placebo). Therefore, introducing a series of tunnel states to account for the additional time spent receiving additional treatment was not necessary for the KEYNOTE-522 model since costs and outcomes can accurately be estimated using the current model structure.

Within the current model for ID1500, patients continue to reside within the LR health state if they do not experience further subsequent metastatic progression or death. Therefore, the need to introduce a series of tunnel states to “hold” disease progression upstream was not required, enabling avoidance of unnecessary model complexity and the need to superimpose time dependency (i.e. that 12 months must be spent in LR before entering “Remission”).

The current model also avoids assumptions which lack clinical relevance, are potentially oversimplifying, and are not supported by the clinical data from KEYNOTE-522 (e.g. no transitions occur from LRR to Death during this time but only from after 12 months and upon patients having entered “Remission”). In fact, in TA424 the manufacturer states that these simplifying assumptions may overestimate QALYs and costs across both arms (CS page 198 of 372). The ERG also raised that whilst it is clinically unrealistic to assume patients will not experience any death events for 12 months once in LRR, the number of these events would be very limited and therefore the impact on the cost-effectiveness would be low.

The current model structure avoids unnecessary complexity and data generalisability issues. This was raised by the ERG in TA424 who queried the generalisability of the Hamilton et al 2014 study used by the company to inform the REM→Met-non-prog health state. **The above considerations mean that the “Remission” state from TA424 in fact resembles the LR state of this submission.**

DM health state not disaggregated further to pre and post-progression within the current model:

With regards to differences in the DM modelling within this submission and TA424, we note the disaggregated modelling for 1st line (1L; metastatic not-progressed) vs 2nd line metastatic disease (2L; metastatic progressed) modelling applied in TA424. Due to data limitations within metastatic TNBC and to avoid unnecessary complexity within the current submission, a single DM state is used to model the efficacy of 1L using primarily the KEYNOTE-355 trial alongside a network meta-analysis.

The % of patients receiving 1st line metastatic therapy is directly informed from KEYNOTE-522 clinical trial data. The process of 1L mTNBC cost calculation is elaborated in question B13c.

Treatment options in the UK for progressed metastatic disease (mTNBC 2L+) were calculated from the chemotherapy mix recorded in the KEYNOTE-355 study (see Table 10 for more information). Clinical experts considered these as generalisable to the UK setting during the ID1546 development state. The cost of 2L+ subsequent therapies is applied as lump sum costs in the current submission to avoid unnecessary complexity.

Table 10: Observed vs adjusted KEYNOTE-355 subsequent therapies from KEYNOTE-355 and applied in the economic model

Subsequent therapy	Patients with new therapy - Observed distribution				Patients with new therapy - Adjusted distribution†			
	Pembrolizumab + Chemo		Placebo + Chemo		Pembrolizumab + Chemo		Placebo + Chemo	
	N=219*	%	N=103*	%	N=216	%	N=100	%
2L	[redacted]							
Capecitabine								
Cyclophosphamide + doxorubicin								
Gemcitabine + carboplatin								
Eribulin								
Paclitaxel								
IO agent								
Mean duration, days (SE)								
3L								
Capecitabine								
Eribulin								
Capecitabine + vinorelbine								
Cyclophosphamide + doxorubicin								
Paclitaxel								
IO agent								
Mean duration, days (SE)								
4L+								
Vinorelbine								
Capecitabine								
Eribulin								
Carboplatin								
Nab-paclitaxel								
IO agent								
Mean duration, days (SE)								

† Adjusted to remove IO and eribulin usage in 2L, and IO usage in 3L and 4L, as these therapies are not used in the 2L setting in the UK. * Please note that the observed estimates are based upon the ITT population. The denominator for subsequent treatment utilisation should be based upon those patients who discontinued therapy, which is captured in the adjusted columns (216 and 100).

As seen in from the subsequent treatment data in KEYNOTE-355, some limited immune-oncology agent or eribulin usage at 2L+ take place in KEYNOTE-355 (see additional information in Table 10). These are not fully reflective of the UK treatment options available. Therefore, subsequent treatment costs have been adjusted by redistributing these agents across other 2L therapies.

The OS endpoint from KEYNOTE-355 has not been adjusted for. Given the limited and balanced IO usage observed across both treatment arms this is unlikely to affect the modelled OS and therefore the cost-effectiveness conclusions. This is a simplifying assumption that was taken for the following reasons:

- to maximise the data available for extrapolations from DM setting,

- ensure consistency with the ongoing ID1546 submission
- to better reflect changes in the pathway as, due to the high unmet medical need, some patients may enter a clinical trial (recognising that KEYNOTE-355 patients were not eligible if they had neo-adjuvant/adjuvant IO therapy before).

The DM OS modelled reflects the 1L+ survival from a contemporary trial that may somewhat overestimate the true OS in the real world setting (i.e. because no IOs are available for 2L+ treatment in the UK but were used in KEYNOTE-355). Therefore, from a costing perspective whilst the DM state in the current model does not explicitly distinguish between 1L and 2L+ costs and effects downstream, it adequately captures these for the purposes of the decision problem whilst avoiding unnecessary complexity and the need to use additional assumptions around the relative efficacy and around treatment sequencing downstream in the metastatic treatment pathway.

Please provide data on how many patients experiencing distant metastasis had progressed metastatic disease.

This level of information is not formally captured within KEYNOTE-522. Patients within KEYNOTE-522 can experience a recurrence, either locoregional or distant. Once patients experienced a recurrence, they continued to be followed for survival status and PROs. Subsequent new oncologic therapies received after recurrence were also collected. Subsequent treatment data may be used as a proxy to explore the level of disease progression once a distant recurrence has been recorded. Table 11 presents the subsequent new oncologic therapy records by disease progression status from the latest DBL (IA4). These demonstrate that subsequent treatment data from KEYNOTE-522 are extremely immature at this stage. This means that the level of information available to inform the later stages of distant metastatic progressed disease diminishes as fewer patients have reached that stage within KEYNOTE-522. At this stage MSD are unable to provide any additional formal analyses to address the request above.

The breakdown of therapies presented in Table 11 is exploratory in nature and reliant upon assumptions of disease progression status over time. As trial follow up

continues to mature new and subsequent oncologic treatment initiation will increase over time. This means that the information provided may not fully reflect the progressed metastatic disease status requested above and only offers a snapshot of subsequent therapies by type of recurrence at the time the database lock took place. It is clear that the exploratory nature of this analysis and the immaturity of subsequent therapies cannot be directly leveraged within the economic modelling.

Table 11: KEYNOTE-522 Breakdown of New Oncologic Therapies after Discontinuing from Study Treatment (All-Subjects-as-Treated Population)

Status	Pembrolizumab + chemotherapy / Pembrolizumab		Placebo + chemotherapy / Placebo		Pooled	
	n (%)†	Treatment duration,[a] Mean (SE)	n (%)†	Treatment duration,[a] Mean (SE)	n (%)†	Treatment duration,[a] Mean (SE)
	(N=783)		(N=389)		(N=1172)	
Subjects with one or more new oncologic therapies	119 (10.2)		85 (7.3)		204 (17.4)	
Status 1 - Before any PD/recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Status 2 - Between first local PD/recurrence and first distant PD/recurrence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD1/PD-L1 therapies ††	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Status 3 - After first distant PD/recurrence - 1L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD1/PD-L1 therapies ††	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Status 3 - After first distant PD/recurrence - 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD1/PD-L1 therapies ††	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Status 3 - After first distant PD/recurrence - 3L+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD1/PD-L1 therapies ††	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† Every subject is counted a single time for each applicable row and column.

†† Anti-PD1/PD-L1 Treatment could be atezolizumab, avelumab or pembrolizumab.

a: Treatment duration is **defined as the days** from start date of the treatment until the stop date of the treatment for each line of therapy or the censored date of overall survival if the stop date is not available.

3L+ refers to any new oncology therapy a subject received from third line after first distant PD/recurrence. The treatment duration is the sum of duration of the line of therapy from third line. (Database Cutoff Date: 23MAR2021)

b. Provide a scenario analysis based on the same model structure as used in TA424

Please see the considerations summarised above. MSD is unable to provide a scenario analysis based on the same structure employed in TA424. The clinical data from KEYNOTE-522 do not support the modelling structure used in TA424. Therefore, providing the requested analysis would increase the complexity of the economic model and data requirements, which are not currently available to inform additional transition probabilities. This would result in increased uncertainty in the economic modelling.

The current economic model sufficiently captures costs and outcomes of the disease evolution over time, including those of locoregional and distant metastatic recurrences. The model structure employed within this submission is similar to other recent IO submissions in the adjuvant melanoma setting (such as TA766)[20] despite there being less data available to inform more complex model modelling of downstream effects in metastatic TNBC setting.

Clinical parameters and variables

B4. Throughout the documentation, references are made to clinical expert opinion, for example on page 74: “Validation of long-term extrapolation was performed by cross checking the estimates at landmark timepoints produced by each model versus estimates provided by clinical experts and those reported in the RWE clinical literature for early-stage or locally advanced treated TNBC patients”. Please provide the meeting report of the UK early-stage TNBC Virtual Advisory Board Meeting, reference 25 in the CS.

An anonymised version of the summary report documenting this advisory board has been provided accompanying this response. This report was developed independently by an external agency and provides a top-line summary of the discussions. Please note that the report does not include a detailed summary of any discussions, and content relating to topics not relevant for this appraisal has been redacted.

B5. On page 77 where selection of distribution and statistical fit per AIC and BIC is discussed, it is stated that “Differences of 5 points or greater are considered

important in terms of distinguishing between models." Please provide a reference or other justification for this.

There is no single universally accepted rule used to assess statistical fit based on AIC and BIC methods. NICE DSU TSD 14 does not provide clear guidance on decision rules beyond stating that the lowest AIC/BIC values indicate the best statistical fit.[21] However, there are some generally accepted 'rules of thumb' which can be used to help assess relative statistical fit among parametric survival models. A recent review of all prior NICE oncology TAs found that 25/152 TAs applied explicit rules of thumb for AIC/BIC when selecting base case models and the 'five-point difference' rule was used most commonly.[22] Other previously-cited rules of thumb were based on publications by Burnham and Anderson (2002; 2004),[23, 24] Raftery (1995),[25] and Kass and Raftery (1995),[26] although the interpretation of these rules was variable reflecting the limited guidance provided in the source publications.[22] The parametric models selected for the base case analysis in the economic model are appropriate based on the five-point difference rule and the typical interpretation of the rules suggested by Burnham/Anderson and Kass/Raftery.

B6. EFS extrapolation: on p76 of the CS, the argumentation for choosing the 50-week cut-off point for the piecewise models is described.

a. Please demonstrate clearly that also for the placebo arm a piecewise model is indicated, with a cut-off point at 50 weeks, as there does not seem to be clear turning point for this arm.

b. Please explain why only the 50-week turning point was taken into account (it seems to be this was only done because of insufficient data at later time points).

c. In the summary of parametric curves fitted to EFS in Appendix O (page 15), parametric models based on the 68-week cut-off point (Pembrolizumab + Chemotherapy: KM68+Log-normal and Chemotherapy: KM68+Log-normal) were also presented as plausible scenario analyses for the curves fitted to the EFS data. Please include these scenarios in the cost-effectiveness model.

MSD would like to take the opportunity to offer more clarity around the selection of the 50 week cut-off point. Within Document B, more emphasis is placed within

Document B on the selection process for the 50 week EFS cut-off point for pembrolizumab + chemotherapy. Page 76 of Document B contains the cumulative hazard and log-cumulative hazard plots over time which are supportive of the ~50 week turning point across both treatment arms. However, more information supporting the presence of a cut-off point for the chemotherapy arm is provided in the confidential Appendix O and is summarised below. In brief, the process used to identify cut-off points included the following steps;

- Exploration of hazard plots for turning points in the hazard function → suggested week 43 for Pembro + chemo and week 68 for chemo arms respectively.
- Visual inspection of cumulative hazard plots were examined → suggested a divergence of curves with a potential turning point at approximately **week 50**.
- Statistical exploration of turning points using Chow tests to explore structural changes to the KM followed by statistical testing for significance → suggested week 93 and 109 as potential turning points.
- Overall the following potential turning points were considered based on the above process: weeks – 43, 50, 68, 93 and 109 (the Appendix O report erroneously reports week 55 due to typographical error in page 10).

Parametric survival modelling using 2-piece models requires a balance between the observed data used directly for economic modelling and the data remaining to inform survival extrapolations. Selecting a timepoint that does not result in sufficient data remaining for survival extrapolations may increase uncertainty. Nonetheless, different timepoints have been included in the model which allow the exploration of structural uncertainty around the timepoint selection and what this entails for the C/E analyses. Please note that the requested parametric models based on the 68-week cut-off point for Pembrolizumab + Chemotherapy and Chemotherapy alone are already included in the economic model and can be selected in the “Specifications” sheet.

B7. PRIORITY QUESTION. The fact that no treatment waning is assumed is only briefly mentioned in Tables 32 and 46 of the CS. The only justification provided

for this is (in Table 32) that it is consistent with previous breast cancer HTAs, such as TA639 (no other explicit references stated). However, in TA639 a time horizon of 15 years was considered, while in this appraisal the time horizon is 51 years. No scenarios analyses were provided to explore the impact of treatment waning on the ICER.

A. Please justify why, from a clinical point of view, waning of the treatment effect would not occur at any point during the 51 year time horizon.

B. Please include a possibility or switch in the model to explore the impact of treatment waning.

From a clinical perspective, there are two plausible mechanisms through which pembrolizumab could be expected to provide a durable treatment effect:

1. **Removal of residual disease**
   The aim of the addition of 1 year of pembrolizumab before and after surgery is to increase the rate of pCR and reduce the risk of local and distant recurrence after surgery by removing any residual disease and/or micrometastases, both of which are expected to increase the rate of pCR and extend EFS and OS. For patients who achieve complete removal of residual disease and any micrometastases, it would be illogical to consider that this treatment effect would be reversed. This is supported by literature available to date whereby pCR has been found to be associated with substantial improved EFS and OS [27-29].

2. **'Immune surveillance' mechanism of action**
   Immunotherapies activate and enhance the ability of the patient's immune system to recognise and destroy tumour cells and micro-metastases.[30] The potential for immune memory enables the activated immune system to continue to identify and remove residual disease after stopping therapy. This 'immune surveillance' effect is therefore expected to be maintained once adjuvant therapy has been completed.

The maintenance of the pembrolizumab treatment effect is supported by evidence from several large clinical studies in TNBC and other solid tumour settings, including:

- KEYNOTE-522: After a median follow-up of 37.8 months, the pembrolizumab and placebo EFS curves remained clearly separated and there was no evidence of the EFS curves converging after stopping treatment. There is therefore no evidence of an increasing relative hazard of recurrence over time for the pembrolizumab arm.[19].

- In stage 3 melanoma, adjuvant treatment with pembrolizumab versus placebo in KEYNOTE-054 has demonstrated a durable separation of RFS curves sustained over the duration of follow-up (median 45.5 months).[31] This effect has also been observed in other adjuvant immunotherapy trials in melanoma: over 4 years with nivolumab in CheckMate238;[32] and over 7 years with ipilimumab in EORTC-18071.[33]

In addition, there is no evidence to indicate that the treatment effect with pembrolizumab would be lost at later follow-ups. In TA639,[34] the ERG and appraisal committee concluded that, in the absence of direct evidence on the duration of treatment effect after stopping therapy, the point at which hazard rates become equal is subjective and application of an arbitrary treatment waning effect was not appropriate. **MSD agree with this position and consequently, given the clinical rationale and the evidence supporting a durable treatment effect, MSD do not consider it appropriate to implement treatment waning in the economic model.**

B8. PRIORITY QUESTION. The selection process for EFS curves resulted in different types of curves for pembrolizumab and placebo. TSD 14 states that: 'Where parametric models are fitted separately to individual treatment arms it is sensible to use the same 'type' of model, that is if a Weibull model is fitted to one treatment arm a Weibull should also be fitted to the other treatment arm. This allows a two-dimensional treatment effect in that the shape and scale parameters can both differ between treatment arms, but does not allow the modelled survival for each treatment arm to follow drastically different distributions. If different types of model seem appropriate for each treatment arm this should be justified using clinical expert judgement, biological plausibility, and robust statistical analysis.' Please provide this justification, or use the same types of distribution for both arms.

Please refer to submission section B.3.3.1.2 for justifications referring to EFS extrapolations. In brief, identification of parametric models included assessment of statistical fit using tests based on the AIC and BIC criterion, combined with visual inspection and assessment of selected models for clinical plausibility.

First, EFS cumulative and log-cumulative hazard plots were generated to assess the proportional hazards assumption (see Doc B Figure 10). From visual inspection, the crossing of the log-cumulative hazard plots of the two treatment arms suggested the implausibility of the proportional hazard assumption; therefore, separate models were used to fit the data for each arm for the projection of EFS in line with the NICE DSU TSD 14. As noted within the submission, the unique mode of action of immunotherapy (with or without chemotherapy) is not comparable to chemotherapy alone; therefore, the underlying hazard assumption for the parametric curve does not need to be the same. This has been observed alongside across a number of metastatic and adjuvant submissions with IO agents to date. As stated in response to question B7 above, clinicians have noted that IO therapies used in the neoadjuvant /adjuvant setting may have an effect of improving 'Immune surveillance' due to their unique mode of action by activating and enhancing the ability of the patient's immune system to recognise and destroy tumour cells and micro-metastases and enhance immune memory.[30] They also may remove residual disease.

Clinical plausibility of different parametric models was discussed during an advisory board. Experts were presented with alternative EFS extrapolations and asked to comment on the most plausible models used to extrapolate the standard of care chemotherapy and the pembrolizumab arm. Based on the unique mode of action of IO therapies as well as the characteristics of patients with early TNBC disease, clinical experts noted that they would expect EFS to start to plateau across both treatment arms since most recurrences occur within the first 3 to 5 years and that pembrolizumab + chemotherapy EFS would sit above that of placebo. Experts noted that **generalised gamma, log-normal and Gompertz** distributions were most realistic for patients with early-stage TNBC treated **with either standard of care or pembrolizumab. Some advisors favoured the Gompertz distribution,**

suggesting it is unlikely that 10% of events will occur between 5 and 10 years as suggested by the log-normal distribution.

Expert opinion was sought alongside assessment of goodness of fit statistics and validation versus long-term real world evidence prior to selecting the alternative parametric models used for long-term EFS extrapolations. Section B.3.10.1.2 discusses the process used to validate the long-term EFS projections in the chemotherapy arm for which data are currently available. A targeted literature review was conducted to identify studies that report long-term EFS in patients with early-stage TNBC following neoadjuvant chemotherapy (NACT). Two external sources were identified: Walsh 2019 [35] and Sikov 2019 (CALGB 40603) [36]. When asked, clinical experts did not suggest any additional sources for model validation purposes and noted that both studies could be appropriate sources of validation for the modelled EFS for placebo. The models selected for the base case and alternative sensitivity analyses all yielded good visual fit to the RWE identified (refer to section B.3.10.1).

B9. Table 36 of the CS presents the probability of the first EFS event for year 1 and years 2+. Please clarify how these percentages (also shown in the 'Raw Effectiveness' sheet of the model) were calculated from the cumulative incidence functions for EFS to LR, DM, or death by treatment arm (sheet Raw_EFtoLR,DM and D (cum.) of the company model), as this is not fully clear from Appendix P[4] that the CS refers to.

CS Document B Table 36 refers to the probability of the first EFS event for year 1 and years 2+. The three EFS components in the KEYNOTE-522 trial – time to LR, time to DM and time to death – were analysed using Gray's method considering competing risks [37]. EFS parametric modelling and cumulative incidence rate plots using competing risks analyses indicated a change in the rates over time for each of the competing events at approximately 1 year (see confidential report P).

To increase the modelling accuracy and capture the plateau in overall EFS extrapolated curves, we estimated transition probabilities from EFS→ LR, EFS→ DM, EFS → Death by splitting the data into year 1 and year 2+ to ensure adequate numbers of events were available across both timepoints. Table 12 below provides

the event breakdown from KEYNOTE-522 which informs the percentages reported in Table 36 of Document B.

Table 12: Breakdown of first EFS event

First EFS event	Pembrolizumab N=784		Placebo N=390		Total N=1174	
	n	%	n	%	n	%
All subjects, ITT						
Any	123	100.0%	93	100.0%	216	100.0%
Local recurrent/PD	*****	*****	*****	*****	*****	*****
Distant recurrent/PD	*****	*****	*****	*****	*****	*****
Death	15	12.2%	6	6.5%	21	9.7%
All subjects, ITT, within 1 year						
Any	*****	*****	*****	*****	*****	*****
Local recurrent/PD	*****	*****	*****	*****	*****	*****
Distant recurrent/PD	*****	*****	*****	*****	*****	*****
Death	*****	*****	*****	*****	*****	*****
All subjects, ITT, after 1 year						
Any	*****	*****	*****	*****	*****	*****
Local recurrent/PD	*****	*****	*****	*****	*****	*****
Distant recurrent/PD	*****	*****	*****	*****	*****	*****
Death	*****	*****	*****	*****	*****	*****

B10. PRIORITY QUESTION: Section B3.3.2 of the CS (page 84) states: "Parametric models were fitted to the time from locoregional recurrence (LR) to distant metastases (DM) or death, and exponential distribution was found to be the best fit. Considering the memoryless feature of the Markov cohort model structure, constant transition probabilities from the LR state were assumed. Furthermore, exponential was also the best fit to the time from LR -> DM or death so this is a reasonable assumption."

a. **Please provide more information on the various parametric models and their fits to both arms and the pooled data, comparable to the information provided for the event-free survival (EFS) curves. This would include cumulative and log-cumulative hazard plots, AIC, BIC and graphical representation of the curves. Please include K-M curves for pembrolizumab, placebo as well as the pooled K-M curves.**

b. **Please explain why the fact that an exponential distribution fits the observed data best would justify an assumption of constant transition probabilities over the entire time horizon of the model. Any assumption on long-term extrapolation would need justification based on clinical**

plausibility, and cannot be based on what is observed in a limited follow-up period.

We thank the ERG for giving us the opportunity to provide additional information with regards to the methodology followed to model transition probabilities from LR→DM or Death. This information should be read as a supplement to section B.3.3.2 of Document B.

As described in document B, the pooled events from KEYNOTE-522 were used to inform the transition probabilities from LR→DM or Death. This is due to the limited number of events that were observed in KEYNOTE-522 which could increase uncertainty if compartmentalised further for separate parametric extrapolations and subsequent calculations of transition probabilities from LR→ DM and LR→ Death Table 12 above provides the breakdown first EFS events that took place demonstrating the limited DM and Death taking place as first events.

Overall, ***** patients experienced LR, of which ***** observations were considered as failed (ie either with a DM or Death event) and ***** were censored (*****% censored).Table 13 below describes the number of first events taking place once patents were confirmed with LR.

Table 13: Breakdown of first LR event

	%	N Events	N Total
% from LR to DM	[redacted]	[redacted]	[redacted]
% from LR to Death	[redacted]	[redacted]	[redacted]

Figure 3 below presents the time to event (TTE) from LR to DM or Death pooled across both treatment arms based on the above information. Figure 4 provides the parametric survival extrapolation curves from the pooled observed LR→ DM or Death data from KEYNOTE-522.

Figure 3: Observed combined KEYNOTE-522 arms time to event (TTE) from LR in weeks (event = distant metastasis or death from LR)

*****

Notes: TTE = Time to Event, reported in Weeks with event being equal to distant metastasis or death.

Within the submission Document B, it is stated that parametric models were fitted to the time from LR to DM or death, and exponential distribution was found to have the

best fit. MSD would like to take the opportunity to clarify that the selection of the exponential parametric distribution selected to model LR → DM or Death was not based in isolation to the AIC/BIC statistics (presented in Table 14 at the ERG's request). Other considerations included the visual fit to the observed KM curve (Figure 4) alongside balanced assessment of clinical plausibility of long term predictions generated by each of the alternative parametric models.

Figure 4: Long term parametric extrapolations using the combined KEYNOTE-522 arms time from LR to DM or Death

Table 14: AIC and BIC statistics of fitted parametric models from LR→ DM or Death

Model	AIC	BIC	Average	Difference in average AIC/BIC
Weibull	419.7952	424.2634	422.0293	-0.227
Exponential	**427.4295**	**429.6636**	**428.5466**	**-6.744**
Gompertz	424.6719	429.1401	426.906	-5.104
Log-logistic	420.733	425.2012	422.9671	-1.165
Log-normal	419.5683	424.0365	421.8024	NA
Gamma	420.0672	424.5354	422.3013	-0.499
Generalized Gamma	421.3584	428.0607	424.7096	-2.907

The very few number of events which have taken place from which extrapolations are based could make the AIC/BIC statistics unreliable and therefore rankings based on AIC/BIC may change as more data become available. Whilst the exponential model yields the highest AIC/BIC statistics this is only ~6.7 points different vs the lowest average AIC/BIC produced by the log-normal model. Although the exponential model sits marginally above the KM data for the duration of the observed period, the exponential model demonstrated a better fit towards the tail of the KM curve better and yielded more conservative estimates of long term time to DM or Death.

As we note within the submission documents, Markov models are memoryless by nature, meaning it is not possible to track individual patients through the model or therefore determine how long patients have been in a particular health state. Considering this limitation, the exponential model was preferred to model transitions from LR→DM or LR →Death. Use of more complex parametric survival models to derive probabilities from intermediate health states such as log-normal or log-logistic

would require additional complexity such as thousands of tunnel states, significantly increasing the computational burden of the model.

The model uses the pooled events to derive transition probabilities and the LY benefit is primarily derived from patients residing within the EFS state. Although the constant transition probability assumption may be simplistic in nature, it does not impact the ability of the model to predict accurate mean long term survival for the purposes of decision making.

B11. PRIORITY QUESTION: Section B3.3.3 of the CS (page 88) states that: "The transition probability of DM --> death was estimated based on the constant hazard assumption.". In Table 44 the transition probabilities are shown as an exponential rate based on weighted mean OS.

a. **Please justify why the probability of DM --> death was estimated based on the constant hazard assumption.**

b. **Please clarify what is meant with the term 'exponential rate' in Tables 44 and 45 (as well as in Table 39).**

c. **Please clarify how these exponential rates were calculated, specifically in the case of the weighted mean OS taken from KEYNOTE-355.**

The model uses a Markov state transition structure in which EF is the starting health state, LR and DM are intermediate health states, and Death is the absorbing health state. Markov models are memoryless by nature, meaning it is not possible to track individual patients through the model or therefore determine how long patients have been in a particular health state. However, to model variable hazards over time from entry into an intermediate health state (in this case, the DM state) it is *necessary* to track time in health state. To achieve this in a Markov model would require thousands of tunnel states and would significantly increase the computational burden of the model. As such, it was deemed an appropriate simplifying assumption to instead apply a constant hazard rate to estimate transitions from the LR (see question B10) and DM health states.

The exponential distribution assumes a constant hazard rate over time and therefore does not depend on time since entry into a health state. As such, the exponential

function is commonly assumed when estimating transition probabilities starting from intermediate health states in a Markov model.[38] The “exponential rate” referenced in CS Table 44 and CS Table 45 refers to the parameter used to define the exponential distribution used to estimate transition probabilities from the DM health state for the corresponding treatment arm.

The exponential rate of DM→Death for each treatment arm was calculated as “1/(weighted mean OS in weeks)”. The “weighted mean OS” was estimated based on the mean OS (in weeks) predicted for each first-line treatment for metastatic TNBC (sourced from the pembrolizumab first-line metastatic TNBC [KEYNOTE-355] cost-effectiveness model), weighted by the treatment mix of first-line treatments for metastatic TNBC in the corresponding arm, as described in CS Table 42. For metastatic treatment regimens not considered in the first-line model, a HR derived from an NMA (described in CS Appendix M) was applied to weekly survival estimates from the first-line model or, alternatively, assumptions of equivalence with another regimen were applied. Full details of these assumptions are provided in CS section B.3.3.3 p87-88. The mean OS for patients who did not receive first-line treatment was sourced from a SEER Medicare study.[39]

B12. PRIORITY QUESTION: OS in the DM state for the proportion of patients that does not receive 1L treatment is derived from ‘no treatment arm’ of the SEER Medicaid study.[7] This is a US study in elderly TNBC patients whose average age at diagnosis was 69 (for the no chemotherapy group).

a. **Please comment on the representativeness of this study, in particular this age group, for OS in the DM state of the current appraisal.**

We would like to thank the ERG for the question and the opportunity to comment further on this part of the appraisal. Only two studies were identified that reported information which was relevant for the economic model; Aly et al 2019 (based on SEER Medicare) and Skinner et al 2020 (US EMR study). These were retrieved from the systematic literature review of health care resource utilisation (Appendix I provided).

Aly et al 2019 is a USA retrospective chart review study of SEER Medicare data [39]. This study was selected as it was based on a larger database that could provide

more reliable information for the survival estimates for patients diagnosed with metastatic TNBC and who did not receive any subsequent line of therapy, and because it included patients from a wide geographical range.

As stated in section B.3.3, patients who did not receive 1L treatment for metastatic TNBC were modelled using the OS data from the recent SEER Medicare database publication by Aly et al 2019 for patients in the 'no treatment' subgroup. (Medicare is the American federal health insurance programme for people aged 65+, certain younger people with disabilities and people with end-stage renal disease [40].)

Given that the study is used to inform OS modelling in the DM state, a comparison of baseline characteristics should be made primarily versus the KEYNOTE-355 study population which forms the basis of evidence for metastatic TNBC. A summary extract of key baseline characteristics from Aly et al 2019 is presented alongside characteristics from Skinner et al 2020, and KEYNOTE-355 below (for full detail please refer to original publications) [39, 41, 42].

Table 15: Comparison of baseline characteristics across Aly et al 2019, Skinner et al 2020, and KEYNOTE-355

Study	**Aly et al 2019[39]**	**Skinner et al 2020**	**KEYNOTE-355**
Patient group:	No chemotherapy (n=308)	No chemo (n=103)	PD-L1 CPS ≥10 score pooled (n= 323)
Age at diagnosis			
Mean (SD)	79.0 (7.7)	61.5 (14.96)	52.7 (13.2)
Median (range)	NR	NR	53 (22-83)
Race, %			
American Indian or Alaska Native	NR	0%	0.6%
Asian	NR	1.0%	19.8%
White	71%	62.1%	69%
Black	21%	30.1%	4.6%
Hispanic	3%	2.9%	NR
Other	3%	3.9%	5.9% (3.1%+2.8%)
Charlson Comorbidity Index, %			
0	46%	NR	NR
1	23%	NR	NR
2	15%	NR	NR
3	17%	NR	NR
Poor Performance Status (proxy)[1] %			
No	75%	76.9%	NR
Yes	25%	23.3%[2]	NR
ECOG performance status %			
0	NR	NR	60.7%
1	NR	NR	39.3%
2	NR	NR	0%

The population of Aly at al 2019 is older versus that of KEYNOTE-522 (mean 79.0 vs 49.1 years). This is expected since KEYNOTE-522 included younger patients at earlier disease stages. Patients in Aly et al 2019 were also older when compared to those of KEYNOTE-355 which recruited an inoperable advanced/metastatic TNBC population (mean: 79.0 vs 52.7 years). The authors state that *"patients were included in this study if they were ≥66 years-old"* which explains skewed age distribution versus that of KEYNOTE-355.

At the same time, the proxy for performance status reported by Aly et al 2019 indicates that most patients (75%) are relatively fit despite being older as they have good performance status. Authors defined this as a claim in the baseline period for wheelchair use, oxygen use, walking aid, hospital bed, hospice, skilled nursing facility or hospitalization. Whilst this definition may not be cancer-specific related performance, when used as a proxy versus ECOG PS reported in KEYNOTE-355 the population is fairly similar to KEYNOTE-355 (60.7%). In addition, the cohort in Aly et al 2019 covers a wider geographical reach and is therefore more likely to be representative of the typical metastatic TNBC population.

By comparison, Skinner et al 2020 reported data for a significantly smaller cohort, and the study population were drawn from nine community oncology practices heavily concentrated in the southern and southeast regions of the US. As such, the cohort was deemed less likely to be representative in terms of factors such as race, income, and treatment patterns than the publication by Aly et al 2019.

For decision making purposes the model needs to be able to predict survival from the DM setting for a proportion of patients that may also not receive subsequent lines of therapy. Whilst Aly et al 2019 included older patients diagnosed with metastatic TNBC which did not receive subsequent therapies, the main source of mortality for would be expected to be primarily attributed to metastatic TNBC. Therefore the mean age of the cohort informing the survival time without mTNBC therapy is unlikely to have a major impact on the cost-effectiveness results.

a. **Please provide a scenario analysis where mortality from DM (for the proportion not treated with 1L therapies) is adjusted to better reflect the target population of the current appraisal.**

Owning to the immaturity of subsequent treatment data from KEYNOTE-522, MSD chose to directly model the observed clinical outcomes for patients not receiving 1st line therapy for metastatic TNBC once in the DM state. Table 40 of Document B presents the proportion of patients that receive 1st line mTNBC therapy assuming that they develop a DM (pembrolizumab: [redacted] placebo: [redacted]). Therefore, the model assumes that [redacted] of patients will not receive 1L treatment for metastatic TNBC in the pembrolizumab arm and [redacted] in the placebo arm.

Currently, the model estimates a mean OS of 21.94 weeks for patients not receiving 1st line treatment for metastatic TNBC (see Model Raw_DM_trt share sheet). This value was calculated from the publication reported median OS and the assumption of an exponential distribution to derived the mean survival that is subsequently applied within the model for this subgroup of patients.

We conducted a one-way sensitivity analysis to assess the impact of the mortality from DM (for the proportion not treated with 1L therapies). We varied the mean OS of patients with DM not treated with 1L therapies by ± 25% of the base-case value. The analysis was conducted manually by multiplying the value in Cell F91 of the "DM Treatment Costs & Efficacy" sheet with 0.75 (lower bound) and 1.25 (upper bound), respectively.

As shown in Table 16, the change in mean OS of patients with DM not treated with 1L therapies does not significantly impact the ICER. The ICER is not sensitive to this variable because 1) Patients gained life years and QALYs mostly in the EF state instead of the DM state; 2) A small proportion of patients did not receive 1L therapies; 3) the change of this variable impact both arms in the same direction.

Table 16: Comparison of ICER when varying the mortality from DM for patients not treated with 1L therapies

Scenarios	ICER (Cost/QALY)*
*Base case (*OS of patients with DM not treated with 1L therapies (21.940 weeks)	*£5,940*
Lower bound: OS of patients with DM not treated with 1L therapies (16.455 weeks)	£5,940

Upper bound: OS of patients with DM not treated with 1L therapies (27.425 weeks)	£5,940

B13. PRIORITY QUESTION: Table 42 provides an overview of the treatment mix among patients who receive 1L in the 'distant metastasis' health state. This information is said to be obtained from UK market research and clinical expert input.

a. **Please provide also treatment mix as observed in KEYNOTE-522 (for patients who received 1L treatment) and KEYNOTE-355, stratified per treatment arm.**

Appendix M1.2 contain a summary table of subsequent treatments derived from KEYNOTE-522 for metastatic disease. These were not deemed as generalisable to the UK setting. A detailed breakdown of treatments from KEYNOTE-522 based on the IA4 database lock is presented below. These have been grouped into the following categories:

- Before any progressive disease (PD) or recurrence
- Between first local PD/recurrence and first distant PD/recurrence
- After first distant PD/recurrence – 1L
- After first distant PD/recurrence – 2L
- After first distant PD/recurrence – 3L+

Patients who received 1L+ treatment options are the categories highlighted below (After first distant PD/recurrence – 1L, 2L or 3L+).

Please note that KEYNOTE-355 can only provide information for the subsequent treatment mix for 2L+ metastatic treatment options since KEYNOTE-355 was conducted in previously untreated locally recurrent inoperable or metastatic TNBC patients. A breakdown of 2L, 3L, and 4L+ metastatic treatment options from KEYNOTE-355 is provided in Table 10 above in response to question B3 above.

Table 17: Utilization of New Oncologic Therapies after Discontinuing from Study Treatment (All-Subjects-as-Treated Population)

	Patients with new therapy	
Line	**Pembrolizumab + chemotherapy / Pembrolizumab**	**Placebo + chemotherapy / Placebo**

Therapy	N = 783	N = 389
Patients with one or more lines of therapy	[redacted]	[redacted]
Status 1 - Before any PD/recurrence	[redacted]	[redacted]
agatolimod (+) monophosphoryl lipid A (+) saponin adjuvant (unspecified)	[redacted]	[redacted]
anastrozole	[redacted]	[redacted]
anastrozole (+) letrozole (+) tamoxifen	[redacted]	[redacted]
cancer multi-epitope folate receptor alpha peptide vaccine (unspecified)	[redacted]	[redacted]
cancer multi-epitope folate receptor alpha peptide vaccine (unspecified) (+	[redacted]	[redacted]
capecitabine	[redacted]	[redacted]
carboplatin (+) cyclophosphamide (+) epirubicin (+) paclitaxel albumin	[redacted]	[redacted]
carboplatin (+) docetaxel	[redacted]	[redacted]
carboplatin (+) gemcitabine	[redacted]	[redacted]
carboplatin (+) paclitaxel	[redacted]	[redacted]
carboplatin (+) paclitaxel albumin	[redacted]	[redacted]
cisplatin	[redacted]	[redacted]
cisplatin (+) cyclophosphamide (+) fluorouracil (+) gemcitabine	[redacted]	[redacted]
cyclophosphamide	[redacted]	[redacted]
cyclophosphamide (+) docetaxel (+) epirubicin	[redacted]	[redacted]
cyclophosphamide (+) doxorubicin	[redacted]	[redacted]
cyclophosphamide (+) doxorubicin hydrochloride	[redacted]	[redacted]
cyclophosphamide (+) epirubicin	[redacted]	[redacted]
cyclophosphamide (+) epirubicin (+) fluorouracil	[redacted]	[redacted]
cyclophosphamide (+) fluorouracil (+) methotrexate	[redacted]	[redacted]
exemestane	[redacted]	[redacted]
letrozole	[redacted]	[redacted]
olaparib	[redacted]	[redacted]
paclitaxel (+) pertuzumab (+) trastuzumab	[redacted]	[redacted]
paclitaxel albumin	[redacted]	[redacted]
tamoxifen	[redacted]	[redacted]
tamoxifen citrate	[redacted]	[redacted]
trastuzumab	[redacted]	[redacted]
trastuzumab (+) vinorelbine tartrate	[redacted]	[redacted]
Status 2 - Between first local PD/recurrence and first distant PD/recurrence	[redacted]	[redacted]
anthracyclines (unspecified)	[redacted]	[redacted]
antineoplastic (unspecified) (+) paclitaxel	[redacted]	[redacted]
atezolizumab (+) paclitaxel	[redacted]	[redacted]
atezolizumab (+) paclitaxel albumin	[redacted]	[redacted]
bevacizumab (+) paclitaxel	[redacted]	[redacted]
capecitabine	[redacted]	[redacted]
capecitabine (+) cyclophosphamide (+) doxorubicin	[redacted]	[redacted]
capecitabine (+) docetaxel	[redacted]	[redacted]
capecitabine (+) gemcitabine	[redacted]	[redacted]
capecitabine (+) investigational drug (unspecified)	[redacted]	[redacted]
capecitabine (+) vinorelbine tartrate	[redacted]	[redacted]
carboplatin	[redacted]	[redacted]
carboplatin (+) gemcitabine	[redacted]	[redacted]
carboplatin (+) paclitaxel	[redacted]	[redacted]
cisplatin	[redacted]	[redacted]
cisplatin (+) gemcitabine	[redacted]	[redacted]
cyclophosphamide (+) docetaxel	[redacted]	[redacted]
cyclophosphamide (+) docetaxel (+) epirubicin	[redacted]	[redacted]
cyclophosphamide (+) doxorubicin	[redacted]	[redacted]
cyclophosphamide (+) epirubicin	[redacted]	[redacted]
docetaxel	[redacted]	[redacted]
eribulin mesylate	[redacted]	[redacted]
fluorouracil (+) vinorelbine tartrate	[redacted]	[redacted]
gemcitabine	[redacted]	[redacted]
olaparib	[redacted]	[redacted]
Status 3 - After first distant PD/recurrence - 1L	[redacted]	[redacted]
anetumab ravtansine	[redacted]	[redacted]
anti-HER2 antibody drug conjugate (DXd conjugate) (+) durvalumab	[redacted]	[redacted]
atezolizumab (+) carboplatin (+) gemcitabine	[redacted]	[redacted]
atezolizumab (+) ipatasertib (+) paclitaxel	[redacted]	[redacted]
atezolizumab (+) paclitaxel	[redacted]	[redacted]
atezolizumab (+) paclitaxel albumin	[redacted]	[redacted]
bevacizumab (+) paclitaxel	[redacted]	[redacted]
capecitabine	[redacted]	[redacted]
capecitabine (+) cyclophosphamide (+) methotrexate	[redacted]	[redacted]
capecitabine (+) paclitaxel	[redacted]	[redacted]
capecitabine (+) vinorelbine tartrate	[redacted]	[redacted]
carboplatin	[redacted]	[redacted]
carboplatin (+) cyclophosphamide (+) vinorelbine tartrate	[redacted]	[redacted]

carboplatin (+) gemcitabine	[redacted]	[redacted]
carboplatin (+) gemcitabine (+) paclitaxel albumin	[redacted]	[redacted]
cisplatin	[redacted]	[redacted]
cisplatin (+) docetaxel	[redacted]	[redacted]
cyclophosphamide (+) docetaxel (+) doxorubicin	[redacted]	[redacted]
cyclophosphamide (+) doxorubicin	[redacted]	[redacted]
cyclophosphamide (+) epirubicin	[redacted]	[redacted]
cyclophosphamide (+) epirubicin (+) fluorouracil	[redacted]	[redacted]
cyclophosphamide (+) fluorouracil (+) methotrexate	[redacted]	[redacted]
cytarabine (+) etoposide (+) idarubicin hydrochloride	[redacted]	[redacted]
denosumab (+) docetaxel	[redacted]	[redacted]
docetaxel	[redacted]	[redacted]
docetaxel (+) zoledronic acid	[redacted]	[redacted]
doxorubicin	[redacted]	[redacted]
eribulin mesylate	[redacted]	[redacted]
fluorouracil	[redacted]	[redacted]
gemcitabine	[redacted]	[redacted]
gemcitabine (+) paclitaxel	[redacted]	[redacted]
gimeracil (+) oteracil potassium (+) tegafur	[redacted]	[redacted]
gimeracil (+) oteracil potassium (+) tegafur (+) oxaliplatin	[redacted]	[redacted]
investigational drug (unspecified) (+) paclitaxel	[redacted]	[redacted]
ladiratuzumab vedotin	[redacted]	[redacted]
letrozole (+) palbociclib	[redacted]	[redacted]
methotrexate	[redacted]	[redacted]
olaparib	[redacted]	[redacted]
paclitaxel	[redacted]	[redacted]
paclitaxel (+) pertuzumab (+) trastuzumab	[redacted]	[redacted]
paclitaxel albumin	[redacted]	[redacted]
palbociclib	[redacted]	[redacted]
pembrolizumab	[redacted]	[redacted]
prexasertib	[redacted]	[redacted]
vinorelbine tartrate	[redacted]	[redacted]
Status 3 - After first distant PD/recurrence - 2L	[redacted]	[redacted]
alpelisib (+) fulvestrant	[redacted]	[redacted]
anti-4-1BB/anti-PDL1 bispecific monoclonal antibody	[redacted]	[redacted]
atezolizumab (+) bevacizumab (+) selicrelumab	[redacted]	[redacted]
atezolizumab (+) paclitaxel albumin	[redacted]	[redacted]
avelumab (+) eribulin mesylate	[redacted]	[redacted]
bevacizumab (+) capecitabine	[redacted]	[redacted]
bevacizumab (+) cisplatin (+) gemcitabine	[redacted]	[redacted]
bevacizumab (+) paclitaxel albumin	[redacted]	[redacted]
capecitabine	[redacted]	[redacted]
capecitabine (+) cyclophosphamide	[redacted]	[redacted]
capecitabine (+) docetaxel	[redacted]	[redacted]
capecitabine (+) lapatinib	[redacted]	[redacted]
carboplatin (+) cyclophosphamide (+) methotrexate	[redacted]	[redacted]
carboplatin (+) docetaxel (+) gimeracil (+) oteracil potassium (+) tegafur	[redacted]	[redacted]
carboplatin (+) gemcitabine	[redacted]	[redacted]
cisplatin	[redacted]	[redacted]
cisplatin (+) gemcitabine	[redacted]	[redacted]
cyclophosphamide	[redacted]	[redacted]
cyclophosphamide (+) docetaxel	[redacted]	[redacted]
cyclophosphamide (+) epirubicin	[redacted]	[redacted]
cyclophosphamide (+) fluorouracil (+) methotrexate	[redacted]	[redacted]
denosumab	[redacted]	[redacted]
docetaxel (+) gemcitabine	[redacted]	[redacted]
doxorubicin	[redacted]	[redacted]
eribulin mesylate	[redacted]	[redacted]
eribulin mesylate (+) pembrolizumab	[redacted]	[redacted]
everolimus	[redacted]	[redacted]
fluorouracil	[redacted]	[redacted]
gemcitabine (+) paclitaxel	[redacted]	[redacted]
ixabepilone	[redacted]	[redacted]
olaparib	[redacted]	[redacted]
paclitaxel albumin	[redacted]	[redacted]
pembrolizumab	[redacted]	[redacted]
sacituzumab	[redacted]	[redacted]
vinorelbine tartrate	[redacted]	[redacted]
Status 3 - After first distant PD/recurrence - 3L+	[redacted]	[redacted]
NLRP3 agonist (unspecified) (+) ipilimumab (+) nivolumab	[redacted]	[redacted]
atezolizumab (+) gemcitabine	[redacted]	[redacted]
atezolizumab (+) paclitaxel	[redacted]	[redacted]
bevacizumab (+) docetaxel	[redacted]	[redacted]

bevacizumab (+) paclitaxel	[redacted]	[redacted]
bevacizumab (+) vinorelbine tartrate	[redacted]	[redacted]
capecitabine	[redacted]	[redacted]
capecitabine (+) docetaxel	[redacted]	[redacted]
capecitabine (+) vinorelbine tartrate	[redacted]	[redacted]
carboplatin	[redacted]	[redacted]
carboplatin (+) eribulin mesylate (+) gimeracil (+) oteracil potassium (+)	[redacted]	[redacted]
cisplatin	[redacted]	[redacted]
cisplatin (+) etoposide	[redacted]	[redacted]
cisplatin (+) gemcitabine	[redacted]	[redacted]
cyclophosphamide	[redacted]	[redacted]
cyclophosphamide (+) epirubicin	[redacted]	[redacted]
cyclophosphamide (+) fluorouracil (+) methotrexate	[redacted]	[redacted]
doxorubicin	[redacted]	[redacted]
doxorubicin hydrochloride	[redacted]	[redacted]
eribulin mesylate	[redacted]	[redacted]
etoposide	[redacted]	[redacted]
gemcitabine	[redacted]	[redacted]
olaparib	[redacted]	[redacted]
olaparib (+) trastuzumab	[redacted]	[redacted]
paclitaxel	[redacted]	[redacted]
picibanil	[redacted]	[redacted]
sacituzumab govitecan	[redacted]	[redacted]
vinorelbine tartrate	[redacted]	[redacted]

Every subject is counted a single time for each applicable row and column.
(Database Cutoff Date: 23MAR2021)

b. Please justify why the treatment mix was not based on the patients receiving 1L treatment for distant metastasis in the KEYNOTE-522 trial, or alternatively based on KEYNOTE-355.

KEYNOTE-522 subsequent treatment data at this stage are very immature as most patients have not experienced a relapse event. KEYNOTE-522 is a multinational RCT, therefore, some of the treatment options received by patients to date do not fully reflect the current UK treatment options.

Overall, [redacted] of patients in the pembrolizumab + chemotherapy arm and [redacted] of patients in the chemotherapy arm have a record for 1L mTNBC recurrence and regardless of PD-L1 status. Limited patient records for subsequent treatments can also impact the time on treatment estimates derived. Of note, the table above demonstrates the very limited use of atezolizumab + nab-paclitaxel or combinations of which is approved and considered the standard of care for 1L mTNBC PD-L1 positive ≥1% IC patients.

Approach of modelling 1L metastatic TNBC treatment mix:

MSD would like to take the opportunity to offer more clarity and justification as to the reasons why KEYNOTE-355 1L data could not directly be fully used to inform the

efficacy of all 1L metastatic TNBC treatment options available in the UK. Pembrolizumab in combination with chemotherapy for previously untreated locally recurrent inoperable advanced or metastatic TNBC patients has received a regulatory approval for patients with PD-L1 positive CPS ≥10 tumors by Dako 22C3 Assay (~38% of overall mTNBC population).

The patient population recruited was previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer. As such the study only includes 1L chemotherapy options that were included in trail design alongside pembrolizumab. Study chemotherapies from KEYNOTE-355 included; gemcitabine/carboplatin, paclitaxel or nab-paclitaxel. These were administered in combination with Pembrolizumab or as standalone comparators.

In KEYNOTE-355 ~38% of patients had PD-L1 positive CPS ≥ 10 tumors and the licence granted for this indication is for untreated patients with PD-L1 positive CPS ≥ 10 tumors. Within the patients with PD-L1 positive mTNBC, alternative IO comparators such as Atezolizumab + nab-paclitaxel have been recommended and are the standard of care currently in the NHS. Some Patients may also receive single taxanes if, due to fitness or comorbidities, IO agents cannot be given to them. The KEYNOTE-355 HTA submission ID1546 is currently ongoing. If approved, Pembrolizumab + taxanes will be an alternative IO comparator for PD-L1 positive mTNBC patients. Therefore, KEYNOTE-355 could be used to inform part of the 1L treatment mix only and for the proportion of patients with PD-L1 positive tumors.

As noted above, the regulatory licence for KEYNOTE-355 covers only ~38% of the total mTNBC population. As per KEYNOTE-355, ~62% of patients would have PD-L1 negative tumors (and would fall outside the TA639 recommendation [or the ongoing ID1546 submission]). It was therefore important to leverage clinical expert opinion to inform the Market Share estimates for the ~62% of the patient population which would have PD-L1 negative tumors. As stated in Document B page 86; "*The base case treatment mix of each scenario was obtained from UK market research and clinical expert input (MSD data on file, 2021), who considered the PD-L1 testing rate, the proportion of PD-L1 positivity, and treatment mix for PD-L1 positive and PD-L1 negative/untested, respectively."* to ensure estimates provide were reflective of the UK treatment pathway.

As explained above, subsequent treatment data from KEYNOTE-522 patients are collected (irrespective of PD-L1 status) but these remain very immature and could not be leveraged to inform the 1L mTNBC treatment mix. In contrast, KEYNOTE-355 provides part of the information required for the 1st line and subsequent treatment options for patients with PD-L1 positive mTNBC. Therefore, some clinical inputs and adjustments were necessary to reflect all mTNBC 1st line treatment options available. Given the KEYNOTE-522 data immaturity for subsequent treatments, we considered it is methodologically more appropriate to inform the 1st Line subsequent treatment utilisation based on clinical expert opinion alongside KEYNOTE-355.

c. **Please clarify which percentages are based on UK market research and which on clinical expert input, and please provide the meeting report of the UK early-stage TNBC Virtual Advisory Board Meeting (reference 25 of the CS) and Market share data and subsequent treatments (reference 37 of the CS) as these do not seem to be provided with the reference pack of the submission.**

MSD welcomes the opportunity to offer more clarity around this aspect of the HTA submission. We have provided the advisory board report which includes a discussion of considerations around 1st line metastatic treatment options. We also include the materials presented alongside a brief description of the methodology followed to guide the discussion as the report in isolation does not provide the level of detail requested by the ERG.

Clinical experts participating in the advisory board were presented with a summary slide containing the % treatment breakdown and market shares for agents used to treat 1st line mTNBC. These were derived from market research with a range of clinicians responding to a structured survey covering a wide geography and hospital settings. For the purposes of the advisory board, treatments were grouped by agent alongside corresponding markets shares and presented for discussion (as presented in Table 18). The original slide used to inform this table is included within the model ("Raw_DM_trt share model sheet").

Table 18: Market share estimates presented for 1L mTNBC patients (Strategic North, MSD data on file)

1L mTNBC subsequent therapy	UK market share	Clinical comments received on the relevance for mTNBC treatment for patients in the UK.

	estimate (n=150)	
Carboplatin (or containing regimens)		
Carboplatin monotherapy	[redacted]	
Carboplatin + Docetaxel	[redacted]	Not commonly used
Gemcitabine + Carboplatin	[redacted]	Usage in early relapsers only; consider separately
Carboplatin + Paclitaxel	[redacted]	
Carboplatin + Epirubicin	[redacted]	Not used in NHS
Atezolizumab-containing regimens		
Atezolizumab + Nab-paclitaxel	[redacted]	Standard of Care in PD-L1 positive patients currently ~38%
Atezolizumab monotherapy	[redacted]	Used with nab-paclitaxel only
Carboplatin + Atezolizumab + Nab-paclitaxel	[redacted]	Not used in NHS
PARP inhibitor + Atezolizumab	[redacted]	Not used in NHS
Atezolizumab + Paclitaxel	[redacted]	Not used in NHS
Taxane single agents		
Paclitaxel monotherapy	[redacted]	Used
Docetaxel monotherapy	[redacted]	Small usage in mTNBC untreated patients due to toxicity
Nab-paclitaxel monotherapy	[redacted]	Small usage in private setting only; COVID guidelines permitted usage instead of paclitaxel due to improved safety
Capecitabine alone		
Capecitabine monotherapy	[redacted]	
Other < 5% market share		
Epirubicin + Paclitaxel	[redacted]	Not used in NHS
Epirubicin monotherapy	[redacted]	Not used in NHS
Docetaxel + Epirubicin	[redacted]	Not used in NHS
Docetaxel + Vinorelbine	[redacted]	Not used in NHS
Vinorelbine + Nab-paclitaxel	[redacted]	Not used – Vinorelbine is 2L/3L agent
Vinorelbine monotherapy	[redacted]	Not used – Vinorelbine is 2L/3L agent
Clinical trial	[redacted]	<1%

Clinical experts noted that the most likely 1st line chemotherapy options for patients included; paclitaxel, carboplatin (or combination of), gemcitabine + carboplatin or capecitabine. These are available regardless of PD-L1 testing status. However, patients with PD-L1 positive mTNBC (>1% immunohistochemistry SP142) would most likely be treated with Atezolizumab + nab-paclitaxel in the UK unless contraindicated due to fitness and/or comorbidities (in that case standard chemotherapies reported above would apply). Clinical experts also noted that treatment options for PD-L1+ve patients [redacted] being widely used in the UK as a result of the wide PD-L1 testing that has already been established for this indication.

Based on clinical feedback received, we conducted the following amendments on the market share estimates to inform the modelling;

- Increased the atezolizumab + nab-paclitaxel market share to reflect the prevalence of PD-L1 positivity at CPS≥10 in mTNBC (~38%)
- Removed chemotherapy treatment options reported in market research which were not considered as being widely used in the NHS
- Grouped and reweighted the remaining chemotherapy market shares as per clinical expert opinion. These would primarily be used to treat patients with PD-L1 negative mTNBC to sum up to 100% or for those in which atezolizumab + nab-paclitaxel is contraindicated due to fitness and/or comorbidities.

The final breakdown of market share estimates used to inform the 1L mTNBC options is included within the model ("Raw_DM_trt share model sheet"; also presented below).

Table 19: Final market share estimates applied within the model for 1L mTNBC (Table 82 of appendix)

Treatment regimen	UK market research share estimate	Model market share estimate validated by HCPs
Paclitaxel	[redacted]	[redacted]
Paclitaxel monotherapy	[redacted]	
Nab-paclitaxel monotherapy	[redacted]	
Carboplatin	[redacted]	[redacted]
Carboplatin monotherapy	[redacted]	
Carboplatin + Docetaxel	[redacted]	
Carboplatin + Epirubicin	[redacted]	
Carboplatin + Paclitaxel	[redacted]	[redacted]
Gemcitabine + Carboplatin	[redacted]	[redacted]
Atezolizumab + Nab-paclitaxel*	[redacted]	38%
Capecitabine	[redacted]	[redacted]
Notes: *uplifted to match the prevalence of PD-L1 positive IC population ~38%		

B14. PRIORITY QUESTION: It is stated that "only a brief summary of the NMA methods and results is provided below to contain the length of this document." in Appendix M of the CS. Please provide the full report of the NMA, making reference to the NICE DSU TSDs.

Please see the full NMA report provided as Commercial and Academic in confidence. As noted within the submission section B.3.3.3 the following assumptions had to be made for chemotherapy comparators for which no evidence base was available to inform an NMA, but clinical experts noted they are used as 1L therapies:

- Paclitaxel: OS assumed to be equal to taxanes (similar to Appraisal committee conclusions in TA639); however it is noted that taxanes differ in AE profile and therefore tolerability

- Capecitabine: OS assumed to be equal to taxanes due to lack of data specific to capecitabine being derived from the metastatic literature review that could be used in evidence synthesis

- Carboplatin + paclitaxel: OS estimated by assuming equal to gemcitabine + carboplatin due to to lack of connected network informing the relative efficacy of carboplatin + paclitaxel versus gemcitabine + carboplatin. This also avoids inconsistencies in long term survival projections versus atezolizumab + nab-paclitaxel.

The above assumptions are unlikely to drastically impact the cost-effectiveness results because these chemotherapies are understood to have limited impact on survival.

B15. In Section 3.3.3.1 the modelled OS curves based on KEYNOTE-355 were validated by the observed OS data.

a. Please clarify whether the KM-curves (observed OS) in Figure 17 of the CS are from KEYNOTE-522 or KEYNOTE-533

b. Please comment on the suitability of observed OS data from KEYNOTE-522 to validate modelled OS data based on KEYNOTE-355 given the differences in population between these two studies.

MSD acknowledge that the caption in CS Figure 17 is unclear and apologise for this. The KM curves in this figure represent the observed OS in KEYNOTE-522, not KEYNOTE-355. The modelled OS projections in the figure are derived based on OS data from KEYNOTE-355.

KEYNOTE-522 is a highly relevant source to validate the OS projections as it directly reflects the patient population considered in the decision problem and is the same source used to model transitions from the EF and LR health states. It enables the validity of the OS projections estimated using an external source (i.e. KEYNOTE-

355) to be assessed relative to the actual OS observed in the relevant patient population.

Adverse events

B16. Section B.3.3.5 (page 93): "The model considers all-cause grade 3+ AEs (incidence rate ≥ 5%). Additional AEs deemed as clinically relevant for inclusion in the economic modelling included:

- Diarrhoea (of Grade 2+)
- Colitis (of Grade 2+)

a. Please explain why these grade 2 AEs were deemed clinically relevant.

b. Provide justification why only grade 3+ AEs with an incidence rate of ≥ 5% were included.

These specific grade 2+ AEs were included in addition to grade 3+ AEs as they are expected to be associated with a high management cost (i.e. hospitalisation) and HRQoL burden, and to ensure consistency with previous NICE appraisals for IO therapies (e.g. TA428, TA766).[20, 43]

MSD would like to take this opportunity to clarify that although only grade 3+ AEs (with the exception of diarrhoea and colitis as explained above) were included in the model, the selection of which AEs to include was determined by the risk at any grade. As such, AEs of any grade which occurred with a frequency of ≥5% in either arm of the KEYNOTE-522 trial were eligible for consideration, and the corresponding grade 3+ event rates for the eligible AEs were incorporated into the model. Only grade 3+ AEs were included, as these are expected to have significant impact on resource utilisation and HRQoL. This selection approach could result in the inclusion of grade 3+ AEs occurring at a frequency of <5%. The cut-off of ≥5% was used to represent AEs occurring 'frequently', in line with common economic modelling methods. Inclusion of AEs occurring at a frequency of <5% would be expected to have a negligible impact on the cost-effectiveness results.

B17. In section B.3.3.5 (page 93) it is stated that: "In line with other IO submissions, the majority of AE costs (at grade 3+) are associated with hospitalization costs."

Please specify to which IO submissions this refers, including the TA identification number.

The specific IO submissions are referenced in CS section B.3.5.5 and in CS Table 66. For clarity, these refer to: TA519 (replaced by TA692; Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy),[44] TA737 (Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer),[45] TA684 (Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease),[46] and TA581 (Nivolumab with ipilimumab for untreated advanced renal cell carcinoma).[47]

Health related quality of life

B18. In the base case pooled health state utilities were used. Though in the CS it is explained that there is no statistically significant or clinically meaningful difference between the treatment arms, it is not clear why treatment-specific utilities could not be used in the base case. Please explain:

a. What could be the reason for the (slightly but consistently) lower utility scores in the pembrolizumab arm.

The slightly but consistently lower utility scores in the pembrolizumab arm may be in part explained by the more complex treatment regimen since pembrolizumab is an add on therapy to the neoadjuvant current standard of care. As such patients randomised in this arm experience more adverse events which subsequently may reduce utility scores.

b. Why treatment-specific utilities were not used in the base case.

Pooled utility results are used to inform the base case since the outputs of the analyses concluded did not show significant or clinically meaningful differences between the two treatment arms. The utility of a patient is more likely to be affected by the disease status, i.e. the patient remaining at the event free survival health state, not experiencing subsequent progression (locoregional or distant). In real life, a patient remaining event free but completing the neoadjuvant/adjuvant treatment course would cease to experience any treatment related AE disutility (applied in the model as one off QALY decrement), therefore experiencing a higher overall utility

regardless of treatment arm. For the purposes of modelling treatment-related HRQoL decrement associated with pembrolizumab is applied through AE disutility. Analysis of KEYNOTE-522 data is supportive of the approach used to estimate utility values (refer to supplementary confidential appendix provided alongside the original submission). Using pooled utilities maximises the data available to inform the analyses and is consistent with previous submissions in the neoadjuvant and adjuvant setting including TA424 but also the more recent TA766.[17, 20] Treatment related utilities have been explored in a scenario analysis.

B19. PRIORITY QUESTION: Based on KEYNOTE-522 the utility for the 'distant metastasis' health state was estimated to be [redacted]. Within the model, no distinction was made between patients with pre-progressed or post-progressed metastatic disease (see also Question B3). As mentioned in Appendix H, one other study (Huang et al. 2020 [ref 185 of the Appendices document]) assessing EQ-5D in metastatic TNBC patients is available, which examined the EQ-5D-3L data collected from patients enrolled in KEYNOTE-119 (previously treated metastatic TNBC patients). The mean utility for progression-free and progressed patients was 0.715 and 0.606 respectively. The difference (0.104) between the two was considered clinically meaningful. The utility used for the 'distant metastasis' health state in the model is very comparable to that of the progressed metastatic TNBC patients in the KEYNOTE-119 trial, however, the 'distant metastasis' state in the current model includes both progressed and not-progressed patients.

a. **Provide justification why this utility is representative for the 'distant metastasis' health state.**

MSD agrees with the ERG's conclusion that the difference reported in Huang et al 2020 can be considered clinically meaningful (since differences exceed 0.08). However, as noted above, this analysis concerns a different population. We do not advocate for direct study utility comparisons since population differences can impact upon the utility results.

The NICE reference case stipulates a preference for HRQoL data collected alongside the pivotal RCT to be used for the decision problem when these are

available. Alternative sources, if available, should be explored in sensitivity analysis where possible.[48]

Whilst we acknowledge that the EQ-5D collection from KEYNOTE-522 is still ongoing since most patients continue to remain relapse free, data from this trial can be considered as representative for this patient population and of the survival profile available to date. Please see separate utility report provided in a confidential appendix for more information.

b. Please provide separate utility estimates for progressed and not-progressed patients with distant metastasis from the KEYNOTE-522.

It is not feasible to estimate separate utility estimates for progressed and not-progressed patients with DM from the KEYNOTE-522 trial. MSD provided a separate confidential Appendix P which provides more information around the utility analyses conducted using patient level data from KEYNOTE-522. Table 3 within that report demonstrates that the number of questionnaires from patients that have experienced distant metastasis is very limited ([redacted] across both treatment arms). In addition, KEYNOTE-522 does not record the progression status for patients with distant metastasis. Whilst subsequent treatment data from KEYNOTE-522 are collected and these could be used to proxy the progression status once at the DM state, these remain immature and considering the limited EQ-5D questionaries available to date, these analyses would not be meaningful if conducted.

However, we have conducted two scenario analyses to assess the impact of the DM utility value. Please see analysis results under the response to B19 c. These scenarios explore a higher utility value in the DM setting within the current model structure.

c. Explain why the utility for the distant metastatic health state from KEYNOTE-522 seems relatively low compared to other studies assessing QoL of metastatic TNBC patients.

Data collected alongside the pivotal RCT is consistent with the NICE reference case requirements and therefore appropriate to inform the economic modelling. Nonetheless, we acknowledge that the EQ-5D collection from KEYNOTE-522 is still

ongoing since most patients continue to remain relapse free, and a small number of questionnaires was available for analyses to estimate utility once at DM setting (***** across both treatment arms). This may in part explain why the utility values at DM setting appear lower than those reported elsewhere in the literature and continued data collection from KEYNOTE-522 will offer more certainty around this model estimate. However we caution against over-interpreting these differences at this stage because the ***** DM derived utility is based upon mapping of 5L to 3L using the *van Hout* algorithm. Once the 5L value set is applied directly the DM utility is *****which is still lower but closer to those values reported elsewhere in the literature.

We would like to take the opportunity to offer some additional information from the KEYNOTE-355 1st line mTNBC study that was not included within the confidential appendix H since ID1546 is still ongoing. Utility results are provided based on disease progression status and on time to death approach (Table 20).

Table 20: Supplementary information reporting utility estimates from KEYNOTE-355

Study (citation)	Population	Progression category	Mean (95% CI) utility value	Time-to-death Category	Mean (95% CI) utility value
KEYNOTE-355	Metastatic TNBC PD-L1 CPS 10 score expression ≥ 10 (using 22C3 Dako Assay)	Progression-free survival	*****	>360 days	*****
				180 to 360 days	*****
				90 to 180 days	*****
		Progressive disease	*****	30 to 90 days	*****
				>30 days	*****
Abbreviations: mTNBC=metastatic triple-negative breast cancer.					

We conducted two scenario analyses using alternative data sources and assumptions to test the impact of the DM utility estimate on ICER using KEYNOTE-355 as a source of evidence for utility in the DM setting:

1. KEYNOTE-355: ***** (a weighted utility based on the total predicted LYs gained during pre-progression (*****) and the post-progression (*****) of the chemotherapy arm; the mean utility for progression-free and progressed patients was 0.761 and 0.647 respectively). The LYs gained were sourced from the cost-effectiveness analysis of pembrolizumab as first-line treatment for TNBC. We conducted this scenario analysis by setting the input in Cell F43 and G43 in the "Utility" sheet to *****.

2. KEYNOTE-119: 0.715 (pre-progression); please note that the utility of pre-progression (vs. the weighted average of pre-progression and post-progression) is used here to test the maximum impact on ICER. We conducted this scenario analysis by setting the input in Cell F43 and G43 in the "Utility" sheet to 0.715.

Results from the scenario analyses demonstrate that the ICER is not sensitive to the utility estimate used in the DM state (Table 21). The ICER increased 1.7% and 1.9% when the two alternative sources were used respectively.

Table 21: Comparison of ICER when varying the DM utility estimate

Scenarios	ICER (Cost £/QALY)
Base case	*5,940*
Scenario 1: Distant metastasis utility - KEYNOTE-355 (weighted)	6,038
Scenario 2: Distant metastasis utility - KEYNOTE-119	6,054

B20. As per the NICE reference case, the health-related quality of life data included in the model was based on EQ-5D data from the KEYNOTE-522 trial. In the KEYNOTE-522 trial, HRQoL data was also collected with the (breast) cancer-specific questionnaires EORTC QLQ-C30 and QLQ-BR23. Mapping methodologies for EORTC QLQ-C30 and QLQ-BR23 to EQ-5D do exist. Please explore the effect on the cost-effectiveness results providing a scenario with HRQoL data based on the mapped EORTC QLQ-C30 and QLQ-BR23 data from KEYNOTE-522.

The NICE Methods Guide[48] states that EQ-5D data from the relevant clinical trial is the preferred source of utility values, although EQ-5D data sourced from the literature can be used if data from the clinical trial are not available. This is considered the reference case for economic analyses. The guide also states that utilities can be estimated by mapping from other HRQoL measures to EQ-5D if EQ-5D data are not available from the trial or the literature, however this may be considered a departure from the reference case. Mapping from one measure to another introduces uncertainty which is not justified when trial-based EQ-5D data are available. Therefore, MSD do not consider it necessary or appropriate to conduct the analyses based on EQ-5D mapped from the EORTC-QLQ-C30 or EORTC-QLQ-BR23.

Whilst MSD acknowledge that the EQ-5D values used in the model were mapped from the EQ-5D-5L to the EQ-5D-3L, this approach is in line with NICE's position statement on the use of EQ-5D in the reference case analysis [49] and has been applied in numerous prior NICE appraisals. Mapping from the 5L to the 3L version of the EQ-5D is expected to introduce significantly less uncertainty compared with mapping to the EQ-5D from a disease-specific measure.

B21. The event-free health state EQ-5D utility values were estimated based on health status (on or off treatment). Additionally, disutilities related to grade 3+ AEs are included based on the difference between the utilities of the event-free on treatment health state with or without grade 3+ AEs (Table 50 of CS).

a. Please confirm that the 'AE disutility' in Table 49 of the CS should be [redacted] instead of [redacted] – or that this is the actual AE disutility and is in the wrong table?

CS Table 49 summarises the estimated utilities in the EF health state by treatment status and reflects the outputs of regression model #2 (on treatment vs off treatment). The AE disutility was calculated from the outputs of regression model #3 (EF with AE vs EF without AE; CS Table 50) and this value has therefore been included in Table 49 in error. MSD apologise for this and confirm that the 'AE disutility' row of that table should be removed – please see Table 22 for a corrected version of the table.

Table 22: Estimated utilities in event-free state by treatment status (pooled treatment arms)

Coefficient	Pooled Value (N=1126 patients#)	SE	95% CI
Event-free, on treatment	*****	*****	*****
Event-free, off treatment	*****	*****	*****

EQ-5D score during baseline is not included. #Number of records analysed per category is provided in Appendix N. Abbreviations: SE, standard error; CI, confidence interval.

b. Please comment if the 'AE disutility' from Table 49 is AE-related and not related to other factors, such as the intravenous administration.

Please see the response to question B21 part a. The AE disutility presented in CS Table 49 was included in the table in error and refers to the disutility associated with a grade 3+ AE.

c. Section 3.4.4: "The disutility associated with AEs from the pooled utility analysis was estimated at [redacted]. The treatment specific disutilities in the event-free state on treatment period was estimated as [redacted] for the pembrolizumab arm and [redacted] for the placebo arm. The pooled disutility associated with AEs are applied in the base case." Please specify here that this is the disutility associated with grade 3+ AEs.

Yes, the disutility of ***** referenced in CS B.3.4.4 refers to the disutility associated with grade 3+ AEs as estimated from regression model #3 described in CS B.3.4.1 and presented in CS Table 50.

d. Section 3.4.4: "The grade 3+ AE disutility were also applied to the grade 2+ AEs included in the model (see section B.3.3.5)." Please justify if the grade 3+ AE disutility is representative for the grade 2+ AEs.

The grade 2+ AEs considered in the model (diarrhoea and colitis) were included as they were deemed to be clinically relevant in terms of healthcare resource use and HRQoL (please see response to question B16). By extension it is therefore considered plausible to assume that the disutility of these grade 2 AEs is comparable to that observed for grade 3+ AEs. As the incidence of these grade 2+ AEs was higher in the pembrolizumab arm than the placebo arm, this is a conservative assumption that may bias against pembrolizumab.

Healthcare resource use and costs

B22. Time on treatment curves.

a. Please explain the seemingly large difference between the time to end of neoadjuvant treatment (figure 18) and the time to end of surgery (figure 20 in the CS). Is there a waiting time before surgery, and if so, how are patients managed in the meantime?

According to the KEYNOTE-522 protocol, patients underwent definitive surgery 2 to 6 weeks after the last cycle of the neoadjuvant phase, and thus there was a waiting time before surgery. In the model, resource use associated with the EF state was applied to patients waiting for surgery.

b. Please explain why, in the time to end of treatment course (figure 19), there is no placebo curve included, and why the end of neoadjuvant treatment is represented here as a fixed point in time.

In the model, patients who are treated with chemotherapy alone do not receive adjuvant therapy. Therefore, the placebo curve was not displayed to avoid confusion. The fixed point in time was introduced in retrospect manually for illustrative purpose to show the end of neoadjuvant treatment for a typical patient according to the KEYNOTE-522 study protocol. Please note that the vertical line introduced in the figure does not affect the model in any case. Following on from the ERG's question, MSD have reviewed this acknowledge that it created confusion in the interpretation of these graphs. Further, this was placed in error on ~week 35 when in fact the end of neoadjuvant treatment is after 8 cycles or 24 weeks). To avoid any confusion we propose that the ERG does not use the original Figure 19 of Document B and instead use the updated graphs supplied below which depict the time to end of treatment by treatment arm.

c. Please provide a figure which includes all 3 types of curves in one (time to end of neoadjuvant treatment, time to end of surgery, and time to end of treatment course).

The requested curves are provided in Figure 5A-B below. Each figure includes all 3 types of curves (time to end of neoadjuvant treatment, time to end of surgery, and time to end of treatment course). Please note that the time to end of treatment course (placebo as adjuvant therapy) was added to Figure 5B for illustrative purpose, however as explained in our response to Question B22b, patients treated with chemotherapy alone do not receive adjuvant therapy.

Figure 5: Time to end of neoadjuvant treatment/surgery/treatment course (Pembrolizumab + chemotherapy)
A) Pembrolizumab + chemotherapy

*****

B) Chemotherapy

*****

B23. Table 54 of the CS shows that relative dose intensity and treatment allocation can be different between treatment arms and were used as observed to feed the model. Given the double-blind nature of the RCT, it may not be very likely that the treatment allocation would be willingly/meaningfully different between treatment arms. Relative dose intensity may have been impacted by AEs (also from pembrolizumab) occurring but may just as well be assumed equal between arms Please explain why using treatment allocation as observed would be the preferred approach.

The RDI and treatment allocations by trial arm were used in the model to accurately reflect the costs associated with the observed trial outcomes which are modelled in the analysis. MSD agree that treatment allocations and RDIs of component regimens should not be meaningfully different between the two arms of the KEYNOTE-522 trial or in the context of this appraisal, and do not have a particular preference for this arm-specific approach over an approach in which these inputs are pooled across treatment arms.

Of the six component regimens presented in CS Table 54, observed RDIs in each arm were identical for four regimens and less than 1 percentage point different for the two carboplatin regimens. Treatment allocations were 100% in both arms for paclitaxel and cyclophosphamide, and the between-arm differences were ***** percentage points for each of the remaining four regimens. MSD do not believe this should be considered a meaningful difference between arms and highlight that assuming the same RDIs and treatment allocations in each treatment arm would have a negligible impact on the ICER.

Company's base-case and sensitivity analyses

B24. PRIORITY QUESTION The incremental cost-effectiveness plane resulting from the probabilistic sensitivity analysis (Figure 21 in the CS) show a couple of quite distinct outliers in the north-east quadrant. Please provide:

1) **A potential explanation for these outliers.**

The outliers in the north-east quadrant were attributed to lower EFS of the chemotherapy arm in some interactions. The base case analysis used the piecewise log-normal distribution to extrapolate the EFS of the chemotherapy arm. For illustrative purpose, we compared the simulated parameters specific to log-normal EFS of chemotherapy (Table 23) and the ICERs (Table 24). Of all three iterations, the simulated EFS parameters resulted in lower EFS for chemotherapy, leading to reduced ICER for pembrolizumab + chemotherapy vs chemotherapy.

Table 23: Simulated parameters for the EFS of chemotherapy

Parameter	Base case	Iteration #28	Iteration #545	Iteration #644
EFS - Chemotherapy - Piecewise - 50 - Log-normal - A - meanlog	[redacted]	[redacted]	[redacted]	[redacted]
EFS - Chemotherapy - Piecewise - 50 - Log-normal - B - log(sdlog)	[redacted]	[redacted]	[redacted]	[redacted]

Table 24: Comparison of results from PSA iterations

	Base case		Iteration #28		Iteration #545		Iteration #644	
	Pembro + CTX	CTX	Pembro + CTX	CTX	Pembro + CTX	CTX	Pembro + CTX	CTX
Total Costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£/QALY)	5,940		795		-2,826		-381	

Abbreviations: CTX, chemotherapy.

