NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

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

# Committee Papers

NICE National Institute for Health and Care Excellence

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

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

**Contents:**

The following documents are made available to consultees and commentators:

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

1. **Company submission** from **Roche Products**

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Breast Cancer Care and Breast Cancer Now

4. **Expert personal perspectives** from:
   a. Prof. Andrew Wardley, Consultant & Professor in Breast Cancer Oncology - clinical expert nominated by UK Breast Cancer Group
   b. Dr Mukesh B Mukesh, Consultant Clinical Oncologist - clinical expert nominated by Roche Products
   c. Holly Heath, Senior Research & Policy Officer – patient expert nominated by Breast Cancer Now *(* see submission from Breast Cancer Care and Breast Cancer Now)*

5. **Evidence Review Group report** prepared by Liverpool Reviews and Implementation Group (LRiG)

6. **Evidence Review Group report – factual accuracy check**

7. **Technical engagement responses from company**
   a. Main response
   b. Appendix 1-3
   c. Appendix 2
   d. Appendix 4

8. **Technical engagement responses from Consultees and Commentators:**
   a. Breast Cancer Care and Breast Cancer Now
   b. NHS England
   c. Pfizer

9. **Evidence Review Group critique of company response to technical engagement** prepared by Liverpool Reviews and Implementation Group (LRiG)

## *10.* Final Technical Report

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

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

# Atezolizumab (Tecentriq®) in combination with nab-paclitaxel for untreated, locally advanced or metastatic, triple negative, PD-L1–positive breast cancer

# [ID1522]

# Document B

# Company evidence submission

**March 2019**

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| **ID1522_First-line atezolizumab plus nab-paclitaxel in mTNBC_Doc B_29032019** | **1.0** | **Yes** | **29th March 2019** |



 

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# Abbreviations

| | |
|---|---|
| ABC | advanced breast cancer |
| ADCC | antibody-dependent cellular cytotoxicity |
| AE | adverse event |
| AESI | adverse event of special interest |
| AIC | Akaike Information Criterion |
| ALK | anaplastic lymphoma kinase |
| AUC | area under curve |
| BC | breast cancer |
| BIC | Bayesian Information Criterion |
| BNF | British National Formulary |
| BRCA | BReast CAncer gene |
| BSA | body surface area |
| CC | complication or comorbidity |
| CCOD | clinical cut-off date |
| CE | cost-effectiveness |
| CEA | cost-effectiveness analysis |
| CHMP | Committee for Medicinal Products for Human Use |
| CI | confidence interval |
| CJEU | Court of Justice of the European Union |
| CMA | cost-minimisation analysis |
| CSR | Clinical Study Report |
| CT | computerized tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CUA | cost-utility analysis |
| DET | data extraction table |
| DOR | duration of response |
| DSU | Decision Support Unit |
| EAMS | early access to medicines scheme |
| ECOG | Eastern Cooperative Oncology Group |
| EG | oestrogen |
| EGFR | epidermal growth factor receptor |
| EMA | European Medicines Agency |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EQ-5D | European Quality of Life-5 Dimensions (-3 Level/-5 Level version) |
| ER | estrogen receptor |
| ERG | Evidence Review Group |
| ESMO | European Society for Medical Oncology |

| | |
|---|---|
| FDA | Food and Drug Administration |
| FF | French franc |
| FFPE | formalin-fixed paraffin-embedded |
| 5-FU | 5-fluorouracil |
| GBP | Great British Pound |
| GP | general practitioner |
| HES | Hospital Episode Statistics |
| HR | hazard ratio |
| HRG | Healthcare Resource Group |
| HRQOL | health-related quality of life |
| HRU | health resource utilisation |
| HS | health state |
| HSUV | health state utility value |
| HTA | health technology assessment |
| IC | immune cell |
| ICER | incremental cost-effectiveness ratio |
| ICTRP | International Clinical Trials Registry Platform |
| IHC | immunohistochemistry |
| IMD | Index of Multiple Deprivation |
| IMRT | intensity-modulated radiation therapy |
| IRC | Independent Review Committee |
| ITC | indirect treatment comparison |
| ITT | intent-to-treat |
| IV | intravenous |
| JPY | Japanese Yen |
| KM | Kaplan-Meier |
| LOS | length of stay |
| LYG | life years gained |
| LYS | life year saved |
| MAIC | matching-adjusted indirect comparisons |
| MBC | metastatic breast cancer |
| MCMC | Markov chain Monte Carlo |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MIMS | Monthly Index of Medical Specialities |
| NA | not applicable |
| NB | Nab-paclitaxel + bevacizumab |
| NCCN | National Comprehensive Cancer Network |
| NCDR | National Cancer Data Repository |
| NCI | National Cancer Institute |

| | |
|---|---|
| ND | not defined |
| NE | not estimable |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NMA | network meta-analysis |
| NR | not reported |
| NSCLC | non-small cell lung cancer |
| NSRC | National Schedules of Reference Costs |
| ORR | objective response rate |
| OS | overall survival |
| PARP | poly ADP ribose polymerase |
| PAS | patient access scheme |
| PB | Paclitaxel + bevacizumab |
| PD | progressive disease |
| PFS | progression free survival |
| PIM | Promising Innovative Medicines |
| PN | placebo with nab-paclitaxel |
| PPE | Palmar-Plantar Erythro-Dysesthesia |
| PPS | post-progression survival |
| PR | progesterone receptor |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PS | performance score |
| PSA | probabilistic sensitivity analysis |
| PSS | personal social services |
| PSSRU | personal social services research unit |
| PTD | Perjeta + Herceptin + docetaxel |
| QALY | quality adjusted life years |
| QLQ | quality of life questionnaire |
| QOL | quality of life |
| RANKL | receptor activator of nuclear factor kappa-B ligand |
| RCT | randomised controlled trial |
| RECIST | response evaluation criteria in solid tumours |
| RW | real world |
| SAE | serious adverse event |
| SD | standard deviation |
| SE | standard error |
| SES | socioeconomic status |
| SG | standard gamble |
| SLR | systematic literature review |

| | |
|---|---|
| SMD | Standardised mean difference |
| SRE | skeletal-related event |
| TA | technical appraisal |
| TC | tumour cell |
| TD | Herceptin + docetaxel |
| TEAE | treatment-emergent adverse event |
| TIL | tumour-infiltrating lymphocyte |
| TKI | tyrosine-kinase inhibitor |
| TNBC | triple-negative breast cancer |
| TP | Herceptin + paclitaxel |
| TPC | treatment of physicians choice |
| TTO | time trade off |
| TTNT | time-to-next-treatment |
| TTOT | time-to-off-treatment |
| UK | United Kingdom |
| US | United States |
| USD | US dollar |

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

## *B.1.1 Decision problem*

The submission covers the technology's full marketing authorisation for this indication, which has a current anticipated regulatory indication of: Tecentriq® in combination with nab-paclitaxel is indicated for the treatment of [redacted]



**Table 1: The decision problem**

| | Final scope issued by NICE | Decision problem addressed in the company submission | Rationale if different from the final NICE scope |
|---|---|---|---|
| **Population** | People with locally advanced or metastatic, triple negative breast cancer whose tumours have PD-L1 expression ≥1% and have not received prior chemotherapy for metastatic disease | 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 | As per NICE final scope and in line with NICE reference case |
| **Intervention** | Atezolizumab (with nab-paclitaxel) | Atezolizumab (with nab-paclitaxel) | As per NICE final scope and in line with NICE reference case |
| **Comparator(s)** | • Single-agent taxane chemotherapy regimens (docetaxel and paclitaxel)<br>• Anthracycline-based chemotherapy | • Single-agent taxane chemotherapy regimens (docetaxel and paclitaxel) | As the IMpassion130 trial did not include any comparators listed in the final scope, an ITC was required. A systematic review (SR) of clinical evidence was conducted to identify potential studies for use in the comparison against paclitaxel, docetaxel and anthracyclines. Whilst RCTs were identified for the comparisons to paclitaxel and docetaxel, no trial evidence could be identified in the SR to allow for a clinical effectiveness (and therefore subsequently a cost-effectiveness) comparison against anthracyclines.<br><br>This is, however, consistent with clinical practice in the UK as eligibility for 1L metastatic TNBC patients to be treated with anthracyclines is limited: Approximately 80–85% of this population will have progressed to the metastatic setting from the eBC setting, where anthracycline-based treatment regimens are preferred. Re-challenge with anthracyclines is hindered by lifetime maximum cumulative dose (e.g. epirubicin (25)) and as such, patients |



| | | | |
|---|---|---|---|
| | | | treated in the eBC setting are unlikely to be eligible for re-challenge. Therefore, these regimens are rarely used within this setting. This is supported by observational data from a UK clinical practice, showing 7.5% usage in 1L mTNBC (32). |
| **Outcomes** | • overall survival<br>• progression-free survival<br>• response rate<br>• adverse effects of treatment<br>• health-related quality of life | • overall survival<br>• progression-free survival<br>• response rate<br>• adverse effects of treatment<br>• health-related quality of life | As per NICE final scope and in line with NICE reference case |
| Economic analysis | • Cost effectiveness expressed in terms of incremental cost per quality-adjusted life year.<br>• Time horizon sufficiently long to reflect any differences in costs or outcomes between the technologies<br>• Costs considered from an NHS and Personal Social Services perspective<br>• Commercial arrangements for the intervention, comparator and subsequent treatment technologies to be taken into account.<br>• The economic modelling should include the costs associated with diagnostic testing for PD-L1<br>• A sensitivity analysis should be provided without the cost of the diagnostic test. | • Cost effectiveness expressed in terms of incremental cost per quality-adjusted life year.<br>• Time horizon sufficiently long to reflect any differences in costs or outcomes between the technologies<br>• Costs considered from an NHS and Personal Social Services perspective<br>• Commercial arrangements for the intervention, comparator and subsequent treatment technologies to be taken into account.<br>• The economic modelling should include the costs associated with diagnostic testing for PD-L1.<br>• A sensitivity analysis should be provided without the cost of the | As per NICE final scope and in line with NICE reference case |

| | | | |
|---|---|---|---|
| | | diagnostic test. | |



## *B.1.2 Description of the technology being appraised*

**Table 2: Technology being appraised**

| | |
|---|---|
| **UK approved name and brand name** | Approved name: Atezolizumab and nab-paclitaxel<br>Brand name: Tecentriq® and Abraxane® |
| **Mechanism of action** | **Atezolizumab:**<br>Atezolizumab is an Fc-engineered, humanised immunoglobulin G1 anti-PD-L1 monoclonal antibody that inhibits binding of PD-L1 to its receptors PD-1 and B7.1 (33).<br><br>The immune checkpoint molecule, PD-L1, is expressed on TC and tumour-infiltrating IC in various tumour types, including breast cancer (4, 34). In TNBC, PD-L1 expression is largely confined to IC (21, 35).<br><br>Binding of PD-L1 to its receptors, PD-1 and B7.1, found on T-cells and antigen-presenting cells, can suppress the T-cell immune response, T-cell proliferation, and cytokine production (36-38). Therefore, the inhibition of PD-L1 can facilitate an anti-tumour response and promote tumour cell killing (33).<br><br>TNBC is suitable for anti-PD-L1 treatment due to:<br>• A higher PD-L1 expression level relative to other breast cancer subtypes (4, 5)<br>• Correlation of increased PD-L1 expression with increased TILs, which are a positive prognostic factor in TNBC and can mediate the immune response (7)(Adams 2018)<br>**Nab-paclitaxel:**<br>Paclitaxel is an inhibitor of mitosis (39), specifically it inhibits the depolymerisation of microtubules which blocks cells at certain phases of the cell cycle, resulting in cell death (40). This means that paclitaxel can target and kill proliferating cells (i.e. tumour cells) (41).<br><br>Solvents must be used with paclitaxel for parenteral administration, however they are associated with hypersensitivity and neurotoxicity (42, 43). To prevent these complications, a pre-medication regimen with steroids prior to paclitaxel administration is recommended (27). Nab-paclitaxel is an albumin-bound paclitaxel that does not require solvents (41) and does not require steroid or antihistamine premedication (44).<br><br>It was selected as a chemotherapy partner for atezolizumab to remove the need for steroid pre-medication which was hypothesised to affect immunotherapy activity (13). |
| **Marketing authorisation/CE mark status** | An application for licence extension was made in [redacted].<br>Marketing authorisation is expected [redacted]. |
| **Indications and any restriction(s) as** | **Current indications:**<br>Atezolizumab is indicated for patients with locally-advanced or |



| | |
|---|---|
| **described in the summary of product characteristics (SmPC)** | metastatic urothelial carcinoma (45):<br>• after prior platinum-containing chemotherapy, or<br>• who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥5%<br>Atezolizumab is indicated for patients with locally advanced or metastatic NSCLC after prior chemotherapy (45)<br>Atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies (45)<br>**Anticipated indication:**<br>[redacted] |
| **Method of administration and dosage** | The recommended dose of atezolizumab is 840 mg administered by intravenous infusion, followed by 100 mg/m$^2$ nab-paclitaxel. For each 28-day cycle, atezolizumab is administered on days 1 and 15, and nab-paclitaxel is administered on days 1, 8, and 15 (45) |
| **Additional tests or investigations** | PD-L1 expression is used as a biomarker for atezolizumab. Patients with previously untreated TNBC should be selected for treatment based on the expression of PD-L1 confirmed by a validated test<br>Cost of a single PD-L1 test: [redacted] |
| **List price and average cost of a course of treatment** | Atezolizumab: [redacted]. Average per 28-day treatment cycle: [redacted]<br>Please note: The above [redacted] vial size PAS will be approved at launch in [redacted]. The [redacted]<br>Nab-paclitaxel: £246.00 per powder vial (100mg). Average price per 28 day treatment cycle: £1,284.12 (assuming body surface area of 1.74m$^2$, as per patients in the IMpassion130 trial) |
| **Patient access scheme (if applicable)** | Atezolizumab: [redacted] discount from list price (existing PAS)<br>Nab-paclitaxel: PAS exists, Roche does not have these details. |

ALK: anaplastic lymphoma kinase; EGFR: epidermal growth factor receptor; IC: immune cells; PAS: patient access scheme; PD-L1: programmed death-ligand 1; TC: tumour cells; NSCLC: non-small cell lung cancer; TIL: tumour-infiltrating lymphocyte; TNBC: triple-negative breast cancer



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

- **TNBC accounts for 15–20% of all breast cancers (18)**
- **TNBC tumours are aggressive with a high proliferation rate and an invasive phenotype (13, 19). The tumours metastasise preferentially to the viscera, which carries a poor prognosis (3)**
- **TNBC accounts for 25% of breast cancer deaths (3)**
- **There are no approved targeted molecular therapies and chemotherapy is the standard of care (3, 18)**
- **Single-agent chemotherapy regimens have shown equivalent OS with less toxicity and improved patient QoL than combination approaches (18)**
- **Chemotherapy agents used in the eBC setting (usually epirubicin + cyclophosphamide +/- 5-fluorouracil, followed by a taxane, usually docetaxel [UK clinical expert opinion (20, 24)]) influence choice of treatment upon metastatic relapse**
- **Anthracyclines have a lifetime maximum cumulative dose (e.g. epirubicin (25, 26)) and as such, patients treated in the eBC 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 (28)**
- **Paclitaxel is often the taxane of choice for 1L mTNBC (UK clinical expert opinion (20)**

### B.1.3.1 Disease overview

Breast cancer is a malignant cancer that originates from the cells of the breast (46); most commonly the ducts, and sometimes the lobules (47). Advanced or metastatic breast cancer is where 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 (48). There were 45,960 new cases of breast cancer diagnosed and 9,685 deaths in 2016 in

England (49, 50). Overall, breast cancer accounted for 7% of cancer deaths in the UK in 2016 (50).

Breast cancer is categorised into 3 main subtypes based on the presence or absence of oestrogen or progesterone receptors and HER2. TNBC, a diagnosis of exclusion characterised by the lack of expression of oestrogen and progesterone receptors as well as the absence of HER2 overexpression, accounts for approximately 15–20% of all breast cancers (2, 3, 18). The specific molecular pathophysiology of TNBC remains poorly understood (18) and this diagnosis comprises a heterogeneous group of malignancies (19).

The main breast cancer subtypes are characterised by distinct prognoses, prevalence and systemic treatment options (18):

- Tumours from TNBC are often aggressive, with a high proliferative rate and an invasive phenotype (19) and thus frequently larger and less differentiated at presentation (3). With a more aggressive natural history compared with other breast cancer subtypes, TNBC is approximately 2.5 times more likely to metastasise (3). It metastasises preferentially to the viscera (which carries a poor prognosis), therefore despite accounting for only approximately 15–20% of breast cancer cases, it accounts for 25% of deaths (3).

- TNBC disproportionally affects younger, premenopausal women and those of African or Hispanic ancestry (3)

- As TNBC tumours lack the classical breast cancer molecular targets (i.e., hormone receptors and HER2), they are difficult to treat. TNBC is usually initially chemosensitive and chemotherapy is the mainstay treatment in early breast cancer (eBC). However, upon relapse, the only available strategy remains to “rechallenge” with systemic chemotherapy. This approach is limited by poor response, toxicity and eventual multi-drug resistance (3).

