STA REPORT ID1522

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Atezolizumab for untreated, locally advanced or metastatic, triple negative, PD-L1 positive breast cancer [ID1522]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 128748

Completed 11th June 2019

CONTAINS [redacted] AND [redacted] DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Atezolizumab for untreated, locally advanced or metastatic, triple negative, PD-L1 breast cancer.

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors: Janette Greenhalgh, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

James Mahon, Director, Coldingham Analytical Services, Berwickshire

Marty Richardson, Research Associate (Medical Statistician), LR*i*G, University of Liverpool

Sophie Beale, Research Associate (Decision Analysis), LR*i*G, University of Liverpool

Angela Boland, Director, LR*i*G, University of Liverpool

Tosin Lambe, Research Associate (Health Economics), LR*i*G, University of Liverpool

Yenal Dundar, Research Fellow (Information Specialist), LR*i*G, University of Liverpool

Joanne McEntee, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

Carlo Palmieri, Consultant in Medical Oncology, The Clatterbridge Cancer Centre NHS Foundation Trust

Correspondence to: Janette Greenhalgh, Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

Date completed: 11th June 2019

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 128748.

Acknowledgements: The authors would like to thank Dr Iain McPherson, Clinical Senior Lecturer in Medical Oncology at the University of Glasgow.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

Declared competing interests of the authors: Within the last 3 years**,** Professor Palmieri has received consultancy fees from Roche UK Ltd for attending an advisory board, speaking at Roche sponsored events, travel, accommodation and registration for attending international meetings. Dr McPherson has received consultancy fees, reimbursement for attending a conference, fees for organising education, fees for speaking and hospitality fees from Roche UK Ltd. Dr McPherson has been an investigator on Roche-funded immunotherapy trials in metastatic triple negative breast cancer. The funding for the trials was awarded to NHS Greater Glasgow and Clyde.

This report should be referenced as follows: Greenhalgh J, Mahon J, Richardson M, Beale S, Boland A, Lambe T, Dundar Y, McEntee J, Palmieri C. Atezolizumab for untreated, locally advanced or metastatic, triple negative, PD-L1 breast cancer [ID1522]: A Single Technology Appraisal. LR*i*G, University of Liverpool, 2019

Contributions of authors:

Janette Greenhalgh	Project lead, critical appraisal of the clinical evidence and supervised the final report
James Mahon	Critical appraisal of the economic model
Marty Richardson	Critical appraisal of the statistical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Tosin Lambe	Critical appraisal of the economic evidence
Yenal Dundar	Critical appraisal of the adverse event data and cross checking of the company search strategies
Joanne McEntee	Critical appraisal of the company submission
Carlo Palmieri	Clinical advice and critical appraisal of the clinical sections of the company submission

Table of contents

List of tables

List of figures

LIST OF ABBREVIATIONS

A+nabPx	atezolizumab plus nab-paclitaxel
AE	adverse event
AEOSI	adverse event of special interest
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BNF	British National Formulary
BRCA	BReast CAncer gene
CCOD	clinical cut-off date
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CrI	credible interval
CSR	clinical study report
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D 3L/5L	European Quality of Life-5 Dimensions (3 Level/5 Level version)
ER	estrogen/oestrogen receptor
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
5-FU	5-fluorouracil
HR	hazard ratio
HR	hormone receptor
HRQOL	health-related quality of life
HTA	health technology assessment
IC	immune cell
ICER	incremental cost-effectiveness ratio
IPD	individual patient data
IRC	Independent Review Committee
ITT	intention-to-treat
KM	Kaplan-Meier
LYG	life years gained
MAIC	matching adjusted indirect comparison
mTNBC	metastatic breast cancer
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NR	not reported
ORR	objective response rate
OS	overall survival
P+nabPx	placebo plus nab-paclitaxel
PAIC	population adjusted indirect comparison
PAS	patient access scheme

PD	progressive disease
PD-L1	Programmed death ligand 1
PFS	progression-free survival
PPS	post-progression survival
PgR	progesterone receptor
PS	performance status
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	quality adjusted life years
QLQ-C30	EORTC quality of life questionnaire –core30
RCT	randomised controlled trial
RECIST	response evaluation criteria in solid tumours
RR	response rate
RWE	real world evidence
SAE	serious adverse event
SD	standard deviation
SLR	systematic literature review
SmPC	summary of product characteristics
TNBC	triple negative breast cancer
TSAP	trial statistical analysis plan
TTOT	time-to-off-treatment

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the Single Technology Appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by Roche Products Ltd in support of the use of atezolizumab (Tecentriq®) in combination with nab-paclitaxel (Abraxane®) for untreated, locally advanced or metastatic, triple negative, PD-L1-positive (PD-L1+) breast cancer. Throughout this ERG report, locally advanced or metastatic triple negative breast cancer is referred to as mTNBC.

1.2 Critique of the decision problem in the company submission

The company has presented data from the IMpassion130 trial. The IMpassion130 trial is a phase III, randomised, international, double-blind, placebo-controlled trial. Patients with untreated mTNBC were randomised to receive atezolizumab plus nab-paclitaxel (A+nabPx) or placebo plus nab-paclitaxel (P+nabPx). A pre-defined subgroup of patients (n=369) in the IMpassion130 trial had tumours that, at baseline, tested positive for PD-L1 expression.

Population

The population described in the final scope issued by NICE is people with locally advanced or metastatic, triple negative breast cancer whose tumours have PD-L1 expression ≥1% and have not received prior chemotherapy for metastatic disease. In the PD-L1+ subgroup of the IMpassion130 trial (A+nabPx: n=185, P+nabPx: n=184), 87.6% of patients in the A+nabPx arm and 86.9% of patients in the P+nabPx arm had metastatic disease.

Currently, PD-L1 testing is not routinely carried out in the NHS for patients with mTNBC. However, clinical advice to the ERG is that, as PD-L1 testing is routinely carried out for patients with advanced non-small cell lung cancer, scaling up testing to include patients with mTNBC should not be problematic, although support and training will be needed to establish the breast-specific assay.

Intervention

The intervention in the final scope issued by NICE and in the company submission (CS) is A+nabPx. The company expects A+nabPx to be granted marketing authorisation by the European Medicines Agency in [redacted]. The company's proposed wording for the licensed indication is:

[redacted]

[redacted]

In the CS, the recommended dose of atezolizumab is 840mg administered intravenously on days 1 and 15 of each 28-day cycle. Nab-paclitaxel is administered intravenously at a dose of 100mg/m^2 on days 1, 8 and 15 of each 28-day cycle. On days 1 and 15, it is administered after atezolizumab. The ERG notes that nab-paclitaxel is only licensed in Europe for use as a second-line, not a first-line, treatment of metastatic breast cancer.

Comparators

The comparators listed in the final scope issued by NICE are anthracycline-based therapy and single agent taxane chemotherapy with paclitaxel or docetaxel. Nab-paclitaxel, the comparator in the IMpassion130 trial, is not specified as a comparator. Clinical advice to the ERG is that, in the NHS, nab-paclitaxel is only prescribed to patients who are intolerant to paclitaxel.

Anthracycline-based chemotherapy

The company has not provided any evidence for the effectiveness (or cost effectiveness) of A+nabPx versus anthracyclines. The company provides two reasons for not submitting this evidence. First, that anthracyclines have a lifetime maximum cumulative dose and, therefore, patients who have been treated with anthracyclines in the early breast cancer setting are unlikely to be eligible for re-challenge in the metastatic setting. Second, that there was an absence of any direct evidence, and a lack of any robust trial data or real-world evidence to allow an indirect comparison.

The ERG considers that anthracyclines may only be a relevant comparator for a limited number of patients but does not consider this to be a reasonable basis for excluding them from the analyses. However, the ERG acknowledges that interpretation of results from any analyses would be problematic due to limited data.

Taxanes

Population adjusted indirect comparisons (PAICs) were carried out so that networks could be formed to allow network meta-analyses (NMAs) to be carried out to generate clinical effectiveness data to compare the effectiveness of A+nabPx versus paclitaxel and docetaxel.

The ERG notes that there is an ongoing trial comparing treatment with atezolizumab+paclitaxel versus placebo+paclitaxel in patients with mTNBC (the IMpassion131 trial); however, the estimated completion date for this trial is not until June 2021.

Outcomes

The company has provided clinical evidence relating to treatment with A+nabPx from the IMpassion130 trial, for all five outcomes specified in the final scope issued by NICE:

- Investigator assessed (RECIST v1.1) progression-free survival (PFS)
- Overall survival (OS) defined as the time from the date of randomisation to the date of death from any cause
- Response rate (RR), specifically objective response rate (ORR) and duration of response (DoR)
- Adverse effects (AEs) of treatment
- Health-related quality of life (HRQoL) using the European Quality of Life-5 Dimensions-5 Level (EQ-5D-5L) questionnaire and the European Organisation for the Research and treatment of Cancer (EORTC) Quality of Life-Core 30 (QLQ-C30) instrument in conjunction with the QLQ-BR23 breast cancer module.

Data from the IMpassion130 trial are available from the April 2018 and January 2019 data cuts. Only descriptive, interim OS results are available for the PD-L1 subgroup due to the statistical approach (hierarchical testing) used to analyse the IMpassion130 trial data.

The company has advised caution when interpreting the results generated by their NMAs. The ERG agrees with the company that the results from the NMAs should be viewed with caution.

Subgroups

No subgroups were specified in the final scope issued by NICE.

Other considerations

The company did not identify any equity or equality issues. However, the company has put forward a case for treatment with A+nabPx to be considered under NICE's End of Life criteria. A Patient Access Scheme (PAS) price is currently in place for 1200mg vials of atezolizumab. The company states that, [redacted]. A PAS is also in place for nab-paclitaxel.

1.3 Summary of the clinical evidence submitted by the company

Direct evidence

At the time of the definitive PFS analysis (data cut-off date: 17th April 2018), treatment with A+nabPx was shown to statistically significantly improve investigator-assessed PFS in comparison to P+nabPx in the PD-L1+ patient population (HR=0.62, 95% confidence interval [CI]: 0.49 to 0.78; p-value<0.001). Median PFS was longer in the A+nabPx arm than in the P+nabPx arm (7.5 months versus 5.0 months, respectively).

[redacted]

The overall frequency of AEs in the PD-L1+ population of the IMpassion130 trial was high in the A+nabPx and P+nabPx treatment arms (100% versus 97.8%). More patients treated with A+nabPx experienced AEs leading to treatment discontinuation. The incidences of AEs of special interest were higher in the A+nabPx arm, most notably hyper- and hypo-thyroidism. Data relevant to treatment-related AEs specific to the PD-L1+ population were not available in the CS, however, in the overall safety population of the trial, the frequency of treatment-related AEs was similar in both arms of the trial. The most commonly experienced AEs (any grade) in both arms were alopecia (56% and 57.3%), nausea (41.2% and 33.8%) and fatigue (40% and 38.1%). The most commonly experienced Grade 3 or Grade 4 treatment-related AEs were neutropenia (8.2% and 8%), peripheral neuropathy (5.5% and 2%) and neutrophil count decrease (4.6% and 3.4%).

The company reports that the AEs reported in the IMpassion130 trial are consistent with the known safety profiles of each treatment with no new AEs identified. However, clinical advice to the ERG is that AEs arising from treatment with atezolizumab and other immunotherapies require tailored training with regard to awareness, as well as careful monitoring by a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs, and that this can place a high burden on NHS staff and systems.

Health-related quality of life was measured during the IMpassion130 trial using the EORTC QLQ-30 and QLQ-BR23 and the EQ-5D-5L questionnaires. The company found no difference between treatment arms (A+nabPx vs P+nabPx) for the outcomes measured by the EORTC QLQ-30 or QLQ-BR23 questionnaires. The ERG considers that the utility values derived from the EQ-5D-5L data collected during the IMpassion130 trial are in line with utilities calculated from data collected during trials of other drugs to treat advanced breast cancer.

Indirect evidence

The company did not identify any relevant RCTs of anthracyclines that could be included in indirect comparisons. The company investigated the possibility of performing indirect comparisons using real-world evidence (the Flatiron Cohort) instead but concluded that this approach was not appropriate for various reasons. These reasons included insufficient data on baseline characteristics for the Flatiron cohort, and differences between the anthracycline treatments used by the Flatiron cohort and those used in UK clinical practice.

The company identified relevant RCTs of paclitaxel and docetaxel that could be included in NMAs. As the networks for both OS and PFS were unconnected, the company performed population adjusted indirect comparisons (PAICs) to form connected networks for both outcomes. The company used discrete time models to summarise treatment effects across the networks of evidence. For OS, a piecewise exponential model with a cut-point at 5 months was chosen as the base-case model. For PFS, the base-case model was a piecewise exponential model with cut-points at 2 and 4 months.

Across the NMAs for OS and PFS, 95% credible intervals (CrIs) for the HRs were wide and mostly included 1 (the point of no difference). The exceptions to this observation were the comparisons of paclitaxel versus A+nabPx for OS after 5 months (HR=1.74, 95% CI: 1.12 to 2.71), paclitaxel versus A+nabPx for PFS after 4 months (HR=1.88, 95% CI: 1.10 to 3.11) and docetaxel versus A+nabPx for PFS after 4 months (HR=2.79, 95% CI: 1.30 to 6.03). For all HRs presented for the comparisons of nab-paclitaxel versus paclitaxel and versus docetaxel, 95% CrIs included 1.

The differences between restricted mean 5-year survival times also had wide CrIs. However, the results suggested that treatment with A+nabPx improved OS versus paclitaxel (29.0 and 20.4 months respectively), and that treatment with A+nabPx improved PFS versus both paclitaxel (11.2 and 7.1 months respectively) and docetaxel (11.2 and 5.9 months respectively). There was no evidence to suggest a difference in restricted mean 5-year survival times between nab-paclitaxel and paclitaxel or docetaxel for either OS or PFS.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

Direct evidence

The ERG is satisfied with the company's search strategy and the stated inclusion and exclusion criteria. The ERG is confident that the literature searching was carried out to an acceptable standard and the ERG is not aware of any additional studies that should have been included in the company's systematic review.

The ERG considers that the IMpassion130 trial is a good quality trial, is well conducted and includes a large number of PD-L1 patients. However, the comparator in the trial (nab-paclitaxel) is not a comparator listed in the final scope issued by NICE.

The ERG is satisfied that the patients recruited to the IMpassion130 trial are generally representative of patients with mTNBC who are treated in the NHS. Clinical advice to the ERG is that most NHS patients treated for early breast cancer who subsequently develop metastatic disease would have been previously treated with a sequential regimen of anthracyclines and taxanes. In the IMpassion130 trial, only 57% of PD-L1 patients had received prior anthracycline treatment and only 51% of PD-L1 patients had received prior taxane treatment.

The ERG considers that the company's statistical approach for the analysis of data from the IMpassion130 trial was appropriate, with the exception that the company presented various results from analyses that, according to the stepwise testing procedure described in the trial statistical analysis plan (TSAP), should not have been performed.

The median PFS was longer for patients in the A+nabPx arm than for patients in the nab-paclitaxel arm (7.5 months versus 5.0 months, respectively); however, clinical advice to the ERG is that a difference in median PFS of 2.5 months is not clinically meaningful.

The ERG highlights that according to the pre-specified stepwise testing procedure described in the TSAP, no analyses of OS in the PD-L1+ population should have been performed at the time of the first interim OS analysis. Furthermore, the results presented by the company are immature as only 34.6% of patients in the A+nabPx arm and 47.8% of patients in the P+nabPx arm had died at the time of this analysis. Due to the immaturity of the data, the ERG is uncertain whether the [redacted] will increase or decrease in the longer-term.

Indirect evidence

In accordance with the company, the ERG did not identify any relevant RCTs of anthracyclines that could be included in indirect comparisons. The ERG agrees with the company's conclusion that it was not appropriate to perform an indirect comparison of A+nabPx versus anthracyclines using the available real-world evidence.

The ERG was unable to determine whether the company's approach to including and excluding studies from the NMAs was appropriate. Furthermore, the company's approach to estimating restricted mean 5-year survival times makes the assumption that the treatment effect of A+nabPx versus each comparator in the comparator trials is identical to the treatment

effect observed in the IMpassion130 trial population. This assumption introduces uncertainty into the results of the NMAs.

Clinical effectiveness evidence for patients with PD-L1 disease treated with A+nabPx and P+nabPx were available from the IMpassion130 trial to populate the company networks. However, for all other treatments in the networks, the company assumed that reported effectiveness results, from patients with unknown PD-L1 disease status, reflected effectiveness in a population with PD-L1 disease.

Finally, the lack of availability of baseline characteristics for patients with mTNBC (for whom data were included in the NMAs) means that a comprehensive evaluation of the comparability of patient populations included in the NMAs is very difficult. The ERG, therefore, considers that the results of the company's NMAs should be interpreted with caution.

1.5 Summary of cost effectiveness evidence submitted by the company

During clarification, the ERG asked the company to re-run their NMAs with P+nabPx as the reference treatment (clarification question A13). The company carried out these analyses. In addition, the company submitted cost effectiveness results using HRs for OS and PFS for paclitaxel and docetaxel from these NMAs and then applied these HRs to the P+nabPx arm of the IMpassion130 trial. The company requested that these cost effectiveness results replace the original results and be considered as the new base case analysis results. Therefore, all of the ERG's changes to the company model are based on the new data submitted by the company during the clarification period.

The company developed a de novo partitioned survival model in Microsoft Excel to compare the cost effectiveness of treatment with A+nabPx versus paclitaxel and versus docetaxel for previously untreated PD-L1+ mTNBC. The model comprises three mutually exclusive health states: progression-free survival (PFS), progressed disease (PD) and death. All patients start in the PFS health state. The model time horizon is set at 15 years with a 7-day cycle length. The model perspective is that of the UK NHS. Outcomes are measured in quality adjusted life years (QALYs) and both costs and QALYs are discounted at an annual rate of 3.5%, as recommended by NICE.

For modelling treatment with A+nabPx, several parametric functions were fitted to the OS, PFS and time to off treatment (TTOT) Kaplan-Meier (K-M) data from A+nabPx arm of the IMpassion130 trial. OS estimates from the fitted Weibull function were used throughout the model time horizon. The PFS K-M data from the IMpassion130 trial were used up to 19.2 months followed by estimates from the fitted Gompertz function. TTOT was separately

calculated for atezolizumab (piecewise K-M plus exponential function) and nab-paclitaxel (piecewise K-M plus gamma function), with cut points at 20.3 months and 12.5 months respectively.

No direct trial evidence was available for the comparison of treatment with A+nabPx versus paclitaxel or versus docetaxel. Therefore, to estimate OS and PFS for these treatments, the time-dependent OS and PFS HRs produced by the company NMAs were applied to the OS and PFS data that were used to model treatment with A+nabPx. The company assumed that, for patients treated with paclitaxel or docetaxel, TTOT was equivalent to PFS.

The AE rates associated with treatment with A+nabPx were obtained from the IMpassion130 trial and rates associated with treatment with paclitaxel or docetaxel were obtained from the published literature. HRQoL data were collected as part of the IMpassion130 trial using the EQ-5D-5L questionnaire. Responses to the questionnaire (stratified by PFS and PD) were converted to EQ-5D-3L utility values using a published algorithm and then used to represent the HRQoL of patients in the PFS and PD health states. Resource use were estimated based on information in previous related technology appraisals of breast cancer while unit costs were obtained from the NHS Reference Cost database and the drugs and pharmaceutical electronic Market Information Tool.

Using the list price of all drugs, results from the company base case deterministic analysis showed that treatment with A+nabPx was more expensive and more effective than paclitaxel or docetaxel. Using the available discounted price for atezolizumab and the list price of other drugs, the incremental cost effectiveness ratio (ICER) for the comparison of treatment with A+nabPx versus treatment with paclitaxel and versus docetaxel were £63,347 and £70,217 per QALY gained respectively.

The results from the company probabilistic sensitivity analysis are consistent with the company's base case (deterministic) analysis. The company carried out a wide range of deterministic sensitivity analyses using the list prices of all treatments. The most influential parameters were the utility values for the PFS and PD health states, discount rate (cost and outcomes) and treatment administration costs.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

Whilst the company economic model was well constructed, the data available to populate the paclitaxel and docetaxel comparator arms were limited. Furthermore, the data presented by the company, as well as that from other published sources identified by the ERG, failed to show that OS and PFS outcomes were statistically significant different for patients treated with

nab-paclitaxel, paclitaxel or docetaxel. Even if the results from the company's NMAs were considered sufficiently robust to populate an economic model, the results provide no evidence that treatment with nab-paclitaxel, paclitaxel and docetaxel lead to different OS and PFS outcomes. The ERG considers that, in the absence of evidence to show that treatment with nab-paclitaxel, paclitaxel and docetaxel are dissimilar, the OS, PFS and TTOT data used to populate the paclitaxel and docetaxel arms of the model should be taken directly from the P+nabPx arm of the IMpassion130 trial.

The ERG also amended resource use and costs in the PFS and PD health states as clinical advice to the ERG was that the frequency, and therefore costs, associated with oncologist appointments were too low.

In the company model, it is assumed that treatment with A+nabPx confers a lifetime treatment effect on OS. The ERG does not consider this plausible; however, there is no direct evidence to indicate the likely duration of treatment effect with A+nabPx. The ERG considered scenarios that limited the duration of treatment effect to 3 and 5 years, noting that, in the IMpassion130 trial, only 3.4% of patients were still progression-free and receiving A+nabPx treatment at 3 years.

1.7 Summary of company's case for End of Life criteria being met

A technology meets NICE End of Life criteria if (i) life expectancy with standard of care treatments for the target population is under 24 months and (ii) the increase in life expectancy with the technology being appraised is at least 3 months.

The estimates generated by the company model are that median life expectancy is 13.8 months for patients treated with paclitaxel and 14.3 months for patients treated with docetaxel. Results from the company model also show that, compared to treatment with paclitaxel and docetaxel, treatment with A+nabPx offers a median extension to life of 12.6 months and 11.6 months respectively.

1.8 ERG commentary on End of Life criteria

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

When duration of effect of treatment with A+nabPx was limited to 3 years (more pessimistic than limiting to 5 years), results from the amended company model showed a gain, compared

with treatment with paclitaxel or docetaxel, in median OS for patients treated with A+nabPx of 5.3 months and a gain in mean OS of 4.8 months.

The ERG is satisfied that treatment with A+nabPx meets both components of the NICE End of Life criteria for the population under consideration when compared with treatment with either paclitaxel or docetaxel.

1.9 ERG commentary on the robustness of evidence submitted by the company

1.9.1 Strengths

Clinical evidence

- The IMpassion130 trial is a good quality RCT.
- EQ-5D-5L data were collected during the IMpassion130 trial.
- The Impassion130 trial included a large number of PD-L1 patients.
- The ERG's requests for additional information were mostly addressed to a good standard.

Cost effectiveness evidence

- The company Excel model was accurately constructed and represented the structure and parameter values detailed in the CS.
- The rationale for the choice of piecewise distributions was well described.
- The EQ-5D-5L data collected during the Impassion130 trial were used in the economic model.

1.9.2 Weaknesses and areas of uncertainty

Clinical evidence

- The ERG advises caution when considering the results presented by the company for OS in the PD-L1+ population. According to the pre-specified stepwise testing procedure of the IMpassion130 trial, no analyses of OS in the PD-L1+ population ought to have been performed at the time of OS analysis.
- There is no direct evidence available to compare the clinical effectiveness of A+nabPx with any of the comparators in the final scope issued by NICE and the ERG considers that the results from the company's NMAs should be interpreted with caution as:
    - the ERG was unable to determine whether the company's approach to including and excluding studies from the NMAs, or their methods to obtain estimates of restricted 5-year mean survival times, were appropriate
    - clinical effectiveness evidence for patients with PD-L1 disease treated with A+nabPx and P+nabPx were available from the IMpassion130 trial to populate the company networks. However, for all other treatments in the networks, the company assumed that reported effectiveness results, from patients with unknown PD-L1 disease status, reflected effectiveness in a population with PD-L1 disease

  - a comprehensive evaluation of the comparability of patient populations included in the NMAs is very difficult due to the lack of availability of baseline characteristics for patients with mTNBC (for whom data were included in the NMAs)

- The company states that no new safety concerns arising from treatment with atezolizumab or nab-paclitaxel were noted during the IMpassion130 trial. However, clinical advice to the ERG is that AEs (Grade 2 or higher) arising from treatment with atezolizumab and other immunotherapies require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs

Cost effectiveness evidence

- The company NMAs did not provide statistically significant evidence that treatment with nab-paclitaxel, paclitaxel or docetaxel lead to different OS or PFS outcomes; however, in the company model, the OS and PFS of patients who received these three treatments are different.
- The company estimates of the frequency of patient visits to an oncologist were too low, leading to underestimates of the health care costs associated with the PD and PFS health states
- The company has assumed that, compared to paclitaxel or docetaxel, the effect of treatment with A+nabPx lasts for a lifetime. The company has not submitted any evidence to support this assumption.

1.10 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG made three amendments to the company base case:

1. Modelling paclitaxel and docetaxel using OS, PFS and TOTT data from the P+nabPx arm of the IMpassion130 trial
2. Increasing patient health care costs in the PFS and PD health states
3. Introducing a limit to the duration of treatment effect of A+nabPx (3- and 5-year durations).

The ERG presents a scenario in which the first two amendments only are applied. For the comparison of A+nabPx versus paclitaxel, this alternative scenario increases incremental costs by [redacted] and reduces incremental QALY gains by [redacted]; the company's base case ICER increases by [redacted] to £85,306 per QALY gained. For the comparison of A+nabPx versus docetaxel, this alternative scenario increases incremental costs by [redacted] and reduces incremental QALY gains by [redacted]; the company's base case ICER increases by [redacted] to £98,506 per QALY gained.

The ERG also presents a scenario when limits to the duration of treatment effect are applied in addition to the first two ERG amendments. For the comparison of A+nabPx versus paclitaxel, using a 3-year duration of treatment effect, the company base case ICER increases by [redacted] to £122,745 per QALY gained; using a 5-year duration of treatment effect, the company base case ICER increases by [redacted] to £96,298. For the comparison of A+nabPx

versus docetaxel, using a 3-year duration of treatment effect, the company base case ICER increases by [redacted] to £142,072 per QALY gained.

The company's cost effectiveness results show that, at a willingness to pay threshold of £50,000 per QALY gained, treatment with A+nabPx versus both paclitaxel and docetaxel is not cost effective. The ERG's revised ICERs per QALY gained are also above this threshold.

Details of ICERs using the PAS price of nab-paclitaxel are provided in a confidential appendix. The appraisal can only assess drugs that are currently available for use by the NHS. It is unknown when, or if, the generic form of paclitaxel will become available for use in the NHS. Furthermore, if it does become available, the impact on the PAS or list price of nab-paclitaxel, is unknown.

2 BACKGROUND

2.1 Summary and critique of company's description of underlying health problem

The company's description of the underlying health problem is presented in Section B1.3 of the company submission (CS).[1] The Evidence Review Group (ERG) considers that the company's description presents a reasonable summary of the underlying health problem. Points made by the company that are considered by the ERG to be of particular relevance to the current appraisal are presented in Box 1.