2) **An update of the model including the tracking of parameter draws used in the PSA simulations, to be able to detect the source of any outliers.**

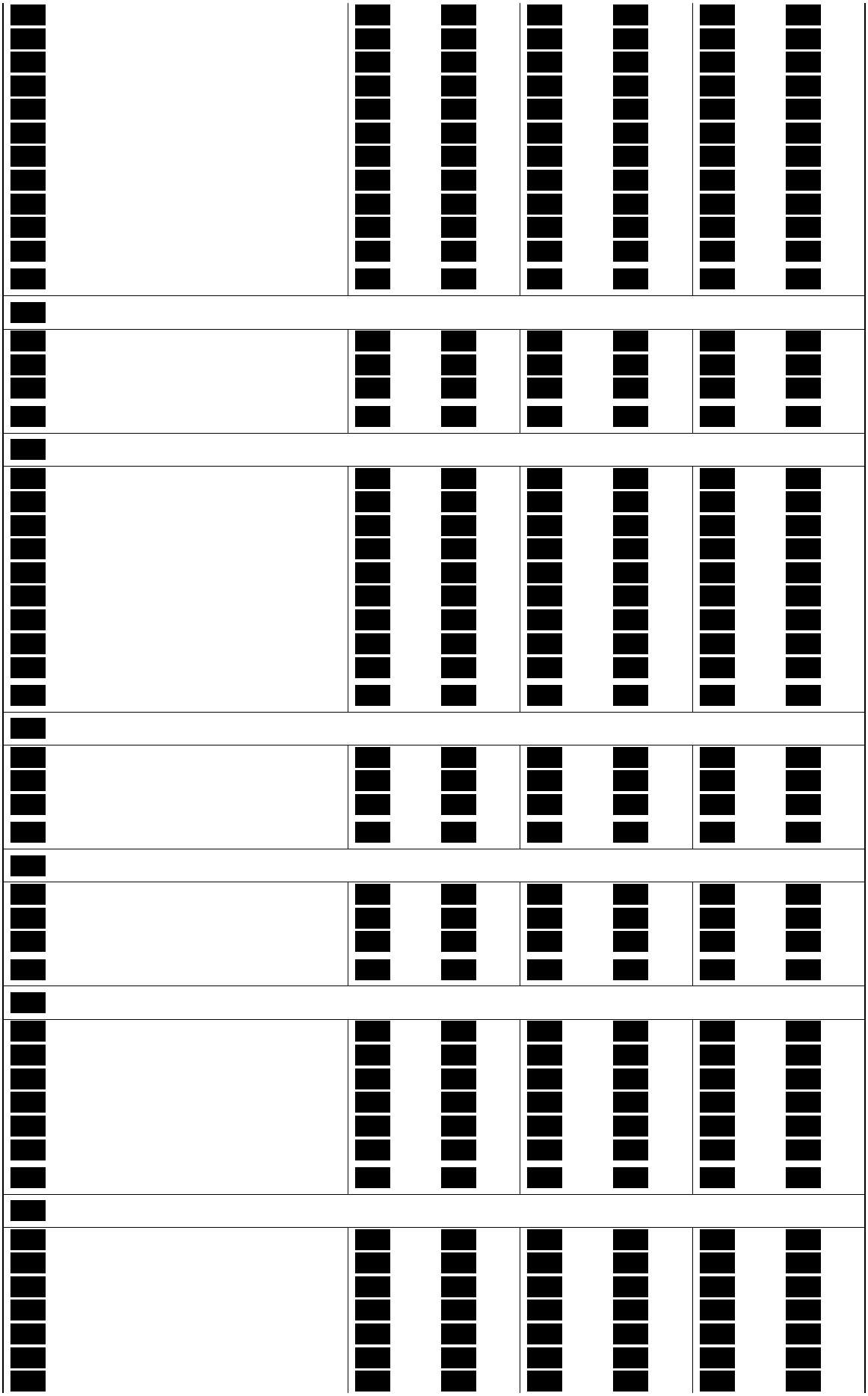
MSD apologises for the lack of tracking of PSA parameter draws used to inform the PSA within the originally submitted model. This was originally done to speed up the computational process. To improve transparency we have added a 'PSA_input' sheet to the model to record sampled values for each parameter and rerun the PSA

results with our current base-case assumptions. A new version of the economic model has been shared as part our clarification questions response.

Appendices

Table 25: Participants With Specific Concomitant Medications (Incidence ≥ 5% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab + chemotherapy / Pembrolizumab		Placebo + chemotherapy / Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	783		389		1,172	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



[redacted]

Every participant is counted a single time for each applicable specific concomitant medication. A participant with multiple concomitant medications within a medication category is counted a single time for that category.

A medication class or specific medication 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.

Database Cutoff Date: 23MAR2021

Table 26: Additional notes for studies excluded for 'study design' reason

Title	In/Excluded	Reason	*Additional Notes*
Efficacy and safety of vinorelbine plus cisplatin vs. Gemcitabine plus cisplatin for treatment of metastatic triple-negative breast cancer after failure with anthracyclines and taxanes	Excluded	Study design	*Non-randomized*
Tumour mutational burden and clinical outcomes with first-line atezolizumab and nab-paclitaxel in triple-negative breast cancer: Exploratory analysis of the phase iii impassion130 trial	Excluded	Study Design	*Prognostic/predictive/genomic/correlative*
No survival benefit of chemotherapy escalation in patients with pcr and "high-immune" triple-negative early breast cancer in the neoadjuvant wsg-adapt-tn trial	Excluded	Study design	*Prognostic/predictive/genomic/correlative*
Pik3ca h1047r mutation associated with a lower pathological complete response rate in triple-negative breast cancer patients treated with anthracycline-taxane-based neoadjuvant chemotherapy	Excluded	Study design	*Prognostic/predictive/genomic/correlative*
Pembrolizumab plus neoadjuvant chemotherapy improves pathologic complete response rates in triple-negative breast cancer	Excluded	Study Design	*Review/Letter/Expert opinion*
Tumor mutational burden and immune infiltration as independent predictors of response to neoadjuvant immune checkpoint inhibition in early tnbc in geparnuevo	Excluded	Study design	*Prognostic/predictive/genomic/correlative*
Genomic profiling and clinical outcomes with first-line atezolizumab and nab-paclitaxel in triple-negative breast cancer: An exploratory analysis from the phase 3 impassion130 trial	Excluded	Study Design	*Prognostic/predictive/genomic/correlative*
Pre-operative pembrolizumab (pembro) with radiation therapy (rt) in patients with operable triple-negative breast cancer (tnbc)	Excluded	Study Design	*Non-randomized*
Tailored neoadjuvant epirubicin, cyclophosphamide and nanoparticle albumin-bound paclitaxel for breast cancer: The phase ii neonab trial-clinical outcomes and molecular determinants of response	Excluded	Study design	*Non-randomized*
Cisplatin plus gemcitabine versus paclitaxel plus gemcitabine as first-line therapy for metastatic triple negative breast cancer	Excluded	Study Design	*Phase not specified*
Association of germline variant status with therapy response in high-risk early-stage breast cancer: A secondary analysis of the geparocto randomized clinical trial	Excluded	Study Design	*Prognostic/predictive/genomic/correlative*
Germline mutation status and therapy response in high-risk early-stage breast cancer: A secondary analysis of the geparocto randomized clinical trial (nct02125344)	Excluded	Study Design	*Prognostic/predictive/genomic/correlative*
Pembrolizumab plus neoadjuvant chemotherapy improves pathologic complete response rates in triple-negative breast cancer	Excluded	Study Design	*Review/Letter/Expert opinion*
Genomic analysis of the calgb 40603(alliance) neoadjuvant trial in tnbc identifies immune features associated with pathological complete response and event-free survival	Excluded	Study Design	*Prognostic/predictive/genomic/correlative*
Combined targeted therapies for first-line treatment of metastatic triple negative breast cancer-a phase ii trial of weekly nab-paclitaxel and bevacizumab followed by maintenance targeted therapy with bevacizumab and erlotinib	Excluded	Study Design	*Non-randomized*
Circulating tumor DNA and biomarker analyse from the lotus randomized trial of first-line ipatasertib and paclitaxel for metastatic triple-negative breast cancer	Excluded	Study Design	*Prognostic/predictive/genomic/correlative*

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of locally advanced non-metastatic triple-negative breast cancer [ID1500]

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 Now is the UK charity that's steered by world-class research and powered by life-changing care. We provide support for today and hope for the future.
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.]	In the last 12 months, Breast Cancer Now has not received any funding from the specific manufacturers listed in the appraisal matrix.

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	N/A
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. Whilst we have so far been unable to find patients with direct experience of this treatment via the clinical trial, we have spoken to patients with high-risk primary triple negative breast cancer to inform our submission.
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?	A diagnosis of breast cancer can cause considerable anxiety to the patient as well as their family and friends. The initial diagnosis can be extremely shocking and impact on people's emotional wellbeing, whilst in the longer-term, the fear of breast cancer returning or spreading to other parts of the body (such as the bone, liver and brain) which is known as secondary breast cancer and is incurable can be extremely frightening and distressing for patients.

	Breast cancer patients tell us about the impact of the disease on their lives, for example the side effects of treatments and visits to hospital taking a significant toll on their general wellbeing, everyday activities, ability to work and relationships. Around 15% of all breast cancers - over 8,000 cases a year in the UK - are triple negative breast cancer. This type of breast cancer is less common but often more aggressive than other types of breast cancer. It is more common in women with an inherited altered BRCA gene, women aged under 40 and black women. A patient has explained to Breast Cancer Now that "when I thought my diagnosis couldn't get an any worse, I was given the news that I had triple negative breast cancer…..which can't be treated with some common treatments such as hormone treatments or trastuzumab, but that chemotherapy would be the only option for my treatment". The risk of triple negative breast cancer returning and spreading to other parts of the body in the first few years after treatment is higher than it is for other breast cancers. A patient with primary triple negative breast cancer told us: "It's daunting to know that your breast cancer is less common and more aggressive than other types of breast cancer, with a higher risk of returning in the years immediately following treatment – but at the same time there are fewer treatment options available to reduce that risk."
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Treatment for triple negative breast cancer is usually a combination of surgery, radiotherapy and chemotherapy. Chemotherapy remains the mainstay of drug treatment for primary breast cancer. Patients with triple negative breast cancer may receive neoadjuvant chemotherapy as their first treatment with a standard combination of an anthracycline and taxane plus an additional platinum (carboplatin). Standard

	adjuvant chemotherapy may include combined anthracycline (epirubicin or doxorubicin) and cyclophosphamide, plus a taxane regime (docetaxel or paclitaxel). A patient with this type of breast cancer who was diagnosed in 2021 explains: "I had chemotherapy with epirubicin and cyclophosphamide followed by paclitaxel. Whilst I feel that I was lucky in relation to the side effects I experienced, I did suffer from dizziness and hair loss as well increasing fatigue as chemotherapy progressed which impacted my day to day life. I was less productive at work, was unable to continue running and was asleep before 8pm most nights." Patients with this type of breast cancer generally feel that there have been fewer advances in the treatment options available to them on the NHS to reduce the risk of recurrence and breast cancer spreading to other parts of the body. They desperately want to see new effective treatments which could significantly reduce the risk of recurrence and provide them with reassurance.
8. Is there an unmet need for patients with this condition?	Yes. People diagnosed with this type of breast cancer are faced with the frightening reality of limited treatment options and a type of breast cancer which can be more aggressive and is associated with an initial higher risk of recurrence than other types of breast cancer and potentially poorer prognosis – with shorter overall survival than other types of breast cancer. This new treatment option could provide an important new milestone in treatment for some patients with primary triple negative breast cancer. There is a significant need for new treatments which can increase the pathologic complete response rate and increase event free survival.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The phase 3 KEYNOTE-522 trial demonstrated that when immunotherapy drug pembrolizumab is given in combination with chemotherapy before surgery, and then as a monotherapy after surgery, it can significantly reduce the likelihood of high-risk triple negative breast cancer recurring or spreading to other parts of the body, where it becomes incurable secondary breast cancer. Crucially, this promising new

	treatment could potentially prevent more lives being lost to breast cancer. A patient with primary triple negative breast cancer explains: “I found it frustrating that there is so much talk about the research going on into potential treatments for triple negative breast cancer, but knowing that my treatment would be limited to standard chemotherapy that had been around for years. It’s so heartening to finally hear that there is a new treatment for triple negative breast cancer that can reduce the risk of it coming back and spreading to other parts of the body that other women should be able to benefit from.” The trial results have shown that: - This treatment had a statistically significant event-free survival (EFS) benefit compared with standard chemotherapy alone. The estimated EFS benefit at three years was 84.5% with pembrolizumab compared to 76.8% in the standard chemotherapy arm. The risk of disease progression was 37% lower with pembrolizumab compared to placebo-chemotherapy. This could have a significant positive impact on a patient’s wellbeing, as we know that the fear of the cancer returning is a significant burden for this group of patients and impacts family and friends too. Also there would be an important benefit in being able to avoid having to go through treatment again if the cancer returned as patients could avoid negative physical and quality of life impacts. - Earlier analysis presented in 2019 also showed the addition of pembrolizumab significantly increased pathological complete response rate (pCR) compared to chemotherapy alone, with pCR observed in 64.8% of patients who received pembrolizumab versus 51.2% in patients who received chemotherapy alone. This could reduce the size of the tumour in the breast and potentially mean less extensive surgery in patients that may have otherwise required a mastectomy. This is significant for patients as it can reduce the treatment burden for them and potentially reduce the impact of surgery on body image and make the recovery quicker. Patients tell us that the impact of a mastectomy can be significant for them so treatments which can potentially allow patients to have less extensive surgery is welcomed.

	- Furthermore, analyses suggest that response to neoadjuvant treatment provides important prognostic information, with pathological complete response potentially correlating to disease-free survival. As set out in the NICE document 'Early and locally advanced breast cancer: diagnosis and management [J] Evidence reviews for neoadjuvant treatment' an improvement in pathological complete response can be a surrogate for improved long-term outcomes in triple negative breast cancer. Therefore, this new treatment could be an important step forward in the options available for a group of patients with a high longstanding unmet need. - The results show that this treatment is beneficial regardless of PDL1 status which differs to this treatment in the metastatic (secondary) setting. This means there is no need for a test to be used which from a patient perspective is positive as waiting for results can be particularly difficult and a stressful time and also from an NHS capacity point of view this is beneficial and will enable chemotherapy to be given as soon as possible in the neoadjuvant setting. We understand that the study continues to follow-up for overall survival (OS) which was a secondary endpoint.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	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 undertake treatments will vary, however, as long as all the side effects are clearly discussed with the patient, they can weigh up the benefits and risks with their healthcare team. Patients may experience more side effects when pembrolizumab is added into their treatment regimen versus chemotherapy alone, which could potentially have a negative impact on some patient's quality of life. Looking across both the neoadjuvant and adjuvant phases of pembrolizumab, the trial highlighted that adverse effects occurred in 77.1% of patients in the pembrolizumab-chemotherapy arm, compared to 73.7% of patients receiving chemotherapy alone. Most common adverse events of any grade included

	fatigue, nausea, alopecia and anaemia. Discontinuation of pembrolizumab-chemotherapy because of adverse events occurred nearly twice the amount in the pembrolizumab-chemotherapy arm versus chemotherapy alone (27.7% versus 14.1%). Immune adverse events of any grade occurred in 33.5% of the patients receiving pembrolizumab-chemotherapy and 11.3% in the chemotherapy alone group. The study highlights that most of these were low grade and managed with treatment interruption or medication which is important to consider. It is important to recognise that patients will often conclude that the benefits of a treatment – in this case the reduction in risk of recurrence - will outweigh the risks associated with potential side effects. A patient with primary triple negative breast cancer told us: “I know with this new treatment that, neo-adjuvantly at least, you would have chemotherapy alongside pembrolizumab, so you may still get all of those chemotherapy side effects, and pembrolizumab may possibly give you the same/other side effects, but if I’d been offered the choice, I would have taken pembrolizumab on the basis of the reduction in risk of recurrence.” This treatment would also require regular trips to the hospital to receive both pembrolizumab and chemotherapy. In the neoadjuvant setting, there wouldn’t be extra appointments, but the chemotherapy appointments would be longer to accommodate giving the additional drug, pembrolizumab. In the adjuvant setting, they would be additional appointments. However, any burden on patients and their families or carers may be outweighed by the benefits of receiving the treatment and there are already examples in breast cancer where there are new adjuvant treatments and patients accept the additional treatment and appointment burden for the known benefits that the treatment could bring.
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.	- The study looked particularly at high-risk primary triple negative breast cancer. - Unlike pembrolizumab in the metastatic (secondary) setting, pembrolizumab in this primary breast cancer indication showed a benefit regardless of PD-L1 expression
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?	N/A.

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • A diagnosis of primary triple negative breast cancer can cause considerable anxiety to patients as well as their family and friends, including fear of recurrence or fear of it spreading to other parts of the body where it becomes incurable. • This fear and anxiety can be heightened for patients diagnosed with triple negative breast cancer as generally treatment options for triple negative breast cancer remain limited, and triple negative breast cancer tends to be more aggressive and is associated with an initial high risk of recurrence and poorer prognosis than other types of breast cancer. • Immunotherapy drug, pembrolizumab in combination with chemotherapy as a neoadjuvant treatment and then followed as a monotherapy as an adjuvant treatment after surgery could be an important new milestone and advancement in the treatment of certain patients with primary triple negative breast cancer by significantly reducing the risk of recurrence, including secondary breast cancer where the breast cancer becomes incurable. • Like with all breast cancer drugs, the treatment can come with some side effects which can impact negatively on patients' day to day lives. It would be important that the risks and benefits of treatment were discussed with the patient and patients may believe that the benefits outweigh the potential of side effects.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of locally advanced non-metastatic triple-negative breast cancer [ID1500]

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 the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NCRI-ACP-RCP-RCR**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NCRI-ACP-RCP-RCR**
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.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Triple negative breast cancer (TNBC) has the worst prognosis amongst breast cancer subtypes, and accounts for 10-20% of new breast cancer diagnoses. Polychemotherapy regimens have been shown to have benefit in improving disease specific and overall survival outcomes, and thus are recommended for most patients with TNBC, with sequential use of a taxane and anthracycline/cyclophosphamide combination being one of the preferred regimens in international guidelines [1] [2] . Although chemotherapy may be given in either the adjuvant or neoadjuvant (pre-operative setting), neoadjuvant chemotherapy is increasingly used as an opportunity to both downstage tumours to facilitate surgical treatments, and to determine tumour sensitivity to treatment, to provide prognostic information and to guide decisions about further systemic therapies. The principal aim of neoadjuvant therapy in TNBC is to induce a pathological complete response (pCR) to systemic therapy. In TNBC, pCR has been shown to be highly correlated with event-free survival [3]. In addition to this prognostic information, it has been shown that failing to achieve a pCR allows the addition of further adjuvant therapy with capecitabine following breast surgery, with a consequent improvement in disease-free survival [4], although the evidence for this is equivocal [5]. Finally, the use of neoadjuvant therapy

	can potentially permit the down-staging of surgery to both the breast and axilla, and such down-staging may reduce both the morbidity and healthcare costs associated with surgery. The pivotal study reporting the use of pembrolizumab in the neoadjuvant setting in early TNBC is the KEYNOTE-522 study, which has recently published an initial interim analysis of the first 602 patients randomised [6]. KEYNOTE-522 compared neoadjuvant paclitaxel/carboplatin with pembrolizumab or placebo, followed by anthracycline/cyclophosphamide chemotherapy prior to surgery. Following definitive surgery, patients continued either pembrolizumab or placebo three weekly for up to 9 cycles. Overall, patients receiving pembrolizumab/chemotherapy had better pCR rates that patients receiving placebo/chemotherapy (64.8% vs 51.2%, p<0.001). At median follow-up of 15.5 months, event-free survival was 11.8% in the placebo arm and 7.4% in the pembrolizumab arm (HR 0.63, 95% CI 0.43-0.93). Pathological complete response rates according to PD-L1 status were 68.9% in the pembrolizumab arm and 54.9% in the placebo arm for PD-L1 positive patients and 45.3% and 30.3% respectively in PD-L1 negative patients. Updated EFS data was presented at the European Society of Medical Oncology meeting in 2021 [7]. This data shows 36-month EFS of 84.5% in the pembrolizumab group versus 76.8% in the placebo group (HR 0.63, 95% CI 0.48-0/82, p=0.0003). There was a trend towards improved overall survival in the pembrolizumab group (HR 0.72, 96% CI 0.51-1.02). This data has however not yet been made available in a peer-reviewed publication.

7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The most significant clinical response for an individual is pathological complete response, as it is highly prognostic for TNBC patients. From the patient's perspective the possibility of surgical de-escalation and breast conservation may be of important psychological value.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	A patient-level meta-analysis of neoadjuvant systemic therapy trials reported a pCR rate of 33.6% in patients with TNBC [3]. More recent data suggests that the addition of platinum salts to neoadjuvant treatment regimens can achieve higher pCR rates, in the region of 53-58% [8 9]. Clearly there remains the potential to improve pCR rates in this context. In addition, the lack of a pCR in the TNBC sub-type categorised using residual cancer burden (RCB) estimates shows that RCB 2 (moderate) and RCB3 (extensive) disease is associated with much higher rates of relapse and death [10]. Many patients in this setting of TNBC non-pCR are essentially peri-metastatic. Therefore, achieving pCR remains the gold standard outcome, and an increase in the percentage of patients achieving this is highly desirable.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	There is currently considerable heterogeneity in the treatment of TNBC in the NHS. Patients with T2 and above tumours will generally be treated with neoadjuvant chemotherapy, as will node positive patients. There is variation in practice nationally in the selection of chemotherapy regimens, with some patients receiving anthracycline-taxane combinations and a proportion receiving platinum-containing regimens. Patients who do not obtain a pathological complete response to neoadjuvant therapy may be considered for capecitabine following definitive breast surgery.

	T1 tumours will generally be treated with primary surgery, with adjuvant chemotherapy given dependent on final histopathology.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Current NICE guidance [NG101] recommends offering neoadjuvant chemotherapy for ER negative breast cancer as an option to reduce tumour size; the guidance for TNBC suggests consideration of a neoadjuvant chemotherapy regimen containing both platinum and anthracycline. International guidelines (St Gallen) recommend neoadjuvant systemic therapy as the preferred initial approach for women with stage 2/3 TNBC [2]. However, at the St Gallen Consensus Conference in March 2021, 90% of those surveyed would not add an immune checkpoint inhibitor to neoadjuvant chemotherapy for TNBC, and 81% do not currently see PD1/PD-L1 testing affecting the recommendation for the use of immune checkpoint inhibitors in the context.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Generally, the pathway of care is well-defined, and most clinicians would agree with the guidance/treatment pathways outlined above. However, there is clearly heterogeneity in the types of neoadjuvant chemotherapy agents used (+/-platinum agents), with some centres routinely giving platinum agents and other not adding it. In addition, treatment of patients with TNBC who do not achieve pCR with neoadjuvant chemotherapy is also non-standardised.
• What impact would the technology have on the current pathway of care?	The benefit of adding pembrolizumab to neoadjuvant chemotherapy is unclear. However, and potentially irrespective of PD-L1 status, the combination of pembrolizumab and chemotherapy achieved a pCR rate of 64.8% versus 51.2% for chemotherapy alone.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Pembrolizumab is not currently approved for use in breast cancer.
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics should deliver systemic anti-cancer therapy, as is currently the case
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Most chemotherapy units are now familiar with giving immunotherapies (IOs) due to their extensive use in other solid cancers, so with respect to training there should be minimal additional training required. Pharmacies will be familiar with handling the drug due to its use in the other disease settings.
11. Do you expect the technology to provide clinically	The addition of neoadjuvant pembrolizumab increased pCR rates from 52.2% to 64.8% in the KEYNOTE-522 trial[6]. Furthermore, interim analysis at a median follow-up of 15.5 months suggested improved EFS in the neoadjuvant/adjuvant pembrolizumab arm of the study (HR0.63). More recently presented data

meaningful benefits compared with current care?	confirms improved EFS at 36 months median follow-up, with a trend towards (but not reaching statistical significance) improved overall survival[7].
• Do you expect the technology to increase length of life more than current care?	The KEYNOTE-522 results presented at ESMO suggest an improved EFS with pembrolizumab plus chemotherapy. However, a significant overall survival benefit was not seen at the 36 month follow up, although there was a trend towards improved survival. Follow-up is ongoing and further data is awaited.
• Do you expect the technology to increase health-related quality of life more than current care?	It is likely that an increased pCR rate will increase the potential for surgical down-staging, as some studies have shown pCR to be a predictor of breast conservation in patients receiving neoadjuvant systemic therapy [11]. Breast conserving surgery has been shown to be associated with better quality of life outcomes than mastectomy +/- breast reconstruction [12]. It therefore seems reasonable to infer that there may be an improvement in HRQoL associated with the potential increase in pCR rates seen from using this technology, although rates of surgical downstaging have not been reported in KEYNOTE-522. This must be considered in the context of a potential increase in adverse events seen with the use of immune checkpoint inhibition.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The KEYNOTE-522 study reported that pCR rates were higher in patients with PD-L1 positive tumours. No other biomarkers predictive of response to pembrolizumab have yet been identified. However, there is significant heterogeneity between the assays used to evaluate PD-L1 expression, with several different antibody clones in use, and different cut-offs for positivity used between the clones. It is clear therefore that there is not yet an optimal biomarker predictive of response to pembrolizumab, although based on the KEYNOTE-522 data it would appear that the 22C3 pharmDx assay is currently the best available predictor of response in this context. Other biomarkers and technologies not yet fully explored in this setting include whole genome sequencing data and related gene expression data.

The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	If the regimen from KEYNOTE-522 were to be used: In the neoadjuvant phase: Intravenous pembrolizumab at 200mg every three weeks, plus paclitaxel 80mg/m^2 once weekly with carboplatin* AUC 5, 3 weekly for 12 weeks, followed by continued intravenous pembrolizumab 200mg every three weeks plus epirubicin 90mg/m^2 with cyclophosphamide 600mg/m^2 once every three weeks for 12 weeks. *Carboplatin could also be given AUC 1.5 on a weekly basis. In the adjuvant phase: Intravenous pembrolizumab 200mg once every three weeks for up to 9 cycles. The standard of care would comparatively be either: 1. Carboplatin AUC 5, 3 weekly and paclitaxel 80mg/m² weekly for 12 weeks followed by Epirubicin 100mg/m² and Cyclophosphamide 600mg/m² for nine weeks

	2. Docetaxel 100mg/m² administered i.v. on day 1 every 21 days for four cycles, followed by epirubicin 90 mg/m² plus cyclophosphamide 600mg/m², both administered intravenously (i.v.) on day 1 every 21 days, for six cycles followed by docetaxel No significant practical differences with respect to time required within treatment units.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Although improved pCR rates appear to be related to PD-L1 positivity in the published data, the benefit (in terms of improved pCR rates or EFS) of pembrolizumab is not restricted to PD-L1 positive patients, and therefore PD-L1 testing would not necessarily be a good biomarker for patient selection. As discussed above there are no other good biomarkers at present which can be used to select patients for immune checkpoint inhibition. A comprehensive review of potential companion biomarkers has not been completed.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Whilst there is early evidence of improved pCR and improved EFS in a single trial, an overall survival benefit has not yet been established. For everyone achieving pCR there would be an improvement in risk of relapse and death.
• Is the technology a 'step-change' in the management of the condition?	Not currently and not until further data is available on longer term outcome and toxicity data related to the adjuvant treatment which of course may impact on outcome.
• Does the use of the technology address any particular unmet need of the patient population?	With required longer term and toxicity data the addition of pembrolizumab may improve pCR rates and potentially longer-term outcome with longer-term EFS and mature OS data awaited
17. How do any side effects or adverse effects of the technology affect the	In the KEYNOTE-522 trial, any-grade adverse events of special interest occurred in 773 (99.0%) patients in the pembrolizumab plus chemotherapy group compared with 388 (99.7%) patients in the placebo plus chemotherapy group[6]. The most common AEs of interest were infusion-related reactions (132 [16.9%] and 43 [11.1%], severe skin reaction (36 [4.4%] and 4 [1.0%], respectively), hypothyroidism (107 [13.7%] and

management of the condition and the patient's quality of life?	two [1%], respectively), hyperthyroidism (36[4.6%] and 2 [0.3%], respectively and adrenal insufficiency (18[2.3%] and 10 [1.3%] respectively). Treatment-related AEs led to death in 3)0.4%) and 1 (0.3%) of patients in the pembrolizumab and control arms respectively.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	The chemotherapy backbone in the KEYNOTE-522 trial is broadly reflective of UK clinical practice, as outlined above. Not all UK units currently use a platinum in the neoadjuvant treatment of breast cancer although given increasing weight of evidence for improved pCR rates using regimens containing this agent, it is likely that this regimen will be increasingly widely used.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Although pCR rates are an important outcome measure in this setting, the key questions surround event-free and overall survival. At a median follow-up of 36 months the presented data suggests a significant EFS benefit for pembrolizumab; however, a significant improvement in overall survival has not yet been shown.
• If surrogate outcome measures were used, do they adequately predict	The primary outcome measure used was pCR. This is a recognised surrogate outcome measure, which has been approved by the US FDA to support the accelerated approval of treatments. However, as discussed above there is no established relationship at a trial level between pCR and long-term outcomes. In addition, the FDA has commented regarding KEYNOTE-522: "The trial continues to evaluate for EFS,

long-term clinical outcomes?	which led the FDA's Oncologic Drugs Advisory Committee to vote 10 to 0 in favor of deferring regulatory decision until more data are available. The next interim analysis will occur at the end of the third quarter of 2021". Published data from the first interim analysis of the trial show an EFS benefit at a relatively early time point of 15 months. The presented, but as yet unpublished data, suggest that this is maintained at 36 months. Mature OS data is awaited.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the	No

publication of NICE technology appraisal guidance?	
21. How do data on real-world experience compare with the trial data?	No relevant real-world data exist.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	

Key messages
23. In up to 5 bullet points, please summarise the key messages of your submission. • The addition of pembrolizumab to neoadjuvant chemotherapy in TNBC appears to improve pathological complete response rates, • Neoadjuvant pembrolizumab given in the neoadjuvant setting and continued into the adjuvant setting appears to improve EFS rates in early TNBC • The chemotherapy backbone in the KEYNOTE-522 study appears broadly comparable to that used in the UK. • The improved pCR rate appears to be related to PD-L1 positivity, although the benefit appears not to be limited to PD-L1 positive tumours. • There is the potential for immune adverse events with the use of ICBs

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University Medical Center Groningen

Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of untreated locally advanced non-metastatic triple negative breast cancer [ID1500]

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Date completed	30/05/2022

Source of funding: This report was commissioned by the National Institute for Health Research (NIHR) Evidence Synthesis Programme as project number 12/99/38.

Declared competing interests of the authors: None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

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Any de-personalised data are highlighted in pink throughout the report.

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.

This report should be referenced as follows:

Perry M, van Asselt T, de Jong LA, al Khayat MNMT, Postma MJ, Riemsma R, Posadzki P, Duffy S, Ahmadu C, Armstrong N, Kleijnen J, Wolff R. Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of untreated locally advanced non-metastatic triple negative breast cancer [ID1500]: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2022.

Contributions of authors

Mark Perry and Robert Wolff acted as project leads and systematic reviewers on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Thea van Asselt acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Lisa de Jong, Mohamed al Khayat, Maarten Postma, Charlotte Ahmadu, and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Rob Riemsma and Pawel Posadzki acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Jos Kleijnen critiqued the company's definition of the decision problem and its description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

1L	First line
2L	Second line
3L	Third line
4L	Fourth line
AAT	Alanine aminotransferase
AC-T	Doxorubicin + cyclophosphamide followed by docetaxel
AC-TH	Doxorubicin + cyclophosphamide followed by docetaxel + trastuzumab
AE	Adverse effect/adverse event
AEOSI	Adverse event of special interest
AHRQ	Agency for Healthcare Research and Quality
AIC	Akaike information criterion
AiC	Academic in confidence
AJCC	American Joint Committee on Cancer
ASaT	All subjects as treated
ASCO	American Society of Clinical Oncology
AUC	Area under the curve
AWMSG	All Wales Medicines Strategy Group
BC	Breast cancer
BI	Budget impact
BIC	Bayesian information criterion
BNF	British National Formulary
BSA	Body surface area
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Clinical Trials
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CiC	Commercial in confidence
COVID-19	Coronavirus disease 2019
CPS	Combined positive score
CS	Company submission
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
DM	Distant metastasis
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
eBC	Early breast cancer
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
FAC	Factual accuracy check
FACT-B-FBSI	Functional Assessment of Cancer Therapy Breast Symptom Index
FAS	Full analysis set
FBC	Full blood count

FDA	Food and Drug Administration
FE	Fixing errors
FEC	Fluorouracil + epirubicin + cyclophosphamide
FEC-THP	Fluorouracil + epirubicin + cyclophosphamide followed by pertuzumab + trastuzumab + taxane
FISH	Fluorescence in situ hybridization
FV	Fixing violations
GP	General practitioner
HAS	Haute Autorité de Santé
HCHS	Hospital and Community Health Services
HER2	Human epidermal growth factor receptor 2
HERC	Health Economics Research Centre
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
HUI	Health utility index
IA	Interim analysis
IC	Indirect comparison
ICER	Incremental cost effectiveness ratio
ICER	Institute for Clinical and Economic Review
IHC	Immunohistochemistry
INAHTA	Health Technology Assessment database of the International Network of Agencies for Health Technology Assessment
IO	Immune oncology
IQWiG	Institute for Quality and Efficiency in Healthcare
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
IV	Intravenous(ly)
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews Ltd
LDH	Lactate dehydrogenase
LPLV	Last patient last visit
LR	Locoregional recurrence
LVEF	Left ventricular ejection fraction
LYs	Life years
LYG	Life years gained
mBC	Metastatic breast cancer
MeSH	Medical Subject Headings
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
MJ	Matters of judgement
MRI	Magnetic resonance imaging
MSD	Merck Sharp & Dohme
mTNBC	Metastatic triple-negative breast cancer
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NL	The Netherlands
NMA	Network meta-analysis
NR	Not reported

NYHA	New York Heart Association
OS	Overall survival
PAS	Patient Access Scheme
pCR	Pathological complete response
PD	Progressed disease
PFS	Progression-free survival
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient reported outcome
PROMIS-Fatigue SF1	Patient-Reported Outcomes Measurement Information System Fatigue Short Form-1
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTC	Pertuzumab + trastuzumab + chemotherapy
Q3W	Every three weeks
QALY	Quality adjusted life year
QLQ-BR23	Breast Cancer-Specific Quality of Life Questionnaire
QLQ-C30	Quality of Life Questionnaire
QoL	Quality of life
QTSQ	Cancer Treatment Satisfaction Questionnaire
QTWIST	Quality-adjusted time without symptoms or toxicity
QW	Once weekly
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
ROB2	Cochrane Risk of Bias tool version 2
RR	Relative risk; Risk ratio
SABCS	San Antonio Breast Cancer Symposium
SAE	Serious adverse effects
ScHARRHUD	School of Health and Related Research health utilities database
SD	Standard deviation
SE	Standard error
SEER	Surveillance, Epidemiology, and End Results
SF-6D	Short-Form Six-Dimension
SF-36	36-Item Short Form Survey;
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SoC	Standard of care
STA	Single technology appraisal
TA	Technology assessment
TCH	Docetaxel + carboplatin + trastuzumab
TC-HP	Docetaxel + carboplatin + trastuzumab + pertuzumab
TEAE	Treatment emergent adverse events
TNBC	Triple-negative breast cancer
UK	United Kingdom
UMC	University Medical Center
VAS	Visual analogue scale
WTP	Willingness-to-pay

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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. If possible, 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 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues relate to the cost effectiveness. A summary is presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main ERG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1: Summary of key issues

Issue #	Summary of issue	Report Section
1	Choice of population: There are major differences between the population defined in the NICE final scope and the decision problem addressed in the CS, e.g. regarding inflammatory disease, early-stage disease, participants being at high risk of recurrence and with a pre-defined ECOG PS.	2.1
2	Choice of comparator: Placebo alone is used while CS indicated that the addition of capecitabine to systemic treatment is associated with improvement in DFS, i.e. the best available comparator in the adjuvant phase might actually be capecitabine.	2.3
3	Geographical effects: Only a small subset of participants were from the UK. Subgroup analysis, based on a small dataset, suggests that geographical area is an important covariate influencing outcome, and so the observed effects may not be applicable to the UK.	3.2.1
4	TNM staging: Details on participants with stage I, II and III disease, respectively, were provided but not for the four detailed TNM grades in the inclusion criteria. As grades relate to prognosis, it is vital to know if the ratio of TNM grades is equivalent to those in the UK population.	3.2.3
5	ECOG staging: Subgroup analyses results indicated potential differences between Eastern Co-operative Oncology Group (ECOG) performance status, especially that compared to ECOG 0 participants, ECOG 1 participants did not demonstrate benefits from pembrolizumab in terms of pCR.	3.2.5.5
6	Adverse effects: Although AEs were described to be comparable between arms, the ERG notes that the risk of deaths in the pembrolizumab arm was three times that of the placebo arm. Furthermore, there was a difference in [redacted], see also Key Issue 8.	3.2.6
7	The company's model structure does not include health states for remission from LR and separate pre- and post-progression states for DM. For the ERG, this does not reflect clinical practice, i.e. the company's model does not capture costs and utilities related to these health states correctly.	4.2.2

Issue #	Summary of issue	Report Section
8	By far the largest gain in survival and QALYs is obtained in the extrapolated EFS part of the model. When using only the observed part (short time horizon), where mortality is increased in the pembrolizumab arm due to adverse events (see Key Issue 6), the ICER increases dramatically. The company has chosen to use different types of parametric distributions for the extrapolations, proper justification for this is lacking according to the ERG.	4.2.6
9	The probabilities of moving to DM (from the LR state) and death (from LR and DM state) are assumed to be constant over the entire time horizon of the model. The ERG is concerned about the lack of clinical justification for this.	4.2.6
10	The ERG considers the use of KEYNOTE-355 data as base case for the DM survival to be a potential source of bias. Although the company argues that KEYNOTE-355 is to be preferred over KEYNOTE-522 data because KEYNOTE-522 data are not sufficiently mature in the DM state, there are quite substantial differences in observed survival between these two studies.	4.2.6
11	The utility for the DM health state is relatively low compared to utilities for comparable health states in literature, which may be due to the limited number of questionnaires from patients who experienced distant metastasis in the KEYNOTE-522 trial which was used to inform this utility value. This causes doubts about the validity of the use of this utility value in the model.	4.2.8

AE = adverse effect; CS = company submission; DM = distant metastasis; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; LR = locoregional recurrence; NICE = National Institute for Health and Care Excellence; pCR = pathological complete response; PS = performance status; QALY = quality-adjusted life year; UK = United Kingdom

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An incremental cost effectiveness ratio (ICER) is the ratio of the extra cost per QALY gained.

Overall, the technology is modelled to affect QALYs by:

- An increase in event free survival (EFS) at a relatively high utility
- A relatively lower utility in the locoregional recurrence (LR) and distant metastasis (DM) states where proportionally more chemotherapy patients reside

Overall, the technology is modelled to affect costs by:

- Its higher treatment acquisition price compared to chemotherapy alone in both the neoadjuvant and the adjuvant phase
- The higher metastatic (one-off) treatment costs for the chemotherapy arm

The inputs that have most impact on the ICERs are those related to parameters linked to EFS extrapolations followed by metastatic treatment costs. Scenarios in the company submission (CS) that have a substantial impact on the ICER are the scenarios varying the distributions for the extrapolation of EFS, and the scenario with a limited time horizon (20 years).

1.3 The decision problem: summary of the ERG's key issues

The decision problem addressed in the CS is in line with the final scope issued by NICE regarding the intervention and the outcomes addressed. However, the population and comparator were not completely aligned with the NICE remit, see Tables 1.2 and 1.3.

Table 1.2: Key issue 1: Choice of population

Report Section	**2.1**
Description of issue and why the ERG has identified it as important	While the ERG acknowledges the need to align with the marketing authorisation, it notes some major differences between the population defined in the NICE final scope and the decision problem addressed in the CS, e.g. regarding inflammatory disease, early-stage disease, participants being at high risk of recurrence and with a pre-defined ECOG PS. Of note, according the CS, *"KEYNOTE-522 is a Phase III pivotal RCT investigating the efficacy of Pembrolizumab plus chemotherapy vs chemotherapy as neoadjuvant therapy followed by pembrolizumab vs placebo as adjuvant therapy in participants with locally advanced, inflammatory, or early-stage triple-negative breast cancer at high risk of recurrence"*. The use of "or" could indicate that different permutations of these factors are possible, e.g. that participants in the trial had inflammatory and early-stage TNBC which was not locally advanced. This ambiguity adds further uncertainty to the differences described before.
What alternative approach has the ERG suggested?	Closer coherence to the NICE scope would have ensured that efficacy and safety were being specifically evaluated in the specified population
What is the expected effect on the cost effectiveness estimates?	The ambiguity around the population breadth, i.e. it is unclear whether the trial population is actually narrower or broader than the NICE scope population, makes it very difficult to estimate effects on cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	Further evidence in a subgroup more closely aligned with the NICE scope population.
CS = company submission; ECOG = Eastern Cooperative Oncology Group; ERG = Evidence Review Group; NICE = National Institute for Health and Care Excellence; PS = performance status; RCT = randomised controlled trial; TNBC = triple-negative breast cancer	

Table 1.3: Key issue 2: Choice of comparator

Report Section	**2.3**
Description of issue and why the ERG has identified it as important	Choice of comparator. In the adjuvant phase of the trial, placebo alone is used as the comparator. This is based on the CS statement that active therapy is not standard treatment in the adjuvant phase according to expert opinion. However, it is stated in the CSR that the addition of capecitabine to systemic treatment is associated with improvement in DFS ([redacted]), which suggests that the best available comparator in the adjuvant phase might actually be capecitabine. Therefore, whilst it may be true that current practice does not commonly use adjuvant therapies (such as capecitabine), it is likely that the trial's use of placebo in the

Report Section	2.3
	adjuvant phase, rather than an active comparator such as capecitabine, may contribute to an increased estimate of benefit for pembrolizumab.
What alternative approach has the ERG suggested?	Including capecitabine as an active comparator in the adjuvant phase could be considered in future trials.
What is the expected effect on the cost effectiveness estimates?	The overly favourable comparator to pembrolizumab in the adjuvant phase (placebo only) may possibly enhance the overall measure of efficacy and thus augment cost effectiveness relative to what might be observed had capecitabine been part of the trial regimen.
What additional evidence or analyses might help to resolve this key issue?	Additional data collection with a subgroup using capecitabine in the adjuvant phase.
CI = confidence interval; CS = company submission; CSR = clinical study report; DFS = disease-free survival; ERG = Evidence Review Group; HR = hazard ratio	

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The ERG identified two major concerns with the evidence presented on the clinical effectiveness, related to quality of life and adverse events

Table 1.4: Key issue 3: Geographical effects

Report Section	3.2.1
Description of issue and why the ERG has identified it as important	Only a small sub-set of participants were from the UK. Crude subgroup analysis suggests that geographical area is an important covariate influencing outcome, and so the overall effects observed may not necessarily be applicable to the UK.
What alternative approach has the ERG suggested?	The ERG also specifically requested all results to be sub-grouped for 1) Europe versus rest of world and 2) UK versus rest of world. The company provided EFS data showing that the Europe subgroup had a less favourable relative effect size for pembroli-zumab (HR [redacted] compared to the rest of the world subgroup (HR [redacted] suggesting that the overall data in the trial might be providing an overly optimistic picture for European patients. The company did not provide similar data for a UK patient subgroup.
What is the expected effect on the cost effectiveness estimates?	Based on the available European data, the trial effectiveness results may be more favourable than they might be for a European-based population (such as the UK), and thus cost effectiveness may be inflated. The ERG implemented a simple fix to the efficacy in the model, assuming the HR to remain constant over time, see Section 6.1.
What additional evidence or analyses might help to resolve this key issue?	UK-specific data would help in addressing this issue. Furthermore, in order to explore the impact of regional difference in effectiveness, the model structure would need to be adapted more elaborately
CI = confidence interval; EFS = event-free survival; ERG = Evidence Review Group; HR = hazard ratio; UK = United Kingdom	

Table 1.5: Key issue 4: TNM staging

Report Section	**3.2.3**
Description of issue and why the ERG has identified it as important	The CS provides details of the numbers of participants in KEYNOTE-522 with Stage I, II and stage III disease, but not the four detailed TNM gradings mentioned in the inclusion criteria. It is likely that stage relates to prognosis, and so it is vital to know if the ratio of TNM stages in the trial is equivalent to ratios of TNM stages in the UK population.
What alternative approach has the ERG suggested?	In response to the request for clarification, the company provided precise data on the TNM stages for the two arms of the trial, but the company were unable to provide data on the UK prevalence of TNM stages, stating that *"data for TNM grading for TNBC patients is not available from publicly available data"*.
What is the expected effect on the cost effectiveness estimates?	Unclear
What additional evidence or analyses might help to resolve this key issue?	Information on the TNM stages in the UK population would allow a better judgement on the external validity of the trial. For example, if the trial contains a greater prevalence of lower TNM stages than the UK population, this may allow more meaningful interpretation of effect sizes.
CS = company submission; ERG = Evidence Review Group; UK = United Kingdom	

Table 1.6: Key issue 5: ECOG staging

Report Section	**3.2.5.5**
Description of issue and why the ERG has identified it as important	The ERG noted that subgroup analyses results indicated potential differences between ECOG PS. In particular, in contrast to the ECOG=0 subgroup, the subgroup with ECOG=1 did not demonstrate benefits from pembrolizumab in terms of pCR. The company stated that numbers were small and that therefore it was difficult to form conclusions, but the data suggest that patients with an ECOG status of 1 are unlikely to benefit from pembrolizumab (and there is a probability that the drug could even cause harm in this group, although this is uncertain).
What alternative approach has the ERG suggested?	When asked to comment on this finding, the company described the characteristics expected to be associated with an ECOG of 1. Attempts to adjust for these covariates were made by the company in post-hoc analyses, which, as expected, removed the negative effects of the highly correlated ECOG variable upon the outcome. These did not show anything other than confirm the evident correlation. The important point is that these correlating characteristics do not prevent people with ECOG 1 being less appropriate candidates for pembrolizumab, and the fact remains that if people have an ECOG score of 1 they are probably not going to experience benefits from pembrolizumab.
What is the expected effect on the cost effectiveness estimates?	For people with an ECOG score of 1, pembrolizumab is unlikely to be cost effective.
What additional evidence or analyses might help to resolve this key issue?	Further evidence with greater numbers of people with an ECOG score of 1.

Report Section	3.2.5.5
ECOG = Eastern Cooperative Oncology Group; ERG = Evidence Review Group; pCR = pathological complete response; PS = performance status	

Table 1.7: Key issue 6: Adverse effects

Report Section	3.2.6
Description of issue and why the ERG has identified it as important	Adverse effects are described as comparable between arms. However, the risk of deaths in the pembrolizumab arm was three times that of the placebo arm. Furthermore, the difference between arms in [redacted], see also Key Issue 8.
What alternative approach has the ERG suggested?	Not applicable
What is the expected effect on the cost effectiveness estimates?	Adverse effects have been included in the economic model, see Section 4.2.7, however, the ERG wanted to bring this is issue to the attention of the committee. This is linked to the Key Issue 8.
What additional evidence or analyses might help to resolve this key issue?	None
ERG = Evidence Review Group	

1.5 The cost effectiveness evidence: summary of the ERG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the ERG's summary and detailed critique in Section 4, and the ERG's amendments to the company's model and results are presented in Section 6. The key issues are discussed in Tables 1.8 to 1.12.

Table 1.8: Key issue 7: Model structure not including locoregional remission and no differentiation between pre-progression and post-progression distant metastatic patients.

Report Section	4.2.2
Description of issue and why the ERG has identified it as important	The company's model structure does not include health states for remission from locoregional recurrence and separate pre- and post-progression states for distant metastasis. The ERG believes this does

Report Section	4.2.2
	not reflect clinical practice, and therefore the company's model does not capture costs and utilities related to these health states correctly.
What alternative approach has the ERG suggested?	The ERG asked for a scenario based on the model structure of TA424, which did include remission from locoregional recurrence and separate pre- and post-progression distant metastasis health states, but this scenario was not provided by the company. The ERG was not able to adjust the model structure, as no data was available to inform remission and separate progression distant metastasis states.
What is the expected effect on the cost effectiveness estimates?	Overall impact on cost-effectiveness is uncertain as adding health states may have consequences in both directions.
What additional evidence or analyses might help to resolve this key issue?	A sensitivity analysis with an alternative model structure, including the remission and separate progression states would help to explore the impact of this issue.
ERG = Evidence Review Group; TA = technology appraisal	

Table 1.9: Key issue 8: Modelled treatment effectiveness and extrapolation for EFS state likely overestimates effectiveness of pembrolizumab

Report Section	4.2.6
Description of issue and why the ERG has identified it as important	By far the largest gain in survival and QALYs is obtained in the extrapolated EFS part of the model. When using only the observed part (short time horizon), where mortality is increased in the pembrolizumab arm due to adverse events (see Key Issue 6), the ICER increases dramatically. The company has chosen to use different types of parametric distributions for the extrapolations, proper justification for this is lacking according to the ERG.
What alternative approach has the ERG suggested?	The ERG base case uses the same type of distribution (but still individually fitted) in both arms to extrapolate EFS. This will not fully eliminate the issue that most of the QALY gain is obtained outside of the observed period.
What is the expected effect on the cost effectiveness estimates?	The ICER increases.
What additional evidence or analyses might help to resolve this key issue?	Mature comparative data on long-term EFS, and more extensive validation of the results by clinical experts.
EFS = Event-free survival; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year	

Table 1.10: Key issue 9: Constant transition probabilities from LR and DM states assumed without clinical justification

Report Section	4.2.6
Description of issue and why the ERG has identified it as important	The probabilities of moving to DM (from the LR state) and death (from LR and DM state) are assumed to be constant over the entire time horizon of the model. The ERG is concerned about the lack of clinical justification for this.

What alternative approach has the ERG suggested?	No alternative approach.
What is the expected effect on the cost effectiveness estimates?	Uncertain.
What additional evidence or analyses might help to resolve this key issue?	Mature data on transition probabilities over time, possibly obtained from further KEYNOTE-522 data cuts, could resolve this uncertainty.
DM = distant metastasis; ERG = Evidence Review Group; LR = locoregional recurrence	

Table 1.11: Key issue 10: The use of KEYNOTE-355 data for DM survival may not be appropriate

Report Section	**4.2.6**
Description of issue and why the ERG has identified it as important	The ERG considers the use of KEYNOTE-355 data as base case for the DM survival to be a potential source of bias. Although the company argues that KEYNOTE-355 is to be preferred over KEYNOTE-522 data because KEYNOTE-522 data are not sufficiently mature in the DM state, there are quite substantial differences in observed survival between these two studies.
What alternative approach has the ERG suggested?	The ERG prefers to use KEYNOTE-522 data to estimate transition probabilities from the DM state to death, as already presented in a company scenario. The ERG has added an additional feature to this scenario where treatment costs are adjusted accordingly.
What is the expected effect on the cost effectiveness estimates?	When only adjusting for DM survival, the ICER changes very little, but when also adjusting for treatment costs, the ICER increases.
What additional evidence or analyses might help to resolve this key issue?	Mature data on transition probabilities over time, possibly obtained from further KEYNOTE-522 data cuts, could resolve this uncertainty.
DM = distant metastasis; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio	

Table 1.12: Key issue 11: Relatively low utility in the DM health state

Report Section	**4.2.8**
Description of issue and why the ERG has identified it as important	The utility for the DM health state is relatively low compared to utilities for comparable health states in literature, which may be due to the limited number of questionnaires from patients who experienced distant metastasis in the KEYNOTE-522 trial which was used to inform this utility value. This causes doubts about the validity of the use of this utility value in the model.
What alternative approach has the ERG suggested?	To provide separate utility estimates for progressed and not-progressed patients with distant metastasis from the KEYNOTE-522. Since this was not possible due to the design of the trial and the limited number of questionnaires available in this group, the ERG considered it appropriate to conduct additional scenario analyses based on utility values for a comparable health state in patients with TNBC from literature.

Report Section	4.2.8
What is the expected effect on the cost effectiveness estimates?	The incremental QALYs are expected to decrease, resulting in an increased ICER. This was confirmed by the scenarios the company conducted in response to clarification question B19c and the scenarios conducted in the ERG model.
What additional evidence or analyses might help to resolve this key issue?	More data on the utility for patients experiencing DM in time, obtained from further KEYNOTE-522 data cuts, could resolve this uncertainty. Additionally, mature subsequent treatment data obtained from further KEYNOTE-522 data cuts may be used to estimate utilities for not-progressed and progressed patients with distant metastasis separately (line of treatment can be used as a proxy for progression status).
DM = distant metastasis; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year	

1.6 Summary of the ERG's view

The following tables summarise the ERG's changes to the company's base case to arrive at an ERG base case (Table 1.13). In addition, Tables 1.14 and 1.15 present the ERG scenarios.

Table 1.13: Deterministic ERG base case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base case					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,940
Fixing errors 1: Enable pembrolizumab 1L treatment in DM state for IO-eligible patients in the placebo arm					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£9,346
Fixing errors 2: Adjustment to formulas correcting for general population mortality					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,976
Matters of judgement 1: Correction for efficacy of pembrolizumab adjusting for Europe versus rest of the world hazard ratio					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£7,801
Matters of judgement 2: Use KEYNOTE-522 data to inform survival in DM state and alongside this adjust treatment costs according to the shorter survival					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£8,976

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Matters of judgement 3: Use lognormal distributions in EFS for both arms					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£16,444

1L = first line; CS = company submission; DM = distant metastasis; EFS = event-free survival; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; IO = immune oncology; QALY = quality-adjusted life year

Table 1.14: Deterministic scenario analyses (conditional on ERG base case)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base case					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£43,621
Scenario 1: Limit time horizon to 5 years (similar to the observed period)					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£397,435
Scenario 2: Set the cut-off of the piecewise model at 68 weeks instead of 50 weeks					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£27,172
Scenario 3: Use generalized gamma distributions for EFS in both arms					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£15,447
Scenario 4: Use lognormal distribution for pembrolizumab and generalized gamma distribution for placebo EFS					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£53,592
Scenario 5: Adjust utility in DM health state based on KEYNOTE-355					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£44,259
Scenario 6: Adjust utility in DM health state based on KEYNOTE-119					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£44,362
ERG base case					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£43,621
CS = company submission; EFS = event-free survival; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 1.15: Probabilistic scenario analyses (conditional on ERG base case)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	Prob-ability
ERG base case						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£43,621	31.9%
Scenario 1: Limit time horizon to 5 years (similar to the observed period)						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£381,768	0.0%
Scenario 2: Set the cut-off of the piecewise model at 68 weeks instead of 50 weeks*						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£37,272	50.8%
Scenario 3: Use generalized gamma distributions for EFS in both arms						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£16,697	79.0%
Scenario 4: Use lognormal distribution for pembrolizumab and generalized gamma distribution for placebo EFS						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£58,421	28.1%
Scenario 5: Adjust utility in DM health state based on KEYNOTE-355						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£44,568	31.4%
Scenario 6: Adjust utility in DM health state based on KEYNOTE-119						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£44,685	31.4%
CS = company submission; DM = distant metastasis; EFS = event-free survival; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year						
*Errors in approximately ten PSA runs. Errors were excluded from the analysis to obtain the results						

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	ERG comment
Population	Adults with previously untreated locally advanced, nonmetastatic triple-negative breast cancer (TNBC).	Adults with locally advanced, inflammatory, or early-stage TNBC at high risk of recurrence.	Wording to reflect licence wording.	There are differences in the population defined in the final scope issued by NICE and the decision problem addressed in the CS which are discussed in Section 2.1.
Intervention	Pembrolizumab in combination with standard neoadjuvant chemotherapy followed by adjuvant pembrolizumab.	Pembrolizumab in combination with standard neoadjuvant chemotherapy followed by adjuvant pembrolizu-mab.	N/A	The ERG has no comments.
Comparator(s)	Standard neoadjuvant/adjuvant therapy without pembrolizumab.	Carboplatin + paclitaxel followed by doxorubicin/epirubicin + cyclo-phosphamide (neoadjuvant phase only) followed by placebo monotherapy (adjuvant phase).	To reflect KEYNOTE-522 and clinical expert opinion which notes that after neoadjuvant chemotherapy patients do not receive additional adjuvant chemotherapy in England.	The comparator might not represent the available comparator in the adjuvant phase, as detailed in Section 2.3.
Outcomes	• Overall survival (OS) • Pathological complete response (pCR) • Event-free survival (EFS) • Adverse effects (AEs) of treatment • Health-related quality of life (HRQoL)	• OS • pCR • EFS • AEs of treatment • HRQoL	N/A	The ERG has no comments.

Based on Table 1 and pages 10 to 12 of the CS[1]
CS = company submission; ERG = Evidence Review Group; N/A = not applicable; NICE = National Institute for Health and Care Excellence; pCR = pathological complete response; TNBC = triple-negative breast cancer

2.1 Population

The population relevant for this submission is defined in four different places:

1. The final scope issued by the National Institute for Health and Care Excellence (NICE) defined the population of interest as *"adults with previously untreated locally advanced, non-metastatic triple-negative breast cancer"* (TNBC).[3]
2. In the decision problem addressed in the company submission (CS), the population is defined as *"adults with locally advanced, inflammatory, or early stage triple-negative breast cancer at high risk of recurrence"*.[1] As noted in Table 2.1, this is *"to reflect licence wording"*.[1]
3. According to Table 4 of Appendix D of the CS, the population of interest for the systematic literature review (SLR) was *"early-stage and locally advanced non-metastatic TNBC"*.[4]
4. According to page 17 of the CS, the *"only relevant study identified by the systematic literature review"*, KEYNOTE-522 was conducted *"...in participants with locally advanced, inflammatory, or early-stage triple-negative breast cancer at high risk of recurrence"*.[1] Table 3 of the CS added that participants with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 were included.[1]

ERG comment: There are a number of differences between the populations assessed in 1) the NICE final scope; 2) the decision problem addressed in the CS; 3) the inclusion criteria for the SLR reported in the CS; and 4) the inclusion criteria of KEYNOTE-522, as detailed in Table 2.2. The Evidence Review Group (ERG) looked into these differences in more detail:

- Adults: Although the term "adults" was not mentioned in either the SLR inclusion criteria or the KEYNOTE-522 inclusion criteria, according to Table 5 of the CS, the range of included participants was 22 to 80 years, i.e., did not include non-adult participants.[1]
- Previously untreated: Although not reflected in the decision problem or the SLR inclusion criteria, the only study identified by the SLR reported in the CS, KEYNOTE-522, included *"untreated newly diagnosed"* patients hence this appears to be in line with the NICE final scope.[1, 3]
- Non-metastatic: According to Table 5 of the CS, 100% of participants included in KEYNOTE-522 were non-metastatic.[1] Therefore, although not clearly stated in the CS decision problem or the inclusion criteria reported for KEYNOTE-522, this is in line with the NICE final scope.[1, 3]
- Inflammatory: According to the Trial Design Overview (reported on page 3308 of the clinical study report (CSR) for KEYNOTE-522), [redacted].[2]
- Early-stage: The NICE final scope did not specify that the population of interest included "early-stage" patients.[3]
- High risk of recurrence: The company has been asked to define the term as this could be considered an important factor defining the population and thus its likely response to the intervention.[5] The company responded by stating that *"within KEYNOTE-522, 'high-risk TNBC' is synonymous with 'locally advanced TNBC', the latter defined as T1c, N1-N2; T2-T4d, N0-N2 (thus, Stage II-III) per the American Joint Committee on Cancer (AJCC) staging criteria for breast cancer"*.[6]

- ECOG PS: While the NICE final scope did not specify the population regarding ECOG PS, the trial inclusion criteria specified participants to have ECOG PS 0 or 1, i.e. the population is narrower than that defined in the NICE scope.

In the clarification letter, the company (Merck Sharp & Dohme (MSD)) has been asked to justify the discrepancies between the NICE final scope and the decision problem addressed in the CS.[5] In response, the company noted that the anticipated marketing authorisation, which the definition used in the decision problem is based on, was included in the response to the draft scope, however, *"this was marked as commercial in confidence and as such NICE were not able to make this wording public"*.[6] According to the response to the request for clarification, the Committee for Medicinal Products for Human Use (CHMP) has now adopted a positive opinion and the wording published on the website of the European Medicines Agency (EMA) is *"KEYTRUDA [pembrolizumab], in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early stage triple negative breast cancer at high risk of recurrence"*.[6, 7]

Furthermore, the company has been asked to discuss how any discrepancy in population definitions may influence how trial results should be extrapolated to clinical practice in the National Health Service (NHS) in England and Wales.[5] The response from the company is that *"MSD understands the definition applied in the KEYNOTE-522 resonates with NHS clinical practice"*.[6]

While the ERG acknowledges the need to align with the marketing authorisation, it notes some major differences between the population defined in the NICE final scope and the decision problem addressed in the CS, e.g. regarding inflammatory disease, early-stage disease, participants being at high risk of recurrence and with a pre-defined ECOG PS (see Table 2.2). These differences are noted as a key issue 1 for consideration of the committee.

Of note, according to page 17 of the CS, *"KEYNOTE-522 is a Phase III pivotal RCT* [randomised controlled trial] *investigating the efficacy of Pembrolizumab plus chemotherapy vs chemotherapy as neoadjuvant therapy followed by pembrolizumab vs placebo as adjuvant therapy in participants with locally advanced, inflammatory, or early-stage triple-negative breast cancer at high risk of recurrence"*.[1] The use of "or" could indicate that different permutations of these factors are possible, e.g. that participants in the trial had inflammatory and early-stage triple-negative breast cancer (TNBC) which was not locally advanced. This ambiguity adds further uncertainty to the differences described before.

Table 2.2: Detailed comparison of population in NICE final scope and CS decision problem

NICE final scope	CS decision problem	SLR inclusion criteria	KEYNOTE-522 inclusion criteria	ERG comment
Table on page 2 of the scope[3]	Table 1 of the CS[1]	Table 4 of Appendix D of the CS[4]	Table 3 and page 17 of the CS[1]	
Adults	Adults	-	-	As detailed above, unlikely that non-adults included
Previously untreated	-	-	Untreated newly diagnosed	"Previously untreated" not reflected in CS decision problem or SLR but in trial
Locally advanced	Locally advanced	Locally advanced	Locally advanced	Identical
-	-	-	Centrally confirmed	Inclusion criterion of trial narrower than NICE final scope
Non-metastatic	-	Non-metastatic	-	"Non-metastatic" not reflected in CS decision problem but no non-metastatic participants in the trial
-	Inflammatory	-	Inflammatory	"Inflammatory" not included in NICE final scope, see comment above
-	Early-stage	Early-stage	Early-stage	"Early stage" not included in NICE final scope
TNBC	TNBC	TNBC	TNBC	Identical
-	High risk of recurrence	-	High risk of recurrence	"High risk of recurrence" not included in NICE final scope
-	-	-	ECOG PS of 0 or 1	Population included in the trial is narrower than NICE final scope

Based on Table 1 of the CS[1]
CS = company submission; ECOG = Eastern Cooperative Oncology Group; ERG = Evidence Review Group; NICE = National Institute for Health and Care Excellence; PS = performance status; SLR = systematic literature review; TNBC = triple-negative breast cancer

2.2 Intervention

The intervention defined in the CS (*"pembrolizumab in combination with standard neoadjuvant chemotherapy followed by adjuvant pembrolizumab"*)[1] is in line with the NICE final scope definition (*"pembrolizumab in combination with standard neoadjuvant chemotherapy followed by adjuvant pembrolizumab"*)[3].

Pembrolizumab is administered in a neoadjuvant and adjuvant phase. In the neoadjuvant phase, 200 mg of pembrolizumab is given intravenously (IV) on day 1 of each 21-day cycle (Q3W) for 8 cycles, alongside:

- Cycles 1 to 4: Carboplatin area under the curve (AUC) 5-day Q3W (or AUC 1.5 weekly) + paclitaxel 80 mg/m^2 once weekly (QW)
- Cycles 5 to 8: Doxorubicin 60 mg/m^2 Q3W or epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 Q3W

In the adjuvant phase, pembrolizumab is given as 200 mg IV Q3W for 9 cycles. No other therapeutic agents are given in this phase.[1]

2.3 Comparators

The description of the comparators in the NICE final scope is *"standard neoadjuvant/adjuvant therapy without pembrolizumab"*.[3] However, the company has set the comparator as *"carboplatin + paclitaxel followed by doxorubicin/epirubicin + cyclophosamide (neoadjuvant phase only) followed by placebo monotherapy (adjuvant phase)"*.[1] Crucially, this involves only placebo monotherapy for the adjuvant phase. This is justified in the CS by the fact that current United Kingdom (UK) practice does not use adjuvant treatment.[1]

ERG comment: The ERG identified the following points:

1. The best available comparator in the adjuvant phase (capecitabine) may have been overlooked.
2. The company had not adequately initially justified the exclusion of taxanes and anthracyclines
3. No justification was initially given for the choice between doxorubicin and epirubicin
4. There is a better efficacy for doxorubicin than epirubicin in the trial, and more received doxorubicin, but it is unclear if this reflects the proportion of doxorubicin use in the population

These points will now be described in detail.

1. *The best available comparator in the adjuvant phase (capecitabine) may have been overlooked.*

It is also stated in the CSR that [redacted]

Whilst it may be true that current practice does not commonly use adjuvant therapies (such as capecitabine), it is likely that the trial's use of placebo in the adjuvant phase, rather than an active comparator such as capecitabine, may contribute to an increased estimate of benefit for pembrolizumab. Thus, whilst this observed benefit may be realistic in terms of comparison to *established* practice,

therefore fulfilling the criteria outlined in the NICE final scope, it might not tell the committee how much better pembrolizumab is than the best available alternative approaches, established or not. This is key issue 2.

In the request for clarification, the ERG asked the company to explain how including capecitabine as a *"an active comparator in the adjuvant phase might have changed findings in the trial (the intervention would have been capecitabine + pembrolizumab)"*.[5] However, the question was not clearly answered as the company appeared to have misunderstood the question, assuming the question was how any *"off-study adjuvant capecitabine use"* might have affected results, which would indeed be very different, because it would assume that capecitabine might be used reactively and off-protocol, such as for people not achieving pathological complete response (pCR), and might thus lead to confounding.[6]

Related to this, another question in the request for clarification asked how any presumed differences in results between the two scenarios, the actual scenario and the scenario where capecitabine is part of the trial, might be accounted for in any sensitivity analyses.[5] Due to the reasons described before, the response did not clarify this issue.[6]

2. *The company had not adequately initially justified the exclusion of taxanes and anthracyclines*

The ERG also noted that for adjuvant treatment after surgery, NICE guidelines for early and locally advanced BC (NG101) recommends offering a regimen that contains both a taxane and an anthracycline, but that the company had not justified the exclusion of taxanes and anthracyclines in the adjuvant phase.[1] Therefore, the company was asked to justify the comparison to only placebo instead of taxane and an anthracycline as adjuvant treatment.[5] The company response was focussed on the point that because the patients had already received the drugs at the neoadjuvant phase it would not be clinically indicated for them to receive them at the adjuvant phase as well:[6]

"A taxane and anthracycline regimen for the treatment of early-stage breast cancer is generally given either before or after surgery with curative intent, but not both before and after surgery as neoadjuvant and adjuvant chemotherapy treatment, respectively. For chemotherapy, neoadjuvant vs adjuvant administration of a taxane and anthracycline regimen is considered equivalent in terms of distant recurrence, breast cancer mortality or death from any cause for breast cancer patients.[8] *The adjuvant guidelines within NG101 do not make a recommendation of what a clinician should do if a patient has already received a taxane and anthracycline in the neoadjuvant setting. As mentioned above and per common clinical practice, such a patient would not be also treated with the same adjuvant chemotherapy regimen. Furthermore, use of anthracycline is limited by a maximum exposure dose due to cardiotoxicity and adjuvant administration of a neoadjuvant chemotherapy regimen that did not result in a pathological complete response (pCR) is not recommended. A relevant clinical practice example comes from the HER2+ breast cancer space, as women who received a neoadjuvant anthracycline + taxane regimen are not treated with the same chemotherapy agents in the adjuvant setting; however, anti-HER2 treatment is given both before and after surgery independent of the surgical outcome (pCR vs not). UK Clinical experts have informed MSD that the treatments used in KEYNOTE-522 reflect the current standard of care for neoadjuvant and adjuvant treatment of TNBC where a taxane and anthracycline regimen given either before or after surgery with curative intent. From the perspective of the clinical evidence base, the early breast cancer systematic literature review conducted to support this submission did not identify any relevant publications that explored the effectiveness and safety of adjuvant taxane and/or anthracycline after administration of a neoadjuvant chemotherapy regimen (see Appendix D1.2.1). Since no relevant publications were retrieved, it was not possible to incorporate neoadjuvant chemotherapy followed by an anthracycline/taxane adjuvant treatment option via an indirect treatment comparison within the model".*

The ERG notes that there is supporting evidence. However, it did not find any papers countering the company's view that chemotherapy should only be given in one phase and not both. The ERG also looked at the SR in the NICE NG 101 guideline, which also did not provide any counterevidence to challenge the company's assertion. The ERG would have preferred to have found more objective data-based backing to confirm the fact that anthracycline/taxane chemotherapy can only be given in one phase but realises that such decisions are often made on the basis of clinical experience and consensus.

The ERG did also consider the point that the chemotherapy need not have been given at the neoadjuvant phase but could have been given at the adjuvant phase instead. The systematic review submitted by the company did support the notion that adjuvant and neoadjuvant chemotherapy are equivalent for the most important outcomes (although adjuvant chemotherapy may be better for local recurrence), thus suggesting that the placing of chemotherapy in the neoadjuvant phase was not disadvantageous. In any event, the ERG realised that any shift of chemotherapy to the adjuvant phase would not have solved the problem of pembrolizumab being compared to placebo alluded to earlier (with its implications for potentially exaggerated pembrolizumab effect sizes).[8] This is because it would simply have shifted the problem of *pembrolizumab versus placebo* in the adjuvant phase to *pembrolizumab versus placebo* in the neoadjuvant phase.

3. *No justification was initially given for the choice between doxorubicin and epirubicin*

For the comparator treatment in the second part of the neoadjuvant phase, a choice is made between doxorubicin and epirubicin, but no justification is given for this in the CS. In the request for clarification, the company was asked why this choice was made, who in the study was responsible for making the choice, and upon which criteria the choice was made.[5] The company responded that *"doxorubicin and epirubicin are commonly used neoadjuvant anthracycline regimens for TNBC. The choice of treatment was made by the investigator at the initiation of the second phase of neoadjuvant treatment and was largely dependent on local/ institutional guidance and guidelines"*.[6]

4. *There is a better efficacy for doxorubicin than epirubicin in the trial, and more received doxorubicin, but it is unclear if this reflects the proportion of doxorubicin use in the population*

Lastly, the ERG requested a comparison with NHS clinical practice in terms of the use of these treatments.[5] The company response was that *"the combination of doxorubicin or epirubicin plus cyclophosamide is available in NHS clinical practice"* but no further information was given.[6] The ERG also requested information on the implications of any difference, and a subgroup analysis of results by doxorubicin / epirubicin use.[5] The company responded with a subgroup analysis for event free-survival (EFS), where within both chemotherapy subgroups a point estimate favouring the pembrolizumab arm was observed. However, the benefit in the doxorubicin subgroup was stronger [pembrolizumab versus placebo HR 0.56. 95% CI 0.40 to 0.80] than the non-significant effect observed in the epirubicin subgroup [pembrolizumab versus placebo HR 0.78, 95% CI 0.47 to 1.31]. These results may be important because more than twice as many participants received doxorubicin (488 versus 238) in the trial. If the distribution of these drugs is different in the UK population, with a more equal distribution, or even a weighting in the opposite direction, then the distribution in the trial may be affecting external validity. More information on the UK distribution would be helpful to address this issue.

2.4 Outcomes

The NICE final scope lists the following outcome measures:[3]

- Overall survival (OS)

- Pathological complete response (pCR)
- Event-free survival (EFS)
- Adverse effects (AEs) of treatment
- Health-related quality of life (HRQoL)

These were all assessed in the KEYNOTE-522 trial.

ERG comment: These outcomes are in line with the NICE scope.

2.5 Other relevant factors

According to the CS, *"pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab monotherapy does not meet the end-of-life criteria"*.[1]

The company does not envisage any equality issues with the use of pembrolizumab in combination with chemotherapy for neoadjuvant and adjuvant treatment of untreated locally advanced non-metastatic TNBC.[1]

According to the company, pembrolizumab in combination with chemotherapy followed by pembrolizumab monotherapy in the adjuvant setting is an innovative treatment option in this therapy area as the first immunotherapy agent to be appraised by NICE for use in early-stage locally advanced BC patients which are at high risk of relapse.[1]

On 26 July 2021, the Food and Drug Administration (FDA) approved pembrolizumab for high-risk, early-stage, TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.[9]

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

A SLR was conducted to identify relevant clinical evidence. Full details of the SLR search strategy, study selection process and results were reported in Appendix D.[4]

3.1.1 Searches

The following section contains a summary and critique of all searches related to clinical effectiveness presented in the CS.[1, 4] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[10, 11] The CS was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[12]

Appendix D of the CS provided details of the literature searches conducted for the SLR of clinical efficacy and safety outcomes.[4] Database searches were conducted on 27 July 2021. A summary of the resources searched is provided in Table 3.1.

Table 3.1: Resources searched for the clinical effectiveness systematic review (as reported in the CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
MEDLINE and In-Process & Other Non-Indexed Citations	Ovid	1946 to July 26, 2021	27/07/21
Embase	Ovid	1974 to 2021 July 27	27/07/21
CENTRAL	EMB Reviews, Ovid	June 2021	27/07/21
Trials registries			
ClinicalTrials.gov	Internet	-	27/07/21
EU Clinical Trial Registry	Internet	-	27/07/21
Conference proceedings			
ASCO	NR	2020-2021	27/07/21
ESMO	NR	2020	27/07/21
SABCS	NR	2020	27/07/21

ASCO = American Society of Clinical Oncology; CENTRAL = Cochrane Central Register of Controlled Clinical Trials; CS = company submission; ESMO = European Society for Medical Oncology; NR = not reported; SABCS = San Antonio Breast Cancer Symposium

ERG comment:

- The CS provided full details of the literature searches for the ERG to appraise.[1, 4]
- A good range of databases, clinical trials registries and conference proceedings were searched.
- Full details of the database searches, including the database name, host platform, date range and date searched, were provided.
- Trials registers were searched, but details of the search strategies or search terms used, dates of searches, and results were not reported in the CS.[1, 4] Details of the ClinicalTrials.gov search strategy, date of search, and results, were provided in response to the ERG clarification letter.

Details of the search results were provided for the EU Clinical Trial Registry; details of the search strategy and date of search were not provided.[6]

- Conference proceedings were searched. The search strategies or search terms used, date of searches, and results, were not reported in the CS.[1, 4] In response to the ERG clarification letter, details of the search terms used, date of searches, URL links, and number of abstracts included in the SLR, were provided.[6]
- The database search strategies were well structured, transparent and reproducible. They included truncation, proximity operators, synonyms, and subject headings (Medical Subject Headings (MeSH) and EMTREE). There were no date limits.
- MeSH terms were used instead of EMTREE in the Embase search strategy, though the Ovid host platform does map to the correct subject heading when the search is conducted. Several MeSH and EMTREE terms were exploded when there were no terms beneath them in the tree hierarchy.
- The population facet of search terms could have been improved with more synonyms, fewer exact phrases, better use of proximity operators, and the removal of redundant terms/phrases. The combination of search terms for 'triple negative breast cancer' with search terms for 'breast cancer' using the Boolean AND was incorrect but had barely any impact on the search results.
- There were a number of redundant search lines in the intervention/comparator facet of search terms.
- The searches were limited to English language only studies and this may have introduced language bias. Best practice states that *"to reduce the risk of introducing bias, searches should not be restricted by language"*.[13] Any limits (including language) should be reported and justified according to PRISMA (Preferred reporting items for systematic reviews and meta-analyses) 2020 and PRISMA-S guidelines.[14-16]
- It would have been preferable for the database search strategies to be presented exactly as run, rather than copied into a tabular format, as item 8 of the PRISMA-S checklist recommends.[16] The Cochrane Handbook also recommends that *"...bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy. The search strategies should not be re-typed, because this can introduce errors"*.[17]
- Study design search filters for randomised controlled trials (RCTs) designed by the Scottish Intercollegiate Guidelines Network (SIGN) were included in the search strategies, and were cited, as current practice recommends.[16]
- Separate searches for safety outcomes were not conducted. It is unlikely that efficacy searches that include study design filters for RCTs will be sensitive enough to identify safety data. Ideally, searches for safety outcomes should be carried out alongside the searches for efficacy.[18]
- The searches were conducted in July 2021. An update of the searches immediately prior to submission to NICE would have been appropriate and could have identified potentially relevant records published since July 2021.

3.1.2 Inclusion criteria

The company conducted a SLR following a pre-defined study eligibility criteria outlined in Table 3.2. Two reviewers independently screened all references retrieved from the search, critiqued in Section 3.1.1 of this report, both at title and abstract, and full text screening stages. To reach consensus, discrepancies in screening results were resolved by involving a third reviewer.

Table 3.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

	Inclusion criteria
Population	Early-stage and locally advanced non-metastatic TNBC
Interventions	**Pembrolizumab regimens:** • Pembrolizumab (200 mg Q3W x 4 cycles) + carboplatin (AUC 5 Q3W x 4 cycles or AUC 1.5 qw x 4 cycles) + paclitaxel (80 mg/ml qw x 4 cycles) • Pembrolizumab (200 mg Q3W x 4 cycles) + doxorubicin (60 mg/m2) or epirubicin (90mg/ml^2) + cyclophosphamide (600mg/ m^2 Q3W x 4 cycles) • Post-surgery: Pembrolizumab (200 mg Q3W x 9 cycles) **Preferred regimens:** • Dose-dense doxorubicin + cyclophosphamide followed by paclitaxel every three weeks • Dose-dense doxorubicin + cyclophosphamide followed by weekly paclitaxel • Docetaxel + cyclophosphamide **Other regimens:** • Dose-dense doxorubicin + cyclophosphamide • Doxorubicin + cyclophosphamide every 3 weeks (category 2B) • Cyclophosphamide + methotrexate + fluorouracil • Doxorubicin + cyclophosphamide followed by docetaxel every 3 weeks • Doxorubicin + cyclophosphamide followed by weekly paclitaxel • Epirubicin + cyclophosphamide • Docetaxel + doxorubicin + cyclophosphamide • Carboplatin + paclitaxel (80 mg/ml QW x 4 cycles) • Paclitaxel every 3 weeks followed by dose-dense doxorubicin + cyclophosphamide/ epirubicin/cyclophosphamide • Paclitaxel weekly followed by dose-dense doxorubicin + cyclophosphamide • Paclitaxel every 3 weeks followed by doxorubicin + cyclophosphamide/ epirubicin/cyclophosphamide • Paclitaxel weekly followed by doxorubicin + cyclophosphamide/ epirubicin/cyclophosphamide • Nab-paclitaxel followed by (dose-dense) doxorubicin + cyclophosphamide/ epirubicin/cyclophosphamide • Nab-paclitaxel + carboplatin followed by (dose-dense) doxorubicin + cyclophosphamide/ epirubicin/cyclophosphamide **Immunotherapy agents:** • Atezolizumab + nab-paclitaxel • Atezolizumab + nab-paclitaxel followed by atezolizumab + dose-dense doxorubicin + cyclophosphamide
Comparators	Any of the interventions listed above
Outcomes	**Efficacy outcomes:** • Pathological complete response (pCR) • Event-free survival (EFS) • Disease-free survival (DFS) • Overall survival (OS) • Landmark survival rates • Landmark EFS • Landmark DFS • Treatment duration/time to treatment discontinuation **Safety outcomes:**

	• Any adverse events • Any Grade 3 or higher adverse events • Immune-related toxicity • Treatment-emergent adverse events (any Grade, and Grade 3 or higher) • Study withdrawals **Patient-reported outcomes, including quality of life measures:** • EQ-5D • EORTC QLQ-C30 • QLQ-BR23 • FACT-B-FBSI
Time	Most recent 15 years
Study design	Phase II and III RCTs Parallel group (triple-blind/double-blind) RCT - cross over (triple-blind/double-blind) RCT - post hoc and open-label extension
Language	Only studies published in English

Based on Table 4 of CS Appendices[4]
AUC = area under the curve; CS = company submission; DFS = disease-free survival; EFS = event-free survival; EQ-5D = European Quality of Life-5 Dimensions; EORTC = European Organisation for Research and Treatment of Cancer; FACT-B-FBSI = Functional Assessment of Cancer Therapy Breast Symptom Index; OS = overall survival; pCR = pathological complete response; Q3W = every three weeks; QLQ-BR23 Breast Cancer-Specific Quality of Life Questionnaire; QLQ-C30 = Quality of Life Questionnaire; QW = once weekly; RCT = randomised controlled trial; TNBC = triple-negative breast cancer

ERG comments:

- Language restrictions: The ERG notes that an English language only restriction was applied to the clinical SLR search. The ERG considers excluding non-English language studies to be inappropriate for obtaining robust evidence on the treatment of adults with previously untreated locally advanced, non-metastatic TNBC as this does not follow-up best practice and potentially relevant studies might have been missed.
- Date restriction: Eligible articles were restricted to those published within 15 years of the SLR commencement. As the term, *"triple-negative breast cancer (TNBC)"* was first used in 2005, this date restriction appears to be appropriate for the SLR.[19]
- Study design restrictions: The study design restriction placed on eligible studies appears to only allow for randomised, controlled, prospective clinical trials above phase 1, open-label studies, and post-hoc analyses of patient sub-groups, to be included in the SLR. This would appear to be appropriate.