Thus, outcomes in metastatic TNBC fall considerably behind those of other breast cancer subtypes, with a median overall survival (OS) of ≤18 months (1, 13, 18, 24) compared with 4–5 years for HR+ and HER2+ subtypes (18). Treatment must balance response with preserving QoL for patients with limited life expectancy, and enrolment in clinical trials remains a priority (28).

### B.1.3.2 Treatment pathway

#### *Introduction*

There are currently no targeted therapies specifically for TNBC and chemotherapy is the standard of care (51). It is internationally recognised that there is no single recommended first-line chemotherapy regimen for mTNBC (18, 28, 52).

The National Institute for Health and Care Excellence (NICE) guideline for advanced breast cancer (CG81) does not address TNBC specifically, however, the NICE pathway for managing advanced breast cancer does have recommendations for TNBC (51, 53).

#### *Single-agent vs. combination chemotherapy*

According to the NICE pathway, systemic sequential therapy should be offered to patients with advanced breast cancer which has progressed (51).

Single-agent chemotherapy regimens have shown equivalent OS with less toxicity and improved patient QoL than combination approaches and thus single-agent sequential chemotherapy can be considered a standard of care for most patients (18).

Indeed, NICE guidelines state that combination chemotherapy should be considered in patients for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity (51). ESMO guidelines endorse that combination chemotherapy should be reserved for patients with rapid clinical progression, life-threatening visceral metastases or need for rapid symptom and/or disease control (28).

#### *Clinical guidelines*

**Choice of chemotherapy agent**

The choice of agent is dependent on an individual patient's characteristics (e.g., performance status, biological age and co-morbidities), disease characteristics (tumour burden, disease-free interval) and importantly, prior treatments the patient has received in the early breast cancer setting (52).

Given the importance of disease history in treatment decisions, it is necessary to first consider treatment in the early breast cancer setting and how this impacts subsequent choice of therapies. Indeed, only 6–7% of breast cancers in the UK are diagnosed at stage 4, i.e. *de novo* metastatic disease (54).

Sequential anthracycline-taxane chemotherapy represents a common standard of care in both the neoadjuvant and adjuvant treatment of moderate/high risk early TNBC (2). In the UK, this tends to be an epirubicin + cyclophosphamide +/- 5-fluorouracil, followed by a taxane, usually docetaxel (UK clinical expert opinion, (20)). 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 (2).

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 (25)) and as such, patients treated in the eBC 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 (28).

**NICE treatment pathway**

According to the NICE treatment pathway, for patients with advanced breast cancer who are not suitable for anthracyclines, systemic chemotherapy treatment should be offered in the following sequence (51):

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)

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 (53).

Similarly, ESMO acknowledges the few treatment options for TNBC and also recommends chemotherapy as standard of care (28). ESMO also recommend patients with advanced breast cancer to participate in trials where possible and the patient is willing to participate (28).

### *UK clinical practice*

Despite the recommendations in the NICE treatment pathway, there is no clear standard of care for patients with metastatic TNBC and treatment in the UK is highly varied and frequently deviates from the described pathway.

A retrospective audit of patients with advanced breast cancer treated at the Mount Vernon Cancer Centre found that only 5/29 patients with HER2-/unknown advanced breast cancer previously treated in the neoadjuvant/adjuvant setting received single-agent docetaxel as first-line therapy for their advanced disease as per the NICE guidelines (55). Across all HER2- patients that were 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 the majority of cases when managing patients with advanced breast cancer (55).

Likewise, a retrospective analysis of patients with mTNBC treated at the Royal Marsden NHS Foundation Trust found that despite 14% of patients in this analysis presenting with *de novo* metastatic disease, only 7.5% received an anthracycline-based regimen. Additionally, only 17.7% patients received a taxane in the first-line setting, however, the specific taxanes used was not reported (32).

### B.1.3.3 UK preferred treatment for 1L mTNBC

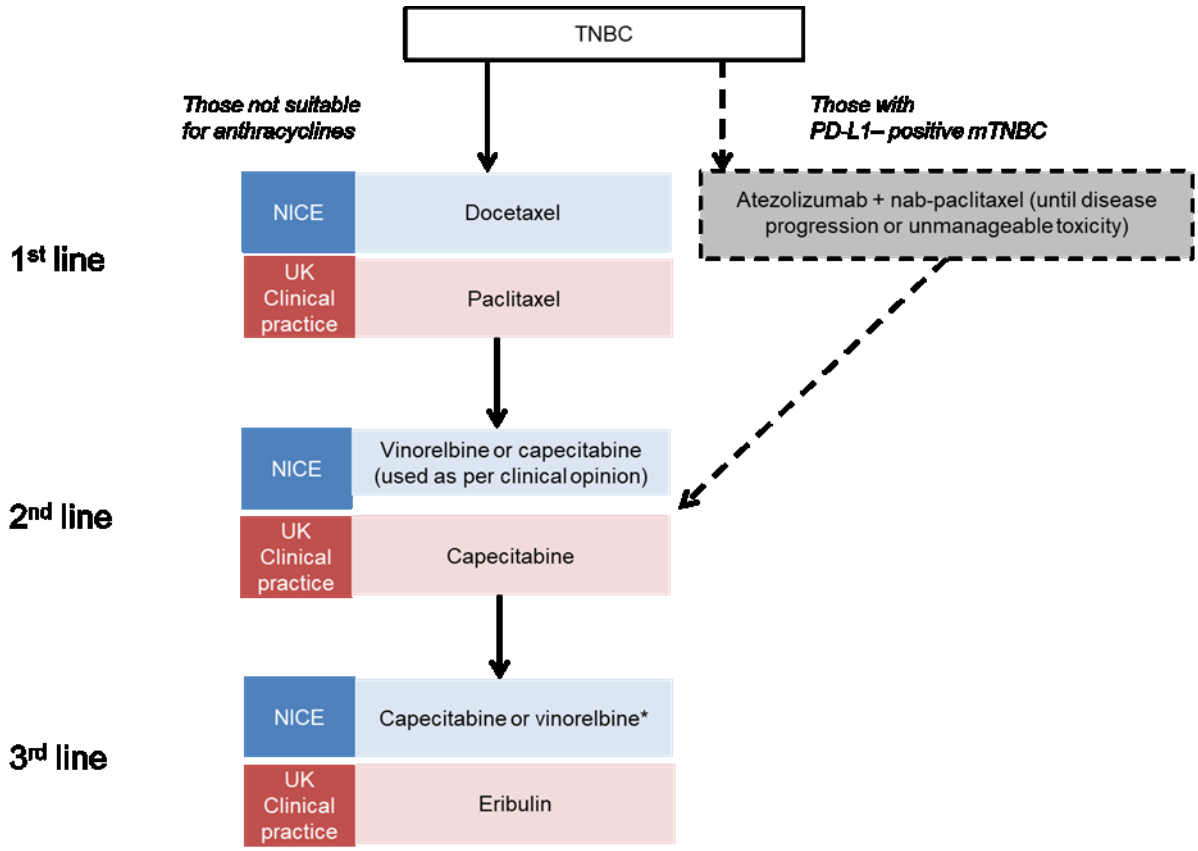
Although it seems unclear which treatments are used in clinical practice, given the variability in the data presented above and in the absence of a robust multi-centre UK real-world data set, Roche consulted UK clinical experts who confirmed that paclitaxel is often the taxane of choice for 1L mTNBC (20). This is due to the favourable toxicity profile of weekly paclitaxel compared with 3-weekly docetaxel which increases tolerability and helps maintain QoL for patients with limited life expectancy (56). Docetaxel is often used in the curative eBC setting where the toxicities of treatment are offset by the aim of cure rather than palliation (UK Clinical expert opinion, (20)). Both *in vitro* and *in vivo* studies have demonstrated only partial cross-resistance between docetaxel and paclitaxel (57-59), increasing the likelihood of additional benefit from a different taxane agent i.e., paclitaxel. Furthermore, re-challenge with docetaxel (following use in eBC) 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 if they have subsequently relapsed.

### B.1.3.4 Metastatic TNBC treatment pathway diagram

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

**Figure 1: Current UK treatment pathway for TNBC and proposed positioning for atezolizumab + nab-paclitaxel for patients with PD-L1-positive metastatic TNBC**




*Whichever was not used as second-line treatment

NICE: National Institute for Health and Care Excellence; TNBC: triple-negative breast cancer

## *B.1.4 Equality considerations*

No equality issues relating to atezolizumab and nab-paclitaxel have been identified.

# B.2 Clinical effectiveness

## *B.2.1 Identification and selection of relevant studies*

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

## *B.2.2 List of relevant clinical effectiveness evidence*

**Phase I/Ib studies**

Phase I/Ib studies have shown proof-of-concept for atezolizumab in advanced or metastatic TNBC:

- A multi-cohort, open-label, Phase I trial (NCT01375842) was carried out in patients with advanced solid and haematologic malignant neoplasms receiving single-agent atezolizumab intravenously every three weeks until unacceptable toxic effects or loss of clinical benefit (35). In the mTNBC cohort, the study found that single-agent atezolizumab was well tolerated and provided durable clinical benefit (35).

- A study of a pre-treated mTNBC cohort from the multi-cohort, open-label, Phase Ib trial (NCT01633970) in patients with advanced solid tumours (n = 33; median safety follow-up, 6.9 months) found that atezolizumab plus nab-paclitaxel was well-tolerated with no treatment-related deaths observed and a safety profile similar to that of atezolizumab or nab-paclitaxel alone (60). Antitumour responses were observed in a significant proportion of patients (31).

These trials will not be discussed further in this submission as the primary evidence on the use of atezolizumab plus nab-paclitaxel in patients with mTNBC is available from the IMpassion130 phase III trial.

**IMpassion130 phase III trial**

The IMpassion130 phase III trial (NCT02425891) is the primary source of evidence for this submission. The study evaluated the efficacy, safety, and pharmacokinetics of atezolizumab with nab-paclitaxel compared with placebo with nab-paclitaxel in patients with metastatic or locally advanced triple negative adenocarcinoma of the breast who have not received prior systemic therapy for metastatic breast cancer (13).

**Table 3: Summary of clinical effectiveness evidence**

| **Study** | Phase I study (35) | Phase Ib study (61) | IMpassion130 (13) |
|---|---|---|---|
| **Study design** | Phase Ia, randomised, open-label study | Phase Ib, randomised, open-label study | Phase III, randomised, double-blind, placebo-controlled study |
| **Population** | Patients with heavily pre-treated mTNBC | Patients with heavily pre-treated mTNBC | Patients with untreated mTNBC |
| **Intervention(s)** | Single-agent atezolizumab | Atezolizumab + nab-paclitaxel | Atezolizumab + nab-paclitaxel |
| **Comparator(s)** | N/A | N/A | Placebo + nab-paclitaxel |
| **Indicate if trial supports application for marketing authorisation** | No | No | Yes |
| **Indicate if trial used in the economic model** | No | No | Yes |
| **Rationale for use/non-use in the model** | Not used in model. This was a study of single-agent atezolizumab | Not used in model. This was a single-arm study of 33 patients | Used in model. A Phase III randomised-controlled trial of atezolizumab + nab-paclitaxel versus placebo + nab-paclitaxel in patients with mTNBC |
| **Reported outcomes specified in the decision problem** | N/A | N/A | • Overall survival<br>• Progression-free survival<br>• Response rate<br>• Adverse effects of treatment<br>• Health-related quality of life |
| **All other reported outcomes** | N/A | N/A | N/A |

mTNBC: metastatic triple-negative breast cancer; N/A: not applicable



### *B.2.3 Summary of methodology – IMpassion130 Phase III trial*

- **PD-L1 is a suitable target for TNBC due to the higher expression levels compared to other breast cancer subtypes, higher mutation rate that can induce an immune response, and a large number of TILs that can mediate the immune response (4, 5) (6) (7-9)**
- **Atezolizumab binds to PD-L1 to prevent the de-activation of T-cells and enhance tumour cell killing (22)**
- **Atezolizumab was combined with chemotherapy (nab-paclitaxel) as this may enhance tumour antigen release and anti-tumour responses to checkpoint inhibition (23)**
- **nab-Paclitaxel was chosen for combination with atezolizumab as it does not require co-administration/pre-medication with steroids (27) and it was hypothesised that the immunosuppressive effects of steroids could potentially inhibit the immune-mediated anti-tumour activity of atezolizumab (30)**
- **The IMpassion130 study enrolled an all-comers population due to activity signals in a non-selected population in early phase studies (31), the hypothesis that the combination of atezolizumab and chemotherapy would enhance tumour-specific T-cell immunity (23), and the lack of robust data for the validity of PD-L1 expression as biomarker for response to anti-PD-L1/PD-L1 therapy at the time of study initiation**
- **Overall, 902 patients (ITT population) were enrolled at 246 sites in 41 countries (including 9 centres in the UK) (13)**
- **Tumour specimens were prospectively tested for PD-L1 expression using the immunohistochemistry (IHC) VENTANA PD-L1 (SP142) assay prior to enrolment (13)**
- **Overall, baseline characteristics were well balanced between arms, and baseline characteristics for the PD-L1–positive population were consistent with the ITT population (13)**

### B.2.3.1 Design rationale

#### *PD-L1 as a biomarker*

PD-L1 is a suitable target for the treatment of TNBC for several reasons:

- Higher PD-L1 expression levels are observed in TNBC relative to other breast cancer subtypes (4, 5) and PD-L1 expression on immune cells (ICs) in particular is hypothesised to play a key role in the activity of atezolizumab (21)
- TNBC tumours tend to have a higher mutation rate than other BC subtypes which could result in tumour-specific antigens that induce an immune response, enhancing the infiltration of anti-tumour T cells (6)
- There are higher levels of TILs (a positive prognostic factor in TNBC) in TNBC compared with other BC subtypes and these can mediate the immune response (7-9). In the Phase Ia PCF4989g study, higher ORR and longer OS were seen with higher baseline tumour-infiltrating lymphocyte (TIL) in the TNBC cohort (62)

PD-L1 downregulates immune responses through binding to its two receptors: PD1 and B7.1 (38). Ligation of PD-L1 with PD1 inhibits T cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (63). Atezolizumab binds to PD-L1 to prevent the de-activation of T-cells and enhance tumour cell killing (22). This means that PD-L2 and PD-1 can interact and potentially preserve immune homeostasis and prevent autoimmune responses (64). In addition, a single amino acid substitution (N298A) has been engineered in the FC region of each heavy chain of atezolizumab to prevent it from triggering antibody-dependent cellular cytotoxicity (ADCC) and therefore maximise the immune response (34, 65, 66). Targeting the PD-L1 pathway with atezolizumab demonstrated activity in early phase studies of patients with advanced malignancies who had failed standard-of-care therapies, including patients with TNBC (61, 67).

#### *Combining anti-PD-L1/PD-1 agents with chemotherapy in TNBC (61)*

Studies have shown that anti–PD-L1/PD-1 agents are clinically active in mTNBC, however low response rates to single-agent treatment have generated interest in combination therapy (35, 68-71). Combination of atezolizumab with chemotherapy may be synergistic by targeting different steps in the cancer immunity (38). Chemotherapy can result in tumour antigen release that may elicit antitumour immunity (38, 72), enhance the antigenicity of

cancer cells by increasing major histocompatibility complex expression, increase PD-L1 expression on tumour cells (73), and increase CD8+ TILs (74). By enhancing T-cell responses, atezolizumab may result in improved response rates and durability vs. chemotherapy alone (38).

### *Choice of chemotherapy partner: nab-paclitaxel*

nab-Paclitaxel is unique among the taxanes in that it does not require co-administration with steroids (27).}. This was considered important for the first definitive study of atezolizumab treatment in breast cancer because it was hypothesised that the immunosuppressive effects of steroids could potentially inhibit the immune-mediated anti-tumour activity of atezolizumab (26, 30). Safety data from the Phase Ib study GP28328 indicated that atezolizumab can be safely combined with chemotherapy (61). No exacerbation of chemotherapy-associated adverse events was reported (61)

### *IMpassion130 ITT population and PD-L1–positive subpopulation*

In the mTNBC cohort of the Phase I PCD4989g atezolizumab monotherapy study, clinical response and OS were associated with PD-L1 IC1/2/3 (≥1% PD-L1 expressing ICs as a percentage of tumour area) (35). Similar trends were observed in a Phase Ib study of mTNBC patients exposed to atezolizumab + nab-paclitaxel (60). However, while the magnitude of benefit was higher in the PD-L1 IC2/3 group, patients with PD-L1 IC 0/1 also derived benefit (62).

This was consistent with atezolizumab trials in other tumour types, whereby expression (or non-expression) of PD-L1 did not distinguish an improved level of response (75-77).

Given this activity in a non-selected population, the hypothesis that the combination of atezolizumab and chemotherapy would enhance tumour-specific T-cell immunity (31), and the fact that PD-L1 was not a validated biomarker at the time of study initiation, an all-comers mTNBC population was deemed the appropriate approach. However, the study design allowed for testing the voracity of the biomarker in a pre-planned exploratory subgroup analysis as demonstrated in the statistical hierarchy of testing for the study.

## B.2.3.2 Methodology

Unless otherwise specified, the information for the IMpassion130 trial comes from the Schmid *et al*. 2018 manuscript, “Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer” (13).