The ERG notes that the patient population specified in the final scope[2] issued by NICE is people with untreated locally advanced or metastatic triple negative PD-L1-positive breast cancer. In the CS, the company uses two different terms to refer to the population of interest, metastatic TNBC (mTNBC) or advanced TNBC. For simplicity, the ERG will use mTNBC to refer to locally advanced or metastatic TNBC.

The ERG highlights that the company's description of the health problem relates to patients with TNBC and that, currently, there are no published epidemiological data specific to patients with mTNBC that tests positive for PD-L1.[3]

Box 1 Key points from the company's description of the underlying health problem

Description of disease

- Breast cancer is a malignant cancer that originates from the cells of the breast; most commonly the ducts, and sometimes the lobules.[4] Advanced and/or metastatic breast cancer occurs when the tumour has spread beyond the breast and lymph nodes; the most common sites of metastasis for breast cancer are the lymph nodes, bones, liver, lungs, and brain.[5]
- Breast cancer is categorised into three main subtypes based on the presence or absence of oestrogen or progesterone receptors and HER2. TNBC is a diagnosis of exclusion characterised by the lack of expression of oestrogen and progesterone receptors as well as the absence of HER2 overexpression. The specific molecular pathophysiology of TNBC remains poorly understood[6] and this diagnosis comprises a heterogeneous group of malignancies.[7]
- TNBC tumours are often aggressive, with a high proliferative rate and an invasive phenotype.[7] They are thus frequently larger and less differentiated at presentation.[8] TNBC metastasises preferentially to the viscera and once this occurs there is a poor prognosis for the patient.[8]
- TNBC disproportionally affects younger, premenopausal women and those of African or Hispanic ancestry.[8]

Epidemiology

- In 2016, there were 45,960 new cases of breast cancer diagnosed and 9685 deaths in England.[9,10]
- TNBC accounts for approximately 15–20% of all breast cancers.[6,8,11]
- 6–7% of breast cancers in the UK are diagnosed as stage IV, i.e., de novo metastatic disease.[12]
- Overall, breast cancer accounted for 7% of cancer deaths in the UK in 2016.[10]
- TNBC accounts for 25% of deaths from breast cancer.[8]

Burden of disease

- As TNBC tumours lack the classical breast cancer molecular targets they are difficult to treat. Chemotherapy is the mainstay of treatment in early breast cancer. However, upon relapse, the only available strategy remains to "re-challenge" with systemic chemotherapy. This approach is limited by poor response, toxicity and eventual multi-drug resistance.[8]

- Outcomes for patients with mTNBC fall considerably behind those for patients with other breast cancer subtypes, with a median overall survival (OS) of ≤18 months[6,13-15] compared with 4–5 years for patients with the HR+ and HER2+ subtypes.[6]

HER2+=human epidermal growth factor receptor 2 positive; HR+=hormone receptor-positive; mTNBC=metastatic triple negative breast cancer; TNBC=triple negative breast cancer
Source: adapted from CS, Section B1.3

2.2 Company's overview of current service provision

The ERG considers that the company's overview (CS, Section B1.3) presents an accurate summary of current service provision. The key points made by the company are provided in Box 2, Box 3 and Box 4 of this ERG report.

Impact of previous treatments

The company (CS, p22) discusses factors that clinicians consider when making decisions about treatment for patients with mTNBC. These factors include patient characteristics, disease characteristics and treatment history. The company highlights that treatments received in earlier breast cancer settings impact on treatment options in the metastatic setting and, therefore, treatment history is important.

Box 2 Adjuvant and neoadjuvant treatment for breast cancer

- Sequential anthracycline-taxane chemotherapy represents a common standard of care in both the neoadjuvant and adjuvant treatment of moderate or high risk early TNBC.[11] In the UK, this tends to be epirubicin + cyclophosphamide +/- 5-fluorouracil, followed by a taxane, usually docetaxel (UK clinical expert opinion[16]). While there is increasing consideration of the role of platinum agents in the neoadjuvant treatment of TNBC, data are not yet available on their impact on long-term outcomes.[11]
- Eligibility for re-challenge with anthracyclines and taxanes in the metastatic setting will depend on several factors; anthracyclines have a lifetime maximum cumulative dose (e.g., epirubicin) and as such, patients treated in the early breast cancer setting are unlikely to be eligible for re-challenge. However, it is generally accepted that re-challenging a patient with a single-agent taxane is reasonable, particularly if there has been a >12 months treatment-free interval.[17]

TNBC=triple negative breast cancer
Source: CS, p22

Clinical advice to the ERG is that in the adjuvant/neoadjuvant setting, most patients (95%) with TNBC are treated with an anthracycline and taxane regimen.

Treatment options for patients with mTNBC

Clinical advice to the ERG is in line with the company view (CS, p22) that there is no targeted therapy for treating mTNBC, chemotherapy is the standard of care and, 'it is internationally recognised that there is no single recommended first-line chemotherapy regimen for mTNBC' (CS, p22).

NICE recommendations

The NICE clinical guideline for advanced breast cancer (CG81[18]) does not include advice for treating TNBC; however, the NICE pathway[19] for managing advanced breast cancer[19] does

include recommendations for treating TNBC. The company discusses the recommendations in the NICE pathway[19] for treating patients with advanced TNBC (Box 3).

Box 3 NICE treatment pathway for advanced TNBC

- Systemic sequential therapy should be offered to patients with advanced breast cancer which has progressed, and combination chemotherapy should be considered as an option for patients for whom a greater probability of response is important and who understand, and are likely to tolerate, the additional toxicity.
- Patients with advanced breast cancer who are not suitable for anthracyclines should be offered systemic chemotherapy treatment in the following sequence:
  - First line: single-agent docetaxel
  -Second line: single-agent vinorelbine or capecitabine
  -Third line: single-agent capecitabine or vinorelbine (whichever was not used at second-line)
- Eribulin is also recommended as an option for treating locally advanced or metastatic breast cancer that has progressed after at least two lines of chemotherapy.

Source: adapted from CS, p23

Clinical advice to the ERG is that very few patients in the NHS are treated with combined chemotherapy.

The ERG notes that in the NICE pathway[19] for advanced breast cancer, patients who are not suitable for treatment with anthracyclines are described as those who have had prior anthracycline treatment (either in the metastatic, adjuvant or neoadjuvant setting) or for whom anthracyclines are contraindicated. The company considers (CS, Table 1) that most patients (80% to 85%) with mTNBC will have progressed from the neoadjuvant or adjuvant setting where treatment with anthracyclines is standard of care. This means that re-challenge with anthracyclines as a first-line treatment for metastatic disease is unlikely. Clinical advice to the ERG agrees with the company's assessment.

Treatment of patients with mTNBC in the NHS

The company contends (CS, p23) that treatment for patients with mTNBC in the NHS does not follow the recommendations in the NICE treatment pathway[19] and that treatment is not uniform across the NHS (Box 4). The company provides evidence to support this viewpoint from two published studies of treatment audits, one conducted at The Mount Vernon Cancer Centre in Middlesex[20] and one conducted at the Royal Marsden NHS Foundation Trust.[21] The company has also conducted its own consultation exercise regarding UK treatments with three UK clinical experts.[16]

Box 4 Clinical practice in the UK

- Results from a retrospective audit of patients with advanced breast cancer treated at the Mount Vernon Cancer Centre (Middlesex) showed that only 5/29 patients with HER2- or unknown advanced breast cancer previously treated in the neoadjuvant or adjuvant setting received single-agent docetaxel as first-line therapy for their advanced disease as per the NICE guidelines.[20] Across all HER2- patients treated with first-line chemotherapy (n=49), 12 received paclitaxel and only 3 received docetaxel. Thus, it was demonstrated that the NICE guidelines are not followed in this centre in the majority of cases patients with advanced breast cancer.[20]
- Results from a retrospective analysis of patients with mTNBC treated at the Royal Marsden NHS Foundation Trust showed that despite 14% of patients in the study presenting with de novo metastatic disease, in the first-line setting only 7.5% received an anthracycline-based regimen. Additionally, only 17.7% of patients received a taxane (type not reported) in the first-line setting.[21]
- Roche Products Ltd consulted 3 UK clinical experts who confirmed that paclitaxel is often the taxane of choice for the first-line treatment of mTNBC.[16] This is due to the favourable toxicity profile of weekly paclitaxel compared with 3-weekly docetaxel, the former is accompanied by less toxicity and this helps maintain QoL for patients with limited life expectancy.[22] Docetaxel is often used in the curative early breast cancer setting where the toxicities of treatment are offset by the aim of cure rather than palliation (UK Clinical expert opinion[16]). Results from both in vitro and in vivo studies have demonstrated only partial cross-resistance between docetaxel and paclitaxel,[23-25] thus patients have the opportunity of additional benefit from treatment with a different taxane agent i.e., paclitaxel. Furthermore, re-challenge with docetaxel (following use in early breast cancer) may be unacceptable to some patients due to the extent of toxicities experienced, possibly coupled with a perception that the treatment was not effective as they have subsequently relapsed.

HER2-=human epidermal growth factor receptor 2 negative; mTNBC=metastatic triple negative breast cancer; QoL=quality of life
Source: adapted from CS, p23

Clinical advice to the ERG is that first-line treatment for most patients in the NHS with mTNBC is weekly paclitaxel and that very few patients are treated with docetaxel as it is not well tolerated. First-line treatment for patients with BReast CAncer (BRCA) gene mutation-positive tumours is carboplatin and patients who do not want an intravenous treatment or who relapse very soon after adjuvant treatment with a sequential anthracycline-taxane regimen are treated with capecitabine. Patients with de novo mTNBC are offered anthracyclines as a first-line treatment, if appropriate.

2.3 Company's proposed position of atezolizumab+nab-paclitaxel in the NHS

The current NICE and UK clinical practice treatment pathway for TNBC is presented in Figure 1 and the company's proposed positioning of atezolizumab + nab-paclitaxel (A+nabPx) for mTNBC is shown.

The ERG is aware that testing breast cancer tumours for PD-L1 status is not currently routine practice in the NHS.

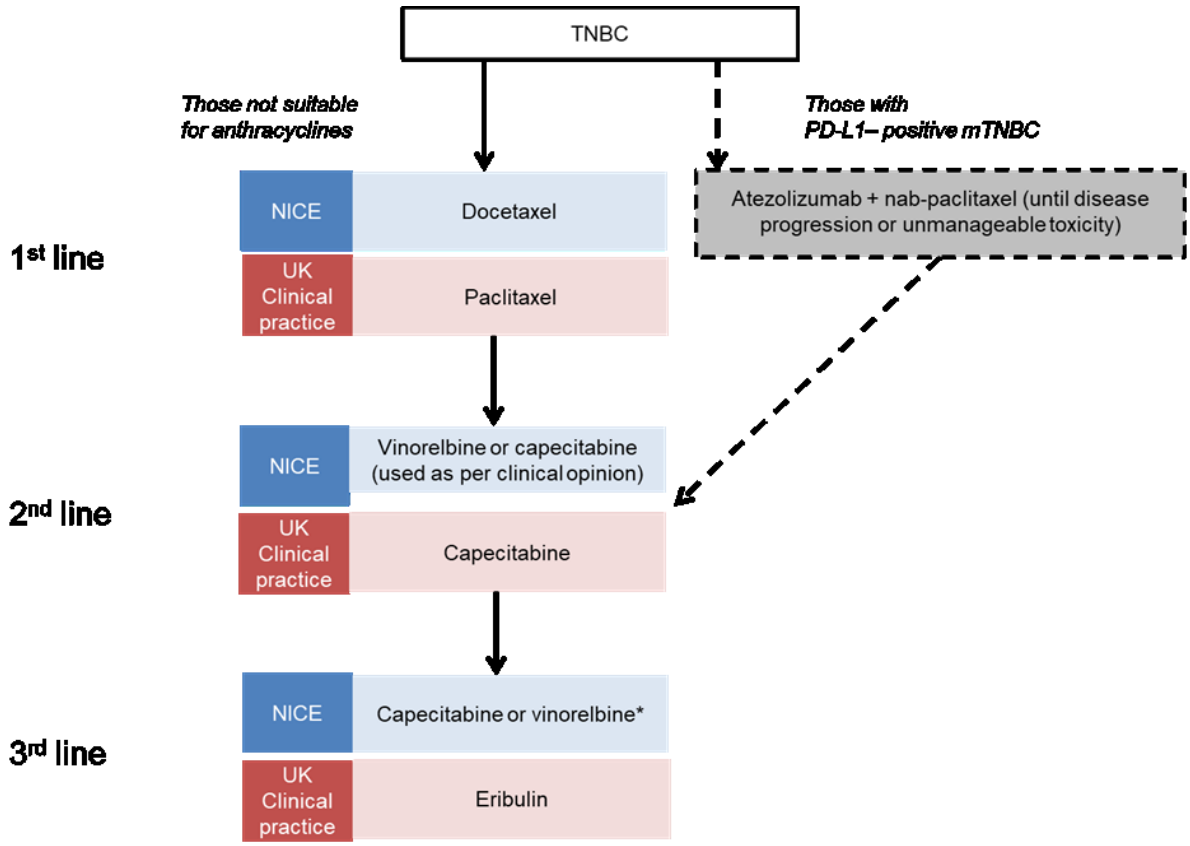

Figure 1 Proposed position of A+nabPx in the NHS treatment pathway

Source: CS, Figure 1

2.4 Innovation

The company considers that A+nabPx is an innovative treatment for patients with PD-L1+ mTNBC. The company's rationale is presented in Box 5.

Box 5 Company's rationale for A+nabPx as an innovative treatment

- There is a clear unmet need for better treatments for mTNBC; with chemotherapy, median OS remains at best in the region of 18 months.
- A+nabPx is the first targeted agent to demonstrate a survival benefit beyond chemotherapy in mTNBC, with a median OS of 25 months in the subset of patients with PD-L1+ disease.
- In recognition of this significant advance, Promising Innovative Medicine designation was granted by the MHRA on 23rd November 2018.
- Following this, MHRA approval for an Early Access to Medicines Scheme was granted on 13th March 2019, meaning that patients with PD-L1+ mTNBC now have access to treatment with A+nabPx.

MHRA=Medicines and Healthcare Products Regulatory Agency; mTNBC=metastatic triple negative breast cancer; OS=overall survival; PD-L1+=programmed death-ligand 1 positive; mTNBC=metastatic triple negative breast cancer
Source: CS, p80

2.5 Number of patients eligible for treatment with A+nabPx

The company's budget impact analysis submission includes an estimate of the number of patients in England who will be eligible for treatment with A+nabPx between 2019 and 2023 (Table 1). The estimates are based on increasing levels of testing for PD-L1 disease in the

NHS. In the absence of any published estimates of PD-L1 prevalence in patients with mTNBC, the company has used the 41% prevalence rate that was observed during recruitment of patients to the IMpassion130 trial.[13] The IMpassion130 trial is the key source of clinical and cost effectiveness evidence presented in the CS.

The ERG considers that the company's estimate of the number of patients eligible for treatment with A+nabPx is reasonable.

Table 1 Company estimate of number of patients in England eligible for treatment with A+nabPx

	2019	2020	2021	2022	2023	Source
Total number of patients with first-line mTNBC in England (84%)	361	365	370	374	378	ECIS[26] CRUK[12] ONS[27]
PD-L1 status (proportion, %)						
Percentage of patients with first-line mTNBC tested for PD-L1 status in England	5%	30%	50%	85%	85%	Roche assumption
Patients with first-line mTNBC tested for PD-L1 status in England	18	110	185	318	322	Calculation
Patients with first-line PD-L1+ mTNBC in England (41%)	7	45	76	130	132	IMpassion130 trial[13]
Patients with first-line PD-L1+ mTNBC fit enough for treatment in England (90%)	7	40	68	117	119	Roche assumption
Total patients eligible for treatment with A+nabPx (100%)	7	40	68	117	119	Calculation

CRUK=Cancer Research UK; ECIS= European Cancer Information System; mTNBC=metastatic triple negative breast cancer; ONS=Office for National Statistics; PD-L1+=programmed death-ligand 1 positive
Source: Company budget impact analysis submission, Table 3

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the ERG's comparison of the decision problem outlined in the final scope[2] issued by NICE and that addressed within the CS is presented in Table 2. Each parameter is discussed in more detail in the text following the table (Section 3.1 to Section 3.7).

Table 2 Comparison between NICE scope and company decision problem

Final scope issued by NICE Parameter and specification	Comparison between the decision problem outlined in the NICE scope and addressed in the company submission
Population People with locally advanced or metastatic, triple negative breast cancer whose tumours have PD-L1 expression ≥1% and have not received prior chemotherapy for metastatic disease	Evidence is presented for the population with mTNBC whose tumours have PD-L1 expression ≥1% and have not received prior chemotherapy for metastatic disease. The ERG notes that almost 90% of PD-L1 patients in the Impassion130 trial had metastatic disease.
Intervention Atezolizumab (with nab-paclitaxel)	Direct evidence for the clinical effectiveness of A+nabPx is available from the IMpassion130 trial. However, the comparator (P+nabPx) used in the trial is not recommended by NICE for the treatment of patients with mTNBC
Comparator • Anthracycline-based chemotherapy • Single agent taxane chemotherapy regimens (docetaxel and paclitaxel)	The company states that anthracycline-based chemotherapy is not standard of care in the UK. The company identified no evidence to allow a reliable comparison of A+nabPx versus anthracyclines The company carried out an indirect comparison of A+nabPx versus docetaxel and versus paclitaxel
Outcomes • OS • PFS • RR • AEs • HRQoL	The company has provided OS, PFS, RR, AEs and HRQoL data for A+nabPx from the IMpassion130 trial. RR is represented by the outcomes of ORR and DoR To allow comparisons with A+nabPx, the company has generated PFS, OS, ORR and AE data for docetaxel and paclitaxel by carrying out NMAs
Economic analysis The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account The economic modelling should include the costs associated with diagnostic testing for PD-L1 in people with locally advanced or metastatic, triple negative breast cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test	The company has provided ICERs per QALY gained for the comparison of A+nabPx versus two single-agent taxanes (docetaxel and paclitaxel) The model time horizon is 15 years. The ERG considers that this is sufficiently long to reflect any differences in costs or outcomes between the technologies being compared The costs have been calculated from the NHS perspective The PAS price for atezolizumab, which is expected to be approved in August 2019, and list prices for the comparator drugs are used in the company calculations Company calculations include the costs associated with diagnostic testing for PD-L1 disease and a sensitivity analysis without these costs has been undertaken
Other considerations Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	The company has not identified any equity issues The company considers that the appraisal of A+nabPx fulfils the conditions laid out for meeting NICE “End of Life” criteria

AE=adverse event; DoR=duration of response; HRQoL=health-related quality of life; ICER=incremental cost-effectiveness ratio; mTNBC=metastatic triple negative breast cancer; NMA=network meta-analysis; OS=overall survival; ORR=objective response rate; PAS=Patient Access Scheme; PD-L1=programmed death-ligand 1; PFS=progression-free survival; QALY=quality adjusted life year; RR=response rate; TNBC=triple negative breast cancer
Source: final scope issued by NICE

The company has presented data from the IMpassion130 trial. The IMpassion130 trial is a phase III randomised, international, double-blind, placebo-controlled trial. Patients with untreated mTNBC were randomised to receive A+nabPx or placebo plus nab-paclitaxel (P+nabPx).

3.1 Population

Prior to enrolment in the IMpassion130 trial, tumour specimens from patients were prospectively stained and evaluated by an external central laboratory using the immunohistochemistry VENTANA PD-L1 (SP142) assay. The assay was developed to optimise staining of tumour-infiltrating immune cells (ICs). The immune checkpoint molecule, PD-L1, is expressed on tumour cells and tumour-infiltrating ICs in various tumour types, including breast cancer[28,29] but in TNBC, PD-L1 expression is largely confined to IC.[30,31] Negative PD-L1 expression (IC0) was defined as <1% IC expressing PD-L1, whilst positive PD-L1 expression was defined as ≥1% ICs expressing PD-L1 (IC1/2/3). Randomisation was stratified by tumour PD-L1 status. The IMpassion130 trial PD-L1+ population comprised 369 patients (40.9%), 185 in the A+nabPx arm and 184 in the P+nabPx arm.

Currently, PD-L1 testing is not routinely carried out in the NHS for patients with mTNBC. However, clinical advice to the ERG is that as PD-L1 testing is routinely carried out for patients with advanced non-small cell lung cancer, scaling up testing to include patients with mTNBC should not be problematic, although support and training will be needed to establish the breast-specific assay.

The population described in the final scope[2] issued by NICE is people with locally advanced or metastatic TNBC whose tumours have PD-L1 expression and have not received prior chemotherapy for metastatic disease. In the PD-L1+ subgroup of the IMpassion130 trial, 12.8% of patients had locally advanced disease and 87.2% had metastatic disease.

Most NHS patients treated for early breast cancer and who subsequently develop metastatic disease would have been pre-treated with a sequential regimen of anthracyclines and taxanes. In the IMpassion130 trial, only 57% of patients had received prior anthracycline treatment and only 51% of patients had received prior taxane treatment.

3.2 Intervention

The intervention specified in the final scope[2] issued by NICE, and discussed in the CS, is A+nabPx. A+nabPx does not currently have a UK marketing authorisation; however, the company made an application to the European Medicines Agency in [redacted] for a licence extension and marketing authorisation is expected in [redacted].

Atezolizumab is a monoclonal antibody that inhibits binding of PD-L1 to its receptors PD-1 and B7.1 (CD80).[32] TNBC is characterised by having a higher PD-L1 expression level relative to other breast cancer subtypes[29,33] and there is a correlation between increased PD-L1 with increased tumour-infiltrating lymphocytes (a positive prognostic factor in TNBC).[34,35]

Paclitaxel is an inhibitor of mitosis,[36] specifically it inhibits the depolymerisation of microtubules which blocks cells at certain phases of the cell cycle, resulting in cell death.[37] This means that paclitaxel can target and kill proliferating cells (i.e., tumour cells).[38] Nab-paclitaxel is a formulation of paclitaxel that negates the need for pre-medication (with steroids or antihistamine).[38,39]

The recommended dose of atezolizumab is 840mg administered by intravenous infusion on days 1 and 15 of each 28-day cycle. In the IMpassion130 trial, nab-paclitaxel is administered by intravenous infusion at a dose of 100mg/m^2 on days 1, 8 and 15 of each 28-day cycle. On days 1 and 15, it is administered after atezolizumab. The ERG notes that nab-paclitaxel is only licensed in Europe for use as a second-line treatment of metastatic breast cancer. The recommended dose of nab-paclitaxel at second-line is 260mg/m^2 every 3 weeks. Clinical advice to the ERG is that, in the NHS, nab-paclitaxel is currently only prescribed as a treatment for patients who are intolerant to paclitaxel.

3.3 Comparators

The comparators outlined in the final scope[2] issued by NICE are anthracyclines and two single-agent taxanes, paclitaxel and docetaxel.

Anthracyclines

The company explains that they have not provided any evidence for the effectiveness (or cost effectiveness) of A+nabPx versus anthracyclines for two reasons. First, because anthracyclines have a lifetime maximum cumulative dose and, therefore, patients who have been treated with anthracyclines in the early breast cancer setting are unlikely to be eligible for re-challenge in the metastatic setting. Second, observational data from a single UK clinical practice have shown that, in the first-line setting, only 7.5% patients with mTNBC were treated with anthracyclines, despite 14% being diagnosed with de novo mTNBC.[21] The authors of the paper emphasised the small size of the study (first-line therapy: n=186) and the ERG cautions that, as a leading cancer research and treatment centre (The Royal Marsden NHS Foundation Trust), their caseload may not be representative of the general population with mTNBC in the UK.

The ERG considers that anthracyclines may only be a relevant comparator for a limited number of patients but does not consider this to be a reasonable basis for excluding them from the appraisal. However, the ERG acknowledges that interpretation of results from any analyses would be problematic due to the absence of any direct evidence and the fact that there are insufficient data to generate robust indirect evidence comparing the effectiveness of treatment with A+nabPx versus an anthracycline (see Section 4.8.1 of this ERG report).

Taxanes

Paclitaxel is not specified as an option within the NICE treatment pathway[19] but clinical advice to the ERG is in agreement with the clinical advice provided to the company, i.e., that paclitaxel is often the taxane of choice for patients with mTNBC[16] in a first-line setting due to the favourable toxicity profile of weekly paclitaxel compared with 3-weekly docetaxel. However, there is no direct effectiveness evidence for the comparison of either docetaxel or paclitaxel versus A+nabPx. The ERG highlights that there is an ongoing trial comparing treatment with atezoliumab+paclitaxel versus placebo+paclitaxel in patients with mTNBC (the IMpassion131 trial); however, the estimated primary completion date for this trial (the date the final subject will be examined for the purposes of final collection of data for the primary outcome measure) is not until 30 January 2020 (estimated study completion date: 30 June 2021).[40]

The NICE guideline for advanced breast cancer (CG81[18]) does not address TNBC specifically; however, the NICE pathway for managing advanced breast cancer[19] does include recommendations for treating patients with TNBC. The NICE treatment pathway for patients with advanced TNBC who are not suitable for anthracyclines[19] is systemic chemotherapy treatment in the following sequence:

1) First line: single-agent docetaxel
2) Second line: single-agent vinorelbine or capecitabine
3) Third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment).

Clinical advice to the ERG is that, in NHS clinical practice, capecitabine is used in the first-line setting to treat people who prefer an oral treatment and carboplatin is used in patients who have tested positive for BRCA genes. The ERG acknowledges, however, that carrying out an indirect comparison of treatment with A+nabPx versus capecitabine or carboplatin may be challenging due to a lack of reliable data.

The ERG cautions that limiting comparisons of cost effectiveness to taxanes may not be an appropriate basis for making a decision about the relative cost effectiveness of A+nabPx

versus NHS standard of care for patients with mTNBC whose tumours are PD-L1+ as there is a range of possible technologies that could be considered appropriate comparators. However, the market share of each of these comparators is unknown as is their effectiveness in a population of patients with mTNBC whose tumours are PD-L1+.

In short, the company did not present any evidence for the comparison of A+nabPx versus anthracyclines. The company only presented evidence for the comparison of A+nabPx versus paclitaxel and versus docetaxel; paclitaxel and docetaxel are likely only to be used in the first-line metastatic setting to treat patients who are not suitable for treatment with anthracyclines (the company argues that most patients in the UK will not suitable for treatment with anthracyclines in the metastatic setting).

3.4 Outcomes

The company has provided clinical evidence relating to treatment with A+nabPx from the IMpassion130 trial, for all five outcomes specified in the final scope[2] issued by NICE:

- Investigator assessed (RECIST v1.1) progression-free survival (PFS)
- Overall survival (OS) defined as the time from the date of randomisation to the date of death from any cause
- Response rate (RR), specifically objective response rate (ORR) and duration of response (DoR)
- Adverse effects (AEs) of treatment
- Health-related quality of life (HRQoL) using the European Quality of Life-5 Dimensions-5 Level (EQ-5D-5L) questionnaire and the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life-Core 30 (QLQ-C30) instrument in conjunction with the QLQ-BR23 breast cancer module.

Data from the IMpassion130 trial are available from the January 2019 data cut. Only descriptive, interim OS results are available due to the statistical approach (hierarchical testing) used to analyse the IMpassion130 trial data. Please see Section 4.4 of this ERG report for a discussion of the hierarchical testing procedure used in the IMpassion130 trial.