3.1.3 Critique of data extraction

Given that the company did not provide any information on the SLR data extraction process, the ERG asked the company to provide more information on how data extraction was conducted.[5] In response to the request for clarification, the company stated that *"two reviewers, working independently, extracted data (…) Following reconciliation between the two reviewers, a third reviewer was included to reach a consensus for any remaining discrepancies"*.[6] This response reassures the ERG that the methodology of data extraction was appropriate.

3.1.4 Quality assessment

The company conducted a quality assessment of the KEYNOTE-522 trial using the Cochrane Risk of Bias tool version 2 (ROB2) and determined the study to be of low risk of bias.[20] The quality of the KEYNOTE-522 trial has been further examined in Section 3.2.4 of this report.

ERG comment: In the request for clarification, the company was asked to provide further details on how the quality assessment process was carried out; in particular, how many reviewers were involved at each stage and how discrepancies in assessment results were resolved.[5] In the response to the request for clarification, the company stated that *"two reviewers, working independently, (...) performed the quality assessment. Following reconciliation between the two reviewers, a third reviewer was included to reach a consensus for any remaining discrepancies"*.[6] The company also provided a detailed breakdown for all ROB2 signalling questions for each paper. This response suggests that the methodology of quality evaluation was appropriate.

3.1.5 Evidence synthesis

The company considered the KEYNOTE-522 trial to be the only study identified by the clinical SLR to explore the effectiveness and safety of pembrolizumab as adjuvant therapy in adults with previously untreated locally advanced, non-metastatic TNBC, and thus did not consider a meta-analysis to be relevant to this submission.[1]

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

In the abstract/title screening phase of the CS SLR, 1383 records were excluded and 142 were retained for full text screening.[1] After an additional 4 articles were found by hand-searching, 12 final citations were included, and the other 134 articles were excluded. From the 12 final citations, 7 unique trials were identified. Of the seven identified trials, only KEYNOTE-522 reported on pembrolizumab as the intervention, as shown in Table 3.3. As such, KEYNOTE-522 was reported by the company to be the only study of relevance to this appraisal.

Table 3.3: Trials included/excluded in CS SLR

Trial	Treatment	Inclusion	CS Comments
ETNA; Gianni et al. 2018[21]	Paclitaxel *versus* Nabpaclitaxel	No	Intervention and comparators differ to KN-522
GeparSepto; Untch et al. 2016[22]	Nab-paclitaxel + epirubicin + cyclophosphamide *versus* Paclitaxel + epirubicin + cyclophosphamide	No	Intervention and comparators differ to KN-522
IMpassion031; Mittendorf et al. 2020[23]	Atezolizumab + nab-Paclitaxel *versus* Placebo + nab-Paclitaxel	No	Intervention and comparators differ or irrelevant to decision problem
KEYNOTE-522; Schmid et al. 2020[24]	Pembrolizumab + chemotherapy + anthracycline *versus* Placebo + chemotherapy + anthracycline	Yes	H2H comparison study directly informing the decision problem
NATT; Chen et al. 2013[25]	Docetaxel + cyclophosphamide + epirubicin *versus* Docetaxel + cyclophosphamide	No	Intervention and comparators differ to KN-522

Trial	Treatment	Inclusion	CS Comments
NCI 10013; Ademuyiwa et al. 2021[26]	Carboplatin + paclitaxel *versus* Atezolizumab + carboplatin + paclitaxel	No	Intervention and comparators differ or irrelevant to decision problem
Vriens et al. 2013[27]	Doxorubicin + cyclophosphamide + docetaxel *versus* Doxorubicin + cyclophosphamide + docetaxel	No	Intervention and comparators differ to KN-522
Adapted from Table 7 in CS Appendices[4] CS = company submission; SLR = systematic literature review			

ERG comment: Given the large number of 20 interventions included in the SLR, the total number of included trials appears to be quite low. Furthermore, the eligibility criteria for the SLR were vague. Therefore, the clarification letter posed four related questions to the company, as follows:[5]

1. Why was the I-Spy2 trial excluded when it involved standard neoadjuvant chemotherapy – 80 mg/m^2 IV paclitaxel, followed by doxorubicin plus IV cyclophosphamide - which is in line with the eligibility criteria?
   The company response was *"to facilitate an understanding of the relative treatment effect of interventions of interest, studies must have included at least two treatment arms of interest to be eligible for inclusion in the SLR of clinical evidence. Patients with TNBC enrolled in ISPY-2 were treated with paclitaxel with or without pembrolizumab followed by doxorubicin plus cyclophosphamide. As one of the treatment arms—pembrolizumab plus paclitaxel followed by doxorubicin plus cyclophosphamide—was not listed in the PICOS criteria, this trial was excluded from the SLR".*[6]
2. The company provided rationale for its decisions on the basis of study design and PICOS outlined and therefore the ERG is satisfied with this response.Why was the PROCEED Trial excluded from the SLR based on outcomes when it reported OS, progression-free survival (PFS), quality of life (QoL) and AEs?
   The company response was that *"the PROCEED trial (KCSG BR 11-01) enrolled patients with HER2-negative metastatic breast cancer. While subgroup results for patients with TNBC were reported for overall survival and progression-free survival in Park et al. 2019, these outcomes were not of interest to the SLR on HRQoL, and subgroup results for these patients were not reported for HRQoL measurements. Thus, this trial was excluded from the SLR of HRQoL studies".*[6]
   The ERG would respond that this approach represents an SLR protocol violation, because at no point in the protocol (Table 4 in appendix D) are eligible outcomes limited to HRQoL. Therefore, the ERG is not clear on why the paper was excluded.
3. What were the 'other' reasons for which 30 studies were excluded?
   The company response was that *"the PRISMA diagram has been updated and excluded publications table of the SLR of clinical evidence to include specific reasons for exclusion with 'Other.' Fourteen citations were excluded because full-text publications superseded them, 13 citations were excluded because they were study protocols, one citation was excluded as a duplicate, one citation was excluded because the full-text was unavailable, and one citation was excluded because it was a pooled analysis and not of interest to the SLR of clinical evidence".*[6] The ERG is satisfied with this response.
4. Why were several phase III trials excluded based on 'inappropriate study design', when phase III studies are listed as eligible in Table 4 of the CS appendices?[4]

The response to clarification was that *"additional notes are provided in Table 22 (appendix), for those references excluded due to 'study design' reasons such as non-randomized study design or prognostic/predictive/genomic/correlative study design"*.[6] The ERG is satisfied with this response.

3.2.1 Details of the included trial: the KEYNOTE-522 trial

The CS identified the KEYNOTE-522 trial as the only RCT evaluating pembrolizumab for TNBC.[1] The publications related to this trial that are cited in the CS are Schmid et al. 2020,[24] the CSR,[28] and a report of the meeting of the virtual advisory board[29].

The following information is taken from the CS.[1] The trial contains 1,174 participants, 1,173 of which are female. The mean (standard deviation, SD) age is 49.1 years (11.8) with a range of 22 to 80 range. Three quarter (75%) of participants were at stage II disease, whilst 24.9% were at stage III disease. Participants were required to be 18 years or over, with newly diagnosed TNBC of either T1c N1-2 or T2-4 N0-2, an ECOG PS 0-1 and a tissue sample for PD-L1 assessment.

Participants were randomly allocated to a treatment or placebo comparator arm, using a 2:1 ratio with stratification for nodal status, tumour size and carboplatin schedule. Participants randomised to the treatment arm (n=784) were administered pembrolizumab in combination with standard neoadjuvant chemotherapy followed by adjuvant pembrolizumab. Participants randomised to the placebo arm (n=390) were administered placebo in combination with standard neoadjuvant chemotherapy followed by placebo in the adjuvant phase. The comparator treatment was designed to reflect current practice in the UK, where no active adjuvant treatment is given, see Section 2.3.

The neoadjuvant phase lasted 24 weeks and the adjuvant phase 27 weeks, with each cycle of treatment lasting 3 weeks. Therefore, the neoadjuvant phase contained 8 treatment cycles and the adjuvant phase contained 9 treatment cycles. Table 3.4 provides extra details of the drugs used in the respective phases.

To date, outcome data have been collected at four IA points, and the IA used for the CS submission appears to be the most recent one (IA4). Median duration of follow up at IA4 is 37.8 months (range 2.7 to 48 months). Although 291 participants have discontinued treatment in the intervention arm and 106 have discontinued treatment in the placebo arm, an intention-to-treat (ITT) approach has been used and follow-up data are currently available for all participants until IA4.

Data have been collected for five patient-relevant outcomes: pCR, EFS, OS, HRQoL and AEs. Attempts to achieve allocation concealment were made by use of an interactive voice response system. Performance and detection bias were minimised by blinding of all study personnel and patients for the duration of the study. A summary of the study methodology from KEYNOTE-522 is presented in Table 3.4.

Table 3.4: Study methodology for KEYNOTE-522

Study	KEYNOTE-522
Study design	Phase III stratified double-blind randomised controlled trial
Location	The study was conducted at 177 centres in 21 countries. There were 54 sites within Europe and of these, six where in the United Kingdom. A total of 434 patients were enrolled in Europe of which 40 were from the UK. All treatments were administered in secondary care setting on an outpatient basis.
Population	Patients with untreated newly diagnosed, locally advanced, centrally confirmed TNBC and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. **Inclusion:** Male and female subjects aged 18 and older who: • Have centrally confirmed TNBC, as defined by the most recent ASCO/CAP guidelines. • Have previously untreated locally advanced non-metastatic (M0) TNBC defined as: - T1c, N1-N2 - T2, N0-N2 - T3, N0-N2 - T4a-d, N0-N2 (These TNM statuses partly equate to stage 2A, 2B and 3A) • Provide a core needle biopsy consisting of at least 2 separate tumour cores from the primary tumour at screening to the central laboratory. • Have ECOG performance status of 0 or 1 performed within 10 days of treatment initiation. • Demonstrate adequate organ function within 10 days of treatment initiation. • Have left ventricular ejection fraction of ≥50% or ≥ institution lower limit of normal (LLN). • Males and female subjects of childbearing potential must be willing to use an adequate method of contraception. **Exclusion:** Subjects were excluded from participating if they had: • history of invasive malignancy ≤5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. • received prior chemotherapy, targeted therapy, and radiation therapy within the past 12 months. • received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor or has previously participated in MK-3475 clinical trials.

Study	KEYNOTE-522
	• participated in an interventional clinical trial with an investigational compound or device within 4 weeks of the first dose of treatment in this current trial. • received a live vaccine within 30 days of the first dose of study treatment. • an active autoimmune disease that has required systemic treatment in past 2 years. Replacement therapy is not considered a form of systemic treatment. • diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. • known history of Human Immunodeficiency Virus (HIV), or known active Hepatitis B or Hepatitis C. • history of (non-infectious) pneumonitis that required steroids or current pneumonitis. • active infection requiring systemic therapy. • significant cardiovascular disease, such as: myocardial infarction, acute coronary syndrome or coronary angioplasty/stenting/bypass grafting within the last 6 months; Congestive heart failure (CHF) New York Heart Association (NYHA) Class II-IV or history of CHF NYHA class III or IV • history or current evidence of any condition, therapy, lab abnormality or other circumstance that might expose the subject to risk by participating in the trial, confound the results of the trial, or interfere with the subject's participation for the full duration of the trial. • known psychiatric or substance abuse disorders • Were pregnant or breastfeeding, or expecting to conceive children within the projected duration of the trial • known hypersensitivity to the components of the study therapy or its analogues. • known history of active TB (Bacillus Tuberculosis)
Intervention(s)	**Neo-adjuvant phase** Pembrolizumab 200 mg IV on day 1 of each 21-day cycle (Q3W) for 8 cycles plus Cycles 1- 4: Carboplatin AUC 5-day Q3W (or AUC 1.5 weekly) + paclitaxel 80mg/m^2 QW Cycles 5 to 8: Doxorubicin 60 mg/m^2 Q3W or epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 Q3W **Adjuvant phase** Pembrolizumab 200 mg Q3W for 9 cycles. Total pembrolizumab cycles across neoadjuvant + adjuvant phase = 17 Q3W infusions.
Comparator(s)	**Neo-adjuvant phase** Placebo (normal saline or dextrose) IV on day 1 of each 21-day cycle (Q3W) for 8 cycles plus

Study	KEYNOTE-522
	Cycles 1- 4: Carboplatin AUC 5-day Q3W (or AUC 1.5 weekly) + paclitaxel 80mg/m^2 QW Cycles 5 to 8: Doxorubicin 60mg/m^2 Q3W or epirubicin 90mg/m^2 and cyclophosphamide 600mg/m^2 Q3W **Adjuvant phase** Placebo (normal saline or dextrose) Q3W for 9 cycles.
Additional treatments	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. Subjects were prohibited from receiving the following therapies from the time of screening until completion of all study therapy: • Immunotherapy not specified in the protocol • Chemotherapy not specified in the protocol • Investigational agents not specified in the protocol • Radiation therapy except as described in the protocol. (Post-operative radiation therapy is acceptable according to the standard of care, as applicable). • Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. • Glucocorticoids for any purpose other than to modulate symptoms from an AE of suspected immunologic aetiology or for use as a pre-medication for chemotherapeutic agents specified in the protocol. Inhaled steroids were allowed for management of asthma. Use of prophylactic corticosteroids to avoid allergic reactions were permitted.
Reported outcomes specified in the decision problem	• Pathological complete response (pCR) • Event-free survival (EFS) • Adverse events (AEs) • Overall survival (OS) • Health-related quality of life (HRQoL)
All other reported outcomes	• Patient reported outcomes (PRO) • Time on treatment

Based on the CS and meeting report of the Virtual Advisory Board[1, 29]
AEs = adverse events; AUC = area under the curve; CS = company submission; EFS = event-free survival; HRQoL = health-related quality of life; OS = overall survival; pCR = pathological complete response; PRO = patient reported outcomes; Q3W = every three weeks, QW = once weekly

ERG comment: Comments below have been separated into sections on duration of follow up, concomitant medications, protocol deviations and external validity. Comments relating to study methodology are covered in Section 3.2.4.

3.2.1.1 Duration of follow up

The short duration of follow-up of only 3 years precludes the assessment of mature survival data and the long-term safety profile. The ERG requested clarification of the reasons for this, along with a discussion of these limitations and the consequences for clinical decision making.[5]

In the response to the request for clarification, the company stated that *"at IA4 with median follow up at IA4 was over three years (39.1 months), the EFS HR of 0.63 (95% CI: 0.48, 0.82), with a one-sided p-value of 0.0003093 that crossed the prespecified boundary for statistical significance (0.00516941), represents a 37% reduction in the risk of disease progression precluding definitive surgery, recurrence, second primary malignancy, or death compared with placebo + NAC / placebo. The information fraction of EFS was approximately 66% [216 of the 327 events needed for the final analysis]. As noted, EFS is an endpoint listed on the FDA surrogate table for breast cancer. By the time of the IA4 Last Patient Last Visit (LPLV) there had been one year since the last exposure which occurred on 11th February 2020. Clinical experts advised MSD the pCR and EFS outcomes from KEYNOTE-522 were good and acknowledged they hoped to use the pembrolizumab combination in the future based upon the trial results. They also suggested that OS events are driven by a reduction in distant recurrences, which equates to a survival benefit in the TNBC setting based on the reduction in distant recurrences observed to date with pembrolizumab in KEYNOTE-522 and therefore, an OS benefit is expected in future analyses"*.

3.2.1.2 Concomitant medications

As shown in Table 3.4, *"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"*. The ERG asked the company to supply a table of the most frequently used concomitant medications during the KEYNOTE-522 trial and to discuss if non-protocol specified concomitant medications were used during the trial.[5]

In response to the request for clarification, the company stated that *"supportive care for the chemotherapeutic agents administered in KEYNOTE-522 could be found in the local product label for each agent. Corticosteroids (such as prednisone), insulin replacement therapy, hormonal replacements, beta blockers, thyroid replacement hormones and other medications were included in the toxicity management guidelines of immune related adverse events. As detailed in B.2.3 of the company submission the protocol specific prohibited concomitant medications. Glucocorticoids were administered to some patients, but in line with the protocol to manage immune-related adverse events, as a pre-medication for chemotherapy or for the management of asthma. Also, a proportion of patients received a vaccine (6.1%), most of which were inactivated though a small number, 3.3%, received an unspecified influenza vaccine"*.[6]

The company directed the ERG to Table 23 in the CS Appendix which was supposed to summarise the most frequently used concomitant medications used during the trial, but this table could not be found (Table 23 in the appendices detailed adverse events). Overall, however, the company responses suggested that concomitant medications were not likely to be a source of significant bias.

3.2.1.3 Protocol deviations

Section 10.2 of the KEYNOTE-522 CSR alluded to [redacted].[2] The ERG asked the company about how 'important', and 'not important' protocol deviations were classified.[5] In response to the request for clarification, the company stated that, *"protocol deviations were classified as '"important or 'not important' by a standard method assessing the potential impact of the protocol deviation on endpoints and safety"*.[6] This statement was supported by any references and more information is required.

The ERG also asked the company to discuss how COVID-19 may have affected the KEYNOTE-522 trial.[5] In response, the company stated that *"part of KEYNOTE-522 was conducted during the COVID-19 pandemic. MSD continued to follow its Standard Operating Procedures (SOPs) for study conduct, monitoring, and oversight during the pandemic. Exceptions and deviations from SOPs were documented. Study sites were advised to follow local and national guidance regarding the pandemic and to share any mitigation plans for study participant management with the Institutional Review Board/Ethics Review Committee and the sponsor. Study sites were also advised to remain in contact with study participants to monitor for safety concerns and to keep participants informed of changes to the study and other study activities. There were no changes in the planned analyses of the study due to the COVID-19 pandemic"*.[6] The ERG is satisfied that appropriate steps were taken to cater for the pandemic and that it is unlikely than the pandemic has had a negative effect on data quality.

The ERG noted that only a proportion of randomised patients in the KEYNOTE-522 trial proceeded onto receiving adjuvant therapy. The ERG requested more information on why this took place and asked for a comparison between the proportion of patients who received surgery/adjuvant therapy in the trial and the proportion of patients that would receive it in NHS clinical practice, along with a discussion of the implications of any difference.[5] In its response to the request for clarification, the company stated that *"about 98% of patients in both treatment arms underwent surgery; therefore, performance of surgery did not differentially impact start of adjuvant therapy. The primary reason for which randomized patients in either treatment arm did not proceed to adjuvant therapy was discontinuation due to adverse events… The higher incidence of discontinuation in the neoadjuvant phase in the pembrolizumab + NAC group was driven primarily by a higher discontinuation rate due to adverse events (14.3%) compared with the placebo + NAC group. Per protocol, if a participant discontinued either pembrolizumab or placebo during the neoadjuvant phase due to toxicity related to pembrolizumab/placebo, the participant was not permitted to receive it in the adjuvant phase of the study. For all other reasons for discontinuation, proportions were similar between groups"*.[6]

Table 3.5 summarises the reasons for drop-out. The company reiterated the important point that the analyses were intention-to-treat (ITT) and that *"despite fewer participants starting adjuvant treatment, KEYNOTE-522 demonstrated that the complete regimen of pembrolizumab + NAC followed by pembrolizumab monotherapy after surgery in the adjuvant phase resulted in a statistically significant and clinically meaningful improvement in both pCR and EFS in the ITT population"*.[6] This explanation reduced ERG concern about the numbers not proceeding to adjuvant therapy. The company was unable to find relevant NHS clinical data to compare the number dropping out of therapy with clinical practice, although it reported data on patients from Scotland who had been given adjuvant chemotherapy had a 20% drop-out rate, similar to that seen with pembrolizumab. However, it correctly cautioned that such data were not directly applicable because *"it included patients with all subtypes of breast cancer, while it did not include those who had neoadjuvant therapy and did not include English hospitals"*.[6] The ERG would also add that the data were from patients where adjuvant chemotherapy had been prescribed for

all, which was completely contrary to the case in this trial, where none were given adjuvant chemotherapy.

Table 3.5: Reasons for discontinuation from all treatments for participants who did not start adjuvant phase - All participants (ITT Population)

	Pembrolizumab + NAC/ Pembrolizumab	%	Placebo + NAC/ Placebo	%
Participants randomised	784		390	
Untreated participants	1	0.1	1	0.3
Treated participants	783	99.9	389	99.7
Participants who started adjuvant phase	588	75.0	331	84.9
Participants who did not start adjuvant phase	195	24.9	58	14.9
Discontinued in neoadjuvant phase	190	24.2	58	14.9
Adverse events	112	14.3	20	5.1
Clinical progression[a]	2	0.3	3	0.8
Physician decision	32	4.1	15	3.8
Progressive disease	8	1.0	7	1.8
Relapse/recurrence	7	0.9	3	0.8
Withdrawal by subject	29	3.7	10	2.6
Had surgery, but did not receive study medication	5	0.6	0	0.0
Still on treatment in neoadjuvant phase	0	0.0	0	0.0
Participants with surgery	768	98.0	381	97.7

Based on Table 5 in the response to the request for clarification[6]
Participants who did receive study medication but had surgery were included in subjects treated.

[a] Clinical progression is disease progression determined by the Investigator. "Progressive disease" is disease progression determined by imaging using RECIST 1.1 criteria.
Database cut-off date: 23 March 2021
ITT = intention-to-treat; NAC = neoadjuvant chemotherapy

In relation to the above point, more than double the number of patients on the pembrolizumab arm (compared to the comparator arm) discontinued study treatment in both the neoadjuvant phase and adjuvant phase of the KEYNOTE-522 trial. This was raised in the clarification letter, and the ERG requested that the company 1) detail and discuss study discontinuation due to adverse effects (AEs), 2) discuss the criteria used to characterise a "clinically important protocol deviation", 3) clarify if the greater number of protocol deviations with study intervention observed on the pembrolizumab arm was due to AEs, and 4) clarify if cross treatment was introduced in the KEYNOTE-522 trial as a protocol deviation.[5]

In its response to clarification, the company clarified that the discontinuation was largely due to adverse events, as detailed in the paragraph above.[6] The company defined clinically important protocol deviations as: *"those that may compromise critical data analyses, especially those pertaining to (1) primary efficacy and/or primary safety endpoints, or (2) the participant's safety"*. The company also confirmed that the protocol deviations were not related to AEs. Finally, in relation to the question about cross-treatments, the company responded with *"universal unblinding upon disease*

progression/recurrence and cross treatment on … was not allowed per protocol; however, off-study treatment with an immune-oncology agent after discontinuation of study treatment due to disease progression/recurrence was at physician's discretion. If this occurred, it was not considered to be a clinically important protocol deviation".[6]

3.2.1.4 External validity of KEYNOTE-522 trial

The ERG noted that the trial inclusion criteria specified that patients would have an ECOG PS of 0 or 1 performed within 10 days of treatment initiation. Thus, the ERG asked the company to confirm if patients in UK clinical practice with an ECOG PS ≥2 would not be expected to receive pembrolizumab as adjuvant therapy.[5] In its response to the request for clarification, the company stated that *"in previous approvals of immunotherapies in oncology a criterion is included on Blueteq forms for only patients who have an ECOG PS of 0 or 1, for example PEMB1 on the baseline funded drugs list".*[6]

The CS states that the KEYNOTE-522 trial recruited 40 participants from six UK study sites and further clarification has been requested on the exact geographical regions used and the specific effect sizes from Europe and UK.[1] This was regarded as particularly important because subgroup analysis results (see Section 3.2.5.5) indicate some potential differences between geographical regions, suggesting that overall findings in the KEYNOTE-522 study may not necessarily be applicable to a single region, and may therefore not be directly applicable to the UK. In the clarification letter, the ERG asked for all results to be sub-grouped for 1) Europe versus rest of world and 2) UK versus rest of world. The company provided EFS data showing that the Europe sub-group had a less favourable relative effect size for pembrolizumab (HR 0.73, 95% CI 0.49 to 1.08) compared to the rest of the world sub-group (HR 0.55, 95% CI 0.38 to 0.80), suggesting that the overall data might be providing an overly optimistic picture for European patients. The company did not provide similar data for a UK patient sub-group, and effectively did not respond to the direct question. Table 3.6 summarises the situation.

Table 3.6: EFS Subgroup analysis

	Effect size of pembrolizumab versus placebo for EFS
Whole cohort	HR: 0.63 (95% CI 0.48 to 0.82)
Europe versus rest of world	Europe: HR [redacted] Rest of the world: HR [redacted]
UK versus rest of world	UK: Data not provided Rest of the world: Data not provided

Based on Table 2 in the response to the request for clarification[6] and Table 13 of the CS[1]
CS = company submission; CI = confidence interval; EFS = event-free survival; HR = hazard ratio; UK = United Kingdom

The company were also asked to provide the baseline characteristics of the 40 UK patients by study arm in comparison with the overall trial ITT population's baseline characteristics. The company provided a table of the baseline characteristics of the 40 UK patients per arm. Comparison of these characteristics to the overall ITT population characteristics published in the CS showed some differences for some characteristics. Notable differences were ethnicity, with the UK data having a higher proportion of white participants (85% in UK data versus 63.5% in overall data), a higher proportion of people with ECOG PS 0 (95% versus 87%), and a greater choice of carboplatin Q3W (67.5% versus 42.8%). Tumour size (70% T1 or T2 versus 74% T1 or T2) and stage (20% stage II versus 25% stage III) were also slightly different. As implied by the company, the small number of UK participants makes such simplistic comparisons prone to sampling error but do suggest uncertainty over the question of how representative the overall data are to the UK population. It is unclear if these

potential differences in characteristics between the UK participants and the overall trial participants would affect outcomes, but they do suggest, in tandem with the EFS sub-group results previously described for Europe versus the rest of the world, that it is possible that the overall results observed in the KEYNOTE-522 trial may not necessarily be relevant to UK patients. This has been identified as key issue 3.

On being asked to discuss the generalisability of the study baseline demographic and disease characteristics to the clinical practice population in England and Wales, the company response was that *"while there is little published data on the demographics of UK patients with early stage triple negative breast cancer, we have not identified any characteristics of subjects in the trial that are not generalisable to patients in the UK. A study on patients in the Northeast London Cancer Network with TNBC (any stage) between 2005 and 2007, reported 82.8% were 69 years and under.[30] The proportion of patients under the age of 65 in KEYNOTE-522 was slightly higher, 88.8%, but this is to be expected as the trial recruited only patients with early-stage non-metastatic disease. Jack et al (2013) reported just over one in five patients were within the Black ethnicity group, which is in line with the UK KEYNOTE-522 participants. Stage at diagnosis for breast cancer data, published by the National Disease Registration Service (NDRS), is reported for all subtypes combined in England.[31] Of the 19,633 patients diagnosed with stage II and III breast cancers, 81.4% were the former, which is in line with KEYNOTE-522 ITT population and UK, 75.0%. and 80.0%, respectively. No major differences are noted between the key baseline demographic and disease characteristics in the UK versus KEYNOTE-522 ITT population, therefore we consider that the trial population is generalisable to that of UK patients."*.[6] These data appear to show that the trial sample is unlikely to spuriously favour the intervention, as might occur if the sample contained a higher proportion of people with a better prognosis than the UK patient population. However, this does not change the conclusion reached in the previous section that UK patients may not have the same reactions as patients in the rest of the world.

The ERG also asked the company to discuss the representativeness of the control arm to England and Wales and to discuss if the trial comparator is consistent with clinical practice. The company responded by stating that *"clinical experts have informed MSD the treatments used in KEYNOTE-522 reflects the current standard of care for neoadjuvant and adjuvant treatment of TNBC where both phases are used. The NICE guidelines for early and locally advanced breast cancer (NG101) recommend "people with triple-negative invasive breast cancer, consider a neoadjuvant chemotherapy regimen that contains both a platinum and an anthracycline". Local NHS cancer guidelines list carboplatin + paclitaxel followed by doxorubicin/epirubicin plus cyclophosamide (or order of chemotherapies is switched) for neoadjuvant treatment of TNBC patients"*.[6] The ERG accepts these points, with the caveat (as has been discussed) that capecitabine should have been considered as part of adjuvant therapy.

The ERG also pointed out that results by BC gene (BRCA1) mutation are missing and requested clarification whether patients would be offered pembrolizumab regardless of the BRCA mutation.[5] The company's response stated that "*determination of BRCA status was not required for KEYNOTE-522. Of the 54 (4.6%) participants with a BRCA1/2 mutation detected, 40 participants were in the pembrolizumab + NAC / pembrolizumab group and 14 participants were in the placebo + NAC / placebo group (as a reminder, randomisation ratio was 2:1). The number of participants with known BRCA status is too small to provide a meaningful assessment for pCR, EFS, or OS. Patients received pembrolizumab regardless of BRCA mutation results in KEYNOTE-522."*.[6]This response suggests that there is reasonable random mixing of this characteristic across arms (expected numbers would be 36 and 18 in the pembrolizumab and control arms as opposed to the observed 40 and 14) and the small imbalance is very unlikely to confound results. It is also clear that numbers are too small to allow any reasonable sub-group analyses.

Other comments relevant to this section have already been made in Section 2.3.

3.2.2 Statistical analyses of the KEYNOTE-522 trial

The statistical analyses used for the primary endpoint, alongside the sample size calculations and methods for handling missing data are presented in Table 3.7.

Table 3.7: Summary of statistical analyses for the primary analysis in KEYNOTE-522

Treatment assignment	Approximately 1,150 subjects will be randomised (double-blind) in a 2:1 ratio between 2 treatment arms: 1. Pembrolizumab plus chemotherapy as neoadjuvant therapy and pembrolizumab as adjuvant therapy, or 2. Placebo plus chemotherapy as neoadjuvant therapy and placebo as adjuvant therapy. Stratification factors are as follows: Nodal status (Positive versus Negative) Tumour size (T1/T2 versus T3/T4) Choice of Carboplatin: Q3W versus Weekly
Analysis populations	Efficacy: Intention-to-Treat Population[32] Safety: All Subjects as Treated (ASaT)
Primary endpoints	1. Pathological complete response (pCR) rate (ypT0/Tis ypN0) 2. Event-free survival (EFS)
Statistical methods for key efficacy analyses	Treatment comparisons of the pCR rate (ypT0/Tis ypN0) will be performed using the stratified Miettinen and Nurminen method. Treatment comparisons for time-to-event endpoints such as EFS and overall survival (OS) will be evaluated 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 are no Tier 1 events for this study. Point estimates and 95% confidence intervals[33] 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	Seven efficacy interim analyses (IAs) are planned. Results will be reviewed by an external DMC. By final analysis (FA) approximately 327 EFS events are expected to have been observed (event driven). It is expected to occur at ~102 months after the first subject is randomised. Primary purpose: final EFS analysis. OS will be tested only when the null hypothesis for EFS is rejected.
Multiplicity	The overall type-I error rate over the 2 primary endpoints will be strongly controlled at 2.5% (one-sided) with 0.5% allocated to the pCR (ypT0/Tis ypN0) and 2.0% allocated to the EFS hypotheses. The graphical approach of Maurer and Bretz will be applied to re-allocate alpha among hypotheses for pCR (ypT0/Tis ypN0), EFS, and OS in subjects with locally advanced TNBC. Group sequential methods will be used to allocate alpha between the interim and final analyses for pCR(ypT0/Tis ypN0), EFS and OS in subjects with locally advanced TNBC.
Sample size and power	The FA of the study is EFS event-driven and will be conducted after approximately 327 EFS events have been observed. It may occur at ~102

	months after the first subject randomized. The planned sample size is approximately 1150 subjects 1. pCR (ypT0/Tis ypN0): the trial has an overall ~95% power to detect a true pCR rate difference of 15 percentage points (pembrolizumab + chemotherapy versus placebo + chemotherapy) at alpha = 0.5% (one-sided) with ~1,000 subjects who have or would have completed surgery after ~6 months neoadjuvant treatment at IA2. 2. EFS: the trial has an overall ~80% power at a one-sided 2.0% alpha level if the true HR is 0.71. 3. OS: the trial has an overall ~79.7% power at a one-sided 2.0% alpha level, if the true HR is 0.70
Based on Table B.2.4 of the CS[1] ASaT = all subjects as treated; CS = company submission; EFS =- event-free survival; HR = hazard ratio; IA = interim analysis; OS = overall survival; pCR = pathological complete response; Q3W = every three weeks; TNBC = triple-negative breast cancer	

ERG comment: Statistical approach appears to be rigorous and correct.

3.2.3 Baseline characteristics of the KEYNOTE-522trial

A total of 1,174 participants were allocated randomly to the two arms in a 2:1 ratio. A summary of the baseline characteristics of patients is presented in Table 3.8.

Table 3.8: Baseline characteristics of patients in the ITT population of KEYNOTE-522

	Pembrolizumab + chemotherapy / Pembrolizumab (n=784)		Placebo + chemotherapy / Placebo (n=390)		Total (n=1,174)	
	n	(%)	n	(%)	n	(%)
Sex						
Male	1	(0.1)	0	(0.0)	1	(0.1)
Female	783	(99.9)	390	(100.0)	1,173	(99.9)
Age (Years)						
< 65	700	(89.3)	342	(87.7)	1,042	(88.8)
≥65	84	(10.7)	48	(12.3)	132	(11.2)
Mean	49.2		49.1		49.1	
SD	11.8		11.9		11.8	
Median	49.0		48.0		49.0	
Range	22 to 80		24 to 79		22 to 80	
Race						
American Indian or AlaskaNative	14	(1.8)	7	(1.8)	21	(1.8)
Asian	149	(19.0)	89	(22.8)	238	(20.3)
Black or African American	38	(4.8)	15	(3.8)	53	(4.5)
Multiple	13	(1.7)	6	(1.5)	19	(1.6)
American Indian or AlaskaNative Black or African American	0	(0.0)	1	(0.3)	1	(0.1)
American Indian or AlaskaNative Black or African American White	2	(0.3)	1	(0.3)	3	(0.3)
American Indian or AlaskaNative White	7	(0.9)	2	(0.5)	9	(0.8)

	Pembrolizumab + chemotherapy / Pembrolizumab (n=784)		Placebo + chemotherapy / Placebo (n=390)		Total (n=1,174)	
	n	(%)	n	(%)	n	(%)
Black Or African AmericanWhite	3	(0.4)	2	(0.5)	5	(0.4)
White Asian	1	(0.1)	0	(0.0)	1	(0.1)
Native Hawaiian or OtherPacific Islander	1	(0.1)	0	(0.0)	1	(0.1)
White	504	(64.3)	242	(62.1)	746	(63.5)
Missing	65	(8.3)	31	(7.9)	96	(8.2)
Geographic Region						
North America	166	(21.2)	78	(20.0)	244	(20.8)
Europe	388	(49.5)	180	(46.2)	568	(48.4)
Australia	23	(2.9)	16	(4.1)	39	(3.3)
Asia	166	(21.2)	91	(23.3)	257	(21.9)
Rest of World	41	(5.2)	25	(6.4)	66	(5.6)
ECOG PS						
0	678	(86.5)	341	(87.4)	1,019	(86.8)
1	106	(13.5)	49	(12.6)	155	(13.2)
Baseline Lactate Dehydrogenase (LDH)						
≤ULN	631	(80.5)	309	(79.2)	940	(80.1)
> ULN	149	(19.0)	80	(20.5)	229	(19.5)
Missing	4	(0.5)	1	(0.3)	5	(0.4)
Menopausal Status						
Pre-menopausal	438	(55.9)	221	(56.7)	659	(56.1)
Post-menopausal	345	(44.0)	169	(43.3)	514	(43.8)
Missing	1	(0.1)	0	(0.0)	1	(0.1)
Choice of Carboplatin (Planned)						
Carboplatin (Cb) Q3W	335	(42.7)	167	(42.8)	502	(42.8)
Carboplatin (Cb) Weekly	449	(57.3)	223	(57.2)	672	(57.2)
Primary Tumour (Planned)						
Tumour Size T1/T2	580	(74.0)	290	(74.4)	870	(74.1)
Tumour Size T3/T4	204	(26.0)	100	(25.6)	304	(25.9)
Nodal Involvement (Planned)						
Nodal Status Positive	405	(51.7)	200	(51.3)	605	(51.5)
Nodal Status Negative	379	(48.3)	190	(48.7)	569	(48.5)
Metastases						
M0	784	(100.0)	390	(100.0)	1,174	(100.0)
Overall Stage						
Stage I	0	(0.0)	1	(0.3)	1	(0.1)
Stage II	590	(75.3)	291	(74.6)	881	(75.0)
Stage III	194	(24.7)	98	(25.1)	292	(24.9)

	Pembrolizumab + chemotherapy / Pembrolizumab (n=784)		Placebo + chemotherapy / Placebo (n=390)		Total (n=1,174)	
	n	(%)	n	(%)	n	(%)
PD-L1 CPS 1 Cut-off						
PD-L1 CPS ≥ 1	656	(83.7)	317	(81.3)	973	(82.9)
PD-L1 CPS < 1	128	(16.3)	69	(17.7)	197	(16.8)
Unknown	0	(0.0)	4	(1.0)	4	(0.3)
PD-L1 CPS 10 Cut-off						
PD-L1 CPS ≥10	[redacted]					
PD-L1 CPS < 10	[redacted]					
Unknown	[redacted]					
PD-L1 CPS 20 Cut-off						
PD-L1 CPS ≥20	[redacted]					
PD-L1 CPS < 20	[redacted]					
Unknown	[redacted]					
HER2 Status						
0-1+ by IHC	595	(75.9)	286	(73.3)	881	(75.0)
2+ by IHC (but FISH-)	188	(24.0)	104	(26.7)	292	(24.9)
Missing	1	(0.1)	0	(0.0)	1	(0.1)

Based on Table 5 of the CS[1]
Missing values in Race and Ethnicity are mainly because France is not permitted to report this information.
The missing value in Menopausal Status is from one male participant.
The missing value in HER2 Status is from the participant with missing IHC, but FISH-.Database Cut-off Date: 23MAR2021
CPS = combined positive score; CS = company submission; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ITT = intention-to-treat; LDH = lactate dehydrogenase; PS = performance status; Q3W = every three weeks; ULN = upper limit of normal

ERG comment: The characteristics listed demonstrate reasonable levels of comparability between arms. Given the law of large numbers and the fact that this was a randomised trial, it can be assumed that other characteristics which were not measured would be similarly distributed. The CS provides details of the numbers of participants in KEYNOTE-522 with stage I, II and stage III disease, but not the four detailed TNM gradings mentioned in the inclusion criteria (page 19 of the CS): T1c, N1-N2; T2, N0-N2; T3, N0-N2; and T4a-d, N0-N2.[1] It is likely that stage relates to prognosis, and so it is vital to know if the ratio of stages in the trial is equivalent to ratios of stages in the UK population. The company has been asked in the clarification letter to provide more details on the numbers with TNM stages T1c, N1-N2; T2, N0-N2; T3, N0-N2; and T4a-d, N0-N2. The company provided the following Table 3.9 that highlights the numbers in each stage.

Table 3.9: Additional participant characteristics (ITT)

	Pembrolizumab + chemotherapy / Pembrolizumab	Placebo + chemotherapy / Placebo	Total
Participants in population (N)	784	390	1,174

	Pembrolizumab + chemotherapy / Pembrolizumab		Placebo + chemotherapy / Placebo		Total	
Tumour Stage and Nodal Involvement Grading						
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
T1b, N1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T1c, N1-N2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T1c, N3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2, N0-N2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2, N3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T3, N0-N2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T4, N0-N2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T4a-d, N0-N2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 7 of the response to request for clarification[6]
Database Cut-off Date: 23MAR2021
The one patient with Stage I disease was considered a protocol deviation, as the inclusion criteria only allowed enrolment of patients with Stage II or III disease
ITT = intention-to-treat

The company has also been asked to provide tumour, node, and metastasis (TNM) grading data on the UK population of patients with TNBC, to allow evaluation of whether the proportions of participants at different stages in the trial are similar to those in the UK population.[5] The response was that *"data for TNM grading for TNBC patients is not available from publicly available data. Information published by the cancer registry is reported as stage 1, 2, 3 and 4."*.[6] This is highlighted as key issue 4.

3.2.4 Risk of bias assessment of the KEYNOTE-522 trial

A quality assessment of the KEYNOTE-522 trial was provided in the CS[1] using the Cochrane risk-of-bias tool for randomised trials (ROB-2),[34] the results of which are presented in Table 3.10. These demonstrate low risk of bias across all areas for both efficacy (EFS) and safety (AE) outcomes.

Table 3.10: Quality assessment of the KEYNOTE-522 against ROB-2 criteria

Area of potential bias	Risk of bias within the specified outcome	
	EFS	**AE**
Randomisation process	Low	Low
Deviations from the intended interventions	Low	Low
Missing outcome data	Low	Low
Measurement of the outcome	Low	Low
Selection of the reported result	Low	Low
Overall risk of bias	Low	Low

Based on Table 11 of the CS appendices[4]
AE = adverse event; CS = company submission; EFS = event-free survival

ERG comment: Neither document B of the CS nor appendices do not provide a rationale for the decisions made on the risk of bias rating.[1, 4] Furthermore, after review of the primary sources the ERG does not agree with the quality assessment in terms of the randomisation process, as detailed below.

The allocation concealment process is very briefly reported and although it is clear that treatment allocation occurred centrally using an interactive response technology system, insufficient information is given to be certain that those recruiting participants were unaware of the allocation sequence. The clarification letter requested further information, but the response did not provide any new information that had not previously been available in the CS: *"Treatment allocation/randomisation occurred centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). Subjects were assigned randomly in a 2:1 ratio to pembrolizumab and placebo, respectively, after stratification. The choice of QW carboplatin or Q3W carboplatin should have been determined prior to randomisation, and carboplatin schedule was a stratification factor".*[6]

Section 10.1.2 of the KEYNOTE-522 CSR states that [redacted].[2] *The ERG requested clarification from the company about the potential effects of premature unblinding during the trial on outcomes measurement. The company response was that* [redacted]

Sponsor-approved non-emergency unblinding requests for participants who had disease progression / recurrence, knowing their study treatment would guide future treatment plans [redacted]

Inadvertent unblinding of investigator site and/or Sponsor personnel [redacted]

Emergency unblinding [redacted]

[redacted]

A summary of participants with or without an EFS event for participants with premature unblinding is provided in [Table 3.11]. [redacted] *out of* [redacted] *participants with premature unblinding already had an EFS event occurred on or prior to the date of unblinding, therefore, unblinding had no impact on the EFS data of those participants. The number of participants with premature unblinding either with an EFS event occurred after the date of unblinding, or without EFS event occurred is small* [redacted] *and generally consistent between the pembrolizumab + NAC / pembrolizumab group and the placebo + NAC / placebo group. There is no evidence to show the premature unblinding of participants without an EFS event at the time of unblinding had an impact on interpretation of the EFS results".*[6]

Table 3.11: Summary of participants with or without an EFS event. All participants with premature unblinding

	Pembrolizumab + chemotherapy/ Pembrolizumab		**Placebo + chemotherapy/ Placebo**		**Total**	
Participants in population (N)	784		390		1,174	
Scenarios						
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
An EFS event occurred on or prior to the date of unblinding	[redacted]					
An EFS event occurred after the date of unblinding	[redacted]					

	Pembrolizumab + chemotherapy/ Pembrolizumab		Placebo + chemotherapy/ Placebo		Total	
No EFS event occurred	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Based on Table 9 of the response to the request for clarification[6] Database Cut-off Date: 23MAR2021 EFS = event-free survival						

It was also unclear if pathologists interpreting surgical specimens for the key outcome of pCR assessment were blinded, and the ERG requested clarification.[5] The company response was that *"all pathologists reviewing and interpreting surgical specimens for assessment of pCR were required to be blinded to treatment assignment"*.[6]

The revised ERG quality assessment, using the Cochrane ROB2 tool,[34] is presented in Table 3.12 for all three completed outcomes.

Table 3.12: ERG revised quality assessment of the KEYNOTE-522 against ROB-2 criteria

Area of potential bias	Risk of bias within the specified outcome		
	EFS	HRQoL	AE
Randomisation process	Unclear	Unclear	Unclear
Deviations from the intended interventions	Low	Low	Low
Missing outcome data	Low	Low	Low
Measurement of the outcome	Low	Low	Low
Selection of the reported result	Low	Low	Low
Overall risk of bias	**Unclear**	**Unclear**	**Unclear**
AE = adverse event; EFS = event-free survival; HRQoL = health-related quality of life			

3.2.5 Efficacy results of the KEYNOTE-522 trial

The final NICE scope lists the following outcomes that need to be covered in the TA:

- Pathological complete response (pCR)
- Event free survival (EFS)
- Adverse events (AEs)
- Overall survival (OS)
- Health related quality of life (HRQoL)

The first four of these outcomes will now be evaluated in turn. Adverse outcomes will be evaluated in Section 3.2.6.

3.2.5.1 Pathological Complete Response (pCR)

The definition for the primary pCR outcome is ypT0/Tis ypN0, meaning the absence of invasive cancer in the breast and axillary nodes. The pembrolizumab arm showed a greater magnitude of pCR events, with an absolute risk difference (95% CI) of 7.5% (1.6 to 13.4). See Table 3.13 below, and Appendix D.1.5 in the CS appendices for further information.[4]

Table 3.13: Analysis of pCR (ypT0/Tis ypN0) (All participants)

Treatment	N	Number of pCR	pCR Rate (%)	Difference in % versus placebo + chemotherapy Estimate (95% CI)[a]
Pembrolizumab + chemotherapy	784	[redacted]	[redacted]	[redacted]
Placebo + chemotherapy	390	[redacted]	[redacted]	

Based on Table 12 of the CS[1], table 12
[a] Based on Miettinen & Nurminen method stratified by nodal status (positive versus negative), tumour size (T1/T2 versus T3/T4) and choice of carboplatin (Cb) (Q3W versus Weekly).
CS = company submission; CI = confidence interval; pCR = pathological complete response; Q3W = every three weeks

ERG comment: The absolute risk difference between treatment arms for pCR (95% CI) of 7.5% (1.6 to 13.4) translates to a number needed to treat of 13.3, which would not normally be regarded as clinically significant.[35]

The CS states that definition for the primary pCR outcome is ypT0/Tis ypN0 (page 17).[1] On page 14 of the CS, this is defined as absence of invasive cancer in the breast and axillary nodes. However, it is also stated on the same page that other commonly used definitions of pCR are ypT0/Tis (absence of invasive cancer in the breast), and ypT0 ypN0 (absence of invasive and in situ cancer in the breast and axillary nodes). The company has been asked to clarify the definitions used, and its response is that *"the definition for the primary outcome of pCR is ypT0/Tis yp N0, meaning the absence of invasive cancer in the breast or all resected lymph nodes. Non-invasive breast residuals were allowed"*.[6]

The company were also asked to discuss why the definition indicative of more complete recovery (absence of invasive and in situ cancer in the breast and axillary nodes) was not used as the primary outcome pCR.[5] The response was that *"FDA guidance recognises ypT0/Tis ypN0 as an acceptable definition of pCR, and so that was selected as the definition used for pCR as the primary outcome. The alternative definition, ypT0 ypN0, was used as the definition for the secondary outcome analysis"*.[6] This confirms that the company used a less testing outcome as its primary outcome. Although potentially misleading, this is not actually a problem as the absolute risk difference (pembrolizumab – control arm) in pCR is actually more favourable to the intervention in the stricter definition: for ypT0ypN0 (the stricter definition) it is +7.6 (95% CI 1.6 to 13.6) and for ypT0/TisypN0 (the primary outcome used in the trial) it is +7.5(95% CI 1.6 to 13.4). Therefore, it could be argued that the company have slightly underestimated (rather than overestimated) its effect by using the ypT0/Tis ypN0 outcome as its primary variable.

3.2.5.2 Event-free survival (EFS)

For the outcome of event-free survival, the HR was 0.63 (95% CI 0.48 to 0.82). This was described by the CS as representing a 37% reduction in the risk of disease progression precluding definitive surgery, recurrence, second primary malignancy, or death compared with placebo + chemotherapy followed by placebo. Table 3.14 summarises the analysis of EFS, and Table 3.15 summarises the first event in EFS analyses.

Table 3.14: Analysis of event free survival (All participants)

Treatment	N	Number of events (%)	Person-months	Event rate/100 person-months	Median EFS [months] (95% CI) [a]	EFS Rate at 42 months % (95% CI)	Versus control Hazard Ratio (95% CI) [b]
Pembrolizumab arm	784	123 (15.7)	26,994.6	0.5	NR	83.5 (80.5, 86.0)	0.63 (0.48, 0.82) p-value [c] 0.0003093
Placebo arm	390	93 (23.8)	12,783.8	0.7	NR	74.9 (69.8, 79.2)	

Based on Table 13 of the CS[1]
[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by nodal status (positive versus negative), tumour size (T1/T2 versus T3/T4) and choice of carboplatin (Q3W versus Weekly).
c One-sided p-value based on log-rank test stratified by nodal status (positive versus negative), tumour size (T1/T2 versus T3/T4) and choice of carboplatin (Cb) (Q3W versus Weekly).
Database Cut-off Date: 23MAR2021
CS = company submission; CI = confidence interval; EFS = event-free survival; NR = not reported; Q3W =every three weeks

Table 3.15: Summary of first event in EFS analyses

Event	Pembrolizumab arm (n=784)	Placebo arm (n=390)
	n (%)	n (%)
Any EFS Event	123 (15.7)	93 (23.8)
Secondary Primary Malignancy	6 (0.8)	4 (1.0)
Local PD Precludes Surgery	[redacted]	[redacted]
Local PD Precludes Definitive Surgery	[redacted]	[redacted]
Distant PD	[redacted]	[redacted]
Positive Margin at Last Surgery	[redacted]	[redacted]
Local Recurrence	28 (3.6)	17 (4.4)
Distant Recurrence	60 (7.7)	51 (13.1)
Death	15 (1.9)	6 (1.5)

Based on Table 15 of the CS[1]
Database Cut-off Date: 23MAR2021.
CS = company submission; EFS = event-free survival; PD = progressed disease

ERG comment: The CS refers to a 37% reduction in risk in relation to the HR of 0.63.[1] However, caution should always be taken with interpretation of the clinical importance of HRs as they cannot be interpreted in the same way as risk ratios.[36] Although the 37% reduction in hazard of recurrence is of large magnitude, this cannot be taken to imply that a similar difference in survival from recurrence will exist between the groups at longer time intervals.[36] Hence the clinical importance of this result is likely to be less clear-cut than that implied by the stated 37% reduction in "risk".

3.2.5.3 Overall Survival (OS)

The OS HR was 0.72 (95% CI 0.51 to 1.02), which was described as representing a 28% reduction in the risk of death compared with the placebo arm (Table 3.16). The median OS was not reached in either arm at month 42 and will need to be analysed in future IA as data matures.

Table 3.16: Analysis of OS (All participants)

Treatment	N	Number of events (%)	Person-months	Event rate/100 person-months (%)	Median OS [a] [months] (95% CI)	OS Rate at month 42 in %[†] (95% CI)	Versus control Hazard Ratio (95% CI) [b] p-value [c]
Pembrolizumab arm	784	80 (10.2)	28,1997.7	0.3	NR	89.2 (86.7, 91.3)	0.72 (0.51, 1.02) 0.0321377
Placebo arm	390	55 (14.1)	13,908.1	0.4	NR	84.1 (79.5, 87.7)	

Based on Table 16 of the CS[1]
[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by nodal status (positive versus negative), tumour size (T1/T2 versus T3/T4) and choice of carboplatin (Q3W versus Weekly).
[c] One-sided p-value based on log-rank test stratified by nodal status (positive versus negative), tumour size (T1/T2 versus T3/T4) and choice of carboplatin (Cb) (Q3W versus Weekly).
Database Cut-off Date: 23MAR2021
CS = company submission; CI = confidence interval; NR = not reached; OS = overall survival; Q3W = every three weeks

ERG comment: The CS refers to a 28% reduction in risk in relation to the HR of 0.72.[1] However, as stated previously, caution should always be taken with interpretation of the clinical importance of HRs as they cannot be interpreted in the same way as risk ratios.[36] Hence the clinical importance of this result is unclear. This is particularly true given that there is insufficient evidence to reject the null hypothesis that the two intervention strategies have the same effects.

3.2.5.4 Quality of life

Three patient reported outcomes (PRO) questionnaires were used to assess patient HRQoL in the study for both the neoadjuvant and adjuvant phases: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), Breast Cancer-Specific Quality of Life Questionnaire (QLQ-BR23) and European Quality of Life-5 Dimensions (EQ-5D visual analogue scale (VAS)) PRO analyses were based on the PRO full analysis set (FAS) population, which included all randomised participants who had at least one PRO assessment available and had received at least one study treatment.

3.2.5.4.1 Neoadjuvant phase

At Week 21, the difference in mean change from baseline in EQ-5D VAS score between the pembrolizumab arm and placebo arm was [redacted] points (95% CI: -[redacted]), as shown in Table 3.17.

Table 3.17: Analysis of change from neoadjuvant baseline in EQ-5D VAS at neoadjuvant week 21 - All participants (FAS population)

Treatment	Baseline		Neoadjuvant Week 21		Change from Baseline at Week 21	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) [a]
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 versus Placebo + chemotherapy					[redacted]	[redacted]

Based on Table 18 of the CS[1]
[a] Based on cLDA model with the PRO score as the response variable, and treatment by timepoint interaction, stratification factors (Nodal status (positive vs negative), Tumour size (T1/T2 vs T3/T4), and Choice of Carboplatin (Q3W vs Weekly)) as covariates.
For Neoadjuvant Baseline and Neoadjuvant Week 21, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from Neoadjuvant Baseline, N is the number of participants in the analysis population in each treatment group.
CI = confidence interval; CS = company submission; EQ-5D = European Quality of Life-5 Dimensions FAS = full analysis set; Q3W = every three weeks; SD = standard deviation; VAS = visual analogue scale

3.2.5.4.2 Adjuvant phase

At Week 24 (of the adjuvant phase) the difference in mean change from baseline in EQ-5D VAS score between the pembrolizumab arm and placebo arm was [redacted] points (95% CI: [redacted], [redacted]), see Table 3.18.

Table 3.18: Analysis of change from adjuvant baseline in EQ-5D VAS at adjuvant week 24 - all participants (FAS population)

Treatment	Baseline		Adjuvant Week 24		Change from Baseline at Week 24	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) [a]
Pembrolizumab monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise comparison					**Difference in LS Means (95% CI)**	**p-Value**
Pembrolizumab + versus Placebo					[redacted]	[redacted]

Based on Table 19 of the CS[1]
[a] Based on cLDA model with the PRO score as the response variable, and treatment by timepoint interaction, stratification factors (Nodal status (positive vs negative), Tumour size (T1/T2 vs T3/T4), and Choice of Carboplatin (Q3W vs Weekly)) as covariates.

Treatment	Baseline		Adjuvant Week 24		Change from Baseline at Week 24	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI) [a]
For Adjuvant Baseline and Adjuvant Week 24, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from Adjuvant Baseline, N is the number of participants in the analysis population in each treatment group. CI = confidence interval; CS = company submission; EQ-5D = European Quality of Life-5 Dimensions FAS = full analysis set; Q3W = every three weeks; SD = standard deviation; VAS = visual analogue scale						

Further details of the EORTC QLQ-C30 and QLQ-BR23 results have been presented in Section 11.2.5 of the KEYNOTE-522 CSR.[28]

ERG comment: The lack of relative benefit for the pembrolizumab arm in terms of quality of life is an important finding. This may reflect the modest benefits observed for the other efficacy outcomes, alongside the significant adverse effect burden of pembrolizumab (see Section 3.2.6).

3.2.5.5 Subgroup analyses

A series of analyses were pre-specified in the KEYNOTE-522 study protocol 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:

- Nodal status (positive versus negative)
- Tumour size (T1/T2 versus T3/T4)
- Choice of carboplatin (Q3W versus weekly)
- PD-L1 CPS (≥1 vs <1, ≥10 versus <10, ≥20 versus <20)
- Overall stage (Stage II versus stage III)
- Menopausal status (Pre versus post)
- Age (<65 years versus ≥ 65)
- Geographic region (Europe/Israel/North America/Australia versus Asia versus Rest of the world)
- Ethnic origin (Hispanic versus non-Hispanic)
- ECOG performance status (0 versus 1)
- HER2 status by IHC (2+ but FISH versus 0-1)
- LDH (>Upper limit of normal (ULN) versus ≤ ULN)

The treatment difference of pembrolizumab + chemotherapy compared with placebo + chemotherapy across prespecified subgroup analysis was generally consistent with the finding in the ITT population, showing directionally favourable improvement in pCR in the pembrolizumab + chemotherapy group (Figure 3.1). The same is also true for EFS (Figure 3.2). Due to the small number of events in subgroups, the results should be interpreted with caution.

ERG comment: The ERG noted that subgroup analyses results indicated potential differences between ECOG PS. In particular, in contrast to the ECOG = 0 sub-group, the sub-group with ECOG = 1 did not demonstrate benefits from pembrolizumab in terms of pCR (Figure 3.1). Thus, the ERG also asked the company to discuss the implications for decision making. The company responded by stating that *"a comparison of baseline characteristics … for all participants in KEYNOTE-522 with an ECOG PS of 1 demonstrated that, compared with the placebo + NAC / placebo group, participants in the pembrolizumab + NAC / pembrolizumab subgroup were older (median age of 53.5 years vs 47.0 years) and included greater proportions (≥5 percentage points) of the*

following parameters: participants who were post-menopausal, participants with PD-L1 positive tumors (CPS cutoff of 10), and participants with a primary tumor size of T3/T4, respectively".[6] This is noted as key issue 5.

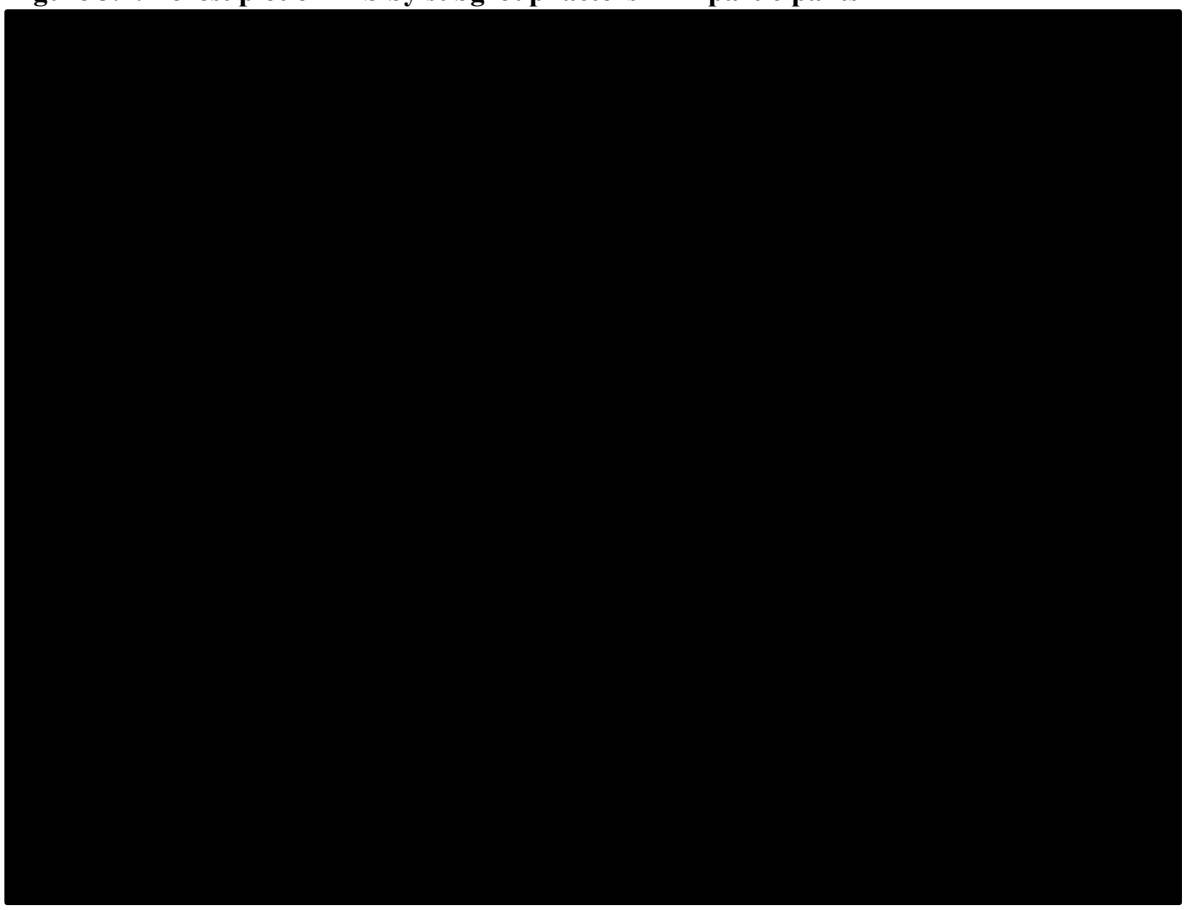
A closely related point was made in the succeeding paragraph. These statements did not provide information relevant to decision-making (in terms of the groups for which pembrolizumab might be, or might not be, useful) and merely described the characteristics expected to be associated with an ECOG of 1. Attempts to adjust for these covariates were made by the company in post-hoc analyses, which of course, removed the negative effects of the highly correlated ECOG variable upon the outcome. These did not show anything other than confirm the evident correlation. Associations of ECOG status with these characteristics are likely to be non-random effects related to the intrinsic nature of ECOG status, and so such an adjustment with these highly correlated variables was inappropriate. This can be demonstrated by considering that the relationship between ECOG status and its correlates of age or menopause status are analogous to the relationship expected between the variable of frailty and its correlates of old age and muscle weakness. One would not adjust frailty for old age and muscle weakness and then claim that frailty does not have an impact on the outcome of falls (because frailty *is* old age and muscle weakness), and in the same way it is not correct to adjust for age and menopause status and then claim that ECOG status has no effect on the outcome of pCR (because you are effectively adjusting ECOG out of the equation through multicollinearity). The important point is that these correlating characteristics do not prevent people with ECOG 1 being less appropriate candidates for pembrolizumab, and it is likely that if people have an ECOG score of 1 they are not going to experience benefits from pembrolizumab. The company stated that numbers were small and that therefore it was difficult to form conclusions, but the data suggest that patients with an ECOG status of 1 are unlikely to benefit from pembrolizumab (and there is a probability that the drug could even cause harm in this group, although this is uncertain).

Sub-group analyses also demonstrated potential differences between geographical regions. This has been commented on in detail in Section 3.2.1.

Figure 3.1: Forest plot of pCR (ypT0/Tis ypN0) by subgroup factors - All participants

Based on Figure 6 of the CS[1]
CI = confidence interval; CPS = combined positive score; CS = company submission; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; pCR = pathological complete response; PS = performance status; Q3W = every three weeks; ULN = upper limit of normal

Figure 3.2: Forest plot of EFS by subgroup factors - All participants



Based on Figure 6 of the CS[1]
CI = confidence interval; CPS = combined positive score; CS = company submission; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; pCR = pathological complete response; PS = performance status; Q3W = every three weeks; ULN = upper limit of normal

3.2.6 Adverse events of the KEYNOTE-522 trial

The CS reported that safety results of KEYNOTE-522 demonstrated pembrolizumab plus chemotherapy followed by pembrolizumab monotherapy had a manageable safety profile in participants with high-risk, early-stage TNBC, and that the safety profile of the pembrolizumab arm is generally consistent with the known safety profile of pembrolizumab monotherapy and a carboplatin-/anthracycline-based chemotherapy regimen.[1] No new safety concerns were identified.

During the combined phases, the overall 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 pembrolizumab arm and the placebo arm. However, there was a higher overall incidence of serious adverse effects (SAEs), serious drug-related AEs, and discontinuations of any drug due to an AE in the pembrolizumab arm compared with the placebo arm, reflecting the contribution of both pembrolizumab and neoadjuvant chemotherapy.

3.2.6.1 Summary of adverse events

According to the CS, comparable proportions of patients in the pembrolizumab and placebo arms experienced AEs (drug-related AEs (98.9% versus 99.7%), Grade 3 to 5 AEs

([redacted]), Grade 3 to 5 drug-related AEs (77.1% versus 73.3%), deaths ([redacted]), deaths due to drug-related AEs (0.5% versus 0.3%), and any dose modification due to an AE ([redacted]).[1]

There was a higher incidence (≥5 percentage points difference) of serious adverse events (SAEs, [redacted]%), serious drug-related AEs ([redacted]%), and discontinuations of any drug due to an AE ([redacted]%) in the pembrolizumab arm compared with the placebo arm.

Included adverse events started from the first treatment including definitive surgery and radiation therapy and up to 30 days of the last treatment including definitive surgery and radiation therapy for the non- SAEs and up to 90 days of the last treatment including definitive surgery and radiation therapy for the SAEs.

Table 3.19 summarises adverse events and effects on continuation.

Table 3.19: Adverse event summary - Combined phases (All participants)

	Pembrolizumab arm (n=789)		Placebo arm (n=389)	
	n	(%)	n	(%)
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse event	[redacted]	[redacted]	[redacted]	[redacted]
with drug-related [a] adverse events	774	(98.9)	388	(99.7)
with toxicity Grade 3-5 adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity Grade 3-5 drug-related adverse events	604	(77.1)	285	(73.3)
with serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
who died	7	(0.9)	1	(0.3)

	Pembrolizumab arm (n=789)		Placebo arm (n=389)	
	n	(%)	n	(%)
who died due to a drug-related adverse event	4	(0.5)	1	(0.3)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]*	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]*	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]*	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 24 of the CS[1]

[a] Determined by the investigator to be related to the drug.

	Pembrolizumab arm (n=789)		Placebo arm (n=389)	
	n	(%)	n	(%)
[b] Defined as an action taken of dose reduced, drug interrupted, or drug withdrawn. Grades are based on NCI CTCAE version 4.0.[37] MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease progression" not related to the drug are excluded. Database Cut-off Date: 23MAR2021 CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; NCI = National Cancer Institute				

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

AEs (incidence ≥15%) with a greater risk difference for pembrolizumab arm (where the lower bound of the 95% CI for the treatment difference was >0) during the combined phases were [redacted]. These events were primarily Grade 1 or 2. There were no AEs (incidence ≥15%) with a greater risk difference for the placebo arm identified during the combined phases. In both treatment arms, most AEs occurred in the first 3 months of initiating study intervention; the exposure-adjusted event rate decreased at 3 to 6 months and continued to decrease beyond 12 months (Table 3.20).

Table 3.20: Participants with AEs by decreasing incidence (incidence ≥10% in at least one arm; ASaT population)

	Pembrolizumab arm		Placebo arm	
	n	(%)	n	(%)
Participants in population	783		389	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Pembrolizumab arm		Placebo arm	
	n	(%)	n	(%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 25 of the CS[1]
Every participant is counted a single time for each applicable specific adverse event.

	Pembrolizumab arm		Placebo arm	
	n	(%)	n	(%)
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Database Cut-off Date: 23MAR2021 CS = company submission; MedDRA = Medical Dictionary for Regulatory Activities;				

ERG comment: The CS reported that the risk of deaths were comparable between arms.[1] However, the risk of deaths in the pembrolizumab arm were three times that of the placebo arm, please see Section 3.2.6.6 for further comments related to this issue.

3.2.6.2 Drug related AEs

The overall incidences of drug-related AEs during the combined phases were similar between the pembrolizumab (98.9%) and placebo (99.7%) arms (Table 3.21).

The incidences of the most frequently reported drug-related AEs (incidence ≥30%) during the combined phases were generally similar between the two treatment groups (Table 3.21) and included:

- Pembrolizumab arm: nausea, alopecia, anaemia, neutropenia, fatigue, and diarrhoea.
- Placebo arm: nausea, alopecia, anaemia, neutropenia, and fatigue.

Table 3.21: Participants with drug related AEs by decreasing incidence (incidence ≥5% in one or more treatment arms; ASaT population)

	Pembrolizumab arm		Placebo arm	
	n	(%)	n	(%)
Participants in population	783		389	
with one or more adverse events	774	(98.9)	388	(99.7)
with no adverse events	9	(1.1)	1	(0.3)
Nausea	495	(63.2)	245	(63)
Alopecia	471	(60.2)	220	(56.6)
Anaemia	429	(54.8)	215	(55.3)
Neutropenia	367	(46.9)	185	(47.6)
Fatigue	330	(42.1)	151	(38.8)
Diarrhoea	238	(30.4)	98	(25.2)
Alanine aminotransferase increased	204	(26.1)	98	(25.2)
Asthenia	198	(25.3)	102	(26.2)
Neutrophil count decreased	185	(23.6)	112	(28.8)
Vomiting	200	(25.5)	86	(22.1)
Constipation	188	(24)	85	(21.9)
Rash	196	(25)	66	(17)
Neuropathy peripheral	154	(19.7)	84	(21.6)
Aspartate aminotransferase increased	157	(20.1)	63	(16.2)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Pembrolizumab arm		Placebo arm	
	n	(%)	n	(%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 26 of the CS[1]
Every participant is counted a single time for each applicable specific adverse event.
Database Cut-off Date: 23MAR2021
CS = company submission

3.2.6.3 Grade 3 to 5 AEs

The overall incidence of Grade 3 to 5 AEs during the combined phases was generally similar between the 2 treatment groups arms (Table 3.22). There were no specific trends noted in the pembrolizumab

arm that suggest any new safety concerns. The types and frequencies of the most common Grade 3 to 5 AEs (incidence ≥5%) during the combined phases were generally similar between the 2 treatment arms. The only risk difference of Grade 3 to 5 AEs (incidence ≥5%) during the combined phases that favoured either treatment group was [redacted], which had a greater risk in the pembrolizumab arm (where the lower bound of the 95% CI for the treatment difference was >0).

Table 3.22: Participants with Grade 3-5 AEs by decreasing incidence (incidence ≥5% in one or more treatment arms; ASaT population)

	Pembrolizumab arm		Placebo arm	
	n	(%)	n	(%)
Participants in population	783		389	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 27 of the CS[1]
Every participant is counted a single time for each applicable specific adverse event.
Grades are based on NCI CTCAE version 4.0.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cut-off Date: 23MAR2021
CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; NCI = National Cancer Institute

ERG comments: No comments

3.2.6.4 Drug related Grade 3-5 AEs

The overall incidences of drug-related Grade 3 to 5 AEs as determined by the investigator during the combined phases were generally similar between the pembrolizumab (77.1%) and placebo arms (73.3%). The incidences of the most frequently reported drug-related Grade 3 to 5 AEs (incidence ≥5%) during the combined phases were generally similar between treatment groups (Table 3.23).

Table 3.23: Participants with drug related Grade 3-5 AEs by decreasing incidence (incidence ≥5% in one or more treatment arms; ASaT population)

	Pembrolizumab arm		Placebo arm	
	n	(%)	n	(%)
Participants in population	783		389	
with one or more adverse events	604	(77.1)	285	(73.3)
with no adverse events	179	(22.9)	104	(26.7)
Neutropenia	270	(34.5)	130	(33.4)
Neutrophil count decreased	146	(18.6)	90	(23.1)

	Pembrolizumab arm		Placebo arm	
	n	**(%)**	**n**	**(%)**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	141	(18)	58	(14.9)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	43	(5.5)	9	(2.3)

Based on Table 28 of the CS[1]
Every participant is counted a single time for each applicable specific adverse event.
Grades are based on NCI CTCAE version 4.0.
Database Cut-off Date: 23MAR2021
CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute

ERG comments: No comments

3.2.6.5 Serious adverse effects

The overall incidence of SAEs was higher in the pembrolizumab arm compared with the placebo arm. The SAEs observed for participants in the pembrolizumab arm were reported by the company [1]to be generally consistent with the known safety profiles of pembrolizumab monotherapy and a carboplatin-/anthracycline-based chemotherapy regimen (Table 3.24).

Table 3.24: Participants with serious AEs up to 90 days after last dose by decreasing incidence (incidence ≥1% in one or more treatment arms; ASaT population)

	Pembrolizumab arm		Placebo arm	
	n	**(%)**	**n**	**(%)**
Participants in population	783		389	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 29 of the CS[1]
Every participant is counted a single time for each applicable specific adverse event.

	Pembrolizumab arm		Placebo arm	
	n	(%)	n	(%)
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Database Cut-off Date: 23MAR2021 CS = company submission; MedDRA = Medical Dictionary for Regulatory Activities				

ERG comments: The difference between arms in SAEs is large and requires consideration in the overall evaluation of the study drug.

3.2.6.6 Deaths due to Adverse Events

Deaths due to AEs during the combined phases occurred in [redacted] ([redacted]%) participants in the pembrolizumab arm and [redacted] ([redacted]%) participant in the placebo arm. There were 4 deaths in the pembrolizumab arm considered drug related. Deaths due to AE in 3 participants were considered related to pembrolizumab (pneumonitis in 1 participant in the neoadjuvant phase, pulmonary embolism in 1 participant in the adjuvant phase, and autoimmune encephalitis in 1 participant in the adjuvant phase). One participant in the neoadjuvant phase experienced 3 AEs resulting in death: sepsis and multiple organ dysfunction syndrome, which were considered related to chemotherapy, and myocardial infarction, which was not considered to be drug related. In the placebo arm, the 1 reported death due to an AE (septic shock) occurred during the neoadjuvant phase and was considered related to chemotherapy by the investigator. No new safety signals were identified upon review of these fatal events.

ERG comments: For pembrolizumab versus placebo, the relative risk of death is 3, which requires consideration in the overall evaluation of the study drug. The probability of a difference this large arising by chance is 0.01. This, together with comments in Section 3.2.6.5, has been noted as key issue 6.

3.2.6.7 Adverse events of special interest (AEOSI)

The overall incidence of AEOSI during the combined phases was higher in the pembrolizumab arm (43.6%) compared with the placebo arm (21.9%).

There were 2 deaths due to an AEOSI (pneumonitis and autoimmune encephalitis) in the pembrolizumab arm, which were considered related to pembrolizumab by the investigator. The most frequently reported AEOSIs (incidence ≥5%) by category, during the combined phases were hypothyroidism, infusion reactions, severe skin reactions, and hyperthyroidism in the pembrolizumab arm and hypothyroidism and infusion reactions in the placebo arm. The incidence of hypothyroidism in the pembrolizumab arm was higher than anticipated based on the known safety profile of pembrolizumab monotherapy and higher than the placebo arm (Table 3.26).

Table 3.25: Participants with AEOSI by category (incidence >0% in one or more treatment arms; ASaT population

	Pembrolizumab arm		Placebo arm	
	n	(%)	n	(%)
Participants in population	783		389	
with one or more adverse events	341	(43.6)	85	(21.9)
with no adverse events	442	(56.4)	304	(78.1)
Infusion Reactions	141	(18)	45	(11.6)

	Pembrolizumab arm		Placebo arm	
	n	**(%)**	**n**	**(%)**
Hypothyroidism	118	(15.1)	22	(5.7)
Severe Skin Reactions	45	(5.7)	4	(1)
Hyperthyroidism	41	(5.2)	7	(1.8)
Adrenal Insufficiency	20	(2.6)	0	(0)
Pneumonitis	17	(2.2)	6	(1.5)
Thyroiditis	16	(2)	5	(1.3)
Hypophysitis	15	(1.9)	1	(0.3)
Colitis	13	(1.7)	3	(0.8)
Hepatitis	11	(1.4)	3	(0.8)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 30 of the CS[1]
Every participant is counted a single time for each applicable specific adverse event. A participant with multiple adverse events within a bolded term is counted a single time for that bolded term.
"Infusion related reaction" includes infusion related reactions due to pembrolizumab and chemotherapy, for example, Paclitaxel.
Database Cut-off Date: 23MAR2021
CS = company submission

ERG comments: No comments.

3.2.7 Included studies: Supporting evidence

Not applicable.

3.2.8 Ongoing studies

The next database cut off (IA5) is calendar-driven and will take place in [redacted].

ERG comment: In the clarification letter, the ERG has requested to know when data from IA5 can be made available.[5] The response from the company is *"as dual-primary endpoints pCR (at IA1) and EFS (at IA4) achieved statistical significance, the study continues to follow OS in a blinded manner. Per the protocol, the next interim analysis (IA5) will occur ~60 months after the first participant was*

randomized, 1 year after IA4. If OS achieves statistical significance, the external DMC will inform MSD and updated efficacy results may be available in Q3 2022. If OS doesn't achieve statistical significance, the study will continue in a blinded manner".[6]

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparison (IC) and/or multiple treatment comparison was carried out.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

According to Section B.2.9 of the CS, *"clinical expert advice sought confirmed that the KEYNOTE-522 study design and choice of comparators is appropriate and generalisable of the treatment pathway in the UK setting".*[1] The ERG asked the company to provide supporting references and please provide a report describing the clinical expert advice solicitation.[5] The response from the company is that *"the report from the advisory board is provided as a separate confidential reference for consideration".*[6]

3.5 Additional work on clinical effectiveness undertaken by the ERG

Not applicable.

3.6 Conclusions of the clinical effectiveness section

The CS and response to clarification provided full details for the ERG to appraise the literature searches conducted to identify studies about the clinical efficacy and safety outcomes of pembrolizumab + chemotherapy and competing interventions for the neoadjuvant treatment of locally advanced non-metastatic TNBC. The searches were conducted in July 2021. Searches were transparent and reproducible, and comprehensive search strategies were used. A good range of databases and grey literature resources were searched. Strategies included an extensive list of search terms for the population and comparators, and validated search filters for study design. The ERG was concerned about the language bias of restricting searches to English language only.