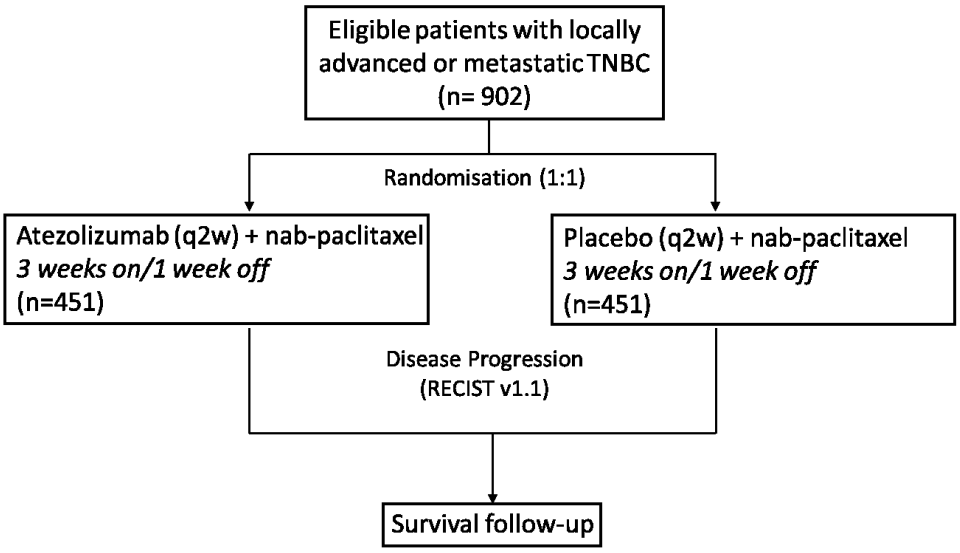

 

From June 2015 through May 2017, 902 patients (ITT population) were enrolled at 246 sites in 41 countries (including 9 centres in the UK). Patients were randomised in a 1:1 ratio using a permuted-block randomisation method (451 patients in each arm). The PD-L1–positive subgroup included 369 patients (40.9%; 185 patients in the A + nabPx arm and 184 in the P + nabPx arm). Patients either received atezolizumab (840 mg) or placebo IV infusions on Days 1 and 15 of every 28-day cycle plus nab-paclitaxel (100 mg/m$^2$) administered via IV infusion on Days 1, 8, and 15 of every 28-day cycle. Randomisation was stratified by the following three factors:

1) Presence of liver metastases (yes vs. no)
2) Prior taxane treatment (yes vs. no)
3) Tumour PD-L1 status (IC0 vs. IC1/2/3)

The study design is shown in Figure 2.

**Figure 2: IMpassion130 study design (29)**




q2w: every 2 weeks; RECIST v1.1: Response Evaluation Criteria in Solid Tumours, version 1.1; TNBC: triple-negative breast cancer

A representative formalin-fixed paraffin-embedded (FFPE) tumour specimen with an associated pathology report documenting ER, PR, and HER2 negativity had to be submitted prior to enrolment (29). Tumour specimens were prospectively tested for PD-L1 expression by a central laboratory using the immunohistochemistry (IHC) VENTANA PD-L1 (SP142) assay prior to enrolment (Ventana Medical Systems, Inc., Tucson, AZ) (13). The SP142 assay was developed specifically for atezolizumab to optimise staining of tumour-infiltrating

ICs (29). PD-L1 expression was scored using the ICs expressing PD-L1 as a percentage of tumour area. Negative PD-L1 expression (IC0) was defined as <1% IC expressing PD-L1; positive PD-L1 expression was defined as ≥1% ICs expressing PD-L1 (IC1/2/3). A summary of the methodology for the IMpassion130 trial is shown in Table 4 (13).

In total, 902 patients underwent randomisation. Overall, baseline characteristics were well balanced between arms, and baseline characteristics for the PD-L1–positive population were consistent with the ITT population (Table 5). The PD-L1–positive population comprised 369 patients (40.9%) (185 in the A + nabPx arm and 184 in the P + nabPx arm).

**Table 4: Summary of methods for IMpassion130 phase III trial (29)**

| **Trial number** | **IMpassion130 phase III Trial** | | |
|---|---|---|---|
| **Trial design** | Phase III, multicentre, double-blind, two-arm, randomised, placebo-controlled study | | |
| **Eligibility criteria for participants** | • Women or men aged ≥ 18 years<br>• Metastatic or unresectable locally advanced, histologically documented TNBC<br>– < 1% ER/PR-positive cells by IHC *and*<br>– HER2 negative by fluorescence in situ hybridisation (non-amplified) or HER2 IHC 0 or 1<br>• No prior chemotherapy or systemic targeted therapy for inoperable locally advanced or metastatic TNBC (radiation therapy for metastatic disease permitted and prior adjuvant/neoadjuvant chemotherapy allowed if completed ≥ 12 months prior to randomisation)<br>• Eligible for taxane monotherapy<br>• Representative FFPE tumour specimen in paraffin blocks or at least 20 unstained slides with an associated pathology report documenting ER, PR, and HER2 negativity<br>• Measurable disease per RECIST v1.1<br>• ECOG performance status 0 or 1<br>• Life expectancy ≥12 weeks<br>• Adequate haematologic and end-organ function, defined by laboratory results obtained within 14 days prior to first study treatment (Cycle 1, Day 1)<br>• Women of childbearing potential who to remain abstinent or use contraceptive methods<br>• Women who are not postmenopausal must have a negative serum pregnancy test within 14 days prior to initiation of study drug<br>• Men who agree to remain abstinent or use contraceptive methods | | |
| **Settings and locations where the data were collected (number of centres in parentheses)** | 246 centres across 41 countries | | |
| | • Argentina (3)<br>• Australia (8) | • France (11)<br>• Germany (20) | • Romania (1)<br>• Russian |

| | | | |
|---|---|---|---|
| | • Austria (3)<br>• Belgium (6)<br>• Bosnia and Herzegovina (1)<br>• Brazil (10)<br>• Canada (11)<br>• Chile (2)<br>• Colombia (2)<br>• Costa Rica (2)<br>• Czech Republic (3)<br>• Estonia (2)<br>• Finland (1) | • Greece (5)<br>• Guatemala (1)<br>• Hong Kong (1)<br>• Hungary (3)<br>• Italy (2)<br>• Japan (27)<br>• Republic of Korea (5)<br>• Latvia (2)<br>• Mexico (5)<br>• Norway (3)<br>• Panama (1)<br>• Poland (6) | Federation (7)<br>• Serbia and Montenegro (1)<br>• Singapore (2)<br>• Slovenia (1)<br>• Spain (8)<br>• Sweden (2)<br>• Switzerland (3)<br>• Taiwan (4)<br>• Thailand (3)<br>• Turkey (5)<br>• Ukraine (4)<br>• United Kingdom (9)<br>• United States (49) |
| **Trial drugs**<br>**Permitted and disallowed concomitant medication** | Patients randomised 1:1 to receive atezolizumab (840 mg) or placebo IV infusions on days 1 and 15 of a 28-day cycle plus nab-paclitaxel (100 mg/m$^2$) on days 1, 8, and 15 of a 28-day cycle.<br><br>**Permitted medication**<br>Premedication with antihistamines could be administered for any atezolizumab/placebo infusions after Cycle 1, Day 1.<br>The following therapies were permitted while patients were in the study:<br>• Prophylactic or therapeutic anticoagulation therapy<br>• Palliative radiotherapy (e.g., treatment of known bone metastases) provided it does not interfere with assessment of tumour target lesions<br>• Inactivated vaccinations (including for influenza)<br>• Megestrol administered as an appetite stimulant<br>• Inhaled corticosteroids for chronic obstructive pulmonary disease<br>• Mineralocorticoids (e.g., fludrocortisone)<br>• Low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency<br>• Bisphosphonates for the prevention of skeletal events<br>• Patients who were receiving denosumab prior to randomisation had to be willing and able to receive a bisphosphonate instead while on study. There was no required minimum washout period for patients who discontinued denosumab<br><br>**Disallowed medication**<br>The following medications were excluded while the patient was receiving study treatment:<br>• Other systemic anti-cancer therapy<br>• RANKL inhibitor<br>• Immunomodulatory agents, including but not limited to interferons or IL 2, during the entire study<br>• Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide<br>• Use of steroids to premedicate patients for whom CT scans with contrast are contraindicated<br>• Any live, attenuated vaccine (e.g., FluMist®) within 28 days prior | | |



| | |
|---|---|
| | to randomisation<br>In addition, other immunomodulatory agents are not permitted for 10 weeks after atezolizumab discontinuation.<br>The concomitant use of herbal therapies is not recommended, however, their use for patients in the study is allowed at the discretion of the investigator |
| **Primary outcomes (including scoring methods and timings of assessments)** | Co-primary efficacy outcome measures in ITT and PD-L1–positive populations:<br>• PFS per investigator assessment (RECIST v1.1)<br>• OS – defined as the time from the date of randomisation to the date of death from any cause |
| **Other outcomes used in the economic model/specified in the scope** | • ORR<br>• DOR<br>• HRQoL |
| **Pre-planned subgroups** | • PD-L1-selected patients (patients in the ITT population whose PD-L1 status was IC1/2/3 at the time of randomisation based on the Ventana SP142 assay)<br>• To assess the consistency of study results in subgroups defined by demographic and baseline characteristics, PFS, ORR, and OS in these subgroups were examined |

CT: computerised tomography; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; ER: oestrogen receptor; FFPE: formalin-fixed paraffin-embedded; HER2: Human epidermal growth factor receptor-2; HRQoL: health-related quality of life; IHC: immunohistochemistry; ITT: intent-to-treat; ORR: objective response rate; OS: overall survival; PD-L1: Programmed death-ligand 1; PFS: progression-free survival; PR: progesterone receptor; RANKL: receptor activator of nuclear factor kappa-B ligand; RECIST v1.1: Response Evaluation Criteria in Solid Tumours, version 1.1; TNBC: triple-negative breast cancer

Tumour assessments per RECIST v1.1 were performed approximately every 8 weeks (± 1 week) for the first 12 months after Cycle 1, Day 1 and every 12 weeks (± 1 week) thereafter until disease progression or treatment discontinuation, whichever was later. A centralised, independent review of response endpoints by an Independent Review Committee (IRC) was carried out on the imaging data used for tumour assessment. For estimation of progression free survival (PFS), objective response rate (ORR), and duration of response (DOR), tumour response was based on RECIST v1.1 (29).

All patients were followed for survival approximately every 3 months after the treatment discontinuation visit until death, withdrawal of consent, loss to follow-up, or study termination. Any subsequent anti-cancer agents used for mTNBC during the survival follow-up period were to be collected (78).

Safety assessments included the incidence, nature, and severity of adverse events and laboratory abnormalities graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0. Laboratory safety assessments included the regular monitoring of haematology and blood chemistry. Serum samples were collected to monitor atezolizumab pharmacokinetics and to detect the presence of antibodies to atezolizumab. An independent data monitoring committee (iDMC) monitored safety and study conduct on a periodic basis (29).

**Table 5: Demographic and baseline characteristics**

| | PD-L1–positive population | | ITT population | |
|---|---|---|---|---|
| | **A + nabPx** | **P + nabPx** | **A + nabPx** | **P + nabPx** |
| **Age (yr)** | | | | |
| n | 185 | 184 | 451 | 451 |
| Mean (SD) | 53.7 (12.9) | 53.6 (12.0) | 54.3 (12.3) | 55.4 (12.1) |
| Median | 53.0 | 53.0 | 55 | 56 |
| 25% and 75%-ile | 44.0 - 63.0 | 44.0 - 63.0 | 46.0 - 64.0 | 47.0 - 65.0 |
| Min - Max | 26 - 82 | 28 - 85 | 20 - 82 | 26 - 86 |
| **Sex** | | | | |
| n | 185 | 184 | 451 | 451 |
| Male | 1 ( 0.5%) | 0 | 3 ( 0.7%) | 1 ( 0.2%) |
| Female | 184 (99.5%) | 184 ( 100%) | 448 (99.3%) | 450 (99.8%) |
| **Race** | | | | |
| n | 185 | 184 | 451 | 451 |
| White | 125 (67.6%) | 31 (16.8%) | 308 (68.3%) | 301 (66.7%) |
| Asian | 38 (20.5%) | 142 (77.2%) | 85 (18.8%) | 76 (16.9%) |
| Black or African American | 9 ( 4.9%) | 7 ( 3.8%) | 26 ( 5.8%) | 33 ( 7.3%) |
| American Indian or Alaska Native | 8 ( 4.3%) | 4 ( 2.2%) | 17 ( 3.8%) | 23 ( 5.1%) |
| Unknown | 5 ( 2.7%) | 184 | 12 ( 2.7%) | 15 ( 3.3%) |
| **Baseline ECOG Performance Status** | | | | |
| n | 185 | 174 | 450 | 450 |
| 0 | 107 (57.8%) | 161.43 (7.65) | 256 (56.9%) | 270 (60.0%) |
| 1 | 77 (41.6%) | 161.00 | 193 (42.9%) | 179 (39.8%) |
| 2 | 1 ( 0.5%) | 156.00 - 167.00 | 1 ( 0.2%) | 1 ( 0.2%) |
| **Metastatic disease** | | | | |
| n | 185 | 183 | 450 | 450 |
| no. (%) | 162 (87.6%) | 159 (86.9%) | 404 (89.8%) | 408 (90.7%) |
| Number of sites | | | | |
| n | 185 | 183 | 450 | 449 |
| 0–3 | 149 (80.5%) | 140 (76.5%) | 332 (73.8%) | 341 (75.9%) |
| ≥4 | 36 (19.5%) | 43 (23.5%) | 118 (26.2%) | 108 (24.1%) |
| **Site of metastatic disease — no. (%)** | | | | |
| n | 185 | 184 | 451 | 451 |
| Liver† | 44 (23.8%) | 39 (21.2%) | 126 (27.9%) | 118 (26.2%) |
| Bone | 54 (29.2%) | 49 (26.6%) | 145 (32.2%) | 141 (31.3%) |
| Brain | 15 (8.1%) | 11 (6.0%) | 30 (6.7%) | 31 (6.9%) |
| Lung | 86 (46.5%) | 98 (53.3%) | 226 (50.1%) | 242 (53.7%) |
| **Prior neoadjuvant or adjuvant treatment** | | | | |
| n | 185 | 184 | 451 | 451 |



| | | | | |
|---|---|---|---|---|
| no. (%) | 125 (67.6%) | 117 (63.6%) | 284 (63.0%) | 286 (63.4%) |
| **Prior taxane use†** | | | | |
| n | 185 | 184 | 451 | 451 |
| no. (%) | 96 (51.9%) | 94 (51.1%) | 231 (51.2%) | 230 (51.0%) |
| **Prior anthracycline use** | | | | |
| n | 185 | 184 | 451 | 451 |
| no. (%) | 109 (58.9%) | 101 (54.9%) | 243 (53.9%) | 242 (53.7%) |

* Two patients had ECOG PS 2 before start of treatment.

† As recorded in the case report form.

A + nabPx: atezolizumab + nab-paclitaxel; ECOG: Eastern Cooperative Oncology Group; ITT: intent-to-treat; PD-L1: programmed death-ligand 1; P + nabPx: placebo + nab-paclitaxel; SD: standard deviation

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

The information in this section comes from the supplementary material of Schmid et al. 2018 (13).

IMpassion130 was designed to randomise approximately 900 patients into the study. A single PFS definitive analysis for the ITT population was planned along with a definitive analysis of PFS in the PD-L1–positive subgroup and a first interim analysis of OS. The definitive PFS analysis and first interim OS analysis will hereafter be called the 'primary analysis'. A second interim OS analyses and a final analysis of OS were also planned. The timing for the first clinical cutoff was chosen based on both the expected number of required events for the definitive PFS analysis and the first interim analysis of OS.

The definitive analysis for the co-primary endpoint of PFS was designed to take place when approximately 600 PFS events had occurred in the ITT population (after approximately 30 months), based on the assumptions presented in Table 6.

**Table 6: Assumptions used in the statistical analysis of PFS and OS**

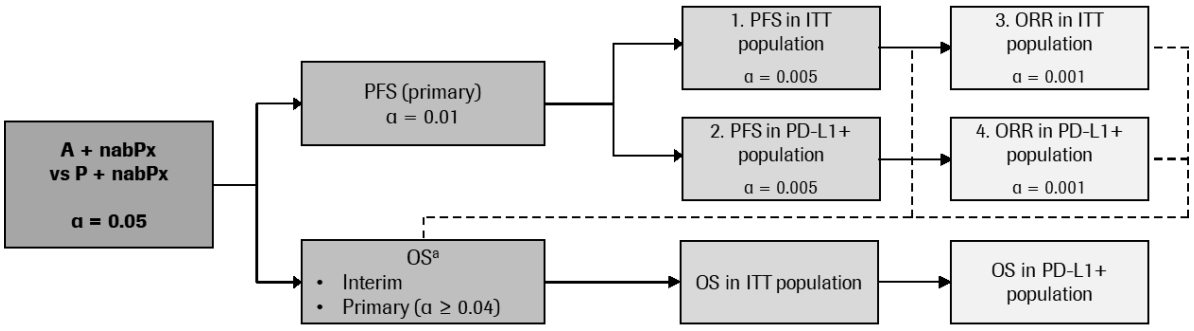
| Co-primary endpoint: Progression-free survival | Co-primary endpoint: Overall survival |
|---|---|
| • Two-sided, stratified log-rank test at the 0.005 significance level (two-sided) in the ITT population<br>• Approximately 95% power for PFS in ITT population<br>• Median PFS of 6 months in the placebo plus nab-paclitaxel arm and 10 months in the atezolizumab plus nab-paclitaxel arm (corresponding to an HR of 0.6) in the ITT population<br>• 2-month initial delay in the onset of the treatment effect<br>• 5% annual loss to follow-up for PFS<br>• No interim analysis for PFS in the ITT population | • Two-sided, stratified log-rank test at the 0.05 significance level (two-sided) in the ITT population<br>• Approximately 88% power for OS in the ITT population<br>• Median OS of 16 months in the placebo plus nab-paclitaxel arm and 20.5 months in the atezolizumab plus nab-paclitaxel arm (corresponding to an HR of 0.78) in the ITT population<br>• Assumption of proportionality<br>• 5% annual loss to follow-up for OS<br>• Two interim analyses, at approximately 50% and 80% of the information fraction |

ITT: intent-to-treat population; OS: overall survival; PFS: progression-free survival

In the primary PFS analysis, PFS was tested in ITT and PD-L1–positive populations in parallel and if both were positive, a small amount of alpha was assigned to test ORR. The first interim OS analysis was done sequentially, first in the ITT population, then if significant, in the PD-L1–positive population.