The company carried out population-adjusted indirect comparisons (PAICs) to facilitate network meta-analyses (NMAs) to generate clinical effectiveness data relating to the effectiveness of A+nabPx versus paclitaxel and docetaxel. It should be noted that the company has advised caution when interpreting the results generated by their statistical analyses due to weaknesses in the methods employed.

3.5 Economic analysis

As specified in the final scope[2] issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained.

Outcomes were assessed over a 15-year time horizon (considered by the company to be long enough to reflect all important differences in costs or outcomes between the technologies being compared) and costs were considered from an NHS perspective. When generating cost effectiveness estimates, the company used the expected patient access scheme (PAS) price for atezolizumab and the list prices of nab-paclitaxel and the comparator drugs. In addition, in line with the final scope[2] issued by NICE, the company presented cost effectiveness estimates that included the costs associated with diagnostic testing for PD-L1 as well as results from a sensitivity analysis that did not include diagnostic testing costs.

3.6 Subgroups

No subgroups were specified in the final scope[2] issued by NICE.

3.7 Other considerations

The company did not identify any equity or equality issues (CS, Section B.1.4).

A PAS is currently in place for 1200mg vials of atezolizumab. The company states that, [redacted].

The company has put forward a case for treatment with A+nabPx to be considered under NICE's End of Life criteria. The ERG supports the company's case (see Section 6).

4 CLINICAL EFFECTIVENESS

4.1 Systematic review methods

Full details of the process and methods used by the company to identify and select the clinical evidence relevant to A+nabPx are presented in Appendix D of the CS. The ERG assessed whether the review was conducted in accordance with the key criteria listed in Table 3.

Table 3 ERG appraisal of systematic review methods

Review process	ERG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Was data extracted by two or more reviewers independently?	Yes
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Not reported
Were appropriate methods used for data synthesis?	Yes

ERG=Evidence Review Group

Overall, the ERG considers that the methods used by the company in the systematic review of clinical effectiveness evidence were satisfactory. The ERG has run its own searches and is confident that no relevant publications were missed.

4.1.1 Literature search

The company explains (CS, Appendix p19) that a description of the IMpassion130 trial, the main source of the company's clinical effectiveness evidence, was published after the searches were complete but before the company submitted evidence for this appraisal to NICE.

4.1.2 Quality assessment methods

To assess the quality of the trials that generated the clinical effectiveness evidence presented in the CS, the company has (appropriately) applied the criteria from the Cochrane Risk of Bias tool[41] to each trial. It is not reported in the CS whether the quality assessment was completed by one reviewer or, independently, by two reviewers.

4.1.3 Data synthesis

The company identified only one randomised controlled trial (RCT), the IMpassion130 trial, [13] [13] that reported clinical effectiveness outcomes for A+nabPx in patients with untreated, PD-L1+ mTNBC.

In the absence of any head-to-head trials comparing the clinical effectiveness of treatment with A+nabPx versus paclitaxel or docetaxel, two of the three comparators listed in the final scope[2] issued by NICE, the company conducted NMAs. Anthracycline-based chemotherapy is also a comparator listed in the final scope[2] issued by NICE; however, the company did not identify any evidence that would allow a comparison of A+nabPx versus anthracycline-based chemotherapy.

4.2 ERG critique of clinical effectiveness evidence

All information presented in this section of the ERG report is taken directly from the CS, unless otherwise stated.

4.2.1 Studies of atezolizumab+nab-paclitaxel

The IMpassion130 trial is the only RCT identified by the company that provides evidence for the use of A+nabPx in patients with PD-L1+ mTNBC. The comparator in the IMpassion130 trial is P+nabPx. Nab-paclitaxel is not listed as a comparator in the final scope[2] issued by NICE.

4.2.2 Studies of comparator treatments

The seven trials included in the company's NMAs (in addition to the IMpassion130 trial) are briefly described in Appendix 3 of this ERG report. The company uses results from the NMAs to compare the effectiveness of treatment with A+nabPx versus paclitaxel and docetaxel. Please see Section 4.8 of this ERG report for discussion and critique of the company's NMAs.

The company was unable to identify any evidence that would allow a comparison of A+nabPx versus anthracycline chemotherapy for patients with untreated, PD-L1+ mTNBC.

4.3 Characteristics of the IMpassion130 trial

4.3.1 Trial characteristics

The IMpassion130 trial is an ongoing, phase III, double-blind, placebo-controlled RCT. The trial is being conducted in 41 countries (246 centres) and patient recruitment took place between June 2015 and May 2017. Nine treatment centres in the UK (46 patients) took part in the IMpassion130 trial. Overall, 902 patients with untreated, locally advanced or metastatic TNBC were randomised in a 1:1 ratio to receive either A+nabPx or P+nabPx. Atezolizumab

840mg, or placebo were given intravenously at a dose of 840mg on days 1 and 15 of a 4-week cycle and nab-paclitaxel was given intravenously on days 1, 8 and 15 at a dose of 100mg/m^2. The ERG notes that nab-paclitaxel is only licensed in Europe as a second-line treatment for metastatic breast cancer and that the licensed dose is 260mg/m^2 every 3 weeks.

All tumours were tested for PD-L1 expression on tumour infiltrating ICs as a percentage of tumour area according to immunohistological testing. Trial stratification factors were: PD-L1+ disease (≥1%), liver metastases (yes or no) and taxane treatment in the neoadjuvant or adjuvant settings (yes or no).

The patient population relevant to this appraisal is the subgroup of patients recruited to the IMpassion130 trial whose tumours tested positive for PD-L1. The PD-L1+ patient subgroup comprised 369 patients, 40.9% of the overall trial population; 185 patients were randomised to receive A+nabPx and 184 were randomised to receive P+nabPx. [redacted] In the CS, the company provides clinical information and clinical effectiveness results from the IMpassion130 trial for the overall (intention-to-treat [ITT]) and PD-L1+ populations. The focus of this appraisal and the ERG report is on the PD-L1+ population.

Clinical advice to the ERG is that the IMpasssion130 trial eligibility criteria are reasonable and that the participating treatment centres are representative of treatment centres in the UK. The ERG is satisfied that the IMpassion130 trial was well designed and well-conducted. However, the ERG notes that the company considered that the subsequent therapies delivered in the IMpassion130 trial were not generally used in clinical practice in the UK.

4.3.2 Baseline characteristics of patients recruited to the IMpassion130 trial

The baseline characteristics of the patients recruited to the IMpassion130 trial are reported in the CS (Table 5, p36); summary details are provided in Table 4.

Table 4 Baseline characteristics of patients recruited to the IMpassion130 trial (PD-L1+ population)

	A+nabPx (N=185)	P+nabPx (N=184)
Age		
Mean (SD)	53.7 (12.9)	53.6 (12.0)
Race n (%)		
White	125 (67.6)	129 (70.1)
Asian	38 (20.5)	28 (15.2)
Black or African American	9 (4.9)	14 (7.6)
Native American	8 (4.3)	9 (4.9)
Unknown	5 (2.7)	4 (2.2)
ECOG PS n (%)		
0	107 (57.8)	112 (60.9)
1	77 (41.6)	72 (39.1)
2	1 (0.5)	0
Prior treatment (neoadjuvant/adjuvant) n (%)	125 (67.6)	117 (63.6)
Taxane	96 (51.9)	94 (51.1)
Anthracycline	109 (58.9)	101 (54.9)

ECOG PS=Eastern Co-operative Oncology Group performance status; SD=standard deviation
Source: adapted from CS Table 5 with additional material from the clinical study report
Note: The values for 'Race' and 'ECOG PS' are taken from the clinical study report as the values presented in the CS contained typographical errors.

Overall, the ERG agrees with the company (CS, p32) that the baseline characteristics of patients participating in the IMpassion130 trial are well balanced between the trial arms. The ERG notes that most patients with PD-L1+ disease in the trial had metastatic disease. Clinical advice to the ERG is that most NHS patients with metastatic disease would have been treated previously with a sequential regimen of anthracyclines and taxanes. In the IMpassion130 trial, 57% of PD-L1 patients had received prior anthracycline treatment and 51% of PD-L1 patients had received prior taxane treatment; this suggests that a substantial proportion of PD-L1 patients in the IMpassion130 trial may have been suitable for anthracycline therapy.

4.3.3 Risk of bias assessment for the IMpassion130 trial

The company assessed the risk of bias of the IMpassion130 trial using the Cochrane Risk of Bias tool[41] (CS, Appendix D, Table 27). The ERG considers that the IMpassion130 trial was generally well designed and well conducted and the ERG agrees with the company's conclusion that the trial has a low risk of bias for all the domains included in the Cochrane Risk of Bias tool[41] (random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias).

4.4 Statistical approach adopted for the IMpassion130 trial

Information relevant to the statistical approach taken by the company has been taken from the clinical study report (CSR),[42] the trial statistical analysis plan (TSAP),[43] the trial protocol,[44] and the CS.

A summary of checks made by the ERG to assess the statistical approach used to analyse data from the IMpassion130 trial is provided in Table 5.

Table 5 ERG assessment of statistical approach used to analyse IMpassion130 trial data

Review process	ERG judgement	ERG comment
Were all the methods used to calculate the sample size correct?	Unclear	The company planned to randomise approximately 900 patients to the IMpassion130 study. The ERG asked the company to provide clarification on how this sample size was calculated as the sample size calculation provided in the TSAP (pp4-8) does not explain how this number of patients (n=900) was determined. However, the ERG did not obtain sufficient information from the company to verify the company's sample size calculation
Were all primary and secondary outcomes presented in the CS pre-specified?	Yes	In the CS, results are presented for the co-primary outcomes of investigator-assessed PFS and OS, and for the secondary outcomes of ORR and DoR. Results for each of these outcomes are presented for both the ITT and PD-L1+ patient population, as was pre-specified in the trial protocol (pp44-45)
Were all relevant outcomes defined and analysed appropriately?	Yes	Definitions for PFS, OS, ORR and DoR are provided in the trial protocol (pp44-45) A stepwise testing procedure was used to control the type I error rate (α=0.05) for the analyses of PFS, OS and ORR; further details are provided in the text that follows this table. The company performed various analyses that were not in accordance with the pre-specified stepwise testing procedure The company used a Cox PH model to analyse the outcomes of PFS and OS. The assumption of PH was assessed by the company; further details are provided in the text that follows this table
Were all protocol amendments carried out prior to analysis?	Yes	Protocol amendments, and the rationale for these changes are provided in the CSR (pp78-82). The ERG is satisfied with the rationale for the amendments and notes that all amendments were made before the data cut-off date for the primary analysis (17th April 2018), so amendments were not driven by trial results
Was a suitable approach employed for handling missing data?	Yes	The company's approach to handling missing data was pre-specified in the protocol (p100). The ERG considers the company's approach to be appropriate
Were all subgroup analyses and sensitivity analyses presented in the CS pre-specified?	Partial	• Results for PFS, OS, ORR and DoR are presented for the PD-L1+ patient subgroup, as was pre-specified in the trial protocol (pp44-45) • The company presented results from subgroup analyses for PFS and OS for various demographic and baseline characteristics (CS, Appendix E). For subgroup analyses, a pre-specified list of the demographic and baseline characteristics of interest was not provided in the protocol or TSAP • The company performed an exploratory analysis of immune biomarker subgroups (CS, pp46-49); this analysis was pre-specified in the TSAP (p14) • The company presented a sensitivity analysis of PFS by IRC assessment in the PD-L1+ patient population (CS, p42); this analysis was pre-specified in the TSAP (p15)

CSR=clinical study report; DoR=duration of response; IRC=Independent Review Committee; ITT=intention-to-treat; ORR=objective response rate; OS=overall survival; PD-L1+=programmed death-ligand 1 positive; PFS=progression-free survival; PH=proportional hazards; TSAP=trial statistical analysis plan
Source: CS, CSR, trial protocol, TSAP and ERG comment

Overall, the ERG considers that the company's statistical approach for the analysis of data from the IMpassion130 trial was appropriate. However, the ERG highlights that it was not possible to verify the sample size calculation as it was not clear from either the TSAP or the

company's response to the ERG clarification letter how the sample size (n=900) was determined.

As described in the TSAP, a single definitive PFS analysis for the ITT population was planned, at which time a definitive analysis of PFS in the PD-L1+ subgroup and the first interim analysis of OS would also be performed. The timing of the first clinical cut-off date was chosen based on both the required number of events for (i) the definitive PFS analysis (approximately n=600) and (ii) the first interim analysis of OS (n=352). From here on, the definitive analyses of PFS in the ITT and PD-L1+ populations and the first interim analysis of OS are referred to as the 'primary analysis'. A second interim analysis of OS was planned, and the timing of this analysis was determined based on results from the primary analysis. The required number of OS events for the second interim analysis of OS was 530. A final analysis of OS is also planned; the timing of this analysis was also determined by results from the primary analysis. The required number of OS events for the final analysis of OS is 662.

A stepwise testing procedure was employed to control the type I error rate (α=0.05) for the analyses of PFS, OS and ORR. At the time of the primary analysis, PFS was tested in parallel for both the ITT and PD-L1+ populations, with α=0.005 assigned to each of these analyses. If both of these analyses produced statistically significant results, ORR would then be tested (α=0.001). For the two interim analyses of OS, and for the final analysis of OS, the company planned to first test OS in the ITT population and, if the difference between trial arms was significant, test OS in the PD-L1+ population. The boundaries for statistical significance at each interim OS analysis and the final OS analysis were determined according to the Lan-DeMets implementation of the O'Brien-Fleming use function.[45] The ERG notes that the company performed various analyses that were not in accordance with the pre-specified testing procedure (see Section 4.5 of this ERG report).

The company used a Cox proportional hazards (PH) model to analyse the outcomes of PFS and OS and presented hazard ratios (HRs) to summarise treatment effect. This method of analysis is only appropriate if the PH assumption is valid, that is, if the event hazards associated with the intervention and comparator data are proportional over time.[46] The company assessed the assumption of PH for the PD-L1+ patient population of the IMpassion130 trial for both PFS and OS (second interim OS analysis, PD-L1+ patient population) using diagnostic plots of log cumulative hazard curves over log time. The company concluded that the PH assumption was violated for OS, but not for PFS. The ERG also assessed the validity of the PH assumption for these two sets of data and concluded that the PH assumption was valid for both OS and PFS (see Appendix 1 to this ERG report). The ERG,

therefore, considers that the OS and PFS HRs calculated by the company for the PD-L1+ population are reliable.

4.5 Efficacy results from the IMpassion130 trial

A summary of OS, PFS and ORR results from the IMpassion130 trial, for the PD-L1+ patient population, is provided in Table 6.

Table 6 Summary of results from the IMpassion130 trial for the PD-L1+ patient population

	PD-L1+ patient population	
	A+nabPx N=185	**P+nabPx N=184**
Co-primary endpoint: Investigator-assessed PFS (CCOD: 17th April 2018)		
No. (%) of patients with events	138 (74.6%)	157 (85.3%)
Median, months	7.5	5
Stratified HR (95% CI) p-value (log-rank)[a]		0.62 (0.49 to 0.78) <0.001
Co-primary endpoint: Investigator-assessed PFS (CCOD: January 2019)		
No. (%) of patients with events	[redacted]	[redacted]
Median, months	[redacted]	[redacted]
Stratified HR (95% CI)[b]	[redacted]	
Co-primary endpoint: OS (CCOD: 17th April 2018)		
No. (%) of patients with events	64 (34.6%)	88 (47.8%)
Median, months	25.0	15.5
Stratified HR (95% CI)[c]		0.62 (0.45 to 0.86)
Co-primary endpoint: OS (CCOD: January 2019)		
No. (%) of patients with events	[redacted]	[redacted]
Median, months	[redacted]	[redacted]
Stratified HR (95% CI)	[redacted]	
Secondary endpoint: Investigator-assessed ORR (CCOD: 17th April 2018)		
No. of evaluable patients	185	183
ORR, n (%)	109 (58.9%)	78 (42.6%)
Difference in ORR, % (95% CI) p-value (Cochran-Mantel-Haenszel)[d]		16.3% (5.7% to 26.9%) p = 0.0016

[a] Significance level=0.005
[b] A p-value is reported for this analysis in the CS (p43); however, no formal testing of PFS ought to have been performed at the time of the second interim OS analysis according to the stepwise testing procedure (see Section 4.4 of this ERG report)
[c] A p-value is reported for this analysis in the CS (Table 7); however, no formal testing of OS in the PD-L1+ population ought to have been performed as no significant differences were observed in the ITT population (see Section 4.4 of this ERG report)
[d] Significance level=0.001
CCOD=clinical cut-off date; CI=confidence interval; HR=hazard ratio; ITT=intention-to-treat; ORR=objective response rate; OS=overall survival; PD-L1+=programmed death-ligand 1 positive; PFS=progression-free survival;
Source: CS, Table 7 and pp43-44

4.5.1 Progression-free survival

At the time of the definitive PFS analysis (data cut-off date: 17th April 2018) treatment with A+nabPx was shown to statistically significantly improve investigator-assessed PFS in comparison to P+nabPx in the PD-L1+ patient population (HR=0.62, 95% confidence interval [CI]: 0.49 to 0.78; p-value<0.001). Although median PFS was longer in the A+nabPx arm than

in the P+nabPx arm (7.5 months versus 5.0 months, respectively), clinical advice to the ERG is that a difference in median PFS of 2.5 months is not clinically meaningful.

A sensitivity analysis based on the Independent Review Committee (IRC) assessment of PFS generated a similar result for the comparison of A+nabPx versus P+nabPx (HR=0.63, 95% CI: 0.49 to 0.81).

[redacted] 4.4 [redacted]

4.5.2 Overall survival

At the time of the first interim OS analysis (data cut-off date: 17th April 2018) no statistically significant difference in OS was observed between the A+nabPx arm and the P+nabPx arm in the ITT population (CS, Table 7). Therefore, according to the pre-specified stepwise testing procedure (see Section 4.4 of this ERG report) no testing of OS in the PD-L1+ patient population should have been performed. Nevertheless, the company tested for OS in the PD-L1+ patient population; the ERG notes that the HR favours treatment with A+nabPx over P+nabPx (HR=0.62, 95% CI: 0.45 to 0.86) and that the difference in median OS between arms was 9.5 months. However, it is important to note that these data are immature; only 34.6% of patients in the A+nabPx arm and 47.8% of patients in the P+nabPx arm had died at the time of this analysis.

[redacted]

A final OS analysis will be conducted when at least 662 OS events have occurred (Appendix 4 to the TSAP[43]). The ERG highlights that it is difficult to predict whether the [redacted]

A summary of cancer therapies received during study follow-up in the ITT population is provided in the supplementary materials to the publication of the IMpassion130 trial. Clinical advice to the ERG is that these treatments, most of which are types of chemotherapy, are the agents generally used in the NHS to treat patients with mTNBC.

4.5.3 Objective response rate

Among patients in the PD-L1+ patient population with measurable disease at baseline, a numerically higher investigator-assessed ORR was seen in patients treated with A+nabPx (58.9%) compared with patients treated with P+nabPx (42.6%). However, the difference in ORR between arms (16.3%, 95% CI: 5.7% to 26.9%) was not statistically significant at the pre-specified significance level of 0.001 (p=0.0016).

4.5.4 Subgroup analyses

The company presented subgroup analyses for PFS and OS for various demographic and baseline characteristics within the PD-L1+ patient population (CS, Appendix E). The ERG did not identify any important subgroup effects for either PFS or OS.

The company also performed an exploratory analysis in immune biomarker subgroups (CS, pp46-49); the ERG considers that there are no important subgroup effects within the PD-L1+ population according to CD8 cells (CD8+ or CD8-), tumour infiltrating lymphocytes (TILs) (TIL+ or TIL-), or BRCA mutation status.

4.6 Adverse events

The company provides an overview of safety data from the IMpassion130 trial in the overall safety population (Section B.2.10.1) and in the PD-L1+ subgroup (Section B.2.10.6). This section of the ERG report focusses on the safety data from the PD-L1+ population. The ERG reiterates that P+nabPx is not a comparator of interest in the appraisal under discussion. There is limited evidence from the company's NMAs to compare the safety of A+nabPx with either paclitaxel, docetaxel or anthracyclines.

4.6.1 Treatment duration

The ERG agrees with the company that the median treatment duration and median number of treatment cycles in the PD-L1+ population (Table 7) are consistent with the overall safety population.

Table 7 Duration of treatment in the IMpassion130 trial (PD-L1+ population)

	A+nabPx (n=185)		**P+nabPx (n=181)**	
	Atezolizumab	**Nab-paclitaxel**	**Placebo**	**Nab-paclitaxel**
Median treatment duration in weeks (range)	26.4 (0 to 139)	22.7 (0 to 137)	16.1 (0 to 109)	16.1 (0 to 103)
Median number of cycles (range)	7 (1 to 35)	6 (1 to 34)	5 (1 to 28)	5 (1 to 26)

Source: CS, Table 29

4.6.2 Overview of adverse events

The ERG agrees with the company that the proportion of patients who reported AEs in the overall safety population (99.3% and 97.9%) and the PD-L1+ population (100% and 97.8%) are similar.

The ERG notes that in the in the PD-L1+ population, patients in the A+nabPx arm experienced higher rates of all categories of AEs compared with patients treated with P+nabPx (Table 8).

Table 8 Overview of adverse events in the IMpassion130 trial (PD-L1+ population)

	A+nabPx (n=185) n (%)	P+nabPx (n=181) n (%)
Total number of patients with at least one AE (any grade)	185 (100)	177 (97.8)
Total number of patients with at least one:		
Grade 5 AE	2 (1.1)	1 (0.6)
Treatment-related Grade 5 AE	1 (0.5)	0
Grade 3 to 4 AE	95 (51.4)	72 (39.8)
Treatment-related Grade 3 to 4 AE	76 (41.1)	49 (27.1)
SAE	42 (22.7)	31 (17.1)
Treatment-related SAE	21 (11.4)	14 (7.7)
AE leading to discontinuation of any study treatment	37 (20.0)	14 (7.7)
AE leading to discontinuation of atezolizumab/placebo	12 (6.5)	4 (2.2)
AE leading to discontinuation of nab-paclitaxel	37 (20.0)	14 (7.7)
AE leading to dose interruption of nab-paclitaxel	60 (32.4)	38 (21)

AE=adverse event; SAE=serious adverse event
Source: CS, Table 30

Treatment-related adverse events

Treatment-related AEs specific to the PD-L1+ population are not reported in the CS. The company provided data from the overall safety population (CS, Table 27) for any grade AEs that were considered to be related to study treatment (Table 9).

Alopecia was the most common treatment-related AE of any grade in both treatment arms (56% versus 57%). The ERG notes that the frequencies of nausea, neutropenia, pyrexia, and hypothyroidism were at least 5% higher in the A+nabPx arm compared to the P+nabPx arm.

The frequencies of treatment-related Grade 3 to Grade 4 AEs were generally similar in each treatment arm except for peripheral neuropathy, which was higher for patients treated with A+nabPx (5.5% versus 2.7%).

Table 9 Treatment-related adverse events (overall safety population)

Adverse event	A+nabPx (n=452)		P+nabPx (n=438)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
All	436 (96.5)	179 (39.6)	410 (93.6)	132 (30.1)
Alopecia	253 (56.0)	3 (0.7)	251 (57.3)	1 (0.2)
Nausea	186 (41.2)	4 (0.9)	148 (33.8)	5 (1.1)
Fatigue	181 (40.0)	16 (3.5)	167 (38.1)	15 (3.4)
Anaemia	112 (24.8)	7 (1.5)	99 (22.6)	7 (1.6)
Diarrhoea	106 (23.5)	6 (1.3)	108 (24.7)	6 (1.4)
Peripheral neuropathy	98 (21.7)	25 (5.5)	94 (21.5)	12 (2.7)
Neutropenia	93 (20.6)	37 (8.2)	66 (15.1)	35 (8.0)
Peripheral sensory neuropathy	71 (15.7)	9 (2.0)	52 (11.9)	8 (1.8)
Decreased appetite	70 (15.5)	2 (0.4)	58 (13.2)	2 (0.5)
Rash	59 (13.1)	2 (0.4)	54 (12.3)	2 (0.5)
Constipation	59 (13.1)	2 (0.4)	52 (11.9)	1 (0.2)
Neutrophil count decrease	57 (12.6)	21 (4.6)	47 (10.7)	15 (3.4)
Hypothyroidism	57 (12.6)	0	12 (2.7)	0
Dysgeusia	56 (12.4)	0	57 (13.0)	0
Vomiting	53 (11.7)	2 (0.4)	49 (11.2)	3 (0.7)
Arthralgia	51 (11.3)	1 (0.2)	42 (9.6)	0
Myalgia	49 (10.8)	1 (0.2)	50 (11.4)	2 (0.5)
Pyrexia	48 (10.6)	1 (0.2)	23 (5.3)	0
Headache	47 (10.4)	1 (0.2)	42 (9.6)	1 (0.2)
Pruritus	46 (10.2)	0	36 (8.2)	0
Asthenia	45 (10.0)	2 (0.4)	39 (8.9)	2 (0.5)
Oedema peripheral	41 (9.1)	1 (0.2)	44 (10.0)	5 (1.1)

Source: CS, Table 27
The company's discussion of treatment-related AEs reported in section B.2.10.4 of the CS is inconsistent with the information provided in CS, Table 27 and in the published paper.[13] The ERG report discusses data from the CS, Table 27 and the published paper.[47]

Immune-related adverse events

The numbers of patients in the PD-L1+ subgroup experiencing specific adverse events of special interest (AEOSI) are presented in Table 10. The ERG notes that A+nabPx is associated with higher AEOSIs of any grade (56.8% versus 36.5) and Grade 3 to Grade 4 AEOSIs (5.4% versus 3.9%) compared to P+nabPx.

The ERG also notes that for any grade of AEOSI, compared with P+nabPx, A+nabPx is associated with a higher frequency of hypothyroidism (20.5% versus 3.3%), hepatitis (10.3% versus 9.9%), hyperthyroidism (3.2% versus 0.6%), pneumonitis (2.2% versus 0%), colitis (1.1% versus 0.6%), meningoencephalitis (2.7% versus 0.6%), adrenal insufficiency (1.6% versus 0%) and pancreatitis (1.1% versus 0%). A+nabPx was also associated with higher rates of immune-related rash (37.3% versus 25.4%).