The evidence from the CS suggests that pembrolizumab given alongside standard neoadjuvant therapy, followed by pembrolizumab given alone in the adjuvant phase, is more clinically effective than placebo given alongside standard neoadjuvant therapy, followed by placebo given alone in the adjuvant phase.[1] The intervention arm demonstrated a benefit in event-free survival (HR 0.63, 95% CI 0.48 to 0.82), a small but significant benefit in pCR (absolute risk difference of 7.5% (95% CI: 1.6% to 13.4%), equating to a number-needed-to-treat of around 13) and a trend for a benefit in OS (HR 0.72, 95% CI 0.51 to 1.02). However, benefits in terms of quality of life were not observed, suggesting that the net positive balance between clinical benefits and harms of pembrolizumab were insufficient to have a positive impact on patients' quality of life.

Although the adverse events of the intervention are reported by the CS to be consistent with expectations, 43.6% of participants in the pembrolizumab arm experienced SAEs, compared to 28.5% of participants in the placebo arm, and three times the proportion of participants died in the pembrolizumab arm (0.9%) compared to the placebo arm (0.3%).[1] The moderate benefits of pembrolizumab therefore need to be considered in the light of its potential harms.

An important issue for consideration is the choice of comparator in the trial. It is likely that the use of placebo in the adjuvant phase, rather than an active comparator such as capecitabine (which is associated with an improvement in DFS) may have contributed to an increased estimate of benefit for

pembrolizumab. Whilst this observed benefit may be realistic in terms of comparison to established practice, it may be over-optimistic in evaluating pembrolizumab in relation to the best available alternative therapies.

4. COST EFFECTIVENESS

4.1 ERG comment on company's review of cost effectiveness evidence

One set of systematic literature searches was performed to identify CE studies, and cost and healthcare resource use studies (CS Appendices G and I), and a separate search was conducted to identify HRQoL studies (Appendix H).[1, 4]

4.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of the searches related to CE presented in the CS. The CADTH evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[10, 11] The CS was checked against the single technology appraisal (STA) specification for company/sponsor submission of evidence.[12]

Appendices G and I of the CS reported the literature searches used to identify CE studies, and cost and healthcare resource use studies.[4] Appendix H reported the literature searches used to identify HRQoL studies.[4] All searches were conducted on 16 May 2021.

A summary of the resources searched for CE studies, HRQoL studies, and cost and healthcare resource use studies is provided in Table 4.1.

Table 4.1: Resources searched for cost effectiveness studies, HRQoL studies, and cost and healthcare resource use studies (as reported in CS)

Resource	Host/Source	Date Ranges	Date Searched
Electronic databases			
MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations	Ovid	1946 to 14 May 2021	16/05/21
Embase	Ovid	1974 to 14 May 2021	16/05/21
CENTRAL	EMB Reviews, Ovid	April 2021	16/05/21
CDSR	EMB Reviews, Ovid	2005 to 12 May 2021	16/05/21
EconLit	Ovid	1886 to 6 May 2021	16/05/21
Additional resources			
HERC Database of Mapping Studies	NR	NR	NR
ScHARRHUD	NR	NR	NR
Conference proceedings			
ASCO	Northern Light, Ovid	2016-2020	16/05/21
ESMO	Northern Light, Ovid	2016-2020	16/05/21
ISPOR Annual European Conference	Northern Light, Ovid	2016-2020	16/05/21
ISPOR Annual Asian Conference	Northern Light, Ovid	2016-2020	16/05/21

Resource	Host/Source	Date Ranges	Date Searched
ISPOR Annual International Meeting North America	Northern Light, Ovid	2016-2020	16/05/21
NCCN	Northern Light, Ovid	2016-2020	16/05/21
SABCS	Northern Light, Ovid	2016-2020	16/05/21
HTA organisations			
AHRQ	NR	NR	NR
NIHR HTA	NR	NR	NR
INAHTA	NR	NR	NR
SMC	NR	NR	NR
AWMSG	NR	NR	NR
CADTH	NR	NR	NR
HAS	NR	NR	NR
IQWIG	NR	NR	NR
ICER	NR	NR	NR
NICE	NR	NR	NR

AHRQ = Agency for Healthcare Research and Quality; ASCO = American Society of Clinical Oncology; AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technologies in Health; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission; ESMO = European Society for Medical Oncology congress; HAS = French National Authority for Health (Haute Autorité de Santé); HERC = Health Economics Research Centre; HTA = health technology assessment; ICER = Institute for Clinical and Economic Review; INAHTA = Health Technology Assessment database of the International Network of Agencies for Health Technology Assessment; IQWIG = Institute for Quality and Efficiency in Healthcare; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NCCN = National Comprehensive Cancer Network Annual Conference; NICE = National Institute for Health and Care Excellence; NIHR = National Institute of Health Research Health; NR = not reported; SABCS = San Antonio Breast Cancer Symposium; ScHARRHUD = School of Health and Related Research health utilities database; SMC = Scottish Medicines Consortium

ERG comment:

- The CS provided full details of the literature searches for the ERG to appraise.[1, 4]
- A comprehensive range of databases, supplementary resources, conference proceedings, and health technology assessment (HTA) organisation websites were searched.
- Full details of the database searches, including the database name, host platform, date range and date searched, were provided.
- Economic specific resources were searched, but details of the search strategies or search terms used, dates of searches, and results were not reported in the CS.[1, 4] The search terms used, and results, were provided in response to the ERG clarification letter; the full search strategies, and dates of searches, were not provided.[6]
- Conference proceedings were searched via the Northern Light Life Sciences Conference Abstracts database. The search strategies, date of searches, and results were not reported in the CS.[1, 4] No further details were provided in response to the ERG request for clarification.[6]
- A comprehensive list of HTA organisation websites was searched. The search strategies or search terms used, date of searches, and results, were not reported in the CS.[1, 4] In response to

the ERG request for clarification, the search terms used were provided. Full details of the search strategies were not provided, because *"across these resources, inconsistent formatting and search functionality often precluded the determination of the magnitude of the available materials. Thus, in accordance with historical precedent, detailed records of grey literature searches were not recorded in a manner analogous to that of the traditional database searches of Embase, MEDLINE, and CENTRAL"*.[6]

- The database search strategies were well structured, transparent and reproducible. They included truncation, proximity operators, synonyms, and subject headings (MeSH and EMTREE). There were no date limits.
- MeSH terms were used instead of EMTREE in the Embase search strategy, though Ovid does map to the correct subject heading when the search is conducted. Several MeSH and EMTREE terms were exploded when there were no terms beneath them in the tree hierarchy.
- The population facet of search terms could have been improved with more synonyms, fewer exact phrases, better use of proximity operators, and the removal of redundant terms/phrases. The combination of search terms for 'triple negative breast cancer' with search terms for 'breast cancer' using the Boolean AND was incorrect but had barely any impact on the search results.
- Study design search filters for economic studies were included in the CE, and costs and healthcare resources search strategies. Study design search filters for utilities studies were included in the health-related quality of life searches. Neither of the search filters used were cited, as current practice recommends.[16]
- The economic studies search filter used was designed to identify CE studies, and not to capture cost and healthcare resource use studies. More relevant search terms such as 'cost', 'resource use', 'employment', 'carers', etc., should have been included in the search strategy.
- The searches were limited to English language only studies and this may have introduced language bias. Best practice states that *"to reduce the risk of introducing bias, searches should not be restricted by language"*.[13] Any limits (including language) should be reported and justified according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 and PRISMA-S guidelines.[14-16]
- It would have been preferable for the database search strategies to be presented exactly as run, rather than copied into a tabular format, as Item 8 of the PRISMA-S checklist recommends.[16] The Cochrane Handbook also recommends that *"...bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy. The search strategies should not be re-typed, because this can introduce errors"*.[17]
- The Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews (CDSR) were searched for economic studies, when one database consists of trials and the other consists of systematic reviews. It is possible that this was a reporting error, and that both databases were searched for the clinical effectiveness SLR.
- The searches were conducted in May 2021. An update of the searches immediately prior to submission to NICE would have been appropriate and could have identified potentially relevant records published since May 2021.
- In order to identify OS data for the economic model the company referred to a SLR conducted for another ongoing NICE submission.[38] Brief details of this SLR were reported in Appendix M.1.3.[4]

4.1.2 Inclusion/exclusion criteria

In- and exclusion criteria for the review on CE studies, HRQoL studies and costs and resource use studies are presented in Table 4.2.

Table 4.2: Eligibility criteria for the systematic literature reviews

	Inclusion criteria	Exclusion criteria
Patient population	• Early-stage locally advanced non-metastatic TNBC • Metastatic TNBC	
Intervention	Not restricted	
Comparator	Not restricted	
Outcomes(s) 1 (Published economic evaluations)	Costs combined with clinical endpoints (e.g. clinical outcomes, utilities, QALY, resource use, burden of illness)	
Outcomes(s) 2 (HRQoL studies)	**Treatment effects in terms of generic and disease-specific patient-reported outcomes and utilities:** • Generic PRO measures (EQ-5D, HUI-2, HUI-3, SF-6D, SF-36, EORTC QLQ-C30, PROMIS-Fatigue SF1, Q-TWIST, CTSQ, etc.) • Disease-specific HRQoL (EORTC QLQ-BR23, FACT-B—FBSI) • Utility measures **Utility values for different health states, disutility associated with AEs, and mapping algorithms:** • Preference measures (both generic and disease-specific non-preference-based measures not converted to utilities will be considered) • Utility values for health states stable disease, pre-progression, post-progression, responders, and by time prior to death • Disutility values associated with AEs **Patient-specific disease burden:** • Recommendations regarding use of PRO measures • PRO measures used in the target populations across different regions	
Outcomes(s) 3 (Cost/resource use studies)	• Direct costs • Indirect costs • Healthcare resource utilisation	
Study design 1 (Cost effectiveness analysis studies)	Primary research studies: • Full economic evaluations (e.g. CEA, cost-utility analyses, cost-benefit analyses, cost-consequence analyses) • Partial economic evaluations (e.g. cost-of-illness analyses, budget impact analyses, cost-minimization analyses) • Observational studies (e.g. prospective and retrospective cohort studies, case-control studies,	• Results are not available • Publication type not of interest (e.g. comment, editorial, letter, case report, animal study)

	Inclusion criteria	Exclusion criteria
	cross-sectional studies, controlled and uncontrolled longitudinal studies) • RCTs and non-RCTs HTAs Pooled analysis presenting the cost or resource use estimates Literature reviews summarizing results of primary research studies and/or economic evaluations	
Study design 2 (HRQoL studies)	**Treatment effects in terms of generic and disease-specific patient-reported outcomes and utilities:** • RCTS and non-RCTs • Economic evaluations reporting patient utility values (studies must provide extractable results) **Utility values for different health states, disutility associated with AEs, and mapping algorithms:** • Mapping algorithms that would allow a non-preference-based measure to be mapped onto a generic preference-based measure • Mapping algorithms between different generic preference-based health state utility values **Patient-specific disease burden:** • Observational studies reporting HRQoL/utility (e.g. controlled before-and-after studies, interrupted time series studies, historically controlled studies, prospective and retrospective cohort studies, case-control studies, cross-sectional studies, controlled and uncontrolled longitudinal studies) **All topics:** • Literature reviews summarizing results of primary research studies • Pooled analyses presenting QoL/utility data	• Results are not available • Publication type not of interest (e.g. comment, editorial, letter, case report, animal study)
Study design 3 (Cost/resource use studies)	• Full economic evaluations (e.g. CEA, cost-utility analyses, cost-benefit analyses, cost-consequence analyses) • Partial economic evaluations (e.g. cost-of-illness analyses, budget impact analyses, cost-minimization analyses) • Observational studies (e.g. prospective and retrospective cohort studies, case-control studies, cross-sectional studies, controlled and uncontrolled longitudinal studies) • RCTs and non-RCTs • Literature reviews summarizing results of primary research studies and/or economic evaluations	
Region	Global	
Publication date	No restriction	

	Inclusion criteria	Exclusion criteria
Language	Studies published in English will be included	

Based on Appendices G, H, and I of the CS[4]
CEA = cost effectiveness analysis, CS = company submission; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D = European Quality of Life-5 Dimensions; FACT-B-FBSI: Functional Assessment of Cancer Therapy Breast Symptom Index; HTA = health technology assessment; HUI = Health Utility Index; PRO = patient-reported outcomes; PROMIS-Fatigue SF1 = Patient-Reported Outcomes Measurement Information System Fatigue Short Form-1; QALY = quality adjusted life year; QLQ-BR23 = Cancer-Specific Quality of Life Questionnaire; QLQ-C30 = Quality of Life Questionnaire-Core 30; QoL = quality of life; CTSQ = Cancer Treatment Satisfaction Questionnaire; Q-TWIST = Quality-adjusted time without symptoms or toxicity; RCTs = randomised controlled trials; SF-6D = Short-Form Six-Dimension; SF-36 = 36-Item Short Form Survey; TNBC = triple-negative breast cancer

ERG comment: The ERG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify CE studies. The rationales for excluding CE studies after full paper reviewing are considered appropriate given the defined in- and exclusion criteria.

4.1.3 Conclusions of the cost effectiveness review

The CS provides an overview of the included CE, HRQoL and resource use and costs studies, but no specific conclusion was formulated.

ERG comment: The CS and response to request for clarification provided sufficient details for the ERG to appraise the literature searches conducted to identify CE, HRQoL, cost and healthcare resource use studies for the treatment of patients in neoadjuvant and adjuvant TNBC.[1, 6] The searches were conducted in May 2021. Searches were transparent and reproducible, and comprehensive strategies were used. A good range of databases and grey literature resources were searched. The search strategies included validated search filters for study design. The ERG was concerned about the language bias of restricting searches to English language only.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 4.3: NICE reference case checklist

Element of HTA	Reference case	ERG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	In line with NICE reference case
Perspective on costs	NHS and PSS	In line with NICE reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	In line with NICE reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	In line with NICE reference case
Synthesis of evidence on health effects	Based on systematic review	In line with NICE reference case

Element of HTA	Reference case	ERG comment on CS
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	In line with NICE reference case
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	In line with NICE reference case
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	In line with NICE reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	In line with NICE reference case
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	In line with NICE reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	In line with NICE reference case

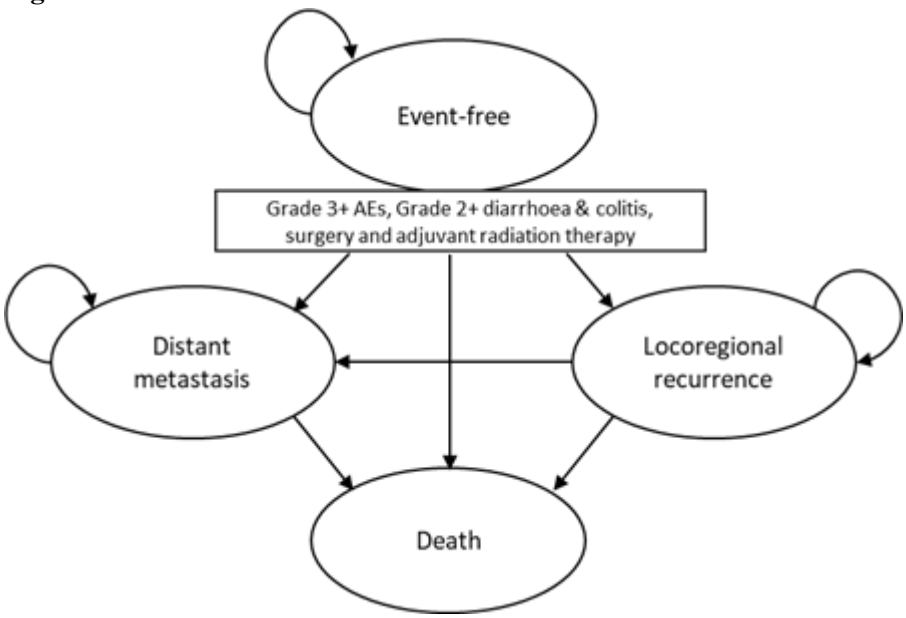
CS = company submission; EQ-5D = European Quality of Life-5 Dimensions; ERG = Evidence Review Group; HTA = health technology assessment; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life-year; UK = United Kingdom

4.2.2 Model structure

A 4-state Markov cohort model was used in the economic analysis. The model was developed in Microsoft Excel™. The model structure consists of four mutually exclusive health states; "event-free (EF)", "locoregional recurrence (LR)", "distant metastasis (DM)", and "death". All patients begin in the "EF" health state. Movement through the model is determined by transition probabilities estimated using patient-level data from KEYNOTE-522 and KEYNOTE-355 (RCT of pembrolizumab + chemotherapy (paclitaxel or nab-paclitaxel or carboplatin/gemcitabine combination) versus chemotherapy for advanced/metastatic PD-L1+ve TNBC) trials. Grade 3+ AEs and Grade 2 AEs diarrhoea and colitis were modelled on the background.

Figure 4.1 shows the model structure of the 4-state Markov cohort model.

Figure 4.1: Model structure



Based on Figure 8 of the CS
AE; adverse effect; CS = company submission

ERG comment: In the CS, it is stated that the model structure of a previous appraisal of pertuzumab for the neoadjuvant treatment in HER2-positive BC (TA424) was used to inform the model structure of the current model.[39] The stage of disease in TA424 was identical to that in the decision problem for this appraisal i.e. locally advanced, inflammatory, or early-stage with a high risk of recurrence. However, the current model is a simplified version of the model structure used in TA424, excluding remission from LR and no differentiation between not progressed and progressed metastatic patients in the DM state. In clarification question B3b, the ERG requested a scenario analysis based on the same model structure as used in TA424.[5] However, the company did not provide the scenario in the response, which was justified by the fact that the clinical data from KEYNOTE-522 do not support the modelling structure used in TA424.[6]

The ERG acknowledges that the model structure of TA424 has its limitations, and it would be complex to use the exact same model structure for the current submission with the available KEYNOTE data. However, the ERG is concerned about the fact that the model: a) does not include the option for remission of LR; and b) does not differentiate between not progressed and progressed DM.

a) In TA424, patients moved from the 'LR' state through tunnel states to the 'remission' health state. The tunnel states (12 months) were used to 'hold' patients in the LR state for a certain duration before progressing to the remission state. In the 'LR' state patients received further treatment with pertuzumab. After completing the treatment, patients were assumed to be in remission and transitioned to the 'remission' health state. Similar to the current model, patient could progress from the remission health state (i.e., after a first LR) to the metastatic not progressed or death states, i.e., a second LR event was not possible. The company justifies the exclusion of a 'remission' health state based on the fact that the 'remission' state from TA424 in fact resembles the LR state in the current submission. The company argues that there are three reasons for this deviation from TA424. First, the NeoSphere trial - which informed TA424 - explored complete response (pCR) as the primary outcome, while the KEYNOTE-522 explored pCR and EFS as primary outcomes.[39, 40] Second, in contrast to TA424, subsequent retreatment with therapy at LR was not allowed in the KEYNOTE-522 trial design. Finally, the

LR health state in TA424 did not allow for patients to move to the death state, which may have led to an overestimation of the QALYs. The current model avoids this unrealistic assumption. The ERG acknowledges the differences between TA424 and the current submission and agrees with the company that the introduction of a remission state is not ideal, as it would increase the model's complexity by introducing multiple tunnel states to the model. However, assuming patients with LR cannot experience remission does simply not reflect clinical practice. Though the company assumes no further treatment effect in the LR state (i.e., transition probabilities to DM and death are treatment independent), the current model assumes that patients remain in the LR state until progression to metastatic disease or death, and therefore patients accrue health utilities and costs related to LR for the remaining time in this state. As patients in the placebo arm have a relatively higher probability to move from the event-free state to the LR state (because of relatively lower EFS and a relatively higher proportion of events being LR (year 1: pembrolizumab [redacted], placebo [redacted] and year 2+: pembrolizumab [redacted], placebo [redacted]) compared with the pembrolizumab arm, the ERG concludes that exclusion of remission from LR may lead to overestimation of pembrolizumab's effect, underestimating the incremental cost effectiveness ratio (ICER). The ERG was not able to include a remission health state within the timeframe of this appraisal, and therefore the exact effect on the ICER is unclear.

b) Differentiating between not progressed and progressed metastatic patients is essential to correctly reflect clinical disease progression and CE, since mortality, costs, and QoL differ considerably between pre-progression and post-progression metastatic patients. In TA424, the model differentiates between a not-progressed metastasis state (first line (1L) treatment) and a progressed metastasis state (>second line (2L+) treatment) using the line of treatment as a proxy. In TA424, non-progressed patients were assumed to have the general population mortality and rate of progression to and death in the progressed metastasis state; >second line (2L+) were estimated based on a weighted average of treatments informed by CLEOPATRA (RCT of trastuzumab and docetaxel versus trastuzumab, docetaxel and Pertuzumab). The current model used one DM state (including both not-progressed and progressed patients) with OS based on patients who received 1L in the KEYNOTE-355. Within the DM health state, patients who receive 1L treatments (% based on the KEYNOTE-355 and expert opinion) were also assumed to receive 2L+ treatment for which a lump sum cost was included in the model based on a weighted average of patients receiving 2L, 3L, or 4L treatments in the cost-effectiveness model for pembrolizumab as 1L treatment in patients with metastatic TNBC (based on KEYNOTE-355 and being used in the NICE appraisal ID1546).[41] It should be noted that OS as estimated from KEYNOTE-355 is a function of death in the 1L state plus rate of progression to and death in the progressed metastasis state (>second line (2L+) and the costs for 1L and 2L+ have been included in the model. However, the company did not account separately for OS, costs, and QoL related to progressed patients (receiving 2L+) as opposed to not progressed (1L) patients. This potentially leads to under or overestimation of the ICER. The ERG was not able to include separate health states for not-progressed and progressed DM since the company was not able to provide the ERG with data on the progression status for patients with DM as this was not recorded in the KEYNOTE-522. Therefore, the exact effect of this remains unclear. The ERG believes that this creates considerable uncertainty in the model.

4.2.3 Population

The patient population included in the economic evaluation consisted of [redacted]

[redacted]. This definition is narrower than the population defined in the final scope issued by NICE, i.e., *"adults with previously untreated locally advanced, nonmetastatic triple-negative breast cancer"*.[3] The proposed marketing authorisation is pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of untreated locally advanced non-metastatic TNBC. The main body of clinical evidence for pembrolizumab was derived from KEYNOTE-522 which included patients with untreated newly diagnosed, locally advanced, centrally confirmed TNBC and have an ECOG PS of 0 or 1, see Section 2.1 for more details.[2] The key baseline patient characteristics in the economic model are listed in Table 4.4 below.

Table 4.4: Key baseline patient characteristics used in the economic model

	Mean (SD)	Source
Starting age (year)	[redacted]	KEYNOTE-522[2]
Female weight (kg), mean	[redacted]	KEYNOTE-522[2]
Female weight (kg), standard deviation	[redacted]	KEYNOTE-522[2]
Body surface area (BSA; m^2), mean	[redacted]	KEYNOTE-522[2]
Body surface area (BSA; m^2), standard deviation	[redacted]	KEYNOTE-522[2]
Based on Table 31 of the CS and the company model BSA = body surface area; CS = company submission; SD = standard deviation		

ERG comment: The population in the economic evaluation is narrower than the population defined in the NICE final scope.[3] The company stated in its response to the request for clarification that 'high-risk TNBC' within KEYNOTE-522 is synonymous with 'locally advanced TNBC'. The ERG agree that the wording is comparable with the final NICE scope.

4.2.4 Interventions and comparators

The intervention considered in the CS was pembrolizumab in combination with standard neoadjuvant chemotherapy followed by adjuvant pembrolizumab as a single regimen, administered IV at a fixed dose of 200 mg over 30 minutes Q3W in the neoadjuvant and adjuvant phases. The neoadjuvant chemotherapy component was: carboplatin (AUC 5 Q3W or AUC 1.5 weekly on days 1, 8 and 15) and paclitaxel (80 mg/m^2 weekly on days 1, 8 and 15) followed by doxorubicin (60 mg/m^2 Q3W) or epirubicin (90 mg/m^2 Q3W) and cyclophosphamide (600mg/m^2 Q3W).

The comparators considered were standard neoadjuvant chemotherapy (as described above) and placebo as adjuvant therapy. The NICE scope listed the following comparators: Standard neoadjuvant/adjuvant chemotherapy without pembrolizumab. The standard neoadjuvant therapy recommended by NICE is: platinum added to an anthracycline-containing neoadjuvant chemotherapy regimen. For adjuvant treatment after surgery, NICE recommends offering a regimen that contains both a taxane and an anthracycline. Standard chemotherapy options used for neoadjuvant and adjuvant treatment of TNBC include doxorubicin, epirubicin, docetaxel, paclitaxel and carboplatin. The company stated that the exclusion of chemotherapy as adjuvant therapy reflects the current UK practice, where no active treatments are given after surgery.

The neoadjuvant and adjuvant therapy was continued until completion of study treatment (17 cycles of pembrolizumab/placebo), disease progression in the neoadjuvant phase or until recurrence (local or distance) after surgery, unacceptable adverse event(s) or physician's decision to withdraw treatment

ERG comment: For adjuvant treatment after surgery, NG101 recommends offering a regimen that contains both a taxane and an anthracycline.[42] Moreover, the CS stated that recent evidence has shown

that capecitabine in the adjuvant phase may improve disease survival and recurrence-free survival, see Section 2.3.[1]

The company stated in its response to the request for clarification that a taxane and anthracycline regimen for the treatment of early-stage BC is generally given either before or after surgery. For chemotherapy, neoadjuvant versus adjuvant administration of a taxane and anthracycline regimen is considered equivalent in terms of distant recurrence, BC mortality or death from any cause for BC patients. Moreover, the company stated that in common clinical practice, a patient would not be treated with the same neoadjuvant and adjuvant chemotherapy regimen. Regarding the treatment with capecitabine as an adjuvant therapy, the company stated in its clarification response that the National Comprehensive Cancer Network (NCCN) guidelines were updated in 2017 to include adjuvant capecitabine as an option for patients with TNBC who do not achieve pCR after neoadjuvant chemotherapy.[43] Optional use of adjuvant capecitabine in patients who do not achieve pCR after neoadjuvant therapy may confound the EFS endpoint, due to the potential for imbalanced capecitabine use between the two treatment arms.

The ERG partly agrees with the company approach of excluding the taxane and anthracycline regimen from the adjuvant phase. Although the statement of the company that a taxane and anthracycline regimen for the treatment of early-stage breast cancer is generally given either before or after surgery, is not supported by any reference, this may still be common clinical practice. However, the use of a taxane and anthracycline regimen as adjuvant treatment could majorly change the EFS and therefore the ICER. The ERG does not agree with excluding capecitabine as adjuvant treatment because of the imbalance between the two arms. Excluding capecitabine as adjuvant therapy for patients who do not achieve pCR after adjuvant chemotherapy does not reflect the general practice and the used guidelines in the UK. The company stated that including capecitabine may increase EFS rate for patients with poor prognosis to 74%. This would majorly change the ICER.

The ERG considers additional scenarios where taxane and anthracycline are used as adjuvant therapy instead of neoadjuvant therapy would have been informative to see the impact on CE, as well as a scenario where capecitabine is used as an adjuvant therapy.

4.2.5 Perspective, time horizon and discounting

The analysis is performed from the NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is 1 week with a time horizon of 51 years and a half-cycle correction is applied.

ERG comment: Perspective, time horizon and discounting are appropriate.

4.2.6 Treatment effectiveness and extrapolation

The primary source of treatment effectiveness for the intervention and comparator is KEYNOTE-522, a phase III RCT to evaluate pembrolizumab in combination with chemotherapy versus chemotherapy alone in the neoadjuvant phase followed by pembrolizumab monotherapy versus placebo in the adjuvant phase.[2] Patient level data of the KEYNOTE-522 trial was used to determine transition probabilities from the event-free and locoregional states. Due to immaturity of the KEYNOTE-522 OS data, transition probabilities from DM to death were based on the KEYNOTE-355 trial for those receiving 1L treatment for metastatic TNBC.[28] For patients who did not receive 1L metastatic TNBC treatment, OS data from the recent Surveillance, Epidemiology, and End Results (SEER) Medicaid database publication ('no treatment' subgroup) was used.[44] Time-on-treatment and relative dose intensity for the intervention and comparator were based on patient-level data from KEYNOTE-522.

4.2.6.1 Transition probabilities from event-free health state

The transition probabilities from the event-free health state were estimated based on the extrapolated EFS data, along with the probabilities of experiencing LR, DM, or death as the first EFS event in each treatment arm derived from the KEYNOTE-522 clinical trial (data cut-off date: 23 March 2021). Extrapolation of the EFS data beyond the trial duration to lifetime horizon was done using survival curve fitting, carried out in line with the NICE Decision Support Unit (DSU) guidelines.[45]

Statistical testing showed that the proportional hazard assumption for EFS did not hold. Therefore, standard parametric models were fitted to the patient level EFS data from the pembrolizumab arm and placebo arm in the KEYNOTE-522 trial separately. All standard parametric models (i.e., exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma) were fitted to the patient level EFS data from the pembrolizumab arm and placebo arm in the KEYNOTE-522 trial to extrapolate the endpoints from the trial over a lifetime time horizon. Since the standard parametric distributions did not provide a good fit to the observed EFS data, two-phase parametric functions fit to the data were conducted. Hazard plots were used to identify potential cut-off points for two-phase models. Visual examination of the cumulative hazard plot suggested week 50 as a potential turning point of the EFS curves in both treatment arms. Hazard plots also suggested week 43 and 68 as turning points for the hazard function. Chow statistical tests showed two additional turning points, 93 and 109 weeks. From these five cut-off points, week 50 was used in the base case as it provides plausible visual fit and has a good balance of robust Kaplan-Meier (KM) data used to directly calculate transition probabilities in the first phase whilst enough data remaining can be used to fit a parametric curve in the second phase (week 50 to life-time horizon). Other cut-off points were included in the economic model.

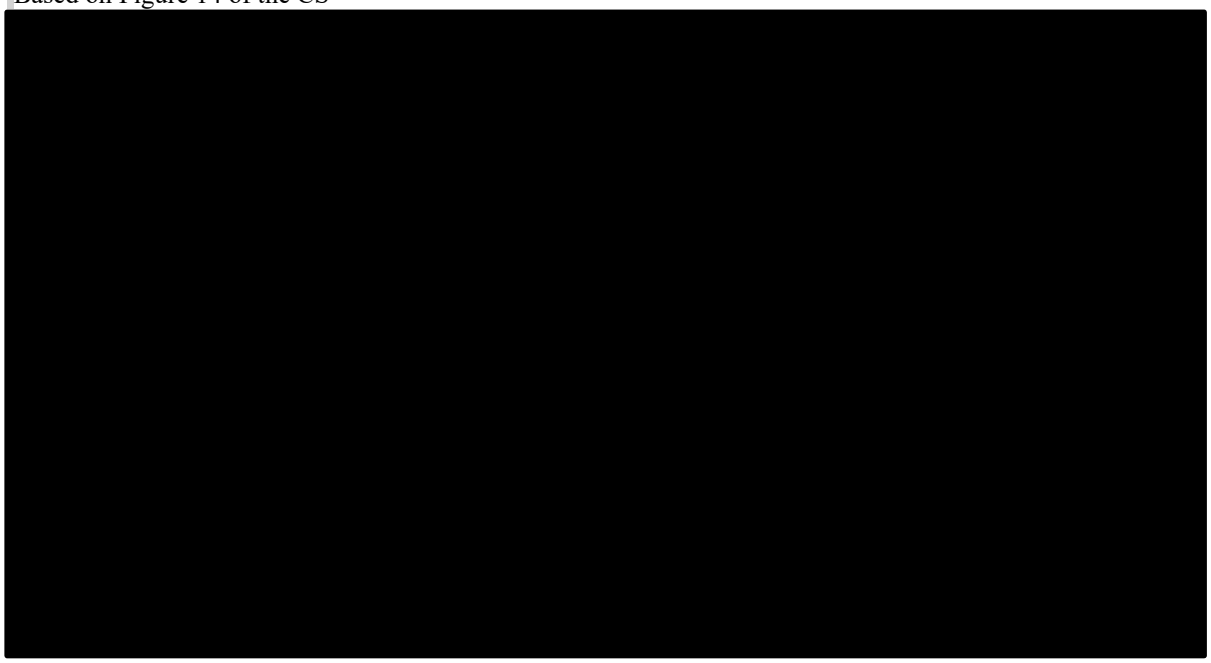
All parametric models were assessed against the Akaike information criterion (AIC) and Bayesian information criterion (BIC) criterion. AIC/BIC statistics, in combination with visual inspection and clinical plausibility based on expert opinion, were used to identify the best-fitted parametric distribution from week 50 onward. As the proportional hazards assumption did not hold, individual distributions were fitted for pembrolizumab and placebo EFS. In addition, the company chose these distributions to be of a different type between the two arms. The company argued that, given the unique mode of action of immunotherapy, pembrolizumab and placebo could have different parametric extrapolations because the underlying hazard for the parametric curves does not need to be the same.

Both AIC/BIC and visual inspection suggested generalised gamma was the best fit for the pembrolizumab arm. A log-normal distribution was suggested as the second-best option and was explored in scenario analysis. For the placebo arm, AIC/BIC statistics were lowest for the Gompertz distribution with log-normal distribution ranked second. However, the Gompertz distribution is associated with a flat tail potentially leading to overestimation of long-term EFS, which suggests an implausible extrapolation. Clinical experts and visual inspection of the curves confirmed the use of log-normal distribution in the base case analysis. Generalised gamma distribution was also suggested as plausible option and was explored in a scenario analysis.

Figure 4.2 shows the modelled and observed EFS extrapolation for the pembrolizumab (generalised gamma distribution) and placebo (log-normal distribution) arm from KEYNOTE-522.

Figure 4.2: Modelled versus observed EFS for pembrolizumab and placebo arm from KEYNOTE-522

Based on Figure 14 of the CS[1]



CS = company submission; EFS = event-free survival; KM = Kaplan-Meier.

The estimation of the transition probabilities from the event-free health state to LR, DM, or death were estimated using Gray's method considering competing risks. Competing risk analysis of the time to first EFS event was used to determine the distribution between the EFS event being LR, DM, or death. Within each cycle, the cause-specific probability of each transition (i.e., EF to LR, EF to DM, and EF to death) was calculated based on the estimated probability of an EFS event, and the probability that the EFS event being LR, DM or death (Table 4.5). The probability of EF to death was constrained by the general population mortality, adjusted for the transition probabilities from EF to LR and EF to DM.

Table 4.5: Probability of the first EFS event being LR, DM, or Death.

Treatment arm	Year 1			Year 2+		
	% LR	% DM	% Death	% LR	% DM	% Death
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 36 of CS[1]
CS = company submission; DM = distant metastasis; LR = locoregional recurrence; % = percentage

The predicted cumulative incidence of EF to LR, EF to DM, and EF to death were validated with the observed cumulative incidence from the KEYNOTE-522 trial. Based on Figures 15 and 16 as well as Tables 37 and 38 of the CS, the company concludes that the modelled cumulative incidence rates are comparable to the observed data.[1]

4.2.6.2 Transition probabilities from locoregional recurrence health state

The transition probabilities of LR to DM and LR to death were estimated based on the pooled data from the two treatment arms from the KEYNOTE-522 trial. Parametric models were fitted to the time from LR to DM or death, and the exponential distribution was found to be the best fit. When asked for statistics of the fit in the clarification phase, the company responded that the selection of the exponential

parametric distribution selected to model LR to DM or death was not based in isolation to the AIC/BIC statistics, but also on visual fit to the observed KM curve alongside balanced assessment of clinical plausibility of long-term predictions generated by each of the alternative parametric models.[6] The company stated that the few number of events which have taken place from which extrapolations are based could make the AIC/BIC statistics unreliable and therefore rankings based on AIC/BIC may change as more data become available. Whilst the exponential model yields the highest AIC/BIC statistics the difference versus the lowest average AIC/BIC produced by the log-normal model was small (6 to 7 points). The company decided to choose the exponential distribution because they considered it to better fit the tail of the KM-curve, despite the fact that it would overestimate OS for the observed period. See also Figure 4.3.

Figure 4.3: Long term parametric extrapolations using the combined KEYNOTE-522 arms time from LR to DM or Death

Based on Figure 4 of the response to the request for clarification[6]
DM = distant metastasis; LR = locoregional recurrence; OS = overall survival

The company assumed constant transition probabilities from the LR state. The transition probabilities to DM and death were calculated based on the transition probabilities of LR to DM *or* death, and the proportions of DM and death respectively, which were all obtained from the KEYNOTE-522 trial. The probability of LR to death was constrained by the general population mortality, adjusted for the transition probability from LR to DM.

4.2.6.3 Transition probabilities from the distant metastasis health state

In the DM state it was assumed that a proportion of patients would receive 1L treatment for metastatic disease. This proportion was obtained from the KEYNOTE-522 trial and was [redacted] for the pembrolizumab arm and [redacted] for the placebo arm.[2] Because of the current immaturity of the KEYNOTE-522 OS data, data from KEYNOTE-355 were used to estimate transition probabilities from DM to death.[28] KEYNOTE-522 data were used in a scenario.

The base case analysis assumed that patients could not be rechallenged with pembrolizumab but could receive other IOs in the DM setting 2 years post initiation of neoadjuvant treatment. This assumption is explored in two scenarios; one where pembrolizumab rechallenge, or treatment with another IO, is possible for the PD-L1 positive population 2 years post initiation of neoadjuvant treatment, and another where patients cannot receive any IOs and would receive a mix of non-IO chemotherapies. Patients in the first two scenarios who relapse within 2 years of neoadjuvant treatment initiation will be managed as in this last 'IO ineligible' scenario. Based on KEYNOTE-355, the proportion of PD-L1 positive patients was estimated at [redacted].

The base case treatment mix of each of the above scenarios was obtained from UK market research and clinical expert input, see Table 4.6 for details on treatment mix per scenario.

Table 4.6: Treatment mix of 1L metastatic TNBC used in the model

Type of 1L treatment	Pembrolizumab + chemotherapy			Chemotherapy
	Pembrolizumab rechallenge for PD-L1 positive	IO-eligible (pembrolizumab ineligible)	IO-ineligible	IO-eligible (pembro ineligible)[#]
Pembrolizumab + taxanes (paclitaxel or nab-paclictaxel)	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin (or containing regimens)	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin + paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine + carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Atezolizumab + Nab-paclitaxel[*]	[redacted]	[redacted]	[redacted]	[redacted]
Capcitabine	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 42 of the CS and company model[1]

[*] assumes PD-L1 SP132 positive as per Impassion130 study; [#] See point f) in the ERG comment below

CS = company submission; 1L = first line; IO = immune oncology; N/A = not applicable; TNBC = triple-negtaive breast cancer

Mean OS in the DM state was estimated as a weighted average of OS for patients who received 1L treatments and OS for patients who did not receive 1L treatments. The transition probability from DM to death was then calculated by fitting an exponential curve to this mean OS and taking the coefficient of this fitted curve as the constant death rate, over the entire time horizon of the model.

The mean OS for patients who did receive 1L treatments was based on the pembrolizumab metastatic TNBC model, with HRs from an NMA (Appendix M of the CS) applied for carboplatin and atezolizumab + nab-paclitaxel.[4, 41] As can be seen in Table 4.7, the company stated that the NMA HRs were versus taxanes. However, the full NMA report provided with the clarification letter response

shows that the comparison was with nab-paclitaxel only. This was because networks were constructed according to subgroups that would be suitable for each of the investigator choice compactors in KEYNOTE 355, i.e., paclitaxel, nab-paclitaxel, and gemcitabine/carboplatin. Therefore, from these sources, it is unclear how this HR versus any taxane was estimated and how valid the estimate is when applied to survival with any taxane. The factual accuracy check (FAC) stated that: *"the studies informing the carboplatin comparison and link carboplatin into the rest of the network, only contain nab-paclitaxel. However, data from the pooled KEYNOTE-355 taxane data were used considering that the AC have previously concluded on taxane efficacy equivalence during prior HTAs"*. The company provided no clarification regarding the comparison with atezolizumab + nab-paclitaxel, but presumably this was also via the pooled KEYNOTE-355 taxane data as opposed to those for nab-paclitaxel only. The ERG considers that, despite the claim that there is equivalence between taxanes, the fact that the KEYNOTE 355 trial was stratified by investigator choice including taxane type (paclitaxel or nab-paclitaxel), which enabled the NMA to also be structured by subgroup according to investigator choice, means that the most appropriate KEYNOTE 355 data source for comparison with carboplatin or atezolizumab-paclitaxel is that for nab-paclitaxel only.

Time on treatment for each of the 1L treatments was derived in a similar way as OS according to the CS. That is, it was based on the pembrolizumab metastatic TNBC model. No further details on this are available.

The study by Aly et al. 2019 used to obtain OS for patients not treated with 1L treatments contained a sample of elderly mBC patients who were on average 79 years of age when they entered the study.[44] The company stated in its response to clarification that this high age should not bias estimates of DM survival since the metastases would likely be the leading cause of death even in high age.

Table 4.7 represents the OS estimates for the different 1L treatment options and Table 4.8 shows the resulting transition probability as used in the model for the base case and in the scenario using KEYNOTE-522 OS data.

Table 4.7: Mean OS by 1L metastatic TNBC treatment

Type of 1L treatment	Mean OS (weeks)	Source/method
Pembrolizumab + taxanes (paclitaxel or nab-paclictaxel)	[redacted]	Taken directly from KEYNOTE-355 1L mTNBC model
Paclitaxel	[redacted]	Taken directly from KEYNOTE-355 1L mTNBC model for taxanes (paclitaxel plus nab-paclitaxel) pooled arm in line with previous NICE assumptions
Carboplatin (or containing regimens)	[redacted]	HR estimated from NMA. Applied OS HR of carboplatin versus taxanes (paclitaxel/nab-paclitaxel) in mTNBC model
Carboplatin + paclitaxel	[redacted]	Assumed equal to gemcitabine + carboplatin arm of KEYNOTE-355 1L mTNBC model
Gemcitabine + carboplatin	[redacted]	Taken directly from KEYNOTE-355 1L mTNBC model
Atezolizumab + Nab-paclitaxel *	[redacted]	HR estimated from NMA. Applied OS HR of atezolizumab + nab-paclitaxel versus taxanes (paclitaxel/nab-paclitaxel) from KEYNOTE-355 1L mTNBC model

Type of 1L treatment	Mean OS (weeks)	Source/method
Capcitabine	[redacted]	Assumed equal to taxanes arm of KEYNOTE-355 1L mTNBC model
No 1L treatment	[redacted]	SEER Medicare, 'no treatment' group[44]

Based on Table 43 of the CS and company model[1]
1L = first line; CS = company submission; HR = hazard ratio; mTNBC = metastatic triple-negative breast cancer; NICE = National Institute for Health and Care Excellence; NMA= network meta-analysis; OS = overall survival

Table 4.8: Transition probabilities used in base case and scenarios

Treatment arm	Eligibility for IOs	Weighted mean OS (weeks)	Transition probability (weekly) from DM to death
Based on KEYNOTE-355 data and NMA			
Pembrolizumab	IO-eligible*	[redacted]	[redacted]
Pembrolizumab	Pembrolizumab rechallenge-eligible	[redacted]	[redacted]
Pembrolizumab	IO ineligible	[redacted]	[redacted]
Placebo	IO-eligible	[redacted]	[redacted]
Based on KEYNOTE-522 data			
Pembrolizumab	N/A^	[redacted]	[redacted]
Placebo	N/A^	[redacted]	[redacted]

Based on Table 44 and 45 of the CS[1]
* IO-eligible assumed in base case for the pembrolizumab arm
^ in the scenario using KEYNOTE-522 data, OS was not based on treatment mix but taken as observed and therefore the scenarios for IO eligibility do not apply
CS = company submission; DM = distant metastasis; N/A = not applicable; NMA = network meta-analysis; OS= overall survival

ERG comment: The main concerns of the ERG relate to: a) the use of differential distributions to extrapolate EFS; b) the difference between EFS gain obtained in the observed period versus EFS gain the extrapolated period; c) the use of constant transitions from LR and DM states; d) the use of the 50-week cut-off point for the EFS curve fitting; e) the use of KEYNOTE-355 as base case for the DM survival; f) no option to receive pembrolizumab as 1L treatment for patients in the placebo arm; and g) adjustment of general mortality in the formula for EF and LR to death by subtracting transitions to other states.

a) The ERG is satisfied that the company has followed the general approach to survival analysis and extrapolation of individual participant data recommended by NICE DSU TSD 14. However, the company used different distributions for the curve fitting for extrapolation of the EFS data. The TSD recommends that where parametric models are fitted separately to individual treatment arms it is sensible to use the same 'type' of model.[45] The use of different types of distributions should be justified using clinical expert judgement, biological plausibility, and robust statistical analysis.

   Therefore, in clarification question B8, the ERG asked for a clear explanation why different distributions in this case would be justifiable.[5] The company justified the use of different distributions based on the argument that the unique mode of action of immunotherapy (with or without chemotherapy) is not comparable to chemotherapy alone; therefore, the underlying hazard

assumption for the parametric curve does not need to be the same.[6] The company argues this has been observed across a number of metastatic and adjuvant submissions with IO agents to date—although they do not mention which—and that clinicians have noted that IO therapies used in neoadjuvant/adjuvant setting may have an effect of improving 'Immune surveillance'. Furthermore, the company explains clinical plausibility of different parametric models was discussed during an advisory board meeting. In response to clarification question B8, the company mentions that clinical experts *"based on the unique mode of action of IO therapies as well as the characteristics of patients with early TNBC disease, clinical experts noted that they would expect EFS to start to plateau across both treatment arms since most recurrences occur within the first 3 to 5 years and that pembrolizumab + chemotherapy EFS would sit above that of placebo"*.[6] The ERG does not consider this the same as the clinical experts confirming that different distributions are clinically plausible. Based on AIC and BIC values, generalised gamma was the best option in the pembrolizumab arm and Gompertz in the placebo arm. However, in both arms lognormal was the second-best option, which does not suggest strong evidence for different distributions. The company mentions in its response to clarification question B8 that the statistical fit was validated using real-world data, however there is only real-world data available for the placebo arm (and not for the pembrolizumab arm) and therefore this validation says nothing about the justification for the use of different distributions.

b) Related to the above issue, the company model and the extrapolations implemented result in a substantial gain in EFS which is mostly obtained in the unobserved part of the time horizon. It is important to take the realism of the extrapolated marginal gain into consideration when selecting the best model as an unrealistic marginal gain would create bias in the economic analysis. To evaluate the realism of the post-extrapolation survival gain, the 'rule-of-thumb' from Tremblay et al., 2015 can be used, stating that the ratio of the marginal relative difference in the extrapolated period (post cut-off) divided by the number of months post-cut-off should not be higher than the ratio of marginal difference on the number of months in the pre-extrapolation period.[46] In other words, the average "rate of survival gain" per month between treatments should be equal or inferior in the post-extrapolation period compared to the pre-extrapolation period. In the current model using different distributions for the extrapolation of EFS, the pre-extrapolation (up to week 205, based on KM data of KEYNOTE-522) rate of survival gain is 0.2367, while the post-extrapolation (from week 206) rate is 0.3340, suggesting lack of realism of the extrapolated marginal gain according to the rule-of-thumb. This is also seen in the model: chancing the time horizon from 51 years to a short-term horizon (e.g. 5 years, which reflects the period for which KM data of the KEYNOTE-522 is available) causes a considerable increase in the ICER. The ERG believes this is a major uncertainty in the model.

   Taken this and the issues discussed under point a) into account, the ERG is not convinced that there is a strong enough justification for using different distributions for the extrapolation of EFS based on the information provided in the CS. Therefore, the ERG uses lognormal distributions (second-best option) in both arms in its base case analysis, and additionally conducted several scenarios to explore the effect of different distributions.

c) The company assumed transition probabilities to move to the DM state (from LR) and to the death state (from LR and DM) to be constant over the entire time horizon of the model. According to page 84 of the CS, this was necessary because of the memoryless feature of the Markov model. The company stated it would be reasonable to assume a constant transition probability since an exponential distribution provided the best fit to the LR survival.[1] For DM, the transition to death was based on the constant hazard assumption without further explanation. No justification based on

clinical plausibility was provided though, also not in response to question B10b of the response to request for clarification.[6] Moreover, from the response to request for clarification to this question, it also became apparent that the exponential distribution did not actually provide the best fit for the LR survival – as almost all other parametric distributions resulted in lower AIC and BIC (although differences were small).[6] The ERG is concerned that oversimplifying assumptions for these transitions, which are mostly relevant to the placebo arm as relatively more patients in the placebo end up in LR and DM, will distort incremental CE while uncertainty around this issue is not captured in the sensitivity analyses.

d) The ERG agrees that the KEYNOTE-522 is the best available source for the extrapolation of EFS data. In accordance with the NICE DSU TSD 21, the company has explored the hazard plots for turning points, which suggested a turning point in week 43 for the pembrolizumab + chemotherapy arm and week 68 for the chemotherapy arm.[47] Visual inspection of the cumulative hazard plots suggested a divergence of curves with a potential turning point at approximately 50 weeks (Figure 10 of the CS).[1] Additionally, the Chow test suggested week 93 and 109 as potential turning points. For the base case analysis, the company used the week 50 cut-off point, justified by the fact that it provides plausible visual fit and a good balance of robust KM data to be used directly in the first phase and enough remaining data to be used to fit a parametric curve in the second phase. However, this does not explain why the week-50 cut-off is preferred over the other cut-off points with sufficient data left to inform survival extrapolations (i.e., week 43 and week 68). Although in response to clarification question B6 the company mentions that the other cut-off points are included in the model, they were not included as scenarios in the CS.[6]

e) The ERG considers the use of KEYNOTE-355 data as base case for the DM survival to be a potential source of bias. Although the company argues that KEYNOTE-355 is to be preferred over KEYNOTE-522 data because KEYNOTE-522 data are not sufficiently mature in the DM state, there are quite substantial differences in observed survival between these two studies (see Table 4.8), which raises doubts about comparability of the populations and therefore on appropriateness of using KEYNOTE-355 OS data for this appraisal. The ERG therefore prefers to use the company's scenario using KEYNOTE-522 data as a base case.

f) In the base case company model, patients in the chemotherapy arm are assumed to not receive pembrolizumab when they metastasize, and so all patients that are IO-eligible receive atezolizumab (see also Table 4.7 above where the treatment mix in 1L metastatic mTNBC is specified – for placebo, the pembrolizumab is set to N/A). The ERG believes this to be an error in the model and corrected for this in its base case.

g) The probabilities of EF and LR to death were constrained by the general population mortality. However, the general mortality in the formula for the transition probability from EF to death was adjusted for the transitions from EF to LR and DM. Similar, the general mortality in the formula for the transition probability from LR to death was adjusted for the transition from LR to DM. The ERG believes the adjustment of the general mortality by subtracting transition probabilities from the EF and LR state to states other than death to be an error in the model and corrected for this in its base case.

4.2.7 Adverse events

The main source of evidence on incidence of treatment-related AEs used for intervention and comparator is the KEYNOTE-522 trial. The model considers all-cause Grade 3+ AEs with an incidence

of ≥5%. Additionally, two Grade 2+ AEs, diarrhoea and colitis, were included in the economic model as these were deemed as clinically relevant.

ERG comment: The main concern of the ERG relates to the inclusion of Grade 2+ AEs colitis and diarrhoea because these were deemed clinically relevant. In response to clarification question B16a, in which the ERG asked for clarification why these Grade 2 AEs were deemed clinically relevant, the company explained that these specific AEs were included in addition to Grade 3+ AEs as they expect these AEs to be associated with a high management cost (i.e. hospitalisation) and HRQoL burden, and to ensure consistency with previous NICE appraisals for IO therapies.[6] The ERG agrees that the inclusion of Grade 2 diarrhoea was indeed in line with other appraisals (e.g. ID1546, pembrolizumab + chemotherapy for untreated, locally recurrent unresectable or metastatic TNBC).[38] However, it remains unclear how the clinical relevance of these AEs was defined.

4.2.8 Health-related quality of life

Health state utility values were estimated for the following health states: EF, LR, and DM and were treatment independent.

4.2.8.1 Health-related quality of life data identified in the review

According to the CS, the SLR identified only one study (Huang et al. 2020) reported EQ-5D-5L utility values for metastatic TNBC.[1, 48] However, no studies reported EQ-5D derived utilities for eBC. Therefore, utility values from the KEYNOTE-522 trial were used to inform the economic model.

4.2.8.2 Health state utility values

In the absence of studies from the SLR (see Section 4.2.8.1), the primary source for the HSUVs was the KEYNOTE-522 trial. HRQoL was collected in KEYNOTE-522 using the EQ-5D-5L questionnaire. In the neoadjuvant phase, the questionnaire was administered on day 1 of cycle 1 of treatment 1 (carboplatin + paclitaxel with or without pembrolizumab) and on day 1 of cycles 1 and 4 of treatment 2 (doxorubicin/epirubicin + cyclophosphamide with or without pembrolizumab). In the adjuvant phase, the questionnaire was administered on day 1 of cycles 1, 5 and 9. Assessments were also conducted at the early discontinuation visits and for long-term follow-up visits every 12 months for 2 years or until progressed disease (PD). The analysis of the EQ-5D-5L data was based on FAS population (pembrolizumab + chemotherapy n=762 and chemotherapy alone n=384) and compliance remained high throughout the trial ([redacted]).

EQ-5D-5L scores were retrieved for: 1) by health state and by treatment status; 2) by treatment status within EF state and by treatment arm, and 3) by AE status within EF on treatment period and by treatment arm. No statistically significant difference in utilities between the two arms was found. Therefore, health state utilities used in the economic model were estimated based on the pooled treatment arm set by health state and for the EF state by treatment status (on or off treatment). For the EFS on treatment health state the utility was only of patients without Grade3+ AE, to avoid double counting as Grade 3+ AE-related disutilities were included in the model separately.

As per the NICE reference case, the EQ-5D-5L data were mapped back to the 3L tool using crosswalk method by van Hout et al., 2012.[49] The 3L value set was used in the base case analysis. The 5L value set was explored in scenario analysis.

A summary of all utility values used in the CEA is provided in Table 4.9.

Table 4.9: Health state utility EQ-5D-3L values used in the model

Health state	Utility value (95% CI)	Reference
Event-free, on treatment	[redacted]	KEYNOTE-522[2] and UK crosswalk tariffs[49]
Event-free, off treatment	[redacted]	
Local recurrence	[redacted]	
Distant metastasis	[redacted]	
Based on base case analysis from Table 52 of the CS[1] CI = confidence interval; CS = company submission		

4.2.8.3 Disutility values

All Grade 3+ events with an incidence of ≥5% were included in the economic model. Additionally, Grade 2 events diarrhoea and colitis were included. Disutilities associated with the AEs were implemented in the model by calculating a QALY loss which was the product of the disutility and the duration of the AE and applied in the first cycle of the model. Grade 3+ AE-related disutilities were obtained from KEYNOTE-522 patient-level data. The disutility associated with AEs from the pooled utility analysis was estimated at [redacted] (standard error (SE): [redacted]). The Grade 3+ AE disutility was also applied to the Grade 2+ AEs included in the model.

An age-related disutility was applied using calculations from Ara and Brazier et al., 2010.[50]

ERG comment: The main concerns of the ERG relate to: a) the use of pooled health state utilities; and b) the relatively low utility value for DM health state.

a) The company used the pooled health state utilities in the base case analysis, as there was no statistically significant or clinically meaningful difference between the treatment arms. However, the HSUVs were slightly but consistently lower in the pembrolizumab + chemotherapy arm compared to the chemotherapy arm (Table 7 in Appendix N of the CS).[4] In response to clarification question B18a, the company explains this may be in part due to the more complex treatment regimen since pembrolizumab is an add on therapy to the neoadjuvant current standard of care (SoC).[6] As such patients randomised in this arm experience more AEs which subsequently may reduce utility scores. However, the company argues that treatment related HRQoL decrement associated with pembrolizumab is applied through AE disutility (modelled as a one-off QALY decrement). The effect of using treatment-related health state utilities was explored in a scenario analysis but showed to have a minimal effect on the ICER. Therefore, the ERG does not consider this is a major issue.
b) The utility for the health state DM is relatively low ([redacted]) compared to other studies. As mentioned in Appendix H of the CS, one other study (Huang et al. 2020) assessing EQ-5D in metastatic TNBC patients is available, which examined the EQ-5D-3L data collected from patients enrolled in KEYNOTE-119 (previously treated metastatic TNBC patients).[48] The mean utility for progression-free and progressed patients was 0.715 and 0.606, respectively. The difference (0.104) between the two was considered clinically meaningful. The utility value used for the 'DM' health state in the model is very comparable to that of the progressed metastatic TNBC patients in the KEYNOTE-119 trial, however, the 'DM' state in the current model includes both progressed and not-progressed patients. The company justifies the use of the relatively low utility value from the KEYNOTE-522 by the fact that as the NICE reference case stipulates a preference for HRQoL data collected alongside the pivotal trial to be used for the decision problem when these are available.[51] However, the company also reported that the number of EQ-5D questionnaires from patients what have experienced DM is very limited ([redacted] across both treatments). Moreover, it is unclear whether the relatively low utility value may be related to a relatively high proportion of patients with PD within

the DM state, because the KEYNOTE-522 does not record the progression status for patients with DM and the company argues that utility data stratified by subsequent treatment line as a proxy for progression status was not possible as these data remain immature and considering the already limited EQ-5D data available, these analyses would not be meaningful if conducted. However, the company did acknowledge that the small number of questionnaires available at DM setting may explain why utility values are relatively lower than reported elsewhere in literature. Therefore, in response to clarification question B19c, the company conducted two scenarios to explore the effect of using alternative data sources to test the impact of the DM utility estimate on the ICER using utility values from: 1) KEYNOTE-355 ([redacted] weighted average based on total predicted LYs gained during pre-progression and post-progression of chemotherapy arm); and 2) KEYNOTE-119 (0.715, pre-progression utility value). In both scenarios the ICER increased, however, the difference was marginal.

4.2.9 Resources and costs

The cost categories included in the model were treatment acquisition costs for intervention, comparator and subsequent treatments, medical costs (treatment administration, disease management, costs of LR and DM states, costs of surgery, and costs of terminal care and end of life), and costs of managing AEs.

Unit prices were based on the NHS reference prices, British National Formulary (BNF), Personal Social Services Research Unit (PSSRU) and the Monthly Index of Medical Specialities (MIMS). Costs were inflated to the current price year using the Hospital and Community Health Services (HCHS) index published by PSSRU where necessary.[52]

4.2.8.1 Resource use and costs data identified in the review

According to the CS, the SLR did not identify any studies reporting UK relevant resource use and cost information for the population of interest.

4.2.8.2 Treatment costs

As per the anticipated license, the model uses a 200 mg fixed dose of pembrolizumab administered as a 30-minute IV infusion Q3W, in combination with chemotherapy (carboplatin + paclitaxel, followed by doxorubicin/epirubicin + cyclophosphamide) in the neoadjuvant phase for 8 cycles, and pembrolizumab monotherapy in the adjuvant phase for 9 cycles.

The intervention and comparator drug acquisition costs used in the model were reported in Table 53 of the CS.[1] The list price for pembrolizumab used is £2,630 per 100 mg/4 ml vial. A confidential PAS is in place.

No vial sharing was included in the base case model, but this assumption was varied in a scenario where vial sharing was allowed.

Relative dose intensity as reflected in the pembrolizumab arm of KEYNOTE-522 was applied to the drug acquisition costs. The detailed dosing schedule, relative dose intensity, and treatment allocation, can be found in Table 54 of the CS.[1]

KEYNOTE-522 patient level data were used to estimate time to end of neoadjuvant treatment, time to end of surgery, and time to end of treatment course. The proportion of patients on neoadjuvant treatment was derived directly from the time to end of neoadjuvant treatment KM curve. The proportion of patients on adjuvant treatment was derived by subtracting the survival function for time to end of surgery from the KM curve for end of treatment course. All three curves are displayed in Figure 4.4

below which was provided by the company in its response to request for clarification.[6] The company also explained in its response to clarification that there is a 2 to 6 week wait time between end of neoadjuvant treatment and surgery, and that resource use associated with the EF state was applied to patients waiting for surgery. In its response to the request for clarification, the company stated that there was a waiting time of about 2 to 6 weeks after the last cycle of the neoadjuvant phase.[6]

Figure 4.4: Time to end of neoadjuvant treatment/surgery/treatment course

Based on Figure 5 of the response to request for clarification[6]

Costs of drug acquisition and administration for subsequent treatments were applied as one-time costs upon entry into the DM state. A proportion of patients entering the DM state were assumed to receive an active 1L treatment. KEYNOTE-355 was used to estimate these 1L treatment costs in the base case, while KEYNOTE-522 was used in a scenario. Patients who received 1L treatments were also assumed to receive subsequent lines (2L, 3L, and 4L). The weighted average costs for each treatment arm was calculated by multiplying the proportion of patients who received 1L treatments (Table 40 of the CS) by the weighted average costs of patients who receive 1L treatments derived from KEYNOTE-355.[1]

Administration costs for intervention/comparators and subsequent treatments were included in the model, depending on complexity and treatment type. Detailed administration costs were presented in Tables 59 and 60 of the CS.[1]

4.2.8.3 Health state costs

Health state costs consisted of disease management costs and included oncologist visits, visits to the general practitioner (GP), clinical nurse specialist and community nurse contacts, imaging (mammogram, computed tomography (CT) and magnetic resonance imaging (MRI) scans), and laboratory monitoring. The frequency for these types of resource use was based on TA424 for the EF health state,[39] TA569 for LR,[53] and ID1546 and TA639 for the DM health state.[38, 54] In addition to these costs which were applied weekly in the model, there were also additional disease management costs for the EF state whilst on treatment (based on assumption from clinical expert opinion), and a one-off cost for the LR and DM states. A one-off cost was also applied at the point of death. Table 4.10 reflects these various health state costs applied.

Table 4.10: Health state costs

Health state	Costs	Reference	Justification
Weekly health state costs			
Event free whilst on treatment (year 0-1) pembrolizumab arm	£81.99	Assumption from clinical expert opinion	Annually 17 oncologist visits, 17 nurse specialist visits, and 25 FBC
Event free whilst on treatment (year 0-1) placebo arm	£38.06	As above adjusted for chemo arm	Annually 8 oncologist visits, 8 nurse specialist visits, and 16 FBC
Event free (year 1-3)	£7.55	TA424 Table 90[39]	Annually 2 oncologist visits, 2 GP visits, 1 mammogram
Event free (year 4-5)	£3.89	TA424 Table 90[39]	Annually 1 oncologist visit, 1 GP visit, 1 mammogram
Event free (year 6-10)	£0.75	TA424 Table 90[39]	Annually 1 GP visit
Locoregional recurrence	£14.50	TA569 Table 42[53]	Annually 2 oncologist visits, 1 mammogram, 2 CT scans, 1 MRI
Distant metastasis	£69.00	ID1546 Table 65[38] and TA 639 Table 64[54]	Annually 12 oncologist visits, 1 GP visit, 4 CT scans, 12 nurse specialist visits, 3 community nurse visits, 17 FBC
One-off costs			
Locoregional recurrence	£474.76	Assumed equal to DM state	Equal to DM

Health state	Costs	Reference	Justification
Distant metastasis	£474.76	ID1546 Table 64[38] and TA639 Table 63[54]	1 oncologist visit, 1 CT scan, 1 FBC, 1 MRI
End of life	£8,347.03	Georghiou & Bardsley et al. 2014 inflated to 2020 value[55]	Including district nurse, nursing and residential care, hospice care, and nursing service
Based on Tables 62, 63, 64 and 65 of the CS[1] CS = company submission; CT = computed tomography; DM = distant metastasis; FBC = full blood count; GP = general practitioner; MRI = magnetic resonance imaging; TA = technology appraisal			

4.2.8.4 Surgery costs and adverse event costs

Surgery costs were applied within the model as a one-time cost calculated based on the unit costs of surgery and the proportion of patients receiving surgery in each arm. A weighted average of £5,823.04 was derived from the unit costs of breast surgery from the NHS reference costs.[56] The proportion of patients receiving surgery was obtained from the KEYNOTE-522 trial and was [redacted] and [redacted] for the pembrolizumab and placebo arm, respectively.

Modelled AEs and its corresponding incidence were presented in Section 4.2.7. The resource use and costing approach was based on previous technology appraisals in IO. See Table 4.11 below for details.

Table 4.11: Unit costs associated with AE management

Type of AE	AE cost	Justification
Grade 3+ AEs		
Neutropenia	£635.68	Costing as per TA519[57]
Neutrophil count decreased	£635.68	Equal to Neutropenia as in TA519[57]
Anaemia	£762.54	Costing as per TA519[57]
Febrile neutropenia	£3,580.80	Costing as per TA737 approach[57]
White blood cell count decreased	£635.68	Equal to Neutropenia as in TA519[57]
AAT increased	£0.00	Costing as per TA684 (previously TA558); Assumption of zero cost for laboratory abnormalities; (already considered under health-state management costs)[58]
Other AEs		
Diarrhoea (Grade 2+)	£2,166.42	Costing as per TA581 approach[59]
Colitis (Grade 2+)	£2,166.42	Equal to Diarrhoea (Grade 2+) as in TA581[59]
Based on Table 66 of the CS[1] AAT = alanine aminotransferase increased; AE = adverse effect; CS = company submission; TA = technology appraisal		

ERG comment: The main concerns of the ERG relate to: a) treatment costs for the DM state may be overestimated; and b) waiting time for surgery seems longer than anticipated

a) As already discussed in Section 4.2.6, modelled survival in the DM state was based on KEYNOTE-355. Given the differences in observed survival between KEYNOTE-355 and KEYNOTE-522, the ERG believes that KEYNOTE-522 would be a more accurate source to inform

DM. However, in the company scenario where KEYNOTE-522 was used for survival in DM, costs (and time on treatment) were still based on KEYNOTE-355 as time on treatment in DM is not a model parameter but assumed to be fixed and costs for DM treatment were implemented as a one-off cost. Therefore, in the scenario where KEYNOTE-522 data are used to inform survival in DM, costs for treatment in DM would be overestimated since patients will have shorter survival while costs are not adjusted. The ERG considers that even when KEYNOTE-355 data would be appropriate, the approach to estimating 1L treatment costs as a one-off in the DM state is not sufficiently precise given the rather substantial impact these costs have on the ICER. An additional comment to this is that the proportion of patients assumed to receive 1L treatment in the DM state was derived from KEYNOTE-522 data in the company base case and was higher for the placebo arm, driving up costs. No clinical or other rationale was provided for the difference in proportion of patients receiving 1L treatment.

b) The ERG asked the company in the clarification phase whether there was a waiting time for surgery after neoadjuvant treatment, and if so, how would patients be managed in the meantime.[5] The company, in its response to the request for clarification, said that indeed according to the KEYNOTE-522 protocol, patients underwent definitive surgery 2 to 6 weeks after the last cycle of the neoadjuvant phase, and thus there was a waiting time before surgery. According to the time on treatment curves however (see Figure 4.4 above), the waiting time appears to be much longer, at least 10 weeks. Although the ERG is puzzled by this apparent difference between protocol and reality, there may not be a large impact on CE as the difference is seen in both arms and in the model the patients waiting for surgery were assumed to have resource use as associated with the EF state.

5. COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The CS base case CE results indicated that pembrolizumab is both more effective (incremental QALYs of [redacted]) and more costly (additional costs of [redacted]) than current care amounting to an ICER of £5,940 per QALY gained (Table 5.1)

Table 5.1: Company's deterministic base case results using pembrolizumab PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Placebo arm	[redacted]	13.82	[redacted]	-	-	-
Pembrolizumab arm	[redacted]	16.89	[redacted]	[redacted]	[redacted]	£5,940

ICER = incremental cost-effectiveness ratio; LYG = life years gained; PAS = Patient Access Scheme; QALY = quality-adjusted life year

Overall, the technology is modelled to affect QALYs by:

- An increase in EF survival at a relatively high utility
- A relatively lower utility in the LR and DM states where proportionally more chemotherapy patients reside

Overall, the technology is modelled to affect costs by:

- Its higher treatment acquisition price compared to chemotherapy alone in both the neoadjuvant and the adjuvant phase
- The higher metastatic (one-off) treatment costs for the chemotherapy arm

ERG comment: The main concerns of the ERG relate to: a) the extrapolated gains being substantially higher than observed gains; and b) the metastatic treatment costs being more than three times higher in the chemotherapy arm compared to pembrolizumab.

a) The issue of the extrapolated versus observed gains was already discussed earlier in Section 4.2.6 (see ERG comment b)
b) The base case model results show that for the chemotherapy arm, almost half of the total costs consisted of metastatic treatment costs. The ERG considers this to be unlikely and may be a result of the potentially biased and imprecise way of estimating the one-off metastatic treatment costs as discussed in Section 4.2.9 (see ERG comment a)

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSAs), deterministic sensitivity analyses (DSAs) as well as scenario analyses. The PSA with 1,000 iterations resulted in a higher ICER. The results of PSA analysis are presented in Table 5.2.

Table 5.2: Company's probabilistic base case results using pembrolizumab PAS price

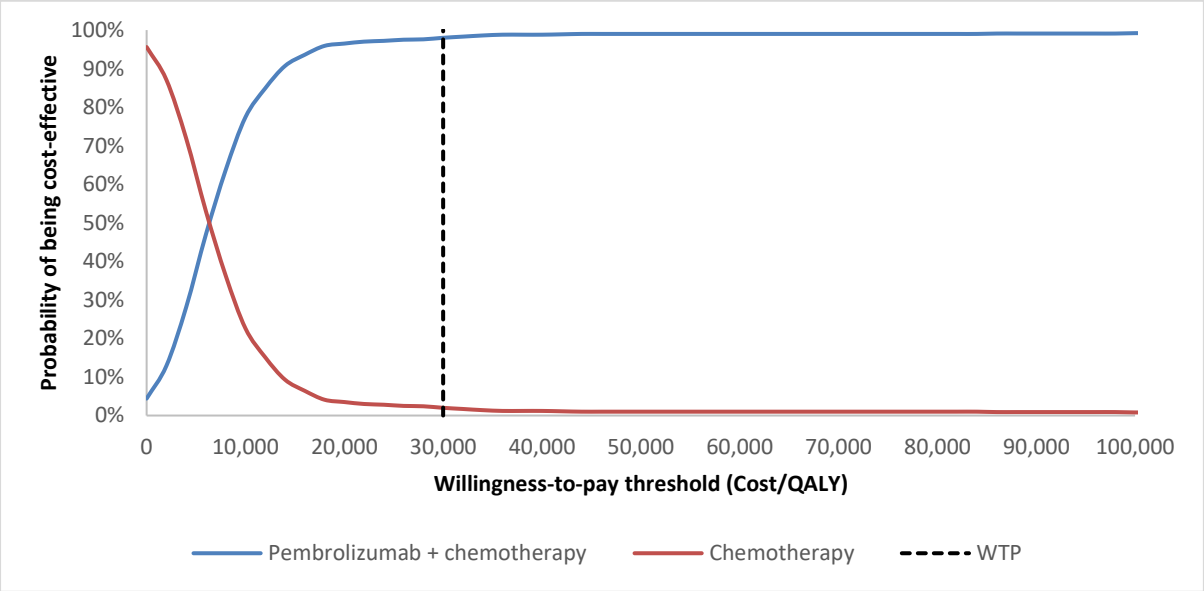
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Placebo arm	[redacted]	13.79	[redacted]	-	-	

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Pembrolizumab arm	[redacted]	16.72	[redacted]	[redacted]	[redacted]	£6,128

ICER = incremental cost-effectiveness ratio; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year

The cost effectiveness acceptability curve (CEAC) in the untreated analysis showed that pembrolizumab had a 98% probability of being cost effective at willingness to pay thresholds of £30,000. The CEAC is presented in Figure 5.1.

Figure 5.1: Company's CEAC with pembrolizumab PAS price

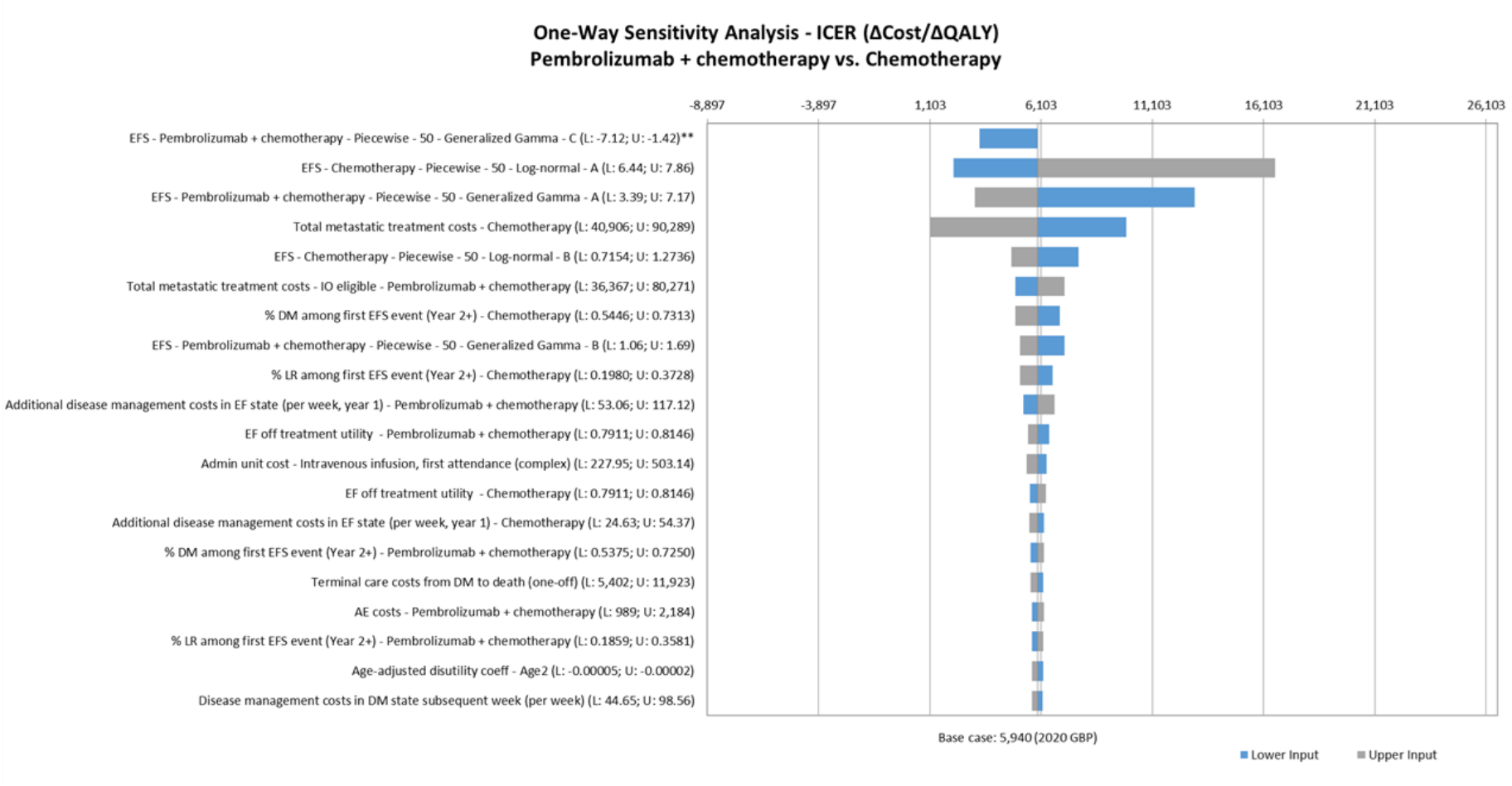


Based on Figure 22 of the CS[1]

CEAC = cost effectiveness acceptability curve; CS = company submission; PAS = patient access scheme; QALY = quality-adjusted life years; WTP = willingness-to-pay

The DSA was performed to investigate key drivers of the base case results. Each input parameter was varied to its respective upper or lower bound and the deterministic results for the model recorded. The base case parameter values were varied across their 95% CI where possible. The results of the DSA are presented in Figure 5.2 below. The inputs that have most impact on the ICERs are those related to parameters linked to EFS extrapolations followed by metastatic treatment costs. CS scenarios that have a substantial impact on the ICER are the scenarios varying the distributions for the extrapolation of EFS, and the scenario with a limited time horizon (20 years).

Figure 5.2: Company's tornado diagram for the 20 most sensitive parameters with pembrolizumab PAS price



**Upper limit parameter pembrolizumab arm is dominated i.e. more costly and less effective; therefore an ICER statistic cannot be presented for the tornado diagram

Based on Figure 23 of the CS[1]

CS = company submission; DM = distant metastasis; EFS = event-free survival; ICER = incremental cost effectiveness analyis; IO = immune oncology; LR = locoregional recurrence; PAS = patient access scheme; QALY = quality-adjusted life year

5.3 Model validation and face validity check

5.3.1 Face validity assessment

Efficacy (EFS) outcomes from KEYNOTE-522 were compared with the modelled EFS curves produced from the economic model. This was possible until a 3-year time horizon, as there were no observed data beyond this point. The company concluded that the modelled EFS curves matched well with the observed EFS curves (Tables 74 and 75 and Figure 24 of the CS).[1]

In addition, OS as modelled in KEYNOTE-355 was compared to OS as observed in KEYNOTE-522. Again, comparison was only possible up until the 3-year time point. The company concluded that the modelled and observed curves matched well. There was slightly more deviation between modelled and observed outcomes than for EFS though.

5.3.2 Technical verification

No details on technical verification were provided, other than a statement that clinical expert opinion was sought to validate certain aspects of the model, including internal review and quality control for model inconsistencies and errors performed.

5.3.3 Comparisons with other technology appraisals

No comparison with other technology appraisals was reported.

5.3.4 Comparison with external data used to develop the economic model

No comparison with external data used to develop the model was reported.

5.3.5 Comparison with external data not used to develop the economic model

For EFS, two external sources were identified as sources of validation for the placebo modelled EFS, a randomized phase II trial reported by Sikov et al. 2019 and a retrospective cohort by Walsh et al. 2019[60, 61] The company concluded that the placebo arm EFS curve matched well with the DFS curve from Walsh et al. 2019 and was reasonably close to the EFS curve from Sikov at al. 2019.

For OS, the same two studies by Sikov et al. 2019 and Walsh et al. 2019 were identified for validation purposes.[60, 61] The company concluded that given reasonable visual alignment, the model produces robust estimates of OS for the chemotherapy arm. The company also noted that using KEYNOTE-522 data provided slightly better visual alignment than using KEYNOTE-355 OS (which was used in the company base case to inform OS).