An overview of the statistical analysis plan is presented in Figure 3.

**Figure 3: Overview of statistical analysis plan**




A: atezolizumab; ITT: intention-to-treat; nabPx: nab-paclitaxel; ORR: overall response rate; OS: overall survival; P: placebo; PD-L1+: programmed death-ligand 1-positive; PFS: progression-free survival

[a]Tested in ITT population and then in PD-L1+ population if PFS/ORR testing was significant. Hazard ratio/p value stopping boundaries dependent on the OS analysis timing.

A second interim OS analysis was carried out when approximately 80% of the information fraction had occurred, with a CCOD of January 2019.

Company evidence document B submission for atezolizumab in combination with paclitaxel for untreated, locally advanced or metastatic, triple negative, PD-L1–positive breast cancer [ID1522].

The final OS analysis is designed to take place approximately 53 months after enrolment of the first patient (see supplementary material from Schmid 2018 for further details (13)).

#### B.2.4.1 Handling of missing data

For PFS, patients without a date of disease progression were analysed as censored observations on the date of last tumour assessment. If no post-baseline tumour assessment was available, PFS was censored at the date of randomisation plus 1 day (29).

For OS, patients who were not reported as having died were analysed as censored observations on the date they were last known to be alive. If no post-baseline data were available, OS was censored at the date of randomisation plus 1 day (29).

For objective response, patients without any post-baseline assessment were considered non-responders (29).

### *B.2.5 Quality assessment of the relevant clinical effectiveness evidence*

Critical appraisal of the included RCTs was performed using established risk of bias tools recommended for health technology assessment (HTA) submissions. The complete quality assessment is provided in Appendix D.

## *B.2.6 Clinical effectiveness results of the relevant trials*

- **IMpassion130 for atezolizumab plus nab-paclitaxel compared with placebo plus nab-paclitaxel in patients with untreated mTNBC is the only trial relevant for this submission**

**At the primary analysis (definitive PFS analysis and first interim OS analysis), in the PD-L1–positive subpopulation:**

- **Treatment with A + nabPx compared with P + nabPx resulted in both a statistically significant and clinically meaningful improvement in PFS with a relative risk reduction of 38% (median PFS: 7.5 months vs. 5.0 months, stratified HR: 0.62; 95% CI: 0.49–0.78, p-value<0.001) (13-15)**

- **A clinically meaningful reduction in the risk of death of 38% was observed with A + nabPx compared with P + nabPx (stratified HR: 0.62; 95% CI: 0.45–0.86) (Figure 5). This was accompanied by a 10-month prolongation in the Kaplan-Meier estimated median OS in the A + nabPx arm vs. P + nabPx (25.0 months vs. 15.5 months)**

- **The risk of disease progression or death was reduced by 40% with A + nabPx relative to P + nabPx (unstratified HR: 0.60; 95% CI; 0.43–0.86), and the median estimated DOR was 3 months longer in the A + nabPx arm (8.5 months vs. 5.5 months in the P + nabPx arm)**

- **HRQoL was similar in both treatment arms in PD-L1–positive patients who were progression free (HSUV in both treatment arms: 0.71)**

**At the second interim analysis, in the PD-L1–positive subpopulation:**

[redacted]



The Phase III results from IMpassion130 presented below were based on the definitive analysis of PFS and first interim analysis of OS (CCOD: 17th April 2018) when 736 PFS events and 389 deaths had occurred. The study enrolled an "all-comer" patient population, therefore the results presented below include both the all-comer population and the PD-L1–selected subpopulation. Unless otherwise stated, the content in this section comes from Schmid et al. 2018 (13).

**Table 7: Overview of IMpassion130 efficacy**

| | **PD-L1–positive** | | **ITT** | |
|---|---|---|---|---|
| | **A + nabPx n=185** | **P + nabPx n=184** | **A + nabPx n=451** | **P + nabPx n=451** |
| **Co-Primary Endpoint: Investigator-Assessed Progression-Free Survival** | | | | |
| No. (%) of patients with events | 138 (74.6%) | 157 (85.3%) | 358 (79.4%) | 378 (83.8%) |
| Median, months | 7.5 | 5 | 7.2 | 5.5 |
| Stratified hazard ratio (95% CI)<br>p-value (log-rank) | 0.62 (0.49–0.78)<br><0.0001 | | 0.80 (0.69–0.92)<br>0.0025 | |
| **Co-Primary Endpoint: Overall Survival** | | | | |
| No. (%) of patients with events | 64 (34.6%) | 88 (47.8%) | 181 (40.1%) | 208 (46.1%) |
| Median, months | 25 | 15.5 | 21.3 | 17.6 |
| Stratified hazard ratio (95% CI)<br>p-value (log-rank) | 0.62 (0.45–0.86)<br>0.0035* | | 0.84 (0.69–1.02)<br>0.0840 | |
| **Secondary Endpoints: Objective Response Rate** | | | | |
| No. of evaluable patients | 185 | 183 | 450 | 449 |
| ORR, N (%) | 109 (58.9%) | 78 (42.6%) | 252 (56.0%) | 206 (45.9%) |
| Difference in ORR, % (95% CI)<br>p-value (Cochran-Mantel-Haenszel) | 16.3% (5.7% –26.9%)<br>p = 0.0016 | | 10.1% (3.4%–16.8%)<br>p = 0.0021 | |
| **Secondary Endpoints: Duration of Response** | | | | |
| No. of evaluable patients | 109 | 78 | 252 | 206 |
| No. (%) of patients with events | 70 (64.2%) | 59 (75.6%) | 174 (69.0%) | 154 (74.8%) |
| Median, months | 8.5 | 5.5 | 7.4 | 5.6 |
| Unstratified hazard ratio (95% CI)<br>p-value (log-rank) | 0.60 (0.43–0.86)<br>0.0047 | | 0.78 (0.63–0.98)<br>0.0285 | |

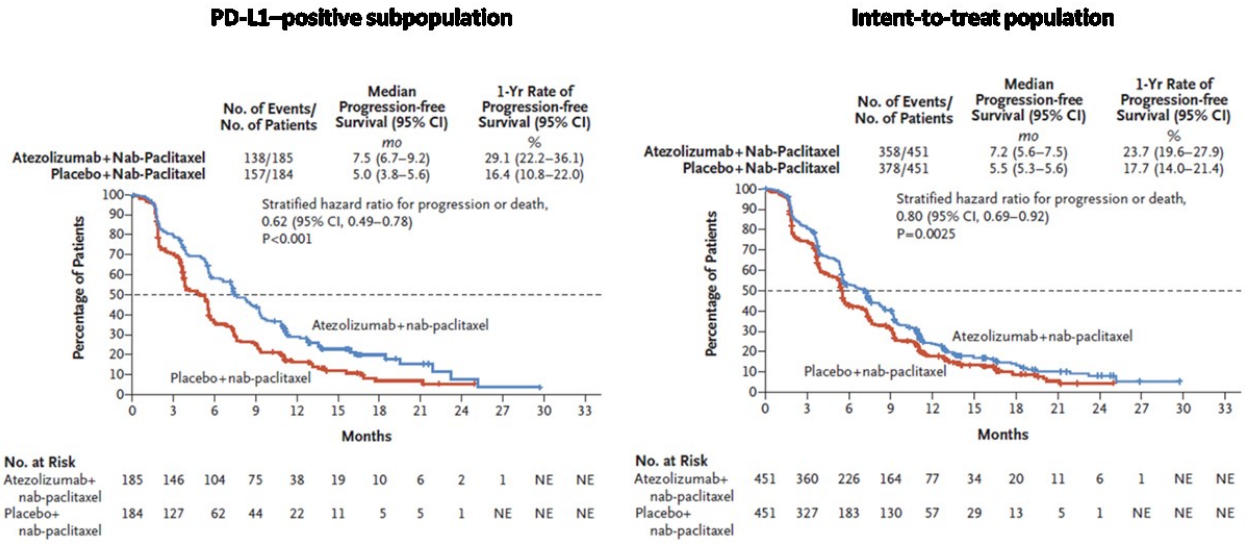

 

A + nabPx: atezolizumab + nab-paclitaxel; CI: confidence interval; HRQoL: health-related quality of life; ITT: intent-to-treat; ORR: objective response rate; PD-L1: programmed death-ligand 1; P + nabPx: placebo + nab-paclitaxel

### B.2.6.1 Co-primary efficacy endpoint: Investigator-assessed progression-free survival

**Definitive PFS analysis**: Compared with the A + nabPx arm, more patients in the P + nabPx arm of the PD-L1–positive subpopulation had progressed or died at the date of data cutoff (74.6% vs. 85.3%). Treatment with A + nabPx compared with P + nabPx resulted in both a statistically significant and clinically meaningful improvement in PFS with a relative risk reduction of 38%; (stratified HR: 0.62; 95% CI: 0.49–0.78, p-value<0.001) (29) (Figure 4). The Kaplan-Meier estimated median PFS was longer in the A + nabPx arm vs. the P + nabPx arm (7.5 months vs. 5.0 months) and the 1-year event free-rate was nearly doubled with A + nabPx (29.1% vs. 16.4%, respectively). Please see Appendix N for a summary of the investigator-assessed PFS results.

**Figure 4: Kaplan-Meier plot of investigator-assessed PFS, date of data cutoff: 17th April 2018**




Censored events are indicated with a + symbol.

CI: confidence interval; mo: months; PD-L1: programmed death-ligand 1

A sensitivity analysis based on the IRC-assessment of PFS was performed and showed a similar benefit for the A + nabPx arm to that seen in the investigator-based analysis (HR: 0.63; 95%CI: 0.49–0. 81).

[redacted]

### B.2.6.2 Co-primary endpoint: overall survival

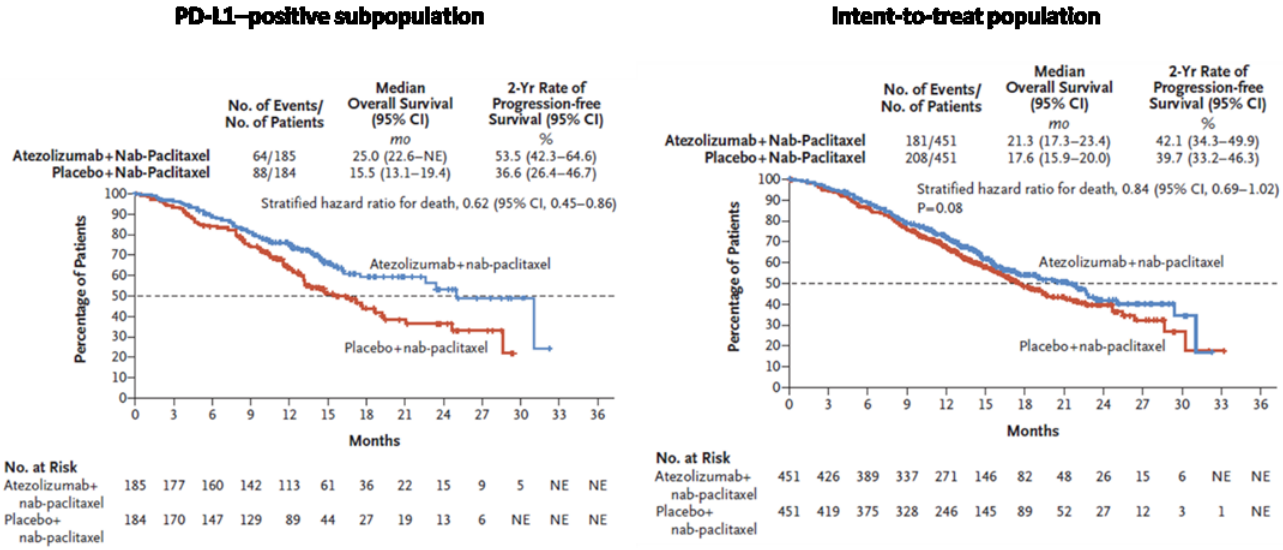
Note: No formal testing of OS was performed in the PD-L1–positive population because hierarchy of testing indicates formal testing can only occur if OS is statistically significant in the ITT population first (29).

**First interim OS analysis**: In the PD-L1–positive population, 64 of 185 patients (34.6%) in the A + nabPx arm and 88 of 184 (47.8%) in the P + nabPx arm had died. A clinically meaningful reduction in the risk of death of 38% was observed with A + nabPx compared with P + nabPx (stratified HR: 0.62; 95% CI: 0.45–0.86) (Figure 5) (29). This was accompanied by a 10-month prolongation in the Kaplan-Meier estimated median OS in the A + nabPx arm vs. P + nabPx (25.0 months vs. 15.5 months). There was a clear separation in the Kaplan-Meier curves favouring A + nabPx from around 3 months, and the separation was maintained over time. Please see Appendix N for a summary of the OS results.

At 2 years, more than half the patients in the PD-L1–positive A + nabPx arm were alive (53.5%) compared with approximately one-third (36.6%) in the P + nabPx arm.

**Figure 5: Kaplan-Meier plot of overall survival, date of data cutoff: 17th April 2018**




Censored events are indicated with a + symbol.

CI: confidence interval; mo: months; NE: not estimable; PD-L1: programmed death-ligand 1

[redacted]

### B.2.6.3 Secondary endpoint: Investigator-assessed objective response rate

Among patients in the PD-L1–positive population with measurable disease at baseline, a numerically higher ORR was seen in the A + nabPx arm (58.9%) compared with the P + nabPx arm (42.6%). The majority of responders achieved a partial response, although there were notably more complete responses in the A + nabPx arm (10.3% vs. 1.1% in the P + nabPx arm). Overall, the proportion of patients with missing or unevaluable response assessments was low and comparable between the arms. Please see Appendix N for a summary of the investigator-assessed ORR results.

### B.2.6.4 Secondary endpoint: Investigator-assessed duration of response

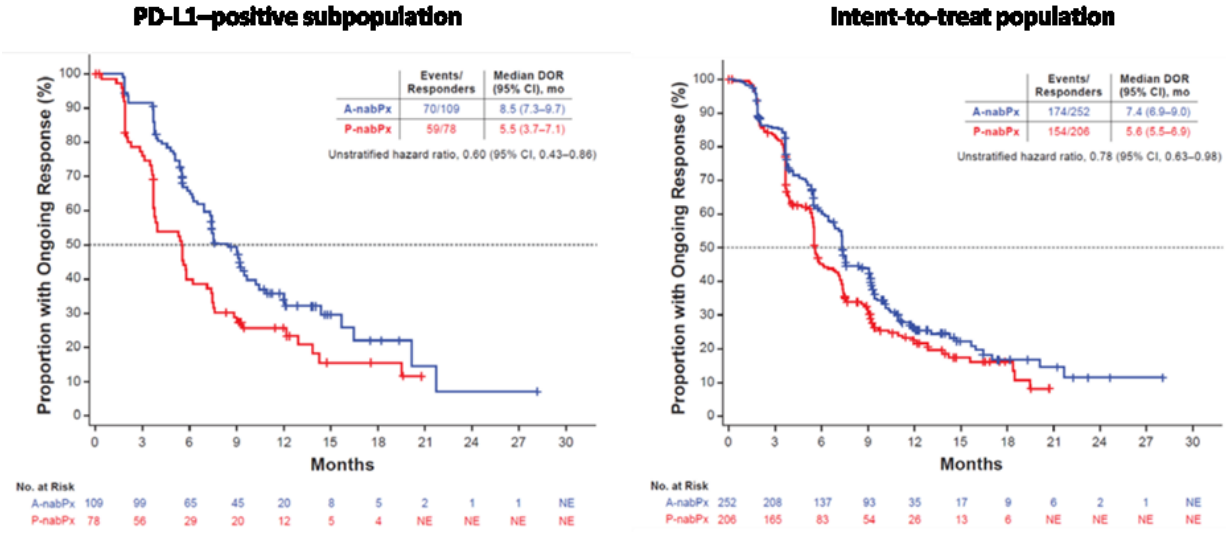
Treatment with A + nabPx resulted in a prolonged DOR compared with P + nabPx. Among responders, more patients in the A + nabPx arm (35.8%) had ongoing responses by the cutoff date compared with the P + nabPx arm (24.4%). The risk of disease progression or

death was reduced by 40% with A + nabPx relative to P + nabPx (unstratified HR: 0.60; 95% CI; 0.43–0.86), and the median estimated DOR was 3 months longer in the A + nabPx arm (8.5 months vs. 5.5 months in the P + nabPx arm, Figure 6). Please see Appendix N for a summary of the investigator-assessed DOR results.