Table 10 Overview of AEOSIs in the IMpassion130 trial (PD-L1+ population)

	A+nabPx (n=185)	P+nabPx (n=181)
Total number of patients with at least one AEOSI (any grade)	105 (56.8)	66 (36.5)
Total number of patients with at least one Grade 3 to 4 AEOSI	10 (5.4)	7 (3.9)
Important AEOSIs by Medical Concept		
Immune-related hypothyroidism	38 (20.5)	6 (3.3)
Immune-related hepatitis (diagnosis and laboratory)	19 (10.3)	18 (9.9)
Immune-related hyperthyroidism	6 (3.2)	1 (0.6)
Immune-related pneumonitis	4 (2.2)	0
Infusion-related reactions	3 (1.6)	4 (2.2)
Immune-related colitis	2 (1.1)	1 (0.6)
Immune-related meningoencephalitis	5 (2.7)	1 (0.6)
Immune-related adrenal insufficiency	3 (1.6)	0
Immune-related pancreatitis	2 (1.1)	0
Immune-related diabetes mellitus	0	1 (0.6)
Immune-related nephritis	0	0
Other AEOSIs by Medical Concept		
Immune-related rash	69 (37.3)	46 (25.4)
Immune-related ocular inflammatory toxicity	1 (0.5)	1 (0.6)
Immune-related severe cutaneous reaction	0	1 (0.6)
Rhabdomyolysis	0	0
Systemic immune activation	1 (0.5)	0
Immune-related myositis	0	1 (0.6)
Immune-related vasculitis	0	1 (0.6)
Autoimmune haemolytic anaemia	0	0

AEOSI=adverse event of special interest
Source: CS, Table 31

Adverse events summary

The AE data from the overall safety population and the PD-L1+ population of the IMpassion130 trial demonstrated similar frequencies of events. The overall frequency of AEs was high in both treatment arms for the overall safety population (99.3% vs 97.9%) and for the PD-L1+ population (100% vs 97.8%). However, the ERG notes that P+nabPx is not a comparator of interest in the appraisal under discussion and there is only limited evidence from the company's NMAs that compares the safety of A+nabPx with either paclitaxel, docetaxel or anthracyclines.

The ERG agrees with the company that AEs reported by patients in the trial appear to be consistent with the known safety profiles of each treatment, with no new AEs identified. However, clinical advice to the ERG is that AEs arising from treatment with atezolizumab and other immunotherapies require careful monitoring by a specialist clinical team with the

experience to provide early recognition and management of immunotherapy-related AEs, and that this can place a high burden on NHS staff and systems.

4.7 Health-related quality of life

The company reports (CS, p45) that HRQoL outcomes were measured during the IMpassion130 trial using the European Quality of Life-5 Dimensions-5 level (EQ-5D-5L[48]) questionnaire and the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life–Core 30 (QLQ-C30[49]) questionnaire with the QLQ-BR23[50] breast cancer module.

The company states (CS, p45 and IMpassion130 protocol, p67) that the data collection schedule was day 1 of cycle 1 (baseline), day 1 of each subsequent treatment cycle, at the treatment discontinuation visit and every 28 days after treatment discontinuation for 1 year.

The company (CS, Table 8, p46) provides a summary of HRQoL estimates for patients in the progression-free state and post-progression state derived from the EQ-5D-5L[48] data collected during the IMpassion130 trial (Table 11); these data were then mapped to EQ-5D-3L.[51] The utility values in Table 11 are derived from the PD-L1+ population of the IMpassion130 trial. The ERG is unable to comment on the generalisability of the results from the company's analysis of the EQ-5D-5L[48] data in the as the number of patients who responded to the questionnaires is not presented in the CS; however, the ERG notes that the utility values reported in Table 11 are in line with utilities calculated from data collected during trials of other drugs used to treat advanced breast cancer. The use of the data from patient responses to the EQ-5D-5L[48] questionnaire is discussed in Section B3.4.1 of the CS.

Table 11 IMpassion130 trial data utility values (EQ-5D-5L data before being mapped to EQ-5D-3L)

Health state	Trial arm	Utility value	95% CI
Progression-free	Both arms	0.726	0.706 to 0.746
	A+nabPx	0.741	0.711 to 0.770
	P+nabPx	0.710	0.684 to 0.736
Progressive disease	Both arms	0.653	0.631 to 0.675

CI=confidence interval
Source: CS, Table 8

The company reports (CSR, p120) that the IMpassion130 trial PD-L1+ population completion rates for the QLQ-C30[49] and the QLQ-BR23[50] questionnaires [redacted]. The ITT population completion rates at baseline were above [redacted] in both trial arms. At cycle 7 [redacted] completion rates in both arms ranged from [redacted] The HRQoL outcomes from the IMpassion130 trial are summarised in Appendix M of the CS. The company found no

difference between treatment arms for any of the EORTC QLQ-30 or QLQ-BR23 outcome measures (Table 12).

Table 12 Summary of EORTC QLQ-30 and QLQ-BR23 outcomes

Parameter	A+nabX	P+nabPx	HR (95% CI)	Company conclusion
Median time to deterioration in global health status/HRQoL	8.2 months	6.4 months	0.94 (0.69 to 1.28)	No difference between treatment arms
Median time to deterioration in role, physical, and cognitive functioning	6.8 months	4.8 months	0.77 (0.57 to 1.04)	No difference between treatment arms

CI=confidence interval; HR=hazard ratio; HRQoL=health-related quality of life
Source: adapted from text in CS, Appendix M

4.8 ERG critique of the indirect evidence

Due to a lack of direct evidence for the comparison of treatment with A+nabPx versus the comparators listed in the final scope[2] issued by NICE (namely, paclitaxel, docetaxel and anthracyclines), the company investigated the possibility of obtaining indirect estimates of clinical effectiveness for each of the relevant comparators.

The search carried out as part of the systematic review described in Section 4.1 was used to identify studies that could be included in indirect comparisons. A total of 54 publications relating to 39 unique trials met the inclusion criteria for the systematic review. The company search identified relevant RCTs that included paclitaxel and docetaxel but did not identify any relevant RCTs that included anthracyclines. The company therefore investigated the possibility of performing indirect comparisons of A+nabPx versus anthracyclines using real-world evidence instead of trial evidence (see Section 4.8.1).

4.8.1 Company's feasibility assessment of an indirect comparison of A+nabPx versus anthracyclines

The company assessed the feasibility of using data from a US-based electronic health record database, Flatiron,[52] in an indirect comparison of A+nabPx versus anthracyclines. Within the Flatiron database, a cohort of mTNBC patients were treated with anthracyclines (n=94). As there is no common treatment comparator between the Flatiron cohort and patients in the IMpassion130 trial, any indirect comparison including data from these two cohorts would need to adjust for differences in the characteristics of the patient populations; this type of indirect comparison is known as a "population-adjusted indirect comparison" (PAIC).

The company observed that only a small number of baseline characteristics were available for the Flatiron cohort. Only age at diagnosis, stage at diagnosis, breast cancer type, time from initial to metastatic diagnosis, race, ECOG status and site of metastases could potentially be

used as covariates in a PAIC. Furthermore, there was a considerable amount of missing data; ECOG status was missing for 51% of patients and time from initial to metastatic diagnosis was missing for 70% of patients. A PAIC effectively assumes that absolute outcomes can be predicted from the measured covariates; that is, it assumes that all effect modifiers and prognostic factors are accounted for. In their response to the ERG clarification letter, the company states that the set of variables available is insufficient to carry out a PAIC. The ERG agrees with this assessment. The company also highlights that such a large amount of missing data would introduce further uncertainty into any PAIC.

In addition, the company had concerns relating to the differences between the anthracycline treatments used by the Flatiron cohort (Table 13) and those used by patients in UK clinical practice. While 95% of patients in the Flatiron cohort received doxorubicin, the company states, in their response to the ERG clarification letter (question A8), that epirubicin is more commonly used than doxorubicin in the UK. Clinical advice to the ERG is that, on balance, it is likely that, in the NHS, epirubicin is more commonly used than doxorubicin. The company also states that fluorouracil is more commonly used in the UK than in the US. However, clinical advice to the ERG is that not many centres in the UK use fluorouracil in the metastatic setting.

Table 13 Anthracycline treatments used in the Flatiron cohort

Anthracycline treatment	n (%) of patients treated (N=94)
Doxorubicin and cyclophosphamide	87 (93%)
Epirubicin, cyclophosphamide and fluorouracil	4 (4%)
Epirubicin and cyclophosphamide	1 (1%)
Doxorubicin, cyclophosphamide and fluorouracil	2 (2%)

Source: company response to the ERG clarification, question A8 (Table 8)

The ERG agrees with the company's conclusion that it was not appropriate to perform a PAIC of A+nabPx versus anthracyclines using the available data from the Flatiron cohort.

4.8.2 Studies identified for inclusion in the company network meta-analyses

In the CS, the company presents results from NMAs that include data from the primary analysis of the IMpassion130 trial (data cut-off date: 17th April 2018). However, in their response to the ERG clarification letter, the company provides results from NMAs that include data from the second interim OS analysis of the IMpassion130 trial (data cut-off date: January 2019). Throughout this ERG report, we discuss the methods and results of the NMAs that include data from the second interim OS analysis of the IMpassion130 trial, unless otherwise stated.

Of the 39 trials that met the inclusion criteria for the systematic review, the company identified 13 trials that provided OS or PFS data that could potentially have been used in the NMAs. As these 13 trials reported either aggregate data or individual patient data (IPD) for OS and/or PFS, they were initially included in the NMAs as the company had not yet determined the most suitable method of summarising treatment effect across the network.

In the CS, the company states that 26 trials were excluded for the following reasons: data were not reported for the TNBC subgroup, the majority (>80%) of TNBC patients were not receiving first-line therapy in the advanced setting, heterogeneity in terms of study design and patient characteristics, and differences in follow-up time points of reported outcomes. During clarification, the ERG asked the company to provide the reason for exclusion for each of the 26 excluded studies. The company responded that an error had been made in the original submission and that 27 studies had been excluded at this stage (company response to the ERG clarification letter, question A9). It is not clear to the ERG how 27 (instead of 26) trials could have been excluded, as the number of included studies remained the same (n=13).

Furthermore, the list of reasons for exclusion provided by the company in their clarification response (company response to the ERG clarification letter, Table 10) does not correspond with the reasons provided in the CS; no trials appear to have been excluded on the basis of heterogeneity in terms of study designs and patient characteristics, or differences in follow-up time points of reported outcomes. Due to the inconsistent information provided about reasons for including or excluding studies from the NMAs it is impossible for the ERG to determine whether the company's approach was appropriate.

The 13 trials that provided OS or PFS data that could potentially have been used in the NMAs (depending on the analysis approach chosen) are listed in Table 14, along with citations of the relevant publications for each trial. Throughout the rest of this ERG report, only the primary reference for each trial is cited.

Table 14 Trials that provided OS or PFS data that could potentially have been used in the NMAs

Study	Citations	Primary citation
IMpassion130	13	13
AVADO	53,54	53
CALGB40502	55,56	55
CARIN	57	57
COLET	58	58
E2100	59,60	60
EGF30001	61,62	62
JapicCTI-090921	63	63
LOTUS	64,65	64
MERiDiAN	66-68	67
RIBBON-1	69	69
TNT	70-73	73
TURANDOT	74-77	77

NMAs=network meta-analyses; OS=overall survival; PFS=progression free-survival

Assessment of proportional hazards

Having identified 13 trials that could have potentially contributed data to the NMAs for OS and PFS, the company assessed how best to summarise treatment effects across networks of evidence (one for each outcome) including these studies. Firstly, the company considered estimating a normal likelihood model using HRs from the included studies; this approach is only appropriate if the PH assumption is valid for each study. The company therefore assessed the PH assumption for both OS and PFS in each study by visually examining plots of the log cumulative hazard over log time by treatment arm and concluded that the PH assumption did not hold due to non-parallel curves in six studies for OS (AVADO,[53] COLET,[58] E2100,[60] LOTUS,[64] TNT,[73] TURANDOT[77] and IMpassion130 [second interim OS analysis, PD-L1+ patient population]), and in six studies for PFS (CALGB40502,[55] COLET,[58] LOTUS,[64] RIBBON-1,[69] TNT[73] and TURANDOT[77]). The company therefore decided not to estimate a normal likelihood model using HRs from the included studies. The ERG agrees with the company that using HRs to summarise treatment effect across these trials is inappropriate due to the violation of the PH assumption in multiple studies.

The company used discrete time models to summarise treatment effect across the identified studies, as these models do not require the assumption of PH. To use discrete time models, the company required either IPD, or Kaplan-Meier (K-M) curves that could be digitised to re-create K-M data for the mTNBC patient subgroup from each trial included in the networks. The JapicCTI-090921,[63] CARIN,[57] and EGF3001[62] trials were excluded from the final networks of evidence as either: IPD data were unavailable, K-M curves were unavailable and/or the

company could not recreate published results from the IPD (company response to the ERG clarification letter, question A10).

Studies of unlicensed therapies

In the updated NMAs, the company excluded the COLET[58] and LOTUS[64] trials from the networks of evidence as they only provide evidence for the relative efficacy of paclitaxel in comparison to unlicensed therapies (paclitaxel+cobimetinib in the COLET trial[58] and paclitaxel+ipatasertib in the LOTUS trial[64]). Furthermore, excluding these studies from the original NMAs (using data from the primary analysis of the IMpassion130 trial) in a scenario analysis had little impact on the estimates of restricted mean PFS and restricted mean OS for paclitaxel and docetaxel (Appendix D to the CS, Table 25 and Table 26).

Networks of evidence

The final networks of evidence for the company's updated NMAs for the outcomes of OS and PFS included eight trials (including IMpassion130), and are provided in Figure 2 and Figure 3, respectively.

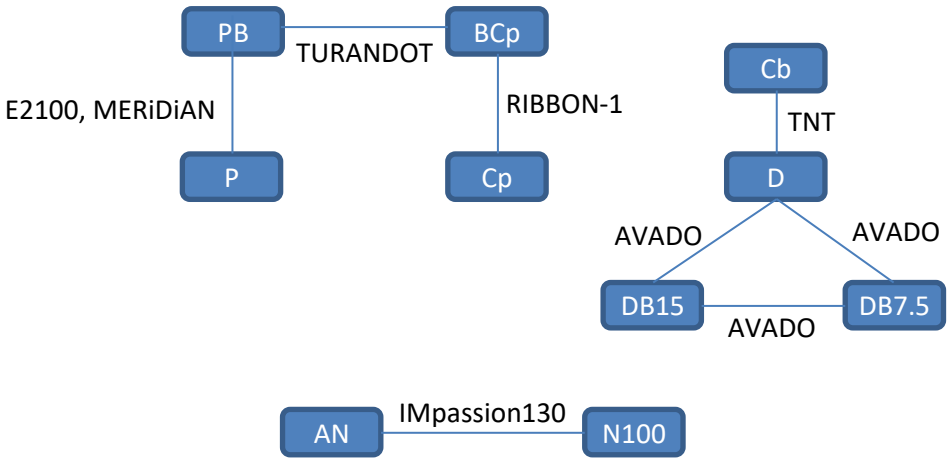

Figure 2 Network of trials for OS

AN=atezolizumab+nab-paclitaxel; BCp=bevacizumab+capecitabine; C=capecitabine; Cb=carboplatin; D=docetaxel; DB7.5=docetaxel+bevacizumab; DB15=docetaxel+bevacizumab; N100=nab-paclitaxel; OS=overall survival; P=paclitaxel; PB=paclitaxel+bevacizumab

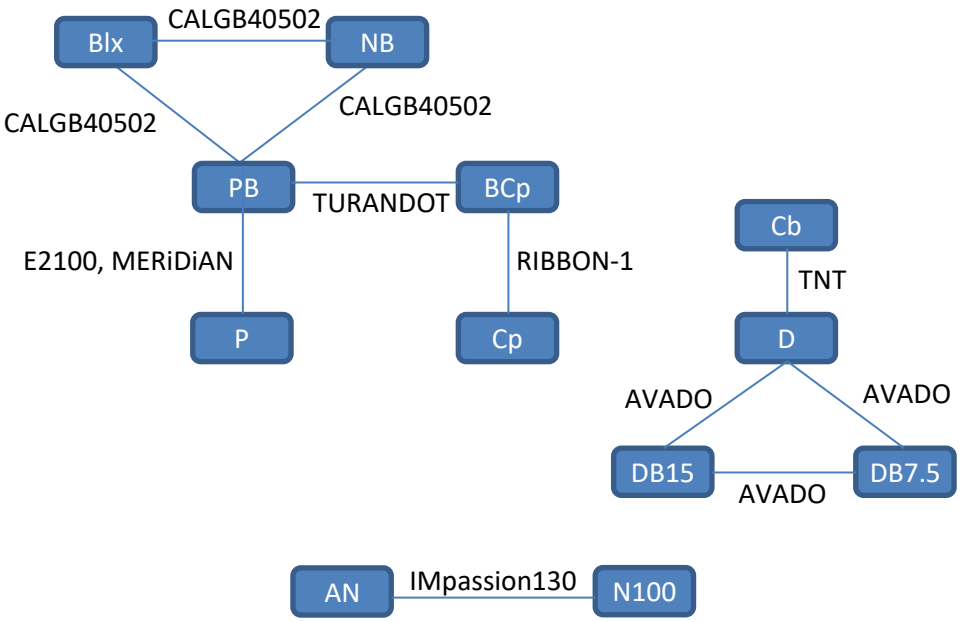

Figure 3 Network of trials for PFS

AN=atezolizumab+nab-paclitaxel; BCp=bevacizumab+capecitabine; Blx=bevacizumab+ixabepilone; C=capecitabine; Cb=carboplatin; D=docetaxel; DB7.5=docetaxel+bevacizumab; DB15=docetaxel+bevacizumab; NB=nab-paclitaxel+bevacizumab; N100=nab-paclitaxel; P=paclitaxel; PB=paclitaxel+bevacizumab; PFS=progression-free survival

For the IMpassion130 trial, the company only used data from the PD-L1+ patient population; for all other trials, the company used data from all patients with mTNBC because testing for PD-L1 status had not been carried out as part of these trials. Clinical effectiveness evidence for patients with PD-L1 disease treated with A+nabPx and P+nabPx were available from the IMpassion130 trial to populate the company networks. However, for all other treatments in the networks, the company assumed that reported effectiveness results, from patients with unknown PD-L1 disease status, reflected effectiveness in a population with PD-L1 disease.

4.8.3 Methodological approach to the indirect comparison

Population-adjusted indirect comparisons

PAICs can be used to link treatments in unconnected networks and thereby facilitate comparisons of two treatments that share no common comparators. As the networks for both OS and PFS (Figure 2, Figure 3) were unconnected, the company considered performing PAICs to form connected networks for both outcomes to enable comparisons of A+nabPx versus paclitaxel and docetaxel.

Firstly, the company assessed which comparators (and trials) should be used to connect the networks for OS and PFS. Of the treatments included in the network, paclitaxel and docetaxel are the only comparators of interest to this appraisal; the company therefore decided to use paclitaxel and docetaxel trials to connect the networks. The company explains that this approach was taken to minimise uncertainty in the estimation of the relative effectiveness of

A+nabPx versus paclitaxel, and A+nabPx versus docetaxel. The ERG considers the company's approach to be appropriate.

The company also decided to only use trials for which IPD were available to connect the networks as population adjustment methods are more robust when IPD data are available for both trials than when only aggregate data are available for one of the trials. The company therefore used data from the E2100[60] and MERiDiAN[67] trials to link A+nabPx to paclitaxel and data from the AVADO trial[53] to link A+nabPx to docetaxel.

The ERG notes that, in the CS, the company repeatedly uses the terminology "matching adjusted indirect comparison (MAIC)". However, "MAIC" refers to a method of PAIC which is applied when IPD are only available for one of the two trials that are included in the indirect comparison. The ERG considers the use of the term "MAIC" to be inappropriate and hereafter refers to the company's approach as a "PAIC".

The company used a covariate balancing propensity score model to adjust survival data from the A+nabPx arm of the IMpassion130 trial. A covariate balancing propensity score model involves the calculation of propensity scores which reflect each IMpassion130 trial patient's likelihood of being enrolled in each comparator trial (E2100,[60] MERiDiAN,[67] and AVADO [53]) based on specific baseline characteristics. Outcome data can then be weighted according to these propensity scores, creating a virtual A+nabPx arm for each of the three comparator studies. The aim of the covariate balancing propensity score model is to optimally balance the number of variables (baseline characteristics), for which matching takes place, with the resulting effective sample size, as weighting always reduces the effective sample size.[78]

In their response to the ERG clarification letter, the company presents comparisons of the adjusted baseline characteristics for the A+nabPx arm of the IMpassion130 trial with the baseline characteristics of patients in each comparator trial (E2100[60]: OS in Table 13 and PFS in Table 14; MERiDiAN[67]: OS in Table 15 and PFS in Table 16; AVADO[53]: OS in Table 17 and PFS in Table 18).

The final networks of evidence, connected by the PAICs, are provided in Figure 4 for OS and Figure 5 for PFS.

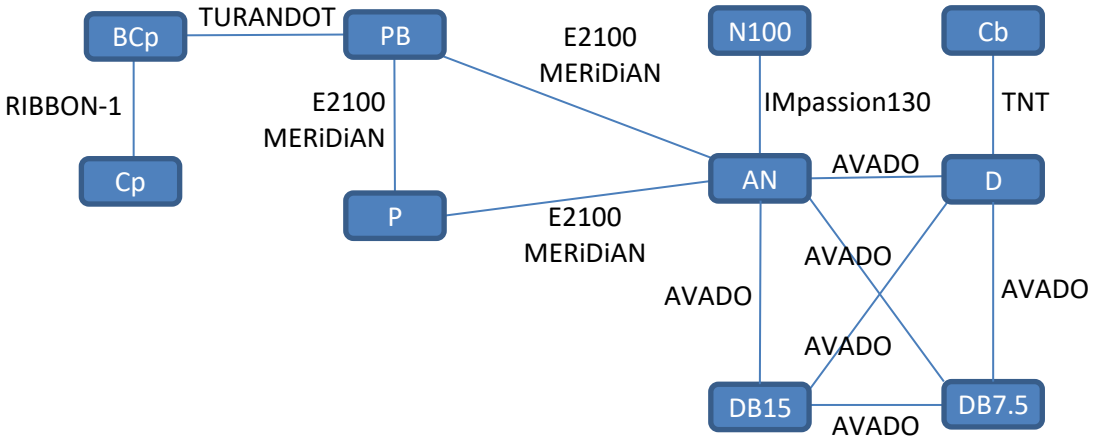

Figure 4 Final connected network for OS

AN=atezolizumab+nab-paclitaxel; BCp=bevacizumab+capecitabine; C=capecitabine; Cb=carboplatin; D=docetaxel; DB7.5=docetaxel+bevacizumab; DB15=docetaxel+bevacizumab; N100=nab-paclitaxel; OS=overall survival; P=paclitaxel; PB=paclitaxel+bevacizumab

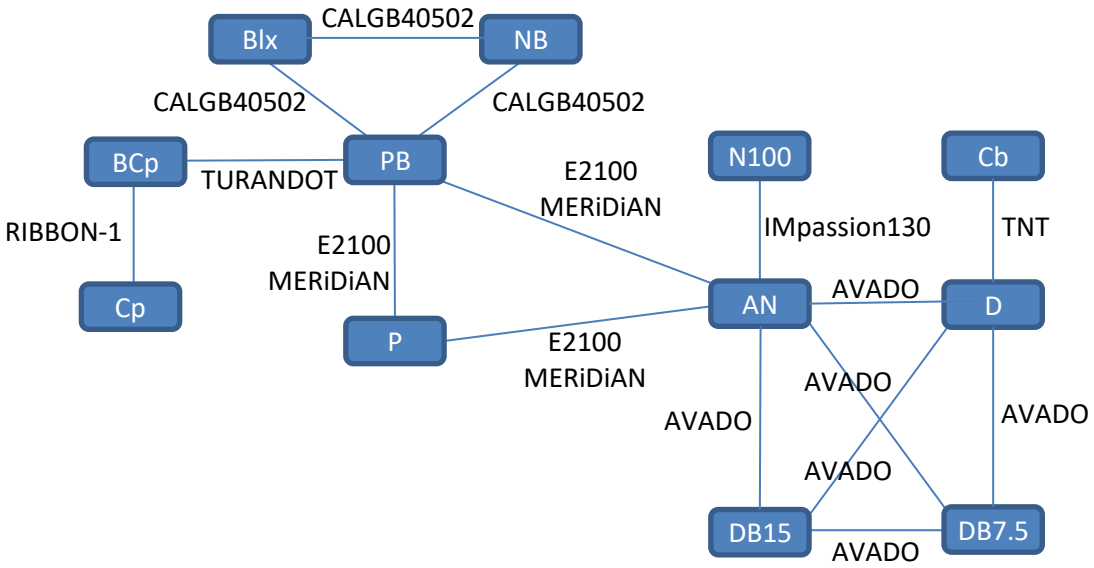

Figure 5 Final connected network for PFS

AN=atezolizumab+nab-paclitaxel; BCp=bevacizumab+capecitabine; Blx=bevacizumab+ixabepilone; C=capecitabine; Cb=carboplatin; D=docetaxel; DB7.5=docetaxel+bevacizumab; DB15=docetaxel+bevacizumab; NB=nab-paclitaxel+bevacizumab; N100=nab-paclitaxel; P=paclitaxel; PB=paclitaxel+bevacizumab; PFS=progression-free survival

Discrete time models

As noted in Section 4.8.2, the company used discrete time models to summarise treatment effects across the networks of evidence. For OS, a piecewise exponential model with a cut-point at 5 months was chosen as the base case model. For PFS, the base case model was a piecewise exponential model with cut-points at 2 and 4 months. The final models were estimated in a Bayesian framework and random effects models were used for both OS and PFS.

Full details of the model selection methods used by the company are provided in Appendix 2 of this ERG report.

The company presents the results of the NMAs in the form of HRs and 95% credible intervals (CrIs) for each "piece" i.e., for OS, 0 to 5 months, greater than 5 months, and for PFS, 0 to 2 months, 2 to 4 months, greater than 4 months. The company also presents restricted mean 5-year survival times for A+nabPx, paclitaxel, docetaxel and nab-paclitaxel, stating that survival probabilities from the IMpassion130 trial were extrapolated over a 5-year time period to obtain these estimates (company response to the ERG clarification letter, question A13). The company extrapolated unadjusted A+nabPx data from the IMpassion130 trial (rather than using adjusted A+nabPx data from the PAICs). The company performed the PAICs in order to generate adjusted A+nabPx data that could be used in the NMAs so the ERG considers it more likely that the company extrapolated adjusted A+nabPx data from the PAICs. The company applied HRs from the NMAs for A+nabPx versus paclitaxel, docetaxel and nab-paclitaxel to the extrapolated IMpassion130 trial data to obtain restricted mean 5-year survival times for paclitaxel, docetaxel and nab-paclitaxel. The ERG notes that these HRs estimate treatment effectiveness in the comparator trial populations (i.e., the populations in the E2100, MERiDiAN, and AVADO trials) rather than in the IMpassion130 trial population (company response to the ERG clarification letter, question A11). The company's approach, therefore, assumes that the treatment effect of A+nabPx versus each comparator in the comparator trial population is identical to the treatment effect observed in the IMpassion130 trial population. The ERG considers that this assumption introduces uncertainty as it is not known whether treatment effectiveness would be comparable across these trial populations.

4.8.4 Characteristics of trials included in the network meta-analyses

Key characteristics of the final eight trials included in the NMAs are provided in Appendix 3 of this ERG report. It is important to note that, although the inclusion criteria vary across the trials, all data included in the NMAs describe the mTNBC patient population only. Therefore, the fact that many studies included patients with non-TNBC types of breast cancer is not an issue of concern. All trials included patients with advanced or metastatic disease only. The ERG did not identify any important differences between the trials in terms of design, location, or drug regimens.