In the absence of clinical or real-world long-term data for early-stage TNBC patients receiving pembrolizumab, plausibility of modelled long-term EFS and OS was validated with clinical experts.[29]

ERG comment: The main concerns of the ERG relate to the absence of explicit clinical validation (using landmark estimates of survival, for instance) and the questionable appropriateness of validating KEYNOTE-355 model OS with KEYNOTE-522 OS given that these are different populations.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

Table 6.1 summarises the key issues related to the CE categorised according to the sources of uncertainty as defined by Grimm et al. 2020:[62]

- Transparency (e.g. lack of clarity in presentation, description, or justification)
- Methods (e.g. violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g. particularly wide CIs, small sample sizes, or immaturity of data)
- Bias & indirectness (e.g. there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g. lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e., whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the CE, whether it is reflected in the ERG base case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this ERG report, the ERG defined a new base case. This base case included multiple adjustments to the original base case presented in the previous sections. These adjustments made by the ERG form the ERG base case and were subdivided into three categories (derived from Kaltenthaler et al. 2016):[63]

- Fixing errors (FE; correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV; correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ; amending the model where the ERG considers that reasonable alternative assumptions are preferred)

6.1.1 ERG base case

Adjustments made by the ERG, to derive the ERG base case (using the CS base case as starting point) are listed below. Table 6.2 shows how individual adjustments impact the results plus the combined effect of all abovementioned adjustments simultaneously, resulting in the ERG base case. The 'FE' adjustments were combined, and the other ERG analyses were performed also incorporating these 'FE' adjustments given the ERG considered that the 'FE' adjustments corrected unequivocally wrong issues.

6.1.1.1 Fixing errors

1. Enable pembrolizumab 1L treatment in DM state for IO-eligible patients in the placebo arm
2. Adjustment to formulas correcting for general population mortality

6.1.1.2 Fixing violations

Not applicable.

6.1.1.3 Matters of judgement

1. Issue 3 (Section 3.2.1)
   Correction for efficacy of pembrolizumab adjusting for Europe versus rest of the world HR. The ERG implemented a simple fix to the efficacy in the model, assuming the HR to remain constant over time.
2. Issue 10 (Section 4.2.6)
   Use KEYNOTE-522 data to inform survival in DM state and alongside this adjust treatment costs according to the shorter survival.
3. Issue 8 (Section 4.2.6)
   Use lognormal distributions in EFS for both arms.

6.1.2 ERG exploratory scenario analyses

The ERG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the ERG base case.

Exploratory scenario analyses

1. Limit time horizon to 5 years (similar to the observed period)
2. Set the cut-off of the piecewise model at 68 weeks instead of 50 weeks
3. Use generalised gamma distributions for EFS in both arms (Issue 8, Section 4.2.6)
4. Use lognormal distribution for pembrolizumab and generalized gamma distribution for placebo EFS (Issue 8, Section 4.2.6)
5. Adjust utility in DM health state to [redacted] based on KEYNOTE-355 (Issue 11, Section 4.2.8)
6. Adjust utility in DM health state to 0.715 based on KEYNOTE-119 (Issue 11, Section 4.2.8)

6.1.3 ERG subgroup analyses

No subgroup analyses were performed by the ERG.

Table 6.1: Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in Section 5.1)

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in ERG base case[b]	Required additional evidence or analyses
Model structure not including locoregional remission and no differentiation between pre-progression and post-progression distant metastatic patients.	4.2.2.	Unavailability	Structural model adjustment	+/-	No	May not be possible with available data
Modelled treatment effectiveness and extrapolation for EFS state likely overestimates effectiveness of pembrolizumab	4.2.6	Bias and indirectness; extrapolated part of the model generates most of the EFS gain compared to observed part	Change distributions	+	Partly in ERG analysis 4, and ERG scenarios 3 and 4	Mature data for better validation of long-term extrapolations
Constant transition probabilities from LR and DM states assumed without clinical justification	4.2.6	Unavailability & imprecision; lack of mature comparative data on OS	Use well-informed OS distributions	+/-	No	Mature LR and DM survival data, clinical justification
The use of KEYNOTE-355 data for DM survival may not be appropriate	4.2.6	Bias and indirectness; lack of mature comparative data observed in KEYNOTE-522	Use KEYNOTE-522 data for OS in DM	+/-	Partly in ERG analysis 3; however, KEYNOTE-522 not mature	Mature LR and DM survival data
Relatively low utility in the DM health state	4.2.8	Bias & indirectness as utility may not be appropriate to the population and health state in question	Explore impact of higher utility	+	Yes, in ERG scenarios 5 and 6, but utility is still an estimate	Not applicable

[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator; [b] Explored
ERG = Evidence Review Group; FE = Fixing errors; FV = fixing violations; MJ = matters of judgement; ICER = incremental cost effectiveness ratio

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

In Section 6.1 the ERG base case was presented, which was based on various changes compared to the company base case. Table 6.2 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.3 deterministically and in Table 6.4 probabilistically. These are all conditional on the ERG base case (except the scenarios where EFS distributions are varied – these override the base case distributions). The analyses numbers in Tables 6.2, 6.3 and 6.4 correspond to the numbers reported in Section 6.1. The CEAC of the ERG base case and the exploratory scenario analyses are presented in Figure 6.1 to 6.7 The submitted model file contains technical details on the analyses performed by the ERG (e.g. the "ERG" sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: Deterministic ERG base case

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base case					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,940
Fixing errors 1: Enable pembrolizumab 1L treatment in DM state for IO-eligible patients in the placebo arm					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£9,346
Fixing errors 2: Adjustment to formulas correcting for general population mortality					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£5,976
Matters of judgement 1: Correction for efficacy of pembrolizumab adjusting for Europe versus rest of the world hazard ratio					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£7,801
Matters of judgement 2: Use KEYNOTE-522 data to inform survival in DM state and alongside this adjust treatment costs according to the shorter survival					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£8,976
Matters of judgement 3: Use lognormal distributions in EFS for both arms					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£16,444

1L = first line; CS = company submission; DM = distant metastasis; EFS = event-free survival; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; IO = immune oncology; QALY = quality-adjusted life year

Table 6.3: Deterministic scenario analyses (conditional on ERG base case)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base case					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£43,621
Scenario 1: Limit time horizon to 5 years (similar to the observed period)					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£397,435
Scenario 2: Set the cut-off of the piecewise model at 68 weeks instead of 50 weeks					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£27,172
Scenario 3: Use generalized gamma distributions for EFS in both arms					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£15,447
Scenario 4: Use lognormal distribution for pembrolizumab and generalized gamma distribution for placebo EFS					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£53,592
Scenario 5: Adjust utility in DM health state based on KEYNOTE-355					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£44,259
Scenario 6: Adjust utility in DM health state based on KEYNOTE-119					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£44,362
ERG base case					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£43,621

CS = company submission; EFS = event-free survival; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year

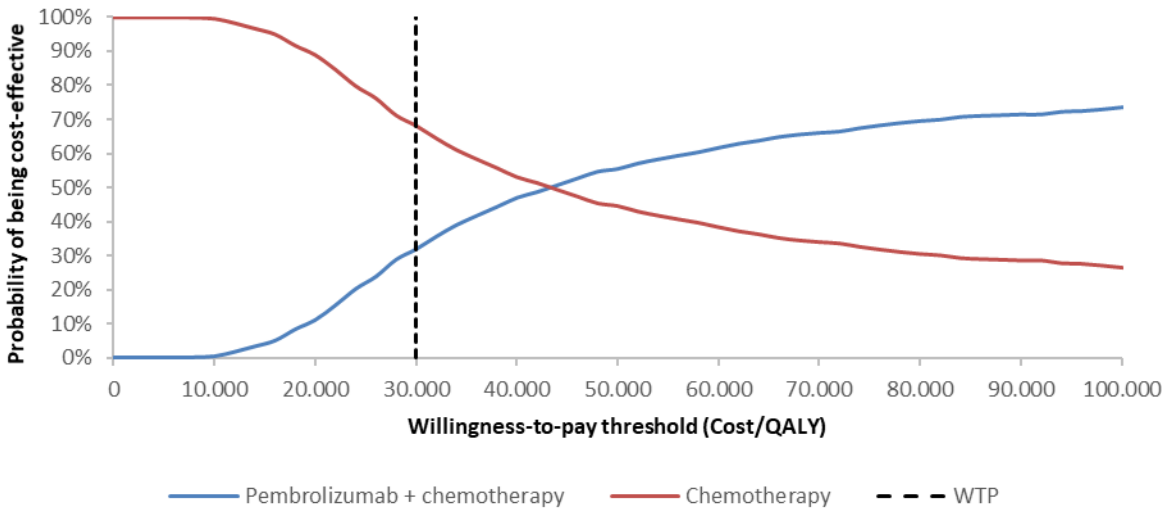
Table 6.4: Probabilistic scenario analyses (conditional on ERG base case)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	Prob-ability
ERG base case						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£43,621	31.9%
Scenario 1: Limit time horizon to 5 years (similar to the observed period)						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£381,768	0.0%
Scenario 2: Set the cut-off of the piecewise model at 68 weeks instead of 50 weeks*						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£37,272	50.8%
Scenario 3: Use generalized gamma distributions for EFS in both arms						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£16,697	79.0%
Scenario 4: Use lognormal distribution for pembrolizumab and generalized gamma distribution for placebo EFS						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£58,421	28.1%
Scenario 5: Adjust utility in DM health state based on KEYNOTE-355						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£44,568	31.4%
Scenario 6: Adjust utility in DM health state based on KEYNOTE-119						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£44,685	31.4%

CS = company submission; DM = distant metastasis; EFS = event-free survival; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year

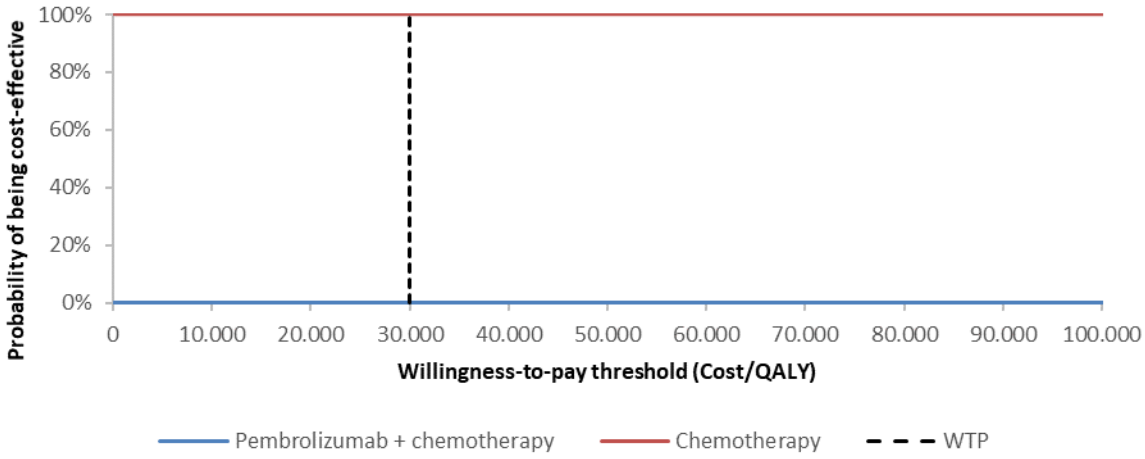
*Errors in approximately ten PSA runs. Errors were excluded from the analysis to obtain the results

Figure 6.1: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on ERG base case



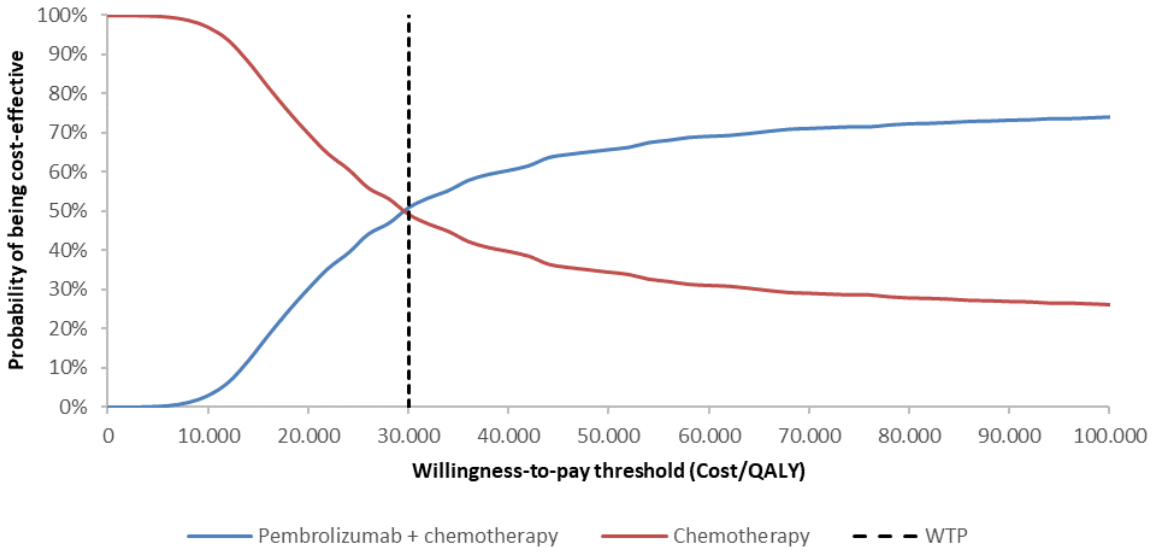
Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 6.2: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 1



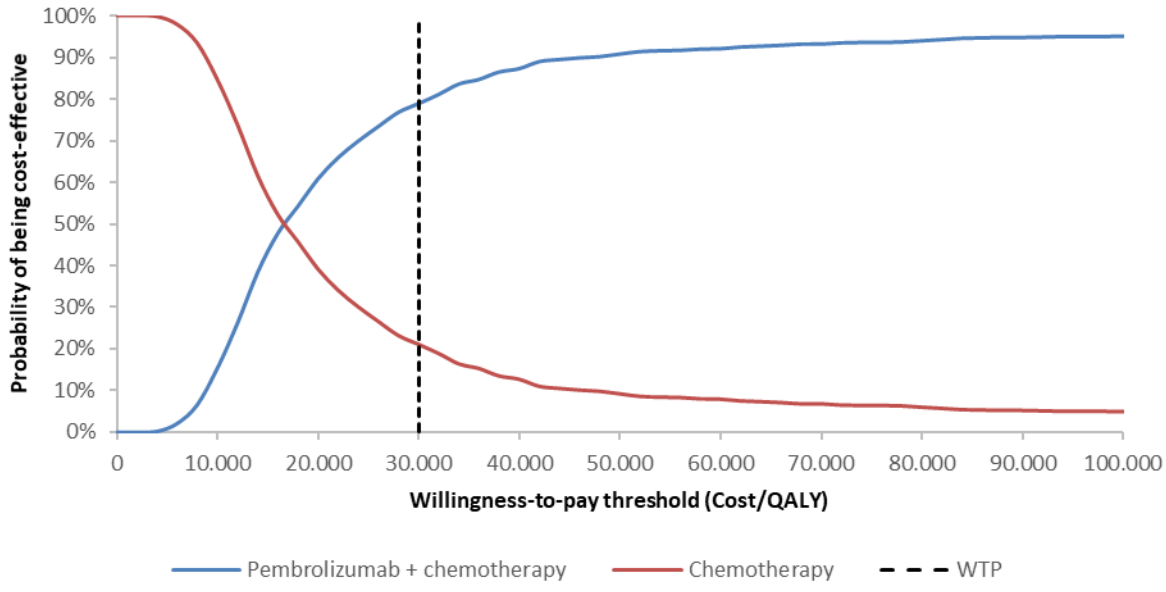
Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 6.3: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 2



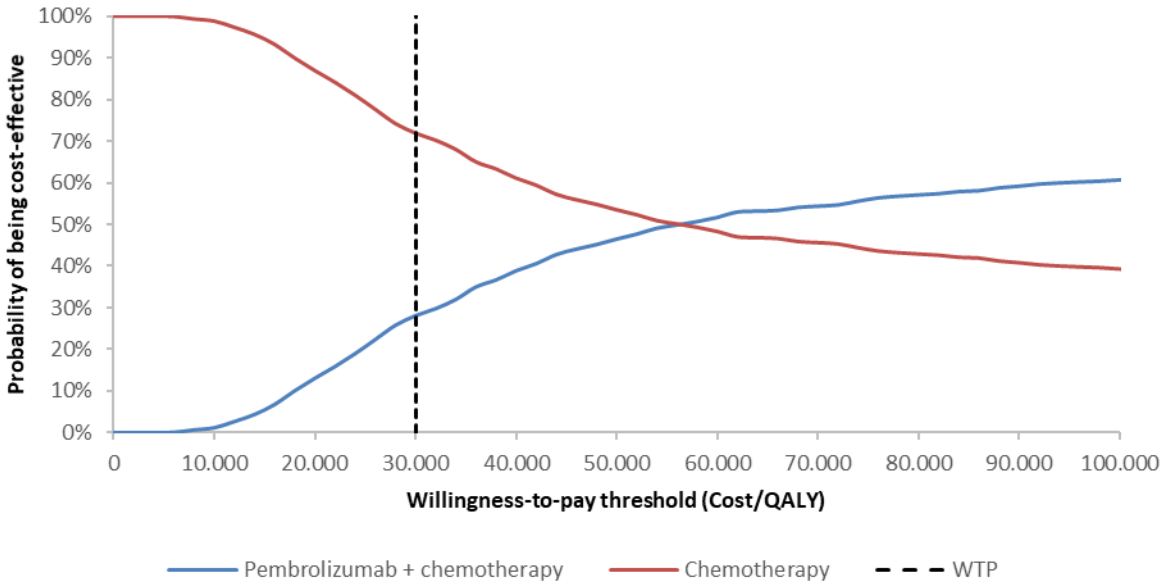
Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 6.4: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 3



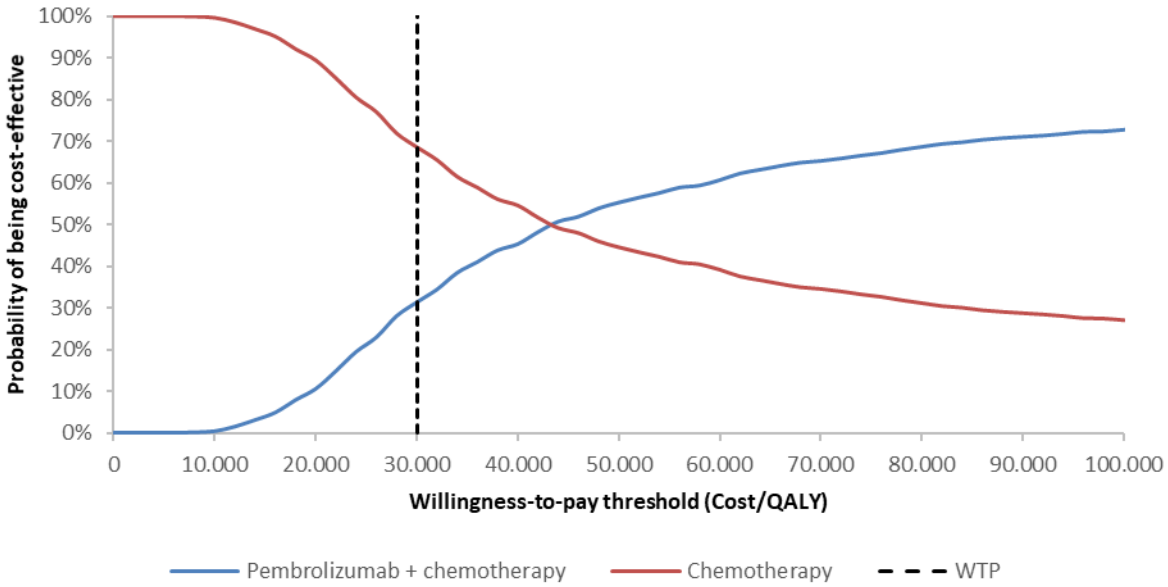
Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 6.5: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 4



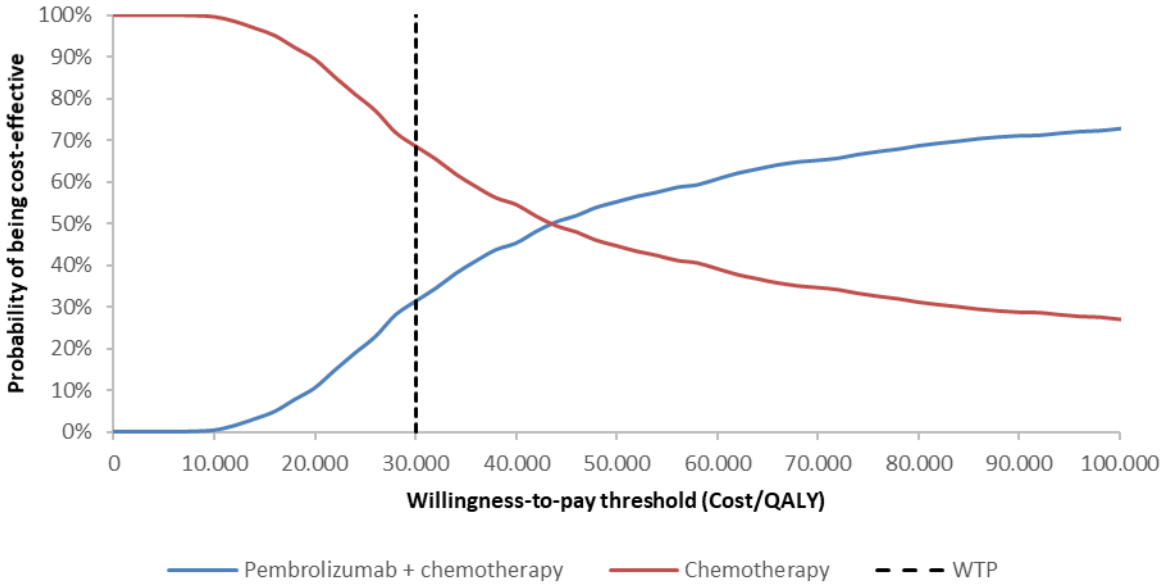
Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 6.6: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 5



Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 6.7: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 6



Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

6.3 ERG's preferred assumptions

The estimated ERG base case ICER (probabilistic), based on the ERG preferred assumptions highlighted in Section 6.1, was £43,621 per QALY gained. The probabilistic ERG base case analysis indicated a CE probability of 31.9% at WTP thresholds of £30,000 per QALY gained. The most influential adjustments were using lognormal distributions in EFS for both arms. The ICER increased most in the scenario analysis with alternative assumptions regarding the time horizon.

6.4 Conclusions of the cost effectiveness section

The company's CE estimates rest heavily on QALY gains in the extrapolated part of the model, while QALY gains in the observed part of the model were only very modest (Issue 8). The ERG adjusted the distributions used for EFS extrapolation in its base case but not all uncertainty caused by this issue may be resolved with this adjustment. As the model structure does not include separate health states for remission from LR and pre- and post-progression in the metastatic phase, it may not sufficiently capture relevant changes in HRQoL and costs in these states (Issue 7). The ERG could not resolve this issue in its analyses. Issue 3, the fact that pembrolizumab may not be as effective in the European population, has been addressed in the ERG model, but to properly explore the impact of regional difference in effectiveness, the model structure would need to be adapted more elaborately. Resolving Issue 2, the exclusion of a potentially relevant comparator, would also require structural changes and additional evidence which was not available.

Given that relatively more patients in the placebo arm reside in the locoregional and metastatic health states (because of the substantial EFS advantage modelled for pembrolizumab), costs and utilities in these states have an important impact on the ICER. However, the way the locoregional and metastatic health states were modelled was quite crude, with transition probabilities assumed constant over the full-time horizon of the model (Issue 9), and the metastatic health state being mostly informed by the KEYNOTE-355 data and model, with treatment costs calculated as one-off based on fixed treatment durations (Issue 10) and a relatively low utility value (Issue 11). Most of the uncertainty around these issues remains in the ERG analyses, although the ERG explores the impact of some assumptions in its scenarios.

In conclusion, with the current model, CE estimates of pembrolizumab + chemotherapy compared with chemotherapy alone are uncertain and likely are subject to bias. Although part of the issues were addressed, substantial uncertainty remains, especially on the long-term EFS benefit and on the costs and QALYs in the metastatic health state. Both are not supported by mature comparative data.

7. END-OF-LIFE

According to the CS, *"pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab monotherapy does not meet the end-of-life criteria"*.[1]

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of untreated locally advanced non-metastatic triple negative breast cancer [ID1500]

'*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 Monday 13 June 2022** 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.

Section 1: Factual inaccuracies

Issue 1 – Decision problem: Choice of population in final scope versus that addressed in the company submission

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
Throughout the ERG report and specifically on; Page 12, 14, 23, 25, 80, 81, "There are major differences between the population defined in the NICE final scope and the decision problem addressed in the CS, e.g. regarding inflammatory disease, early-stage disease, participants being at high risk of recurrence and with a pre-defined ECOG PS" "The use of "or" could indicate that different permutations of these factors are possible, e.g. that participants in the trial had inflammatory and early-stage TNBC which was not locally advanced. This ambiguity adds further uncertainty to the differences described before" "The ambiguity around the population breadth, i.e. it is unclear whether the trial population is actually narrower or broader than the NICE scope population, makes it very difficult to estimate effects on cost effectiveness".	Please replace all references to this text with the following; ***"During the regulatory assessment process, minor changes in the wording of the anticipated licensed indication took place but the final MA granted resonates with clinical practice for the treatment of patients with early-stage or locally advanced TNBC. Within the submission, the company addressed the C/E of the indication pertaining to the final licensed indication and had noted inconsistencies in the final scope issued early on in the process. The ERG does not anticipate this to have any major implications for the C/E since the final licensed indication is reflective of NHS patients."***	This technology was rescoped in September 2021 – The draft scope being issued by NICE for consultation at the time stated the population of interest as "Adults with previously untreated locally advanced, non-metastatic triple-negative breast cancer". At that stage MSD responded to the draft scope asking that NICE update the final scope population to reflect the anticipated licensed wording at that time to "MSD suggests the population should be [redacted] MSD raised again the population inconsistency in the final scope issued by NICE at the DPM. In its response to MSD's comment pertaining to the amendment of the population to reflect the anticipated licensed	This is not a factual inaccuracy. In Section 2.1 of the ERG report, the differences between scope and the decision problem addressed in the CS as well as the inclusion criteria of the SLR and the trials have been highlighted for the attention of the committee.

"Closer coherence to the NICE scope would have ensured that efficacy and safety were being specifically evaluated in the specified population" KN522 license includes both early-stage and locally advanced, the trial recruited patients with stage II-IIIb patients which would fall under the definition of early-stage and locally advanced. Inflammatory breast cancer patients were allowed onto the trial however these patients were not included within the EMA and MHRA marketing authorization for KN522, therefore this should no longer be a concern. Considering the above, all references pertaining to ambiguity around the final scope population and the population addressed in the decision problem are factually incorrect and should be removed from the ERG report altogether or more text should be added to explain that MSD noted minor inconsistencies in the draft scope, but this was not updated by NICE. Finally, it should be made clear that the population addressed in the CS is fully relevant to NHS patients for decision making purposes.		indication NICE notes that "As the information on the population provided has been marked commercial in confidence, this change cannot be made. No change to scope made.". During the Clarification response stage MSD provided the final wording of the licensed indication since a +ve CHMP has been granted at the time; ***"KEYTRUDA, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early stage triple negative breast cancer at high risk of recurrence"***. As we explained within at the clarification response stage the final population addressed within our submission is in line with the +CMHP granted and reflects fully the patients that would receive this intervention	

		within the NHS (includes those with ECOG PS status = 1).	

Issue 2 – Decision problem: Choice of comparator and queries on systematic literature reviews

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
Page 12, 23, 28, 82 Statements around the addition of capecitabine to systemic treatment being associated with improvement in DFS and or likelihood of capecitabine being a relevant adjuvant chemotherapy comparator that might better reflect the adjuvant setting. Page 30, 82 – potentially misleading claims on magnitude of survival benefit when capecitabine is used in the adjuvant setting. Within our submission and clarification question response we explained that capecitabine may be used in some patients who have not achieved a pathological complete response. This is based on the results from the CREATE-X study. This data was published in 2017 and so capecitabine would not have been widely used at the time when KN522 had started recruiting. There are a number of differences (both	We have provided context that capecitabine may only be used in patients that do not achieve a pCR and that generally adjuvant chemotherapies post neoadjuvant chemotherapy are not extensively used in the UK. Please amend all capecitabine related statements to make clear that "*Capecitabine may be used in some cases where pathological Complete Response (pCR) is not achieved by patients. It is also unlikely this can have a major impact in terms of survival benefit as noted by UK clinicians within the CS, although the ERG has a*	The current description of the potential use of capecitabine is not balanced and potentially exaggerates the perceived impact on the relative treatment effect. Capecitabine is used within only non-pCR patients at small % and experts have noted that the KEYNOTE-522 trial design reflets the UK treatment pathway for these patients. Amendments proposed reflect this to offer a more balanced view around this matter. In addition, the CREATE-X trial was published in 2017, capecitabine would not have been widely used at the time when KEYNOTE-522 had started recruiting.[i]	This is not a factual inaccuracy. The ERG was very careful to point out that while current practice does not commonly use adjuvant therapies, it is likely that the use of placebo in the trial, rather than capecitabine, may have contributed to an increased estimate of benefit for pembrolizumab. This statement is cautiously worded and based on the meta-analysis showing a small but significant improvement in disease-free survival when capecitabine is added to systemic treatment.

methodological and population wise between the KEYNOTE-522 and CREATE-X such as the limited overlap in TNBC patients from CREATE-X, which preclude the ability to draw such conclusions.[i] Finally, clinicians noted that the use of capecitabine in the UK is very limited and it is unlikely that this would have a major impact on survival benefit. Therefore capecitabine should not be considered as a "relevant adjuvant comparator". Page 14, 71 ; "However, it is stated in the CSR that the addition of capecitabine to systemic treatment is associated with improvement in DFS ([redacted]), which suggests that the best available comparator in the adjuvant phase might actually be capecitabine." And "placebo in the adjuvant phase, rather than an active comparator such as capecitabine (which is associated with an improvement in DFS) may have contributed to an increased estimate of benefit for pembrolizumab" Page 15; recommendations for future research of collection of data around the use and impact of capecitabine are unrealistic.	*diverging opinion on this matter".* Please delete sentence in page 15; "Including capecitabine as an active comparator in the adjuvant phase could be considered in future trials". It is neither realistic not appropriate to conduct an additional trials. Please delete sentence in page 15; "Additional data collection with a subgroup using capecitabine in the adjuvant phase." Both of these sentences are irrelevant.		

Page 28 – "*The best available comparator in the adjuvant phase (capecitabine) may have been overlooked."* *"it is likely that the trial's use of placebo in the adjuvant phase, rather than an active comparator such as capecitabine, may contribute to an increased estimate of benefit for pembrolizumab."*	Please delete sentence which states that *"the best available comparator in the adjuvant setting may have been overlooked by the company".* This is factually incorrect and rationale for the study design of KEYNOTE-522 has been provided to explain this. Capecitabine use in the UK is very limited to the patients which do not achieve pCR. Further, please add more context to explain that off-study capecitabine use was limited but also balanced across both arms therefore its effects on the EFS estimates would be limited. This is demonstrated by the EFS sensitivity analyses results presented in the clarification questions response.	The current description of the potential use of capecitabine is not balanced and potentially exaggerates the perceived impact on the relative treatment effect. It also raises concerns on the study design of KEYNOTE-522 which has factored in regulatory authority considerations and scientific literature available at the time of conceptualisation and does not contradict the limited use of capecitabine in non pCR patients in the UK.	This is not a factual inaccuracy. Please see the statements above.

Page 29, *82* – *"….*might be used reactively and off-protocol, such as for people not achieving pathological complete response (pCR), and might thus lead to confounding".	Please delete any references to potential confounding as these are misleading. No such evidence exists to support these statements. Only a small % of patients received off-study treatments and these were balanced between the two different arms as explained in our clarification question response.	Please remove references to potential confounding as they are irrelevant.	This is not a factual inaccuracy.
Page 30 – "…would not have solved the problem of pembrolizumab being compared to placebo alluded to earlier (with its implications for potentially exaggerated pembrolizumab effect sizes)"	Capecitabine use in the UK is very limited to the patients which do not achieve pCR, off study treatment was well balanced and KEYNOTE-522 fully reflect the UK clinical practice – therefore please delete "(with its implications for potentially exaggerated pembrolizumab effect sizes)" as it is not factually correct.	The current description of the potential use of capecitabine is not balanced and potentially exaggerates the perceived impact on the relative treatment effect and raises unnecessary concerns on the study design of KEYNOTE-522 which factored in regulatory authority considerations and scientific literature available at the time of conceptualisation.	This is not a factual inaccuracy. Please see previous comments.
Page 37 – queries pertaining to the I-Spy2 and the PROCEED trials[ii], [iii]. We provide further rationale below.	We consider that the additional context provided has clarified to the ERG why these two studies were not considered further.	The pivotal RCT informing this indication is KEYNOTE-522. Sufficient rationale which makes clear the differences between I-	Changed accordingly

The aim of the SLR was to identify studies that could be used to estimate (directly or via an indirect comparison) relative treatment effects for the pembrolizumab regimen approved in the UK (neoadjuvant pembrolizumab + carboplatin + paclitaxel followed by doxorubicin–cyclophosphamide or epirubicin–cyclophosphamide and adjuvant pembrolizumab) versus other treatments used in the UK setting for the population of interest. Because the pembrolizumab regimen in ISPY-2 did not contain carboplatin, it does not align with the approved regimen and does not contribute direct or indirect evidence on the treatment regimen of interest. Further, adjuvant treatment in the ISPY-2 trial was left to the discretion of the treating oncologist. Pooling this study with Keynote-522, which evaluates the regimen of interest, would not be appropriate as the addition of carboplatin is expected to modify the treatment effect relative to the control arm. Separate SLRs were conducted for clinical endpoints and HRQoL studies. The reasons for exclusion given in Table 56 pertain to the HRQoL review only. The PROCEED trial was excluded from this review because no	Please revise the concluding remarking to reflect this “The company provided rationale for its decisions on the basis of study design and PICOS outlined and therefore the ERG is satisfied with this response.”	SPY-2 and KEYNOTE-522 is provided for its exclusion.	

HRQoL outcomes in the population of interest were reported. The PICOS criteria given in Table 4 pertains to the SLR conducted for clinical endpoints of interest for the NMA. This review was restricted by interventions used for the population of interest in relevant countries. The treatments evaluated in the PROCEED trial (irinotecan + capecitabine and capecitabine monotherapy) were not prespecified in the study protocol.			

Issue 3 – KEYNOTE-522 clinical data (Geographical effects; TNM staging, ECOG staging and subgroup analyses)

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
Page 44, 45, 46 & key issue 3 – Misleading statement - "It is unclear if these potential differences in characteristics between the UK participants and the overall trial participants would affect outcomes, but they do suggest, in tandem with the EFS sub-group results previously described for Europe versus the rest of the world, that it is possible that the overall results observed in the KEYNOTE-522 trial may not necessarily be relevant to UK patients."	Please delete or amend to include that the study was not powered to perform this type of analysis and a conclusion can't be made	Wording is misleading - stating that UK patients may not receive EFS benefit based on the lower HR for the Europe vs rest of the world. This conclusion should not be made as the study was not designed to compare UK (or Europe) only patients with the rest of the world and so any analysis would be invalid.	This is not a factual inaccuracy. The ERG has not made conclusions about the applicability of the trial, but instead has raised concerns, based on the evidence, that the overall results may not be fully applicable to UK patients. The company is correct to state that the study was not powered to detect differences between

			ECOG types, but it is important to recognise that this makes it all the more important to watch for possible type II errors, and to raise awareness of them if there is good reason to suspect their presence.
Page 57, 58 & key issue 5 – Misleading statements “and it is likely that if people have an ECOG score of 1 they are not going to experience benefits from pembrolizumab.” “the data suggest that patients with an ECOG status of 1 are unlikely to benefit from pembrolizumab (and there is a probability that the drug could even cause harm in this group, although this is uncertain).”	Please delete or amend to include that the study was not powered to perform this type of analysis and a conclusion can’t be made	Wording is misleading - Difference in the baseline characteristics between treatment groups in the subgroup of ECOG=1 may have an impact on the results due to the small sample size and therefore not all variables are balanced. However, subgroup analyses are not intended to be used for inferential testing as the study was not powered for definitive demonstrations of efficacy in these subgroups. The results of these exploratory analyses should be interpreted with caution.	This is not a factual inaccuracy. See point above about lack of analysis power.
Page 102, - preference for Europe EFS HR to be applied in the base-case	Please amend to include acknowledgement that the study was not powered to perform this type of analysis and is purely descriptive in nature.	The study was not designed to compare EFS for Europe vs rest of the world and therefore it would not be appropriate to	This is not a factual inaccuracy.

		apply the HR from this analysis in the base-case.	
Page 38 – “clinical effectiveness appears to be derived”	Please change to “is derived from the IA4 dataset”, as this is the case as explained clearly in the submission.	Wording is misleading – the IA4 dataset which is the latest available data has been presented in the submission documents.	The highlighted quote has not been used in the ERG report.
Page - 45 “Europe versus rest of world EFS estimate, overly simplistic estimate” “The company did not provide similar data for a UK patient sub-group, and effectively did not respond” “UK vs rest of world data not provided”. It is unrealistic for the ERG to expect a survival analysis to derive HRs based on 40 patients.	Estimate is not overly simplistic vs European patients as confidence intervals overlap between ITT and Europe patients. The study was not powered to detect differences in EFS by geographic region subgroups so all these analyses are purely exploratory in nature. Please add a footnote to explain that such a request is unrealistic and probably meaningless given the small samples size of the UK subgroup.	Please add more clarity as to why this request was not fulfilled. It is misleading to report and base the preferred cost-effectiveness results in a geographic location subgroup. The study was not powered to detect significant differences and this is purely exploratory.	This is not a factual inaccuracy. The ERG is aware that the study is not powered to detect differences between small subgroups but wished to gain an overview of the point-estimates to assist the committee with interpretation.
Page 55 – “Hence the clinical importance of this result is unclear” – please rewrite – EFS benefit has remained consistent throughout each analysis. EFS is clinically relevant for patients and very important from a decision perspective	KEYNOTE-522 has demonstrated a statistically significant EFS benefit in favour of the intervention. This has remained consistent throughout. Whilst the final OS analysis has not taken place, yet the intervention has demonstrated	Please amend –EFS remains clinically relevant and consistent results with most information fraction having taken place means that it is highly unlikely that the EFS benefit will not continue to be sustained. Whilst OS is	This is not a factual inaccuracy. The ERG was highlighting that it is misleading to describe HR data in terms of ‘reductions in risk’ as this can heighten the impression of clinical

and given that there is a 66% information fraction, the EFS is considered mature. Page 55 “The median OS was not reached in either arm at month 42 and will need to be analysed in future IA as data matures”. This is a potentially curative-intent disease setting, therefore median OS may never reached. Unlike metastatic disease, median OS reached or not cannot be a criterion to decide data mature or not in isolation, especially given the sufficient EFS follow up and the statistically significant benefit.	evidence that it also extends OS although the final analysis results will take place at a later DBL. Therefore, the OS results, even based on an interim analysis, are clinically relevant and important for both patients, carers, doctors and decision makers. It is also not uncommon for median OS not to be reached in the neoadjuvant and adjuvant setting. Please amend statements accordingly.	immature at this stage, this is not uncommon given the pathway setting but even so the study demonstrated a numerical OS benefit which is clinically relevant and important. The current wording does not reflect the above aspects.	importance. This is important to ensure that the committee interpret data appropriately. The ERG highlighted that more mature OS data would support a more informed decision.
Page 58, 71 – “The lack of relative benefit for the pembrolizumab arm in terms of quality of life is an important finding. This may reflect the modest benefits observed for the other efficacy outcomes, alongside the significant adverse effect burden of pembrolizumab” “benefits in terms of quality of life were not observed, suggesting that the net positive balance between clinical benefits	Please delete or amend to reflect that clinical trials are not powered to detect differences in PROs in general and that PROs are used descriptively to assess broad concepts of quality of life. The results from these exploratory endpoints demonstrate that the addition of pembrolizumab does not have a statistically significant burden on the quality of life.	The current wording does not reflect the true aim of PRO collection alongside an RCT and only offers a conservative interpretation of the clinical trial results. Please correct working to reflect that the addition of pembrolizumab results in statistically significant EFS benefit and numerical OS benefit at this stage but does	This is not a factual inaccuracy.

and harms of pembrolizumab were insufficient to have a positive impact on patients' quality of life"		not have a detrimental impact on the QoL of patients.	
Page 58: "and it is likely that if people have an ECOG score of 1 they are not going to experience benefits from pembrolizumab" – please amend or delete statement as this conclusion cannot be reached by the ERG when the current trial design or data are considered. Page -58 "but the data suggest that patients with an ECOG status of 1 are unlikely to benefit from pembrolizumab (and there is a probability that the drug could even cause harm in this group, although this is uncertain)". Please delete the statement above – no such claim was ever made by the company, rather we cautioned against intrepretting small subgroups.	The regulatory authority has been satisfied or the +ve risk benefit profile associated with the intervention led to a +ve CHMP opinion being granted. The ERG should exercise caution when interpreting results of analyses based on small sample sizes as well as the risk/benefit profile within those subgroups, which again has been explored by the regulatory authority.	Please amend or delete statements as they are misleading.	This is not a factual, inaccuracy. This is the ERG's interpretation of the data in Fig 3.1 and discussed in Section 3.2.5.5.

Issue 4 – Safety: Adverse effects

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
Page 17, 68 , 69 Inferences around the risk of death for patients treated with pembrolizumab. "difference between arms in SAEs is large and requires consideration in the overall evaluation of the study drug" "For pembrolizumab versus placebo, the relative risk of death is 3, which requires consideration in the overall evaluation of the study drug. The probability of a difference this large arising by chance is 0.01."	The safety and risk benefit profile of the intervention has been assessed and deemed as favourable by the regulatory authority which resulted in a +ve CHMP opinion has been issued. No specific AE resulting in death was reported in more than 1 participant. No new safety signals were identified upon review of these fatal events. Please supplement the sentences to note that "no new safety concerns were identified as per the published EPAR."	The sentences in question are linked to the risk/benefit profile of the intervention which has been deemed as positive but as written currently, may be misinterpreted. No specific AE resulting in death was reported in more than 1 participant. No new safety signals were identified upon review of these fatal events.	This is not a factual inaccuracy.
Page 90 – "Grade 2+ AEs, diarrhoea and colitis, were included in the economic model as these were deemed as clinically relevant" "The main concern of the ERG relates to the inclusion of Grade 2+ AEs colitis and diarrhoea because these were deemed	The inclusion of Grade 2+ AEs colitis and diarrhoea because these were deemed clinically relevant from clinical perspective to ensure that AE costs estimates accurately reflect that there may be a need for some level of management within health care setting. This is	The inclusion of these two additional AEs can be removed from the base-case if the ERG is concerned. Our current approach is in agreement with previous TAs. AE management costs in general have very small impact on the ICER.	This is not a factual inaccuracy. The ERG is mainly concerned about the reasoning for why these two Grade 2+ AEs are considered clinically relevant (which is also not

clinically relevant. In response to clarification question B16a, in which the ERG asked for clarification why these Grade 2 AEs were deemed clinically relevant, the company explained that these specific AEs were included in addition to Grade 3+ AEs as they expect these AEs to be associated with a high management cost (i.e. hospitalisation)"	consistent with ID1546 but also across a number of other IO HTAs.		clearly explained in the company submission for TA ID1546). However, as explained in the ERG report, this is expected to have very limited impact on the ICER and therefore there is no need to remove this from the base-case.

Issue 5 – Model structure criticism: lack of remission post LR and differentiation between pre and post progression at DM state

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
Page 17, Table 1.8: Key issue 7; 79, 80, 104 The ERG states that "…model structure does not include health states for remission from locoregional recurrence and separate pre- and post-progression states for distant metastasis and that the current model does not reflect clinical practice, and therefore the company's model does not capture costs and utilities	MSD proposes the following amendments to be made in key Issue 7 given the substantial justification provided to the ERG during the clarification question response stage that fully justifies the model structure (amended text in ***bold***); "The ERG was not able to adjust the model structure, as no data was available to inform remission and separate progression distant metastasis states ***because as explained by the company the breadth of data necessary to do***	As written currently, Issue 7 does not fully reflect the fact that MSD has fully justified the model structure is adequate and that the choice of assumptions used aimed to strike a balance between data availability and model complexity (when referring to Remission from LR request). Remission from LR is not clinically justified when considering that TNBC is an aggressive type of cancer. We have provided the full methodology on how this was	This is not a factual inaccuracy. The ERG specifically state that the overall impact of this issue on the ICER is uncertain but the main concern is that costs and QoL are not accurately captured. In addition, although the company did offer basic explanation on how costs in DM were calculated, the costs were taken from the

related to these health states correctly..." "The ERG was not able to adjust the model structure, as no data was available to inform remission and separate progression distant metastasis states". As presented currently the issue offers an unbalanced view pertaining the economic modelling.	***this is not available for mTNBC. The company considers that the current evidence from KEYNOTE-522 does not support the addition of remission post LR within the economic considering that TNBC is an aggressive type of cancer and most patients with LR would continue to develop a DM. The current model assumptions likely to bias against pembrolizumab, since pooled transition probabilities have been applied across both treatment arms.*** "The ERG believes this ***may not*** reflect clinical practice, and therefore the company's model does not capture costs and utilities related to these health states correctly, ***although the company provided full explanation as to how the costs are estimated in the DM health state. This adds certainty that the pre-progression DM and post-progression DM costs are ascertained correctly form a methodological point of view (although still reliant on KEYNOTE-355 and expert opinion).***"	conducted which included data from KEYNOTE-355 to which this ERG is privy and/or clinical expert opinion where necessary. MSD is concerned by the fact that the current write up of this issue leaves ambiguity to the read as to whether the DM health state can adequately capture the costs associated at pre- and post-progression whilst on DM. The proposed changes add more context with regards to these elements of the modelling and therefore remove any potential misinterpretation around the suitability of the model for decision making purposes.	KEYNOTE-355 model which was not made available to the ERG and so the ERG did not have any means to check the exact methods or validity of these calculations.
Page 80; The ERG claims that the lack of a remission tunnel state may lead to an over-	We propose the following text is added; "exclusion of remission from LR may lead to ***an underestimation*** of	The proposed amendment clarifies the current assumptions are likely to bias against	This is not a factual inaccuracy.

estimation of QALYs in favor of pembrolizumab. We disagree with this statement and we see that remission is more relevant for patients which remain in the EF health state.	pembrolizumab's effect***, but is justified given based on the KEYNOTE-522 clinical data. Considering that TNBC is an aggressive type of cancer and most patients with LR would continue to develop a DM. The current model assumptions likely to bias against pembrolizumab, since pooled transition probabilities have been applied across both treatment arms.***	pembrolizumab considering the current clinical data and that the aggressiveness of TNBC.	As acknowledged in the ERG report, the company's model assumed no further treatment effect (i.e. transition probabilities to DM and death are treatment independent) in the LR state. However, since patients in the placebo arm have a relatively higher probability to move from the event-free state to the LR state compared with the pembrolizumab arm, the assumption of no remission from LR affects the placebo group more than the pembrolizumab group, leading to a difference between the costs and utilities in this state in favor of pembrolizumab. The fact that KEYNOTE-522 did not allow for retreatment with therapy in patients experiencing LR does not mean this is not done in clinical practice, therefore it may be

			incorrect to assume based on only KEYNOTE-522 that patients cannot go into remission.

Issue 6 – Cost-effectiveness analysis: EFS extrapolation may overestimate the effectiveness of the intervention

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
Page 13, 18, Table 1.9: Key issue 8; The ERG states that "…When using only the observed part (short time horizon), where mortality is increased in the pembrolizumab arm due to adverse events (see Key Issue 6), the ICER increases dramatically." Pembrolizumab is not associated with increased mortality. Clinical data from KEYNOTE-522 have demonstrated a numerical OS benefit and AE related deaths were not dissimilar between the two treatment arms.	We request that inferences to mortality over the observed period which may be misinterpreted as an ERG's view towards the risk/benefit are completely removed. The above suggested edits cover this aspect. If the ERG wish to raise the choice of exploring alternative parametric curves with regards to EFS in their base-case this can be done in isolation in a manner that does not rely for justification on the basis of risk/benefit. The regulatory authority has been satisfied that the intervention has a +ve risk/benefit on the basis of the clinical data itself reviewed in its totality during the regulatory assessment. We request that the ERG change the wording of this issue by amending the sentence "When using only the observed part (short time horizon), of ~5 years , ***as***	We strongly request that any inferences alluding to the risk/benefit profile are removed as they miss-represent the clinical data and the risk benefit profile. Alternative scenarios on parametric extrapolations can be explored in isolation by the ERG provided that justification is included for these scenarios. With regards to short time horizon analyses presented; MSD wants to raise the following points to justify the amendments requested. As with most oncology submissions, most QALY gains are derived from the extrapolated period of the economic model considering the follow up in oncology trials. It is neither possible not realistic to follow up	This is not a factual inaccuracy. The ERG used the scenario with the limited time horizon to illustrate that the cost-effectiveness of pembrolizumab very heavily relies on the long-term extrapolations. The ERG is aware that a 5 year time horizon is not as per NICE reference case and therefore only performed this analysis as a scenario. The company in their submission performed scenarios using discount rates which were not per NICE reference case either, for a scenario this

The ERG raises the issue of EFS extrapolation but is also mixing it with perceived Issue 6 which focuses on patients experiencing AEs. The regulatory authorities have endorsed that there is a +ve risk benefit profile for this indication and granted an authorization and there have been no new safety concerns identified. We ask that the ERG revisits the Issue and focuses in EFS extrapolations alone. We also ask that the ERG provides a narrative that short time horizon analyses are not relevant for decision making.	***expected, the ICER increases. However, this analysis is crude and deviates from the NICE methods of HTA evaluation which aim to ascertain costs and benefits over a lifetime horizon".***	patients indefinitely to acquire mature data (noting that there are differences on what constitutes data maturity). Simply conducting a C/E analysis by resting the time horizon to the followed up period deviates from the NICE methods of evaluation.	is not necessarily a problem.
Page 18; - different parametric model preferences to extrapolate EFS The ERG claims that justification was not provided for the use of alternative parametric curves to model EFS. This is not the case since the choice of parametric extrapolations was informed by clinical experts.	Please amend the sentence; "Mature comparative data on long-term EFS, and more extensive validation of the results by clinical experts, ***which may support the use of different parametric functions to model the long term EFS, as advocated by the company currently".*** With regards to QALY accrual over the extrapolated period, the following change	The suggested addition will add more context around these issues for the reader. The ERG does not provide its own clinical expect opinion in the matter of EFS extrapolations and preferences for alternative	This is not a factual inaccuracy

Justification has been provided – the underlying hazard of relapse or death would differ between the two arms therefor the justification of different functions to model EFS is justified. The choice of same type of model to be used for EFS extrapolation, whilst may be preferred by the ERG, it would still not resolve the fact that most QALY gains take place beyond the trial follow up as per every oncology indication.	should be implemented; "This will not fully eliminate the issue that most of the QALY gain is obtained outside of the observed period, ***which is usually the case with oncology submissions due to the need to use extrapolations to model costs and effects over a life time."***	models but the company has within the submission. Is not uncommon for most QALY gains to be derived from the extrapolated period of the model. Not explicitly stating this may raise concerns as to whether the mode is fit for decision making purposes. This is clearly not the case based on the validation we have conducted and is included in the submission.	
Page 89 – "… the statistical fit was validated using real-world data, however there is only real-world data available for the placebo arm (and not for the pembrolizumab arm) and therefore this validation says nothing about the justification for the use of different distributions" MSD considers it highly relevant to validate the comparator arm	Please amend the statement in question to add more context around the choice of different parametric extrapolation models used to extrapolate EFS as explained within the submission. Please add the following text; "however there is only real-world data available for the placebo arm (and not for the pembrolizumab arm) and therefore this validation says nothing about the justification for the use of different distributions, ***although differences in the underlying hazard assumptions over time between the two treatment***	Please add more context for the concluding remarks of this sentence. Please also provide details of the expert opinion sought by the ERG during the critical appraisal process.	This is not a factual inaccuracy.

for which more evidence is available, and it is not uncommon for new technologies to lack historical data for model validation purposes. Further, it is well accepted that the unique mode of action of immunotherapy (with or without chemotherapy) is not comparable to chemotherapy alone; therefore, the underlying hazard assumptions for the parametric curves can differ between the two interventions.	***arms may warrant different choice of parametric functions to extrapolate the EFS.***		
Page 89 – sentence around the accrual of QALYs beyond the observed period from extrapolation; "extrapolations implemented result in a substantial gain in EFS which is mostly obtained in the unobserved part of the time horizon" followed by analyses caping the time horizon to that of the observed period; "….chancing the time horizon from 51 years to a short-term horizon (e.g. 5 years, which reflects the period for which KM data of the KEYNOTE-522 is	The ERG does not state that it is not uncommon in oncology HTAs most of the benefits are derived from the extrapolated portion of the economic model since NICE is interested to explore the c/e of an intervention over a life time. It is natural that restricting the TH would artificially inflate the ICER because the intervention costs are front loaded but benefits take time to accumulate in the form of QALYs. The analysis presented therefore is exploratory in nature and should be positioned as such since it deviates from the NICE reference case.	The analysis presented should be positioned as exploratory in nature since it deviates from the NICE reference case. This should be made clear to the reader.	This is not a factual inaccuracy, see also response above.

available) causes a considerable increase in the ICER. The ERG believes this is a major uncertainty in the model.".	Please add to the sentence to reflect this "This is also seen in the model: chancing the time horizon from 51 years to a short-term horizon (e.g. 5 years, which reflects the period for which KM data of the KEYNOTE-522 is available) causes a considerable increase in the ICER, ***but this is expected and this analysis deviates from the NICE reference case."***		
Page 89 – "*from Tremblay et al., 2015*[iv] *can be used, stating that the ratio of the marginal relative difference in the extrapolated period (post cut-off) divided by the number of months post-cut-off should not be higher than the ratio of marginal difference on the number of months in the pre-extrapolation period*" "rate of survival gain" per month between treatments should be equal or inferior in the post-extrapolation period compared to the pre-extrapolation period. In the current model using different distributions for the extrapolation of EFS, the pre-	The ERG does not explicitly state that the authors use a case study from the metastatic BC setting to derive their conclusions and apply this accordingly. KEYNOTE-522 is not a metastatic setting trial and therefore this "rule of thumb" is both misleading and irrelevant in this instance. It is not uncommon for most benefits to be accrued in the extrapolated period when it comes to oncology submissions. Please add clarity regarding the context of Tremblay et al 2015 to make clear these limitations to the reader otherwise this assessment is irrelevant as it cannot be applied in this context.	As written currently this offers a single sided view which challenges the validity of extrapolations using examples which are irrelevant for the neo-adjuvant/adjuvant setting. Considering the key differences between the provided reference and this submission, this is a completely irrelevant assessment.	This is not a factual inaccuracy. The conclusions of Tremblay do not exclusively apply to metastatic settings. The company state that: *" It is not uncommon for most benefits to be accrued in the extrapolated period when it comes to oncology submissions."* The ERG would like to point out that similar *rate* of survival gain in the post- to pre- extrapolation period is not inconsistent with more benefit in terms of total life years gained in the post-extrapolation period, depending on life-expectancy.

extrapolation (up to week 205, based on KM data of KEYNOTE-522) rate of survival gain is 0.2367, while the post-extrapolation (from week 206) rate is 0.3340, suggesting lack of realism of the extrapolated marginal gain according to the rule-of-thumb".			
Page 89, 103 – preference for log-normal to be used across both treatment arms to extrapolate EFS. We kindly ask that the ERG provide the results of the clinical expert elicitation they conducted to support their preference for a log-normal distribution. As is currently, the preference for log-normal to be applied across both arms is on the basis of QALY accrual over the extrapolated period which the ERG argues is unrealistic.	Based on clinical expert opinion and review of the breadth of data MSD believes that it is well accepted that the unique mode of action of immunotherapy (with or without chemotherapy) is not comparable to chemotherapy alone; therefore, the underlying hazard assumptions for the parametric curves can differ between the two interventions. This is in line with the NICE DSU survival analysis TSD14. It is not uncommon for the QALY accrual to take place In the extrapolated part of the economic model, especially for neoadjuvant/adjuvant submissions. Please provide more evidence to support the ERG's justification for choosing log-normal across both treatment arms.	Please add more context to justify the preference for log-normal. Please also note that QALY accrual does In majority take place during the extrapolated period of a model, especially when it comes to a neoadjuvant/adjuvant therapy. Please also provide details of the expert opinion sought by the ERG during the critical appraisal process.	This is not a factual inaccuracy. The ERG does not agree with the line of reasoning of the company that the unique mode of action of immunotherapy and the fact that underlying hazard assumptions 'can' differ between the interventions would necessitate the use of different parametric functions over using individually fit curves of the same type. The ERG also does not agree that this is in line with TSD14.

Issue 7 – Cost-effectiveness: Assumptions around constant transition probabilities from LR and DM health states

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
Page 18, Table 1.10: Key issue 9; The ERG states that they are concerned with the use of constant transition probabilities from LRà DM, LR and DM à Death. This element has been explained by the company during the clarification questions. In brief, we are limited by the memoryless nature of Markov modelling and the need to strike a balance between data availability and model complexity as well as consistency with other prior submissions. The current wording used by the ERG does not take into consideration any of these aspects.	MSD proposes the addition of the following text in ***bold*** "The ERG is concerned about the lack of clinical justification for this; ***The company explained the choice of exponential distribution was necessitated by the memoryless feature of Markov modelling to avoid unnecessary complexity but also due to the limited number of events observed in KEYNOTE-522, although the ERG still maintains its position*** ."	The amendment proposed offers a more balanced view explaining the reasons why the company chose to model these transition probabilities using assuming an exponential function whilst it still allows for the ERG to maintain its opinion around this matter.	This is not a factual inaccuracy.
Page 85 – the discussion around the assumptions pertaining to constant hazards	We propose the addition of some text in the following sentence "*The company decided to choose the exponential*	The amendment proposed offers a more balanced view explaining the reasons why the	This is not a factual inaccuracy.

from LR→ DM and LR→ Death does not provide any notion on the Markov memoryless feature that precludes more complex time varying modelling without the introduction of additional model complexity which is also not justified by the availability of the current data.	*distribution because they considered it to better fit the tail of the KM-curve, despite the fact that it would overestimate OS for the observed period,* ***however, a full discussion of the limitations of Markov modelling with regards to its memoryless nature as well as the breadth of the current data, both which preclude any alternative modelling without introducing additional complexity and assumptions".***	exponential function was used to model LR to DM and LR to death using pooled data from KEYNOTE-522.	
Page 89 and 90 – "The ERG is concerned that oversimplifying assumptions for these transitions, which are mostly relevant to the placebo arm as relatively more patients in the placebo arm and up in LR and DM, will distort incremental CE while uncertainty around this issue is not captured in the sensitivity analyses." There is no over-simplifying assumption. We have explained the restrictions of Markov modelling.	It is unlikely that this assumption has a major impact in the c/e since pooled data are used to model the transition probabilities and the assumption of constant hazards equality applies across both arms. Therefore, if there is underestimation in QALYs and/or Costs this happens to the same degree across both treatment arms and therefore it is unlikely to have a major impact on the ICER. However, considering the clinical evidence, this assumption is conservative against pembrolizumab since probably the LR or DM costs & QALYs may be slightly underestimated but considering the limited survival associated with TNBC it is unlikely that this assumption "distorts" the ICER.	The ERG reaches conclusions without presenting any additional evidence on this matter.	Not factual inaccuracy. The ERG stated that it is concerned that it will distort the outcomes, which does not mean a certain impact in a certain direction. Also, exclusion of a relevant health state is, in the opinion of the ERG, a simplification.

	The ERG has not presented any evidence to prove that this assumption may distort the C/E therefore the "will distort incremental CE" should be changed to "***might affect incremental CE but the impact of this is likely to be limited***".		

Issue 8 – Cost-effectiveness modelling of DM: appropriateness of KEYNOTE-355 data

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
Page 18, Table 1.11: Key issue 10; MSD has provided full justification for the choice to use KEYNOTE-355 to model DM à Death survival for the patients which receive subsequent treatments. Further, the ERG does not mention the discrepancies that result from adjusting the immature OS data from KEYNOTE-522 to estimate the treatment costs. This information is derived from KEYNOTE-355 which is what MSD used in the base-case to avoid over imposing additional	MSD proposes the addition of the following text in bold to account for this limitation "***However, the ERG notes that its preferred methodology may potentially be introducing uncertainty since two different sources are used (KEYNOTE-522 immature OS data for efficacy and costs based on Time on Treatment (ToT) which is derived from the KEYNOTE-355 RCT***."	The amendment proposed offers a more balanced view explaining the reasons why the company chose to model costs and survival using a single source of evidence – that being KEYNOTE-355 which was recently appraised by NICE.	This is not a factual inaccuracy.

assumptions pertaining to the time on treatment for DM patients from KEYNOTE-522. This discrepancy should be added in this issue.			
On page 19: “Mature data on transition probabilities over time, possibly obtained from further KEYNOTE-522 data cuts, could resolve this uncertainty” Whilst more mature OS data may allow for the use of KEYNOTE-522 to model survival and costs for patients whilst at DM, the ERG does not raise the limitations associated with the collection of mature OS data in the neoadjuvant/adjuvant setting. At this stage MSD has presented the latest OS to NICE which was derived from IA4 and cannot comment as to when the company will be unblinded to data interim analysis if the number of OS events is reached to do a formal analysis.	To account for this limitation we ask that the ERG add the following text in the sentence; “,***noting that the company has presented the latest IA4 data for assessment and that it is not known when the formal OS analysis results may become available to inform the HTA process”.***	The amendment proposed offers a more balanced view explaining availability of OS data that that could be used to derive the DMà death transition probabilities as alluded by the ERG is not currently known. At this stage MSD have presented the latest OS data to NICE and cannot comment as to when the OS events will be reached for a formal analysis which may help resolve this issue.	This is not a factual inaccuracy.
Page 80; The ERG does not address the fact that the	Please add further text to the sentence: “the company was not able to provide the	The proposed amendment offers a balanced view of why	This is not a factual inaccuracy.

company explained that the immaturity of KEYNOTE-522 OS data and subsequent treatment data further prevented any additional exploratory analyses such as use of start of subsequent lines of therapy for metastatic disease to define pre and post progression as proxy, that could be used to fulfil the ERGs request.	ERG with data on the progression status for patients with DM as this was not recorded in the KEYNOTE-522, ***and the company also explained that the OS data maturity at this stage does not allow for exploratory analyses to be conducted to attempt to address this perceived limitation (such as use of start of subsequent lines of therapy for metastatic disease to define pre and post progression as proxy).***	this request could not be fulfilled and it also adds further justification as to why the company preferred the use of KEYNOTE-355 in the base-case.	
Page 82; Information around time on treatment and data used for subsequent therapies needs to be added.	Please add the following statement to make clear that ToT for 1L DM therapies was taken from KEYNOTTE-355 or public information where available (such as in the case of TA639 for Atezolizumab + nab-paclitaxel)	Proposed amendment adds clarity for the reader.	This is not a factual inaccuracy. Also, it is not clear to the ERG what statement the company suggests to add.
Page 87; The sentence "*The full NMA report provided with the clarification letter response shows that the comparison was with nab-paclitaxel only"* is unclear currently and edits should be made to reflect some aspects noted below which arise by the availability of data used to inform the comparators. There appears to be confusion in the HRs derived from the NMA, what the common	Please edit the sentence *"The full NMA report provided with the clarification letter response shows that the comparison was with nab-paclitaxel only"* *to* *"The full NMA report provided with the clarification letter response shows that* ***the studies informing the carboplatin comparison and link carboplatin into the rest of the network, only contain nab-paclitaxel. However, data from the pooled KEYNOTE-355 taxane data were***	Proposed amendment provide further clarity to resolve ambiguity. As written currently the sentence is misleading considering that full justification and NMA report have been provided.	This is not a factual inaccuracy. However, the ERG has added this clarification to the ERG report.

comparison was and what was applied within the economic model versus what is reported in the submission. We understand that the full NMA provided at clarification stage contains a large number of analyses which may have created a confusion. We also understand that the studies which inform the carboplatin comparison (TNT and JapicCTI-090921) only include nab-paclitaxel as a taxane. This is not the case for KEYNOTE-355 which allows us to generate HRs either using pooled taxanes or by specifically exploring nab-paclitaxel alone. However, we preferred the use of pooled taxanes to increase the sample size leveraged from KEYNOTE-355 which is also aligned with prior deliberations regarding the of perceived equivalence between the different taxanes (including docetaxel and paclitaxel). Finally, the applied HRs are located within the "Raw_DM trt TOT OS sheet".	***used considering that the AC have previously concluded on taxane efficacy equivalence during prior HTAs.*** KEYNOTE-355 included the information for the efficacy of pembrolizumab + taxanes versus taxanes alone. The rest of the estimates were derived from a systematic review and NMA conducted in line to NICE DSU. Please amend the sentence "*Therefore, it is unclear how this HR versus any taxane was estimated and how valid the estimate is when applied to survival with any taxane"* by adding the following text: "***although given the perceived equivalence in survival between taxanes and the similar HRs for using nab-paclitaxel alone from KEYNOTE-355, it is unlikely this would have any major implications for the c/e results.***		

Page 88 – statements around the lack of pembrolizumab 1L usage for RS treated patients once they progress to the DM setting "*no option to receive pembrolizumab as 1L treatment for patients in the placebo arm".* As explained within Document B p86 of 147 – *"In the base case, pembrolizumab rechallenge is not permitted to reflect the current standard of care in the UK where atezolizumab + nab-paclitaxel is the only IO therapy currently available for metastatic TNBC".*	Please amend the current statement "no option to receive pembrolizumab as 1L treatment for patients in the placebo arm" to "***The company did not pembrolizumab as 1L treatment for patients in the placebo arm considering that at the time of developing the submission, ID1546 was ongoing (although the company did allow for alternative IO utilisation). Given the recent ve recommendation issued by NICE for a restricted population, the company should now explore alternative assumptions which better reflect the UK treatment pathway".***	Proposed amendment provide further clarity to which explains why this assumption was used to inform the economic modelling.	This is not a factual inaccuracy. This explanation was not provided to the ERG at submission. Also, there was an inconsistency in the model regarding this point, see also response below at issue 10.
Page 90 – "there are quite substantial differences in observed survival between these two studies (see Table 4.7), which raises doubts about comparability of the populations and therefore on appropriateness of using KEYNOTE-355 OS data for this appraisal". Table 4.7 refers to treatment specific survival as derived from the NMA not as applied. It is 4.8 that contains the weighted	Please correct the table referred to in the text. The weighted survival estimate applied in the actual model is reported in table 4.8 depending on the scenario that is selected regarding IO eligibility.	Please correct the table source referenced.	Amended as suggested

survival applied in the model that factors in the mix of 1L metastatic therapies. Please correct this.			
Page 94 – "KEYNOTE-355 was used to estimate these 1L treatment costs in the base case, while KEYNOTE-522 was used in a scenario."	KEYNOTE-355 was used for % PD-L1 +ve patients to ascertain 1L costs and assumptions were made with to derive the costs 1L patients with were PD-L1-ve and would therefore only be eligible for chemotherapies because they fall outside ID1546 and TA639 (mainly those receiving carboplatin monotherapy, carboplatin + paclitaxel or capecitabine alone). KEYNOTE-355 was used to estimate these 1L treatment costs ***(ToT and OS)*** in the base case, ***alongside assumptions for the ToT pertaining to carboplatin monotherapy, carboplatin + paclitaxel or capecitabine alone) since these chemotherapies would primarily be used in the PD-L1 -ve patients not covered by TA639 or ID1546***, while KEYNOTE-522 was used in a scenario."	Please add more clarity on the estimation of 1L metastatic costs.	This is not a factual inaccuracy. The CS was not very clear on this matter, stating that ToT was used but the actual ToT estimates could not be found in the submission nor in the model – as also mentioned in the ERG report in section 4.2.6.3.
Page 96 – ".Given the differences in observed survival between KEYNOTE-355 and KEYNOTE-522, the ERG believes that KEYNOTE-522	The KEYNOTE-522 OS data are currently immature, therefore DM à death OS estimates are also immature. Please make this clear.	Please add more clarity on the estimation of 1L metastatic costs – the model currently captures costs for 1L and 2L from KEYNOTE-355 very accurately without	This is not a factual inaccuracy. Also, the ERG does not agree that the company has provided extended methodology of how 1L

would be a more accurate source to inform DM." The KEYNOTE-522 OS data are currently immature and therefore cannot be used to inform the base-case. We understand that differences in survival noted by the ERG are related to survival from DM not from randomization, however, this is not clear in the sentence. Page 97 – "The ERG considers that even when KEYNOTE-533 data would be appropriate, the approach to estimating 1L treatment costs as a one-off in the DM state is not sufficiently precise given the rather substantial impact these costs have on the ICER. An additional comment to this is that the proportion of patients assumed to receive 1L treatment in the DM state was derived from KEYNOTE-522 data in the company base case and was higher for the placebo arm, driving up costs.."	Please amend statement to add more context as survival comparisons are not fully relevant. KEYNOTE-522 OS is immature at this stage therefore robust transition probabilities on DM→ Death cannot be calculated to inform the base-case. We have provided extended methodology of how the 1L mTNBC treatment costs were estimated and the approach followed strikes a balance between model complexity and accuracy given the data availability for mTNBC.	overcomplicating the model structure.	treatment costs were estimated (since these were all derived from the KEYNOTE-355 model which was not made available) and so there was no way for the ERG to see whether the current model captured 1L and 2L costs 'very accurately'.

Page 101 – Please note that the OS validation carried out factored in the modeled OS from the NMA which is reliant upon market share estimates for patients being treated as well as those that do not receive subsequent therapy based on KEYTNOTE-522. "…validation (using landmark estimates of survival, for instance) and the questionable appropriateness of validating KEYNOTE-355 model OS with KEYNOTE-522 OS given that these are different populations".	Please amend the relevant sentence to add more clarity; " *".. **standard validation using landmark estimates of survival, for instance was not provided by the company. The appropriateness of approach followed for OS validation is reliant upon the modelled OS output which is derived from an NMA and assumptions around market share estimates as well as % of patients that do not receive any subsequent therapies versus the KEYNOTE-522 OS. The ERG has concerns given that these are different populations."***	The proposed change offers more clarity as to what the company did and why the ERG is concerned.	This is not a factual inaccuracy.
Page 97 – ". Although the ERG is puzzled by this apparent difference between protocol and reality, there may not be a large impact on CE as the difference is seen in both arms and in the model the patients waiting for surgery were assumed to have resource use as associated with the EF state"	We do not believe this to have major implications of the C/E as concluded by the ERG. Although the protocol states that definitive surgery should be done 3-6 weeks after the end of NA therapy (see section 7.1.2.9 Definitive Surgery), whether the surgery happens in that time frame is subject to many factors, such as additional time needed for recovery from NA treatment, complications like COVID, etc. Please add more context to the sentence.	Please add more context to the sentence.	This is not a factual inaccuracy. The ERG asked the company in clarification phase and used the information provided by the company at the time.

Issue 9 – Utility: appropriateness of utility values used in DM setting

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
Page 19, Table 1.12: Key issue 11; The ERG queries the validity of utility values that are used to inform the DM heath state of the economic model. The company has explained that KEYNOTE-522 data collection is currently ongoing and that a limited number of observations is available to inform the utility estimation for patients in the DM. We do not agree with the ERG's view which questions the validity of the utility values used to inform the economic model on the above basis. The value derived is reflective of the poor prognosis these patients experience once they develop a DM but also of the large % of patients which end up not receiving subsequent therapies for mTNBC which affects the DM utility generated	We propose the following sentence is amended from; "This causes doubts about the validity of the use of this utility value in the model." to ***"Therefore there may be uncertainty with regards to the DM utility value, although the company adhered to the NICE reference case to inform health state utilities". Whilst the company explored higher DM utility values from KEYNOTE-355 and KEYNOTE-119 as per ERG's request and these increased the ICERs, use of both sources to mode utilities has its own limitations."***	The proposed amendment offers a balanced view of why the use of KEYNOTE-522 data was preferred for the estimation of DM utility versus other sources, although exploration of other sources was conducted at the request of the ERG.	This is not a factual inaccuracy.

due to survival. The ERG's criticism also fails to account for the limitations associated with the use of alternative utility sources most notably that of KEYNOTE-119 which was conducted in 2L mTNBC patients.			
Page 92 – "b) the relatively low utility value for DM health state." "The utility for the health state DM is relatively low ([redacted]) compared to other studies". We explained why this may be the case. The utility value derived is reflective of the poor prognosis these patients experience once they develop a DM but also of the large % of patients which end up not receiving subsequent therapies for mTNBC which affects the DM utility generated considering the limited survival of those patients.	Please add more context to explain why the DM utility appears to be low, which is however reflective of the clinical data itself from KEYNOTE-522. Please add the following text; ***"A large % of patients across both treatment arms did not receive subsequent therapy in KEYNOTE-522 (see submission table 40) and therefore the limited survival profile may have affected the DM derived utility. Further, the PRO data collection is currently ongoing which may affect the values derived."***	As above	This is not a factual inaccuracy. The ERG worked with the explanations why DM utility appears to be low given by the company in the clarification phase, which did not mention their explanation suggested here.

Page 80; claims that the lack of desegregation of DM to pre and post -progression may lead to underestimation of the ICER is misleading "This potentially leads to under or overestimation of the ICER."	Please amend text to make clear that costs for 1L and 2L plus have been accurately reflected upon within the economic model using the latest data from KEYNOTE-355 and assumptions that have been critiqued by the AC. Whilst we understand that a single aggregate DM utility from KEYNOTE-522 applied in the model currently may not be fully representative, exploration of using inflated values whilst it increased the ICER marginally, therefore we would not expect the separation of DM to two health states and application of alternative utility values for these to have a significant impact on the ICER beyond what has already been quantified. We therefore request the addition of the following text "This potentially leads to under or overestimation of the ICER, ***although the company provided additional scenarios around DM utility which demonstrated a marginal increase in the ICER".***	MSD is concerned by the fact that the current write up of this issue leaves ambiguity to the read as to whether the DM health state can adequately capture the costs associated at pre- and post-progression whilst on DM which is not the case. Scenarios with alternative utilities are explored to address the utility impact at DM setting.	This is not a factual inaccuracy.

Issue 10 – Comments on perceived model errors corrected by the ERG

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
ERG perceived error 1: Page 90, 102, 105, The base case company model assumed patients in the chemotherapy arm to not receive pembrolizumab when they metastasize. The EAG revised the model to enable pembrolizumab 1L treatment in the DM state for patients in the chemotherapy arm. The ERG believes this to be an error in the model and corrected for this in its base case."	This is not error but reflected the actual treatment pathway when the submission took place in November 2021 since NICE had not recommended at that time pembrolizumab in combination with Taxanes (ID1546)[v] which is the case currently. Please add this to make clear the justification around this assumption. We note that some assumptions pertaining to scenarios around the downstream treatment pathway may need to be revisited which may affect options across both treatment arms.	Add more context and note that revisions may need to be made on the base-case assumptions during the TE process to reflect the pathway updates.	In the company base-case, there was a difference regarding the possibility for pembrolizumab between the 50/50 and 17/83 split scenarios for pembrolizumab and atezolizumab. This is visible on worksheet 'Raw_DM trt share' where for chemotherapy the pembrolizumab share was 0% for the 50/50 scenario (base-case) in line with IO-eligible share, but 6% for the 17/83 scenario, in line with rechallenge-eligible share. This made the ERG conclude that chemotherapy patients would be eligible for pembrolizumab overall. If the company believes this is not correct then the 17/83 scenario was also not correct in the first place, or the description of the scenarios was not clear as there were other

			differences between them then only the proportion pembrolizumab versus atezolizumab.
ERG perceived error 2: Page 88 and 90, 102 - adjustment of transition probabilities from competing risks to account for all-cause mortality *"adjustment of general mortality in the formula for EF and LR to death by subtracting transitions to other states."* In the company model, the probabilities of EF and LR to death were constrained by the general population mortality. The adjustment of the general mortality was made by subtracting transition probabilities from the EF and LR state to states other than death. The EAG revised the formula to cap probability of EF and LR to death by the general population mortality directly.	We disagree with the change made by the EAG. The approach to adjust the general mortality should be reverted back to one used in the original company model. Please add the following context for clarity; This is NOT a programming error. The transition probability of EF à death in the model does not mean "the probability of death", instead it represents "the probability that patients die AND death occurs before LR/DM". For example, if patients in the EF state are subject to the risk of three events: natural death, LR and DM, some patients will experience LR/DM before natural death and therefore contribute to the transitions of EF à LR or EF à DM. In this case, the proportion of patients having EF à death (death before LR/DM) are lower than the natural mortality rate. More natural death events will happen after the cohort experience LR/DM, which are taken into account in the transitions LRà death and DM à death. The same logic applies to transition probability formular for LR à death. If the	LR, DM, and death are competing risks for patients who are event-free. The probability from EF to death should be constrained by general mortality, subtracting probability from EF to LR and EF to DM. Similarly, the probability from LR to death should be constrained by general mortality, subtracting probability from LR to DM. **Please revert the formula in the model back to the original given the explanation which has been provided.**	The ERG still perceives this to be logical error, if not programming error. The main aim of correcting for general population mortality is that mortality of the model population does not fall below mortality of the general population. By correcting the general population mortality downwards, the resulting mortality actually applied in the health state could still end up being lower than general population mortality. And so the whole idea of the correction does not work out in this way. The mortality rate used for this correction can only be the crude general population mortality, without any changes.

	formular for the transition probabilities are changed to the ones suggested by ERG, the mortality rates will be overestimated. However, this change should not result in a higher ICER. Instead it should favor against chemotherapy arm which has higher recurrence rate.		

Issue 11 – Analyses presented by the ERG are not in line with NICE's HTA evaluation manual.