There was a clear separation in the Kaplan-Meier curves in favour of A + nabPx at around 2.5 months, which was maintained over time.

**Figure 6: Kaplan-Meier plot of duration of response (Investigator-assessed), date of data cutoff: 17th April 2018**




Ongoing response refers to no progressive disease or death. Hazard ratios for progression or death are reported along with P values.

Censored events are indicated with a + symbol.

A-nabpx: atezolizumab + nab-paclitaxel; CI: confidence interval; PD-L1: programmed death-ligand 1; P-nabPx: placebo + nab-paclitaxel

### B.2.6.5 Health-related quality of life and patient-reported outcomes

Health-related quality of life (HR-QoL) outcomes data were collected within the IMPassion130 trial. The instruments used were: the European Quality of Life-5 Dimensions-5 Level (EQ-5D-5L) 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.

EQ-5D-5L questionnaires were completed at baseline (Cycle 1, Day 1), and then Day 1 of each 28-day subsequent cycle thereafter, at the treatment discontinuation visit, and during survival follow-up. Patients also completed EQ-5D-5L every 28 days for 1 year after

treatment discontinuation. Quality of life (QoL) estimates on progression-free and post-progression states have been collected. The results are provided in Table 8.

**Table 8: EQ-5D-5L utility estimates from IMpassion130**

| Health state | Health state | Utility value | 95% Confidence Intervals |
|---|---|---|---|
| Progression Free | Both treatment arms | 0.726 | 0.706, 0.746 |
| | A + nabPx | 0.741 | 0.711, 0.770 |
| | P + nabPx | 0.710 | 0.684, 0.736 |
| Progressive disease | Both treatment arms | 0.653 | 0.631, 0.675 |

A + nabPx: atezolizumab plus nab-paclitaxel; P + nabPx: placebo plus nab-paclitaxel

Health state utility values are scored on a scale that assigns a value of 1 to a state equivalent to full health and 0 to a state equivalent to death

For further results of the HRQoL analysis and patient-reported outcomes from the IMpassion130 study, please see Section B.3.4.1 and Appendix N.

## *B.2.7 Subgroup analysis*

**Exploratory analysis: efficacy in immune biomarker subgroups**

- **Expression of PD-L1 on ICs was predictive of clinical benefit with A + nabPx, regardless of BRCA status (21)**
- **In CD8+ and TIL+ subgroups, clinical benefit was only evident if tumours were also PD-L1 IC+ (21)**
- **The exploratory analysis confirms the role of PD-L1 IC expression as a biomarker for benefit from A + nabPx in 1L mTNBC (21)**

To assess the consistency of study results in subgroups defined by demographic and baseline characteristics, PFS, ORR, and OS in these subgroups were examined. A summary of these results is available in appendix E. In addition, an exploratory analysis of biomarker subgroups was carried out and is detailed below.

### Exploratory analysis: Efficacy in immune biomarker subgroups

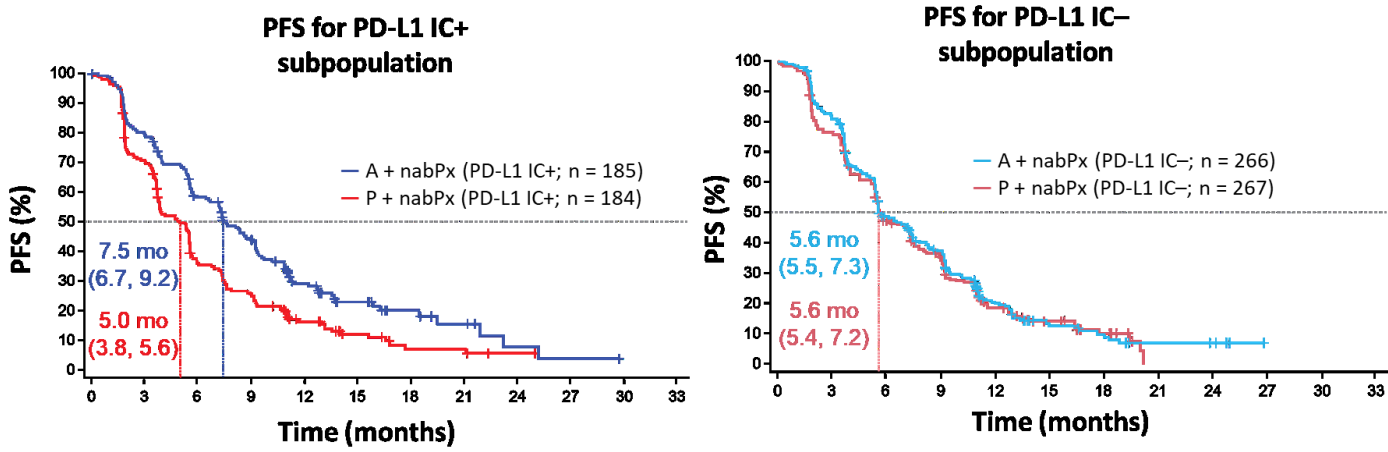
The IMpassion130 study demonstrated that expression of PD-L1 on tumour-infiltrating ICs was predictive of benefit with A + nabPx (13). An exploratory analysis was also carried out to assess PD-L1 in IC-positive (IC+) subgroups, PD-L1 on TCs, CD8+ T cells, stromal TILs and BReast CAncer gene (BRCA) 1/2 mutation status as other potential biomarkers (21).

This analysis confirmed the efficacy of A + nabPx in the PD-L1 IC+ subpopulation compared with the PD-L1 IC-negative (IC-) subpopulation (Figure 7, Figure 8, Table 9, Table 10) (21). For the CD8+ and TIL+ subgroups, clinical benefit was evident only if the tumours were also PD-L1 IC+ (Table 11). Furthermore, patients with PD-L1–positive tumours derived clinical benefit regardless of BRCA status (Table 11) (21).

The results confirm the role of PD-L1 IC expression as a biomarker for clinical benefit from A + nabPx in 1L mTNBC (21).

**Figure 7: Kaplan-Meier plot of progression-free survival, date of data cutoff: 17th April 2018 (21)**




A + nabPx: atezolizumab + nab-paclitaxel; IC: immune cells; P + nabPx: atezolizumab + nab-paclitaxel; PD-L1: programmed death-ligand 1; PFS: progression-free survival

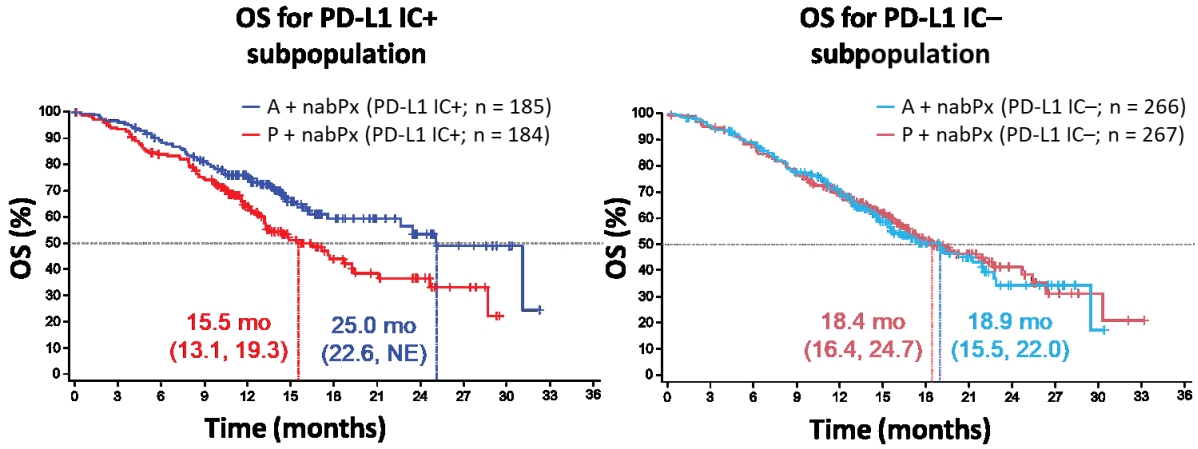
**Table 9: Progression-free survival hazard ratios for the PD-L1 IC+ and IC- subpopulations, date of data cutoff: 17th April 2018 (21)**

| Subpopulation | PFS HR (95% CI) | HR *P* Value | Interaction Test (treatment × PD-L1 IC) P Value |
|---|---|---|---|
| PD-L1 IC+ | 0.62 (0.49, 0.78) | <0.0001 | 0.0055 |
| PD-L1 IC– | 0.94 (0.78, 1.13) | 0.5152 | |

Stratified HRs are shown. All *P* values except for PD-L1 IC+ PFS are nominal *P* values.

HR: hazard ratio; IC: immune cells; PFS: progression-free survival

**Figure 8: Kaplan-Meier plot of overall survival, date of data cutoff: 17th April 2018 (21)**




A + nabPx: atezolizumab + nab-paclitaxel; Mo: months; NE: not estimable; OS: overall survival; P + nabPx; placebo + nab-paclitaxel; PD-L1: programmed death-ligand 1

**Table 10: Overall survival hazard ratios for the PD-L1 IC+ and IC- subpopulations , date of data cutoff: 17th April 2018 (21)**

| Population | OS HR (95% CI) | HR *P* Value | Interaction Test (treatment × PD-L1 IC) *P* Value |
|---|---|---|---|
| PD-L1 IC+ | 0.62 (0.45, 0.86) | 0.0035 | 0.0178 |
| PD-L1 IC– | 1.02 (0.79, 1.31) | 0.9068 | |

Stratified HRs are shown. All *P* values except for PD-L1 IC+ PFS are nominal *P* values.

CI: confidence interval; HR: hazard ratio; IC: immune cells; OS: overall survival; PD-L1: programmed death-ligand 1; PFS: progression-free survival

**Table 11: Clinical benefit derived by PD-L1 IC+/- patients depending on their CD8, TIL, or BRCA mutation status**

| | PFS HR (95% CI, p-value) | OS HR (95% CI, p-value) |
|---|---|---|
| CD8–/PD-L1 IC+ (n = 37) | 0.33 (0.13, 0.87, p=0.03) | 0.25 (0.06, 1.02, p=0.05) |
| CD8+/PD-L1 IC+ (n = 280) | 0.61 (0.46, 0.80, p≤0.005) | 0.55 (0.38, 0.80, p≤0.005) |
| CD8+/PD-L1 IC– (n = 220) | 0.89 (0.66, 1.20, p=0.45) | 0.77 (0.50, 1.17, p=0.21) |
| TIL–/PD-L1 IC+ (n = 176) | 0.74 (0.54, 1.03, p=0.07) | 0.65 (0.41, 1.02, p=0.06) |
| TIL+/PD-L1 IC+ (n = 190) | 0.53 (0.38, 0.74, p≤0.005) | 0.57 (0.35, 0.92, p=0.02) |
| TIL+/PD-L1 IC– (n = 94) | 0.99 (0.62, 1.57, p=0.97) | 1.53 (0.76, 3.08, p=0.24) |

Company evidence document B submission for atezolizumab in combination with paclitaxel for untreated, locally advanced or metastatic, triple negative, PD-L1–positive breast cancer [ID1522].

| | | |
|---|---|---|
| BRCA1/2 non-mut/PD-L1 IC+ (n = 257) | 0.63 (0.48, 0.83, p≤0.005) | 0.62 (0.43, 0.91, p=0.01) |
| BRCA1/2 mut/PD-L1 IC+ (n = 45) | 0.45 (0.21, 0.96, p=0.04) | 0.87 (0.26, 2.85, p=0.82) |
| BRCA1/2 mut/PD-L1 IC– (n = 44) | 0.77 (0.37, 1.61, p=0.49) | 0.85 (0.29, 2.43, p=0.76) |

CI: confidence interval; HR: hazard ratio; IC: immune cells; OS: overall survival; PD-L1: programmed death-ligand 1; PFS: progression-free survival; TIL: tumour infiltrating lymphocyte

### *B.2.8 Meta-analysis*

The evidence source for atezolizumab in combination with nab-paclitaxel in untreated mTNBC is made up of one clinical randomised controlled trial: the IMpassion130 phase III study, which compared atezolizumab in combination with nab-paclitaxel to placebo in combination with atezolizumab. However, the trial comparator (nab-paclitaxel) is not a comparator in the final scope. Therefore, a simple pairwise comparison meta-analysis was not feasible and an indirect treatment comparison (ITC) was considered to be appropriate.

## *B.2.9 Indirect and mixed treatment comparisons*

- **Due to the unconnected networks for each of OS and PFS, it was necessary to conduct matching adjusted indirect comparisons (MAICs) to enable a comparison of atezolizumab in combination with nab-paclitaxel to comparators of interest from the NICE scope**
- **Sufficient evidence to enable a comparison to paclitaxel and docetaxel were identified, but no RCTs were identified to allow a comparison to anthracyclines**
- **Three trials were used in the matching adjustments: E2100 (10, 11) and MERIDIAN (for a paclitaxel comparison) (12) and AVADO (for docetaxel comparison) (16, 17)**
- **For OS, the piecewise exponential with one cut point at 5 months was considered the best fitting model, with random effects utilised in the base case to account for heterogeneity**
- **For PFS, the piecewise exponential with cut points at 4 and 7 months was selected as the most suitable model, with random effects utilised in the base case to account for heterogeneity**
- **The posterior median restricted mean 5-year OS survival gains of atezolizumab in combination with nab-paclitaxel compared with paclitaxel and docetaxel were 12.13 and 11.74 months, respectively**
- **The posterior median restricted mean 5-year PFS gains compared with paclitaxel and docetaxel were 2.63 and 3.32 months, respectively**

A systematic review (SR) of clinical evidence was conducted to identify potential studies for use in indirect comparisons between atezolizumab in combination with nab-paclitaxel, and the comparators of interest for this NICE appraisal: paclitaxel, docetaxel and anthracyclines. The methodology of this SR is detailed in Appendix D.

The electronic databases Medline, Embase, and the Cochrane library were searched on 27th July 2018. Additional searches of congress proceedings from the past three years, reference lists of included publications, Health Technology Assessment (HTA) bodies, and Company evidence document B submission for atezolizumab in combination with paclitaxel for untreated, locally advanced or metastatic, triple negative, PD-L1–positive breast cancer [ID1522].

the International Clinical Trials Registry Platform (ICTRP) were conducted to identify relevant evidence. The SR included trials conducted in adult patients (≥ 18 years) with locally advanced/metastatic HER2-negative breast cancer, receiving treatment in the first-line setting that included at least a proportion of patients with TNBC (any study not reporting the proportion of patients with TNBC was excluded). The trials searched for contained the following interventions: atezolizumab, nab-paclitaxel, paclitaxel, docetaxel, anthracycline therapies as well as several other chemotherapies (beyond the final scope of this appraisal).

Records were reviewed based on title and abstract in the first instance, and those included were reviewed based on the full publication. Data pertaining to study design, baseline characteristics, and treatment outcomes were extracted from the included publications into a data extraction table (DET) by an analyst. All extracted data were independently checked against the source document by a second analyst. Quality (risk of bias) assessment of RCTs was conducted as per the NICE user guide for company evidence submissions (Appendix D D.1.3). For full details on the eligibility criteria and process, please see Appendix D.

The electronic database search identified a total of 7,316 articles. In total, 6,534 articles were excluded, and 121 articles were deemed potentially relevant. Upon review of the full publications, a further 78 articles were excluded, and 47 publications were included in the systematic review. Hand searching yielded an additional seven publications for inclusion. A total of 54 publications relating to 39 unique trials met the inclusion criteria for the systematic review. Of the 39 trials included in the systematic review 25 were categorised as ‘mixed studies’ conducted in patients with advanced or metastatic breast cancer that included a proportion of patients with TNBC and 14 trials were conducted exclusively in TNBC populations.

Paclitaxel (single agent) and docetaxel (single agent) randomised controlled trials (RCTs) were identified – however, no anthracyclines RCTs were identified.

As detailed in section B1.3, eligibility for 1L metastatic TNBC patients for anthracyclines is limited: Approximately 80% of this population will have progressed to the metastatic setting from the eBC setting, where anthracyclines are a preferred treatment regimen. Re-challenge with anthracyclines is hindered by lifetime maximum cumulative dose (e.g. epirubicin (25)) and as such, patients treated in the eBC setting are unlikely to be eligible for re-challenge. As such, these regimens are rarely used within this setting. This is supported by observational data from a UK clinical practice demonstrating a mere 7.5% usage in 1L mTNBC (32).

Nevertheless, an effort was made to explore a comparison through the use of RWE. Appendix P details the approach taken, and baseline characteristics assessment. The population available for such a comparison was too distinct from the IMpassion130 patient population for a robust comparison. Given the limited real world usage, the lack of trial evidence identified in the clinical SR to provide a comparison, and insufficient alignment of populations in the RWE to provide a comparison, no clinical effectiveness comparisons can be made to anthracyclines and subsequently, no cost-effectiveness analyses can be generated for this comparison.