A summary of the patient characteristics of the eight trials included in the NMAs is provided in Appendix 3 of this ERG report. For the IMpassion130 trial, baseline characteristics are presented for the PD-L1+ patient population as only data from this subgroup of the IMpassion130 trial were included in the NMAs. For the TURANDOT trial,[77] baseline characteristics are presented for the mTNBC patient population; these values are reported in

the Brodowicz et al publication.[74] For the remaining six trials, baseline characteristics are presented for the whole trial populations, even though only data from the mTNBC patient subgroups of these trials were included in the NMAs. The ERG notes that for the AVADO,[53] E2100,[60] MERiDiAN,[67] and RIBBON-1 [69] trials, all of which were supported by Roche, the company could have perhaps been able to obtain and present the baseline characteristics for the mTNBC subgroups.

Incomplete baseline characteristics for the mTNBC patient subgroups means that a comprehensive evaluation of the comparability of patient populations included in the NMAs is very difficult. However, based on an assessment of the limited information available, the ERG does not consider there to be any important differences in patient characteristics across the included studies.

4.8.5 Assessment of risk of bias of the trials included in the network meta-analyses

The company carried out risk of bias assessments for the final eight trials included in the NMAs using the risk of bias assessment tool for RCTs recommended by the Cochrane Collaboration.[41] The results of the company's risk of bias assessments are provided in Table 15.

As noted in Section 4.1 of this ERG report, the company and the ERG consider that the IMpassion130 trial has a low risk of bias across all seven domains of the assessment tool (random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting and any other bias). For the seven other trials included in the company's NMAs, the ERG's assessment of the risk of bias differs to the company's assessment for some domains as described in Table 15. Full details of the ERG's comments on the company's risk of bias assessment is provided in Appendix 4 of this ERG report.

Table 15 Company assessment of risk of bias for trials included in the NMAs with ERG comment

Risk of bias criterion	IMpassion130[13]	E2100[60]	MERiDiAN[67]	AVADO[53]	RIBBON-1[69]	CALGB40502[55]	TNT[73]	TURANDOT[77]	ERG comment
Random sequence generation	Low	Low	Low	Low	Low	Low	Low	Low	Unclear risk for MERiDiAN CALGB40502 E2100
Allocation concealment	Low	High	Low	Low	Low	High	High	High	Unclear risk for MERiDiAN Low risk for TURANDOT
Blinding of participants	Low	High	Low	Low	Low	High	High	High	Agree
Blinding of outcome assessment	Low	High	Low	Low	Low	High	High	High	Agree
Incomplete outcome data	Low	Low	Low	Low	Low	Low	Low	Low	Agree
Selective reporting	Low	Low	Low	Low	Low	Low	Low	Low	Unclear risk for all trials except IMpassion130
Any other sources of bias	Low	Low	Low	Low	Low	High	Low	Low	Unclear risk for all trials

Source: Adapted from Table 27 of Appendix D to the CS

4.8.6 Results from the network meta-analyses

In this section, results are presented for paclitaxel and docetaxel versus A+nabPx and paclitaxel and docetaxel versus nab-paclitaxel as these are the comparisons of interest in this appraisal. However, the company highlights that the methodology used for each NMA incorporates data for all treatments included in the final network of evidence for the relevant outcome.

Paclitaxel and docetaxel versus A+nabPx

HRs and 95% CrIs are presented by piece for the outcomes of OS and PFS in Table 16 and Table 17, respectively.

Table 16 OS HRs of paclitaxel and docetaxel versus A+nabPx, by piece

	t<5months		5months≤t	
	HR (median)	95% CrI	HR (median)	95% CrI
Paclitaxel	1.19	0.43 to 3.41	1.74	1.12 to 2.71
Docetaxel	1.67	0.61 to 4.78	1.72	0.8 to 3.53

A+nabPx=atezolizumab+nab-paclitaxel; CrI=credible interval; HR=hazard ratio; OS=overall survival
Source: company response to the ERG clarification letter, Table 22

Table 17 PFS HRs of paclitaxel and docetaxel versus A+nabPx, by piece

	0 months ≤t< 2months		2 months ≤t< 4months		4 months ≤t	
	HR (median)	**95% CrI**	**HR (median)**	**95% CrI**	**HR (median)**	**95% CrI**
Paclitaxel	0.95	0.42 to 2.09	1.65	0.82 to 3.27	1.88	1.10 to 3.11
Docetaxel	1.23	0.44 to 3.48	1.01	0.31 to 3.07	2.79	1.30 to 6.03

A+nabPx=atezolizumab+nab-paclitaxel; CrI=credible interval; HR=hazard ratio; PFS=progression-free survival
Source: company response to the ERG clarification letter, Table 23

The posterior median restricted mean 5-year survival times for A+nabPx, paclitaxel and docetaxel based on extrapolations over a 5-year time horizon are presented in Figure 6 for OS and Figure 7 for PFS; differences between these restricted mean survival times for paclitaxel and docetaxel versus A+nabPx are presented in Figure 8 for OS and Figure 9 for PFS. As previously discussed in Section 4.8.3, it is not clear to the ERG how these extrapolations were performed.

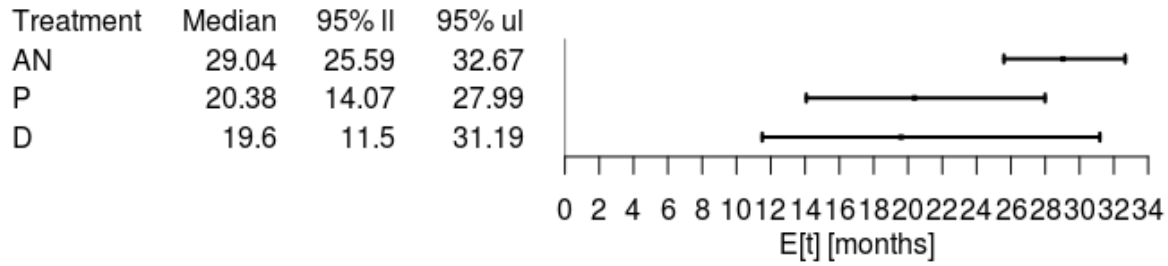

Figure 6 Restricted mean 5-year OS times based on extrapolations over a 5-year time horizon

AN=atezolizumab+nab-paclitaxel; D=docetaxel; OS=overall survival; P=paclitaxel; 95% ll=95% credible interval lower limit; 95% ul=95% credible interval upper limit
Source: company response to the ERG clarification letter, Figure 5

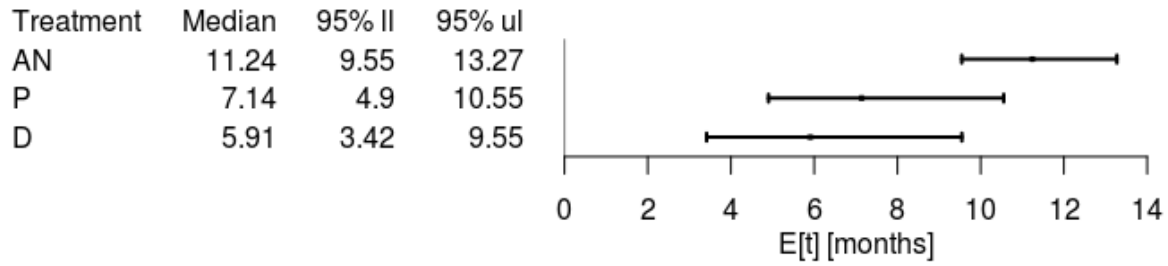

Figure 7 Restricted mean 5-year PFS times based on extrapolations over a 5-year time horizon

AN=atezolizumab+nab-paclitaxel; D=docetaxel; P=paclitaxel; PFS=progression-free survival; 95% ll=95% credible interval lower limit; 95% ul=95% credible interval upper limit
Source: company response to the ERG clarification letter, Figure 8

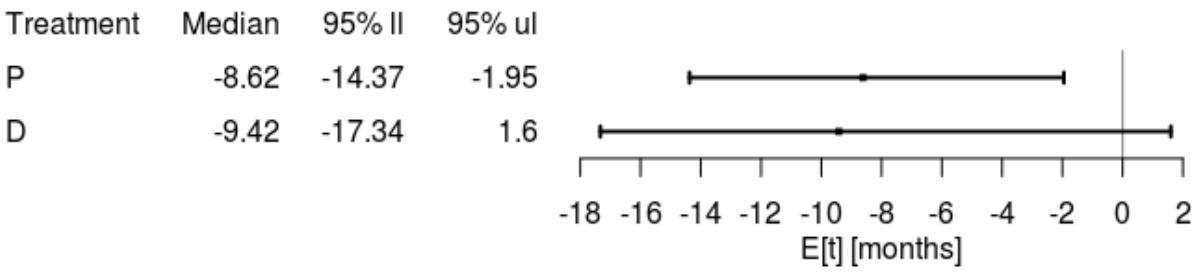

Figure 8 Differences between restricted mean OS times for paclitaxel and docetaxel versus A+nabPx

A+nabPx=atezolizumab+nab-paclitaxel; D=docetaxel; OS=overall survival; P=paclitaxel; 95% ll=95% credible interval lower limit; 95% ul=95% credible interval upper limit
Source: company response to the ERG clarification letter, Figure 6

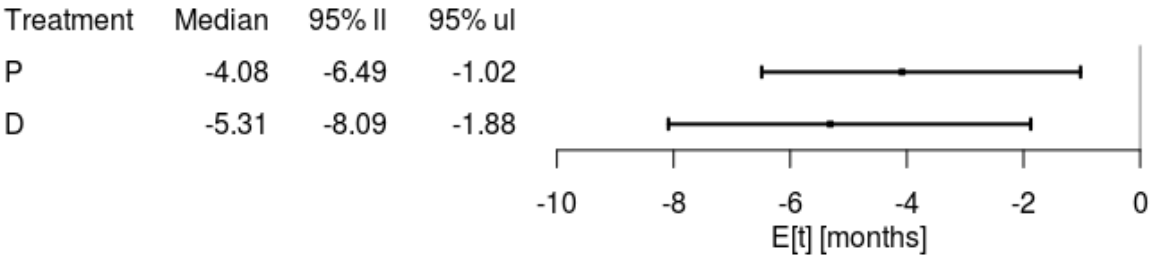

Figure 9 Differences between restricted mean PFS times for paclitaxel and docetaxel versus A+nabPx

A+nabPx=atezolizumab+nab-paclitaxel; D=docetaxel; P=paclitaxel; PFS=progression-free survival; 95% ll=95% credible interval lower limit; 95% ul=95% credible interval upper limit
Source: company response to the ERG clarification letter, Figure 9

Paclitaxel, docetaxel and A+nabPx versus nab-paclitaxel

HRs and 95% CrIs are presented by piece for the outcomes of OS and PFS in Table 18 and Table 19, respectively.

Table 18 OS HRs of paclitaxel, docetaxel, and A+nabPx versus nab-paclitaxel, by piece

	t<5months		5months≤t	
	HR (median)	95% CrI	HR (median)	95% CrI
Paclitaxel	0.63	0.18 to 2.2	1.33	0.72 to 2.46
Docetaxel	0.89	0.25 to 3.14	1.32	0.56 to 3.00
A+nabPx	0.53	0.26 to 1.07	0.76	0.5 to 1.18

CrI=credible interval; HR=hazard ratio; OS=overall survival
Source: Company response to the ERG clarification letter, Table 24

Table 19 PFS HRs of paclitaxel, docetaxel and A+nabPx versus nab-paclitaxel, by piece

	0 months ≤t< 2months		2 months ≤t< 4months		4 months ≤t	
	HR (median)	95% CrI	HR (median)	95% CrI	HR (median)	95% CrI
Paclitaxel	0.56	0.19 to 1.64	0.95	0.34 to 2.63	1.35	0.57 to 2.99
Docetaxel	0.74	0.21 to 2.59	0.57	0.14 to 2.24	2	0.72 to 5.44
A+nabPx	0.59	0.29 to 1.22	0.57	0.27 to 1.22	0.72	0.37 to 1.36

A+nabPx=atezolizumab+nab-paclitaxel; CrI=credible interval; HR=hazard ratio; nabPx=nab-paclitaxel; PFS=progression-free survival
Source: Company response to the ERG clarification letter, Table 25

The posterior median restricted mean 5-year survival times for A+nabPx, nab-paclitaxel, paclitaxel and docetaxel based on extrapolations of the IMpassion130 trial data over a 5-year time horizon are presented in Figure 10 for OS and in Figure 11 for PFS; differences between restricted mean 5-year OS times for paclitaxel and docetaxel versus nab-paclitaxel are presented in Figure 12, and differences between restricted mean 5-year PFS times for paclitaxel, docetaxel and A+nabPx versus nab-paclitaxel are presented in Figure 13. As previously discussed in Section 4.8.3, it is not clear to the ERG how these extrapolations were performed.

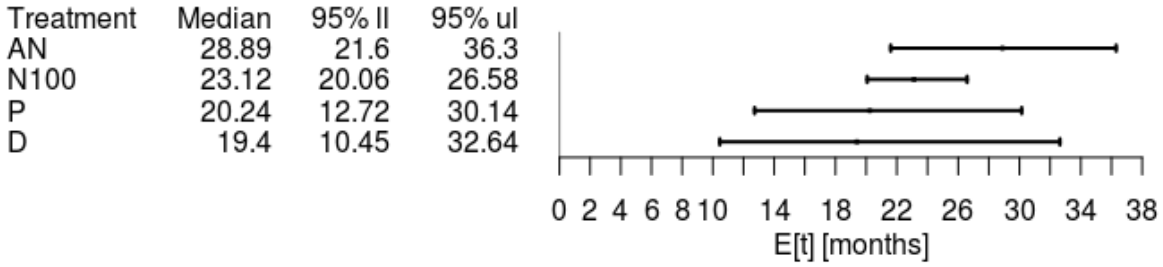

Figure 10 Restricted mean 5-year OS times based on extrapolations over a 5-year time horizon

AN=atezolizumab+nab-paclitaxel; D=docetaxel; N100=nab-paclitaxel; OS=overall survival; P=paclitaxel; 95% ll=95% credible interval lower limit; 95% ul=95% credible interval upper limit
Source: company response to the ERG clarification letter, Figure 11

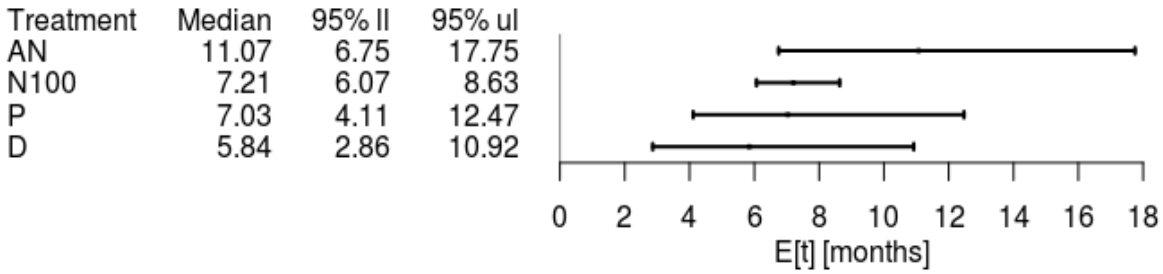

Figure 11 Restricted mean 5-year PFS times based on extrapolations over a 5-year time horizon

AN=atezolizumab+nab-paclitaxel; D=docetaxel; N100=nab-paclitaxel; P=paclitaxel; PFS=progression-free survival; 95% ll=95% credible interval lower limit; 95% ul=95% credible interval upper limit
Source: company response to the ERG clarification letter, Figure 14

Treatment	Median	95% ll	95% ul
P	-2.86	-10.19	6.43
D	-3.74	-12.57	8.9

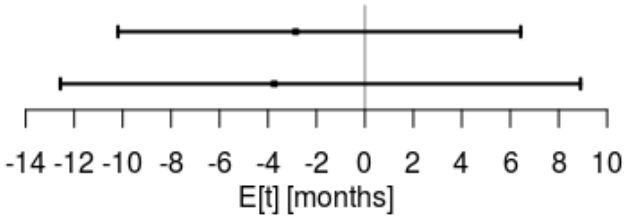

Figure 12 Differences between restricted mean OS times for paclitaxel and docetaxel versus nabPx

D=docetaxel; OS=overall survival; P=paclitaxel; nabPx=nab-paclitaxel; 95% ll=95% credible interval lower limit; 95% ul=95% credible interval upper limit
Source: company response to the ERG clarification letter, Figure 12

Treatment	Median	95% ll	95% ul
AN	3.85	-0.29	10.16
P	-0.18	-3.13	5.09
D	-1.36	-4.38	3.54

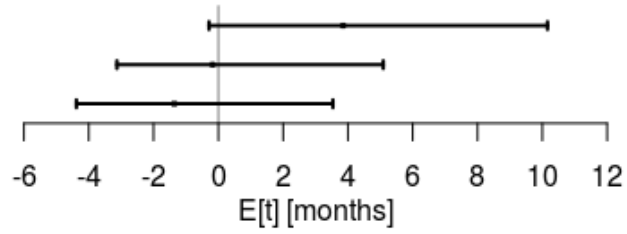

Figure 13 Differences between restricted mean PFS times for A+nabPx, paclitaxel and docetaxel versus nabPx

A+nabPx=atezolizumab+nab-paclitaxel; D=docetaxel; nabPx=nab-paclitaxel; P=paclitaxel; PFS=progression-free survival; 95% ll=95% credible interval lower limit; 95% ul=95% credible interval upper limit
Source: company response to the ERG clarification letter, Figure 15

Network meta-analyses for objective response rate and adverse events

The company also performed NMAs for the outcomes of ORR and Grade 3 to 5 AEs. The methodology used to perform these NMAs is provided in Appendix D to the CS (pp98-102). No clear information is provided on how studies were selected for inclusion in these NMAs.

The results of the NMA for ORR suggest that A+nabPx improves ORR in comparison to both paclitaxel and docetaxel. No statistically significant differences were observed between A+nabPx and paclitaxel or docetaxel in terms of Grade 3 to 5 AEs. Full numerical results are provided in Appendix D to the CS (pp100-104).

4.8.7 ERG interpretation of the company's network meta-analyses

The ERG considers that it is difficult to draw conclusions about the overall relative efficacy of paclitaxel and docetaxel versus A+nabPx, and paclitaxel and docetaxel versus nabPx; the results are uncertain as there are several HRs available which correspond to different periods of time.

Furthermore, the ERG notes that, across the analyses for OS and PFS, 95% CrIs for the HRs are wide and mostly include 1 (the point of no difference). The exceptions to this observation are the comparisons of paclitaxel versus A+nabPx for OS after 5 months, paclitaxel versus A+nabPx for PFS after 4 months and docetaxel versus A+nabPx for PFS after 4 months. Notably, 95% CrIs for all HRs presented for the comparisons of nab-paclitaxel versus paclitaxel and docetaxel include 1.

The differences between restricted mean 5-year survival times also have wide CrIs. However, the results suggest that treatment with A+nabPx improves OS versus paclitaxel, and that treatment with A+nabPx improves PFS versus both paclitaxel and docetaxel. There was no evidence to suggest any difference in restricted mean 5-year survival times between nab-paclitaxel and paclitaxel or docetaxel for either OS or PFS.

The ERG has serious reservations about the reliability of all the results generated by the company's NMAs as:

- the inconsistent information provided to the ERG regarding studies identified for inclusion in the NMAs has made it impossible for the ERG to determine whether the company's approach to including and excluding studies was appropriate
- clinical effectiveness evidence for patients with PD-L1 disease treated with A+nabPx and P+nabPx were available from the IMpassion130 trial to populate the company networks. However, for all other treatments in the networks, the company assumed that reported effectiveness results, from patients with unknown PD-L1 disease status, reflected effectiveness in a population with PD-L1 disease. The ERG considers that this assumption introduces considerable uncertainty as it is not known whether PD-L1 status has an impact on the efficacy of other treatments included in the networks
- the company's approach to obtaining estimates of restricted 5-year mean survival times assumes that the treatment effect of A+nabPx versus each comparator in the comparator trial population is identical to the treatment effect observed in the IMpassion130 trial population. The ERG considers that this assumption introduces uncertainty as it is not known whether treatment effectiveness is comparable across these trial populations
- the lack of baseline characteristics information for patients with mTNBC whose data were included in the NMAs means that a comprehensive evaluation of the comparability of patient populations included in the NMAs was not possible.

4.9 Conclusions of the clinical effectiveness section

Direct evidence
The direct clinical effectiveness evidence for A+nabPx was derived from the IMpassion130 trial. The ERG highlights the following points:

- The IMpassion130 trial is a well-designed and good quality trial with an appropriate, pre-defined statistical approach to the analysis of efficacy, safety and patient reported outcomes.
- The comparator in the IMpassion130 trial is P+nabPx. Nab-paclitaxel is not a comparator listed in the final scope[2] issued by NICE. Nab-paclitaxel is not licensed in Europe as a first-line treatment for metastatic breast cancer. The dose and delivery of nab-paclitaxel used in the IMpassion130 trial differs from the dose that is recommended in the second-line indication.
- The clinical effectiveness outcomes for the subgroup of patients (n=369) in the IMpassion130 trial with PD-L1+ disease are the focus of this appraisal. The ERG considers that, based on the numbers of patients in the PD-L1+ subgroup, these subgroup data can be used to inform decision making; however, decision making is hampered by the lack of a relevant comparator in the IMpassion130 trial.
- Clinical advice to the ERG is that most NHS patients with metastatic disease would have been previously treated with a sequential regimen of anthracyclines and taxanes. In the IMpassion130 trial, 57% of PD-L1 patients had received prior anthracycline treatment and 51% of PD-L1 patients had received prior taxane treatment. This suggests that a substantial proportion of patients might have been suitable for anthracycline therapy.
- Results from the definitive PFS analysis suggest that treatment with A+nabPx statistically significantly improves investigator-assessed PFS in comparison to P+nabPx in the PD-L1+ patient population (HR=0.62, 95% CI: 0.49 to 0.78; p-value<0.001). Median PFS was longer in the A+nabPx arm than in the P+nabPx arm (7.5 months versus 5.0 months, respectively). However, clinical advice to the ERG is that a difference in median PFS of 2.5 months is not clinically meaningful.
- [redacted]. A final OS analysis will be conducted when at least 662 OS events have occurred The ERG highlights that it is difficult to predict whether the [redacted]
- The ERG agrees with the company that AEs reported in the trial appear to be consistent with the known safety profiles of atezolizumab and nab-paclitaxel with no new AEs identified. However, clinical advice to the ERG is that AEs arising from treatment with atezolizumab and other immunotherapies require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs and that this can place a high burden on NHS staff and systems.
- HRQoL data were collected as part of the IMpassion130 trial using the EQ-5D-5L[48] questionnaire and the EORTC QLQ-C30[49] questionnaire with the QLQ-BR23[50] breast cancer module. The company mapped the EQ-5D-5L data to EQ-5D-3L.[51] The ERG considers that the resultant utility values are in line with utilities calculated from data

collected during trials of other drugs to treat advanced breast cancer. The company found no difference between treatment arms for any of the EORTC QLQ-30[49] or QLQ-BR23[50] outcome measures.

Indirect evidence

The IMpassion130 trial was not designed to assess the effectiveness of any of the comparators specified in the final scope issued by NICE (paclitaxel, docetaxel and anthracyclines). It was, therefore, necessary for the company to carry out NMAs to generate this evidence.

- The company did not identify any relevant RCTs of anthracyclines that could be included in the indirect comparisons. The company investigated the possibility of performing indirect comparisons of A+nabPx versus anthracyclines using real-world, instead of trial, evidence but concluded that this approach was not appropriate. The ERG agrees with the company's conclusion.
- The company performed NMAs to obtain indirect estimates of effect for A+nabPx versus paclitaxel and versus docetaxel. However, the ERG has serious reservations about the reliability of all the results generated by the company's NMAs as:
  - the ERG was unable to validate the company's approach to including and excluding studies from their NMAs
  - clinical effectiveness evidence for patients with PD-L1 disease treated with A+nabPx and P+nabPx were available from the IMpassion130 trial to populate the company networks. However, for all other treatments in the networks, the company assumed that reported effectiveness results, from patients with unknown PD-L1 disease status, reflected effectiveness in a population with PD-L1 disease
  - the company's method of obtaining estimates of restricted 5-year mean survival times assumes that the treatment effect of A+nabPx versus each comparator in the comparator trial populations is identical to the treatment effect observed in the IMpassion130 trial population
  - the NMAs included subgroups of patients with mTNBC from different trials; however, the lack of baseline characteristics information about these patients made checking the comparability of trials problematic.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by the company in support of the use of A+nabPx versus paclitaxel and docetaxel for treating people with mTNBC whose tumours have PD-L1+ expression and have not received prior chemotherapy for metastatic disease. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel

5.2 Company's systematic review of cost effectiveness evidence

5.2.1 Objective of the company's systematic review

The company performed a systematic review of the literature to identify published studies that evaluated the cost effectiveness of first-line treatments for advanced or metastatic breast cancer. The search was not restricted to people with mTNBC to ensure all relevant publications were captured.

5.2.2 Company searches

The company searched for articles that had been published since 1 January 2007. The databases listed in Table 20 were searched on 23 July 2018. Details of the search strategies used by the company are provided in Appendix G of the CS.

Table 20 Databases searched for economic evidence

Database	Interface
Excerpta Medical Database (Embase)	Ovid
Medical Literature Analysis and Retrieval System Online (MEDLINE)	Ovid
Health Technology Assessment database (HTA)	Ovid
National Health Service Economic Evaluation Database (NHS EED)	Ovid
EconLit	Ovid

Source: CS, adapted from Appendix G

The company also carried out searches to identify relevant proceedings from the following conferences held between 2016 and 2018:

- American Society of Clinical Oncology (ASCO)
- European Society for Medical Oncology (ESMO)
- Health Technology Assessment International (HTAi)
- International Society of Pharmacoeconomic and Outcomes Research (ISPOR): European and International Congresses
- The Society for Medical Decision Making (SMDM).

In addition, the company searched the following websites for potentially relevant technology appraisals: NICE, Scottish Medicine Consortium (SMC), All Wales Medicine Strategy Group (AWMSG), Pharmaceutical Benefits Advisory Committee (PBAC), Canadian Agency for Drugs and Technologies in Health (CADTH), Institut National d'Excellence en Sante et en Services Sociaux (INESSS) and Hauté Autorite de Santé (HAS).

The following sources were also searched for relevant studies: Cost Effectiveness Analysis (CEA) Registry and the health technology assessment database of the International Network of Agencies for Health Technology Assessment (INAHTA).

5.2.3 Eligibility criteria used in study selection

The main inclusion criteria used by the company to select studies are shown in Table 21.