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
Page 12, 15 - Inferences around the perceived geographical effects on HR of EFS and preference of subgroup results to be used to inform the base-case assumptions. Specific text includes; *"small subset of participants were from the UK. Subgroup analysis, based on a small dataset, suggests that geographical area is an important covariate influencing outcome, and so the observed effects may not be applicable to the UK."*	Please note that subgroup analyses are not intended to be used for inferential testing as the study was not powered for definitive demonstrations of efficacy in these subgroups. Therefore, the results of these exploratory analyses should be interpreted with caution and should not be used by the ERG to inform the C/E assumptions formulating the base-case. Please add the following text to reflect this; " … and so the observed effects may not be applicable to the UK. ***However, the extend of this influence cannot be ascertained because the study was not powered to detect differences between subgroups and therefore the C/E results using this***	MSD is concerned with the ERG's interpretation around the presence of geographical effects when the study was not powered to detect such differences. We are also extremely concerned for the fact that this preference is then carried through to the C/E base-case assumptions.	This is not a factual inaccuracy. Moreover, the ERG did not use any UK-specific estimate in the economic model, as no UK-specific estimate was made available. The economic model uses the 'Europe versus rest of the world' HR as a proxy for a potential UK specific estimate.

	estimate should also be interpreted with caution."		
Page 20, 21, 104, 106, 107, 112 – scenario presented restricting the time horizon to 5 years is irrelevant and against the NICE methods manual whereby it is stated that "Analyses that limit the time horizon to periods shorter than the expected effect of the technology do not usually provide the best estimates of benefits and costs"[vi]. Please remove this scenario and any notions around this altogether from the ERG report or position it in a way that makes clear to the reader these violations. MSD is very concerned that such a scenario has been included in the ERG report and explored a number of times.	The scenario presented by the ERG whereby the TH is truncated to 5 years is altogether irrelevant and violates the NICE methods of evaluation manual. It is therefore also highly misleading for the reader and should be completely removed or positioned in a way that makes this clear to the reader.	The scenario presented by the ERG is altogether irrelevant and violates the NICE methods of evaluation manual. It is therefore also highly misleading for the reader and should be completely removed or positioned in a way that makes this clear to the reader.	This is not a factual inaccuracy. See also response to issue 6.
Page 15, 104, 45 – "The company did not provide similar data for a UK patient subgroup."	Please note that subgroup analyses are not intended to be used for inferential testing as the study was not powered for definitive demonstrations of efficacy in these subgroups. Therefore, the results	The scenario presented by the ERG is altogether irrelevant and violates the NICE methods of evaluation manual. It is therefore also highly misleading	This is not a factual inaccuracy, see also above.

"UK-specific data would help in addressing this issue." The company has explained that it is not feasible to conduct a survival analysis on a very small subgroup of UK patients only (n=[redacted]). The numbers of participants are too small for a meaningful subgroup efficacy analysis.	of these exploratory analyses should be interpreted with caution and should not be used by the ERG to inform the C/E assumptions formulating the base-case. The number of UK participants is too small for a meaningful subgroup efficacy analysis. Please add clarity that it is neither feasible nor possible to conduct a UK specific subgroup analysis and delete such statements from the issue deception. Please also add a note to state that; "***The manufacturer explained that the UK specific subgroup is too small for a meaningful efficacy subgroup analysis. The study was not powered to detect differences between subgroups and therefore the C/E results using this estimate should also be interpreted with caution.***"	for the reader and should be completely removed or positioned in a way that makes this clear to the reader.	
Page 16, 17 - The ERG states that "but the data suggest that patients with an ECOG status of 1 are unlikely to benefit from pembrolizumab (and there is a probability that the drug could even cause harm in this group, although this is uncertain)." , "…	Please note that subgroup analyses are not intended to be used for inferential testing as the study was not powered for definitive demonstrations of efficacy in these subgroups. Therefore, the results of these exploratory analyses should be interpreted with caution. There is no biological reason as to why an ECOG =1 patient would not be expected to benefit	We are very concerned with the ERG's interpretation of the clinical evidence and its attempt to interpret the risk/benefit profile of the intervention which has been already ascertained by the regulatory authority. We are also very concerned by the ERG's statement that ECOG =1	This is not a factual inaccuracy, please note earlier comments regarding power.

ECOG = 1 they are probably not going to experience benefits from pembrolizumab." Please note that subgroup analyses are not intended to be used for inferential testing as the study was not powered for definitive demonstrations of efficacy in these subgroups. Therefore, the results of these exploratory analyses should be interpreted with caution. There is no biological reason as to why an ECOG =1 patient would not be expected to benefit from neoadjuvant followed by adjuvant therapy. Please remove any references associated with the risk/benefit profile of the intervention. The regulatory authority has concluded on the benefits outweighing risks.	from neoadjuvant followed by adjuvant therapy. Please remove any references associated with the risk/benefit profile of the intervention. The regulatory authority has concluded on the benefits outweighing risks. Please amend the wording of this issue accordingly noting the above limitations.	patients may not experience the benefit of pembrolizumab.	

Issue 12 – Data availability

Description of problem	Description of proposed amendment	Justification for amendment	ERG comments
Page 70, section 3.2.8 – ongoing studies; The EAG report includes the response provided from MSD pertaining to the availability of IA5 from KEYNOTE-522. [redacted]	Please add as commercial in confidence the following working pertaining to the availability of IA5. “MSD have informed the ERG that [redacted]	The proposed amendment adds clarity with regards to the availability of IA5 for further processing[redacted]	This is not a factual inaccuracy

Section 2: Marking of confidential information

Location of incorrect marking	Description of incorrect marking	Amended marking
NA	NA	NA

Section 3: Typographical errors

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG comment
Page 46 - cyclophosamide	Please correct typographical error to “cyclophosphamide”	This is error in our part that was carried over in the ERG report.	Changed accordingly
Page 48 - KEYNOTE-52	Please change to KEYNOTE-522	Typographical error	Changed accordingly
Page 60 – the trial under consideration is KEYNOTE-522	Please change to KEYNOTE-522	Typographical error	Changed accordingly
Page 6, 47, 50, 51 52 – KEYNOTE 716	Please change to KEYNOTE-522	Typographical error	Changed accordingly
Page 53 – “Randomisation process stated as “Unclear” on ERG’s assessment	Bias assessment should be changed to “Low” – study was double-blinded.	Please correct assessment or justify further.	The process of randomisation and the state of being ‘double blinded’ are quite different, please refer to the Cochrane Handbook for further details, see https://training.cochrane.org/handbook/current/chapter-08

			Randomisation was stated as 'unclear' because allocation concealment was not adequately reported.
Page 57 - CCOG	Please change to ECOG	Typographical error	Changed accordingly
Page 90 – "arm and up in LR and DM"	"end up in LR and DM"	Typographical error	Changed accordingly
Page 97 – typographical error - "The ERG considers that even when KEYNOTE-533…"	The ERG is referring to KEYNOTE-355 – please correct this.	Typographical error	Changed accordingly
Page 42 "The company directed the ERG to "Table 23 in the CS Appendix which was supposed to summarise the most frequently used concomitant medications …. (Table 23 in the appendices detailed adverse events"	We apologise for the error in our part. This can be provided at TE stage.	N/A	N/A

References

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[ii] Nanda, R., Liu, M.C., Yau, C., Shatsky, R., Pusztai, L., Wallace, A., Chien, A.J., Forero-Torres, A., Ellis, E., Han, H. and Clark, A., 2020. Effect of pembrolizumab plus neoadjuvant chemotherapy on pathologic complete response in women with early-stage breast cancer: an analysis of the ongoing phase 2 adaptively randomized I-SPY2 trial. *JAMA oncology*, *6*(5), pp.676-684.

[iii] Park, I.H., Im, S.A., Jung, K.H., Sohn, J.H., Park, Y.H., Lee, K.S., Sim, S.H., Park, K.H., Kim, J.H., Nam, B.H. and Kim, H.J., 2019. Randomized open label phase III trial of irinotecan plus capecitabine versus capecitabine monotherapy in patients with metastatic breast cancer previously treated with anthracycline and taxane: PROCEED trial (KCSG BR 11-01). *Cancer Research and Treatment: Official Journal of Korean Cancer Association*, *51*(1), p.43.

[iv] Haines, P., Tremblay, G. and Briggs, A., 2015. A criterion-based approach for the systematic and transparent extrapolation of clinical trial survival data. *Journal of Health Economics and Outcomes Research*, *2*(2), pp.147-160.

[v] NICE ID1546: https://www.nice.org.uk/guidance/indevelopment/gid-ta10417/documents

[vi] NICE methods manual – 2022; https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation#the-reference-case-framework

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pembrolizumab in combination with chemotherapy for neoadjuvant and adjuvant treatment of triple negative breast cancer [ID1500]

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 **Wednesday 20 July.** 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.

NICE National Institute for Health and Care Excellence

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.	**None**

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
1. Choice of population	No	**MSD would like to highlight the reasons for the differences between the company submission and the original NICE Scope detailed in the ERG report. An updated final scope has since been issued by NICE to reflect the final marketing authorisation licence as it had omitted the word 'early'. The population stated in the company submission is in line with the final licensed population.** The population is different as during the scoping process the EMA dossier was being assessed and therefore the anticipated licence was marked as Commercial In Confidence (CIC). The data presented by MSD is in line with the licence issued by the MHRA. The licence wording is as follows "[pembrolizumab] in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence"

		• **Centrally confirmed:** Centrally confirmed is not part of the licence wording and is reflective of the trial design. It not anticipated that patients will be required to have their TNBC status confirmed by a central NHS laboratory. • **Inflammatory**: The use of the word inflammatory was not to provide a second category of patients, but to show that patients with inflammatory breast cancer were eligible for the study if they met the other criteria. • **High risk of recurrence**: The wording regarding high risk of recurrence was provided to NICE but was marked as CIC and therefore could not be publicly shared in the final scope. • **Early stage**: During the Technical Engagement call on the 30th of June 2022, it was noted by NICE that the words 'early stage' had been inadvertently omitted from the population wording in the scope document. A new scope was issued on 5th July 2022 which means this issue can be resolved. • **PS 0 or 1**: Patients needed to have a performance status of 0 to 1 to be eligible for the trial. PS is not included as part of the licence wording in any pembrolizumab indications. There is no data from KEYNOTE-522 for patients with PS 2. **MSD considers that the population stated in the company submission is in line with the final licensed population.**
2. Choice of comparator	No	The ERG discussed the implication of the potential use of adjuvant capecitabine instead of placebo. MSD has provided scientific rationale as to why capecitabine as active comparator in the adjuvant phase is irrelevant for this submission. **MSD disagrees that capecitabine should be considered a comparator in the adjuvant setting for the population under consideration**. Our arguments are below. We note the ERG's comment that 'current practice does not commonly use adjuvant therapies (such as capecitabine)' therefore the trial is generalisable to the UK setting and the efficacy result reported is reflective of the efficacy gain expected in routine clinical practice in the UK. To include

capecitabine, which is not standard of care, would provide information extraneous to the decision problem. MSD provides additional detail of why capecitabine cannot and should not be included in the appraisal.

There are population and trial design differences between KEYNOTE-522 and CREATE-X, please see table 1 for details. In the CREATE-X study, the neoadjuvant chemotherapy did not include carboplatin, so it is not known whether post-neoadjuvant capecitabine provides similar benefit after a platinum-containing neoadjuvant regimen (as in KN522) compared to a platinum-free neoadjuvant regimen (as in CREATE-X). Furthermore, it is unclear whether post-neoadjuvant capecitabine improves long term survival after neoadjuvant use of immunotherapy (as in KN522) compared to CREATE-X where neoadjuvant treatment was only chemotherapy.

It is not possible to compare the use of pembrolizumab in the adjuvant phase with adjuvant capecitabine as these patients also received pembrolizumab in the neoadjuvant phase. The CREATE-X study results and the recommendation by oncology societies that capecitabine is an option for patients with TNBC and non-pCR after neoadjuvant chemotherapy came while KN522 was actively accruing patients, about mid-way during the enrolment period. At that time, the FDA was consulted about possibly including post-neoadjuvant capecitabine in KN522, but the feedback was that such a change while the study was already ongoing and at an advanced stage would negativity impact the interpretability and regulatory validity of the results. (1)

Table 1: Comparison of KEYNOTE-522 and CREATE-X trials

	KEYNOTE-522 n=1,174	**CREATE-X n=910 (2)**
Population	Patients with untreated newly diagnosed, locally advanced, centrally confirmed TNBC.	Patients with HER2-negative residual invasive breast cancer after neoadjuvant chemotherapy and surgery

Intervention	Pembrolizumab plus chemotherapy in the neoadjuvant phase followed by monotherapy pembrolizumab in the adjuvant phase.	Adjuvant capecitabine
Comparator	Placebo plus chemotherapy in the neoadjuvant phase followed by monotherapy placebo in the adjuvant phase	Placebo
Primary Outcomes	pCR, EFS	DFS
Number of patients from centres in Europe	434	0
Abbreviations: DFS (and definition), EFS, pCR		

MSD is aware that capecitabine as adjuvant therapy is not indicated specifically for TNBC patients (3). The cost of adjuvant capecitabine is very limited (capecitabine has a very low drug acquisition cost and is administered orally). From a costing perspective, hospital treatment protocols dictate 6 to 8 cycles or capecitabine as adjuvant (however, again this is not TNBC specific) (4). Since this may only be used in a limited subset of patients (as noted by clinical opinion) the implications form a costing and cost-effectiveness perspective are extremely limited. Clinical experts consulted during the technical engagement process, reiterated the statements made in the company submission, and that the use of adjuvant capecitabine is very limited and associated with limited survival benefit. They also noted that it was only offered because of the lack of effective alternative treatment options.

MSD does not consider that capecitabine in the adjuvant setting is a relevant comparator for this submission and for the population under consideration. It is neither possible nor appropriate to leverage the results from the CREATE-X study to inform such comparisons.

3. Geographical effects	No	**MSD disagrees that 'overall data in the trial might be providing an overly optimistic picture for European patients.' Also, the subgroup analyses are not intended to be used for inferential testing as the study was not powered for definitive demonstrations of efficacy in these subgroups. Therefore, the results of these exploratory analyses should be interpreted with caution.** In KEYNOTE-522, 40 (3.4%) participants were from UK: 27 participants were in the pembrolizumab group and 13 participants were in the placebo group. The numbers of participants are too small for a meaningful subgroup efficacy analysis. The ad-hoc analyses of testing interactions of treatment and subgroup variable of geographic region (Europe/Israel/North America/Australia, Asia, and Rest of World) were performed. The study was not powered to carry out statistical testing for interaction and there were no multiplicity adjustments for multiple testing in the subgroup analyses. Therefore, the results need to be interpreted with caution. A Cox regression model with covariates for treatment, a subgroup variable, and treatment by subgroup variable interaction was performed. The p-value of 0.1843 was greater than 0.1, which indicates the treatment effect is not likely to differ across strata within geographic region (no plausible quantitative effect modifier observed of geographic region). **To MSD's knowledge there is no robust evidence which suggests that geographical region is a treatment effect modifier in the context of neoadjuvant and adjuvant therapy in this population. MSD asserts that the base-case should be based on the full trial population as the basis of the cost-effectiveness analysis.**
4. TNM staging	Yes	**MSD is able to provide reassurance to the ERG the ratio of TNM in KEYNOTE-522 is equivalent to ratios of TNM in the UK population to allow a better judgement on the external validity of the trial.**

		MSD is currently undertaking a study using data from the English Cancer Registry investigating those patients diagnosed with TNBC between 01/01/2015 and 31/12/2018. TNM information on patients is displayed below (Figure 1) and shows a similar distribution to that observed in KEYNOTE-522. **Figure 1: Comparison of TNM in KEYNOTE-522 and patients in England**  **The data presented provides external validation that the TNM ratios in England are similar to those in KEYNOTE-522 and there would be no reason to assume outcomes would be different.**
5. ECOG staging	No	The ERG concludes that for people with an ECOG score of 1, pembrolizumab is unlikely to be cost effective after looking at subgroup analysis results for EFS. The ERG argues that more evidence may be required for ECOG PS=1 for decision purposes. **MSD considers that the population of KEYNOTE-522 covers ECOG PS 0 and 1 patients. KEYNOTE-522 was not statistically powered to ascertain clinical differences within this subgroup. There is no biological rationale on why the clinical benefit of PS =1 patients would differ, noting that PS clinical distinction between these two subgroups can be sometimes vague.** MSD would like to reiterate the clarification questions response: subgroup analyses were not intended to be used for inferential testing as the study was not powered for definitive demonstrations of efficacy in these subgroups or formally compare efficacy between subgroups. Therefore, the results of these exploratory analyses should be interpreted with caution. In addition, the number of patients with ECOG PS of 1 is relatively small (106 participants in pembrolizumab group and 49 participants in placebo group), and so caution should be taken in interpreting efficacy

		differences between these two groups. The treatment difference for pCR, Hazard Ratios (HRs) for EFS and OS between treatments had overlapping confidence intervals in participants with ECOG PS of 1 and ECOG PS of 0 (as shown in figures 3.1 and 3.2 of the ERG report). **MSD asserts that the base-case should be based on the full trial population as the basis of the cost-effectiveness analysis.**
6. Adverse events	No	**MSD acknowledges there is a difference between the percentage of serious adverse events between the two arms in KEYNOTE-522. This reflects the safety profile of adding pembrolizumab to neoadjuvant chemotherapy administered.** As noted by the EAG, the incidence of AEs leading to death was 0.9% in the experimental arm compared to 0.3% in the control arm. No specific AE resulting in death was reported in more than 1 participant. No new safety signals were identified upon review of these fatal events. Pembrolizumab is established in other tumour groups and recently approved for metastatic TNBC where clinicians are comfortable in its use and management of adverse events. **There were no specific trends noted for the pembrolizumab group that suggest a new safety concern.**

7. Model structure not including locoregional remission and no differentiation between pre-progression and post-progression distant metastatic patients. Model may not adequately capture costs and benefits.	No	It is important the structure and the rationale for the structure of the economic model are well understood. MSD's response to this issue aims to address some missing information and possibly clear any misunderstanding about why the model is structured as it is and around the model mechanics. Points raised below include "Remission" after locoregional recurrence (LR) and the value of separating the pre and post-progression at distant metastasis (DM) health state. The ERG states that current model structure which does not include a "Remission from locoregional recurrence (LR)" and separate "pre- and post-progression states for distant metastasis (DM)" may not reflect clinical practice. The ERG argues that the current model may not capture correctly subsequent costs and health benefits associated with these health states. The criticism in the current model structure arises from the fact that MSD's model deviates from the TA424 model structure which was designed to explore the cost-effectiveness of pertuzumab as neoadjuvant treatment for early-stage HER2-positive breast cancer. **MSD disagrees with the ERG's opinion and is confident that the current model structure adequately captures costs and benefits of the TNBC pathway. As with all models, balancing optimal model structure with available data is key. Driving the structure of this model, and where it is different to other breast cancer models, is that there is substantial less data for TNBC. We note that TNBC data in contrast to other BCs such as HER2+ve are limited. This does not allow more complex modelling and multiple health states without imposing assumptions adding to the model complexity and uncertainty (such as explicit "Remission" modelling after locoregional recurrence (LR) or for the differentiation of the distant metastasis (DM) in pre and post-progression. The current model adequately captures downstream costs and benefits for decision making purposes without adding to unnecessary complexity and is similar to that of other recent adjuvant submissions including TA766.** The justification to deviate from the published TA424 model structure is re-iterated below alongside some additional explanation pertaining to the functionality of the current model. We demonstrate that the current model structure sufficiently

		captures all relevant costs and outcomes associated with the management TNBC in both the locoregional and distant setting. The current submission leverages a Markov model to estimate costs and outcomes, consisting of four mutually exclusive health states; event-free (EF), locoregional recurrence (LR), distant metastasis (DM), and death, to track the disease course and survival of patients over time. This model structure explicitly captures the disease pathway of patients with early-stage TNBC as well as including the functionality to model metastatic outcomes with appropriate accuracy. The model can differentiate health states by type of recurrence (either LR or DM) because the co-primary endpoint of the KEYNOTE-522 (i.e., EFS) trial encompasses both types of recurrence events and because these are relevant for the clinical management of patients. These two types of recurrences have different implications on patients' prognoses, and therefore result in different health outcomes and costs which is important from a decision-making perspective. Lack of "Remission" after locoregional recurrence (LR) in ID1500: **MSD interprets "Remission" as the absence of cancer specific symptoms or evidence of detectable disease at a specific timepoint. Remission does not necessarily preclude further progression to metastatic disease and subsequent death from cancer. Clinical experts consider that the exclusion of "Remission" after LR is clinically valid due the aggressiveness of TNBC versus other types of breast cancer. They indicated that the majority of patients with locoregional recurrence would not be salvageable with subsequent surgical resection and therefore have poor prognosis (i.e., develop a DM or die). Therefore, we consider the lack of remission modelling after LR to be appropriate and therefore the model can accurately capture costs and outcomes associated with TNBC.** The current clinical data from KEYNOTE-522 do not provide any evidence of remission after a locoregional recurrence. Analysis of pooled treatment arm clinical trial data from KEYNOTE-522 shows that most patients which develop an LR event, experience DM or death (Figure 2).

		Therefore, Remission after a LR is not substantiated by the clinical trial data itself and would be reliant upon additional assumptions being imposed in the economic model itself. This assumption alongside the current model structure were both validated during a global advisory board which took place during the submission development process ([redacted]). UK clinical experts were also presented with the CE model structure at a UK advisory board during the submission development process and considered the model structure appropriate in the context of TNBC. **Figure 2: Observed combined KEYNOTE-522 arms time to event (TTE) from LR in weeks (event = distant metastasis or death from LR).** [redacted] Notes: TTE = Time to Event, reported in Weeks with event being equal to distant metastasis or death. MSD is limited to the extend it can comment on a manufacturer's submission without visibility of the full data. In the NICE TA424 (Pertuzumab for Neoadjuvant Treatment of Early-Stage HER2-Positive Breast Cancer) patients could enter the "Remission" health state after locoregional recurrence. In TA424, the manufacturer introduced a series of tunnel states to model locoregional recurrence, therefore artificially superimposing a time dependency (i.e., that 12 months must be spent in LR before entering "Remission") in part of the economic model. Only after LR had taken place could these patients enter the "Remission" health state and therefore influence the subsequent health state occupancy. Whilst patients remained in the LR tunnel states, they could not experience a further progression or death event for 12 months which is a simplistic and implausible assumption considering the KEYNOTE-522 clinical trial data and expert opinion. **Therefore, the** "**Remission" health state in TA424 in fact resembles the "Locoregional recurrence" of this submission without adding unnecessary complexity with the introduction of tunnel states that may not be appropriate for TNBC considering its aggressiveness and poor prognosis vs HER2+ve BC.** The overall approach used in TA424 was relevant for decision making purposes at the time, this assessment took into consideration the RCT design and trial endpoints support the TA424

		recommendation. This does not necessarily mean that the same modelling approach would be appropriate for TNBC given the population and trial differences (primary outcome differences, re-challenge in adjuvant setting). The availability of clinical data and clinical endpoints reported in TNBC is not as extensive as in HER2+ve BC since very limited changes in the TNBC treatment pathway have taken place over the last 2 decades. Therefore, evidence would not be derived from clinical studies but rather be based upon arbitrary assumptions leading to model complexity (and thus inflate uncertainty further in contract to the KEYNOTE-522 clinical data itself). Page 79 of the ERG report reads; *"The ERG acknowledges the differences between TA424 and the current submission and agrees with the company that the introduction of a remission state is not ideal, as it would increase the model's complexity by introducing multiple tunnel states to the model."* However, the ERG still concludes that omitting the "Remission" post LR may not reflect clinical practice (page 79); "*However, assuming patients with LR cannot experience remission does simply not reflect clinical practice*". This thesis appears to be counter-intuitive considering the evidence base and the justification provided by MSD in terms of modelling. During the technical engagement process a UK clinical expert was consulted by MSD to test further the validity of this assumption at the request of the ERG (expressed during the technical engagement call). Considering the differences between HER-2+ve cancer (TA424) and TNBC, the clinical expert concluded that it is clinically justified not to model a "Remission" health state after a locoregional recurrence in TNBC. The support of this was on the basis that TNBC is more aggressive versus other early breast cancer such as HER-2+ve. Based on their clinical experience, the clinical expert noted that the majority of TNBC patients with LR would not be salvageable with subsequent surgical resection (i.e., they would not have an isolated LR recurrence) and would therefore be anticipated to experience a poor prognosis once at LR with wither progression to DM or death. They noted that only a very small proportion of patients with isolated LR would be surgically salvageable (therefore the implications in the C/E are likely to be very limited). The clinical expert concluded that the TA424 model structure is not reflective of TNBC's aggressiveness and availability of data in TNBC versus other early BC tumours.

		The current model employs a conservative assumption which assumes equal transition probabilities for patients within LR using pooled trial arm data and therefore, no further potential treatment benefit once patients depart from the EF health state (owning to limited data available to inform treatment specific estimates. **The exclusion of "Remission" from current model structure is appropriate considering the current KEYNOTE-522 clinical data, data from overall TNBC patients and the clinical expert option. MSD therefore considers that the current model structure adequately captures the clinical outcomes experienced by patients and avoids introducing unnecessary complexity and uncertainty.** <u>No differentiation between pre and post-progression at distant metastasis (DM) health state:</u> The current economic model does not disaggregate the DM health state to pre-progressed and post-progressed DM and instead a single DM health state is used to model the survival from that health state which is based on the recent KEYNOTE-355 trial (alongside a network meta-analysis [NMA] to inform some comparisons). Costs for 1L mTNBC were calculated from KEYNOTE-355 and results from the NMA for some comparators. Costs for 2L+ subsequent therapies have been accounted for by using the most recent data from KEYNOTE-355 (TA801). MSD acknowledges that the current single DM health state approach may introduce some limitations with regards to ascertaining the impact of DM-post-progression utility (discussed separately below). The decision for single DM health state was taken to avoid unnecessary complexity within the current submission since the evidence base for mTNBC in contrast to HER2-ve BC is more limited and would therefore require assumptions and more complex artificially increasing uncertainty. UK clinical experts were presented with the CE model structure at a UK advisory board during the submission development process and considered the model structure appropriate in the context of TNBC.

		Metastatic TNBC lacked effective treatment options until recently with the introduction of anti-PD-1 and anti-PD-L1 agents such as Atezolizumab + nab-paclitaxel and pembrolizumab + taxanes for 1L mTNBC treatment options in PD-L1 +ve tumours (PD-L1 +ve ascertainment differs between options). The above approvals had a positive impact on patient long term survival but are treatment options for ~38% of patients with PD-L1 +ve tumours. The majority of patients (~62%) are PD-L1 -ve (or for whom PD-L1 test is not preformed) would therefore continue to be treated with standard of care chemotherapy options (such as taxanes or platins) for 1L mTNBC disease. Overall, for these patients treatment options may include gemcitabine with or without carboplatin or taxanes (paclitaxel or, nab-paclitaxel). However, it is understood that all standard 1L mTNBC and subsequent chemotherapy treatments offer limited survival extension (i.e., the survival benefit is primarily conferred by the 1L mTNBC option received once patients develop a distant metastasis). **The current DM modelling is not dissimilar with previous adjuvant submissions recently reviewed by NICE (some brief examples presented below). A few examples briefly described included TA766, TA544 and the ongoing ID3810. The methodology of the current model and its functionality is explained in more detail below.** • In TA766 - pembrolizumab as adjuvant treatment for stage 3 resected melanoma; a single DM health state was constructed; survival from DM was based upon a composite OS curve derived from OS NMA results weighted by market shares validated by HCPs. Subsequent treatment cost for 1L mMEL were estimated based on a PFS NMA weighted by the same market shares, one off weighted 2L+ costs were applied assuming a maximum treatment duration of 21 weeks (5). • In TA544 - dabrafenib/trametinib adjuvant resected stage 3 melanoma; the manufacturer applied a one off cost and QALY gain for 1L+ therapies extracted from previous TA not formally incorporating DM survival within the economic model (6). • Ongoing ID3810 – Pembrolizumab for adjuvant RCC; 1L line costs ad 2nd line costs were estimated and applied in a single DM health state; efficacy from DM to death is derived based upon 1 1L mRCC NMA for PFS and OS (7).

		The current single DM health state allows for the incorporation of the AC's recent preferences pertaining to anticipated DM survival based on TA801 for key 1L comparators. This ensures that the model predicts robust survival estimates for the DM patients. Therefore the current single DM health state adequately captures metastatic treatment and disease management costs appropriately. <u>Approach to model 1L+ survival:</u> Market research was conducted to understand the utilisation of 1L mTNBC treatment options across the UK. Clinical experts noted that the most likely 1st line chemotherapy options for patients with 1L mTNBC included; paclitaxel, carboplatin (or combination of), gemcitabine + carboplatin or capecitabine. These are available regardless of PD-L1 tumour status. However, patients with PD-L1 positive mTNBC (≥1% immunohistochemistry SP142) would at the time of this submission would likely be treated with Atezolizumab + nab-paclitaxel in the UK since TA801 was ongoing. Clinical experts were consulted to validate the market share (MS) treatment mix of 1L mTNBC during an advisory board (final values used in the model are presented in Table 2). **Table 2: UK market shares for 1L mTNBC treatment options validated by UK HCPs**

Treatment regimen	UK market research share estimate	Updated TE model market share estimates with rechallenge validated by HCPs
Pembrolizumab + taxanes	0% (unavailable at time of submission)	~6.46% (17% of PD-L1 +ve patients)#
Paclitaxel	[redacted]	[redacted]
Paclitaxel monotherapy	[redacted]	
Nab-paclitaxel monotherapy	[redacted]	
Carboplatin	[redacted]	[redacted]
Carboplatin monotherapy	[redacted]	
Carboplatin + Docetaxel	[redacted]	
Carboplatin + Epirubicin	[redacted]	
Carboplatin + Paclitaxel	[redacted]	[redacted]
Gemcitabine + Carboplatin	[redacted]	[redacted]
Atezolizumab + Nab-paclitaxel*	[redacted]	~31.54% (~83% of 38% of mTNBC PD-L1 +ve patients overall)#
Capecitabine	[redacted]	[redacted]

Notes: *Final estimates uplifted to match the prevalence of PD-L1 positive IC population ~38%, # The original base-case did not assume pembrolizumab rechallenge for DM disease due to the lack of pembrolizumab + taxanes at the time - the table above presents the actual market share data with pembrolizumab rechallenge and assuming that pembrolizumab + taxanes is available for 22C2+ve/SP=142-ve patients only (17%)

KEYNOTE-355 overall survival data (total life year estimates) were extracted from the TA801 cost-effectiveness model where available. This included 1L mTNBC survival estimates from the Pembrolizumab + taxanes (paclitaxel or nab-paclitaxel) and paclitaxel chemotherapy arms which were recently discussed by the AC. The TA801 model also included survival projections for alternative comparators such as gemcitabine + carboplatin. The carboplatin + paclitaxel comparator was not directly modelled in TA801 CEA and upon expert opinion was assumed to have equal survival benefit to gemcitabine + carboplatin due to lack of clinical trials in the metastatic setting to inform alternative assumptions. For carboplatin monotherapy (or

		combinations with epirubicin) survival was estimated by applying a NMA derived OS HR versus taxanes (it is assumed that add on epirubicin does not to confer an additional survival benefit due to lack of clinical trials in the mTNBC to inform alternative assumptions). Capecitabine for 1L mTNBC disease not directly modelled in TA801 CEA. Due to lack of clinical literature in mTNBC to inform an indirect comparison versus other 1LMTNBC options, it was assumed to have equal survival benefit to taxanes from KEYNOTE-355. Survival of Atezolizumab + nab-paclitaxel was estimated using the NMA OS HR results of Atezolizumab + nab-paclitaxel versus Pembrolizumab + taxanes (paclitaxel/nab-paclitaxel). Based on clinical expert opinion sought by MSD and AC deliberations during TA639 and TA801, MSD understands that taxanes can be perceived to be equally efficacious (although differences in the toxicity/safety profile may exist). Therefore the use of pooled taxane arm data from KEYNOTE-355 to inform the NMA estimates is appropriate. The average survival benefit for all 1L mTNBC treatment options was finally weighted by the clinical expert validated MS estimates to derive an average survival for proportion of patients at the DM setting which received 1L+ metastatic therapy. No differences in the distribution of 1L mTNBC treatment received, apart from allowing for Pembrolizumab rechallenge for 1L mTNBC in PD-L1 +ve patients after 2 years of neoadjuvant/adjuvant initiation (this assumption was informed based on previous clinical experience from adjuvant melanoma). In KEYNOTE-522, [redacted] of patients will not receive 1L treatment for metastatic TNBC in the pembrolizumab arm and [redacted] in the placebo arm. Therefore, RWE evidence was sourced to inform the mean DM survival for those patients (Aly et al 2019) as these patients are likely to experience a shorter survival. <u>Estimation of mTNBC treatment costs (1L and subsequent 2L+ costs):</u> We provide additional information on the method used to estimate the 1L mTNBC treatment costs to alleviate the ERG's concerns of imprecision around these (page 97 of ERG report). In brief, an approach similar to that outlined above for survival was used.

		Time of treatment data (ToT) from KEYNOTE-355 were extracted from the TA801 cost-effectiveness model where available. This included 1L mTNBC ToT from the Pembrolizumab + taxanes (paclitaxel or nab-paclitaxel) and paclitaxel chemotherapy arms (equal efficacy is assumed between paclitaxel and nab-paclitaxel) which were recently discussed by the AC. The TA801 model also included actual ToT data for alternative comparators such as gemcitabine + carboplatin where available. The carboplatin + paclitaxel comparator was not directly modelled in TA801 CEA. Since equal survival benefit assumed with gemcitabine + carboplatin, equal ToT was also assumed. For carboplatin monotherapy (or combinations with epirubicin) ToT was estimated by applying a NMA derived PFS HR versus taxanes. No evidence was derived for capecitabine as 1L mTNBC, therefore ToT was assumed to have equal survival benefit to taxanes from KEYNOTE-355. The ToT data for Atezolizumab + nab-paclitaxel were assumed to be equal to PFS projections estimated through an NMA of Pembrolizumab + taxanes versus Atezolizumab + nab-paclitaxel. During the TE process, an alternative exploratory scenario for Atezolizumab + nab-paclitaxel ToT was introduced which uses directly the ToT data from pembrolizumab + taxanes instead of the PFS NMA. The area under the curve was estimated for each of the 1L mTNBC treatment options to derive the mean ToT for each of these comparators. The total drug acquisition cost for each of the 1st line mTNBC treatment options modelled (including IV infusion costs where appropriate) were then estimated. A weighted total 1L mTNBC treatment cost was then derived based on the anticipated market shares presented in Table 2 . These were validated by UK HCPs and factor in pembrolizumab rechallenge for 1L metastatic disease (2 years post neoadjuvant treatment initiation). MSD acknowledges that this methodology may lead to some overestimation of the 1L mTNBC drug acquisition costs because these are not adjusted for discounting rate, vial sharing, and half cycle correction. However, this is not dissimilar to the approach used in other NICE submissions whereby PFS is used as a time on treatment proxy to assign 1L metastatic costs (and therefore in those occasions costs remain unadjusted for discounting half cycle correction and vial sharing).

		As noted above, the current KEYNOTE-522 OS data remain immature. The same is the case for the subsequent treatment records available for analysis from KEYNOTE-522 to inform the DM setting post-progression (2L+ costs). Therefore, KEYNOTE-522 data cannot be used to provide robust estimates for subsequent treatments by progression status for patients with DM. For the purposes of economic modelling it is important that subsequent treatment costs for 2L+ mTNBC treatment options are also captured. Clinical experts have concluded that KEYNOTE-355 data with minor adjustments to account for subsequent IO usage, would be generalisable to the UK setting. For patients which received 1L mTNBC treatment a lump sum cost of 2L, 3L, 4L+ subsequent treatment options was applied. This was derived from the KEYNOTE-355 trial data based on the % of patients which received each of these lines of therapy. The mean ToT was derived from KEYNOTE-355. IO subsequent treatment utilisation in KEYNOTE-355 was limited and very well balanced, and therefore it is unlikely to affect the C/E results (IO records were distributed across other therapies to adjust the subsequent treatment costs). It should be noted that the KEYNOTE-355 subsequent treatment data are PD-L1 agnostic and primarily consist of chemotherapies already available to the NHS (refer to Table 10 of B3 clarification question response). The table below presents the mean estimated 2L+ subsequent treatment costs applied in the model for patients that go on to receive 1L therapy for mTNBC by the type of regimen in the 1L mTNBC setting. Please note that during the TE process MSD conducted a minor update in the subsequent lump sum treatment costs for 2L+. We clarify that previous 2L+ lump sum costs included within this submission were incorrectly extracted from the original KEYNOTE-355 model which used interim OS (IA2 DBL) and subsequent treatment cost estimates. However, MSD subsequently updated KEYNOTE-355 model with the final OS results including updated subsequent treatment data which was provided to NICE during the technical engagement process of TA801. The updated lump sum 2L+ mTNBC costs are applied (minor uplift to the original values) in the latest model version, however the impact of these on the ICER is fairly limited.

Table 3: Subsequent treatment line costs by type of 1L mTNBC therapy received

1L mTNBC treatment regimen received	UPDATED subsequent treatment (2L+) costs	Original subsequent treatment (2L+) costs	Source
Pembrolizumab + taxanes (paclitaxel/nab-paclitaxel)	[redacted]	[redacted]	KEYNOTE-355 1L mTNBC CEM (8)
Paclitaxel	[redacted]	[redacted]	KEYNOTE-355 1L mTNBC CEM (8) (taxanes pooled arm)
Carboplatin†	[redacted]	[redacted]	Assumed same as gemcitabine + carboplatin from KEYNOTE-355 1L mTNBC CEM (8)
Carboplatin + paclitaxel†	[redacted]	[redacted]	Assumed same as gemcitabine + carboplatin from KEYNOTE-355 1L mTNBC CEM (8)
Gemcitabine + carboplatin	[redacted]	[redacted]	KEYNOTE-355 1L mTNBC CEM (8)
Atezolizumab + nab-paclitaxel	[redacted]	[redacted]	KEYNOTE-355 1L mTNBC CEM (8)
Capecitabine*	[redacted]	[redacted]	Assumed same as taxanes from KEYNOTE-355 1L mTNBC CEM (8)

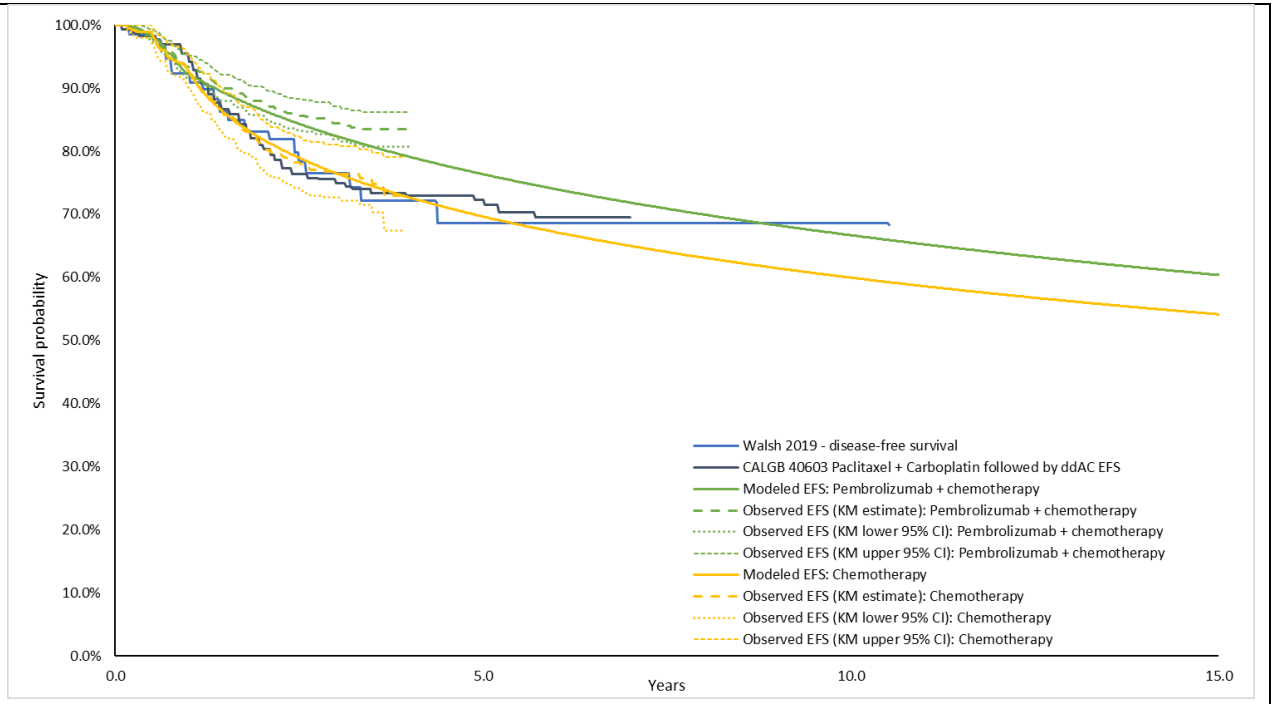
		Metastatic TNBC lacked effective treatment options until very recently with the approval of Atezolizumab + nab-paclitaxel became in July 2020 (TA639) followed by Pembrolizumab + chemotherapy (taxanes) in June 2022 (TA801) (9, 10). These two treatment options are only available for patients with untreated PD-L1-positive tumours (approximately 38%; PD-L1 ascertainment differs; refer to TA801). The majority of patients in practice are PD-L1 negative (or are not tested for PD-L1 status; approximately 62% are negative], and therefore most patients with 1Lm TNBC would receive standard chemotherapy options, all of which are understood to be associated with limited survival benefit. During the technical engagement process a further UK clinical expert was consulted by MSD with regards to the DM health state. The clinical expert noted that TNBC is a very aggressive tumour and therefore once patients develop a DM, their survival is mainly determined by the choice of 1L mTNBC treatment received noting that standard chemotherapies used for 2L+ result in limited survival benefit. The clinical expert also noted that with the exception of IOs for PD-L1+ve 1L mTNBC patients, standard 1L mTNBC chemotherapies also resulted in limited survival benefit. The clinical expert concluded that it is reasonable to model a single DM health state given the availability of TNBC evidence versus other early BC tumours but to account for 2L+ subsequent treatment costs. The current DM heath state modelling reflects the OS for patients with 1L mTNBC using data from a large multinational Phase 3 RCT which explored the efficacy of key 1st line chemotherapy treatment alongside pembrolizumab + taxanes. Subsequent treatment costs for 2L+ were derived from the same source and are fully reflective of NHS treatment practice. Whilst the DM state in the current model does not explicitly distinguish between 1L and 2L+ costs, from a costing perspective it adequately captures all TNBC associated costs relevant to the decision problem. **MD is confident that the model structure adequately captures the relevant cost and outcomes associated with TNBC progression. The current model structure does not make explicit claims on any additional benefit (or, conversely, a detriment) depending on the prior treatment received in the neo-adjuvant/adjuvant setting. To this end, MSD**

		considers the model structure to be adequately structured to inform decision making, and a more complex model structure would only introduce superfluous complexity and rely on weak data/assumptions.
8. Modelled treatment effectiveness and extrapolation for EFS state likely overestimates effectiveness of pembrolizumab	No	The ERG disagrees with the parametric curves selected by the company to model Event Free Survival (EFS) and suggests that the same type of distribution (in this case log-normal) may be more appropriate across both treatment arms. The ERG also notes that QALY gains continue to be accrued from the extrapolated part of the model. Analyses with shorter time horizon are presented which are inappropriate and discordant with the NICE reference case that stipulates that costs and benefits are assessed over lifetime. MSD accepts that choosing the most suitable parametric curves is a topic that features in many appraisals conducted by NICE, and therefore is likely a matter for the committee to consider, but for completeness below is a summary of the process taken to determine the base-case approach used in MSD's submission. **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 (11). MSD's base-case parametric curve selection for EFS extrapolation in the Pembrolizumab + chemotherapy arm was that of Generalised Gamma. The log-normal distribution was selected to model EFS extrapolation in the chemotherapy arm. MSD considers that the unique mode of action of immunotherapy agents (IO) such as pembrolizumab + chemotherapy warrants alternative parametric distributions for valid EFS extrapolations.** <u>Model selection process:</u> Patient level data from KEYNOTE-522 IA4 were used. Prior to model fitting, EFS cumulative and log-cumulative hazard plots were generated to assess the proportional hazards assumption. 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. Further interrogation of cumulative hazard plots revealed the crossing the log-cumulative hazards of the two treatment arms,

		therefore suggesting the implausibility of the proportional hazard assumption. For this reason, separate models were explored to fit the data for each arm for the projection of EFS. Visual inspection of log-cumulative hazard plots and statistical tests identified potential cut-off points for two-phase models were identified to capture potential turning points of the EFS curves in both treatment arms. The base-case used a 50-week timepoint for piecewise extrapolations in both treatment arms to ensure that sufficient data remained beyond this point for EFS extrapolation. Finally, the suitability of alternative models was assessed both by considering internal and external validity from RWE sources and the clinical plausibility of the extrapolated results. The AIC/BIC statistics are presented in Table 9 below. <u>Justification for different models:</u> MSD's current base-case model selected for Pembrolizumab + chemotherapy based on statistical fit to the observed data ranks 1st. Although the log-normal distribution ranks 2nd, the AIC/BIC difference versus the 1st best curve is 4.93 points (refer to Table 9). This is indicative of the poorer fit to the observed data, despite ranking as second in terms of statistical fit. The Generalised-gamma model was also preferred by clinical experts versus that of log-normal because it was unlikely that 10% of events will occur between 5 and 10 years which is suggested by the choice of the log-normal for pembrolizumab + chemotherapy arm. For this reason MSD selected the choice of generalised-gamma to model EFS extrapolations for pembrolizumab + chemotherapy. The unique mode of action of IO agents cannot be perceived to be comparable to that of chemotherapy alone; therefore, the underlying hazard assumption for the parametric curve does not need to be the same. This has been observed alongside across a number of metastatic and adjuvant submissions with IO agents to date (5, 12). During the submission development process clinical experts advised MSD that IO therapies used in the neoadjuvant /adjuvant setting may have an effect of improving 'Immune surveillance' due to their unique mode of action by activating, therefore enhancing the ability of the patient's immune system to recognise and destroy tumour cells and micro-metastases and enhance immune memory, resulting in the removal of any residual disease (13).

		MSD is therefore of the opinion that alternative parametric models are appropriate for EFS extrapolations for the two treatment arms. The ERG's approach (which uses the same parametric model to extrapolate EFS for both arms) implicitly assumes that the same parametric function can be used to describe the hazard function for two mechanistically different treatment strategies. It is MSD's view that the choice of setting the EFS curve for the pembrolizumab arm to align with the choice for the control arm likely leads to biased estimates of cost-effectiveness against pembrolizumab, given that the effect of this change leads to reduced survival gains versus MSD's base-case analysis. **Figure 3: EFS standard parametric curve fitting in the pembrolizumab + chemotherapy arm for week 50+** [redacted] **Figure 4: EFS standard parametric curve fitting in the placebo arm for week 50+** [redacted] <u>Validation of EFS projections vs RWE and clinical opinion:</u> The clinical plausibility of different EFS parametric models was discussed during an advisory board. Experts were presented with alternative EFS extrapolations and asked to comment on the most plausible models used to extrapolate the standard of care chemotherapy and the pembrolizumab arm. Clinical experts noted that an EFS plateau would be seen across both treatment arms since most recurrences would be expected occur within the first 3 to 5 years based on prior experience from other adjuvant IO trials (5, 12). Overall, clinical experts noted that the generalised gamma, log-normal and Gompertz distributions were most realistic for patients with early-stage TNBC treated with either pembrolizumab or standard of care chemotherapy. However, some experts favoured distributions other than log-normal (that is Gompertz or Generalised-Gamma), noting concerns and that it was unlikely that that 10% of EFS events will occur between 5 and 10 years as suggested by the log-normal distribution (14). Based on this information and due to the unique mode of action of IO + chemotherapy separate models were selected to extrapolate EFS from KEYNOTE-522. The log-normal model was not

		explored in the base-case for Pembrolizumab + chemotherapy because due to the % of EFS events which take place between years 5 and 10 (as noted above). Gompertz was also not explored in the base-case because of the plateau it generates for EFS extrapolations which takes place very early on in the extrapolation period. Considering these limitations the base-case using generalised-gamma to model long term EFS for pembrolizumab + chemotherapy. All experts noted that for patients treated with pembrolizumab + chemotherapy EFS would be higher than that of placebo as observed in other adjuvant trials, most notably in melanoma (5, 6). Long term EFS projections were also validated for the chemotherapy standard of care arm for which long term data are currently available. Two publications of long-term EFS in patients with early-stage TNBC following neoadjuvant chemotherapy (NACT) were retrieved from a targeted literature review; Walsh 2019 (15) and Sikov 2019 (CALGB 40603) (16). No other sources were suggested by clinical experts for model validation purposes and noted that both studies could be appropriate sources of validation for the modelled EFS for placebo. The models selected for the base case and alternative sensitivity analyses all yielded good visual fit to the RWE identified and observed EFS estimates from KEYNOTE-522 (refer to section B.3.10.1). One further discrepancy with regards to the selection of log-normal to model EFS across both treatment arms is also observed when the 10 year EFS estimates generated for Pembrolizumab + chemotherapy are compared versus the disease-free survival (DFS) estimates reported by Walsh et al 2019. This can be attributed to the EFS events which are estimated using the log-normal from year 5 onwards that were deemed by clinicians to be unrealistic (14). The authors report ~68.6% DFS at year 10 vs 66.7% generated by the log-normal EFS extrapolation. The use of log-normal for EFS does not generate an EFS plateau which was noted by clinical experts and has also been observed in Walsh et al 2019 and Sikov et al 2019 (15, 16). These elements clearly demonstrate the conservatism of log-normal to extrapolate EFS which biases against Pembrolizumab + chemotherapy alongside the expert advice presented above (see Figure 5 below). **Figure 5: Impact of log-normal for Pembro + chemotherapy EFS versus RWE data for standard of care**



MSD followed the NICE TSD methodology and clinical expert option to identify the most appropriate EFS parametric models for survival extrapolations. We consider that the unique mode of action of immunotherapy agents (IO) such as pembrolizumab + chemotherapy warrants alternative parametric distributions for EFS extrapolations. We have also demonstrated that the use of log-normal to extrapolate EFS for pembrolizumab + chemotherapy may not capture the full benefit of the intervention based on clinical expert opinion and may bias the cost-effectiveness estimates against Pembrolizumab + chemotherapy.

9. Constant transition probabilities from LR and DM states assumed without clinical justification	No	The ERG is concerned around the constant transition probabilities applied over the model's time horizon to model LR→ DM, LR→ Death and DM→ Death. The ERG requested MSD provides additional clinical justification around this assumption to demonstrate its clinical validity. **MSD has discussed the limitations associated with the Markov modelling framework above. The KEYNOTE-522 data currently do not support complex modelling of transitions from LR. Clinical experts confirmed the assumption of constant transition probabilities is clinically justified considering the aggressiveness of TNBC and the overall poor prognosis for patients presenting with a LR.** These elements are discussed further below. The current model uses a Markov state transition structure in which EF is the starting health state, LR and DM are intermediate health states, and Death is the absorbing health state. Markov models are memoryless by nature, meaning it is not possible to track individual patients through the model or therefore determine how long patients have been in a particular health state. However, to model variable hazards over time from entry into an intermediate health state (in this case, the DM state) it is *necessary* to track time in health state. To achieve this in a Markov model would require thousands of tunnel states and would significantly increase the computational burden of the model. As such, it was deemed an appropriate simplifying assumption to instead apply a constant hazard rate to estimate transitions from the LR and DM health states. In KEYNOTE-522, [redacted] patients experienced LR, of which [redacted] observations were considered as failed (i.e. either with a DM or Death event) and [redacted] were censored ([redacted]% censored; refer to Table 4 below describes the number of first events taking place once patents were confirmed with LR). Due to the limited number of events between the two treatment arms, the pooled events from KEYNOTE-522 were used to inform the transition probabilities from LR→DM or Death. This is due to the limited number of events that were observed in KEYNOTE-522 which could increase uncertainty if compartmentalised further for separate parametric extrapolations

and subsequent calculations of transition probabilities from LR→ DM and LR→ Death (see Table 4 below for a breakdown first EFS events that took place from LR).

Table 4: Breakdown of first LR event

	%	N Events	N Total
% from LR to DM	[redacted]	[redacted]	[redacted]
% from LR to Death	[redacted]	[redacted]	[redacted]

MSD clarified that the selection of the exponential parametric distribution selected to model LR → DM or Death was not based in isolation to the AIC/BIC statistics. Other considerations such as visual fit to the observed KM curve (Figure 6) alongside balanced assessment of clinical plausibility of long term predictions generated by each of the alternative parametric models. Although the exponential model sits marginally above the KM data for the duration of the observed period, it demonstrated a better fit towards the tail of the KM curve better and yielded more conservative estimates of long term time to DM or Death.

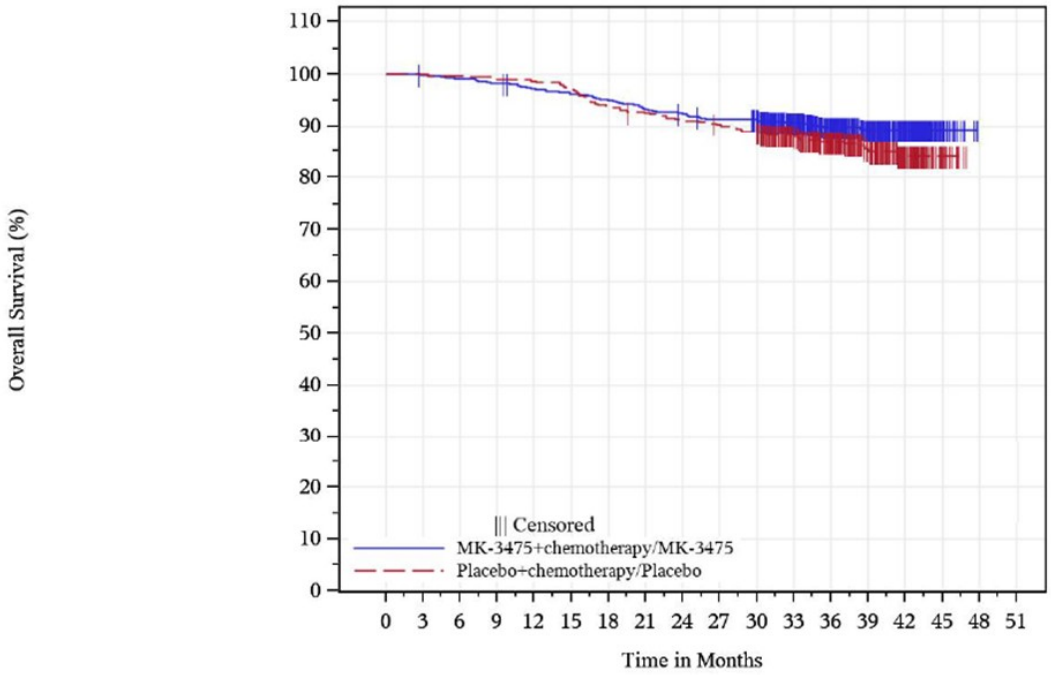
Figure 6: Long term parametric extrapolations using the combined KEYNOTE-522 arms time from LR to DM or Death

[redacted]

Based on the data presented above from KEYNOTE-522, a weekly exponential rate was calculated; [redacted] alongside (95% CIs: [redacted] Please note that the model is largely insensitive to this assumption as demonstrated by the DSA results which tested the upper and lower 95%CIs of this value (refer to new scenarios 22 and 23 in updates sensitivity analyses presented below). Markov models are memoryless by nature, meaning it is not possible to track the time individual patients may spend in a particular health state. Therefore, the exponential model was preferred to model transitions from LR→DM or LR →Death. The approach of constant transition probabilities is also on par with that of TA424 transition from all health states apparent from that of EFS (17).

		During the technical engagement process a UK clinical expert was consulted by MSD to test further the validity of this assumption at the request of the ERG (expressed during the technical engagement call). The clinical expert noted the aggressiveness of TNBC versus other early BC tumours including those which are HER2+ve. The expert stated that once patients develop a locoregional recurrence, only a very small proportion of patients with LR would be surgically salvageable due to developing an isolated LR which would result in them experiencing a decrease in the probability of DM or death. The clinical expert noted that the majority of patients with LR would not be surgically salvageable and therefore the probability of them developing a DM or death would remain fairly constant over time considering the aggressiveness of TNBC. The expert noted that due to the very small proportion of patients presenting with isolated LR which is surgically salvageable, the assumption of constant transition probabilities from LR was clinically justified and was unlikely this would have a major impact in the cost-effectiveness. **The KEYNOTE-522 data currently do not support complex modelling of transitions from LR. Clinical experts confirmed the assumption of constant transition probabilities is clinically justified considering the aggressiveness of TNBC and the overall poor prognosis for patients presenting with a LR.**
10. The use of KEYNOTE-355 data for DM survival may not be appropriate	No	The ERG is concerned that the company's preferred approach to model survival from DM→ Death using the KEYNOTE-355 dataset may not be appropriate. Instead the ERG prefers to use the KEYNOTE-522 dataset to inform the DM→ Death survival. **MSD has discussed the limitations associated with the use of immature OS data from KEYNOTE-522 for HTA purposes. MSD leveraged the KEYNOTE-355 OS data recently reviewed by NICE during TA801 to model the survival from DM→Death. The decision to use multiple sources to inform transition probabilities for health economic modelling is not unjustified and is in line with previous submission in the adjuvant space that either lacked OS in totality or reported immature OS.**

		The OS data from IA4 of KEYNOTE-522 were presented within the main submission Document B. At IA4, considering that the primary hypothesis of EFS was successful, the secondary hypothesis of OS was formally tested at the same alpha level of 2.5% according to the protocol multiplicity strategy. The analysis showed improvement in OS that favoured the pembrolizumab arm over the placebo arm at month 42. However, due to the relative early time of the analysis with respect to the OS endpoint [redacted]information fraction of approximately [redacted][135 of the [redacted]events needed for the final analysis]) the observed one-sided p-value did not cross the multiplicity-adjusted, one-sided prespecified p-value boundary at IA4. Therefore, the success criterion for the secondary OS hypothesis was not met. The OS HR of 0.72 (95% CI: 0.51, 1.02), with a one-sided p-value of 0.0321377 that did not cross the prespecified boundary for statistical significance of p=[redacted], represents a 28% reduction in the risk of death compared with the placebo arm (refer to Table 10 and Table 11 for detailed results presented within Document B). The median OS was not reached in either arm at month 42 and will be analysed in future interim analysis as data matures. The OS Kaplan-Meier and HRs are presented below. Please note that the final analysis for the trial (for all endpoints) is due to take place in [redacted], however, [redacted]OS events, the number of events required to conduct a formal statistical analysis may not be reached. This is due to the fact that OS maturity may be delayed for patients obtaining a pCR and subsequently remaining EFS, whilst for those who relapse, OS may in part be confounded by the availability of other anti-PD-1/anti-PD-L1 agents for treatment of metastatic disease similar to what has been observed across other adjuvant IO trials including (KEYNOTE-054 and Checkmate-238) (5, 12). **Figure 7: KEYNOTE-522 Overall Survival data (All Participants)**



n at risk

MK-3475+chemotherapy/MK-3475	784	782	777	770	759	752	742	729	720	712	701	586	461	323	178	30	0	0
Placebo+chemotherapy/Placebo	390	390	389	386	385	380	366	360	354	350	343	286	223	157	89	17	0	0

Database Cutoff Date: 23MAR2021

		Please note that the null-hypothesis for EFS has been rejected at IA4, therefore EFS will not be further tested formally. OS has been formally tested from IA4. [redacted] From a health economic modelling perspective, the use of the immature OS data from KEYNOTE-522 directly in the economic model carries its own limitations which are associated with potentially increased uncertainty. To mitigate against the immature OS data from KEYNOTE-522, an alternative approach was followed to model the DM→ Death which leveraging data from KEYNOTE-355. This study is a contemporary 1L mTNBC study which investigated the efficacy and safety of Pembrolizumab + chemotherapy versus chemotherapy alone in PD-L1+ve CPS ≥10 patients. KEYNOTE-355 formed the basis of the recent +ve recommendation for TA801 (Pembrolizumab + taxanes) for previously untreated locally recurrent unresectable or metastatic TNBC adults whose tumours express PD-L1 with a CPS of 10 or more and an immune cell staining (IC) of less than 1% (Atezolizumab + nab-paclitaxel ineligible). KEYNOTE-355 was preferred for the base-case because it offered a source for 1L+ mTNBC survival specific to PD-L1 +ve patients but also a single source of inputs for subsequent treatment costs. <u>DM→ Death methodology from KEYNOTE-355:</u> We have provided sufficient information in Issue 7 above around the methodology used to estimate survival using KEYNOTE-355. In brief, survival estimates for other 1L mTNBC comparators other than Pembrolizumab + taxanes (directly derived from KEYNOTE-355) were estimated based on a mTNBC NMA alongside the clinical expert input on market research for the anticipated utilisation of 1L mTNBC treatment options. This allowed the estimation of a weighted DM→Death survival which accounted for the subsequent treatment mix at 1L mTNBC and was then applied in the model. This approach was necessary since only ~38% of KEYNOTE-355 patients had PD-L1 positive CPS ≥ 10 tumours under the granted marketing authorisation. Within the patients with PD-L1 positive mTNBC, alternative IO comparators such as Atezolizumab + nab-paclitaxel have been recommended and are the standard of care currently in the NHS. The remaining 62% of patients which are PD-L1 negative and would go to otherwise receive a standard chemotherapy. The DM OS modelled reflects the 1L+ survival from a contemporary trial and the methodology captures the current treatment pathway for

		mTNBC in the UK. Finally, the approach used to model the of DM→Death in this submission is not dissimilar to that used in previous IO adjuvant submissions such as TA766 which leverages metastatic OS from clinical trials to estimate DM survival. **Robust DM survival for PD-L1+ve patients can only be derived from KEYNOTE-355. MSD has modelled the efficacy and costs in the DM setting for 1L+ mTNBC by leveraging the same source of data where possible to avoid discrepancies. The current approach ensures consistency between IO 1L mTNBC survival estimates discussed during TA801 and those modelled from DM→ Death in the current submission. The impact of using immature OS from KEYNOTE-522 was explored in scenarios presented within Document B and resulted in a marginal ICER increase.**
11. The utility value used in the DM health state may be relatively low when compared to literature reported values.	No	The ERG raised concerns with regards to the DM utility derived from the KEYNOTE-522 data and questioned its validity for use in the economic model. The ERG justified its criticism on the basis of comparing the DM utility estimate from KEYNOTE-522 versus utilities reported elsewhere for mTNBC patients at pre-progression (KEYNOTE-355 and KEYNOTE-119 [2L mTNBC study]). **As per the ERG's request MSD commented on the representativeness of the DM utility value derived from KEYNOTE-522 highlighting some uncertainties that should be considered when cross study comparisons of utility sources and values are performed. MSD provided additional justification on why the DM utility value from KEYNOTE-522 is appropriate for consideration, noting its limited impact on the ICER.** MSD would like to reiterate that the current DM health state utility (mean = [redacted]) was derived from the KEYNOTE-522 data which is consistent with the NICE reference case (18). This value is reflective of the KEYNOTE-522 patient population based on the IA4 database lock. Alternative values were explored during the CQ response stage using higher utility estimates for DM.

We acknowledge that there are some of the limitations associated with the DM utility value calculated from KEYNOTE-522. Most notably, the EQ-5D collection from KEYNOTE-522 is still ongoing since most patients continue to remain relapse free and OS data continue to remain immature. EQ-5D collection from KEYNOTE-522 is still ongoing, and a small number of questionnaires was available for analyses to estimate utility once at DM setting ([redacted] across both treatment arms).

This may in part explain why the utility values at DM setting appear lower than those reported elsewhere in the literature and continued data collection from KEYNOTE-522 will add more certainty around this model estimate. However, we also caution against over-interpreting differences between studies because the [redacted] DM derived utility was also based upon mapping of 5L to 3L using the *van Hout* algorithm. When the EQ-5D-5L value set was applied directly, the DM utility value was higher ([redacted]) but still lower to values reported elsewhere in the literature.

Taking into account the EQ-5D data maturity, an analysis of utility values from KEYNOTE-522 by DM progression status could not be performed as per the ERG's request. To understand the impact on the C/E results of a higher utility for patients in the DM setting MSD presented some additional utility estimates from KEYNOTE-355 (1L mTNBC population) and conducted alternative scenarios with different utility values from KEYNOTE-355 and KEYNOTE-119. The utility values from KEYNOTE-355 study population and KEYNOTE-119 are presented in the table below.

Table 5: Supplementary information reporting utility estimates from KEYNOTE-355 and KEYNOTE-119

Health state	Mean utility value (95% CI)	Time-to-death Category	Mean utility value (95% CI)
KEYNOTE-355: 1L mTNBC PD-L1 CPS 10 population			

Progression-free survival	[redacted]	>360 days	[redacted]	
		180 to 360 days	[redacted]	
		90 to 180 days	[redacted]	
Progressive disease	[redacted]	30 to 90 days	[redacted]	
		>30 days	[redacted]	
KEYNOTE-119: Patients with previously treated mTNBC (2L mTNBC) (19)*				
Progression-free survival	0.715 (0.701-0.730)	>360 days	0.765 (0.750, 0.779)	
		180 to 360 days	0.655 (0.624, 0.687)	
		90 to 180 days	0.586 (0.549, 0.624)	
Progressive disease	0.601 (0.571-0.631)	30 to 90 days	0.517 (0.471, 0.564)	
		>30 days	0.264 (0.128, 0.401)	
**N.B. Publication does not explicitly state that the USA population tariff used to derive the utility estimates.*				

Based on the above utility sources, two scenario analyses were conducted alternative data sources and assumptions to test the impact of the DM utility estimate on ICER for utility in the DM setting:

- KEYNOTE-355 (1L mTNBC population): Scenario #1 whereby the DM utility is set to [redacted]. This value represents a weighted utility based on the total predicted LYs gained during pre-progression ([redacted]) and the post-progression ([redacted]) of the chemotherapy arm; the mean pooled utility for progression-free and progressed patients was [redacted] and [redacted] respectively). The LYs gained were sourced from the cost-effectiveness analysis of pembrolizumab as first-line treatment for TNBC.

		• KEYNOTE-119 (2L mTNBC population): Scenario #2 tests the utility value of 0.715 which is specific to the pre-progression utility from KEYNOTE-119; (vs. the weighted average of pre-progression and post-progression tested using KEYNOTE-355 data). This scenario was used to test the maximum impact on ICER considering that KEYNOTE-119 was conducted in a 2L mTNBC study population. MSD does not agree with KEYNOTE-119 data being relevant to inform the DM utility in this submission due to the population differences from which the pre-progression utility was derived versus the DM population modelled within ID1500. It is also worth noting that the utility values reported within KEYNOTE-119 used the US tariff and therefore of limited generalisability to the UK population (confirmed with authors in personal communication during the TE process). Results from the scenario analyses described above demonstrate that the ICER is not overly sensitive to the utility estimate used in the DM state. Using the KEYNOTE-355 utility data, the company base-case ICER increased from £5,940/QALY gained to £6,038/QALY gained in the scenario whereby a KEYNOTE-355 DM weighted average utility was used (please refer to QC response B19). The pre-progression KEYNOTE-119 data increased the ICER from £5,940/QALY gained to £6,054/QALY gained (please refer to QC response B19). The limited impact of DM utility in the ICER was also noted by the EGR in its report. **MSD acknowledges that EQ-5D collection from KEYNOTE-522 is still ongoing since most patients continue to be followed up and a small sample size was available to inform the DM utility. We caution against cross study comparisons of utility data considering the different study populations. The two exploratory analyses demonstrated that a higher DM utility does not have a great impact on the ICERs. The DM utility derived from KEYNOTE-522 remains relevant for economic modelling purposes as it is line with the NICE reference case.**

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: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

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

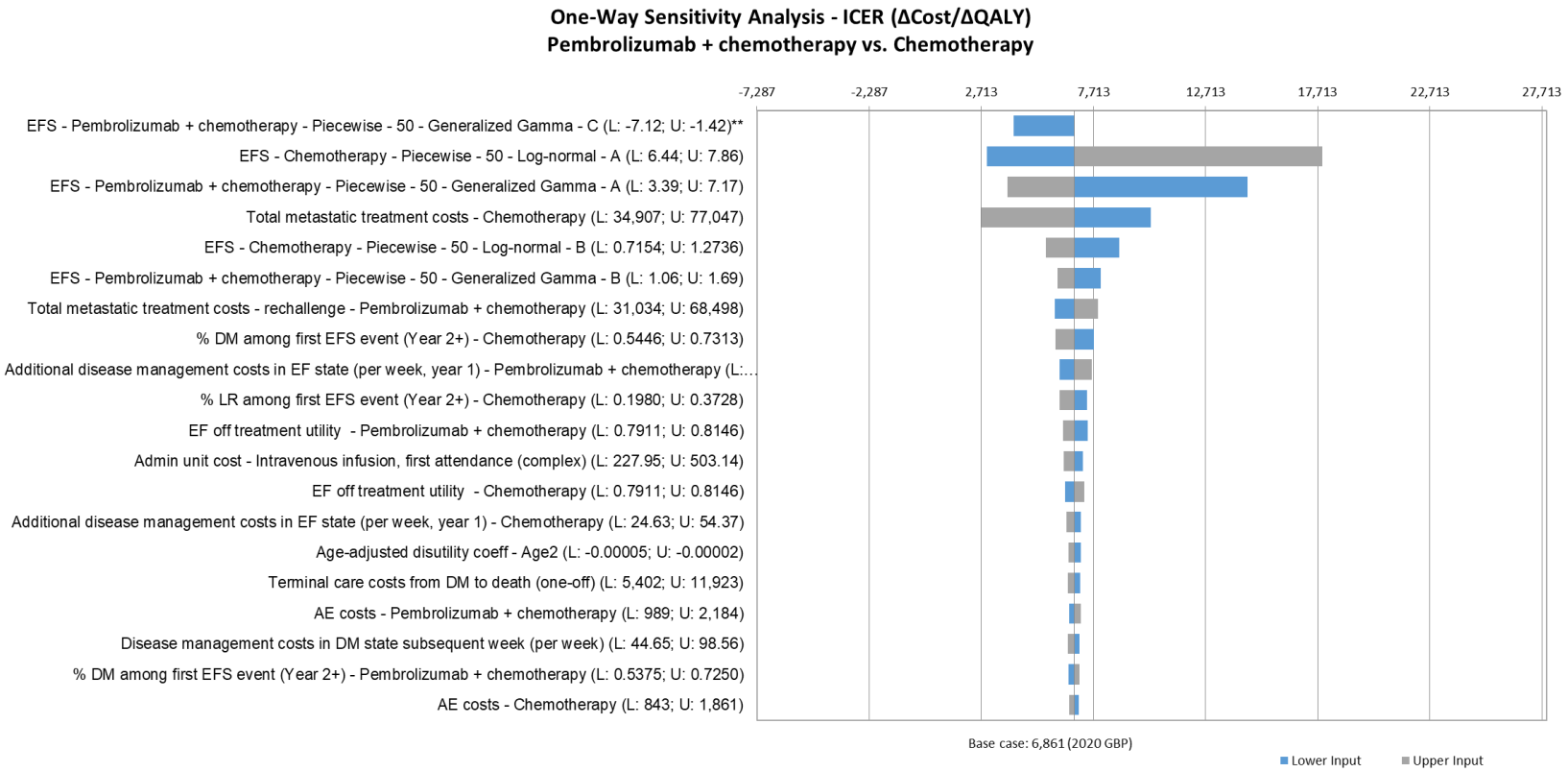
Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
[redacted]	[redacted]	[redacted]	[redacted]
In part affects; Issue 7: Model structure (ascertainment of costs in ***pre-progression*** DM health state) *and* Issue 10: KEYNOTE-355 trial data used to model DM→ Death.	The base-case previously did not allow pembrolizumab rechallenge for metastatic disease (TA801) following on from pembrolizumab + chemotherapy in the neoadjuvant/adjuvant setting (ID1500).	The new base-case allows for rechallenge with pembrolizumab + taxanes for metastatic disease to account for recent changes in the metastatic pathway (TA801). Rechallenge is allowed with pembrolizumab after 2 years of neoadjuvant treatment initiation. This assumption was confirmed by a to be reflective of the new treatment pathway given experience in other IO adjuvant → metastatic HTA assumptions (primarily melanoma; TA766 and TA684).	[redacted]

Updated assumptions pertaining to pembrolizumab IO rechallenge from neoadj/adj → metastatic setting.			
In part affects; Issue 7: Model structure (ascertainment of costs in pre-progression DM health state) *and* Issue 10: KEYNOTE-355 trial data used to model DM→ Death. **Updated market share split for IO agents in 1L mTNBC for PD-L1+ve patients.**	The base-case previously assumed a 50-50% market share mix between Atezolizumab + nab-paclitaxel and Pembrolizumab + taxanes for 1L mTNBC for PD-L1 +ve patients. This assumption was used since TA801 was ongoing at the time. These estimates affect DM→ Death estimates applied in the model.	The new base-case assumes a ~83% Atezolizumab + nab-paclitaxel and ~17% for Pembrolizumab + taxanes to reflect the recent TA801 recommendation. This assumption was reflected by a clinical expert to be reflective of the new treatment pathway. Whilst update is not directly linked to any ERG criticisms this change in the base-case assumptions for IO usage for 1L mTNBC is now necessary to reflect the current treatment pathway.	[redacted]
In part affects; Issue 7: Model structure (ascertainment of costs in pre-progression DM health state)	Drug acquisition costs for capecitabine were incorrectly estimated not adjust the pack size overestimating capecitabine costs.	Updated capecitabine costs now reflect the pack size – extracts from eMIT added into "raw_Drug Costs" sheet for clarity.	[redacted]

Capecitabine 1L mTNBC cost correction – error identified during TE stage.			
In part affects; Issue 7: Model structure (ascertainment of costs post-progression DM health state) **Minor update of 2L+lump sum costs to reflect latest KN-355 data presented during TA801 assessment.**	Minor update in the subsequent lump sum treatment costs for 2L+. Previous 2L+ lump sum costs were incorrectly extracted from the KN-355 model with interim OS but the NICE AC reviewed the FA KN-355 model during TA801. These costs have now been revised upwards.	Minor updates 2L+ subsequent treatment costs carried out to align these with the latest 2L+ subsequent treatment costs included in the final KN-355 model.	[redacted]
Cumulative impact of base-case changes noted above.	All changes above implemented	All changes above implemented	**£6,861 (all above changes to company base-case included)**

Sensitivity analyses around revised base case

Figure 8: Tornado diagram for the 20 most sensitive parameters with pembrolizumab PAS price after technical engagement



**Upper limit parameter pembrolizumab arm is dominated i.e. more costly and less effective; therefore an ICER statistic cannot be presented for the tornado diagram

Table 6: Scenario analyses with pembrolizumab PAS price after technical engagement

Scenario No.	Description	Pembrolizumab arm		Placebo arm		Pembrolizumab vs. placebo arm		
		Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
0	Updated base case – deterministic*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£6,861**
0	Updated base case – probabilistic*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£7,089**
1	EFS function - Pembrolizumab + chemotherapy - Piecewise - Week 50 - ***Log-normal*** (second best option of pembrolizumab arm curve by clinical experts)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,398
2	EFS function - Chemotherapy - Piecewise - Week 50 - ***Generalized Gamma*** (second best option of placebo arm curve by clinical experts)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,693
3	EFS function - Pembrolizumab + chemotherapy - Piecewise - Week 50 - ***Log-normal*** **and** Chemotherapy - Piecewise - Week 50 – ***Generalized Gamma*** (combined second best option of pembrolizumab arm and placebo arm curves by clinical experts)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,178
4	Time horizon (20 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,451
5	Allow vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,051
6	Utility by treatment arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,140
7	Utility algorithm (UK 5L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,396
8	TOT measure - Pembrolizumab + chemotherapy - KM lower 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,413
9	TOT measure - Pembrolizumab + chemotherapy - KM upper 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,345

Scenario No.	Description	Pembrolizumab arm		Placebo arm		Pembrolizumab vs. placebo arm		
		Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
10	TOT measure - Chemotherapy - KM lower 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,915
11	TOT measure - Chemotherapy - KM upper 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,808
12	Annual discount rate - costs (1.5%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,868
13	Annual discount rate - effects (1.5%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,710
14	Annual discount rate – costs and effects (1.5%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,028
15	Remission after 8 years (note: remission assumes the probability of EFS event for both treatment arms = 0, only transition applied is background mortality; based on clinical expert opinion)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,595
16	Remission after 10 years (note: remission assumes the probability of EFS event for both treatment arms = 0, only transition applied is background mortality; based on clinical expert opinion)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,061
17	KEYNOTE-522 OS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,825
18	Pembrolizumab 400mg Q6W dosing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,310
19	Pembrolizumab rechallenge scenario with atezolizumab 50:50 split for both treatment arms	No longer relevant considering the treatment pathway and recommendations within TA801, therefore not re-run.						
20	Pembrolizumab rechallenge scenario with atezolizumab 17:83 split for both treatment arms	**New base-case** assumes a split of 17:83 between Atezolizumab + nab-paclitaxel and Pembrolizumab + taxanes in the DM setting. This assumption was justified by clinical experts.						
21	Do not allow pembrolizumab rechallenge in DM setting after 2 years from neoadjuvant initiation.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,152

Scenario No.	Description	Pembrolizumab arm		Placebo arm		Pembrolizumab vs. placebo arm		
		Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
22	Lower 95%CI of exponential rate for LR→DM or Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,045
23	Upper 95%CI of exponential rate for LR→DM or Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,747
24	New option: explore ToT for Atezo + nab-paclitaxel = Pembrolizumab + taxanes CPS ≥10 population from KEYNOTE-355.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,916
25	New option: explore alternative mean survival for Pembro + Taxanes derived using an exponential parametric model (3.52 years predicted versus 4.51 using the log-normal derived estimate applied in base-case).	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,858
26	Assumption of equal efficacy for Atezolizumab + taxanes = Pembrolizumab + taxanes.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,886

*Updated base-case assumptions include; pembrolizumab rechallenge in the metastatic setting, IO split in metastatic reflective of TA801 guidance, correction in 2L+ mTNBC lump sum costs, correction on capecitabine 1L mTNBC costs.

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Appendix A: Model updates and new options included by MSD during the TE process

Some changes have been implemented in the new base-case but these cannot explicitly be linked to any of the specific issues raised by the ERG in isolation. The table below provides a full list model updates including but not limited to calculation corrections, base-case assumptions changes and introduction of new modelling options to reflect recent changes in the mTNBC pathway alongside the justification for these changes feeding into the updated base-case assumptions. Light grey shaded changes impact the new base-case presented by MSD; all other options presented as alternatives for exploration.