Thirteen of the trials included in the clinical evidence SR contained, at a minimum, OS or PFS data that could be used for indirect comparisons. Twenty-six trials were excluded from the network meta-analysis (NMA) (see Appendix D for full methods).

Table 12 provides a summary of the 13 trials included in the final network (bold text details the trials of relevance to the final scope comparators), and **Figure 9** and **Figure 10** demonstrate the resulting OS and PFS networks. Beyond the IMpassion130 trial, no trials reported outcomes for patients with PD-L1–positive mTNBC, and so it is assumed that the chemotherapy treatments perform equivalently across PD-L1–positive and negative patients. Based upon the IMpassion130 trial, where patients PD-L1–positive and negative patients were enrolled, this assumption may not hold true.

The present evidence synthesis uses data from the “primary analysis” of the IMpassion130 trial. The methodology features the full network of evidence, however for clarity, the results presented only feature the comparators of interest for this appraisal: paclitaxel and docetaxel.

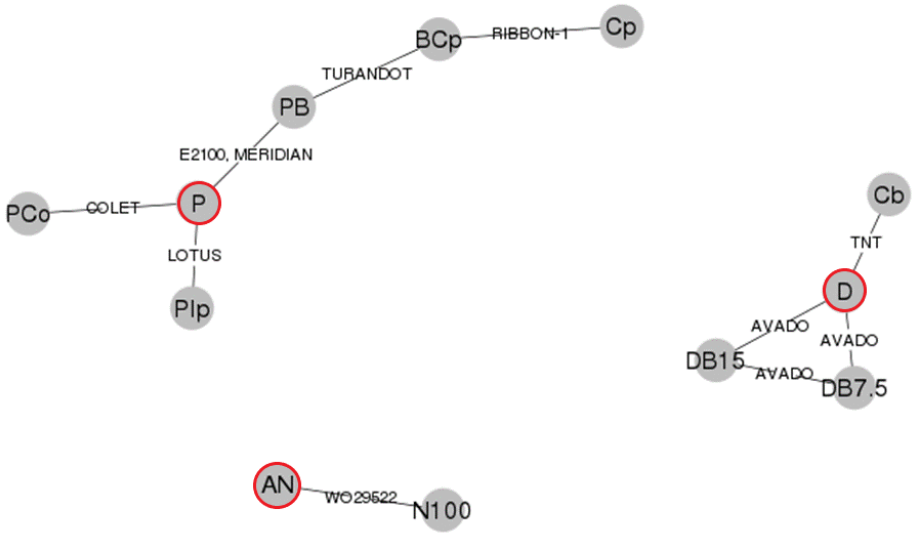
**Table 12: Summary of the trials for conduct of the indirect comparisons**

| References of trial | Atezolizumab + paclitaxel | Nab-paclitaxel | Paclitaxel | Docetaxel | Anthracycline therapies | Bevacizumab + paclitaxel | Capecitabine + bevacizumab | Capecitabine | Bevacizumab + nab-paclitaxel | Ixabepilone + bevacizumab | Capecitabine + bevacizumab + vinorelbine | Cobimetinib + paclitaxel | Ipataserib + paclitaxel | Carboplatin | Lapatinib |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IMpassion130 (Primary analysis: data cutoff April 2018) (13) | ✓ | ✓ | | | | | | | | | | | | | |
| AVADO (16, 17) | | | | ✓ | | | | | | | | | | | |
| CALGB40502 (79, 80) | | | | | | ✓ | | | ✓ | | | | | | |
| CARIN (81) | | | | | | | ✓ | | | | ✓ | | | | |
| COLET [13](82) | | | ✓ | | | | | | | | | ✓ | | | |
| E2100 [14, 15](10, 11) | | | ✓ | | | ✓ | | | | | | | | | |
| EGF30001 (83, 84) | | | ✓ | | | | | | | | | | | | ✓ |
| JapicCTI-090921 (85) | | ✓ | | ✓ | | | | | | | | | | | |
| LOTUS (86, 87) | | | ✓ | | | | | | | | | | ✓ | | |
| MERIDIAN (12, 14, 15) | | | ✓ | | | ✓ | | | | | | | | | |
| RIBBON-1 (88) | | | | | | | ✓ | ✓ | | | | | | | |
| TNT (89-92) | | | | ✓ | | | | | | | | | | ✓ | |
| TURANDOT (93-96) | | | | | | ✓ | ✓ | | | | | | | | |



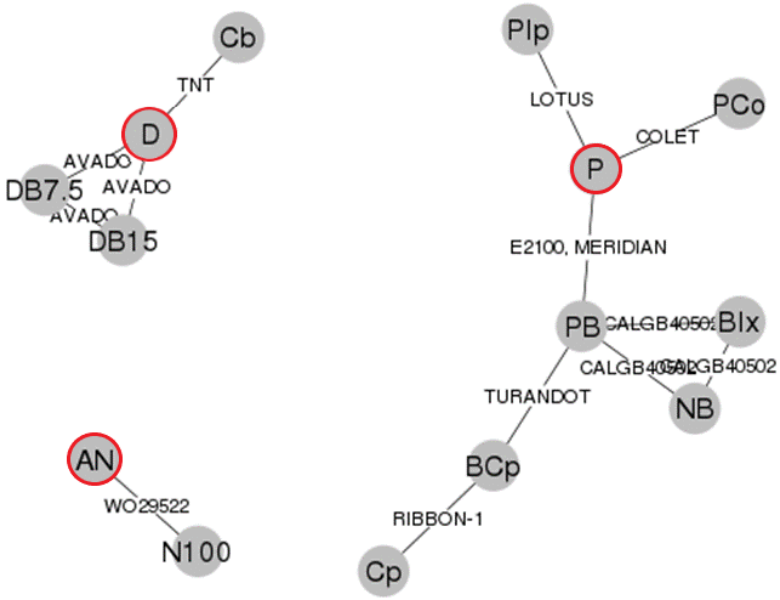
 

**Figure 9: Network of trials for OS (unconnected)**




AN: Atezolizumab + nab-paclitaxel; P: Paclitaxel; D: Docetaxel; BCp: Bevacizumab + Capecitabine; Bix: Bevacizumab + Ixabepilone; Cb: Carboplatin; C: Capecitabine; DB15: Docetaxel + Bevacizumab; DB7.5: Docetaxel + Bevacizumab; N100: Nab-paclitaxel; NB: Nab-paclitaxel; + Bevacizumab; PB: Paclitaxel + bevacizumab; PCo: Paclitaxel + cobimetinib; Pip: Paclitaxel + ipatasertib

**Figure 10: Network of trials for PFS (unconnected)**




AN: Atezolizumab + nab-paclitaxel; P: Paclitaxel; D: Docetaxel; BCp: Bevacizumab + Capecitabine; Bix: Bevacizumab + Ixabepilone; Cb: Carboplatin; C: Capecitabine; DB15: Docetaxel+ Bevacizumab; DB7.5: Docetaxel + Bevacizumab; N100: Nab-paclitaxel; NB: Nab-paclitaxel + Bevacizumab; P: Paclitaxel; PB: Paclitaxel + bevacizumab; PCo: Paclitaxel + cobimetinib; Pip: Paclitaxel + ipatasertib

### B.2.9.1 Method of Matching adjustment

Due to the unconnected networks for each of OS and PFS (Figure 9, Figure 10), it was necessary to conduct matching adjusted indirect comparisons (MAICs) to enable a comparison of atezolizumab in combination with nab-paclitaxel to both paclitaxel and docetaxel.

From the 13 trials incorporated in the network, an assessment was undergone to determine which comparators (and resulting trials) should be utilised to connect the network. Given both paclitaxel and docetaxel were considered the most critical comparators for a number of countries (including the UK), these became the linking trials to connect the network. By connecting directly to the paclitaxel and docetaxel studies, as opposed to any of the others within the ITC allowed for any additional uncertainty to be reduced within the analysis.

Three trials were used in the matching adjustments: E2100 (10, 11) and MERIDIAN (for a paclitaxel comparison) (12, 14, 15) and AVADO (for docetaxel comparison) (16, 17). All three studies were Roche-sponsored studies; hence individual patient level data could be accessed. The TNT trial was also assessed for the docetaxel comparison, however due to lack of individual patient level data was excluded in favour of more robust methods of matching covariates.

All trials were Roche-sponsored studies, allowing for access to individual patient level data. The E2100 study was particularly appropriate because of the high number of TNBC cases (n=230). The MERIDIAN study included fewer TNBC (n=78) but provided more variables than E2100 and was a more recent study. Both trials had generally similar patient characteristics to the IMpassion130 trial. AVADO was the only trial investigating docetaxel for which individual-patient level data were available to Roche. Its patients also generally had similar patient characteristics to the IMpassion130 trial. Patient characteristics between these three trials were directly compared with IMpassion130 trial using frequency distributions (Appendix D).

A covariate balancing propensity score model was used for estimating the weights used in the matching of atezolizumab + nab paclitaxel patients to comparison studies. The results of the baseline characteristics that were matched for the comparison with paclitaxel (E2100 and MERIDIAN trials) are provided in Table 13 to Table 16. The baseline characteristics that were matched for the comparison with docetaxel (AVADO trial) are provided in Table 17 and Table 18.

**Table 13: Weighted summary statistics of matching variables for matching to the E2100 (paclitaxel) trial - OS**

| | E2100 (paclitaxel) | Atezolizumab + nab-paclitaxel | p | SMD |
|---|---|---|---|---|
| **neff (Effective sample size)** | 230.00 | 59.43 | | |
| **Age** | 54.69 (11.59) | 54.64 (12.35) | 0.977 | 0.004 |
| **Race: White** | 0.74 (0.44) | 0.74 (0.44) | 0.990 | 0.002 |
| **Race: Black** | 0.13 (0.34) | 0.13 (0.34) | 0.998 | <0.001 |
| **Race: Asian** | 0.01 (0.09) | 0.01 (0.10) | 0.861 | 0.012 |
| **Time from treatment initiation to metastatic diagnosis** | 3.49 (3.74) | 3.46 (4.31) | 0.970 | 0.007 |
| **Time from metastatic diagnosis to randomisation** | 0.33 (0.93) | 0.31 (0.28) | 0.848 | 0.022 |
| **Metastatic disease** | 0.97 (0.18) | 0.97 (0.18) | 0.998 | <0.001 |
| **Number of disease sites** | 2.47 (1.17) | 2.46 (1.07) | 0.992 | 0.001 |
| **Bone metastases** | 0.37 (0.48) | 0.36 (0.48) | 0.980 | 0.004 |
| **Liver metastases** | 0.28 (0.45) | 0.28 (0.45) | 0.969 | 0.005 |
| **Lung metastases** | 0.53 (0.50) | 0.53 (0.50) | 0.996 | 0.001 |
| **Prior anthracycline treatment** | 0.57 (0.50) | 0.57 (0.50) | 0.983 | 0.003 |
| **Prior adjuvant taxane treatment** | 0.28 (0.45) | 0.28 (0.45) | 0.984 | 0.002 |

P-value from a Chi-square test; SMD: Standardized mean difference defined as the difference in means divided by the pooled standard deviation; neff: Effective sample size as defined in Phillippo et al. (97).

**Table 14: Weighted summary statistics of matching variables for matching to the E2100 (paclitaxel) trial – PFS**

| | E2100 (paclitaxel) | Atezolizumab + nab-paclitaxel | p | SMD |
|---|---|---|---|---|
| **$n_{eff}$ (Effective sample size)** | 230.00 | 79.06 | | |
| **Age** | 54.69 (11.59) | 54.69 (12.05) | 1.000 | <0.001 |
| **Race: White** | 0.74 (0.44) | 0.74 (0.44) | 0.998 | <0.001 |
| **Race: Black** | 0.13 (0.34) | 0.13 (0.34) | 0.999 | <0.001 |
| **Race: Asian** | 0.01 (0.09) | 0.01 (0.09) | 0.970 | 0.003 |
| **Time from treatment initiation to metastatic diagnosis** | 3.49 (3.74) | 3.49 (4.40) | 1.000 | <0.001 |
| **Time from metastatic diagnosis to randomisation** | 2.47 (1.17) | 2.47 (1.14) | 1.000 | <0.001 |
| **Metastatic disease** | 0.37 (0.48) | 0.37 (0.48) | 1.000 | <0.001 |

| | | | | |
|---|---|---|---|---|
| **Number of disease sites** | 0.28 (0.45) | 0.28 (0.45) | 1.000 | <0.001 |
| **Bone metastases** | 0.53 (0.50) | 0.53 (0.50) | 1.000 | <0.001 |
| **Liver metastases** | 0.57 (0.50) | 0.57 (0.50) | 1.000 | <0.001 |
| **Lung metastases** | 0.28 (0.45) | 0.28 (0.45) | 0.999 | <0.001 |

P-value from a Chi-square test; SMD: Standardized mean difference defined as the difference in means divided by the pooled standard deviation; neff: Effective sample size as defined in Phillippo et al. (97).

### Table 15: Weighted summary statistics of matching variables for matching to the MERIDIAN trial - OS

| | MERIDIAN (paclitaxel) | Atezolizumab + nab-paclitaxel | p | SMD |
|---|---|---|---|---|
| **$n_{eff}$ (Effective sample size)** | 78.00 | 87.67 | | |
| **Age** | 54.83 (11.41) | 54.83 (13.70) | 1.000 | <0.001 |
| **Height** | 160.88 (7.71) | 160.88 (8.95) | 1.000 | <0.001 |
| **Bmi** | 28.09 (6.11) | 28.09 (6.80) | 1.000 | <0.001 |
| **Region: North America & Europe** | 0.42 (0.50) | 0.42 (0.50) | 1.000 | <0.001 |
| **Region: Asia** | 0.24 (0.43) | 0.24 (0.43) | 1.000 | <0.001 |
| **Race: White** | 0.56 (0.50) | 0.56 (0.50) | 1.000 | <0.001 |
| **Race: Black** | 0.14 (0.35) | 0.14 (0.35) | 1.000 | <0.001 |
| **Race: Asian** | 0.24 (0.43) | 0.24 (0.43) | 1.000 | <0.001 |
| **ECOG = 0** | 0.64 (0.48) | 0.64 (0.48) | 1.000 | <0.001 |
| **Number of disease sites** | 2.41 (1.13) | 2.41 (1.06) | 1.000 | <0.001 |
| **Sum of longest diameters of lesions** | 69.32 (52.43) | 69.32 (66.00) | 1.000 | <0.001 |
| **Time from metastatic diagnosis to randomisation** | 0.27 (0.62) | 0.27 (0.29) | 1.000 | <0.001 |
| **Bone metastases** | 0.26 (0.44) | 0.26 (0.44) | 1.000 | <0.001 |
| **Liver metastases** | 0.26 (0.44) | 0.26 (0.44) | 1.000 | <0.001 |
| **Lung metastases** | 0.47 (0.50) | 0.47 (0.50) | 1.000 | <0.001 |
| **Prior anthracycline therapy** | 0.50 (0.50) | 0.50 (0.50) | 1.000 | <0.001 |
| **Prior adjuvant taxane treatment** | 0.33 (0.47) | 0.33 (0.47) | 1.000 | <0.001 |
| **Diastolic blood pressure** | 75.72 (10.51) | 75.72 (9.38) | 1.000 | <0.001 |
| **Respiratory rate** | 36.46 (0.40) | 36.46 (0.44) | 1.000 | <0.001 |
| **Body temperature** | 36.46 (0.40) | 36.46 (0.46) | 1.000 | <0.001 |

p: P-value from a Chi-square test; SMD: Standardized mean difference defined as the difference in means divided by the pooled standard deviation. neff: Effective sample size as defined in Phillippo et al. (97).

**Table 16: Weighted summary statistics of matching variables for matching to the MERIDIAN trial - PFS**

| | MERIDIAN (paclitaxel) | Atezolizumab + nab-paclitaxel | p | SMD |
|---|---|---|---|---|
| $n_{eff}$ (Effective sample size) | 78.00 | 87.67 | | |
| Age | 54.83 (11.41) | 54.83 (13.70) | 1.000 | <0.001 |
| Height | 160.88 (7.71) | 160.88 (8.95) | 1.000 | <0.001 |
| Bmi | 28.09 (6.11) | 28.09 (6.80) | 1.000 | <0.001 |
| Region: North America & Europe | 0.42 (0.50) | 0.42 (0.50) | 1.000 | <0.001 |
| Region: Asia | 0.24 (0.43) | 0.24 (0.43) | 1.000 | <0.001 |
| Race: White | 0.56 (0.50) | 0.56 (0.50) | 1.000 | <0.001 |
| Race: Black | 0.14 (0.35) | 0.14 (0.35) | 1.000 | <0.001 |
| Race: Asian | 0.24 (0.43) | 0.24 (0.43) | 1.000 | <0.001 |
| ECOG = 0 | 0.64 (0.48) | 0.64 (0.48) | 1.000 | <0.001 |
| Number of disease sites | 2.41 (1.13) | 2.41 (1.06) | 1.000 | <0.001 |
| Sum of longest diameters of lesions | 69.32 (52.43) | 69.32 (66.00) | 1.000 | <0.001 |
| Time from metastatic diagnosis to randomisation | 0.27 (0.62) | 0.27 (0.29) | 1.000 | <0.001 |
| Bone metastases | 0.26 (0.44) | 0.26 (0.44) | 1.000 | <0.001 |
| Liver metastases | 0.26 (0.44) | 0.26 (0.44) | 1.000 | <0.001 |
| Lung metastases | 0.47 (0.50) | 0.47 (0.50) | 1.000 | <0.001 |
| Prior anthracycline therapy | 0.50 (0.50) | 0.50 (0.50) | 1.000 | <0.001 |
| Prior adjuvant taxane treatment | 0.33 (0.47) | 0.33 (0.47) | 1.000 | <0.001 |
| Diastolic blood pressure | 75.72 (10.51) | 75.72 (9.38) | 1.000 | <0.001 |
| Respiratory rate | 36.46 (0.40) | 36.46 (0.44) | 1.000 | <0.001 |
| Body temperature | 36.46 (0.40) | 36.46 (0.46) | 1.000 | <0.001 |

p: P-value from a Chi-square test; SMD: Standardized mean difference defined as the difference in means divided by the pooled standard deviation. neff: Effective sample size as defined in Phillippo et al. (97).