Table 21 Key criteria for identification of cost effectiveness studies

Characteristic	Inclusion criteria
Population	• Adult patients with locally advanced or metastatic BC who have received no prior chemotherapy or targeted therapy
Intervention(s) / comparator	Investigational products of interest: atezolizumab, paclitaxel and nab-paclitaxel Additional interventions of interest, either as single agents or as combination therapy: bevacizumab, ipatasertib, cobimetinib, pembrolizumab, paclitaxel, emcitabine, docetaxel, cisplatin, capecitabine, carboplatin, cyclophosphamide, vinorelbine, eribulin, anthracycline, ixabepilone, doxorubicin or (pegylated) liposomal doxorubicin, epirubicin, cyclophosphamide+doxorubicin+fluorouracil or doxorubicin+fluorouracil, fluorouracil+epirubicin+cyclophosphamide or epirubicin+cyclophosphamide, cyclophosphamide+methotrexate+fluorouracil, gemcitabine+paclitaxel
Outcomes	• Incremental costs, LYs gained, QALYs, and any other measure of effectiveness reported together with costs • Model type, structure, source of input parameters and assumptions • Cost drivers as reported in sensitivity analyses
Study design	• Cost effectiveness analyses • Cost utility analyses • Cost minimisation analyses • Cost benefit analyses
Country	• No restrictions
Language	• Studies published in English, or non-English publications with an abstract in English

BC=breast cancer; LY=life year; QALY=quality adjusted life year
Source: CS Appendix G, Table 31

The company search identified 27 economic evaluations published as full reports and 23 abstracts. None of the published full-text economic evaluations considered people with mTNBC. Two of the identified abstracts (references not available) did consider people with TNBC but these were people in the early (adjuvant) breast cancer setting and people who had received at least one prior chemotherapy for advanced/metastatic breast cancer.

Details of the company screening process and the reasons for the exclusion of studies are presented in the CS (Section B.3.1 and Appendix G).

5.2.4 Findings from cost effectiveness review

The company did not identify any cost effectiveness studies that met the eligibility criteria of the systematic review.

5.3 ERG critique of the company's literature review

A summary of the ERG appraisal of the company search and selection processes is provided in Table 22. The ERG considers that the databases searched, and the search terms used, appear to be reasonable. However, the ERG notes that the justification for the data search period/timespan chosen by the company for some databases was not stated. Apart from study selection and data extraction, it was unclear from information provided in the main body of the CS and Appendix G of the CS whether other aspects of the systematic review (including quality assessment of studies) were conducted by two or more reviewers. Finally, details provided in Appendix G of the CS suggest that the databases were last accessed in July 2018 and it was not stated whether the search has been updated.

Overall, the ERG is satisfied that the company has not missed any relevant economic studies.

Table 22 ERG appraisal of the company's cost effectiveness systematic review methods

Review process	ERG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Partly
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Was data extracted by two or more reviewers independently?	Yes
Were appropriate criteria used to assess the quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Not reported
Were any relevant studies identified?	No

Source: in-house LRiG checklist

5.4 ERG summary of the company's submitted economic evaluation

The company developed a de novo economic model to compare the cost effectiveness of treatment with A+nabPx versus paclitaxel and versus docetaxel as a first-line treatment for adults with PD-L1+ mTNBC.

5.4.1 Model structure

The company model structure (a partitioned survival model) is shown in Figure 14. It comprises three mutually exclusive health states that are designed to reflect the natural course of the disease. The modelled population enters the model in the PFS health state. At the end of each 7-day cycle, patients in the PFS health state can remain in that health state or experience disease progression and enter the progressed disease (PD) health state. Patients in the PD health state can, at the end of each cycle, remain in that health state but they cannot return to the PFS health state. Transitions to the death health state can occur from either the PFS health state or the PD health state. Death is an absorbing health state from which transitions to other health states are not permitted.

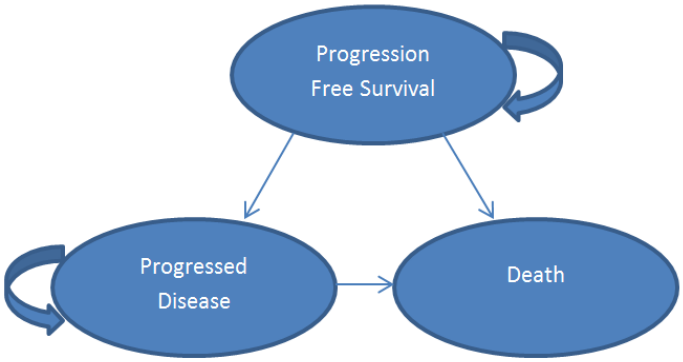

Figure 14 Structure of the company model

Source: CS, Section B.3.2 Figure 19

5.4.2 Population

The population reflected in the company model comprises people with mTNBC whose tumours have PD-L1 expression in the first-line setting. The population is consistent with the IMpassion130 trial population and similar to that described in the final scope[2] issued by NICE. The population described in the final scope[2] is people with locally advanced or mTNBC whose tumours have PD-L1+ expression.

5.4.3 Interventions and comparators

Intervention

Treatment with A+nabPx is implemented in the model in line with the anticipated Summary of Product Characteristics (SmPC) as described in the CS[1] i.e., IV infusion of 840mg of atezolizumab on days 1 and 15 of every 28 cycle followed by 100mg/m^2 nab-paclitaxel on days 1 and 15 of every 28 cycle. 100mg/m^2 of nab-paclitaxel is also implemented (by IV infusion) on day 8 of each 28-day cycle.

Comparators

The company notes that treatment with paclitaxel monotherapy is not licensed for use in the first-line setting for patients with mTNBC. However, the company were advised by clinicians that it was standard of care in the NHS and the most frequently used dosing regimen was 90mg/m^2 every week. The company has assumed that NHS patients would receive 18 cycles of paclitaxel.

Treatment with docetaxel is not implemented in the model in line with the dosing regimen specified in the SmPC[79] (100mg/m^2 IV infusion every 3 weeks). Based on clinical advice, the company has modelled patients to receive docetaxel at a dose of 75mg/m^2 every 3 weeks, with a maximum of six cycles.

The company has not provided any cost effectiveness evidence for the comparison of A+nabPx versus anthracyclines.

5.4.4 Perspective, time horizon and discounting

The company states that the economic evaluation has been undertaken from the perspective of the NHS and Personal Social Services (PSS). In line with the NICE Guide to the Methods of Technology Appraisal,[80] the base case analysis excludes out-of-pocket expenses, informal costs and productivity costs. The model cycle length is 1 week, and the time horizon is set at 15 years which, the company considers, is long enough to reflect all important differences in costs or outcomes between the technologies being compared. Relevant costs and outcomes have been discounted at 3.5% per annum.

5.4.5 Treatment effectiveness and extrapolation in the base case

Parameter values used in the company model have, primarily, been estimated using IPD from the IMpassion130 trial. The follow-up period in this trial was shorter than the required length of the economic evaluation and, therefore, extrapolation of the trial OS, PFS and time to off treatment (TTOT) data was necessary; this involved identifying suitable parametric functions.

Overall survival

The company initially fitted six parametric functions (exponential, gamma, Gompertz, log-normal, log-logistic and Weibull) to the OS data from the A+nabPx arm of the IMpassion130 trial. The gamma, log-logistic and Weibull functions were identified as being more suitable than the other functions based on goodness-of-fit statistics (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]) and visual inspection. The Weibull parametric function was used in the economic model as the company considered the OS projection from that parametric function (5 years=9.9%; 10 years=0.3%) to be consistent with expert opinion (5 years=8%; 10 years=0.2%). A noteworthy point is that, in the base case, the preferred parametric function was used for the entire model time horizon to represent the effectiveness of treatment with A+nabPx. The parametric function selection criteria used by the company are shown in Section B.3.3.2 of the CS.

To estimate OS for patients treated with paclitaxel and docetaxel, the time-dependent OS HRs generated by the company's NMAs (see section 4.8.6 of this report) were applied to the A+nabPx OS data used in the model. The data used in the company model to represent OS for patients treated with A+nabPx, paclitaxel and docetaxel are shown in

[redacted]

Figure 15 OS in the economic model for treatment with atezolizumab plus nab-paclitaxel, paclitaxel and docetaxel .

Source: Company model, overall survival overall chart

Progression-free survival

Similar to the methods used to identify an OS extrapolation, the company fitted six parametric functions to the PFS data from the A+nabPx arm of the IMpassion130 trial and then assessed their suitability based on goodness-of-fit statistics, visual inspection and clinical opinion. The company states that the parametric functions with the best goodness-of-fit statistics (gamma and log-normal) and visual fit (gamma, log-logistic and log-normal) were excluded because the extrapolations produced implausible scenarios (the uncapped PFS extrapolations exceeded OS).

The remaining parametric functions (exponential, Weibull and Gompertz) were then assessed against clinical expert opinion elicited by the company. Clinical opinion was that at 3 years and 5 years the proportions of patients likely to still be in the PFS health state were 13% and 2% respectively. The company considered that, although the Gompertz function provided the closest estimates to clinical opinion (3 years=5.6%; 5 years=2.5%), it had the poorest goodness-of-fit statistics compared with the observed PFS data from the IMpassion130 trial. The company, therefore, considered that, given the maturity of the PFS data from IMpassion130 trial and precedence from a previous NICE appraisal (TA520[81]), it was appropriate to use a piecewise model. This involved appending a Gompertz function to K-M PFS data from A+nabPx arm of the IMpassion130 trial at 19.2 months (at which point 15% of patients were still at risk of progression). The parametric function selection criteria used by the company are shown in section B.3.3.3 of the CS. To estimate PFS for patients treated with paclitaxel and docetaxel, the time-dependent PFS HRs generated by the company's NMAs

(see section 4.8.6 of this report) were applied to the data used in the model to represent PFS for patients treated with A+nabPx.

The data used to represent PFS in the intervention and comparator arms of the company model are shown in

Figure 16.

Figure 16 PFS in the economic model for treatment with A+nabPx, paclitaxel and docetaxel

Source: Company model, progression-free survival overall chart

Time to off treatment

When modelling TTOT for the A+nabPx arm of the company model, the TTOT for atezolizumab and nab-paclitaxel were modelled separately. The approach used to select the most appropriate representation to use in the model for each treatment was the same as that used to select a PFS representation. The parametric function preferred by the company on the basis of goodness-of-fit statistics, visual fit and clinical opinion were K-M data plus an exponential function (from 20.3 months) for treatment with atezolizumab and K-M data plus a gamma function (from 12.5 months) for treatment with nab-paclitaxel.

TTOT for patients treated with either paclitaxel or docetaxel was assumed to be the same as PFS, which implies that all patients in the comparator arms are treated until disease progression (see CS, section B.3.3.4).

The model does not permit treatment continuation beyond disease progression in either the intervention or comparator arm. The justifications presented by the company behind the

decision for the modelling of A+nabPx are that the anticipated licence will only allow for treatment until disease progression or unacceptable toxicity and that available data from the IMpassion130 trial show that TTOT is consistently shorter than PFS. For patients treated with either paclitaxel or docetaxel, since TTOT has been set to be the same as PFS, a treatment cap is, effectively, in place. The company then assumed in the model that people treated with paclitaxel and docetaxel would receive treatment for a maximum of 18 weeks and 24 weeks respectively.

5.4.6 Health-related quality of life

Patients in the IMpassion130 trial completed the EQ-5D-5L[48] questionnaire at baseline and then on the first day of each 28-day treatment cycle. Trial participants also completed the questionnaire during survival follow-up contacts, at the treatment discontinuation visit and every 28 days for 1 year after treatment discontinuation. Patient responses to the EQ-5D-5L[48] questionnaire were mapped onto the EQ-5D-3L domain scores using the van Hout algorithm.[82] This approach is consistent with the NICE position statement on the use EQ-5D-5L[48] data within its technology appraisal process. A mixed model linear regression was then used, with subjects being a random factor. The fixed factors in the regression were the treatment arm and the pre- versus post-progression indicator flag. The utility values used in the economic model are shown in Table 23.

Table 23 Utility values used in the company model

Health state	Treatment arm	Utility value (95% CI)
Progression-free	A+nabPx and P+nabPx	0.726 (0.706 to 0.746)
Progressive disease	A+nabPx and P+nabPx	0.653 (0.631 to 0.675)

CI=confidence interval
Source: CS, Section B3.4.2 (Table 50)

5.4.7 Adverse events

Adverse event rates occurring at Grade 3 or 4 in ≥2% of patients in the A+nabPx arm of the IMpassion130 trial were used to represent the experience of patients in the A+nabPx arm of the company model. Rates for those treated with paclitaxel were obtained from the E2100 trial,[59,60] LOTUS trial[64,65] and the MERIDIAN trial,[66-68] whilst rates for those treated with docetaxel were obtained from the AVADO trial[53,54] and the JapicCTI-090921 trial.[63] Table 24 shows the unit costs associated with the occurrence of the different modelled AEs.

Table 24 Adverse event rates and associated costs used in the company model

Event	Unit cost	Unit Cost period	Cost per week	A+nabPx, n (%)	Paclitaxel, n (%)	Docetaxel, n (%)
Anaemia*	£1,748.10	Per month	£402.00	8 (2.0)	2 (3)	-
Bone pain#	£0.00	-	£0.00	2 (0.4)	1 (2)	-
Venous thrombotic event⌂	£288.00	Per episode	£288.00	0 (0.0)	-	7 (3)
Diarrhoea#	£0.00	-	£0.00	6 (1.0)	-	2 (2)
Fatigue*	£932.75	Per month	£215.00	16 (3.4)	23(6)	-
Febrile neutropenia*	£1,612.55	Per month	£371.00	6 (13.0)	30(13)	26 (11)
Allergic reaction⌂	£438.00	Per episode	£438.00	1 (0.2)	9(3)	-
Hypertension⌂	£659.00	Per episode	£659.00	0 (0.0)	12 (4)	-
Infection*	£1,612.55	Per month	£371.00	0 (0.0)	10(3)	-
Leukopenia*	£273.83	Per month	£63.00	8 (2.0)	-	90 (90)
Nausea*	£568.33	Per month	£131.00	4 (-)	1 (2)	-
Peripheral neuropathy*	£874.80	Per month	£201.00	25 (5.5)	72(18)	-
Neutropenia*	£1,222.85	Per month	£281.00	37 (8.2)	4 (6)	138 (42)
Oedema⌂	£544.00	Per episode	£544.00	0 (0.0)	-	4 (4)
Vomiting*	£568.33	Per month	£131.00	2 (0.4)	7(2)	-
Total cost per cycle				**£113.99**	**£210.75**	**£246.10**

*=unit cost obtained from Majethia (2014)[83] are considered to be out of pocket cost and therefore not incurred by the NHS; ⌂=unit cost obtained from NHS reference cost[84]
Source: adapted from CS, Section B3.5.3 (Table 68 and Table 69)

5.4.8 Resources and costs

Drug costs

Confidential PAS discounts are available for both atezolizumab and nab-paclitaxel. However, the PAS discount for nab-paclitaxel is not known to the company. The dosing schedules used in the company model for A+nabPx, paclitaxel and docetaxel are reported in Section 5.4.3 of this report. A+nabPx, paclitaxel and docetaxel are administered via IV infusion. Vial sharing was assumed in the base case analysis. Details of intervention and comparator drug costs, including administration costs, are presented in Section B3.5.2 of the CS and reproduced in Table 25 of this ERG report.

Table 25 Drug acquisition costs (list price) and administration cost used in the company model

Drug	Drug acquisition		Drug administration	
	Vial concentration	Cost per vial (source)	Type of administration	Cost (Source)
A+nabPx: atezolizumab	840mg	[redacted] (proposed list price)	Complex administration cost: complexities associated with administering a combination of atezolizumab and nab-paclitaxel on days 1 and 15	£336.55 (NHS Reference Cost – SB14Z)[84]
A+nabPx: nab-paclitaxel	100mg	£246.00 (BNF)[85]		
Atezolizumab: nab-paclitaxel discontinued	840mg	[redacted] (proposed list price)	Simple administration cost	£228.99 (NHS Reference Cost – SB12Z)[84]
Nab-paclitaxel: atezolizumab discontinued	100mg	£246.00 (BNF)[85]	Simple administration cost	£228.99 (NHS Reference Cost – SB12Z)[84]
Paclitaxel	30mg / 8ml	£3.41 (eMIT 2018[86])	Complex administration cost: pre-medication required and prolonged infusion	£336.55 (NHS Reference Cost – SB14Z)[84]
	100mg / 16.7ml	£7.35 (eMIT 2018)[86]		
	150mg / 25ml	£10.48 (eMIT 2018)[86]		
	300mg / 50ml	£22.82 (eMIT 2018)[86]		
Docetaxel	20mg / 1ml	£5.75 (eMIT 2018)[86]	Simple administration cost	£228.99 (NHS Reference Cost – SB12Z)[84]
	80mg / 4ml	£11.95 (eMIT 2018)[86]		
	160mg / 8ml	£30.82 (eMIT 2018)[86]		

BNF=British National Formulary; eMIT=electronic market information tool; mg=milligram; ml=millilitre; SB12Z=healthcare resource code for deliver simple parenteral chemotherapy at first attendance; SB14Z=healthcare resource code for deliver complex chemotherapy, including prolonged infusional treatment, at first attendance
Source: adapted from CS, Section B3.4.2 (Table 56 and Table 60)

Subsequent treatment costs

A £300 cost was applied weekly to patients in the PD health state to account for subsequent therapy costs. The company states that this approach is consistent with a previous relevant NICE appraisal (palbociclib for previously untreated HER2+ advanced BC [TA495][87]). The company considered it inappropriate to use subsequent therapy data from the IMpassion130 trial because a high proportion of patients in the trial received treatments that are unlicensed, not recommended by NICE, or not generally used in clinical practice in the UK. The company also considered that an explicit modelling of second-, third-, and fourth-line treatments would be complex and result in additional uncertainty.

Resource use by health state

In addition to drug costs, patients in the PFS and PD health states incurred costs of £33.16 and £46.02 per week respectively for routine care (Table 26). Further, a one-off cost of £245.64 was applied in the model when patients entered the first cycle of the PFS and PD health states to account for diagnostic costs (oncologist visit, computed tomography scan and full blood count).

Table 26 Weekly resource use costs used in the company model

Resource	Number required	Duration	Unit cost	Cost per month	Cost per weekly model cycle
Progression-free health state					**£33.16**
Oncologist visit	1 per 6 months	Unknown	£136.25	£22.71	£5.22
General practitioner visit (surgery)	1 per month	9.22 minutes	£37.00	£37.00	£8.51
Clinical nurse specialist	1 per month	1 hour	£74.00	£74.00	£17.02
Community nurse	1 per 4 months	20 minutes	£42.00	£10.50	£2.41
Progressed disease health state					**£46.02**
Oncologist visit	1 per 2 months	Unknown	£136.25	£68.13	£15.67
General practitioner visit (surgery)	1 per month	9.22 minutes	£37.00	£37.00	£8.51
Clinical nurse specialist	1 per month	1 hour	£74.00	£74.00	£17.02
Community nurse	1 per 2 months	20 minutes	£42.00	£21.00	£4.83

Source: adapted from CS, Section B3.4.2 (Table 64 and Table 65)

Other costs

The company states that PD-L1+ status would need to be confirmed before patients were treated with A+nabPx. The cost of a single test is [redacted]. Since only 41% of the randomised participants in the IMpassion130 trial are PD-L1+, the unit cost of the PD-L1 test was re-weighted to 100% (i.e., £295.32) and then applied as a one-off cost in the first cycle to the A+nabPx arm of the model. The company also applied a one-off end of life/terminal care cost of £5,617.85 as patients entered the death health state.

5.4.9 Cost effectiveness results

As part of the clarification process, the ERG asked the company to populate their model with data from the second interim OS analysis (January 2019 data cut) of the IMpassion130 trial (OS, PFS, TTOT and NMA results). The company provided two versions of its model, one using NMA results that had been generated using A+nabPx as the reference treatment (model 1) and the other using nab-paclitaxel as the reference treatment (model 2).

In line with the preference stated by the company in its clarification response, results from model 2 are presented in this report as the base case (referred to as the 'Updated base case').

Updated base case results

Table 27 shows the pairwise base case incremental cost effectiveness ratios (ICERs) per QALY gained for the comparison of treatment with A+nabPx versus paclitaxel and docetaxel. Results have been generated using list prices for all treatments.

Table 28 shows the pairwise cost effectiveness results for the comparison of the cost effectiveness of treatment with A+nabPx versus paclitaxel and docetaxel. The PAS discounted price has been used when costing the treatment with atezolizumab and list prices have been used for nab-paclitaxel, paclitaxel and docetaxel.

Table 27 Base case pairwise incremental cost effectiveness results – with list prices for atezolizumab, nab-paclitaxel, paclitaxel and docetaxel

Treatment	Total cost	Total LYG	Total QALYs	Incremental			Incremental cost per QALY gained (A+nabPx versus comparators)
				Cost	LYG	QALYs	
A+nabPx	[redacted]	2.43	[redacted]				
Paclitaxel	£17,127	1.60	1.06	[redacted]	0.83	[redacted]	[redacted]
Docetaxel	£11,047	1.55	1.02	[redacted]	0.88	[redacted]	[redacted]

LYG=life year gained; QALY=quality adjusted life year
Source: updated company base case model

Table 28 Base case pairwise incremental cost effectiveness results – with PAS prices for atezolizumab and list prices for nab-paclitaxel, paclitaxel and docetaxel

Treatment	Total cost	Total LYG	Total QALYs	Incremental			Incremental cost per QALY gained (A+nabPx versus comparators
				Cost	LYG	QALYs	
A+nabPx	[redacted]	2.43	[redacted]				
Paclitaxel	£17,127	1.60	1.06	[redacted]	0.83	[redacted]	£63,347
Docetaxel	£11,047	1.55	1.02	[redacted]	0.88	[redacted]	£70,217

LYG=life year gained; QALY=quality adjusted life year

5.4.10 Source: Updated company base case model: Sensitivity analyses

Updated deterministic sensitivity analyses

The company states that the choice of parameters included in its one-way sensitivity analyses (OWSAs) was considered a priori. Results from the OWSAs show that PFS and PD health state utility values, discount rate (cost and outcomes) and treatment administration costs have the greatest impact on the magnitude of the cost effectiveness results (see Figure 17 and Figure 18).

[redacted]

Figure 17 Tornado diagram showing OWSA results for the comparison of treatment with A+nabPx versus paclitaxel

Admin=administration; OWSA=one-way sensitivity analysis; PD=progressed disease; PF=progression-free
Source: Updated company base case model

inty
sus
ab,
ER
xel.
sus
stic

ncer
522]
eport
114

Figure 20 Cost effectiveness acceptability curve of treatment with A+nabPx versus paclitaxel and docetaxel at a willingness-to-pay threshold of £100,000 per additional QALY gained

Source: Updated company base case model

5.4.11 Model validation and face validity check

The company states that input from clinical experts was sought during the model development. Additionally, an external consultancy team assessed the model for coding errors and validated the model.

5.5 ERG detailed critique of company economic model

5.5.1 NICE reference case checklist

Table 29 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by NICE	Yes. The company considers people with locally advanced or metastatic, triple negative breast cancer whose tumours have PD-L1 expression ≥1% and have not received prior chemotherapy for metastatic disease
Comparator(s)	As listed in the scope developed by NICE	Partly. The company analyses only include paclitaxel and docetaxel; anthracyclines were not included in the analyses
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Partly. PSS costs were not considered
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on outcomes	Based on systematic review	Partly. Data were primarily taken from the IMpassion130 trial and the company NMAs; the ERG has concerns about the reliability of the results from the company NMAs
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to the NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Partly. PSS costs were not considered
Discounting	The same annual rate for both costs and health effects (3.5%)	Yes

HRQoL=health-related quality of life; NHS=National Health Service; NMA=network meta-analysis; PD-L1=programmed death ligand 1; PSS=personal social services; QALY=quality adjusted life year

5.5.2 Drummond checklist

Table 30 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partly	Effectiveness was only established over the 24-month period for which data from the IMpassion130 trial were available. Lifetime treatment effect - notably OS - was not established
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	No	Costs associated with being in the PFS or PD health states were implausibly low
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

5.6 ERG critique of the company model

The ERG commends the company for producing an MS Excel based model that is easy to understand and accurately represents the model structure described in the CS. The ERG confirms that the company model produces accurate ICERs per QALY gained for the parameter values described in the CS.

The ERG has identified three areas where amendments to the company model will generate more credible cost effectiveness results. The three areas are:

4. Modelling PFS, OS and TTOT for patients treated with paclitaxel or docetaxel using data from the P+nabPx arm of the IMpassion130 trial
5. Increasing the implausibly low health care costs for patients in the PFS and PD health states
6. Introducing a limit to the duration of treatment effect on OS for patients receiving A+nabPx.

5.6.1 Modelling paclitaxel and docetaxel using data from the P+nabPx arm of the IMpassion130 trial

During clarification, the ERG asked the company to re-run their NMAs with P+nabPx as the reference treatment (clarification question A13). The company carried out these analyses. In addition, the company submitted cost effectiveness results using HRs for OS and PFS for paclitaxel and docetaxel from these NMAs and then applied these HRs to the P+nabPx arm of the IMpassion130 trial. The company requested that these cost effectiveness results replace the original results and be considered as the new base case analysis results. Therefore, all of the ERG's changes to the company model are based on the new data submitted by the company during the clarification period.

The results of the NMAs with P+nabPx as the reference treatment provided during clarification (Table 31 and Table 32) do not show any statistically significant evidence (CrIs overlap) to support differences in OS and PFS for patients treated with A+nabPx, paclitaxel or docetaxel compared to P+nabPx.

Table 31 Overall survival hazard ratios by piece from NMA centred on P+nabPx

Treatment	t<5months			5months≤t		
	Hazard ratio (median)	95% lower credible interval	95% upper credible intervals	Hazard ratio (median)	95% lower credible interval	95% upper credible intervals
Paclitaxel	0.63	0.18	2.20	1.33	0.72	2.46
Docetaxel	0.89	0.25	3.14	1.32	0.56	3.00
A+nabPx	0.53	0.26	1.07	0.76	0.50	1.18

Source: company response to LRiG clarification questions, Table 24

Table 32 Progression-free survival hazard ratios by piece from NMA centred on P+nabPx

	0 months ≤t< 2months			2months ≤t< 4months			4months ≤t		
	Hazard ratio (median)	95% lower credible interval	95% upper credible intervals	Hazard ratio (median)	95% lower credible interval	95% upper credible intervals	Hazard ratio (median)	95% lower credible interval	95% upper credible intervals
P	0.56	0.19	1.64	0.95	0.34	2.63	1.35	0.57	2.99
D	0.74	0.21	2.59	0.57	0.14	2.24	2	0.72	5.44
AN	0.59	0.29	1.22	0.57	0.27	1.22	0.72	0.37	1.36

P=paclitaxel; D=docetaxel; AN=A+nabPx
Source: company response to LRiG clarification questions, Table 26

The published evidence describing the efficacy of paclitaxel or docetaxel compared to nab-paclitaxel is limited and can be summarised as follows:

- A phase II trial published in 2017[63] included in the company NMAs found no statistically significant difference in PFS, ORR or OS for nab-paclitaxel (150mg/m^2 3 weeks out of 4 weeks) versus docetaxel (75mg/m^2 once every 3 weeks) as first-line chemotherapy for patients with HER2- mBC.

- A meta-analysis published in 2017[88] that included four RCTs (1506 patients with mBC) found no statistically significant evidence that nab-paclitaxel was more efficacious than paclitaxel or docetaxel in terms of 1 year or 2 year OS (risk ratio at 1 year: 1.00 [95% CI: 0.83 to 1.21]; risk ratio at 2 years 1.04 [95% CI: 0.90 to 1.21]) or ORR (risk ratio: 1.36 [95% CI 0.94 to 1.98]). There was also no evidence that treatment with nab-paclitaxel resulted in statistically significantly different rates of Grade 3 or 4 toxicities compared with treatment with either paclitaxel or docetaxel.