Table 7: Updates carried out by MSD in the C/E model during the TE process

#	Description	Rationale	Model Sheet
[redacted]	[redacted]	[redacted]	[redacted]
2	Allowed for Pembrolizumab re-challenge for distant metastatic disease	Previous base-case did not allow for pembrolizumab re-challenge in the DM setting since TA801 has not concluded. This assumption has now been revised in the new base-case	"Specifications" sheet G87 drop down set to "Yes", G89 input cell set to "2 Years"
3	New assumptions DM IO market share	At time of ID1500, TA801 has not concluded and therefore Atezo + nab-pacl vs Pembro + taxane market share distribution was unknown. Updated to reflect TA801 positioning within the pathway. Change of drop down menu selection for DM setting to set Pembro to Atezo split to 17%-83% from 50%-50% assumed previously.	"DM Treatment Costs & Efficacy" F94 drop down set to 17%-83%
4	Correction of Capecitabine drug cost	Cost per pack was used to estimate DM capecitabine costs - changed by MSD during TE to factor pack size of 120 tablets to derive cost/mg	“Raw drug Cost” cell F12 divided to 120 tablets – change carried over to "DM Trt Costs" – cell AM16 and into "DM Tx costs & Efficacy – cell R57"
5	Minor update of 2L+ subsequent treatment costs	Minor update in the subsequent lump sum treatment costs for 2L+. Previous 2L+ lump sum costs were incorrectly extracted from the KN-355 model with interim OS but the NICE AC reviewed the FA KN-355 model during TA801. These costs have now been revised	"DM Treatment Costs & Efficacy" – cells F67:F73 updated (original values in cells J67: J73) - New menu introduced in cell “M68” and select “New Lump sum costs”.

		upward (original values are reported in the model to aid the review process).	
6	New option for Pembro + taxanes survival at DM	The AC discussed Pembro + Taxane LY estimates with exponential model - this has been added in the updated model	"Raw_DM trt TOT OS" - new option
7	New option for Atezo + nab-paclitaxel ToT at DM	During ACM1 the AC discussed the most plausible Atezo + nab-paclitaxel ToT estimation. MSD originally assumed this would equal to the PFS projections generated but presented a new analysis whereby this was assumed to be equal to KEYNOTE-355 Pembro +taxane ToT from KEYNOTE-355; this has been added into the updated model	"Raw_DM trt TOT OS" - new option
8	New base-case assumptions	Cumulative impact of 1 + 2 + 3 + 4 + 5	NA

Table 8: Instructions to revert back to ERG original base-case

#	Description	Rationale	Model Sheet and change
1	[redacted]	[redacted]	[redacted]
2	Remove Pembrolizumab re-challenge for distant metastatic disease	Previous base-case did not allow for pembrolizumab re-challenge in the DM setting since TA801 has not concluded. This assumption has now been revised in the new base-case	Select "Specifications" sheet G87 drop down set to "No", G89 input cell set to "0 Years"
3	Revert back to 50-50 for DM IO market share	At time of ID1500, TA801 has not concluded and therefore Atezo + nab-pacl vs Pembro + taxane market share distribution was unknown. Revert back to IO DM MS to 50%-50% assumed previously.	"DM Treatment Costs & Efficacy" – cell “F94” drop down set to 50%-50%
4	Undo cost correction of Capecitabine drug cost	Undo cost per pack correction for DM capecitabine costs - changed by MSD during TE to factor pack size of 120 tablets to derive cost/mg	Navigate to “Raw drug Cost” cell F12 and delete the value of “ 120” which adjusted for pack size.
5	Revert back to old 2L+ subsequent treatment costs pre-correction	Revert back to older subsequent lump sum treatment costs for 2L+.	Navigate to "DM Treatment Costs & Efficacy" – M68 new menu introduced and select “Old Lump sum costs”.

6	Apply ERG selections	Navigate to ERG sheet and click checkbox “F9” to apply all other settings.	ERG Sheet – cell “F9” should be checked.

Appendix B: Additional data referred within the TE pro-forma

Table 9: Summary of goodness of fit for EFS: pembrolizumab arm and placebo comparator arm from KEYNOTE-522 (week 50+)

Parametric distribution for EFS	Pembrolizumab arm				Placebo arm			
	AIC	BIC	AVG	Rank	AIC	BIC	AVG	Rank
Exponential	1140.24	1144.84	1142.54	4	980.85	984.75	982.80	7
Weibull	1140.71	1149.89	1145.30	6	972.61	980.39	976.50	4
Log-normal	1134.58	1143.76	1139.17	2	969.91	977.69	973.80	2
Log-logistic	1139.91	1149.09	1144.50	5	971.70	979.48	975.59	3
Gompertz	1134.88	1144.06	1139.47	3	968.49	976.27	972.38	1
Gamma	1140.95	1150.13	1145.54	7	973.15	980.94	977.05	5
Generalized Gamma	**1127.35**	**1141.12**	**1134.24**	**1**	971.87	983.54	977.71	6
Abbreviations: AIC: Akaike Information Criteria, BIC: Bayesian Information Criteria; AVRG: Average, Ranking is based on the average AIC/BIC statistic.								

Table 10: Analysis of OS (All participants)

Treatment	N	Number of events (%)	Person-months	Event rate/100 person-months (%)	Median OS [a] [months] (95% CI)	OS Rate at month 42 in %[†] (95% CI)	Vs. control Hazard Ratio (95% CI) [b] p-value [c]
Pembrolizumab arm	784	80 (10.2)	28,1997.7	0.3	NR	89.2 (86.7, 91.3)	0.72 (0.51, 1.02)
Placebo arm	390	55 (14.1)	13,908.1	0.4	NR	84.1 (79.5, 87.7)	p-value: 0.0321377

NR = Not reached
[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron’s method of tie handling with treatment as a covariate stratified by nodal status (positive vs. negative), tumour size (T1/T2 vs. T3/T4) and choice of carboplatin (Q3W vs. Weekly).
[c] One-sided p-value based on log-rank test stratified by nodal status (positive vs. negative), tumour size (T1/T2 vs. T3/T4) and choice of carboplatin (Cb) (Q3W vs. Weekly).
Database Cutoff Date: 23MAR2021

Table 11: Summary of OS rate over time (All participants)

	Pembrolizumab arm (n=784) % (95% CI)	Placebo arm (n=390) % (95% CI)
Summary of overall survival rate at time point		
12 months	97.2 (95.8, 98.1)	98.7 (96.9, 99.5)
24 months	92.3 (90.2, 94.0)	91.0 (87.7, 93.5)
36 months	89.7 (87.3, 91.7)	86.9 (83.0, 89.9)
42 months	89.2 (86.7, 91.3)	84.1 (79.5, 87.7)
Database Cutoff Date: 23MAR2021		

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Pembrolizumab in combination with chemotherapy for neoadjuvant and adjuvant treatment of triple negative breast cancer [ID1500]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder 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

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 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 (see sections 1.3 to 1.5). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

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. 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 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' 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.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Clinical expert statement

Pembrolizumab in combination with chemotherapy for neoadjuvant and adjuvant treatment of triple negative breast cancer [ID1500]

NICE National Institute for Health and Care Excellence

Deadline for comments by **5pm** on **Wednesday 20 July.** 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.

NICE National Institute for Health and Care Excellence

Part 1: Treating early-stage and locally advanced triple negative breast cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	
2. Name of organisation	
3. Job title or position	
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☐ A specialist in the treatment of people with triple negative breast cancer? ☐ A specialist in the clinical evidence base for triple negative breast cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes

7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for early-stage or locally advanced triple negative breast cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The principal aim of treatment in early TNBC is curative, and usually comprises polychemotherapy (either in the adjuvant/neoadjuvant setting), surgery and often breast radiotherapy (always following breast conserving surgery, and after mastectomy in selected cases).
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	The principal aim of neoadjuvant therapy in TNBC is to induce a pathological complete response (pCR) to systemic therapy. In TNBC, pCR has been shown to be highly correlated with event-free survival. In addition to this prognostic information, it has been shown that failing to achieve a pCR allows the addition of further adjuvant therapy with capecitabine following breast surgery, with a consequent improvement in disease-free survival, although the evidence for this is equivocal. Finally, the use of neoadjuvant therapy can potentially permit the down-staging of surgery to both the breast and axilla, and such down-staging may reduce both the morbidity and healthcare costs associated with surgery.
10. In your view, is there an unmet need for patients and healthcare professionals in early-stage or locally advanced triple negative breast cancer?	Yes
11a. How is early-stage or locally advanced triple negative breast cancer currently treated in the NHS? **11b. Is chemotherapy used as adjuvant treatment for early-stage or locally advanced triple negative breast cancer in the NHS?** **11c. Please specify the chemotherapy options which are available for neoadjuvant and adjuvant (if**	There is currently considerable heterogeneity in the treatment of TNBC in the NHS. Patients with T2 and above tumours will generally be treated with neoadjuvant chemotherapy, as will node positive patients (patients with smaller tumours will generally undergo surgery as their primary treatment but the majority of these will still receive chemotherapy in the adjuvant setting). There is variation in practice nationally in the selection of chemotherapy regimens, with

applicable) treatment and which are most commonly used in practice in the NHS. **11d. KEYNOTE-522 included 67% doxorubicin use and 33% use in the neoadjuvant phase – is this reflective of clinical practice?** Please also consider: • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	the majority of patients receiving anthracycline-taxane combinations and substantial proportion receiving platinum-containing regimens. Patients who do not obtain a pathological complete response to neoadjuvant therapy may be considered for capecitabine following definitive breast surgery. Patients in KN-522 received treatment with 4 cycles of neoadjuvant paclitaxel and carboplatin, followed by 4 cycles of doxorubicin-cyclophosphamide or epirubicin-cyclophosphamide with either pembrolizumab or placebo. All chemotherapy was given in the neoadjuvant phase. These treatment regimens are broadly reflective of clinical practice in the UK, with most patients receiving anthracycline/taxane combinations and an increasing proportion of patients receiving platinum salts following the publication of data demonstrating higher pCR rates with the addition of platinum (1). There is heterogeneity in the choice of neoadjuvant chemotherapy regimens in the UK at present; however, it is fair to say that both epirubicin and doxorubicin are used in this context currently. Clinical guidelines (including NICE guidance [NG101]) suggest that neoadjuvant systemic therapy be used in the treatment of T2 or N+ TNBC and that a regimen containing both anthracycline and a platinum should be considered. Similarly, international guidelines such as St Gallen guidance recommend neoadjuvant systemic therapy as the preferred initial approach for women with stage 2/3 TNBC (2). Thus, the overall pathway of care (neoadjuvant systemic therapy followed by surgery) is well-defined, and the addition of pembrolizumab would not alter this pathway.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Pembrolizumab is already in use in the treatment of other solid tumours and therefore there is experience within the NHS with the use of this agent. Therefore, no additional training or equipment should be required. The technology should be used in specialist clinics as is currently the case for the delivery of systemic anti-cancer therapy.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The addition of pembrolizumab to chemotherapy increased pCR rates in KN-522 by 7.4% (95% CI 1.6=13.4%), from 55.6% in the placebo arm to 63% in the experimental arm. Furthermore, the most recently published analysis of KN-522 confirmed a significant improvement in event-free survival in patients treated with pembrolizumab, with a HR of 0.63 (95% CI 0.48-0.82, p<0.001) (3). First events consisted of progression of disease that precluded definitive surgery in 1.8% vs 3.8% of patients, local recurrence in 3.6% vs 4.4%, distant recurrence in 7.7% vs 13.1%, second primary cancer in 0.8% vs 1.0%, and death from any cause in 1.9% vs 1.5%. Overall survival data however remains immature; however, given that the most common event in the EFS analysis was distant relapse (7.7% in the pembrolizumab arm versus 13.1% in the control arm) it is possible that an OS benefit may be seen in future analyses. HRQoL scores did not decrease with the addition of pembrolizumab to chemotherapy, suggesting that an improved EFS with this agent may well have a positive impact on HRQoL.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The KEYNOTE-522 study reported that pCR rates were higher in patients with PD-L1 positive tumours. No other biomarkers predictive of response to pembrolizumab have as yet been identified. However, KEYNOTE-522 did not require that patients were PDL-1 positive to access immunotherapy.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	If the regimen from KEYNOTE-522 were to be used: In the neoadjuvant phase: Intravenous pembrolizumab at 200mg every three weeks, plus paclitaxel 80mg/m^2 once weekly with carboplatin* AUC 5, 3 weekly for 12 weeks, followed by continued intravenous pembrolizumab 200mg every three weeks plus epirubicin 90mg/m^2 with cyclophosphamide 600mg/m^2 once every three weeks for 12 weeks. *Carboplatin could also be given AUC 1.5 on a weekly basis. In the adjuvant phase: Intravenous pembrolizumab 200mg once every three weeks for up to 9 cycles.

	The standard of care would comparatively be either: 1. Carboplatin AUC 5, 3 weekly and paclitaxel 80mg/m² weekly for 12 weeks followed by Epirubicin 100mg/m² and Cyclophosphamide 600mg/m² for nine weeks 2. Docetaxel 100mg/m² administered i.v. on day 1 every 21 days for four cycles, followed by epirubicin 90 mg/m² plus cyclophosphamide 600mg/m², both administered intravenously (i.v.) on day 1 every 21 days, for six cycles followed by docetaxel No significant practical differences with respect to time required within treatment units.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Although improved pCR rates appear to be related to PD-L1 positivity in the published data, the benefit (in terms of improved pCR rates or EFS) of pembrolizumab is not restricted to PD-L1 positive patients, and therefore PD-L1 testing would not necessarily be a good biomarker for patient selection. As discussed above there are no other good biomarkers at present which can be used to select patients for immune checkpoint inhibition. A comprehensive review of potential companion biomarkers has not been completed.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No

• Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Whilst there is early evidence of improved pCR and improved EFS in a single trial, an overall survival benefit has not yet been established. It would also be important for the trial to provide details of deaths from all causes, to exclude immunotherapy related sequelae contributing to this. For each individual achieving pCR there would be an improvement in risk of relapse and death.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	In the KEYNOTE-522 trial, any-grade adverse events of special interest occurred in 773 (99.0%) patients in the pembrolizumab plus chemotherapy group compared with 388 (99.7%) patients in the placebo plus chemotherapy group(4). The most common AEs of interest were infusion-related reactions (132 [16.9%] and 43 [11.1%], severe skin reaction (36 [4.4%] and 4 [1.0%], respectively), hypothyroidism (107 [13.7%] and two [1%], respectively), hyperthyroidism (36[4.6%] and 2 [0.3%], respectively and adrenal insufficiency (18[2.3%] and 10 [1.3%] respectively). Treatment-related AEs led to death in 3)0.4%) and 1 (0.3%) of patients in the pembrolizumab and control arms respectively.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting?	Yes – the placebo arm of KN-522 could be considered to be broadly reflective of current UK clinical practice in this setting, not withstanding the comments above regarding some degree of treatment heterogeneity in this setting. Not all UK units currently use a platinum in the neoadjuvant treatment of breast cancer although given increasing weight of evidence for improved pCR rates using

• What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	regimens containing this agent, it is likely that this regimen will be increasingly widely used. Although pCR rates are an important outcome measure in this setting, the key questions surround event-free and overall survival. At a median follow-up of 36 months the presented data suggests a significant EFS benefit for pembrolizumab; however, a significant improvement in overall survival has not yet been shown. The primary outcome measure used was pCR. This is a recognised surrogate outcome measure, which has been approved by the US FDA to support the accelerated approval of treatments. However, as discussed above there is no established relationship at a trial level between pCR and long-term outcomes. EFS data has now been published, as noted above.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	No real-world data exist
23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	No

people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

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Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Choice of population: There are differences between the population defined in the NICE final scope (locally advanced non-metastatic disease) and the decision problem addressed in the company decision problem (also including inflammatory disease and early-stage disease at high risk of recurrence).	TNBC is considered an aggressive form of breast cancer and is at a disproportionately high risk of early recurrence, most commonly distant recurrence, as noted in the Technical Engagement Papers. Therefore, early TNBC as described here (cT1, N1-2 or cT2, N0-2) disease would be considered high risk and would be deemed at high risk of recurrence. cT4 disease (either inflammatory or involving skin/chest wall) would be considered locally advanced; however, if confirmed as non-metastatic by staging investigations, the treatment approach would be similar, with neoadjuvant systemic therapies followed by surgery, using similar regimens as non-locally advanced disease. Therefore the addition of pembrolizumab to chemotherapy for patients with non-locally advanced early TNBC, as well as for locally advanced or inflammatory disease, would be considered appropriate.

Clinical expert statement

Please define triple negative breast cancer that is 'locally-advanced non-metastatic', 'inflammatory' and 'early-stage with high risk of recurrence'. For example, is Tc, N1-N2 and T2, N0-N2 deemed early-stage disease at high risk of recurrence (aligned with inclusion criteria in KEYNOTE-522)? Are different treatments used for the different stages of disease described? Is pembrolizumab in combination a potentially appropriate option for people with early-stage or inflammatory triple negative breast cancer as well as locally advanced disease?	
Choice of comparator: The best available comparator in the adjuvant phase might be capecitabine rather than placebo.	Capecitabine is occasionally used in the adjuvant treatment of TNBC where there has been a non-pCR following neoadjuvant chemotherapy. However, this is based on data from the CREATE-X study, where patients with non-pCR following neoadjuvant anthracycline/taxane combinations received adjuvant capecitabine (5). No patients in CREATE-X received neoadjuvant platinum-containing regimen, so there is a lack of data to support this approach.

Is capecitabine (or any other chemotherapy) used for treatment of triple negative breast cancer in the adjuvant phase?	Nevertheless, anecdotally, some UK sites are known to be offering capecitabine in patients with non-pCR following neoadjuvant treatment with platinum-containing regimens.
Geographical effects: A small subset of participants in KEYNOTE-522 were from the UK. Subgroup analysis, based on a small dataset, suggests that geographical area is an important covariate influencing outcome, and so the observed effects may not be applicable to the UK. Is there any biological reason or differences in the care pathway which may mean evidence from the rest of the world are not generalisable to the UK?	A small subset of patients in KN-522 were from the UK; however, 50% of the trial patients were from Europe and a further 21% from North America, and the majority were white. The findings from the unplanned subgroup analysis may be a chance finding; given the overall composition of the trial participants there is no obvious biological rationale to suppose that the observed effects may not be applicable to the UK population.
TNM staging: Details of the 4 detailed TNM grades in KEYNOTE-522 were not provided. This information will inform the generalisability of the prognosis of the trial	

population to people seen in UK practice.	
ECOG staging: Subgroup analyses results indicated potential differences between Eastern Co-operative Oncology Group (ECOG) performance status, especially that compared to ECOG 0 participants, ECOG 1 participants did not demonstrate benefits from pembrolizumab in terms of pCR. Is there a biological reason that ECOG status (0 or 1) would influence the outcome of pathological complete response?	Only a small proportion of patients in KN-522 had ECOG PS 1 (~13%) – it seems unlikely that there is any reason that ECOG PS would influence the likelihood of achieving a pCR.
Adverse events: Risk of death was higher in the pembrolizumab arm than the placebo arm of KEYNOTE-522. Are there differences in the number and severity of adverse events (including death) seen in practice with pembrolizumab in	This increase in risk of death is something that needs to be looked at carefully as the data matures, in case any increase in death is attributable to longer term adverse effects secondary to adjuvant immunotherapy. At the moment there is insufficient evidence to ascribe such causality. Across all treatment phases, the incidence of treatment-related adverse events of grade 3 or higher was 78.0% in the pembrolizumab–chemotherapy group and 73.0% in the placebo–

combination compared with current practice?	chemotherapy group, including death in 0.4% (3 patients) and 0.3% (1 patient), respectively. The incidence rate is not significantly worse than for other neoadjuvant chemotherapy studies.
Model does not include health states for remission from locoregional recurrence or separate pre- and post-progression states for distant metastasis.	
Most health gains are obtained in the extrapolated event-free survival part of the model and is therefore uncertain. Use of different types of parametric distribution for extrapolation of event-free survival in the pembrolizumab + current treatment and the current treatment alone arms is not justified by the company.	
Probability of moving to distant metastasis (from locoregional recurrence state) and death (from locoregional recurrence state and distant metastasis state) is assumed to be constant over time.	

KEYNOTE-355 data is used to estimate survival in the distant metastasis state rather than KEYNOTE-522 data. KEYNOTE-522 data on distant metastasis is immature but there are substantial differences in observed survival between KEYNOTE-522 and KEYNOTE-355. Is the use of data from KEYNOTE-355 to estimate overall survival in people with distant metastasis appropriate?	KEYNOTE 355: **The final** overall survival results from the KEYNOTE-355 study showed a statistically significant 27% reduction in the risk of death for patients with metastatic triple-negative breast cancer whose tumors were strongly positive for PD-L1, defined as a combined positive score (CPS) of at least 10 and who received pembrolizumab vs placebo combined with chemotherapy as first-line therapy. Whilst these are important results for first line metastatic treatment extrapolating this to comment on KEYNOTE-522 seems an over-reach. The patients in KN-522 received adjuvant immunotherapy alone for 27 weeks, so the two trials are not comparable.
Utility values for the distant metastasis state (including progressed and non-progressed disease) appears relatively low (see ERG report table 4.9). A small number of people experienced distant metastasis in KEYNOTE-522 and there are doubts about the validity of the use of this utility value in model.	
Are there any important issues that have been missed in ERG report?	

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Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

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Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

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For more information about how we process your personal data please see our privacy notice.

Commented [ja1]: I would say that there is evidence that neoadjuvant pembro does provide additional benefit to pCR rates. There is evidence to suggest that EFS may also be improved. There is a need to understand with greater clarity whether all patients require 27 weeks of adjuvant pembro. Ultimately I think we should probably approve it but with further reviews as data matures. Again happy to chat.

1. Loibl S, O'Shaughnessy J, Untch M, Sikov WM, Rugo HS, McKee MD, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. The lancet oncology. 2018;19(4):497-509.
2. Burstein HJ, Curigliano G, Loibl S, Dubsky P, Gnant M, Poortmans P, et al. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2019;30(10):1541-57.
3. Schmid P, Cortes J, Dent R, Pusztai L, McArthur H, Kummel S, et al. Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer. N Engl J Med. 2022;386(6):556-67.
4. Schmid P, Cortes J, Pusztai L, McArthur H, Kummel S, Bergh J, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020;382(9):810-21.
5. Masuda N, Lee S-J, Ohtani S, Im Y-H, Lee E-S, Yokota I, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. New England Journal of Medicine. 2017;376(22):2147-59.

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Technical engagement response form

Pembrolizumab in combination with chemotherapy for neoadjuvant and adjuvant treatment of triple negative breast cancer [ID1500]

As a stakeholder you have been invited to comment on the evidence assessment group (EAG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The EAG 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 EAG 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 EAG 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 EAG 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 **Wednesday 20 July.** 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.

Technical engagement response form

Pembrolizumab in combination with chemotherapy for neoadjuvant and adjuvant treatment of triple negative breast cancer [ID1500]

NICE National Institute for Health and Care Excellence

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.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response	EAG response
1. Choice of population	No	**MSD would like to highlight the reasons for the differences between the company submission and the original NICE Scope detailed in the ERG report. An updated final scope has since been issued by NICE to reflect the final marketing authorisation licence as it had omitted the word 'early'. The population stated in the company submission is in line with the final licensed population.** The population is different as during the scoping process the EMA dossier was being assessed and therefore the anticipated licence was marked as Commercial In Confidence (CIC). The data	Thank you for the clarification. Our responses are as follows: **Centrally confirmed** The EAG agrees that this difference is not of importance. Whilst in theory this difference narrows the trial scope relative to the NICE scope, in practice it simply confirms that the trial evaluated the correctly and/or clearly-specified population, which is exactly what a trial would be expected to do. This may lead to a mismatch with the patient population but that is less of a problem than trial results from an incorrect or poorly-specified population. **Inflammatory**

		presented by MSD is in line with the licence issued by the MHRA. The licence wording is as follows "[pembrolizumab] in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence" • **Centrally confirmed:** Centrally confirmed is not part of the licence wording and is reflective of the trial design. It not anticipated that patients will be required to have their TNBC status confirmed by a central NHS laboratory. • **Inflammatory**: The use of the word inflammatory was not to provide a second category of patients, but to show that patients with inflammatory breast cancer were eligible for the study if they met the other criteria. • **High risk of recurrence**: The wording regarding high risk of recurrence was provided to NICE but was marked as CIC and therefore could not be publicly shared in the final scope. • **Early stage**: During the Technical Engagement call on the 30th of June 2022, it was noted by NICE that the words 'early stage' had been inadvertently omitted from	Had the trial used the Boolean operator 'and' in relation to 'inflammatory' then the population of the trial would have been made narrower than the patient population. However, this did not occur. Instead, it was stated that, [redacted]", implying the Boolean operator "or". Therefore, the EAG agrees that the term 'inflammatory' does not present a problem. **High risk of recurrence** In the response to clarification the company stated that the term 'high risk of recurrence is synonymous with 'locally advanced'. If correct, this would make the term compatible with the NICE scope, which specifies 'locally advanced'. However, the EAG would like to have further evidence that this is the case. If 'high risk of recurrence' and 'locally advanced' do indeed have identical meanings it seems strange that both terms have been used as inclusion criteria in KEYNOTE 522. **Early stage** As this term has now been added to the new NICE document the EAG is satisfied that this is resolved. **PS 0 or 1** The EAG does not think that the company has justified this mismatch adequately. As it stands, the restriction of the trial population

		the population wording in the scope document. A new scope was issued on 5th July 2022 which means this issue can be resolved. • **PS 0 or 1**: Patients needed to have a performance status of 0 to 1 to be eligible for the trial. PS is not included as part of the licence wording in any pembrolizumab indications. There is no data from KEYNOTE-522 for patients with PS 2. **MSD considers that the population stated in the company submission is in line with the final licensed population.**	to PS 0 or 1 is at odds with the NICE scope, which makes no such restriction on the basis of PS score, and this represents a clear case of the trial population being narrower than the patient population.
2. Choice of comparator	No	The ERG discussed the implication of the potential use of adjuvant capecitabine instead of placebo. MSD has provided scientific rationale as to why capecitabine as active comparator in the adjuvant phase is irrelevant for this submission. **MSD disagrees that capecitabine should be considered a comparator in the adjuvant setting for the population under consideration**. Our arguments are below. We note the ERG's comment that 'current practice does not commonly use adjuvant therapies (such as capecitabine)' therefore the trial is generalisable to the UK setting and the	The EAG accepts the differences between the KEYNOTE 522 and CREATE X trials but does not accept the company's argument that capecitabine is an inappropriate comparator. The differences cited could lead to capecitabine being less effective when used alongside pembrolizumab, but, equally, they could also accentuate efficacy, or make no difference at all. What the CREATE-X trial tells us is that capecitabine may have a role in the adjuvant phase, and that evaluation of pembrolizumab without taking this possibility into account makes the evaluation incomplete.

		efficacy result reported is reflective of the efficacy gain expected in routine clinical practice in the UK. To include capecitabine, which is not standard of care, would provide information extraneous to the decision problem. MSD provides additional detail of why capecitabine cannot and should not be included in the appraisal. There are population and trial design differences between KEYNOTE-522 and CREATE-X, please see table 1 for details. In the CREATE-X study, the neoadjuvant chemotherapy did not include carboplatin, so it is not known whether post-neoadjuvant capecitabine provides similar benefit after a platinum-containing neoadjuvant regimen (as in KN522) compared to a platinum-free neoadjuvant regimen (as in CREATE-X). Furthermore, it is unclear whether post-neoadjuvant capecitabine improves long term survival after neoadjuvant use of immunotherapy (as in KN522) compared to CREATE-X where neoadjuvant treatment was only chemotherapy. It is not possible to compare the use of pembrolizumab in the adjuvant phase with adjuvant capecitabine as these patients also received pembrolizumab in the neoadjuvant phase. The CREATE-X study results and the recommendation by oncology societies that	Whilst it may be true that current practice does not commonly use adjuvant therapies (such as capecitabine), it is likely that the trial's use of placebo in the adjuvant phase, rather than an active comparator such as capecitabine, may contribute to an increased estimate of benefit for pembrolizumab. Thus, whilst this observed benefit may be realistic in terms of comparison to established practice, therefore fulfilling the criteria outlined in the NICE final scope, it might not tell the committee how much better pembrolizumab is than the best available alternative approaches, established or not. This is the information that the committee need in order to make their decision.

capecitabine is an option for patients with TNBC and non-pCR after neoadjuvant chemotherapy came while KN522 was actively accruing patients, about mid-way during the enrolment period. At that time, the FDA was consulted about possibly including post-neoadjuvant capecitabine in KN522, but the feedback was that such a change while the study was already ongoing and at an advanced stage would negativity impact the interpretability and regulatory validity of the results. (1)

Table 1: Comparison of KEYNOTE-522 and CREATE-X trials

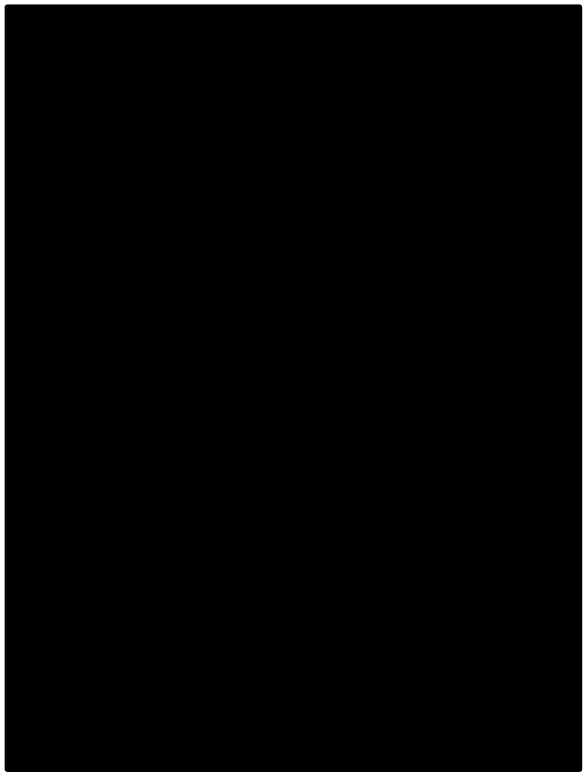
	KEYNOTE-522 n=1,174	**CREATE-X n=910 (2)**
Population	Patients with untreated newly diagnosed, locally advanced, centrally confirmed TNBC.	Patients with HER2-negative residual invasive breast cancer after neoadjuvant chemotherapy and surgery
Intervention	Pembrolizumab plus chemotherapy in the neoadjuvant	Adjuvant capecitabine

			phase followed by monotherapy pembrolizumab in the adjuvant phase.	
		Comparator	Placebo plus chemotherapy in the neoadjuvant phase followed by monotherapy placebo in the adjuvant phase	Placebo
		Primary Outcomes	pCR, EFS	DFS
		Number of patients from centres in Europe	434	0
		Abbreviations: DFS (and definition), EFS, pCR		
		MSD is aware that capecitabine as adjuvant therapy is not indicated specifically for TNBC patients (3). The cost of adjuvant capecitabine is very limited (capecitabine has a very low drug acquisition cost and is administered orally). From a costing perspective, hospital treatment protocols dictate 6 to 8 cycles or capecitabine as adjuvant (however, again this is not TNBC		

		specific) (4). Since this may only be used in a limited subset of patients (as noted by clinical opinion) the implications form a costing and cost-effectiveness perspective are extremely limited. Clinical experts consulted during the technical engagement process, reiterated the statements made in the company submission, and that the use of adjuvant capecitabine is very limited and associated with limited survival benefit. They also noted that it was only offered because of the lack of effective alternative treatment options. **MSD does not consider that capecitabine in the adjuvant setting is a relevant comparator for this submission and for the population under consideration. It is neither possible nor appropriate to leverage the results from the CREATE-X study to inform such comparisons**.	
3. Geographical effects	No	**MSD disagrees that 'overall data in the trial might be providing an overly optimistic picture for European patients.' Also, the subgroup analyses are not intended to be used for inferential testing as the study was not powered for definitive demonstrations of efficacy in these subgroups. Therefore, the results of these exploratory analyses should be interpreted with caution.** In KEYNOTE-522, 40 (3.4%) participants were from UK: 27 participants were in the	The EAG reiterates the important point that *because the sub-group analyses were underpowered it is particularly vital for the committee to be aware of the potential for a type II error*; that is, that European and non-European patient populations may actually differ in outcomes, and so the trial results may be unrepresentative of the UK population. As for the economic model, the EAG chose to maintain their base-case of the adjusted HR for Europe versus rest of the world since

		pembrolizumab group and 13 participants were in the placebo group. The numbers of participants are too small for a meaningful subgroup efficacy analysis. The ad-hoc analyses of testing interactions of treatment and subgroup variable of geographic region (Europe/Israel/North America/Australia, Asia, and Rest of World) were performed. The study was not powered to carry out statistical testing for interaction and there were no multiplicity adjustments for multiple testing in the subgroup analyses. Therefore, the results need to be interpreted with caution. A Cox regression model with covariates for treatment, a subgroup variable, and treatment by subgroup variable interaction was performed. The p-value of 0.1843 was greater than 0.1, which indicates the treatment effect is not likely to differ across strata within geographic region (no plausible quantitative effect modifier observed of geographic region). **To MSD's knowledge there is no robust evidence which suggests that geographical region is a treatment effect modifier in the context of neoadjuvant and adjuvant therapy in this population. MSD asserts that the base-case should be based on the full trial population as the basis of the cost-effectiveness analysis.**	this may be considered a more plausible effect size than what was used in the company base-case. Although the EAG acknowledges that this approach may not be very precise, it provides an idea of the magnitude of the impact on the ICER when effectiveness is less than now assumed by the company.

4. TNM staging	Yes	**MSD is able to provide reassurance to the ERG the ratio of TNM in KEYNOTE-522 is equivalent to ratios of TNM in the UK population to allow a better judgement on the external validity of the trial.** MSD is currently undertaking a study using data from the English Cancer Registry investigating those patients diagnosed with TNBC between 01/01/2015 and 31/12/2018. TNM information on patients is displayed below (Figure 1) and shows a similar distribution to that observed in KEYNOTE-522. **Figure 1: Comparison of TNM in KEYNOTE-522 and patients in England**	The EAG is reassured by the data below, which appear to demonstrate that the trial sample had a larger proportion of participants at a higher level of severity than the UK population, and a lower proportion of participants at a lower level of severity than the UK population. These point estimate differences are in the opposite direction to those which would cause the EAG concern.

		 **The data presented provides external validation that the TNM ratios in England are similar to those in KEYNOTE-522 and there**	

		would be no reason to assume outcomes would be different.	
5. ECOG staging	No	The ERG concludes that for people with an ECOG score of 1, pembrolizumab is unlikely to be cost effective after looking at subgroup analysis results for EFS. The ERG argues that more evidence may be required for ECOG PS=1 for decision purposes. **MSD considers that the population of KEYNOTE-522 covers ECOG PS 0 and 1 patients. KEYNOTE-522 was not statistically powered to ascertain clinical differences within this subgroup. There is no biological rationale on why the clinical benefit of PS =1 patients would differ, noting that PS clinical distinction between these two subgroups can be sometimes vague.** MSD would like to reiterate the clarification questions response: subgroup analyses were not intended to be used for inferential testing as the study was not powered for definitive demonstrations of efficacy in these subgroups or formally compare efficacy between subgroups. Therefore, the results of these exploratory analyses should be interpreted with caution. In addition, the number of patients with ECOG PS of 1 is relatively small (106 participants in	The ERG reiterates the important point that because the sub-group analyses were underpowered it is particularly vital for the committee to be aware of the potential for a type II error; that is, that ECOG 0 and ECOG 1 populations may actually differ in outcomes, to the extent that for the ECOG 1 group pembrolizumab may not be cost-effective, although the EAG was not able to take the uncertainty caused by this issue into account in the economic model.

		pembrolizumab group and 49 participants in placebo group), and so caution should be taken in interpreting efficacy differences between these two groups. The treatment difference for pCR, Hazard Ratios (HRs) for EFS and OS between treatments had overlapping confidence intervals in participants with ECOG PS of 1 and ECOG PS of 0 (as shown in figures 3.1 and 3.2 of the ERG report). **MSD asserts that the base-case should be based on the full trial population as the basis of the cost-effectiveness analysis.**	
6. Adverse events	No	**MSD acknowledges there is a difference between the percentage of serious adverse events between the two arms in KEYNOTE-522. This reflects the safety profile of adding pembrolizumab to neoadjuvant chemotherapy administered.** As noted by the EAG, the incidence of AEs leading to death was 0.9% in the experimental arm compared to 0.3% in the control arm. No specific AE resulting in death was reported in more than 1 participant. No new safety signals were identified upon review of these fatal events. Pembrolizumab is established in other tumour groups and recently approved for metastatic	The EAG acknowledge the small risk difference of 0.6%, but the risk ratio of 3 cannot be ignored because over the entire population and over time this could equate to a significant number of lives (whilst acknowledging the uncertainty around this point estimate). The EAG therefore think it is relevant to make this statistic clear to the committee so that they can incorporate it into their weighing up of benefits and risks.

		TNBC where clinicians are comfortable in its use and management of adverse events. **There were no specific trends noted for the pembrolizumab group that suggest a new safety concern.**	

7. Model structure not including locoregional remission and no differentiation between pre-progression and post-progression distant metastatic patients. Model may not adequately capture costs and benefits.	No	It is important the structure and the rationale for the structure of the economic model are well understood. MSD's response to this issue aims to address some missing information and possibly clear any misunderstanding about why the model is structured as it is and around the model mechanics. Points raised below include "Remission" after locoregional recurrence (LR) and the value of separating the pre and post-progression at distant metastasis (DM) health state. The ERG states that current model structure which does not include a "Remission from locoregional recurrence (LR)" and separate "pre- and post-progression states for distant metastasis (DM)" may not reflect clinical practice. The ERG argues that the current model may not capture correctly subsequent costs and health benefits associated with these health states. The criticism in the current model structure arises from the fact that MSD's model deviates from the TA424 model structure which was designed to explore the cost-effectiveness of pertuzumab as neoadjuvant treatment for early-stage HER2-positive breast cancer. **MSD disagrees with the ERG's opinion and is confident that the current model structure adequately captures costs and benefits of the TNBC pathway. As with all models, balancing optimal model structure with available data is key. Driving the structure of this model, and where it is different to other breast cancer models, is that there is substantial less data for TNBC. We note that TNBC data in contrast to other BCs such as HER2+ve are limited. This does not allow more complex modelling and multiple health states without imposing assumptions adding to the model complexity and uncertainty (such as explicit "Remission" modelling after locoregional recurrence (LR) or for the differentiation of the distant metastasis (DM) in pre and post-progression. The current model adequately captures downstream costs and benefits for decision making purposes without adding to unnecessary complexity and is** [redacted] The justification to deviate from the published TA424 model structure is re-iterated below alongside some	Thank you for the clarification. Our responses are as follows: **Lack of "Remission" after locoregional recurrence (LR):** The EAG appreciates that the company provided data on the transitions from the LR state in the KEYNOTE-522 trial. However, this graph does not provide any information on remission after LR as the events were either DM or death, and not remission. After around 70 days, a stable proportion of around 25% of patients remain in the LR state. It is unclear whether there were no remissions from LR, or that it was not

		additional explanation pertaining to the functionality of the current model. We demonstrate that the current model structure sufficiently captures all relevant costs and outcomes associated with the management TNBC in both the locoregional and distant setting. The current submission leverages a Markov model to estimate costs and outcomes, consisting of four mutually exclusive health states; event-free (EF), locoregional recurrence (LR), distant metastasis (DM), and death, to track the disease course and survival of patients over time. This model structure explicitly captures the disease pathway of patients with early-stage TNBC as well as including the functionality to model metastatic outcomes with appropriate accuracy. The model can differentiate health states by type of recurrence (either LR or DM) because the co-primary endpoint of the KEYNOTE-522 (i.e., EFS) trial encompasses both types of recurrence events and because these are relevant for the clinical management of patients. These two types of recurrences have different implications on patients' prognoses, and therefore result in different health outcomes and costs which is important from a decision-making perspective. <u>Lack of "Remission" after locoregional recurrence (LR) in ID1500:</u> **MSD interprets "Remission" as the absence of cancer specific symptoms or evidence of detectable disease at a specific timepoint. Remission does not necessarily preclude further progression to metastatic disease and subsequent death from cancer. Clinical experts consider that the exclusion of "Remission" after LR is clinically valid due the aggressiveness of TNBC versus other types of breast cancer. They indicated that the majority of patients with locoregional recurrence would not be salvageable with subsequent surgical resection and therefore have poor prognosis (i.e., develop a DM or die). Therefore, we consider the lack of remission modelling after LR to be appropriate and therefore the model can accurately capture costs and outcomes associated with TNBC.**	measured. Therefore, the EAG is not convinced on the company claiming that remission after an LR is not substantiated based on these data. The EAG is more reassured by the further validation of assumption of no remission after LR by consultation with an expert, confirming that the chance of remission after LR is small given the aggressive nature of TNBC. Since only a small percentage of patients will experience remission from LR according to experts and there is no data available on how many patients it concerns, and the fact that no further treatment effect was assumed in the LR

		The current clinical data from KEYNOTE-522 do not provide any evidence of remission after a locoregional recurrence. Analysis of pooled treatment arm clinical trial data from KEYNOTE-522 shows that most patients which develop an LR event, experience DM or death (Figure 2). Therefore, Remission after a LR is not substantiated by the clinical trial data itself and would be reliant upon additional assumptions being imposed in the economic model itself. This assumption alongside the current model structure were both validated during a global advisory board which took place during the submission development process ([redacted]). UK clinical experts were also presented with the CE model structure at a UK advisory board during the submission development process and considered the model structure appropriate in the context of TNBC. **Figure 2: Observed combined KEYNOTE-522 arms time to event (TTE) from LR in weeks (event = distant metastasis or death from LR).**	health state, the EAG considers the lack of a remission health state from LR acceptable. **No differentiation between pre and post-progression at distant metastasis (DM) health state:** The EAG acknowledges that due to the design of the KEYNOTE-522 and its available data it is not possible to model pre-progressed and post-progressed DM state separately without making assumptions that would cause uncertainty. However, the EAG wants to reiterate that pre-progression and post-progression costs and utilities differ and combining

		 Notes: TTE = Time to Event, reported in Weeks with event being equal to distant metastasis or death. MSD is limited to the extend it can comment on a manufacturer's submission without visibility of the full data. In the NICE TA424 (Pertuzumab for Neoadjuvant Treatment of Early-Stage HER2-Positive Breast Cancer) patients could enter the "Remission" health state after locoregional recurrence. In TA424, the manufacturer introduced a series of tunnel states to model locoregional recurrence, therefore artificially superimposing a time dependency (i.e., that 12 months must be spent in LR before entering "Remission") in part of the economic model. Only after LR had taken place could these patients enter the "Remission" health state and therefore influence the subsequent health state occupancy. Whilst patients remained in the LR tunnel states, they could not experience a further progression or death event for 12 months which is a simplistic and implausible assumption considering the KEYNOTE-522 clinical trial data and expert opinion. **Therefore, the** "**Remission" health state in TA424 in fact**	these into one DM state has its limitations. The company has included treatment costs for pre-progressed (1L) and post-progressed (2L+) DM patients. However, as the company also acknowledges, this approach does not allow for costs being corrected for discounting and half-cycle correction. In addition, utilities could not be corrected for the DM progression status. The company explains in issue 11 that an analysis of utility values from KEYNOTE-522 by DM progression status could not be performed. Although the company argues that this approach is

		resembles the "Locoregional recurrence" of this submission without adding unnecessary complexity with the introduction of tunnel states that may not be appropriate for TNBC considering its aggressiveness and poor prognosis vs HER2+ve BC. The overall approach used in TA424 was relevant for decision making purposes at the time, this assessment took into consideration the RCT design and trial endpoints support the TA424 recommendation. This does not necessarily mean that the same modelling approach would be appropriate for TNBC given the population and trial differences (primary outcome differences, re-challenge in adjuvant setting). The availability of clinical data and clinical endpoints reported in TNBC is not as extensive as in HER2+ve BC since very limited changes in the TNBC treatment pathway have taken place over the last 2 decades. Therefore, evidence would not be derived from clinical studies but rather be based upon arbitrary assumptions leading to model complexity (and thus inflate uncertainty further in contract to the KEYNOTE-522 clinical data itself). Page 79 of the ERG report reads; *"The ERG acknowledges the differences between TA424 and the current submission and agrees with the company that the introduction of a remission state is not ideal, as it would increase the model's complexity by introducing multiple tunnel states to the model."* However, the ERG still concludes that omitting the "Remission" post LR may not reflect clinical practice (page 79); "*However, assuming patients with LR cannot experience remission does simply not reflect clinical practice*". This thesis appears to be counter-intuitive considering the evidence base and the justification provided by MSD in terms of modelling. During the technical engagement process a UK clinical expert was consulted by MSD to test further the validity of this assumption at the request of the ERG (expressed during the technical engagement call). Considering the differences between HER-2+ve cancer (TA424) and TNBC, the clinical expert concluded that it is clinically	in line with other TAs, the EAG considers this a limitation of the model structure and feels that if the trial was designed to differentiate between pre-progressed and post-progressed patients in the DM state, cost-effectiveness outcomes could have been calculated more accurately. All in all, with the limitations of the data available it was not possible for the EAG to include a remission state (or to substantiate exclusion of the state) and to differentiate between pre- and post-progressed in the DM state. Therefore, uncertainty with regard to the model structure remains

		justified not to model a “Remission” health state after a locoregional recurrence in TNBC. The support of this was on the basis that TNBC is more aggressive versus other early breast cancer such as HER-2+ve. Based on their clinical experience, the clinical expert noted that the majority of TNBC patients with LR would not be salvageable with subsequent surgical resection (i.e., they would not have an isolated LR recurrence) and would therefore be anticipated to experience a poor prognosis once at LR with wither progression to DM or death. They noted that only a very small proportion of patients with isolated LR would be surgically salvageable (therefore the implications in the C/E are likely to be very limited). The clinical expert concluded that the TA424 model structure is not reflective of TNBC’s aggressiveness and availability of data in TNBC versus other early BC tumours. The current model employs a conservative assumption which assumes equal transition probabilities for patients within LR using pooled trial arm data and therefore, no further potential treatment benefit once patients depart from the EF health state (owning to limited data available to inform treatment specific estimates. **The exclusion of “Remission” from current model structure is appropriate considering the current KEYNOTE-522 clinical data, data from overall TNBC patients and the clinical expert option. MSD therefore considers that the current model structure adequately captures the clinical outcomes experienced by patients and avoids introducing unnecessary complexity and uncertainty.** <u>No differentiation between pre and post-progression at distant metastasis (DM) health state:</u> The current economic model does not disaggregate the DM health state to pre-progressed and post-progressed DM and instead a single DM health state is used to model the survival from that health state which is based on the recent KEYNOTE-355 trial (alongside a network meta-analysis [NMA] to inform some comparisons). Costs for 1L mTNBC were calculated from KEYNOTE-355 and results from the NMA for some comparators. Costs for 2L+ subsequent therapies have been accounted for by using the most recent data from KEYNOTE-355 (TA801). MSD acknowledges that the	and the magnitude and direction of the impact on the ICER are unknown. The EAG appreciates that market shares have been updated to the current situation, but is not sure whether also updated survival incorporating treatment waning of pembrolizumab in the metastatic setting (as per committee discussion of TA801) was included in the estimates of OS here. The EAG takes note of the fact that the company has included an additional option in the model where OS in the metastatic setting is based on

		current single DM health state approach may introduce some limitations with regards to ascertaining the impact of DM-post-progression utility (discussed separately below). The decision for single DM health state was taken to avoid unnecessary complexity within the current submission since the evidence base for mTNBC in contrast to HER2-ve BC is more limited and would therefore require assumptions and more complex artificially increasing uncertainty. UK clinical experts were presented with the CE model structure at a UK advisory board during the submission development process and considered the model structure appropriate in the context of TNBC. Metastatic TNBC lacked effective treatment options until recently with the introduction of anti-PD-1 and anti-PD-L1 agents such as Atezolizumab + nab-paclitaxel and pembrolizumab + taxanes for 1L mTNBC treatment options in PD-L1 +ve tumours (PD-L1 +ve ascertainment differs between options). The above approvals had a positive impact on patient long term survival but are treatment options for ~38% of patients with PD-L1 +ve tumours. The majority of patients (~62%) are PD-L1 -ve (or for whom PD-L1 test is not preformed) would therefore continue to be treated with standard of care chemotherapy options (such as taxanes or platins) for 1L mTNBC disease. Overall, for these patients treatment options may include gemcitabine with or without carboplatin or taxanes (paclitaxel or, nab-paclitaxel). However, it is understood that all standard 1L mTNBC and subsequent chemotherapy treatments offer limited survival extension (i.e., the survival benefit is primarily conferred by the 1L mTNBC option received once patients develop a distant metastasis). **The current DM modelling is not dissimilar with previous adjuvant submissions recently reviewed by NICE (some brief examples presented below). A few examples briefly described included TA766, TA544 and the ongoing ID3810. The methodology of the current model and its functionality is explained in more detail below.** • In TA766 - pembrolizumab as adjuvant treatment for stage 3 resected melanoma; a single DM health state was constructed; survival from DM was	the exponential function (also as per committee discussion of TA801) but this option does not seem to change anything in the results of the economic model, while committee discussion of TA801 states that changing the distribution had a substantial impact on the ICER there. So the EAG is not sure whether this option is fully functional. Taken together, the way of estimating survival is in itself sufficiently clear but the EAG still has worries about the appropriateness of the numbers taken from KEYNOTE-355 to this appraisal. Minor comment: the EAG believes that in Table 2 to the left, the original

		based upon a composite OS curve derived from OS NMA results weighted by market shares validated by HCPs. Subsequent treatment cost for 1L mMEL were estimated based on a PFS NMA weighted by the same market shares, one off weighted 2L+ costs were applied assuming a maximum treatment duration of 21 weeks (5). • In TA544 - dabrafenib/trametinib adjuvant resected stage 3 melanoma; the manufacturer applied a one off cost and QALY gain for 1L+ therapies extracted from previous TA not formally incorporating DM survival within the economic model (6). • Ongoing ID3810 – Pembrolizumab for adjuvant RCC; 1L line costs ad 2nd line costs were estimated and applied in a single DM health state; efficacy from DM to death is derived based upon 1 1L mRCC NMA for PFS and OS (7). **The current single DM health state allows for the incorporation of the AC's recent preferences pertaining to anticipated DM survival based on TA801 for key 1L comparators. This ensures that the model predicts robust survival estimates for the DM patients. Therefore the current single DM health state adequately captures metastatic treatment and disease management costs appropriately.** <u>Approach to model 1L+ survival:</u> Market research was conducted to understand the utilisation of 1L mTNBC treatment options across the UK. Clinical experts noted that the most likely 1st line chemotherapy options for patients with 1L mTNBC included; paclitaxel, carboplatin (or combination of), gemcitabine + carboplatin or capecitabine. These are available regardless of PD-L1 tumour status. However, patients with PD-L1 positive mTNBC (≥1% immunohistochemistry SP142) would at the time of this submission would likely be treated with Atezolizumab + nab-paclitaxel in the UK since TA801 was ongoing. Clinical experts were consulted to validate the market share (MS) treatment mix of 1L	market share for atezolizumab +nab-paclitaxel should be 38% (consistent with CS Table 42). This does not have any implications for the analyses run and is probably only a typo. The EAG appreciates the additional explanation but still has concerns regarding imprecision of the mTNBC costs. The EAG does not object to using PFS as a proxy for ToT per se, but disagrees with the statement that using PFS would imply that discounting, half cycle correction, an vial sharing could not be applied – although the Markov model structure could complicate things again. The main

mTNBC during an advisory board (final values used in the model are presented in Table 2).

Table 2: UK market shares for 1L mTNBC treatment options validated by UK HCPs

Treatment regimen	UK market research share estimate	Updated TE model market share estimates with rechallenge validated HCPs
Pembrolizumab + taxanes	0% (unavailable at time of submission)	~6.46% (17% of PD-L1 +ve patients)#
Paclitaxel		
Paclitaxel monotherapy		
Nab-paclitaxel monotherapy		
Carboplatin		
Carboplatin monotherapy		
Carboplatin + Docetaxel		
Carboplatin + Epirubicin		
Carboplatin + Paclitaxel		
Gemcitabine + Carboplatin		
Atezolizumab + Nab-paclitaxel*		~31.54% (~83% of 38% of mTNBC PD-L1 +v patients overall)#
Capecitabine		

Notes: *Final estimates uplifted to match the prevalence of PD-L1 positive IC population ~38%, # The origi base-case did not assume pembrolizumab rechallenge for DM disease due to the lack of pembrolizumab + taxanes at the time - the table above presents the actual market share data with pembrolizumab rechallen and assuming that pembrolizumab + taxanes is available for 22C2+ve/SP=142-ve patients only (17%)

concern of the EAG is in lumping everything together as a one off cost – and using data from multiple sources (not from KEYNOTE-522) and assumptions to get to these. Especially because the metastatic treatment costs make up about one third of all costs in the chemotherapy arm and are twice as high for the chemotherapy arm compared to the pembrolizumab arm, precision should be important here.

		KEYNOTE-355 overall survival data (total life year estimates) were extracted from the TA801 cost-effectiveness model where available. This included 1L mTNBC survival estimates from the Pembrolizumab + taxanes (paclitaxel or nab-paclitaxel) and paclitaxel chemotherapy arms which were recently discussed by the AC. The TA801 model also included survival projections for alternative comparators such as gemcitabine + carboplatin. The carboplatin + paclitaxel comparator was not directly modelled in TA801 CEA and upon expert opinion was assumed to have equal survival benefit to gemcitabine + carboplatin due to lack of clinical trials in the metastatic setting to inform alternative assumptions. For carboplatin monotherapy (or combinations with epirubicin) survival was estimated by applying a NMA derived OS HR versus taxanes (it is assumed that add on epirubicin does not to confer an additional survival benefit due to lack of clinical trials in the mTNBC to inform alternative assumptions). Capecitabine for 1L mTNBC disease not directly modelled in TA801 CEA. Due to lack of clinical literature in mTNBC to inform an indirect comparison versus other 1LMTNBC options, it was assumed to have equal survival benefit to taxanes from KEYNOTE-355. Survival of Atezolizumab + nab-paclitaxel was estimated using the NMA OS HR results of Atezolizumab + nab-paclitaxel versus Pembrolizumab + taxanes (paclitaxel/nab-paclitaxel). Based on clinical expert opinion sought by MSD and AC deliberations during TA639 and TA801, MSD understands that taxanes can be perceived to be equally efficacious (although differences in the toxicity/safety profile may exist). Therefore the use of pooled taxane arm data from KEYNOTE-355 to inform the NMA estimates is appropriate. The average survival benefit for all 1L mTNBC treatment options was finally weighted by the clinical expert validated MS estimates to derive an average survival for proportion of patients at the DM setting which received 1L+ metastatic therapy. No differences in the distribution of 1L mTNBC treatment received, apart from allowing for Pembrolizumab rechallenge for 1L mTNBC in PD-L1 +ve patients after 2 years of neoadjuvant/adjuvant initiation (this assumption was informed based on previous clinical experience from adjuvant melanoma). In KEYNOTE-522, [redacted] of patients will not receive 1L treatment for metastatic TNBC in the pembrolizumab arm and [redacted] in	

		the placebo arm. Therefore, RWE evidence was sourced to inform the mean DM survival for those patients (Aly et al 2019) as these patients are likely to experience a shorter survival. <u>Estimation of mTNBC treatment costs (1L and subsequent 2L+ costs):</u> We provide additional information on the method used to estimate the 1L mTNBC treatment costs to alleviate the ERG's concerns of imprecision around these (page 97 of ERG report). In brief, an approach similar to that outlined above for survival was used. Time of treatment data (ToT) from KEYNOTE-355 were extracted from the TA801 cost-effectiveness model where available. This included 1L mTNBC ToT from the Pembrolizumab + taxanes (paclitaxel or nab-paclitaxel) and paclitaxel chemotherapy arms (equal efficacy is assumed between paclitaxel and nab-paclitaxel) which were recently discussed by the AC. The TA801 model also included actual ToT data for alternative comparators such as gemcitabine + carboplatin where available. The carboplatin + paclitaxel comparator was not directly modelled in TA801 CEA. Since equal survival benefit assumed with gemcitabine + carboplatin, equal ToT was also assumed. For carboplatin monotherapy (or combinations with epirubicin) ToT was estimated by applying a NMA derived PFS HR versus taxanes. No evidence was derived for capecitabine as 1L mTNBC, therefore ToT was assumed to have equal survival benefit to taxanes from KEYNOTE-355. The ToT data for Atezolizumab + nab-paclitaxel were assumed to be equal to PFS projections estimated through an NMA of Pembrolizumab + taxanes versus Atezolizumab + nab-paclitaxel. During the TE process, an alternative exploratory scenario for Atezolizumab + nab-paclitaxel ToT was introduced which uses directly the ToT data from pembrolizumab + taxanes instead of the PFS NMA.	

		The area under the curve was estimated for each of the 1L mTNBC treatment options to derive the mean ToT for each of these comparators. The total drug acquisition cost for each of the 1st line mTNBC treatment options modelled (including IV infusion costs where appropriate) were then estimated. A weighted total 1L mTNBC treatment cost was then derived based on the anticipated market shares presented in Table 2 . These were validated by UK HCPs and factor in pembrolizumab rechallenge for 1L metastatic disease (2 years post neoadjuvant treatment initiation). MSD acknowledges that this methodology may lead to some overestimation of the 1L mTNBC drug acquisition costs because these are not adjusted for discounting rate, vial sharing, and half cycle correction. However, this is not dissimilar to the approach used in other NICE submissions whereby PFS is used as a time on treatment proxy to assign 1L metastatic costs (and therefore in those occasions costs remain unadjusted for discounting half cycle correction and vial sharing). As noted above, the current KEYNOTE-522 OS data remain immature. The same is the case for the subsequent treatment records available for analysis from KEYNOTE-522 to inform the DM setting post-progression (2L+ costs). Therefore, KEYNOTE-522 data cannot be used to provide robust estimates for subsequent treatments by progression status for patients with DM. For the purposes of economic modelling it is important that subsequent treatment costs for 2L+ mTNBC treatment options are also captured. Clinical experts have concluded that KEYNOTE-355 data with minor adjustments to account for subsequent IO usage, would be generalisable to the UK setting. For patients which received 1L mTNBC treatment a lump sum cost of 2L, 3L, 4L+ subsequent treatment options was applied. This was derived from the KEYNOTE-355 trial data based on the % of patients which received each of these lines of therapy. The mean ToT was derived from KEYNOTE-355. IO subsequent treatment utilisation in KEYNOTE-355 was limited and very well balanced, and therefore it is unlikely to affect the C/E results (IO records were distributed across other therapies to adjust the	

subsequent treatment costs). It should be noted that the KEYNOTE-355 subsequent treatment data are PD-L1 agnostic and primarily consist of chemotherapies already available to the NHS (refer to Table 10 of B3 clarification question response).

The table below presents the mean estimated 2L+ subsequent treatment costs applied in the model for patients that go on to receive 1L therapy for mTNBC by the type of regimen in the 1L mTNBC setting. Please note that during the TE process MSD conducted a minor update in the subsequent lump sum treatment costs for 2L+. We clarify that previous 2L+ lump sum costs included within this submission were incorrectly extracted from the original KEYNOTE-355 model which used interim OS (IA2 DBL) and subsequent treatment cost estimates. However, MSD subsequently updated KEYNOTE-355 model with the final OS results including updated subsequent treatment data which was provided to NICE during the technical engagement process of TA801. The updated lump sum 2L+ mTNBC costs are applied (minor uplift to the original values) in the latest model version, however the impact of these on the ICER is fairly limited.

Table 3: Subsequent treatment line costs by type of 1L mTNBC therapy received

1L mTNBC treatment regimen received	**UPDATED subsequent treatment (2L+) costs**	**Original subsequent treatment (2L+) costs**	**Source**
Pembrolizumab + taxanes (paclitaxel/nab-paclitaxel)	[redacted]	[redacted]	KEYNOTE-355 1L mTNBC CEM (8)
Paclitaxel	[redacted]	[redacted]	KEYNOTE-355 1L mTNBC CEM (8) (taxanes pooled arm)

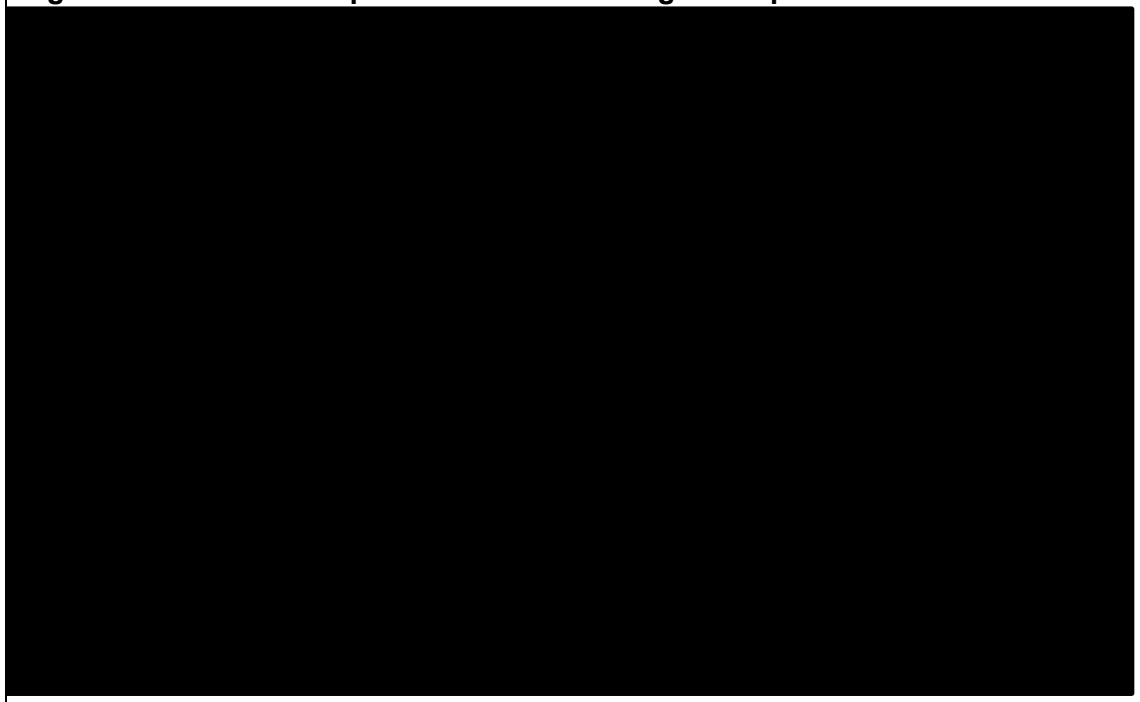
		Carboplatin†	[redacted]	[redacted]	Assumed same as gemcitabine + carboplatin from KEYNOTE-355 1L mTNBC CEM (8)
		Carboplatin + paclitaxel†	[redacted]	[redacted]	Assumed same as gemcitabine + carboplatin from KEYNOTE-355 1L mTNBC CEM (8)
		Gemcitabine + carboplatin	[redacted]	[redacted]	KEYNOTE-355 1L mTNBC CEM (8)
		Atezolizumab + nab-paclitaxel	[redacted]	[redacted]	KEYNOTE-355 1L mTNBC CEM (8)
		Capecitabine*	[redacted]	[redacted]	Assumed same as taxanes from KEYNOTE-355 1L mTNBC CEM (8)
		Metastatic TNBC lacked effective treatment options until very recently with the approval of Atezolizumab + nab-paclitaxel became in July 2020 (TA639) followed by Pembrolizumab + chemotherapy (taxanes) in June 2022 (TA801) (9, 10). These two treatment options are only available for patients with untreated PD-L1-positive tumours (approximately 38%; PD-L1 ascertainment differs; refer to TA801). The majority of patients in practice are PD-L1 negative (or are not tested for PD-L1 status; approximately 62% are negative], and therefore most patients with 1Lm TNBC would receive standard chemotherapy options, all of which are understood to be associated with limited survival benefit.			

		During the technical engagement process a further UK clinical expert was consulted by MSD with regards to the DM health state. The clinical expert noted that TNBC is a very aggressive tumour and therefore once patients develop a DM, their survival is mainly determined by the choice of 1L mTNBC treatment received noting that standard chemotherapies used for 2L+ result in limited survival benefit. The clinical expert also noted that with the exception of IOs for PD-L1+ve 1L mTNBC patients, standard 1L mTNBC chemotherapies also resulted in limited survival benefit. The clinical expert concluded that it is reasonable to model a single DM health state given the availability of TNBC evidence versus other early BC tumours but to account for 2L+ subsequent treatment costs. The current DM heath state modelling reflects the OS for patients with 1L mTNBC using data from a large multinational Phase 3 RCT which explored the efficacy of key 1st line chemotherapy treatment alongside pembrolizumab + taxanes. Subsequent treatment costs for 2L+ were derived from the same source and are fully reflective of NHS treatment practice. Whilst the DM state in the current model does not explicitly distinguish between 1L and 2L+ costs, from a costing perspective it adequately captures all TNBC associated costs relevant to the decision problem. **MD is confident that the model structure adequately captures the relevant cost and outcomes associated with TNBC progression. The current model structure does not make explicit claims on any additional benefit (or, conversely, a detriment) depending on the prior treatment received in the neo-adjuvant/adjuvant setting. To this end, MSD considers the model structure to be adequately structured to inform decision making, and a more complex model structure would only introduce superfluous complexity and rely on weak data/assumptions.**	
8. Modelled treatment effectiveness and	No	The ERG disagrees with the parametric curves selected by the company to model Event Free Survival (EFS) and suggests that the same type of distribution (in this case log-normal) may be more appropriate across both treatment arms. The ERG also notes that QALY gains continue to be accrued from the extrapolated part of the model. Analyses with shorter time horizon are presented which are inappropriate and discordant with the NICE reference case that stipulates that costs and benefits are	The EAG acknowledges that the company followed the methods for survival extrapolation as

extrapolation for EFS state likely overestimates effectiveness of pembrolizumab		assessed over lifetime. MSD accepts that choosing the most suitable parametric curves is a topic that features in many appraisals conducted by NICE, and therefore is likely a matter for the committee to consider, but for completeness below is a summary of the process taken to determine the base-case approach used in MSD's submission. **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 (11). MSD's base-case parametric curve selection for EFS extrapolation in the Pembrolizumab + chemotherapy arm was that of Generalised Gamma. The log-normal distribution was selected to model EFS extrapolation in the chemotherapy arm. MSD considers that the unique mode of action of immunotherapy agents (IO) such as pembrolizumab + chemotherapy warrants alternative parametric distributions for valid EFS extrapolations.** <u>Model selection process:</u> Patient level data from KEYNOTE-522 IA4 were used. Prior to model fitting, EFS cumulative and log-cumulative hazard plots were generated to assess the proportional hazards assumption. 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. Further interrogation of cumulative hazard plots revealed the crossing the log-cumulative hazards of the two treatment arms, therefore suggesting the implausibility of the proportional hazard assumption. For this reason, separate models were explored to fit the data for each arm for the projection of EFS. Visual inspection of log-cumulative hazard plots and statistical tests identified potential cut-off points for two-phase models were identified to capture potential turning points of the EFS curves in both treatment arms. The base-case used a 50-week timepoint for piecewise extrapolations in both treatment arms to ensure that sufficient data remained beyond	described in the NICE TSD DSU. However, the EAG questions the use of arm-specific parametric distributions for EFS extrapolation. The company bases the use of alternative distributions on the following argument: *"The unique mode of action of IO agents cannot be perceived to be comparable to that of chemotherapy alone; therefore, the underlying hazard assumption for the parametric curve does not need to be the same."* However, the company does not provide any reference for this, nor does the NICE TSD DSU recommend that one should use alternative distributions across

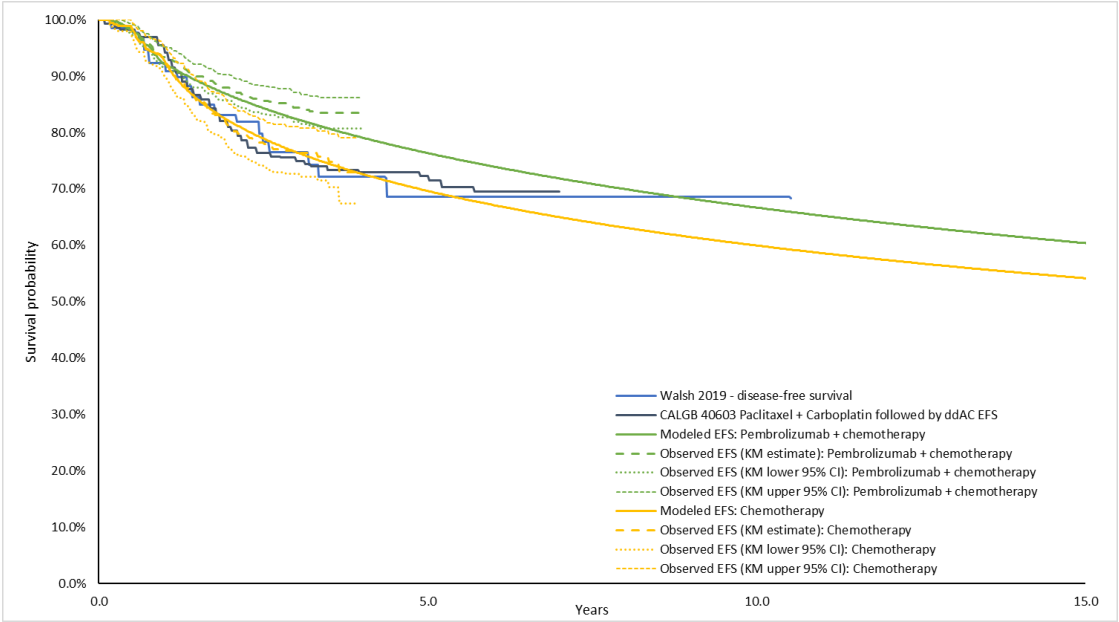
		this point for EFS extrapolation. Finally, the suitability of alternative models was assessed both by considering internal and external validity from RWE sources and the clinical plausibility of the extrapolated results. The AIC/BIC statistics are presented in Table 9 below. <u>Justification for different models:</u> MSD's current base-case model selected for Pembrolizumab + chemotherapy based on statistical fit to the observed data ranks 1st. Although the log-normal distribution ranks 2nd, the AIC/BIC difference versus the 1st best curve is 4.93 points (refer to Table 9). This is indicative of the poorer fit to the observed data, despite ranking as second in terms of statistical fit. The Generalised-gamma model was also preferred by clinical experts versus that of log-normal because it was unlikely that 10% of events will occur between 5 and 10 years which is suggested by the choice of the log-normal for pembrolizumab + chemotherapy arm. For this reason MSD selected the choice of generalised-gamma to model EFS extrapolations for pembrolizumab + chemotherapy. The unique mode of action of IO agents cannot be perceived to be comparable to that of chemotherapy alone; therefore, the underlying hazard assumption for the parametric curve does not need to be the same. This has been observed alongside across a number of metastatic and adjuvant submissions with IO agents to date (5, 12). During the submission development process clinical experts advised MSD that IO therapies used in the neoadjuvant /adjuvant setting may have an effect of improving 'Immune surveillance' due to their unique mode of action by activating, therefore enhancing the ability of the patient's immune system to recognise and destroy tumour cells and micro-metastases and enhance immune memory, resulting in the removal of any residual disease (13). MSD is therefore of the opinion that alternative parametric models are appropriate for EFS extrapolations for the two treatment arms. The ERG's approach (which uses the same parametric model to extrapolate EFS for both arms) implicitly assumes that the same parametric function can be used to describe the hazard function for two	treatment arms in case of a unique mode of action. The company does refer to two other TAs with IO agents: TA766 and TA684. However, these TAs did not use the same approach. In TA766 the models were selected such that the same combination of parametric models could be used in the pembrolizumab and routine surveillance arms, though the company does mention that this is a conservative approach potentially biasing against pembrolizumab due to the potential for immune memory due to the unique mode of action of IO agents. In the original submission of TA684

		mechanistically different treatment strategies. It is MSD's view that the choice of setting the EFS curve for the pembrolizumab arm to align with the choice for the control arm likely leads to biased estimates of cost-effectiveness against pembrolizumab, given that the effect of this change leads to reduced survival gains versus MSD's base-case analysis. **Figure 3: EFS standard parametric curve fitting in the pembrolizumab + chemotherapy arm for week 50+** 	both arms were fitted with the same distribution for extrapolation of RFS and OS and the argument of the unique mode of action of IO agents for alternative distributions was not mentioned. Therefore, the EAG is of the opinion that this is a matter of judgement and not an evidence-based approach. The EAG wants to reiterate that in the current model using different distributions for the extrapolation of EFS, the pre-extrapolation (up to week 205, based on KM data of KEYNOTE-522) rate of survival gain is 0.2367, while the post-extrapolation

		Figure 4: EFS standard parametric curve fitting in the placebo arm for week 50+  Validation of EFS projections vs RWE and clinical opinion: The clinical plausibility of different EFS parametric models was discussed during an advisory board. Experts were presented with alternative EFS extrapolations and asked to comment on the most plausible models used to extrapolate the standard of care chemotherapy and the pembrolizumab arm. Clinical experts noted that an EFS plateau	(from week 206) rate is 0.3340, suggesting lack of realism of the extrapolated marginal gain according to the rule-of-thumb from Tremblay et al., 2015. Based on the lack of evidence-based justification of the approach, the lack of realism of the extrapolated marginal QALY gain, and the fact that no treatment waning was taken into account in the model, the EAG considers a more conservative approach of using the same distribution for both arms to model EFS more suitable for the base-case analysis.

		would be seen across both treatment arms since most recurrences would be expected occur within the first 3 to 5 years based on prior experience from other adjuvant IO trials (5, 12). Overall, clinical experts noted that the generalised gamma, log-normal and Gompertz distributions were most realistic for patients with early-stage TNBC treated with either pembrolizumab or standard of care chemotherapy. However, some experts favoured distributions other than log-normal (that is Gompertz or Generalised-Gamma), noting concerns and that it was unlikely that that 10% of EFS events will occur between 5 and 10 years as suggested by the log-normal distribution (14). Based on this information and due to the unique mode of action of IO + chemotherapy separate models were selected to extrapolate EFS from KEYNOTE-522. The log-normal model was not explored in the base-case for Pembrolizumab + chemotherapy because due to the % of EFS events which take place between years 5 and 10 (as noted above). Gompertz was also not explored in the base-case because of the plateau it generates for EFS extrapolations which takes place very early on in the extrapolation period. Considering these limitations the base-case using generalised-gamma to model long term EFS for pembrolizumab + chemotherapy. All experts noted that for patients treated with pembrolizumab + chemotherapy EFS would be higher than that of placebo as observed in other adjuvant trials, most notably in melanoma (5, 6). Long term EFS projections were also validated for the chemotherapy standard of care arm for which long term data are currently available. Two publications of long-term EFS in patients with early-stage TNBC following neoadjuvant chemotherapy (NACT) were retrieved from a targeted literature review; Walsh 2019 (15) and Sikov 2019 (CALGB 40603) (16). No other sources were suggested by clinical experts for model validation purposes and noted that both studies could be appropriate sources of validation for the modelled EFS for placebo. The models selected for the base case and alternative sensitivity analyses all yielded good visual fit to the RWE identified and observed EFS estimates from KEYNOTE-522 (refer to section B.3.10.1). One further discrepancy with regards to the selection of log-normal to model EFS across both	Since the log-normal distribution is the preferred option for the placebo arm and the second-best option for the pembrolizumab arm according to AIC/BIC values the EAG has used this distribution in their base-case. Although the company argues that a log-normal distribution is not suitable for the pembrolizumab arm because experts say that it is unlikely that between 5 and 10 years 10% of the events will take place, it is unclear to the EAG why the same argument does not apply to the placebo arm, for which the company does use log-normal

		treatment arms is also observed when the 10 year EFS estimates generated for Pembrolizumab + chemotherapy are compared versus the disease-free survival (DFS) estimates reported by Walsh et al 2019. This can be attributed to the EFS events which are estimated using the log-normal from year 5 onwards that were deemed by clinicians to be unrealistic (14). The authors report ~68.6% DFS at year 10 vs 66.7% generated by the log-normal EFS extrapolation. The use of log-normal for EFS does not generate an EFS plateau which was noted by clinical experts and has also been observed in Walsh et al 2019 and Sikov et al 2019 (15, 16). These elements clearly demonstrate the conservatism of log-normal to extrapolate EFS which biases against Pembrolizumab + chemotherapy alongside the expert advice presented above (see Figure 5 below).	distribution. Therefore, the EAG maintains that using a log-normal distribution for both arms for EFS extrapolation appears to be the most appropriate. The use of generalized gamma distributions for EFS in both arms was explored in a scenario analysis. The EAG remains concerned about the large marginal gain in QALYs obtained in the unobserved period of the model (compared to the gain in the observed period) and believes that the scenarios presented do not fully capture the uncertainty around this issue. Clinical experts should

		Figure 5: Impact of log-normal for Pembro + chemotherapy EFS versus RWE data for standard of care  **MSD followed the NICE TSD methodology and clinical expert option to identify the most appropriate EFS parametric models for survival extrapolations. We consider that the unique mode of action of immunotherapy agents (IO) such as pembrolizumab + chemotherapy warrants alternative parametric distributions for EFS extrapolations. We have also demonstrated that the use of log-normal to extrapolate EFS for pembrolizumab + chemotherapy may not capture the full benefit of the intervention based on clinical expert opinion and may bias the cost-effectiveness estimates against Pembrolizumab + chemotherapy.**	evaluate whether it is plausible that what does not seem very beneficial in the short run, turns out to be very (cost-)effective over a lifetime.

9. Constant transition probabilities from LR and DM states assumed without clinical justification	No	The ERG is concerned around the constant transition probabilities applied over the model's time horizon to model LR→ DM, LR→ Death and DM→ Death. The ERG requested MSD provides additional clinical justification around this assumption to demonstrate its clinical validity. **MSD has discussed the limitations associated with the Markov modelling framework above. The KEYNOTE-522 data currently do not support complex modelling of transitions from LR. Clinical experts confirmed the assumption of constant transition probabilities is clinically justified considering the aggressiveness of TNBC and the overall poor prognosis for patients presenting with a LR.** These elements are discussed further below. The current model uses a Markov state transition structure in which EF is the starting health state, LR and DM are intermediate health states, and Death is the absorbing health state. Markov models are memoryless by nature, meaning it is not possible to track individual patients through the model or therefore determine how long patients have been in a particular health state. However, to model variable hazards over time from entry into an intermediate health state (in this case, the DM state) it is *necessary* to track time in health state. To achieve this in a Markov model would require thousands of tunnel states and would significantly increase the computational burden of the model. As such, it was deemed an appropriate simplifying assumption to instead apply a constant hazard rate to estimate transitions from the LR and DM health states. In KEYNOTE-522, [redacted] patients experienced LR, of which [redacted] observations were considered as failed (i.e. either with a DM or Death event) and [redacted] were censored ([redacted]% censored; refer to Table 4 below describes the number of first events taking place once patents were confirmed with LR). Due to the limited number of events between the two treatment arms, the pooled events from KEYNOTE-522 were used to inform the transition probabilities from LR→DM or Death. This is due to the limited number of events that were observed in KEYNOTE-522 which could increase	The EAG can follow the reasons given by the company to choose for constant probabilities: - limited number of events - The clinical expert opinion noted that the majority of patients with LR would not be surgically salvageable and therefore the probability of them developing a DM or death would remain fairly constant over time considering the aggressiveness of TNBC. However, this is still a matter of

<table>
<tr>
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<td>uncertainty if compartmentalised further for separate parametric extrapolations and subsequent calculations of transition probabilities from LR→ DM and LR→ Death (see Table 4 below for a breakdown first EFS events that took place from LR).