**Table 17: Weighted summary statistics of matching variables for matching to the AVADO trial - OS**

| | AVADO (docetaxel) | Atezolizumab + nab-paclitaxel | p | SMD |
|---|---|---|---|---|
| **$n_{eff}$ (Effective sample size)** | 164.00 | 64.84 | | |
| **Age** | 53.13 (11.21) | 53.13 (12.88) | 1.000 | <0.001 |
| **Weight** | 67.50 (14.07) | 67.50 (15.55) | 1.000 | <0.001 |
| **Race: White** | 0.78 (0.42) | 0.78 (0.42) | 1.000 | <0.001 |
| **Race: Black** | 0.02 (0.13) | 0.02 (0.13) | 1.000 | <0.001 |
| **Race: Asian** | 0.15 (0.36) | 0.15 (0.36) | 1.000 | <0.001 |
| **ECOG = 0** | 0.59 (0.49) | 0.59 (0.49) | 1.000 | <0.001 |
| **Number of disease sites >3** | 0.51 (0.50) | 0.51 (0.50) | 1.000 | <0.001 |
| **Time from treatment initiation to metastases diagnosis** | 40.47 (57.84) | 40.46 (51.71) | 1.000 | <0.001 |
| **Time from metastases diagnosis to randomisation** | 1.96 (4.16) | 1.96 (1.83) | 1.000 | <0.001 |
| **Liver metastases** | 0.30 (0.46) | 0.30 (0.46) | 1.000 | <0.001 |
| **Lung metastases** | 0.50 (0.50) | 0.50 (0.50) | 1.000 | <0.001 |
| **Prior anthracycline therapy** | 0.60 (0.49) | 0.60 (0.49) | 1.000 | <0.001 |
| **Prior adjuvant taxane treatment** | 0.24 (0.43) | 0.24 (0.43) | 1.000 | <0.001 |
| **Region:Asia** | 0.14 (0.35) | 0.14 (0.35) | 1.000 | <0.001 |
| **BMI** | 26.05 (5.08) | 26.05 (5.39) | 1.000 | <0.001 |

p: P-value from a Chi-square test; SMD: Standardized mean difference defined as the difference in means divided by the pooled standard deviation; neff: Effective sample size as defined in Phillippo et al. (97).

**Table 18: Weighted summary statistics of matching variables for matching to the AVADO trial - PFS**

| | AVADO (docetaxel) | Atezolizumab + nab-paclitaxel | p | SMD |
|---|---|---|---|---|
| $n_{eff}$ (Effective sample size) | 164.00 | 72.80 | | |
| Age | 53.13 (11.21) | 53.13 (12.89) | 1.000 | <0.001 |
| Weight | 0.78 (0.42) | 0.78 (0.42) | 1.000 | <0.001 |
| Race: White | 0.02 (0.13) | 0.02 (0.13) | 1.000 | <0.001 |
| Race: Black | 0.15 (0.36) | 0.15 (0.36) | 1.000 | <0.001 |
| Race: Asian | 0.59 (0.49) | 0.59 (0.49) | 1.000 | <0.001 |
| ECOG = 0 | 0.51 (0.50) | 0.51 (0.50) | 1.000 | <0.001 |
| Number of disease sites >3 | 37.84 (53.62) | 37.84 (47.69) | 1.000 | <0.001 |
| Time from treatment initiation to metastases diagnosis | 1.92 (4.16) | 1.92 (1.81) | 1.000 | <0.001 |
| Time from metastases diagnosis to randomisation | 0.30 (0.46) | 0.30 (0.46) | 1.000 | <0.001 |
| Liver metastases | 0.50 (0.50) | 0.50 (0.50) | 1.000 | <0.001 |
| Lung metastases | 0.60 (0.49) | 0.60 (0.49) | 1.000 | <0.001 |
| Prior anthracycline therapy | 0.59 (0.49) | 0.59 (0.49) | 1.000 | <0.001 |
| Prior adjuvant taxane treatment | 0.24 (0.43) | 0.24 (0.43) | 1.000 | <0.001 |
| Region:Asia | 0.14 (0.35) | 0.14 (0.35) | 1.000 | <0.001 |
| BMI | 26.05 (5.08) | 26.05 (5.55) | 1.000 | <0.001 |

Propensity scores (the probability of being assigned to a treatment based upon observed patient baseline characteristics (covariates)) were generated to estimate each IMpassion130 patient's tendency to be enrolled in the comparator trials (E2100, MERIDIAN, AVADO), which generated "weights". The weights were then used to obtain an estimation of outcomes in the three comparator trials. This generated a virtual atezolizumab in combination with nab-paclitaxel arm within these three studies. The propensity scores for each patient in the atezolizumab + nab-paclitaxel arm of the IMpassion130 (WO29522) were then transformed into odds ratios, which were subsequently used to re-estimate the hazard ratios of

atezolizumab in combination with nab-paclitaxel versus the comparators (paclitaxel and docetaxel). The aim was to optimally balance the matching of variables with the optimal effective sample size of patients created, to arrive at the most robust feasible estimates.

For E2100 and AVADO, the covariate balancing propensity score model achieved between a reasonable balance and almost perfect matching of covariates at the cost of a low effective sample size. For MERIDIAN, sample size was maintained well as compared with the comparator arm for both PFS and OS.

Further details of the methods of matching adjustments and rationales for approaches are provided in Appendix D.

### B.2.9.2 Model selection process

Following adjustment of the atezolizumab in combination with nab-paclitaxel arm, a set of candidate statistical models for OS and PFS were fitted. For OS and PFS, the statistical model for each outcome was selected from the set of candidate models based on evidence on the proportionality of hazard rates; the goodness of fit in a frequentist framework; the validity of extrapolations based on 12-month data; Bayesian model diagnostics; a comparison of extrapolated and observed survival curves and a comparison of the goodness of fit of fixed and random effects models.

### B.2.9.3 Priors used in NMA

For the basic parameters, in all Bayesian analyses, non-informative priors for the piecewise exponential were used for the study baseline (μ) and treatment effect parameters (d) (Table 19).

**Table 19: Non-informative priors for time-to-event models**

| Model | Prior (normal distribution parametrised with mean and precision) |
|---|---|
| **Discrete time piecewise exponential** | $\mu_k \sim dnorm(0, 0.0001)$ …piece k<br>$d_k \sim dnorm(0, 0.0001)$ … piece k |

Furthermore, informative priors proposed by Turner et al. (98) were used in the random effects model, to address heterogeneity (Table 20).

**Table 20: Informative priors for between study heterogeneity**

| Endpoint | Base case | Sensitivity analyses |
|---|---|---|
| **Overall survival** | $\tau^2 \sim dlnorm(-4.18, 1.41^{-2})$<br><br>Turner (2015) | $\tau^2 \sim dlnorm(-4.18, 1.8^{-2})$<br><br>Log-normal with same median as main prior but 2x larger upper 95% quantile. |
| **Progression-free survival** | $\tau^2 \sim dlnorm(-2.94, 1.79^{-2})$<br><br>Turner (2015) | $\tau^2 \sim dlnorm(-2.94, 2.2^{-2})$<br><br>Log-normal with same median as main prior but 2x larger upper 95% quantile. |

### B.2.9.4 Proportional Hazards assumption (OS and PFS)

The proportional hazards assumption was assessed using diagnostic plots of log cumulative hazard curves over log time. The diagnostic plots within each study were examined – these are provided in Appendix D, for each of OS and PFS. The atezolizumab + nab-paclitaxel arm of the IMpassion130 study was compared to all other study arms included in the network for which KMs were available. Proportionality of hazard rates was rejected if at least one within- or cross-study comparison demonstrated a violation.

For OS, assessment of the diagnostic plots demonstrated that there were non-parallel curves (indicating the proportional hazards assumption was not met) in multiple studies: AVADO, COLET, E2100, LOTUS, TNT, TURANDOT and the IMpassion130 trial. For PFS, there were non-parallel curves (proportional hazards assumption not met) within CALGB40502, COLET, LOTUS, RIBBON-1, TNT and TURANDOT studies.

### B.2.9.5 Bayesian and Frequentist models assessment

All discrete time candidate models were estimated (piecewise exponential, fractional polynomial models) in a frequentist network meta-analysis framework. This framework is considered to be consistent with a fixed effect model in the Bayesian framework and as such, allows a range of models to be simply assessed without loss of information. The model fit was compared using the Akaike information criterion and the Bayesian information criterion. The best fitting candidate models were then assessed based on goodness of fit to the observed data and validity of extrapolations. To allow the models to capture possible anticipated changes in hazard – in particular, at the point at which the treatment effect is realised as well as a point at which the treatment effect diminishes, the candidate piecewise exponential models considered were models with one or two cut-points. The choice of cut

points was assessed empirically and therefore included all potential month cuts from 2 months up to the maximum based on the KM curves available, leading to cut points at 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 months where one cut point was allowed, and for two cut-points at all combinations of 2, 3, 4, 5 months and 7, 8, 9, 10, 11, 12 months.

Candidate fractional polynomial models were also considered – and included 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).

The best fitting model(s) in a Bayesian framework was estimated and the Bayesian model diagnostics examined, comparing fixed effects and random effects models. The model with the lowest deviance information criterion was selected as the base case model. A difference in the deviance information criterion of 5 or more was considered indicative of better model fit (99). Where there were differences of less than 5, a random effects model was selected as the base case model.

#### B.2.9.6 Model selection results

For OS, the proportional hazards investigation demonstrated clear non-proportionality of curves for six of the comparator studies as well as IMpassion 130. The discrete time candidate models were fitted and based on AIC primarily, the five best fitting candidate models were the three second order fractional polynomials, the first order fractional polynomial (power 0) and a piecewise exponential with cut points at 5 and 7 months. Based on visual fit to the observed data and five year extrapolations the second order fractional polynomial models were excluded due to high plateaus and poor fit to the tails of the observed data. The remaining two models showed clear convergence towards zero. However, Bayesian model diagnostics indicated poor convergence for both models and alternative best fitting (based on Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]) models were reconsidered. The piecewise exponential with one cut point at 5 months had similarly low AIC and BIC values (to the best fitting piecewise exponential), converged appropriately and was considered a sufficiently good fit to the data and was selected as the final model. The deviance information criteria of the fixed and random effects models were very similar, as such, random effects were used as the base case. Further supporting information for the model assessment process can be found in Appendix D.

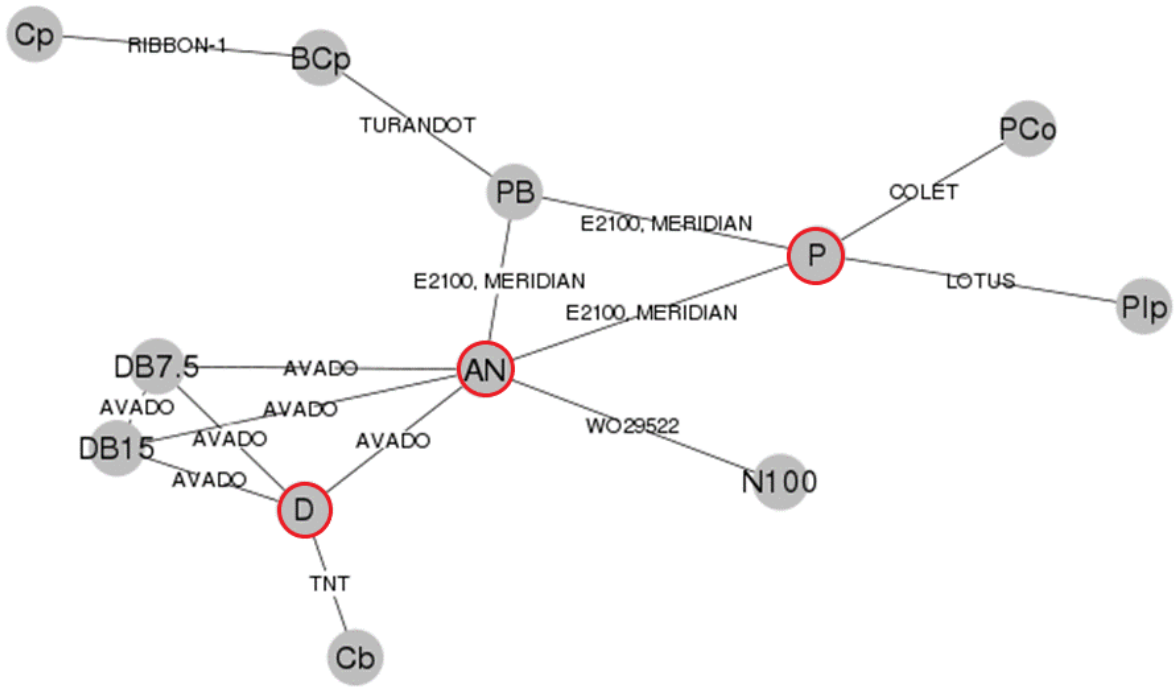
For PFS, the same model assessment stages were performed. Following AIC and BIC assessment of model fit, the five best fitting candidate models were the three second order

fractional polynomials, the first order fractional polynomial (power 0) and a piecewise exponential with cut points at 4 and 7 months were identified. As for OS, the second order fractional polynomials were discounted due to poor fits to the tails of the observed data and implausible high plateaus in the extrapolated period. The remaining first order fractional polynomial was discounted due to poor convergence in the Bayesian framework. The piecewise exponential with cut points at 4 and 7 months showed appropriate convergence and was selected as the most suitable model for PFS. As with OS, the deviance information criteria of the fixed and random effects models were very similar, as such, random effects were used as the base case. Further supporting information for the model assessment process can be found in Appendix D.

The final networks, utilising the matching adjusted indirect comparisons are provided in Figure 11 (OS) and Figure 12 (PFS).

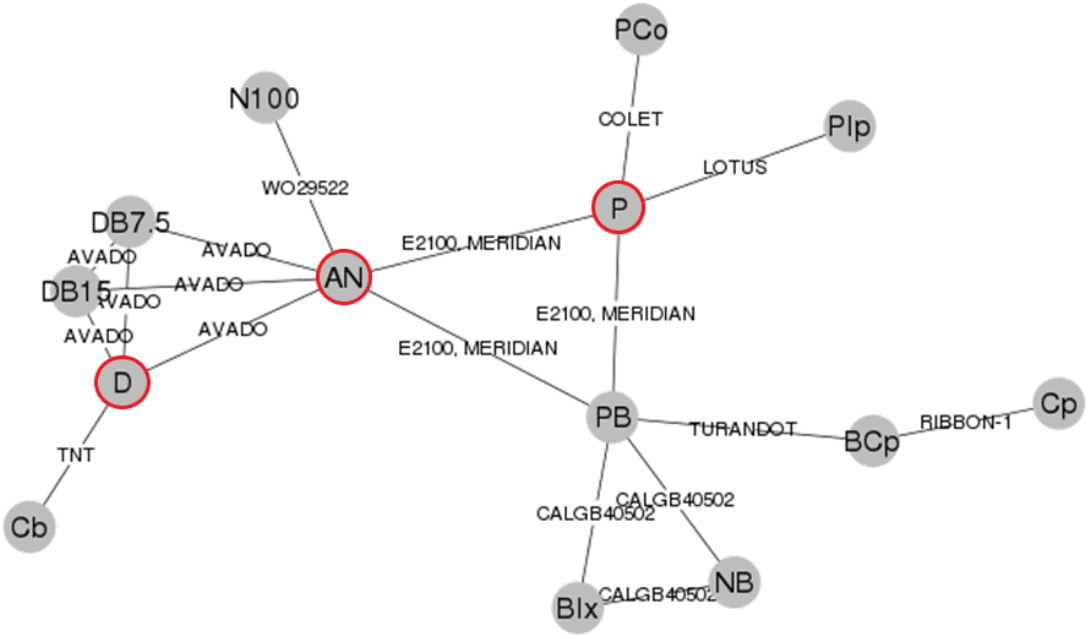
**Figure 11: OS Final connected network, included matching adjusted indirect comparisons**




AN: Atezolizumab + nab-paclitaxel; P: Paclitaxel; D: Docetaxel; BCp: Bevacizumab + Capecitabine; Bix: Bevacizumab + Ixabepilone; Cb: Carboplatin; C: Capecitabine; DB15: Docetaxel+ Bevacizumab' DB7.5: Docetaxel + Bevacizumab; N100: Nab-paclitaxel; NB: Nab-paclitaxel + Bevacizumab; P: Paclitaxel; PB: Paclitaxel + bevacizumab; PCo: Paclitaxel + cobimetinib; Pip: Paclitaxel + ipatasertib.