- Real world data[89] from the US that were highlighted in the company submission (CS, p121) suggested that there was no statistically significant difference in time to next treatment (a proxy for PFS) for women with mTNBC treated with nab-paclitaxel or paclitaxel.

Having reviewed the OS and PFS evidence from these three sources,[63,88,89] the ERG considers that there are two reasonable courses of action.

- (i) Consider the results from the company NMAs are robust enough for it to be appropriate to use them to populate the economic model; if so, the CrIs from the NMAs support the available published evidence that OS and PFS for patients treated with nab-paclitaxel, paclitaxel or docetaxel are not statistically significantly different from each other

- (ii) Consider the NMA results to be so uncertain that they should not be used to populate the economic model; if so, the available published evidence suggests OS and PFS for patients treated with nab-paclitaxel, paclitaxel and docetaxel are equivalent.

No matter the option supported, the P+nabPx arm of the Impassion130 trial can be used as the basis for modelling PFS and OS for patients treated with paclitaxel or docetaxel. The ERG considers that this also means that TTOT for patients treated with paclitaxel or docetaxel can be modelled using TTOT data from P+nabPx arm of the IMpassion130 trial, instead of linking TTOT for patients receiving paclitaxel or docetaxel to PFS (the approach used in the company base case analysis). Clinical advice to the ERG is that nab-paclitaxel is less toxic than paclitaxel, which is less toxic than docetaxel. However, in the absence of TTOT data for patients receiving paclitaxel or docetaxel, the ERG has assumed that TTOT is similar for all three treatments. To model OS for patients receiving A+nabPx or P+nabPx, the company approach was to fit a parametric distribution to IMpassion130 trial K-M data. This distribution was used to represent OS for the whole model time horizon. The ERG's preference to modelling survival is, generally, to use K-M data whilst it is robust and then append a distribution to extrapolate past this point. However, in this case, use of the ERG's exploratory survival models made minimal difference to the company's cost effectiveness results. The ERG is, therefore, satisfied that the company's approach of using parametric distributions to represent OS for the whole model time horizon is acceptable.

In choosing distributions to model OS for both A+nabPx and P+nabPx, the company considered the Weibull distribution to be the most suitable. Visual inspection shows that the Weibull distribution chosen by the company closely matches the IMpassion130 trial K-M OS data for both A+nabPx and P+nabPx and does not produce implausibly long survival tails; the ERG is, therefore, satisfied that the company's choice of Weibull distribution is appropriate, whilst noting that all distributions (with the exception of the exponential distribution and, to a lesser extent, the log-normal distribution) are largely indistinguishable in terms of visual fit to the first 20 months of IMpassion130 trial K-M OS data (for A+nabPx see CS, Figure 21 which is reproduced in Figure 21).

Figure 21 Visual fit of OS distributions to second interim K-M OS data (A+nabPx)

Source: CS, Figure 21, p104

The ERG considered that the company approach (predominantly using K-M data and using a distribution when K-M data were essentially censoring events) to modelling PFS and TTOT for patients treated with A+nabPx or P+nabPx was appropriate.

For the comparison of A+nabPx versus paclitaxel, using data from the P+nabPx arm of the IMpassion130 trial to estimate OS, PFS and TTOT for paclitaxel, increases incremental costs by [redacted] and reduces incremental QALY gains by [redacted]; the ICER increases by [redacted] to £83,624 per QALY gained.

For the comparison of A+nabPx versus docetaxel, using data from the P+nabPx arm of the IMpassion130 trial to estimate OS, PFS and TTOT for docetaxel, increases incremental costs by [redacted] and reduces incremental QALY gains by [redacted]; the ICER increases by [redacted] to £96,824 per QALY gained.

Health care costs applied in the PFS and PD health states

In the company model it is assumed that, in the PFS and PD health states, patients have appointments with an oncologist once every 6 months and once every 2 months respectively. Clinical advice to the ERG is that these assumptions are underestimates and that, in the NHS, patients have appointments with an oncologist once a month irrespective of health state. Changing the frequency of oncologist appointments increases the weekly cost of these appointments from £33.16 to £59.28 in the PFS health state and from £46.02 to £61.69 in the PD health state.

For the comparison of A+nabPx versus paclitaxel, applying the ERG's oncologist appointment costs increases incremental costs by £[redacted]; the ICER increases by [redacted] to £64,969 per QALY gained.

For the comparison of A+nabPx versus docetaxel, applying the ERG's oncologist appointment costs increases incremental costs by [redacted]the ICER increases by [redacted] to £71,864 per QALY gained.

Lifetime duration of treatment effect

In the company model, for the entire model time horizon, the mortality rate for patients treated with A+nabPx is lower than the mortality rate for patients treated with docetaxel or paclitaxel. The ERG notes that, in the CS (Table 35, p98), it is stated that a scenario with waning of treatment effect for A+nabPx would be explored 'to acknowledge the uncertainty regarding long term benefit'. However, the company did not present a waning/limited treatment duration scenario. The capability to run waning scenarios has been built into the company model, this allows treatment waning to occur instantaneously at the start of a specific cycle (i.e., the hazard rates for OS become equal for all arms in the model at that time point) or waning to occur between cycles (i.e., the hazard rates for OS become equal for all arms by converging between two not necessarily consecutive cycles).

Limiting the duration of treatment effect for A+nabPx would be in line with the approach supported by the NICE Appraisal Committee (AC) during TA520[81] (Atezolizumab for treating locally advanced or metastatic NSCLC after chemotherapy), although it is noted that in TA520[81] treatment waning was applied at various time points after a 2 year stopping point for treatment had been reached. No stopping rule is considered in the current submission but the ERG notes that in the IMpassion130 trial only [redacted] of patients were still receiving A+nabPx at 2 years. During TA520,[81] the AC reached the conclusion that it was implausible that atezolizumab would deliver a lifetime treatment effect.

With no direct evidence on duration of treatment effect or waning of effect, any point at which OS hazard rates are set to become equal for all treatments is subjective. Further, the company's submitted partitioned survival model can, by design, only assume that the duration of treatment effect is the same for all people regardless of response or duration of treatment itself. In this situation, the ERG considers that scenario analyses with different durations of treatment effect provide a means by which the importance of the company assumption of a lifetime effect can be explored.

Choosing when treatment effect stops or treatment effect waning begins is subjective, the ERG considers that there is likely to be a link between the duration of treatment effect and the percentage of patients who have progressed and/or who are still on treatment. Results from the company model suggest that at 3 years 6.0% of patients in the A+nabPx arm of the model are in the PFS health state, with 3.4% still receiving atezolizumab and 0.8% still receiving nab-paclitaxel. Given the majority of patients in the A+nabPx arm of the model have, therefore, progressed or died and are off initial treatment, the ERG considers that a scenario applying a duration of treatment effect of 3 years is reasonable. However, the ERG has also run a scenario with treatment effect limited to 5 years.

For the comparison of A+nabPx versus paclitaxel, applying a 3 year duration of treatment effect increases the ICER by [redacted] to [redacted] per QALY gained; applying a 5 year duration of treatment effect increases the ICER by [redacted] to £69,444 per QALY gained.

For the comparison of A+nabPx versus docetaxel, applying a 3 year duration of treatment effect increases the ICER by [redacted] to [redacted] per QALY gained; applying a 5 year duration of treatment effect increases the ICER by [redacted] to £76,544 per QALY gained.

5.7 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Using the revised company base case provided at clarification, A+nabPx was estimated to generate an additional [redacted] QALYs at an additional cost of [redacted] compared to paclitaxel, with an ICER of £63,347 per QALY gained.

Using the revised company base case provided at clarification, A+nabPx was estimated to generate an additional [redacted] QALYs at an additional cost of [redacted] compared with docetaxel with an ICER of £70,217 per QALY gained.

The ERG has made three amendments to the company base case:

7. Modelling paclitaxel and docetaxel using OS, PFS and TOTT data from the P+nabPx arm of the IMpassion130 trial
8. Increasing patient health care costs in the PFS and PD health states
9. Introducing a limit to the duration of treatment effect of A+nabPx (3- and 5-year durations).

The ERG's revised ICERs per QALY gained are shown in Table 33 and Table 34.

The ERG presents an alternative scenario: applying the first two amendments only. For the comparison of A+nabPx versus paclitaxel, this alternative scenario increases incremental costs by [redacted] and reduces incremental QALY gains by [redacted]; the ICER increases by [redacted] to

£85,306 per QALY gained. For the comparison of A+nabPx versus docetaxel, this alternative scenario increases incremental costs by [redacted] and reduces incremental QALY gains by [redacted]; the ICER increases by [redacted] to £98,506 per QALY gained.

The ERG also presents the results of the alternative scenario when limits to the duration of treatment effect are applied. For the comparison of A+nabPx versus paclitaxel, using a 3 year duration of treatment effect, the ICER increases by [redacted] to £122,745 per QALY gained; using a 5 year duration of treatment effect, the ICER increases by [redacted] to [redacted]. For the comparison of A+nabPx versus docetaxel, using a 3 year duration of treatment effect, the ICER increases by [redacted] to [redacted] per QALY gained; using a 5 year duration of treatment effect, the ICER increases by [redacted] to £111,297.

No cost effectiveness evidence was presented by the company, or has been generated by the ERG, to compare A+nabPx to anthracyclines.

Details of all Microsoft Excel revisions carried out by the ERG to the company model are provided in Appendix 5.

Table 33 ERG adjustments to company base case: A+nabPx versus paclitaxel (confidential PAS for atezolizumab)

Scenario/ERG amendment	A+nabPx			Paclitaxel			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	***2.433***	***£17,127***	***1.060***	***1.600***	[redacted]	[redacted]	***0.833***	***£63,347***	
R1) Use of P+nabPx arm for OS, PFS and TTOT estimation for paclitaxel	[redacted]	[redacted]	2.433	£16,619	1.181	1.797	[redacted]	[redacted]	0.636	£83,624	+£20,277
R2) Revised PFS and PD health state costs	[redacted]	[redacted]	2.433	£18,700	1.060	1.600	[redacted]	[redacted]	0.833	£64,969	+£1,622
R3) 3-year duration of treatment effect	[redacted]	[redacted]	2.201	£17,127	1.060	1.600	[redacted]	[redacted]	0.601	£82,686	+£19,339
R4) 5-year duration of treatment effect	[redacted]	[redacted]	2.341	£17,127	1.060	1.600	[redacted]	[redacted]	0.741	£69,444	+£6,097
B. ERG alternative scenario (R1-R2)	[redacted]	[redacted]	**2.433**	**£18,369**	**1.181**	**1.797**	[redacted]	[redacted]	**0.636**	**£85,306**	**+£21,959**
C. ERG alternative scenario (B) plus 3-year duration of treatment effect	[redacted]	[redacted]	**2.201**	**£18,369**	**1.181**	**1.797**	[redacted]	[redacted]	**0.404**	**£122,745**	**+£59,398**
D. ERG alternative scenario (B) plus 5-year duration of treatment effect	[redacted]	[redacted]	**2.341**	**£18,369**	**1.181**	**1.797**	[redacted]	[redacted]	**0.544**	**£96,298**	**+£32,951**

ICER=incremental cost-effectiveness ratio; OS=overall survival; PFS=progression-free survival; PD=progressed disease; TTOT=time to off treatment; QALY=quality adjusted life year

Table 34 ERG adjustments to company base case: A+nabPx versus docetaxel (confidential PAS for atezolizumab)

Scenario/ERG amendment	A+nabPx			Docetaxel			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	***2.433***	***£17,127***	***1.025***	***1.551***	[redacted]	[redacted]	***0.882***	***£70,217***	
R1) Use of P+nabPx arm for OS, PFS and TTOT estimation for docetaxel	[redacted]	[redacted]	2.433	£11,288	1.181	1.797	[redacted]	[redacted]	0.636	£96,824	+£26,607
R2) Revised PFS and PD health state costs	[redacted]	[redacted]	2.433	£12,553	1.025	1.551	[redacted]	[redacted]	0.882	£71,864	+£1,647
R3) 3-year duration of treatment effect	[redacted]	[redacted]	2.201	£17,127	1.025	1.551	[redacted]	[redacted]	0.649	£90,015	+£19,798
R4) 5-year duration of treatment effect	[redacted]	[redacted]	2.341	£17,127	1.025	1.551	[redacted]	[redacted]	0.789	£76,544	+£6,327
B. ERG alternative scenario (R1-R2)	[redacted]	[redacted]	**2.433**	**£13,037**	**1.181**	**1.797**	[redacted]	[redacted]	**0.636**	**£98,506**	**+£28,289**
C. ERG alternative scenario (B) plus 3-year duration of treatment effect	[redacted]	[redacted]	**2.201**	**£13,037**	**1.181**	**1.797**	[redacted]	[redacted]	**0.404**	**£142,072**	**+£71,855**
D. ERG alternative scenario (B) plus 5-year duration of treatment effect	[redacted]	[redacted]	**2.341**	**£13,037**	**1.181**	**1.797**	[redacted]	[redacted]	**0.544**	**£111,297**	**+£41,080**

ICER=incremental cost-effectiveness ratio; OS=overall survival; PFS=progression-free survival; PD=progressed disease; TTOT=time to off treatment; QALY=quality adjusted life year

5.8 Conclusions of the cost effectiveness section

The company's cost effectiveness results show that, at a willingness to pay threshold of £50,000 per QALY gained, treatment with A+nabPx versus both paclitaxel and docetaxel is not cost effective. The ERG's revised ICERs per QALY gained are also above this threshold.

Details of ICERs using the PAS price of nab-paclitaxel are provided in a confidential appendix. The appraisal can only assess drugs that are currently available for use by the NHS. It is unknown when, or if, the generic form of paclitaxel will become available for use in the NHS. Furthermore, if it does become available, the impact on the PAS or list price of nab-paclitaxel, is unknown.

6 END OF LIFE CRITERIA

A technology meets NICE End of Life criteria[80] if (i) life expectancy with standard of care treatments for the target population is under 24 months and (ii) the increase in life expectancy with the technology being appraised is at least 3 months.

In the CS (Table 33, p85) the company puts forward a case that, for the population under consideration, treatment with A+nabPx meets NICE End of Life criteria.[80] The estimates generated by the company model are that median life expectancy is 13.8 months for patients treated with paclitaxel and 14.3 months for patients treated with docetaxel. Results from the company model also show that, compared to treatment with paclitaxel and docetaxel, treatment with A+nabPx offers a median extension to life of 12.6 months and 11.6 months respectively.

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

When the duration of effect of treatment with A+nabPx is limited to 3 years, results from the amended company model predicts a gain, compared with treatment with paclitaxel or docetaxel, in median OS for patients treated with A+nabPx of 5.3 months and a gain in mean OS of 4.8 months.

The ERG is, therefore, satisfied that A+nabPx meets both components of the NICE End of Life criteria[80] for the population under consideration when compared with treatment with either paclitaxel or docetaxel.

7 REFERENCES

1. Roche UK. Atezolizumab (Tecentriq®) in combination with nab-paclitaxel for untreated, locally advanced or metastatic, triple negative, PD-L1- positive breast cancer. Company submission to NICE. 2019.
2. National Institute for Health and Care Excellence (NICE). Atezolizumab for untreated, locally advanced or metastatic, triple negative, PD-L1 positive breast cancer [ID1522]: Final scope. 2019; Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10433/documents. Accessed April 2019.
3. Roche UK. Atezolizumab (Tecentriq®) in combination with nab-paclitaxel for untreated, locally advanced or metastatic, triple negative, PD-L1–positive breast cancer [ID1522]: Company budget impact analysis submission. 2019.
4. Sharma GN, Dave R, Sanadya J, Sharma P, Sharma KK. Varous types and management of breast cancer: an overview. J Adv Pharm Technol Res. 2010; 1:109-26.
5. Cancer Research UK. Symptoms of advanced breast cancer. CRUK; 2017; Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/advanced/symptoms?_ga=2.102484097.1886212571.1556015338-1721115417.1553768149. Accessed April 2019.
6. Waks AG, Winer EP. Breast Cancer Treatment: A Review. JAMA. 2019; 321:288-300.
7. Lebert JM, Lester R, Powell E, Seal M, McCarthy J. Advances in the systemic treatment of triple-negative breast cancer. Curr Oncol. 2018; 25:S142-50.
8. Lee A, Djamgoz MBA. Triple negative breast cancer: Emerging therapeutic modalities and novel combination therapies. Cancer Treat Rev. 2018; 62:110-22.
9. Office for National Statistics. Cancer registration statistics, England: first release, 2016. 2018; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2016. Accessed April 2019.
10. Cancer Research UK. Breast cancer statistics. 2018; Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer. Accessed April 2019.
11. Stover D, Bell CF, Tolaney SM. Neoadjuvant and adjuvant chemotherapy considerations for triple-negative breast cancer. Am J Hematol Oncol. 2016; 12:6-12.
12. Cancer Research UK. Breast cancer incidence (invasive) statistics. 2018; Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive#heading-Three. Accessed April 2019.
13. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H*, et al.* Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med. 2018; 379:2108-21.
14. Yardley DA, Coleman R, Conte P, Cortes J, Brufsky A, Shtivelband M*, et al.* nab-Paclitaxel plus carboplatin or gemcitabine versus gemcitabine plus carboplatin as first-line treatment of patients with triple-negative metastatic breast cancer: results from the tnAcity trial. Ann Oncol. 2018; 29:1763-70.
15. Delaloge S, Ezzalfani M, Dieras V, Bachelot TD, Debled M, Jacot W. Evolution of overall survival according to year of diagnosis (2008-2014) and subtypes, among

16703 metastatic breast cancer (MBC) patients included in the real-life "ESME" cohort. J Clin Oncol. 2017; 35:1078.
16. Roche UK. Data on File. Clinical Expert Opinion. 2019.
17. Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, Andre F, *et al.* 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). Ann Oncol. 2018; 29:1634-57.
18. National Institute for Health and Care Excellence (NICE). Advanced breast cancer: diagnosis and treatment: CG81. NICE; 2009; Available from: https://www.nice.org.uk/guidance/cg81 Accessed April 2019.
19. National Institute for Health and Care Excellence (NICE). Managing advanced breast cancer. NICE; 2018; Available from: https://pathways.nice.org.uk/pathways/advanced-breast-cancer#path=view%3A/pathways/advanced-breast-cancer/managing-advanced-breast-cancer.xml&content=view-node%3Anodes-triple-negative-disease Accessed April 2019.
20. Chiu MKL, Miles D, Samani A, Swinton M, Makris A. NICE chemotherapy guidelines in advanced breast cancer (ABC) in practice: experience of Mount Vernon Cancer Centre. Clin Oncol. 2015; 27:e10-1.
21. Battisti NML, Okonji D, Manickavasagar T, Mohammed K, Allen M, Ring A. Outcomes of systemic therapy for advanced triple-negative breast cancer: A single centre experience. Breast. 2018; 40:60-6.
22. Sparano JA, Wang M, Martino S, Jones V, Perez EA, Saphner T, *et al.* Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med. 2008; 358:1663-71.
23. Hanauske AR, Degen D, Hilsenbeck SG, Bissery MC, Von Hoff DD. Effects of taxotere and taxol on in vitro colony formation of freshly explanted human tumor cells. Anti-Cancer Drugs. 1992; 3:121-4.
24. Untch M, Untch A, Sevin BU, Angioli R, Perras JP, Koechli O. Comparison of paclitaxel and docetaxel (Taxotere) in gynecologic and breast cancer cell lines with the ATP-cell viability assay. Anti-Cancer Drugs. 1994; 5:24-30.
25. Valero V, Jones SE, Von Hoff DD, Booser DJ, Mennel RG, Ravdin PM. A phase II study of docetaxel in patients with paclitaxel-resistant metastatic breast cancer. J Clin Oncol. 1998; 16:3362-8.
26. European Commission. European Cancer Information System. Measuring cancer burden and its time trends across Europe. 2018; Available from: https://ecis.jrc.ec.europa.eu/. Accessed April 2019.
27. Office for National Statistics. Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2017. 2018; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2017. Accessed April 2019.
28. Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, *et al.* Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014; 515:563-7.
29. Mittendorf EA, Philips AV, Meric-Bernstam F, Qiao N, Wu Y, Harrington S, *et al.* PD-L1 expression in triple-negative breast cancer. Cancer Immunol Res. 2014; 2:361-70.
30. Emens LA, Loi S, Rugo HS, Schneeweiss A, Diéras V, Iwata H, *et al.* IMpassion130: Efficacy in immune biomarker subgroups from the global, randomized, double-blind, placebo- controlled, Phase III study of atezolizumab + nab-paclitaxel in patients with treatment-naive, locally advanced or metastatic triple-negative breast cancer. San Antonio Breast Cancer Symposium; 4th-8th December 2018.
31. Emens LA, Cruz C, Eder JP, Braiteh F, Chung C, Tolaney SM, *et al.* Long-term clinical outcomes and biomarker analyses of atezolizumab therapy for patients with

metastatic triple-negative breast cancer: A Phase 1 study. JAMA Oncol. 2019; 5:74-82.
32. Shah NJ, Kelly WJ, Liu SV, Choquette K, Spira A. Product review on the Anti-PD-L1 antibody atezolizumab. Hum Vaccin Immunother. 2018; 14:269-76.
33. Muenst S, Schaerli AR, Gao F, Daster S, Trella E, Droeser RA*, et al.* Expression of programmed death ligand 1 (PD-L1) is associated with poor prognosis in human breast cancer. Breast Cancer Res Treat. 2014; 146:15-24.
34. Adams S, Diamond JR, Hamilton E, Pohlmann PR, Tolaney SM, Chang CW*, et al.* Atezolizumab plus nab-paclitaxel in the treatment of metastatic triple-negative breast cancer with 2-year survival follow-up: A Phase 1b clinical trial. JAMA Oncol. 2018.
35. Denkert C, von Minckwitz G, Brase JC, Sinn BV, Gade S, Kronenwett R*, et al.* Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. J Clin Oncol. 2015; 33:983-91.
36. Schiff PB, Fant J, Horwitz SB. Promotion of microtubule assembly in vitro by taxol. Nature (London). 1979; 277:665-7.
37. Long BH, Fairchild CR. Paclitaxel inhibits progression of mitotic cells to G1 phase by interference with spindle formation without affecting other microtubule functions during anaphase and telephase. Cancer Res. 1994; 54:4355-61.
38. Yardley DA. nab-Paclitaxel mechanisms of action and delivery. J Control Release. 2013; 170:365-72.
39. Joerger M. Prevention and handling of acute allergic and infusion reactions in oncology. Ann Oncol. 2012; 23:x313-x9.
40. US National Library of Medicine. A study of atezolizumab and paclitaxel versus placebo and paclitaxel in participants with previously untreated locally advanced or metastatic triple negative breast cancer (TNBC) (IMpassion131). 2019; Available from: https://clinicaltrials.gov/ct2/show/NCT03125902 [accessed April 2019]. Accessed.
41. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions Version 5.1.0 [updated March 2011]. . The Cochrane Collaboration; 2011; Available from: www.handbook.cochrane.org. Accessed April 2019.
42. F. Hoffmann-La Roche Ltd. Primary CSR: Study WO29522 (IMpassion130). 2018.
43. F. Hoffmann-La Roche Ltd. Statistical Analysis Plan: Study WO29522 (IMpassion130).
44. F. Hoffmann-La Roche Ltd. Protocol: Study WO29522 (IMpassion130). 2018.
45. Demets DL, Lan KG. Interim analysis: the alpha spending function approach. Stat Med. 1994; 13:1341-52.
46. Collett D. Modelling survival data in medical research. Texts in Statistical Science. Second ed. Florida, USA: Chapman & Hall; 2003.
47. Schmid P, Abraham J, Chan S, Wheatly D, Brunt M, Nemsadze G. AZD5363 plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (PAKT): A randomised, double-blind, placebo-controlled, phase II trial. J Clin Oncol. 2018; 36:Suppl Abstract 1007.
48. EuroQoL Research Foundation. EQ-5D-5L. 2019; Available from: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/. Accessed May 2019.
49. EORTC. EORTC QLQ-C30 Available from: https://qol.eortc.org/questionnaire/eortc-qlq-c30/. Accessed May 2019.
50. EORTC. QLQ-BR23 Breast. Available from: https://qol.eortc.org/questionnaire/qlq-br23/. Accessed May 2019.
51. EuroQol Research Foundation. EQ-5D-3L. 2019; Available from: https://euroqol.org/eq-5d-instruments/eq-5d-3l-available-modes-of-administration/. Accessed 2019 May.
52. Flatiron. Flatiron. 2019; Available from: https://flatiron.com/about-us/. Accessed May 2019.