Table 4: Breakdown of first LR event
<table><tr><th></th><th>%</th><th>N Events</th><th>N Total</th></tr><tr><td>% from LR to DM</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>% from LR to Death</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table>
MSD clarified that the selection of the exponential parametric distribution selected to model LR → DM or Death was not based in isolation to the AIC/BIC statistics. Other considerations such as visual fit to the observed KM curve (Figure 6) alongside balanced assessment of clinical plausibility of long term predictions generated by each of the alternative parametric models. Although the exponential model sits marginally above the KM data for the duration of the observed period, it demonstrated a better fit towards the tail of the KM curve better and yielded more conservative estimates of long term time to DM or Death.

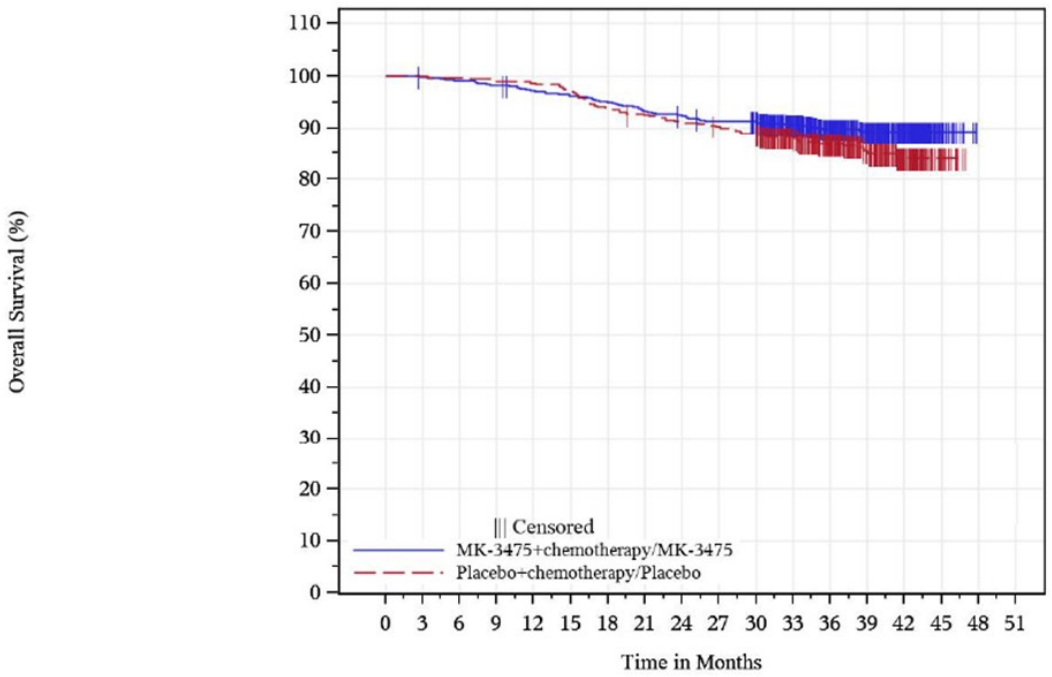
Figure 6: Long term parametric extrapolations using the combined KEYNOTE-522 arms time from LR to DM or Death</td>
<td>substantial uncertainty
Also, in TA801 the company argued that probabilities of dying from the metastatic phase were not constant and therefore chose to use a log-normal distribution, stating the exponential distribution was overly simple.</td>
</tr>
</table>

		 Based on the data presented above from KEYNOTE-522, a weekly exponential rate was calculated; [redacted] alongside (95% CIs: [redacted] Please note that the model is largely insensitive to this assumption as demonstrated by the DSA results which tested the upper and lower 95%CIs of this value (refer to new scenarios 22 and 23 in updates sensitivity analyses presented below). Markov models are memoryless by nature, meaning it is not possible to track the time individual patients may spend in	

		a particular health state. Therefore, the exponential model was preferred to model transitions from LR→DM or LR →Death. The approach of constant transition probabilities is also on par with that of TA424 transition from all health states apparent from that of EFS (17). During the technical engagement process a UK clinical expert was consulted by MSD to test further the validity of this assumption at the request of the ERG (expressed during the technical engagement call). The clinical expert noted the aggressiveness of TNBC versus other early BC tumours including those which are HER2+ve. The expert stated that once patients develop a locoregional recurrence, only a very small proportion of patients with LR would be surgically salvageable due to developing an isolated LR which would result in them experiencing a decrease in the probability of DM or death. The clinical expert noted that the majority of patients with LR would not be surgically salvageable and therefore the probability of them developing a DM or death would remain fairly constant over time considering the aggressiveness of TNBC. The expert noted that due to the very small proportion of patients presenting with isolated LR which is surgically salvageable, the assumption of constant transition probabilities from LR was clinically justified and was unlikely this would have a major impact in the cost-effectiveness. **The KEYNOTE-522 data currently do not support complex modelling of transitions from LR. Clinical experts confirmed the assumption of constant transition probabilities is clinically justified considering the aggressiveness of TNBC and the overall poor prognosis for patients presenting with a LR.**	
10. The use of KEYNOTE-355 data for DM	No	The ERG is concerned that the company's preferred approach to model survival from DM→ Death using the KEYNOTE-355 dataset may not be appropriate. Instead the ERG prefers to use the KEYNOTE-522 dataset to inform the DM→ Death survival.	The EAG agrees with the company that the use of the immature OS data from the KEYNOTE-522 to

survival may not be appropriate		**MSD has discussed the limitations associated with the use of immature OS data from KEYNOTE-522 for HTA purposes. MSD leveraged the KEYNOTE-355 OS data recently reviewed by NICE during TA801 to model the survival from DM→Death. The decision to use multiple sources to inform transition probabilities for health economic modelling is not unjustified and is in line with previous submission in the adjuvant space that either lacked OS in totality or reported immature OS.** The OS data from IA4 of KEYNOTE-522 were presented within the main submission Document B. At IA4, considering that the primary hypothesis of EFS was successful, the secondary hypothesis of OS was formally tested at the same alpha level of 2.5% according to the protocol multiplicity strategy. The analysis showed improvement in OS that favoured the pembrolizumab arm over the placebo arm at month 42. However, due to the relative early time of the analysis with respect to the OS endpoint [redacted]information fraction of approximately [redacted][135 of the [redacted]events needed for the final analysis]) the observed one-sided p-value did not cross the multiplicity-adjusted, one-sided prespecified p-value boundary at IA4. Therefore, the success criterion for the secondary OS hypothesis was not met. The OS HR of 0.72 (95% CI: 0.51, 1.02), with a one-sided p-value of 0.0321377 that did not cross the prespecified boundary for statistical significance of p=[redacted], represents a 28% reduction in the risk of death compared with the placebo arm (refer to Table 10 and Table 11 for detailed results presented within Document B). The median OS was not reached in either arm at month 42 and will be analysed in future interim analysis as data matures. The OS Kaplan-Meier and HRs are presented below. Please note that the final analysis for the trial (for all endpoints) is due to take place in [redacted], however, [redacted]OS events, the number of events required to conduct a formal statistical analysis may not be reached. This is due to the fact that OS maturity may be delayed for patients obtaining a pCR and subsequently	model survival from DM --> Death has its limitations. However, the EAG considers the use of KEYNOTE-355 data as base case for the DM survival to be a potential source of bias. Although the company argues that KEYNOTE-355 is to be preferred over KEYNOTE-522 data because KEYNOTE-522 data are not sufficiently mature in the DM state, there are quite substantial differences in observed survival between these two studies (Table 4.7 of the EAG report), which raises doubts about comparability of the populations and therefore on appropriateness of using KEYNOTE-355 OS data for this

		remaining EFS, whilst for those who relapse, OS may in part be confounded by the availability of other anti-PD-1/anti-PD-L1 agents for treatment of metastatic disease similar to what has been observed across other adjuvant IO trials including (KEYNOTE-054 and Checkmate-238) (5, 12). **Figure 7: KEYNOTE-522 Overall Survival data (All Participants)**	appraisal. The EAG maintains to use of OS KEYNOTE-522 data for DM survival as a base case.



n at risk

MK-3475+chemotherapy/MK-3475	784	782	777	770	759	752	742	729	720	712	701	586	461	323	178	30	0	0
Placebo+chemotherapy/Placebo	390	390	389	386	385	380	366	360	354	350	343	286	223	157	89	17	0	0

Database Cutoff Date: 23MAR2021

		Please note that the null-hypothesis for EFS has been rejected at IA4, therefore EFS will not be further tested formally. OS has been formally tested from IA4. [redacted] From a health economic modelling perspective, the use of the immature OS data from KEYNOTE-522 directly in the economic model carries its own limitations which are associated with potentially increased uncertainty. To mitigate against the immature OS data from KEYNOTE-522, an alternative approach was followed to model the DM→ Death which leveraging data from KEYNOTE-355. This study is a contemporary 1L mTNBC study which investigated the efficacy and safety of Pembrolizumab + chemotherapy versus chemotherapy alone in PD-L1+ve CPS ≥10 patients. KEYNOTE-355 formed the basis of the recent +ve recommendation for TA801 (Pembrolizumab + taxanes) for previously untreated locally recurrent unresectable or metastatic TNBC adults whose tumours express PD-L1 with a CPS of 10 or more and an immune cell staining (IC) of less than 1% (Atezolizumab + nab-paclitaxel ineligible). KEYNOTE-355 was preferred for the base-case because it offered a source for 1L+ mTNBC survival specific to PD-L1 +ve patients but also a single source of inputs for subsequent treatment costs. <u>DM→ Death methodology from KEYNOTE-355:</u>	

		We have provided sufficient information in Issue 7 above around the methodology used to estimate survival using KEYNOTE-355. In brief, survival estimates for other 1L mTNBC comparators other than Pembrolizumab + taxanes (directly derived from KEYNOTE-355) were estimated based on a mTNBC NMA alongside the clinical expert input on market research for the anticipated utilisation of 1L mTNBC treatment options. This allowed the estimation of a weighted DM→Death survival which accounted for the subsequent treatment mix at 1L mTNBC and was then applied in the model. This approach was necessary since only ~38% of KEYNOTE-355 patients had PD-L1 positive CPS ≥ 10 tumours under the granted marketing authorisation. Within the patients with PD-L1 positive mTNBC, alternative IO comparators such as Atezolizumab + nab-paclitaxel have been recommended and are the standard of care currently in the NHS. The remaining 62% of patients which are PD-L1 negative and would go to otherwise receive a standard chemotherapy. The DM OS modelled reflects the 1L+ survival from a contemporary trial and the methodology captures the current treatment pathway for mTNBC in the UK. Finally, the approach used to model the of DM→Death in this submission is not dissimilar to that used in previous IO adjuvant submissions such as TA766 which leverages metastatic OS from clinical trials to estimate DM survival. **Robust DM survival for PD-L1+ve patients can only be derived from KEYNOTE-355. MSD has modelled the efficacy and costs in the DM setting for 1L+ mTNBC by leveraging the same source of data where possible to avoid discrepancies. The current approach ensures consistency between IO 1L mTNBC survival estimates discussed during TA801 and those modelled from DM→ Death in the current submission. The impact of using immature OS from KEYNOTE-522 was explored in scenarios presented within Document B and resulted in a marginal ICER increase.**	
11. The utility value used in	No	The ERG raised concerns with regards to the DM utility derived from the KEYNOTE-522 data and questioned its validity for use in the economic model. The ERG justified	Thank you for the clarification. Our

the DM health state may be relatively low when compared to literature reported values.		its criticism on the basis of comparing the DM utility estimate from KEYNOTE-522 versus utilities reported elsewhere for mTNBC patients at pre-progression (KEYNOTE-355 and KEYNOTE-119 [2L mTNBC study]). **As per the ERG's request MSD commented on the representativeness of the DM utility value derived from KEYNOTE-522 highlighting some uncertainties that should be considered when cross study comparisons of utility sources and values are performed. MSD provided additional justification on why the DM utility value from KEYNOTE-522 is appropriate for consideration, noting its limited impact on the ICER.** MSD would like to reiterate that the current DM health state utility (mean = [redacted]) was derived from the KEYNOTE-522 data which is consistent with the NICE reference case (18). This value is reflective of the KEYNOTE-522 patient population based on the IA4 database lock. Alternative values were explored during the CQ response stage using higher utility estimates for DM. We acknowledge that there are some of the limitations associated with the DM utility value calculated from KEYNOTE-522. Most notably, the EQ-5D collection from KEYNOTE-522 is still ongoing since most patients continue to remain relapse free and OS data continue to remain immature. EQ-5D collection from KEYNOTE-522 is still ongoing, and a small number of questionnaires was available for analyses to estimate utility once at DM setting ([redacted] across both treatment arms). This may in part explain why the utility values at DM setting appear lower than those reported elsewhere in the literature and continued data collection from KEYNOTE-522 will add more certainty around this model estimate. However, we also caution against over-interpreting differences between studies because the [redacted] DM derived utility was also based upon mapping of 5L to 3L using the *van Hout* algorithm. When the EQ-5D-	responses are as follows: Since the DM utility value calculated from KEYNOTE-522 is associated with limitations as small sample size and the EQ-5D collection is still ongoing, the EAG added two scenarios with different utility values from KEYNOTE-355 and KEYNOTE-119 to estimate the effect on the ICER. As the company mentions, the effect on the ICER is limited.

5L value set was applied directly, the DM utility value was higher ([redacted]) but still lower to values reported elsewhere in the literature.

Taking into account the EQ-5D data maturity, an analysis of utility values from KEYNOTE-522 by DM progression status could not be performed as per the ERG's request. To understand the impact on the C/E results of a higher utility for patients in the DM setting MSD presented some additional utility estimates from KEYNOTE-355 (1L mTNBC population) and conducted alternative scenarios with different utility values from KEYNOTE-355 and KEYNOTE-119. The utility values from KEYNOTE-355 study population and KEYNOTE-119 are presented in the table below.

Table 5: Supplementary information reporting utility estimates from KEYNOTE-355 and KEYNOTE-119

Health state	Mean utility value (95% CI)	Time-to-death Category	Mean utility value (95% CI)
KEYNOTE-355: 1L mTNBC PD-L1 CPS 10 population			
Progression-free survival	[redacted]	>360 days	[redacted]
		180 to 360 days	[redacted]
		90 to 180 days	[redacted]
Progressive disease	[redacted]	30 to 90 days	[redacted]
		>30 days	[redacted]
KEYNOTE-119: Patients with previously treated mTNBC (2L mTNBC) (19)*			
Progression-free survival	0.715 (0.701-0.730)	>360 days	0.765 (0.750, 0.779)
		180 to 360 days	0.655 (0.624, 0.687)

			90 to 180 days	0.586 (0.549, 0.624)
Progressive disease	0.601 (0.571-0.631)		30 to 90 days	0.517 (0.471, 0.564)
			>30 days	0.264 (0.128, 0.401)
**N.B. Publication does not explicitly state that the USA population tariff used to derive the utility estimates.*				

Based on the above utility sources, two scenario analyses were conducted alternative data sources and assumptions to test the impact of the DM utility estimate on ICER for utility in the DM setting:

- KEYNOTE-355 (1L mTNBC population): Scenario #1 whereby the DM utility is set to [redacted]. This value represents a weighted utility based on the total predicted LYs gained during pre-progression ([redacted]) and the post-progression ([redacted]) of the chemotherapy arm; the mean pooled utility for progression-free and progressed patients was [redacted] and [redacted] respectively). The LYs gained were sourced from the cost-effectiveness analysis of pembrolizumab as first-line treatment for TNBC.

- KEYNOTE-119 (2L mTNBC population): Scenario #2 tests the utility value of 0.715 which is specific to the pre-progression utility from KEYNOTE-119; (vs. the weighted average of pre-progression and post-progression tested using KEYNOTE-355 data). This scenario was used to test the maximum impact on ICER considering that KEYNOTE-119 was conducted in a 2L mTNBC study population. MSD does not agree with KEYNOTE-119 data being relevant to inform the DM utility in this submission due to the population differences from which the pre-progression utility was derived versus the DM population modelled within ID1500. It is also worth noting that the utility values reported within KEYNOTE-119 used the US tariff and therefore of limited generalisability to the UK population (confirmed with authors in personal communication during the TE process).

		Results from the scenario analyses described above demonstrate that the ICER is not overly sensitive to the utility estimate used in the DM state. Using the KEYNOTE-355 utility data, the company base-case ICER increased from £5,940/QALY gained to £6,038/QALY gained in the scenario whereby a KEYNOTE-355 DM weighted average utility was used (please refer to QC response B19). The pre-progression KEYNOTE-119 data increased the ICER from £5,940/QALY gained to £6,054/QALY gained (please refer to QC response B19). The limited impact of DM utility in the ICER was also noted by the EGR in its report. **MSD acknowledges that EQ-5D collection from KEYNOTE-522 is still ongoing since most patients continue to be followed up and a small sample size was available to inform the DM utility. We caution against cross study comparisons of utility data considering the different study populations. The two exploratory analyses demonstrated that a higher DM utility does not have a great impact on the ICERs. The DM utility derived from KEYNOTE-522 remains relevant for economic modelling purposes as it is line with the NICE reference case.**	

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: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

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)
[redacted]	[redacted]	[redacted]	[redacted]
In part affects; Issue 7: Model structure (ascertainment of costs in ***pre-progression*** DM health state) *and* Issue 10: KEYNOTE-355	The base-case previously did not allow pembrolizumab rechallenge for metastatic disease (TA801) following on from pembrolizumab + chemotherapy in the neoadjuvant/adjuvant setting (ID1500).	The new base-case allows for rechallenge with pembrolizumab + taxanes for metastatic disease to account for recent changes in the metastatic pathway (TA801). Rechallenge is allowed with pembrolizumab after 2 years of neoadjuvant treatment initiation. This	[redacted]

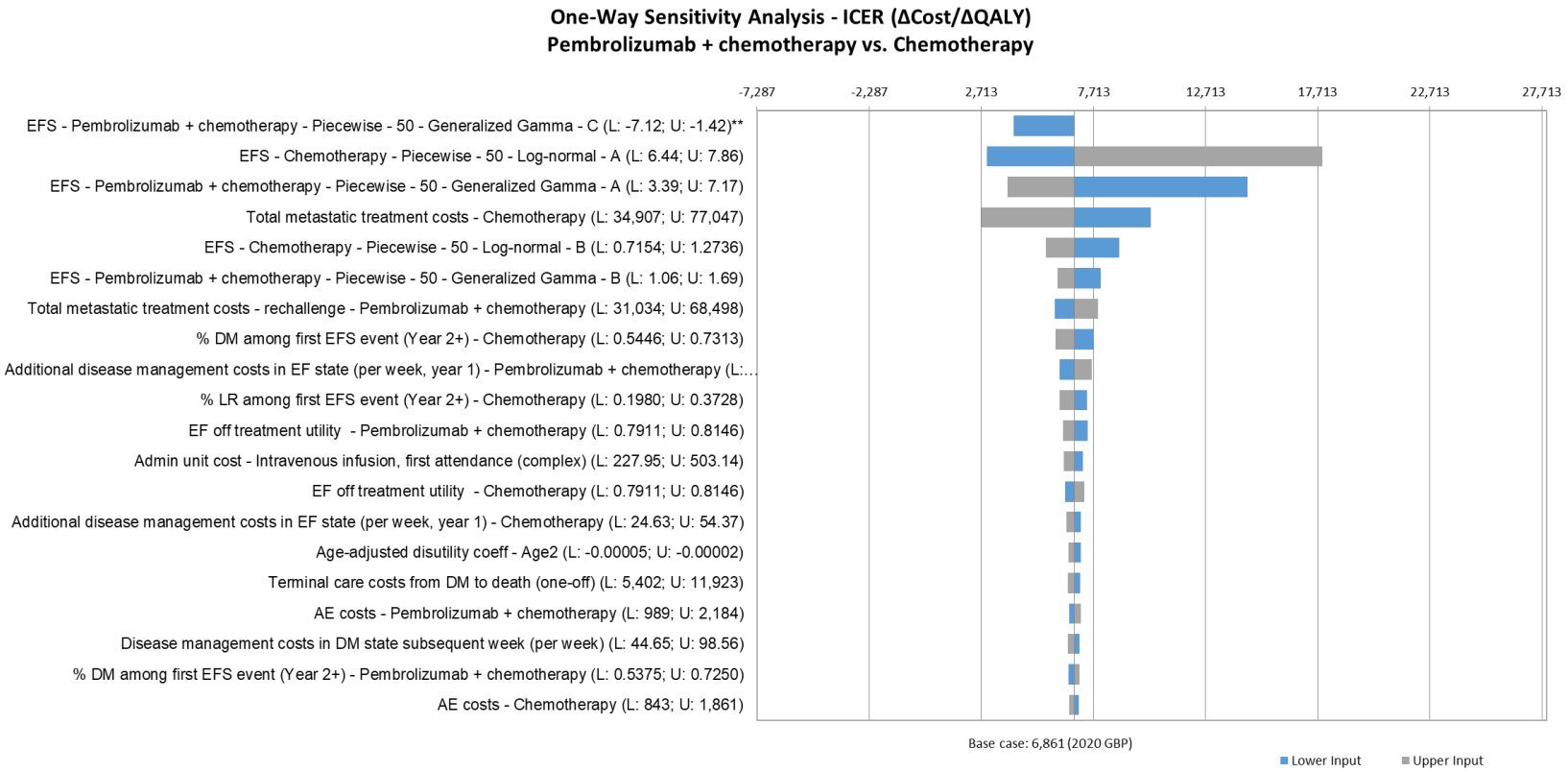
trial data used to model DM→ Death. **Updated assumptions pertaining to pembrolizumab IO rechallenge from neoadj/adj → metastatic setting.**		assumption was confirmed by a to be reflective of the new treatment pathway given experience in other IO adjuvant → metastatic HTA assumptions (primarily melanoma; TA766 and TA684).	
In part affects; Issue 7: Model structure (ascertainment of costs in pre-progression DM health state) *and* Issue 10: KEYNOTE-355 trial data used to model DM→ Death.	The base-case previously assumed a 50-50% market share mix between Atezolizumab + nab-paclitaxel and Pembrolizumab + taxanes for 1L mTNBC for PD-L1 +ve patients. This assumption was used since TA801 was ongoing at the time. These estimates affect DM→ Death estimates applied in the model.	The new base-case assumes a ~83% Atezolizumab + nab-paclitaxel and ~17% for Pembrolizumab + taxanes to reflect the recent TA801 recommendation. This assumption was reflected by a clinical expert to be reflective of the new treatment pathway. Whilst update is not directly linked to any ERG criticisms this change in the base-case assumptions for IO usage for 1L mTNBC is now	[redacted]

Updated market share split for IO agents in 1L mTNBC for PD-L1+ve patients.		necessary to reflect the current treatment pathway.	
In part affects; Issue 7: Model structure (ascertainment of costs in pre-progression DM health state) **Capecitabine 1L mTNBC cost correction – error identified during TE stage.**	Drug acquisition costs for capecitabine were incorrectly estimated not adjust the pack size overestimating capecitabine costs.	Updated capecitabine costs now reflect the pack size – extracts from eMIT added into "raw_Drug Costs" sheet for clarity.	[redacted]
In part affects; Issue 7: Model structure (ascertainment of costs post-progression DM health state) **Minor update of 2L+lump sum**	Minor update in the subsequent lump sum treatment costs for 2L+. Previous 2L+ lump sum costs were incorrectly extracted from the KN-355 model with interim OS but the NICE AC reviewed the FA KN-355 model during	Minor updates 2L+ subsequent treatment costs carried out to align these with the latest 2L+ subsequent treatment costs included in the final KN-355 model.	[redacted]

costs to reflect latest KN-355 data presented during TA801 assessment.	TA801. These costs have now been revised upwards.		
Cumulative impact of base-case changes noted above.	All changes above implemented	All changes above implemented	**£6,861 (all above changes to company base-case included)**

Sensitivity analyses around revised base case

Figure 8: Tornado diagram for the 20 most sensitive parameters with pembrolizumab PAS price after technical engagement



**Upper limit parameter pembrolizumab arm is dominated i.e. more costly and less effective; therefore an ICER statistic cannot be presented for the tornado diagram

Table 6: Scenario analyses with pembrolizumab PAS price after technical engagement

Scenario No.	Description	Pembrolizumab arm		Placebo arm		Pembrolizumab vs. placebo arm		
		Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
0	Updated base case – deterministic*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£6,861**
0	Updated base case – probabilistic*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£7,089**
1	EFS function - Pembrolizumab + chemotherapy - Piecewise - Week 50 - ***Log-normal*** (second best option of pembrolizumab arm curve by clinical experts)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,398
2	EFS function - Chemotherapy - Piecewise - Week 50 - ***Generalized Gamma*** (second best option of placebo arm curve by clinical experts)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,693
3	EFS function - Pembrolizumab + chemotherapy - Piecewise - Week 50 - ***Log-normal*** **and** Chemotherapy - Piecewise - Week 50 – ***Generalized Gamma*** (combined second best option of pembrolizumab arm and placebo arm curves by clinical experts)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,178
4	Time horizon (20 years)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£12,451
5	Allow vial sharing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,051
6	Utility by treatment arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,140
7	Utility algorithm (UK 5L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,396
8	TOT measure - Pembrolizumab + chemotherapy - KM lower 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,413
9	TOT measure - Pembrolizumab + chemotherapy - KM upper 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,345

Scenario No.	Description	Pembrolizumab arm		Placebo arm		Pembrolizumab vs. placebo arm		
		Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
10	TOT measure - Chemotherapy - KM lower 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,915
11	TOT measure - Chemotherapy - KM upper 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,808
12	Annual discount rate - costs (1.5%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£5,868
13	Annual discount rate - effects (1.5%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,710
14	Annual discount rate – costs and effects (1.5%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,028
15	Remission after 8 years (note: remission assumes the probability of EFS event for both treatment arms = 0, only transition applied is background mortality; based on clinical expert opinion)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£11,595
16	Remission after 10 years (note: remission assumes the probability of EFS event for both treatment arms = 0, only transition applied is background mortality; based on clinical expert opinion)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,061
17	KEYNOTE-522 OS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,825
18	Pembrolizumab 400mg Q6W dosing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,310
19	Pembrolizumab rechallenge scenario with atezolizumab 50:50 split for both treatment arms	No longer relevant considering the treatment pathway and recommendations within TA801, therefore not re-run.						
20	Pembrolizumab rechallenge scenario with atezolizumab 17:83 split for both treatment arms	**New base-case** assumes a split of 17:83 between Atezolizumab + nab-paclitaxel and Pembrolizumab + taxanes in the DM setting. This assumption was justified by clinical experts.						
21	Do not allow pembrolizumab rechallenge in DM setting after 2 years from neoadjuvant initiation.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,152

Scenario No.	Description	Pembrolizumab arm		Placebo arm		Pembrolizumab vs. placebo arm		
		Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
22	Lower 95%CI of exponential rate for LR→DM or Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£7,045
23	Upper 95%CI of exponential rate for LR→DM or Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,747
24	New option: explore ToT for Atezo + nab-paclitaxel = Pembrolizumab + taxanes CPS ≥10 population from KEYNOTE-355.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£9,916
25	New option: explore alternative mean survival for Pembro + Taxanes derived using an exponential parametric model (3.52 years predicted versus 4.51 using the log-normal derived estimate applied in base-case).	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,858
26	Assumption of equal efficacy for Atezolizumab + taxanes = Pembrolizumab + taxanes.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£6,886

*Updated base-case assumptions include; pembrolizumab rechallenge in the metastatic setting, IO split in metastatic reflective of TA801 guidance, correction in 2L+ mTNBC lump sum costs, correction on capecitabine 1L mTNBC costs.

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Appendix A: Model updates and new options included by MSD during the TE process

Some changes have been implemented in the new base-case but these cannot explicitly be linked to any of the specific issues raised by the ERG in isolation. The table below provides a full list model updates including but not limited to calculation corrections, base-case assumptions changes and introduction of new modelling options to reflect recent changes in the mTNBC pathway alongside the justification for these changes feeding into the updated base-case assumptions. Light grey shaded changes impact the new base-case presented by MSD; all other options presented as alternatives for exploration.

Table 7: Updates carried out by MSD in the C/E model during the TE process

#	Description	Rationale	Model Sheet
[redacted]	[redacted]	[redacted]	[redacted]
2	Allowed for Pembrolizumab re-challenge for distant metastatic disease	Previous base-case did not allow for pembrolizumab re-challenge in the DM setting since TA801 has not concluded. This assumption has now been revised in the new base-case	"Specifications" sheet G87 drop down set to "Yes", G89 input cell set to "2 Years"
3	New assumptions DM IO market share	At time of ID1500, TA801 has not concluded and therefore Atezo + nab-pacl vs Pembro + taxane market share distribution was unknown. Updated to reflect TA801 positioning within the pathway. Change of drop down menu selection for DM setting to set Pembro to Atezo split to 17%-83% from 50%-50% assumed previously.	"DM Treatment Costs & Efficacy" F94 drop down set to 17%-83%
4	Correction of Capecitabine drug cost	Cost per pack was used to estimate DM capecitabine costs - changed by MSD during TE to factor pack size of 120 tablets to derive cost/mg	“Raw drug Cost” cell F12 divided to 120 tablets – change carried over to "DM Trt Costs" – cell AM16 and into "DM Tx costs & Efficacy – cell R57"
5	Minor update of 2L+ subsequent treatment costs	Minor update in the subsequent lump sum treatment costs for 2L+. Previous 2L+ lump sum costs were incorrectly extracted from the KN-355 model with interim OS but the NICE AC reviewed the FA KN-355 model during TA801. These costs have now been revised upward (original values are reported in the model to aid the review process).	"DM Treatment Costs & Efficacy" – cells F67:F73 updated (original values in cells J67: J73) - New menu introduced in cell “M68” and select “New Lump sum costs”.

6	New option for Pembro + taxanes survival at DM	The AC discussed Pembro + Taxane LY estimates with exponential model - this has been added in the updated model	"Raw_DM trt TOT OS" - new option
7	New option for Atezo + nab-paclitaxel ToT at DM	During ACM1 the AC discussed the most plausible Atezo + nab-paclitaxel ToT estimation. MSD originally assumed this would equal to the PFS projections generated but presented a new analysis whereby this was assumed to be equal to KEYNOTE-355 Pembro +taxane ToT from KEYNOTE-355; this has been added into the updated model	"Raw_DM trt TOT OS" - new option
8	New base-case assumptions	Cumulative impact of 1 + 2 + 3 + 4 + 5	NA

Table 8: Instructions to revert back to ERG original base-case

#	Description	Rationale	Model Sheet and change
1	[redacted]	[redacted]	[redacted]
2	Remove Pembrolizumab re-challenge for distant metastatic disease	Previous base-case did not allow for pembrolizumab re-challenge in the DM setting since TA801 has not concluded. This assumption has now been revised in the new base-case	Select "Specifications" sheet G87 drop down set to "No", G89 input cell set to "0 Years"
3	Revert back to 50-50 for DM IO market share	At time of ID1500, TA801 has not concluded and therefore Atezo + nab-pacl vs Pembro + taxane market share distribution was unknown. Revert back to IO DM MS to 50%-50% assumed previously.	"DM Treatment Costs & Efficacy" – cell “F94” drop down set to 50%-50%
4	Undo cost correction of Capecitabine drug cost	Undo cost per pack correction for DM capecitabine costs - changed by MSD during TE to factor pack size of 120 tablets to derive cost/mg	Navigate to “Raw drug Cost” cell F12 and delete the value of “ 120” which adjusted for pack size.
5	Revert back to old 2L+ subsequent treatment costs pre-correction	Revert back to older subsequent lump sum treatment costs for 2L+.	Navigate to "DM Treatment Costs & Efficacy" – M68 new menu introduced and select “Old Lump sum costs”.
6	Apply ERG selections	Navigate to ERG sheet and click checkbox “F9” to apply all other settings.	ERG Sheet – cell “F9” should be checked.

Appendix B: Additional data referred within the TE pro-forma

Table 9: Summary of goodness of fit for EFS: pembrolizumab arm and placebo comparator arm from KEYNOTE-522 (week 50+)

Parametric distribution for EFS	Pembrolizumab arm				Placebo arm			
	AIC	BIC	AVG	Rank	AIC	BIC	AVG	Rank
Exponential	1140.24	1144.84	1142.54	4	980.85	984.75	982.80	7
Weibull	1140.71	1149.89	1145.30	6	972.61	980.39	976.50	4
Log-normal	1134.58	1143.76	1139.17	2	969.91	977.69	973.80	2
Log-logistic	1139.91	1149.09	1144.50	5	971.70	979.48	975.59	3
Gompertz	1134.88	1144.06	1139.47	3	968.49	976.27	972.38	1
Gamma	1140.95	1150.13	1145.54	7	973.15	980.94	977.05	5
Generalized Gamma	**1127.35**	**1141.12**	**1134.24**	**1**	971.87	983.54	977.71	6
Abbreviations: AIC: Akaike Information Criteria, BIC: Bayesian Information Criteria; AVRG: Average, Ranking is based on the average AIC/BIC statistic.								

Table 10: Analysis of OS (All participants)

Treatment	N	Number of events (%)	Person-months	Event rate/100 person-months (%)	Median OS [a] [months] (95% CI)	OS Rate at month 42 in %† (95% CI)	Vs. control Hazard Ratio (95% CI) [b] p-value [c]
Pembrolizumab arm	784	80 (10.2)	28,1997.7	0.3	NR	89.2 (86.7, 91.3)	0.72 (0.51, 1.02)
Placebo arm	390	55 (14.1)	13,908.1	0.4	NR	84.1 (79.5, 87.7)	p-value: 0.0321377
NR = Not reached [a] From product-limit (Kaplan-Meier) method for censored data. [b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by nodal status (positive vs. negative), tumour size (T1/T2 vs. T3/T4) and choice of carboplatin (Q3W vs. Weekly). [c] One-sided p-value based on log-rank test stratified by nodal status (positive vs. negative), tumour size (T1/T2 vs. T3/T4) and choice of carboplatin (Cb) (Q3W vs. Weekly). Database Cutoff Date: 23MAR2021							

Table 11: Summary of OS rate over time (All participants)

	Pembrolizumab arm (n=784) % (95% CI)	Placebo arm (n=390) % (95% CI)
Summary of overall survival rate at time point		
12 months	97.2 (95.8, 98.1)	98.7 (96.9, 99.5)
24 months	92.3 (90.2, 94.0)	91.0 (87.7, 93.5)
36 months	89.7 (87.3, 91.7)	86.9 (83.0, 89.9)
42 months	89.2 (86.7, 91.3)	84.1 (79.5, 87.7)
Database Cutoff Date: 23MAR2021		

in collaboration with:

university of groningen

University Medical Center Groningen

Addendum post technical engagement to:

Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of untreated locally advanced non-metastatic triple negative breast cancer [ID1500]

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Date completed 02/08/2022

Source of funding: This report was commissioned by the National Institute for Health Research (NIHR) Evidence Synthesis Programme as project number 12/99/38.

Declared competing interests of the authors: None.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

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.

This report should be referenced as follows:

Perry M, van Asselt T, de Jong LA, al Khayat MNMT, Postma MJ, Riemsma R, Posadzki P, Duffy S, Ahmadu C, Armstrong N, Kleijnen J, Wolff R. Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of untreated locally advanced non-metastatic triple negative breast cancer [ID1500]: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2022.

Contributions of authors

Mark Perry and Robert Wolff acted as project leads and systematic reviewers on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Thea van Asselt acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Lisa de Jong, Mohamed al Khayat, Maarten Postma, Charlotte Ahmadu, and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Rob Riemsma and Pawel Posadzki acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Jos Kleijnen critiqued the company's definition of the decision problem and its description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Addendum to ERG report

This addendum presents the cost-effectiveness results of pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of untreated locally advanced non-metastatic triple negative breast cancer. In this addendum, the ERG have re-run their original analyses with the adjustments the company made to their model in response to technical engagement, i.e. with updated metastatic treatment costs, the possibility for rechallenge with pembrolizumab after 2 years of neoadjuvant treatment initiation, updated market shares for pembrolizumab and atezolizumab + nab-paclitaxel for 1L mTNBC, and an updated PAS price.

See Table 1 for results of company and ERG base case analyses, Table 2 for deterministic scenario results, and Table 3 for results of probabilistic analyses. Cost-effectiveness acceptability curves for probabilistic analyses are presented in Figures 1 -7.

Table 1: Deterministic CS and ERG base case (as per technical engagement)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base case					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£6,861
Fixing errors 1: Enable pembrolizumab 1L treatment in DM state for IO-eligible patients in the placebo arm*					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£6,861
Fixing errors 2: Adjustment to formulas correcting for general population mortality					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£6,863
Matters of judgement 1: Correction for efficacy of pembrolizumab adjusting for Europe versus rest of the world hazard ratio					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£8,828
Matters of judgement 2: Use KEYNOTE-522 data to inform survival in DM state and alongside this adjust treatment costs according to the shorter survival					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£9,554
Matters of judgement 3: Use lognormal distributions in EFS for both arms					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£17,398

1L = first line; CS = company submission; DM = distant metastasis; EFS = event-free survival; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; IO = immune oncology; QALY = quality-adjusted life year

* No longer relevant after technical engagement as the error was in the scenario where patients were not re-challenged with pembrolizumab in the DM health state. As per TE, patients were allowed re-challenge of pembrolizumab in the base case.

Table 2: Deterministic scenario analyses (conditional on ERG base case; as per technical engagement)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base case					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£36,284

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Scenario 1: Limit time horizon to 5 years (similar to the observed period)					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£355,514
Scenario 2: Set the cut-off of the piecewise model at 68 weeks instead of 50 weeks					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£22,694
Scenario 3: Use generalized gamma distributions for EFS in both arms					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£12,864
Scenario 4: Use lognormal distribution for pembrolizumab and generalized gamma distribution for placebo EFS					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£44,849
Scenario 5: Adjust utility in DM health state based on KEYNOTE-355					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£36,814
Scenario 6: Adjust utility in DM health state based on KEYNOTE-119					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£36,900

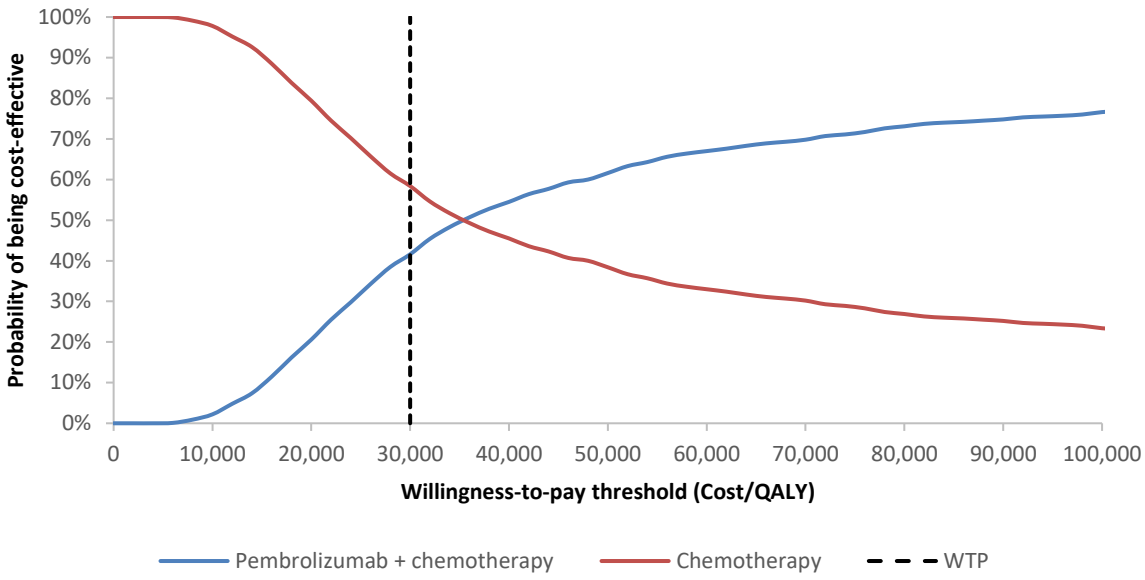
CS = company submission; EFS = event-free survival; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year

Table 3: Probabilistic scenario analyses (conditional on ERG base case; as per technical engagement)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	Prob-ability
ERG base case						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£36,358	41.6%
Scenario 1: Limit time horizon to 5 years (similar to the observed period)						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£340,273	0.0%

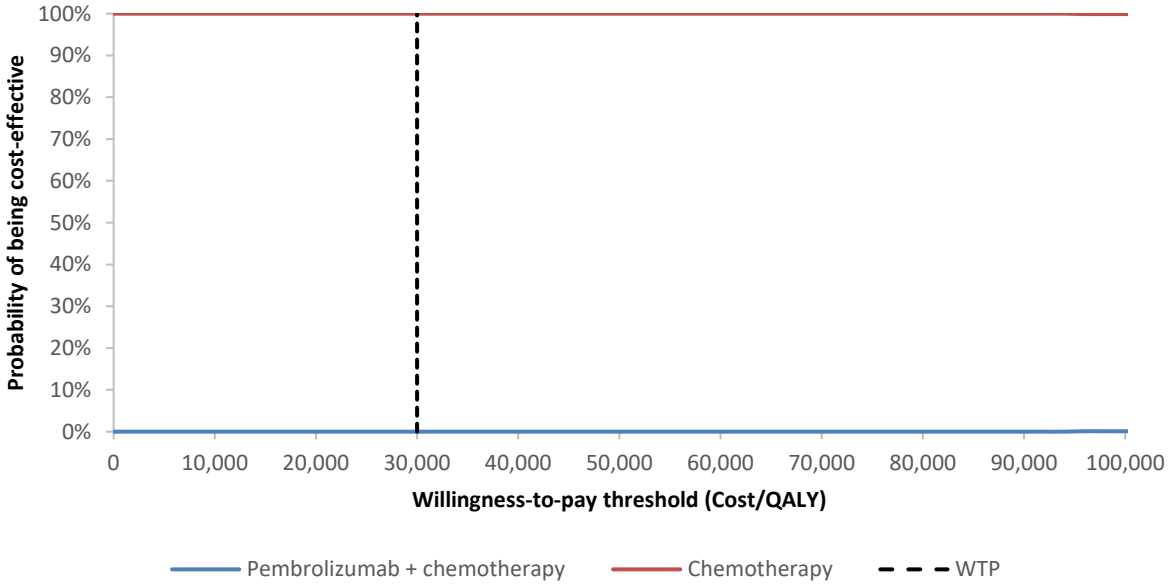
Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	Prob-ability
Scenario 2: Set the cut-off of the piecewise model at 68 weeks instead of 50 weeks*						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£31,053	58.1%
Scenario 3: Use generalized gamma distributions for EFS in both arms						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£13,883	84.7%
Scenario 4: Use lognormal distribution for pembrolizumab and generalized gamma distribution for placebo EFS						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£48,828	35.7%
Scenario 5: Adjust utility in DM health state based on KEYNOTE-355						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£36,958	41.3%
Scenario 6: Adjust utility in DM health state based on KEYNOTE-119						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£37,053	41.2%
CS = company submission; DM = distant metastasis; EFS = event-free survival; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year						
*Errors in approximately ten PSA runs. Errors were excluded from the analysis to obtain the results						

Figure 1: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on ERG base case (as per technical engagement)



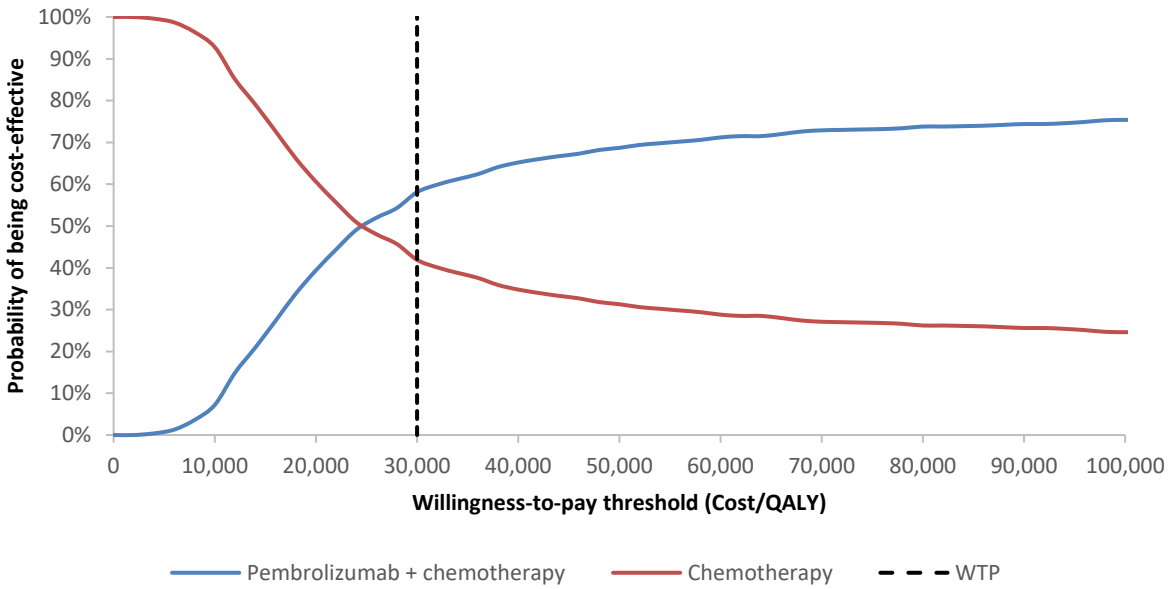
Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 2: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 1 (as per technical engagement)



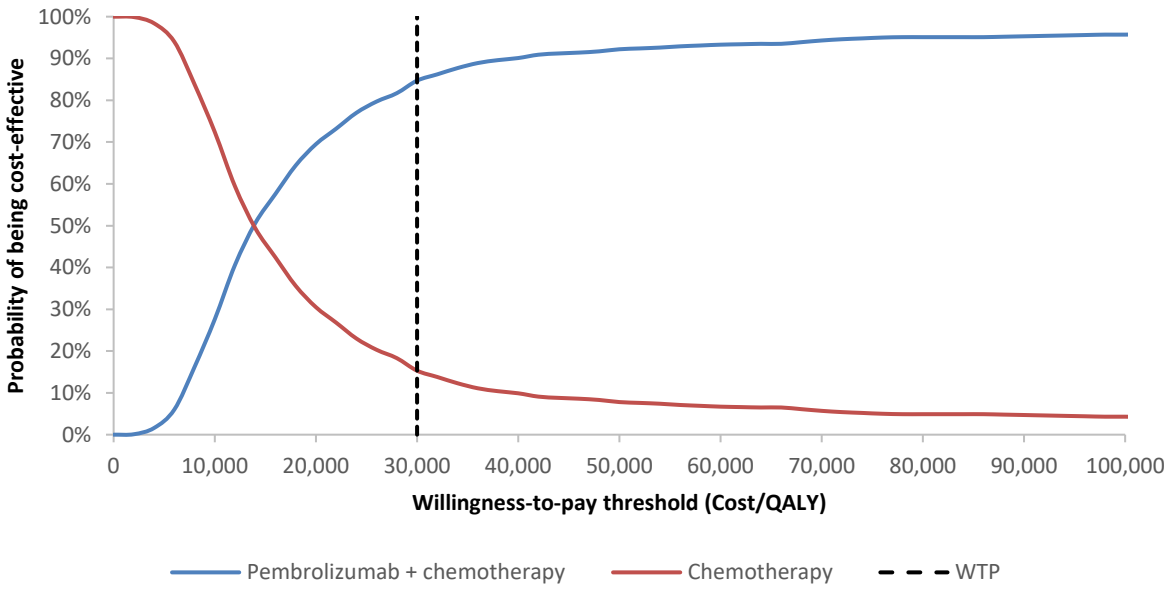
Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 3: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 2 (as per technical engagement)



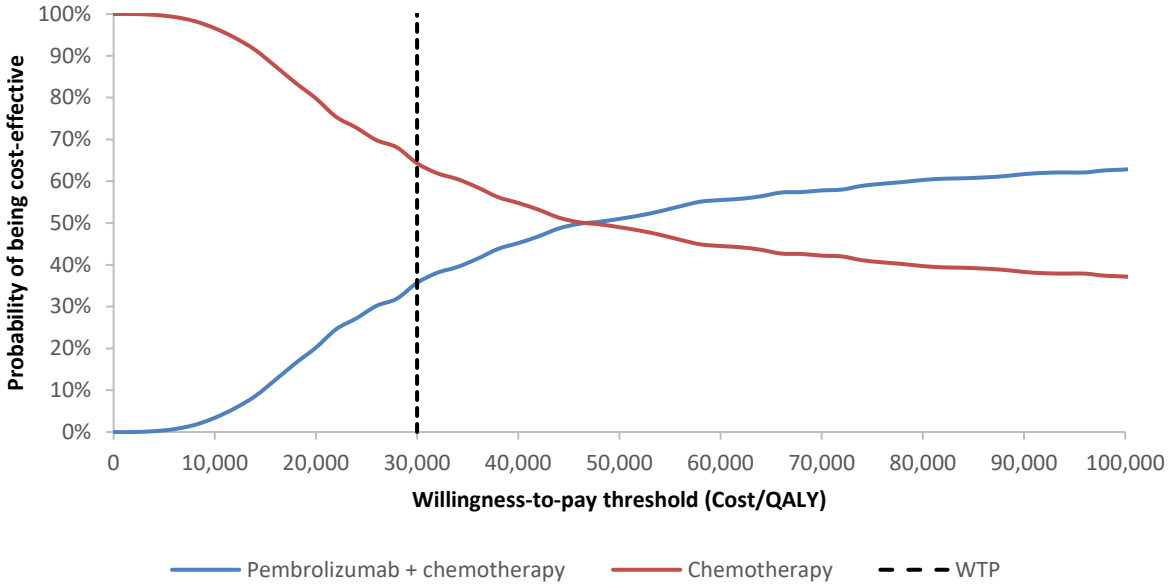
Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 4: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 3 (as per technical engagement)



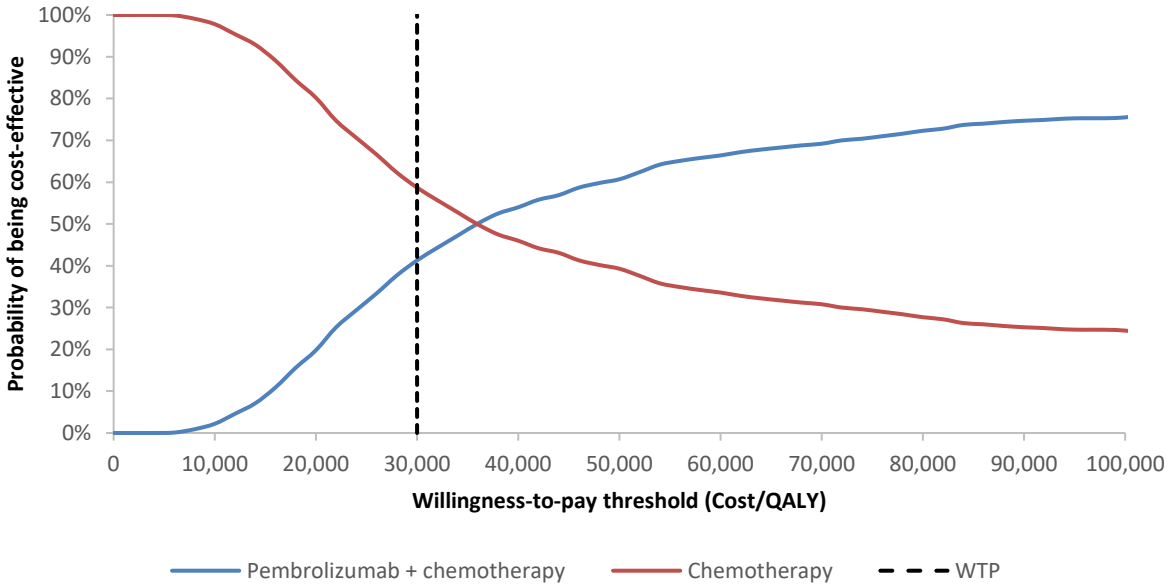
Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 5: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 4 (as per technical engagement)



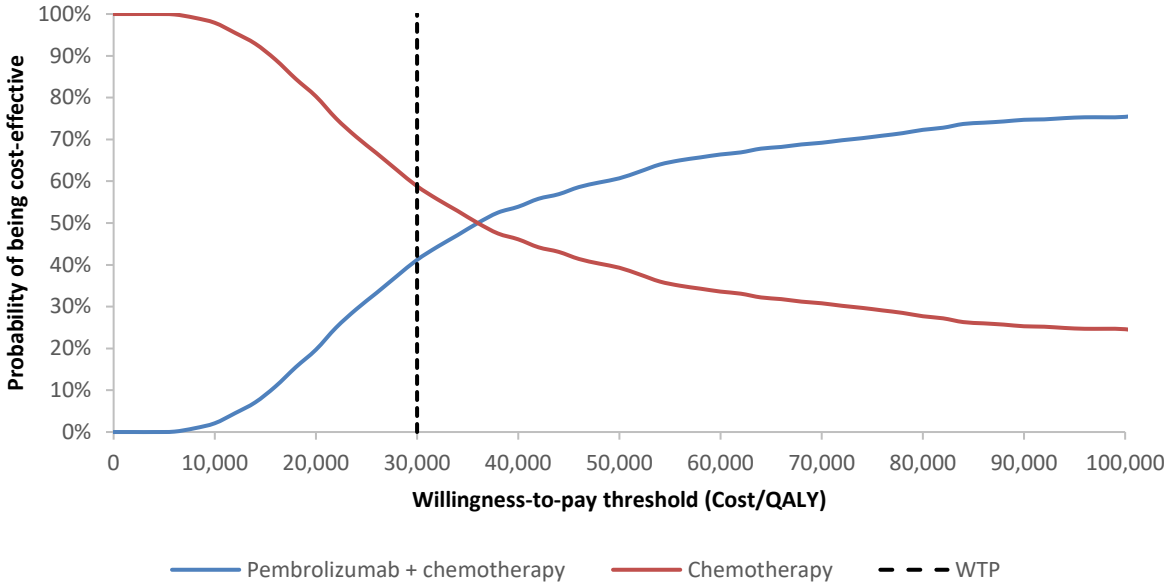
Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 6: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 5 (as per technical engagement)



Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 7: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 6 (as per technical engagement)



Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

in collaboration with:

university of groningen

University Medical Center Groningen

Addendum post PMB to:

Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of untreated locally advanced non-metastatic triple negative breast cancer [ID1500]

Produced by Kleijnen Systematic Reviews (KSR) Ltd in collaboration with University Medical Center (UMC) Groningen, the Netherlands (NL)

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Date completed 29/08/2022

Source of funding: This report was commissioned by the National Institute for Health Research (NIHR) Evidence Synthesis Programme as project number 12/99/38.

Declared competing interests of the authors: None.

[redacted]

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.

This report should be referenced as follows:

Perry M, van Asselt T, de Jong LA, al Khayat MNMT, Postma MJ, Riemsma R, Posadzki P, Duffy S, Ahmadu C, Armstrong N, Kleijnen J, Wolff R. Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of untreated locally advanced non-metastatic triple negative breast cancer [ID1500]: a Single Technology Assessment. York: Kleijnen Systematic Reviews Ltd, 2022.

Contributions of authors

Mark Perry and Robert Wolff acted as project leads and systematic reviewers on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Thea van Asselt acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Lisa de Jong, Mohamed al Khayat, Maarten Postma, Charlotte Ahmadu, and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Rob Riemsma and Pawel Posadzki acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Jos Kleijnen critiqued the company's definition of the decision problem and its description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Addendum to ERG report

This addendum presents the cost-effectiveness results of pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of untreated locally advanced non-metastatic triple negative breast cancer. In this addendum, the ERG have re-run their original analyses in response to PMB, i.e. without the correction for efficacy of pembrolizumab adjusting for Europe versus rest of the world hazard ratio in the ERG base-case, and instead run as a scenario.

See Table 1 for results of company and ERG base case analyses, Table 2 for deterministic scenario results, and Table 3 for results of probabilistic analyses. Cost-effectiveness acceptability curves for probabilistic analyses are presented in Figures 1-8.

Table 1: Deterministic CS and ERG base case (as per PMB)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base case					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£6,861
Fixing errors 1: Enable pembrolizumab 1L treatment in DM state for IO-eligible patients in the placebo arm*					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£6,861
Fixing errors 2: Adjustment to formulas correcting for general population mortality					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£6,863
Matters of judgement 1: Use KEYNOTE-522 data to inform survival in DM state and alongside this adjust treatment costs according to the shorter survival					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£9,554
Matters of judgement 2: Use lognormal distributions in EFS for both arms					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£17,398

1L = first line; CS = company submission; DM = distant metastasis; EFS = event-free survival; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; IO = immune oncology; QALY = quality-adjusted life year

* No longer relevant after technical engagement as the error was in the scenario where patients were not re-challenged with pembrolizumab in the DM health state. As per TE, patients were allowed re-challenge of pembrolizumab in the base case.

Table 2: Deterministic scenario analyses (conditional on ERG base case; as per PMB)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base case					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£21,005
Scenario 1: Limit time horizon to 5 years (similar to the observed period)					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£221,330
Scenario 2: Set the cut-off of the piecewise model at 68 weeks instead of 50 weeks					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£15,699
Scenario 3: Use generalized gamma distributions for EFS in both arms					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			

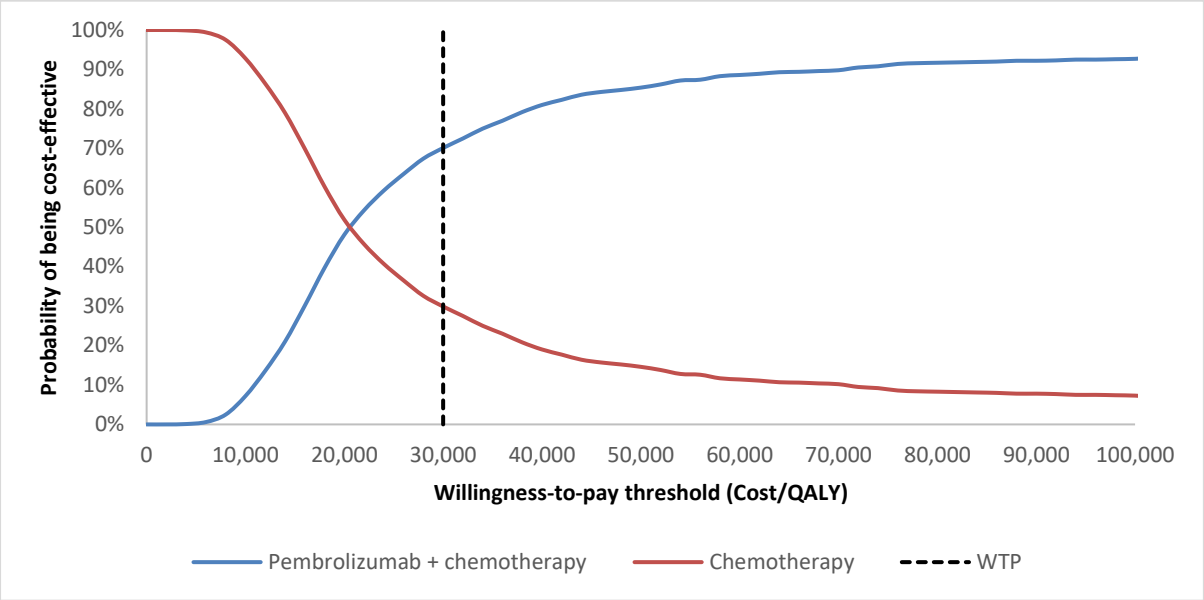
Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£10,276
Scenario 4: Use lognormal distribution for pembrolizumab and generalized gamma distribution for placebo EFS					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£23,962
Scenario 5: Adjust utility in DM health state based on KEYNOTE-355					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£21,244
Scenario 6: Adjust utility in DM health state based on KEYNOTE-119					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£21,283
Scenario 7: Correction for efficacy of pembrolizumab adjusting for Europe versus rest of the world hazard ratio					
Pembrolizumab + chemotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£36,284
CS = company submission; EFS = event-free survival; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year					

Table 3: Probabilistic scenario analyses (conditional on ERG base case; as per PMB)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	Prob-ability
ERG base case						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£20,944	70.1%
Scenario 1: Limit time horizon to 5 years (similar to the observed period)						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£215,133	0.0%
Scenario 2: Set the cut-off of the piecewise model at 68 weeks instead of 50 weeks*						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£19,417	72.6%
Scenario 3: Use generalized gamma distributions for EFS in both arms						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£10,870	93.5%

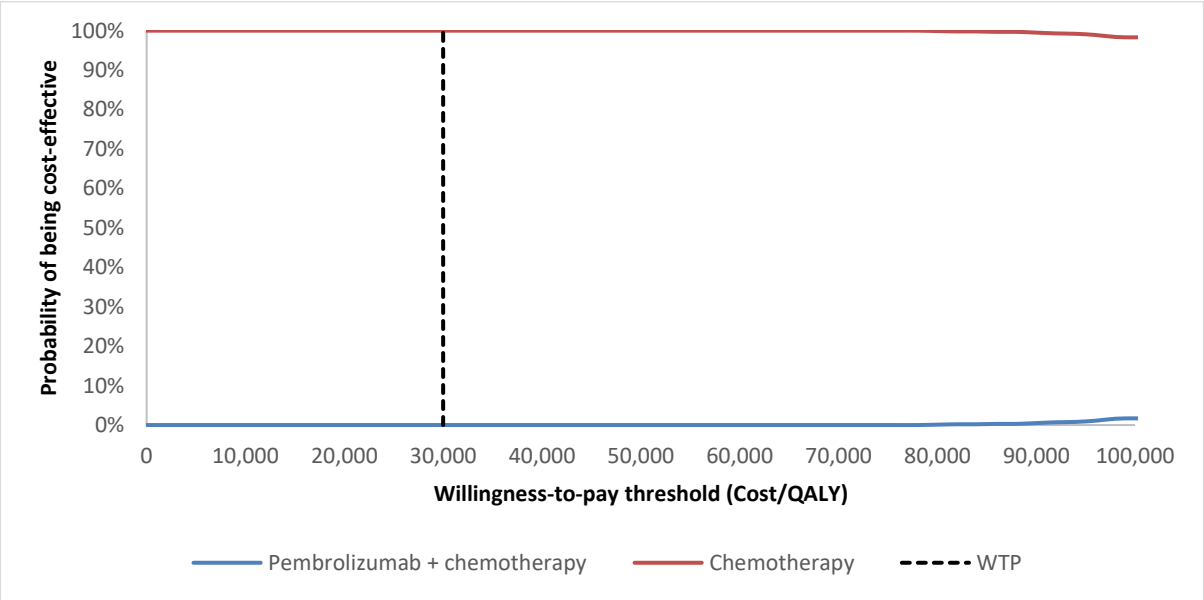
Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)	Prob-ability
Scenario 4: Use lognormal distribution for pembrolizumab and generalized gamma distribution for placebo EFS						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£25,053	56.9%
Scenario 5: Adjust utility in DM health state based on KEYNOTE-355						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£21,208	70.0%
Scenario 6: Adjust utility in DM health state based on KEYNOTE-119						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£21,250	69.8%
Scenario 7: Correction for efficacy of pembrolizumab adjusting for Europe versus rest of the world hazard ratio (original ERG base-case post TE)						
Pembrolizumab + chemotherapy	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£36,358	41.6%
CS = company submission; DM = distant metastasis; EFS = event-free survival; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year						
*Errors in approximately ten PSA runs. Errors were excluded from the analysis to obtain the results						

Figure 1: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on ERG base case (as per PMB)



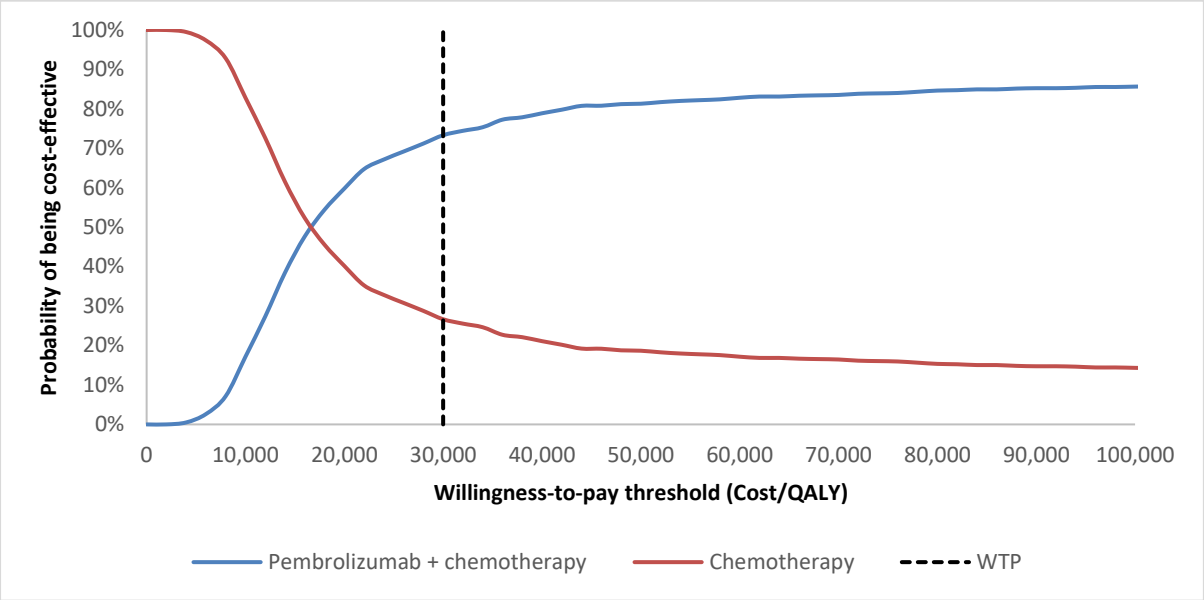
Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 2: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 1 (as per PMB)



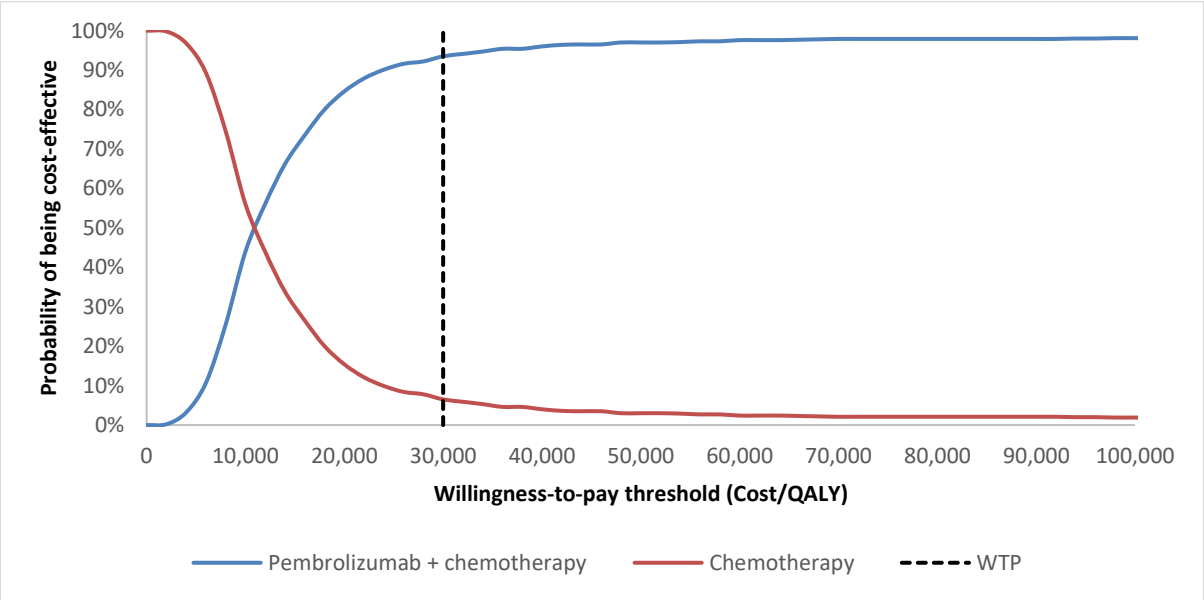
Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 3: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 2 (as per PMB)



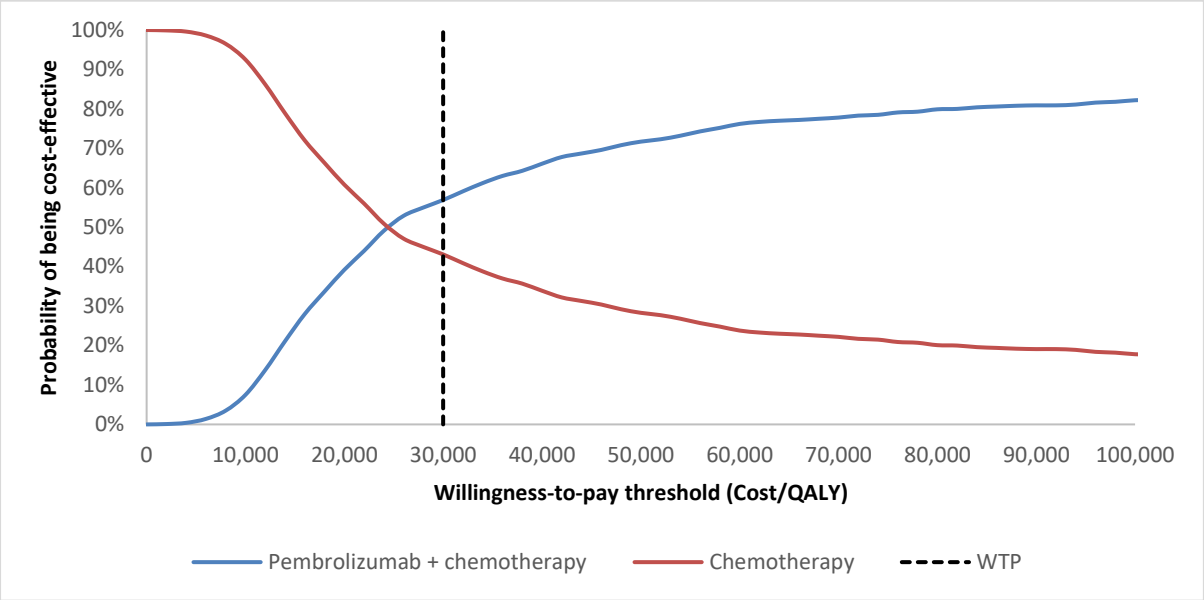
Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 4: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 3 (as per PMB)



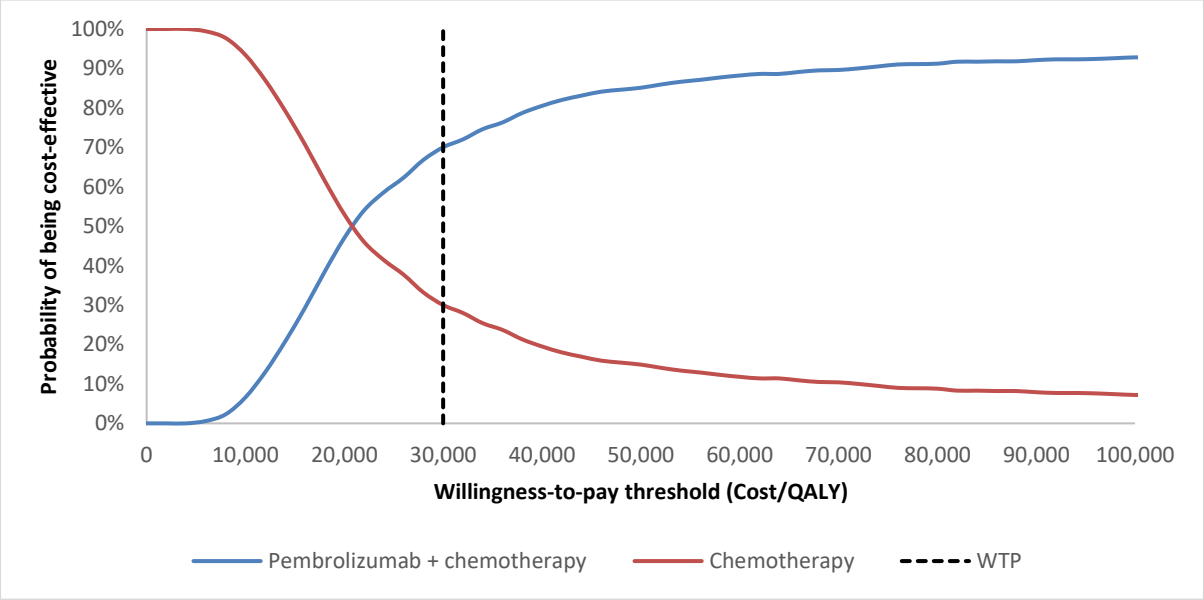
Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 5: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 4 (as per PMB)



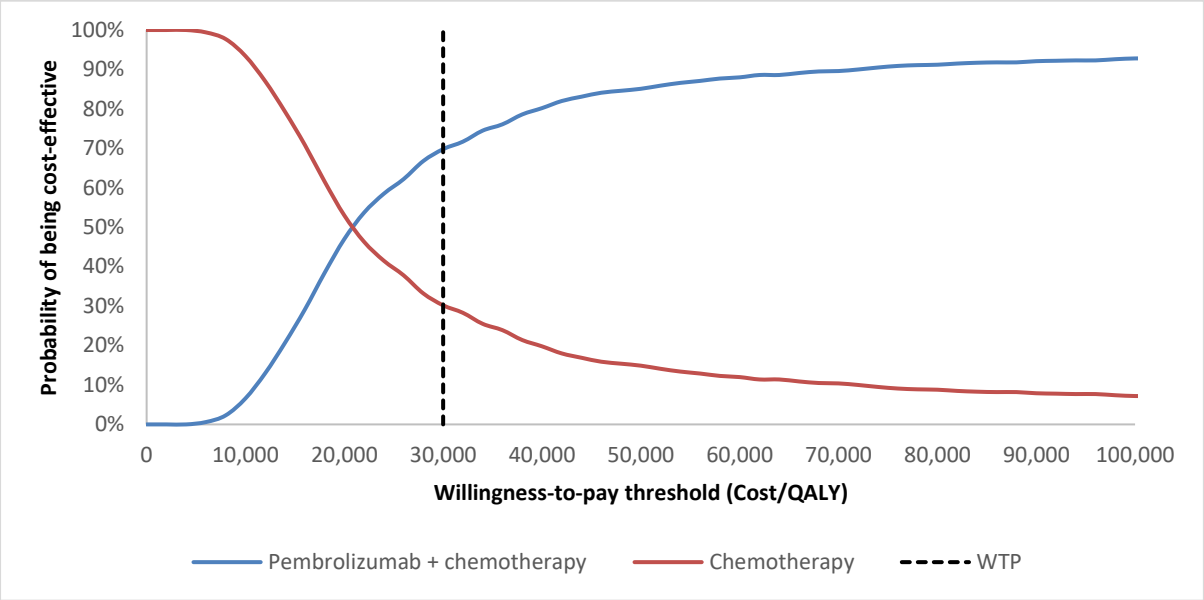
Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 6: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 5 (as per PMB)



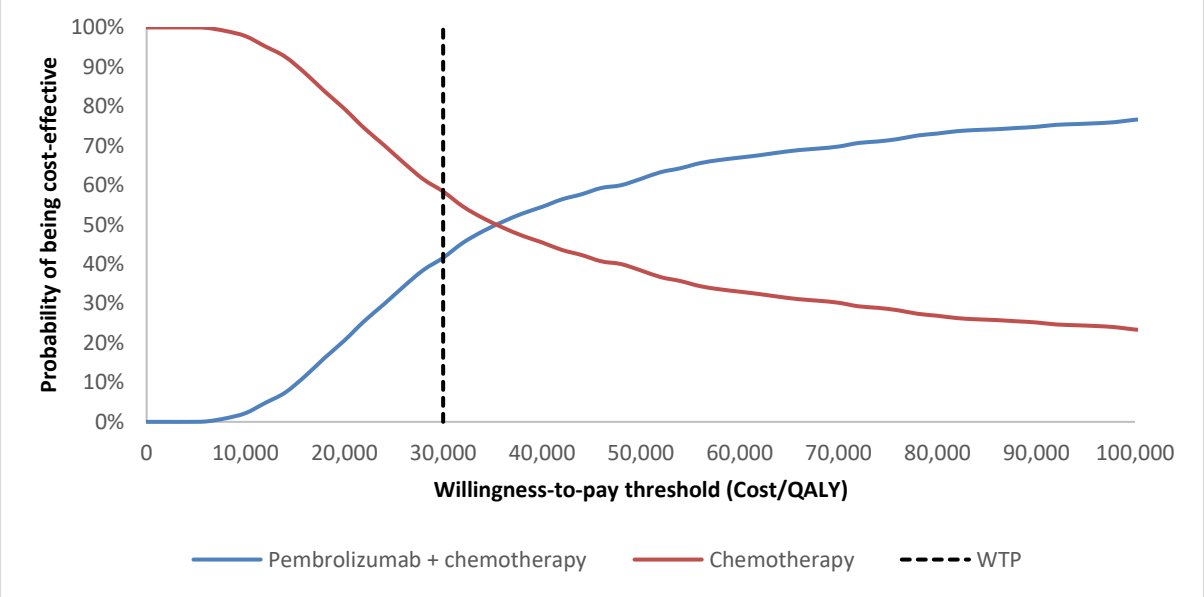
Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 7: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 6 (as per PMB)



Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 8: Cost-effectiveness acceptability curve of pembrolizumab + chemotherapy versus chemotherapy based on scenario 7 (original ERG base-case post TE)



Based on the company model with ERG adjustments
ERG = Evidence Review Group; QALY = quality-adjusted life year; WTP = willingness-to-pay