53. Miles DW, Chan A, Dirix LY, Cortes J, Pivot X, Tomczak P*, et al.* Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol. 2010; 28:3239-47.
54. Pivot X, Schneeweiss A, Verma S, Thomssen C, Passos-Coelho JL, Benedetti G*, et al.* Efficacy and safety of bevacizumab in combination with docetaxel for the first-line treatment of elderly patients with locally recurrent or metastatic breast cancer: results from AVADO. Eur J Cancer. 2011; 47:2387-95.
55. Rugo HS, Barry WT, Moreno-Aspitia A, Lyss AP, Cirrincione C, Leung E*, et al.* Randomized Phase III trial of paclitaxel once per week compared with nanoparticle albumin-bound nab-paclitaxel once per week or ixabepilone with bevacizumab as first-line chemotherapy for locally recurrent or metastatic breast cancer: CALGB 40502/NCCTG N063H (Alliance). J Clin Oncol. 2015; 33:2361-9.
56. Rugo HS BW, Moreno-Aspitia A, Lyss A, Huebner L, Mayer EL, Naughton M, Layman RM, Carey LA, Somer RA, Toppmeyer D, Velasco M, Perez EA, Hudis CA, Winer E. Long-term follow-up of CALGB 40502/NCCTG N063H (Alliance): a randomized phase III trial of weekly paclitaxel (P) compared to weekly nanoparticle albumin bound nab-Paclitaxel (NP) or ixabepilone (Ix) +/- bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer (MBC). Cancer research Conference: San Antonio Breast Cancer Symposium, SABCS. 2017; 78.
57. Welt A, Marschner N, Lerchenmueller C, Decker T, Steffens CC, Koehler A*, et al.* Capecitabine and bevacizumab with or without vinorelbine in first-line treatment of HER2/neu-negative metastatic or locally advanced breast cancer: final efficacy and safety data of the randomised, open-label superiority phase 3 CARIN trial. Breast Cancer Res Treat. 2016; 156:97-107.
58. Brufsky A, Miles D, Zvirbule Z, Eniu A, Lopez-Miranda E, Seo J*, et al.* Abstract P5-21-01: Cobimetinib combined with paclitaxel as first-line treatment for patients with advanced triple-negative breast cancer (COLET study): Primary analysis of cohort I. Cancer Res. 2018; 78:P5-21-01.
59. Gray R, Bhattacharya S, Bowden C, Miller K, Comis RL. Independent review of E2100: a phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer. J Clin Oncol. 2009; 27:4966-72.
60. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA*, et al.* Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 2007; 357:2666-76.
61. Finn RS, Press MF, Dering J, Arbushites M, Koehler M, Oliva C*, et al.* Estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (HER2), and epidermal growth factor receptor expression and benefit from lapatinib in a randomized trial of paclitaxel with lapatinib or placebo as first-line treatment in HER2-negative or unknown metastatic breast cancer. J Clin Oncol. 2009; 27:3908-15.
62. Di Leo A, Gomez HL, Aziz Z, Zvirbule Z, Bines J, Arbushites MC*, et al.* Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. J Clin Oncol. 2008; 26:5544-52.
63. Tamura K, Inoue K, Masuda N, Takao S, Kashiwaba M, Tokuda Y*, et al.* Randomized phase II study of nab-paclitaxel as first-line chemotherapy in patients with HER2-negative metastatic breast cancer. Cancer Sci. 2017; 108:987-94.
64. Kim S-B, Dent R, Im S-A, Espié M, Blau S, Tan AR*, et al.* Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet Oncology. 2017; 18:1360-72.
65. Dent R, Schmid P, Cortes J, Kim SB, Andre F, Abramson V*, et al.* Overall survival (OS) update of the double-blind placebo (PBO)-controlled randomized phase 2 LOTUS trial of first-line ipatasertib (IPAT) + paclitaxel (PAC) for locally

advanced/metastatic triple-negative breast cancer (mTNBC). J Clin Oncol. 2018; 36:Suppl. 1008.
66. Masuda N, Takahashi M, Nakagami K, Okumura Y, Nakayama T, Sato N*, et al.* First-line bevacizumab plus paclitaxel in Japanese patients with HER2-negative metastatic breast cancer: subgroup results from the randomized Phase III MERiDiAN trial. Jpn J Clin Oncol. 2017; 47:385-92.
67. Miles D, Cameron D, Bondarenko I, Manzyuk L, Alcedo JC, Lopez RI*, et al.* Bevacizumab plus paclitaxel versus placebo plus paclitaxel as first-line therapy for HER2-negative metastatic breast cancer (MERiDiAN): A double-blind placebo-controlled randomised phase III trial with prospective biomarker evaluation. Eur J Cancer. 2017; 70:146-55.
68. Miles D, Cameron D, Hilton M, Garcia J, O'Shaughnessy J. Overall survival in MERiDiAN, a double-blind placebo-controlled randomised phase III trial evaluating first-line bevacizumab plus paclitaxel for HER2-negative metastatic breast cancer. Eur J Cancer. 2018; 90:153-5.
69. Robert NJ, Dieras V, Glaspy J, Brufsky AM, Bondarenko I, Lipatov ON*, et al.* RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol. 2011; 29:1252-60.
70. Tovey H, Bliss J, Tutt A, Morden J, Jarman K, Martin S*, et al.* Managing non-proportionality of hazards (PH) within TNT: a randomised phase III trial of carboplatin compared to docetaxel for patients with metastatic or recurrent locally advanced triple negative (TN) or brca1/2 breast cancer (BC). Trials. 2015; 16.
71. Tutt A, Cheang MCU, Kilburn L, Tovey H, Gillett C, Pinder S*, et al.* Abstract S6-01:BRCA1methylation status, silencing and treatment effect in the TNT trial: A randomized phase III trial of carboplatin compared with docetaxel for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer (CRUK/07/012). Cancer Res. 2017; 77:S6-01.
72. Tutt A, Ellis P, Kilburn L, Gilett C, Pinder S, Abraham J*, et al.* Abstract S3-01: The TNT trial: A randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative orBRCA1/2breast cancer (CRUK/07/012). Cancer Res. 2015; 75:S3-01-S3-.
73. Tutt A, Tovey H, Cheang MCU, Kernaghan S, Kilburn L, Gazinska P*, et al.* Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. Nat Med. 2018; 24:628-37.
74. Brodowicz T, Lang I, Kahan Z, Greil R, Beslija S, Stemmer SM*, et al.* Selecting first-line bevacizumab-containing therapy for advanced breast cancer: TURANDOT risk factor analyses. Br J Cancer. 2014; 111:2051-7.
75. Lang I, Brodowicz T, Ryvo L, Kahan Z, Greil R, Beslija S*, et al.* Bevacizumab plus paclitaxel versus bevacizumab plus capecitabine as first-line treatment for HER2-negative metastatic breast cancer: interim efficacy results of the randomised, open-label, non-inferiority, phase 3 TURANDOT trial. The Lancet Oncology. 2013; 14:125-33.
76. Lang I, Inbar MJ, Kahan Z, Greil R, Beslija S, Stemmer SM*, et al.* Safety results from a phase III study (TURANDOT trial by CECOG) of first-line bevacizumab in combination with capecitabine or paclitaxel for HER-2-negative locally recurrent or metastatic breast cancer. Eur J Cancer. 2012; 48:3140-9.
77. Zielinski C, Láng I, Inbar M, Kahán Z, Greil R, Beslija S*, et al.* Bevacizumab plus paclitaxel versus bevacizumab plus capecitabine as first-line treatment for HER2-negative metastatic breast cancer (TURANDOT): primary endpoint results of a randomised, open-label, non-inferiority, phase 3 trial. The Lancet Oncology. 2016; 17:1230-9.

78. Phillippo D, Ades T, Dias S, Palmer S, Abrams KR, Welton N. NICE DSU technical support document 18: methods for population-adjusted indirect comparisons in submissions to NICE. 2016.
79. Datapharm Communications Limited. electronic Medicines Compendium (eMC): SmPC-docetaxel. Datapharm; 2018; SmPC]. Available from: https://www.medicines.org.uk/emc/product/7206/smpc. Accessed 2019 09 May.
80. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. Process and methods [PMG9]. Published date: April 2013 2013; Available from: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case. Accessed 2019 09 May.
81. National Institute for Health and Excellence (NICE). Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy. Technology appraisal guidance [TA520] NICE; 2018; Available from: https://www.nice.org.uk/guidance/ta520/. Accessed May 2019.
82. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D*, et al.* Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012; 15:708-15.
83. Majethia U, Tremblay G, He YP, Faria C, McCutcheon S, Kopenhafer L*, et al.* Economic Burden of Chemotherapy Related Toxicities in Third Line Metastatic Breast Cancer Patients. Value Health. 2014; 17:A628.
84. Department of Health. National schedule of reference costs 2017/18. 2018; Available from: https://improvement.nhs.uk/documents/1973/2_-_National_schedule_of_reference_costs_v2.xlsx. Accessed May 2019.
85. British National Formulary (BNF). British National Formulary 2019. 2019; Available from: https://www.medicinescomplete.com/mc/bnf/current/. Accessed May 2019.
86. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). 2018; Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/773877/emit-national-database-june-2018.xlsx. Accessed 2019 08 May.
87. National Institute for Health and Care Excellence (NICE). Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer: TA495. 2017; Available from: https://www.nice.org.uk/guidance/ta495/history Accessed May 2019.
88. Liu Y, Ye G, Yan D, Zhang L, Fan F, Feng J. Role of nab-paclitaxel in metastatic breast cancer: a meta-analysis of randomized clinical trials. Oncotarget. 2017; 8:72950-58.
89. Luhn P, Chui S, Hsieh A, Yi J, Mecke A, Bajaj P*, et al.* Comparative effectiveness of nab-paclitaxel vs paclitaxel as first-line treatment of triple-negative breast cancer in US clinical practice. European Society for Medical Oncology; 2018 19th to 23rd October; Munich.
90. Welton NJ, Sutton AJ, Cooper N, Ades A, Abrams KR. Evidence synthesis for decision making in healthcare: John Wiley & Sons; 2012.
91. Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JP. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Stat Med. 2015; 34:984-98.

8 APPENDICES

8.1 Appendix 1 ERG assessment of the proportional hazards assumption for data from the IMpassion130 trial

The validity of the PH assumption within a trial is best assessed by considering the H-H plot which shows the relationship between the cumulative hazard for each trial event at common time points in the two trial arms. For the PH assumption to be valid, two criteria must be met:

- the data should follow a straight line trend, with individual data points randomly distributed close to and on either side of the trend line
- the linear trend line should pass through the graph origin (zero value on both axes).

As part of the ERG's clarification letter to the company, the ERG requested K-M data for the outcomes of investigator-assessed PFS and OS to inform the ERG's critique of the company's economic model. The ERG also used this K-M data to assess the validity of the PH assumption for these outcomes.

8.1.1 Progression-free survival by investigator assessment

The H-H plot for PFS by investigator assessment from the IMpassion130 trial (second interim OS analysis, PD-L1+ patient population) is provided in

Figure 22. The data are distributed fairly evenly about the linear trend line, and the estimated constant (-0.08) of the linear model is close to zero (95% CI: -0.11 to -0.06). The ERG therefore considers that the PH assumption holds for PFS by investigator assessment in the IMpassion130 trial.

Figure 22 H-H plot for investigator-assessed PFS data from the IMpassion130 trial (second interim OS analysis, PD-L1+ patient population)

A+nabPx=atezolizumab+nab-paclitaxel; OS=overall survival; PD-L1+=programmed death-ligand 1-positive; PFS=progression-free survival; P+nabPx=placebo+nab-paclitaxel

8.1.2 Overall survival

The H-H plot for OS from the IMpassion130 trial (second interim OS analysis, PD-L1+ patient population) is provided in

Figure 22. The data are distributed fairly evenly about the linear trend line, and the estimated constant (-0.02) of the linear model is close to zero (95% CI: -0.03 to 0.00). The ERG therefore considers that the PH assumption holds for OS in the IMpassion130 trial.

Figure 23 H-H plot for OS data from the IMpassion130 trial (second interim OS analysis, PD-L1+ patient population)

A+nabPx=atezolizumab+nab-paclitaxel; OS=overall survival; PD-L1+=programmed death-ligand 1-positive; P+nabPx=placebo+nab-paclitaxel

8.2 Appendix 2: Discrete time models: model selection methods and results

8.2.1 Discrete time models: model selection methods

The company considered piecewise exponential models with one cut-point at 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months, and two cut-points at all combinations of 2, 3, 4, 5 months and 7, 8, 9, 10, 11, 12 months. The company also considered fractional polynomial models, including a zero order model without any time dependent effect (exponential model), first order models with powers 0 (Weibull) and 1 (Gompertz) and second order models with powers (0, 0), (0, 1) and (1, 1).

All discrete time models were firstly estimated in a frequentist NMA framework. This allowed the company to simply assess model fit, using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), for a range of different models. The best fitting models were then assessed based on visual fit to the observed data and validity of extrapolations. Finally, the company estimated the best fitting model(s) from the previous stage in a Bayesian framework, examined Bayesian model diagnostics, and compared fixed and random effects models. The company examined the deviance information criterion in order to determine whether a fixed or random effects model would be used as the base case model. Differences in the deviance information criterion of 5 or more were considered indicative of a better model fit.[90] If differences in the deviation information criterion were less than 5, the company selected the random effects model to be the base case model, as the company considered the assumption of identical treatment effects across studies that compared the same treatments to be unrealistic.

In all Bayesian analyses, non-informative priors were used for the study baseline (μ) and treatment effect parameters (d) (Table 35). Informative priors proposed by Turner et al[91] were used in the random effects models to address between-study heterogeneity (Table 36).

Table 35 Non-informative priors used in all Bayesian analyses

Model	Prior (normal distribution parametrised with mean and precision)
Discrete time piecewise exponential	$\mu_k \sim dnorm(0, 0.0001)$ …piece k $d_k \sim dnorm(0, 0.0001)$ … piece k
Fractional polynomials	$\begin{pmatrix}\mu_1\\ \mu_2\\ \mu_3\end{pmatrix} \sim dmnorm(\mathrm{M}, \Sigma)$ $\begin{pmatrix}d_1\\ d_2\\ d_3\end{pmatrix} \sim dmnorm(\mathrm{M}, \Sigma)$ $\mathrm{M} \sim \begin{matrix}0\\0\\0\end{matrix}$ $\Sigma \sim \begin{matrix}0.0001 & 0 & 0\\ 0 & 0.0001 & 0\\ 0 & 0 & 0.0001\end{matrix}$

Source: adapted from CS Appendix D, Table 11

Table 36 Informative priors for between study heterogeneity

Endpoint	Base case	Sensitivity analyses
OS	$\tau^2 \sim dlnorm(-4.18, 1.41^{-2})$	$\tau^2 \sim dlnorm(-4.18, 1.8^{-2})$ Log-normal with same median as main prior but 2x larger upper 95% quantile
PFS	$\tau^2 \sim dlnorm(-2.94, 1.79^{-2})$	$\tau^2 \sim dlnorm(-2.94, 2.2^{-2})$ Log-normal with same median as main prior but 2x larger than the upper 95% quantile.

OS=overall survival; PFS=progression-free survival
Source: CS, Table 10

8.2.2 Discrete time models: model selection results

For OS, the five best fitting candidate models based primarily on AIC were: one first order fractional polynomial model; two second order fractional polynomial models; and two piecewise exponential models, one with a cut-point of 5 months and one with cut-points at 3 and 6 months (Table 19 of the company's response to the ERG clarification letter). Based on visual fit to the observed data and 5-year extrapolations (based on 12-month data), the second order fractional polynomial models were excluded due to poor fit to the tails of the observed data and high plateaus. The remaining three models demonstrated a better fit to the tails of the observed data and showed clear convergence towards zero in the IMpassion130 trial over a 5-year horizon.

The company next considered Bayesian model diagnostic plots; the piecewise exponential model with a cut-point at 5 months showed the most stable running means of study baselines and treatment effects, converged appropriately, and was consequently chosen as the base case model for OS.

For PFS, the five best fitting candidate models based primarily on AIC were: three second order fractional polynomial models; one first order fractional polynomial model; and one piecewise exponential model with cut-points at 2 and 4 months (Table 20 of the company's response to the ERG clarification letter). Based on visual fit to the observed data and 5-year extrapolations (based on 12-month data), the three second order fractional polynomial models were rejected due to poor fit to the tails of the observed data and high plateaus. The remaining two models fit the tails of the observed data well and showed clear convergence towards zero in the IMpassion130 trial over a 5-year horizon.

The company deemed the piecewise exponential model with cut-points at 2 and 4 months to be the most suitable model for PFS based on Bayesian model diagnostic plots; this model converged well and there were no issues of correlation between iterations (this was a problem for the first order fractional polynomial model).

In their response to the ERG clarification letter (Table 21), the company states that the models fitted for OS and PFS were random effects models, which were chosen after comparing the goodness of fit of fixed and random effects models.

8.3 Appendix 3: Characteristics of trials included in the NMAs

Table 37 Key characteristics of trials included in the NMAs

Study	Design	Location	Inclusion criteria	Treatment arms
AVADO[53]	Phase III, double-blind RCT	International (24 countries)	HER2- LR or MBC Age ≥18 years ECOG PS 0 or 1 Previous chemotherapy for LR or metastatic disease not permitted	Docetaxel, 100 mg/m^2 on day 1 3-week cycles
				Docetaxel, 100 mg/m^2 on day 1 Bevacizumab, 7.5 mg/kg on day 1 3-week cycles
				Docetaxel, 100 mg/m^2 on day 1 Bevacizumab, 15.0 mg/kg on day 1 3-week cycles
CALGB40502[55]	Phase III, open-label RCT	USA	Stage IV or IIIC BC not amenable to local therapy Age ≥18 years ECOG PS 0 or 1 No prior chemotherapy for metastatic disease or prior treatment with bevacizumab was allowed	Paclitaxel, 90/m^2 on days 1, 8 and 15 Bevacizumab, 10mg/kg on days 1 and 15 28-day cycles
				Nab-paclitaxel, 1500/m^2 on days 1, 8 and 15 Bevacizumab, 10mg/kg on days 1 and 15 28-day cycles
				Ixabepilone, 16/m^2 on days 1, 8 and 15 Bevacizumab, 10mg/kg on days 1 and 15 28-day cycles
E2100[60]	Phase III, open-label RCT	US and Canada	MBC Females Age ≥18 years ECOG PS 0 or 1 No prior cytotoxic therapy for MBC	Paclitaxel, 90/m^2 on days 1, 8 and 15 Bevacizumab, 10mg/kg on days 1 and 15 28-day cycles
				Paclitaxel, 90mg/m^2 on day 1, 8 and 15 28-day cycles
IMpassion130	Phase III, double-blind RCT	International (41 countries)	LA or metastatic TNBC Age ≥18 years ECOG PS 0 or 1 No prior chemotherapy or prior targeted systemic therapy for inoperable LA or metastatic TNBC	Nab-paclitaxel 100 mg/m^2 (IV) on days 1, 8 and 15 Atezolizumab, 840 mg (IV) on days 1 and 15 28 day cycles
				Nab-paclitaxel 100 mg/m^2 (IV) on days 1, 8 and 15 28 day cycles
MERiDiAN[67]			HER2- LR or MBC	Paclitaxel, 90/m^2 on days 1, 8 and 15

Study	Design	Location	Inclusion criteria	Treatment arms
	Phase III, double-blind RCT	International (USA, Russian, Europe and South America)	Age ≥18 years ECOG PS ≤2 No previous chemotherapy for LR or metastatic disease permitted	28-day cycles
				Paclitaxel, 90/m^2 on days 1, 8 and 15 Bevacizumab, 10mg/kg on days 1 and 15 28-day cycles
RIBBON-1[69]	Phase III, double-blind RCT	International (22 countries)	LR or MBC Age ≥18 years ECOG PS 0 or 1 Previous chemotherapy for LR or metastatic disease not permitted	Capecitabine, 1000 mg/m2 bd on days 1 and 14 21-day cycle
				Capecitabine, 1000 mg/m2 bd on days 1 and 14 Bevacizumab, 15mg/kg (IV) once every cycle 21-day cycle
TNT[73]	Phase III, open-label RCT	UK	TNBC or BRCA1 or BRCA2 mutation carrier with any ER, PgR, HER2 status Females Age ≥18 years ECOG PS 0-2	Carboplatin AUC 6 every 3 weeks for six cycles
				Docetaxel 100 mg/m^2 every 3 weeks for six cycles
TURANDOT [77]	Phase III, open-label RCT	International (Europe and Israel)	HER2- LR or MBC Females Age ≥18 years ECOG PS 0-2 No prior chemotherapy for LR or MBC	Paclitaxel, 90mg/m^2 on days 1, 8 and 15 Bevacizumab, 10mg/kg on days 1 and 15 28-day cycles
				Capecitabine, 1000/m^2 bd on days 1-14 Bevacizumab, 10mg/kg on days 1 and 15 21-day cycles

BC=breast cancer; BRCA=BReast CAncer gene; ECOG PS= Eastern Cooperative Oncology Group performance status; ER=estrogen receptor; HER2= human epidermal growth factor receptor-2; HER2-= human epidermal growth factor receptor-2 negative; LA=locally advanced; LR=locally recurrent; MBC=metastatic breast cancer; NMAs=network meta-analyses; PgR=progesterone receptor; RCT=randomised controlled trial; TNBC=triple negative breast cancer
Source: Adapted from Table 8 of Appendix D to the CS

Table 38 Patient characteristics of trials included in the NMAs

Study	Arm	N	TNBC, n (%)	Age, median (range)	ECOG PS, n (%)			Presence of liver metastases, n (%)	Prior chemotherapy in the (neo) adjuvant setting, n (%)
					0	1	2		
AVADO[53]	D	241	43 (22)	44 (29-83)	147 (62)	91 (38)	NA	120 (50)	156 (65)
	DB7.5	248	55 (22)	54 (26-83)	149 (61)	94 (39)	NA	98 (40)	162 (65)
	DB15	247	60 (24)	54 (27-76)	150 (61)	94 (39)	NA	112 (46)	167 (68)
CALGB40502[55]	PB	275	73 (26)	66% of pts aged 50-69	NR	NR	NR	NR	Adjuvant taxane: 125 (44)
	NB	267	65 (24)	60% of pts aged 50-69	NR	NR	NR	NR	Adjuvant taxane: 120 (44)
	BIx	241	63 (26)	63% of pts aged 50-69	NR	NR	NR	NR	Adjuvant taxane: 107 (44)
E2100[60]	PB	347	121 (35)	56 (29-84)	NR	NR	NR	NR	224 (64.6)
	P	326	109 (33)	55 (27-85)	NR	NR	NR	NR	212 (65)
IMpassion130 PD-L1+ population	AN	185	185 (100)	53 (26-82)	107 (58)	77 (42)	1 (1)	44 (24)	125 (68)
	N100	184	184 (100)	53 (28-85)	112 (61)	72 (39)	0	39 (21)	117 (64)
MERiDiAN[67]	P	242	39 (16.1)	56 (28-77)	141 (58.5)	100 (41.5)	NA	NR	118 (48.8)
	PB	239	39 (16.3)	55 (28-85)	23 (51.5)	116 (48.5)	NA	NR	116 (48.5)
RIBBON-1[69]	Cp	206	50 (24.3)	57 (23-88)	NR		NR	NR	NR
	BCp	409	87 (21.3)	56 (28-91)	NR		NR	NR	NR
TNT[73]	Cb	188	174 (92.5)	55.7 (IQR 47.6-62.9)	174 (92.6)		14 (7.4)	98 (52.1)	147 (78.2)
	D	188	180 (95.8)	54.9 (IQR 47.9-63.5)	176 (93.6)		12 (6.4)	100 (53.2)	136 (72.3)
TURANDOT[77]	PB	285	63 (22)	54 (29-84)*	47 (75)*	13 (21)*	3 (5)*	113 (40)	45 (71)*
	BCp	279	67 (24)	56 (28-87)*	401 (60)*	24 (36)*	3 (4)*	126 (45)	42 (63)*

ECOG PS= Eastern Cooperative Oncology Group performance status; IQR=interquartile range; NA=not applicable; NMAs=network meta-analyses; NR=not reported; PD-L1+= programmed death-ligand 1-positive; TNBC=triple negative breast cancer
*Values reported are for the TNBC population of the TURANDOT trial [77]
Source: Adapted from Table 8 of Appendix D to the CS; company response to the ERG clarification letter (question A11)

8.4 Appendix 4 ERG comment on the company's risk of bias assessment for the trials included in the NMAs

Random sequence generation

The company considers all seven included trials have a low risk of bias for the domain of random sequence generation. As there is no information available from the published papers about the randomisation methods used in the MERiDiAN and CALGB40502 trials, the ERG considers that the risk of bias for these trials is unclear. In the E2100 trial, the randomisation process was carried out using permuted blocks within strata, however, the process of block selection is not reported. The ERG, therefore, considers that the risk of bias for the E2100 trial is also unclear.

Allocation concealment

The company considers that three of the included trials have a low risk of bias (MERiDiAN, AVADO and RIBBON-1) for the domain of allocation concealment. The ERG agrees with the company's assessment for AVADO and RIBBON-1 and notes that the trials used a centralised randomisation system. The ERG considers the risk of bias for the MERiDiAN trial is unclear as the method of randomisation was not described.

The company has rated four trials (E2100, CALGB40502, TNT and TURANDOT) as having a high risk of bias. The ERG considers that the TURANDOT trial has a low risk of bias as an inter-active web-based system was used to enrol patients.

Blinding of participants

The company rated the MERiDiAN, AVADO and RIBBON-1 trials as having a low risk of bias for the domain of blinding of participants. The ERG agrees with the company's assessment as the three trials included a placebo treatment.

The company rated the remaining four trials (E2100, CALGB40502, TNT and TURANDOT) as having a high risk of bias. The ERG agrees with the company's assessment.

Blinding of outcome assessment

The company rated the MERiDiAN, AVADO and RIBBON-1 trials as having a low risk of bias for the domain of blinding of outcome assessment. The ERG agrees with the company that these trials are likely to have a low risk of bias as they were double-blind, placebo-controlled trials.

The ERG agrees with the company assessment that the E2100, CALGB40502, TNT and TURANDOT trials have a high risk of bias for the domain of outcome assessment as none included blinded assessment of radiographic outcomes.

Incomplete outcome data and selective reporting.

The ERG agrees with the company that the risk of bias is low for all seven trials for the outcome of incomplete outcome data. All trials report the patient flow through the trial. The company has rated the risk of bias for selective reporting as low for all trials. As the ERG has not seen the protocol for any of the trials, the ERG considers that the risk of bias rating for the domain of selective reporting is unclear. However, the ERG considers that the details given in the published trial reports suggest that selective reporting is not an issue in any of the trials.

Any other sources of bias

The company has rated all trials as having a low risk of bias for the domain of any other sources of bias. The ERG notes that all trials, with the exception of the CALGB40502 and the TNT trials, were funded by pharmaceutical companies. The ERG considers that there is an unclear risk of bias for the domain of sources of other bias.

8.5 ERG revisions to the company model

This appendix contains details of the changes that the ERG made to the company model.

ERG revisions	Implementation instructions
R1 (**paclitaxel**): setting efficacy of paclitaxel to be equal to nab-paclitaxel (by setting the costs of nab-paclitaxel to be the same as paclitaxel)	In Sheets 'nappac' Insert formula in cell BP11 =IF(AND('Cost Inputs'!$A$33=TRUE,E11>=18),0,INDEX(new_admin_cost,IF(MOD(E11+1,4)=0,4,MOD(E11+1,4)),4)*BL11*BN11) Copy cell formula to range = BP11:BP1835 Insert formula in cell BQ11 =IF(E11>=18,0,'Dosing Calc'!$AM$8*BL11*BN11) Copy cell formula to range = BQ11:BQ1835 Insert formula in cell BR11 =IF(E11=0,p_c_ae_com2,0) Copy cell formula to range = BR11:BR1835
R1 (**docetaxel**): setting efficacy of paclitaxel to be equal to nab-paclitaxel (by setting the costs of nab-paclitaxel to be the same as docetaxel)	In Sheets 'nappac' Insert formula in cell BP11 = IF(E11>=18,0,IF(MOD(E11,3)=0,'Administration Cost'!$H$13,0)*BL11*BN11) Copy cell formula to range = BP11:BP1835 Insert formula in cell BQ11 = IF(BP11=0,0,BL11*BN11*'Dosing Calc'!$AN$8) Copy cell formula to range = BQ11:BQ1835 Insert formula in cell BR11 =IF(E11=0,p_c_ae_com3,0) Copy cell formula to range = BR11:BR1835

ERG revisions	Implementation instructions
R2 Costs in PFS and PD state	In Sheets 'Supportive Care Cost' Insert formula in cell G71 =(p_SCC_Oncologist_visit*D71)/month2week Insert formula in cell H71 =(p_SCC_Oncologist_visit*E71)/month2week Insert formula in cell I71 =(p_SCC_Oncologist_visit*F71)/month2week Insert formula in cell G40 =(p_SCC_Oncologist_visit*D40)/month2week Insert formula in cell H40 =(p_SCC_Oncologist_visit*E40)/month2week Insert formula in cell I40 =(p_SCC_Oncologist_visit*F40)/month2week
R3 and R4 Waning scenarios for OS	In Sheets 'Model Inputs' Set named range 'effect_os' to 'Effect is limited in time' Three year duration of treatment effect Set cell value I174 = 36 Set cell value I175 = 36 Five year duration of treatment effect Set cell value I174 = 60 Set cell value I175 = 60