**Figure 12: PFS Final connected network, included matching adjusted indirect comparisons**




AN: Atezolizumab + nab-paclitaxel; P: Paclitaxel; D: Docetaxel; BCp: Bevacizumab + Capecitabine; Bix: Bevacizumab + Ixabepilone; Cb: Carboplatin; C: Capecitabine; DB15: Docetaxel+ Bevacizumab' DB7.5: Docetaxel + Bevacizumab; N100: Nab-paclitaxel; NB: Nab-paclitaxel + Bevacizumab; P: Paclitaxel; PB: Paclitaxel + bevacizumab; PCo: Paclitaxel + cobimetinib; Pip: Paclitaxel + ipatasertib.

### B.2.9.7 Rationale for exclusion of trials identified in the clinical SR from indirect comparisons

Thirteen of the trials included in the clinical evidence SR contained, at a minimum, OS or PFS data that could be used in the indirect comparisons. Twenty-six trials, identified in the SR, were excluded from the NMA, based upon the NMA feasibility assessment. The reasons for exclusion were: Data was not reported for TNBC subgroups, majority (>80%) of patients with TNBC were not receiving first line therapy in the advanced setting, assessment of heterogeneity (study designs and patient characteristics) and sufficiently similar follow up time points of reported outcomes. Further details of the systematic approach to the selection of studies included in the systematic review for inclusion into the evidence networks are provided in Appendix D.

### B.2.9.8 Results of indirect comparisons

Results of the MAIC are presented below. Hazard ratios for each "piece" are used directly in the cost-effectiveness model. As detailed in section B.2.9.1, the following time points were

selected in the piecewise exponential ITC: cut-points at 5 months (OS) and 4 and 7 months (PFS).

### *OS (base case results)*

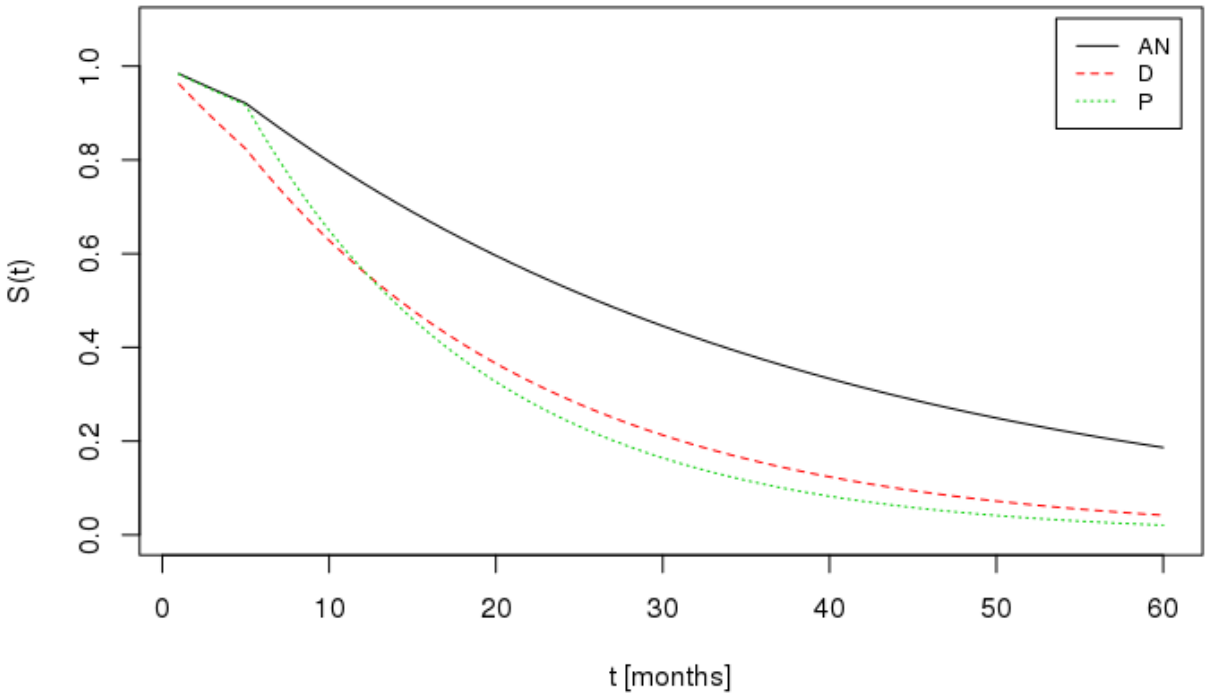
Table 21 provides the resulting Hazard Ratios, by piece (0 to 5 months, greater than 5 months). The resulting OS curve can be found in Figure 13.

**Table 21: Overall survival hazard ratios of atezolizumab + nab-paclitaxel vs. docetaxel and paclitaxel, by piece**

| | **t<5months** | | | **5months≤t** | | |
|---|---|---|---|---|---|---|
| | Hazard ratio (median) | 95% lower credible interval | 95% upper credible intervals | median | 95% lower credible interval | 95% upper credible intervals |
| P | 1.06 | 0.39 | 2.82 | 2.38 | 1.39 | 4.12 |
| D | 2.35 | 0.76 | 8.31 | 1.86 | 0.8 | 4.25 |

D: Docetaxel (100mg/m2 every three weeks), P: Paclitaxel (80 - 90mg/m2 on days 1, 8, and 15 of 28-day cycles)

**Figure 13: Overall survival probabilities extrapolated using median basic parameters**



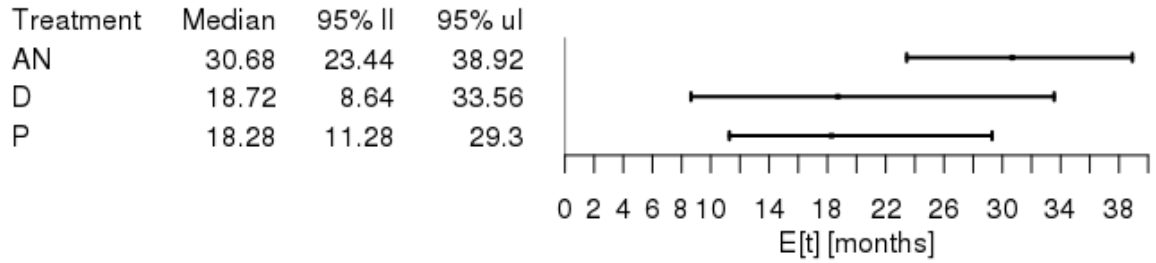

As demonstrated in Figure 13, there is divergence of the survival curves from initiation versus docetaxel, and from 5 months versus paclitaxel.

The posterior median restricted mean 5-year OS survival gains of atezolizumab in combination with nab-paclitaxel compared with paclitaxel and docetaxel over the illustrated presented 5-year time period were 12.13, and 11.74 months respectively (see Figure 14 and

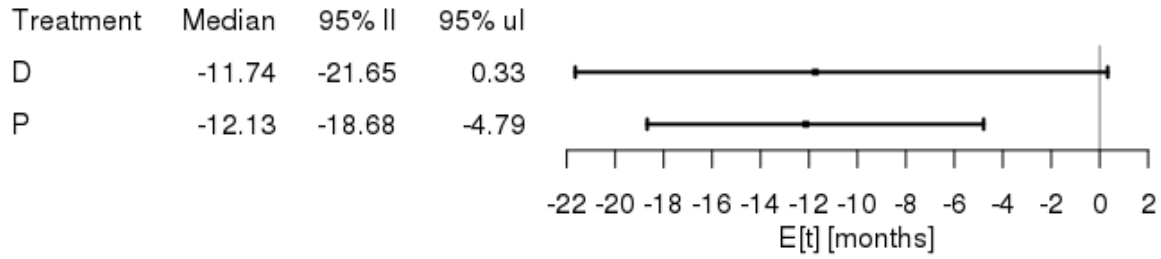
Figure 15). Both comparisons demonstrate a clinically meaningful improvement. In addition, the benefit atezolizumab in combination with nab-paclitaxel demonstrates over paclitaxel is statistically significant. It is not uncommon for indirect comparisons, which require a matching adjusted approach, to produce wide 95% credible intervals, due the uncertainty associated with the methodology.

**Figure 14: Restricted mean overall survival times from extrapolations in the IMpassion130 study over a 5-year time horizon**




D: Docetaxel (100 mg/m2 every three weeks), P: Paclitaxel (80 – 90 mg/m2 on days 1, 8, and 15 of 28-day cycles)

**Figure 15: Differences to atezolizumab + nab-paclitaxel in restricted mean overall survival times from extrapolations in the IMpassion130 study over a 5-year time horizon**




D: Docetaxel (100 mg/m2 every three weeks), P: Paclitaxel (80 – 90 mg/m2 on days 1, 8, and 15 of 28-day cycles)

Full details of the OS scenario analyses and results are provided in Appendix D.

### *PFS (base case results)*

Table 22 provides the resulting Hazard Ratios, by piece (0 to 4 months, 4 to 7 months, greater than 7 months). The resulting PFS curve can be found in Figure 16.

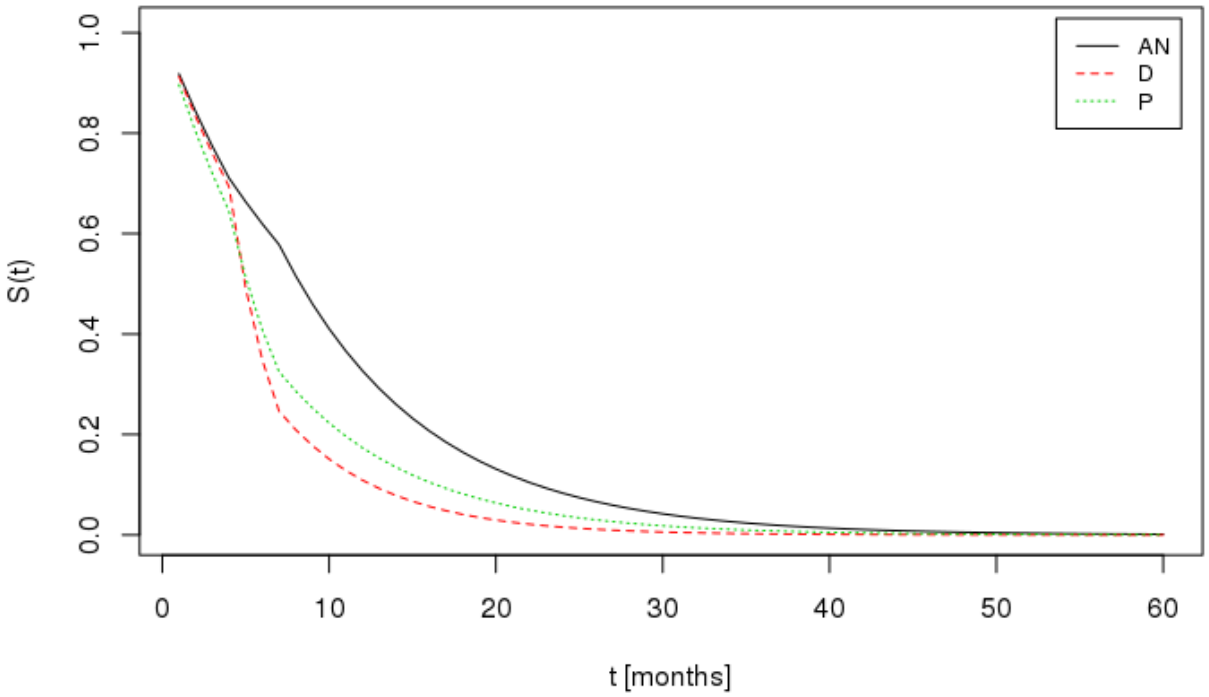

 

**Table 22: Progression-free survival hazard ratios of atezolizumab with nab-paclitaxel vs. docetaxel monotherapy and paclitaxel monotherapy, by piece**

| | 0≤t<4 months | | | 4 months ≤t< 7 months | | | 7 months ≤t | | |
|---|---|---|---|---|---|---|---|---|---|
| | Hazard ratio (median) | 95% lower credible interval | 95% upper credible intervals | median | 95% lower credible interval | 95% upper credible intervals | median | 95% lower credible interval | 95% upper credible intervals |
| P | 1.28 | 0.69 | 2.32 | 3.33 | 1.62 | 7.01 | 1.1 | 0.58 | 1.99 |
| D | 1.07 | 0.46 | 2.47 | 5.00 | 1.75 | 15.08 | 1.43 | 0.48 | 3.93 |

D: Docetaxel (100 mg/m2 every three weeks), P: Paclitaxel (80 – 90 mg/m2 on days 1, 8, and 15 of 28-day cycles)

**Figure 16: Progression-free survival probabilities extrapolated using median basic parameters**



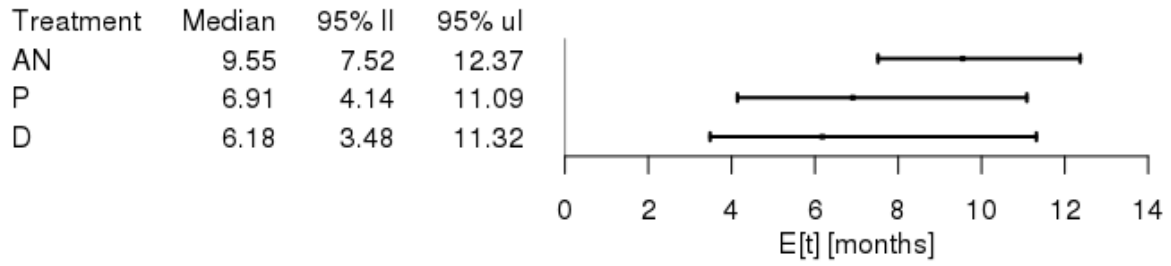

As demonstrated in (Figure 16), there is divergence of the progression-free survival curves from approximately 4 months for both paclitaxel and docetaxel.

The posterior median restricted mean 5-year PFS gains compared with paclitaxel and docetaxel presented over a 5 year time period were 2.63 and 3.32 months (Figure 17 and Figure 18). Although these results were not statistically significant, atezolizumab with nab-paclitaxel provided a clinically meaningfully improvement in PFS, compared with paclitaxel and docetaxel. Similarly to the OS analysis, it is not uncommon for indirect comparisons,

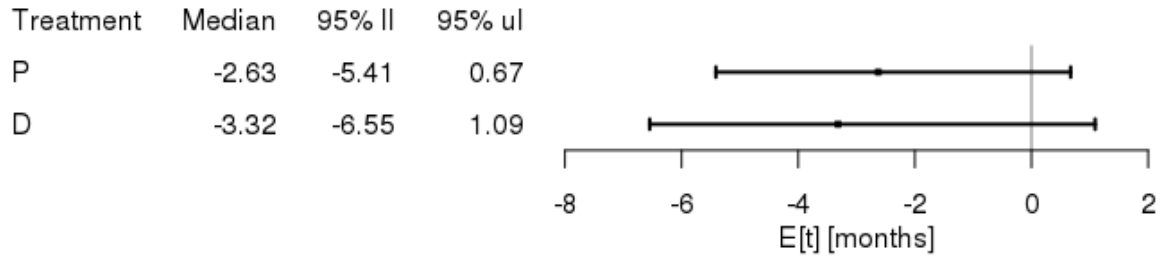
which require a matching adjusted approach, to produce wide 95% credible intervals, due the uncertainty associated with the methodology.

**Figure 17: Restricted mean progression-free survival times from extrapolations in the IMpassion130 study over a 5-year time horizon**




D: Docetaxel (100mg/m2 every three weeks), P: Paclitaxel (80 - 90mg/m2 on days 1, 8, and 15 of 28-day cycles)

**Figure 18: Differences to atezolizumab + nab-paclitaxel in restricted mean progression-free survival times from extrapolations in the IMpassion130 study over a 5-year time horizon**




D: Docetaxel (100mg/m2 every three weeks), P: Paclitaxel (80 - 90mg/m2 on days 1, 8, and 15 of 28-day cycles

Details of the PFS scenario analyses methods and results are provided in Appendix D.

### *Further indirect comparison outcomes*

Methods and results of 1) objective response rates and 2) adverse events for each of docetaxel and paclitaxel are provided in Appendix D.

### *Uncertainties in the indirect comparisons*

Multiple scenario analyses were explored to identify possible sources of uncertainty.

Beyond the IMpassion130 trials, no trials in the final networks contained data specifically for patients who had PD-L1 positive TNBC. It is therefore assumed in all results that PD-L1 status does not act as an effect modifier of treatment for all the therapies included in the indirect comparisons. To the best of our knowledge, the only published evidence on the relative effects of PD-L1 status in TNBC is the IMpassion130 trial. Based on the Impassion130 trial results, a modest impact on outcomes of the placebo + nab-paclitaxel treatment arm can be witnessed based on PDL1 expression levels. However, there is insufficient evidence to draw conclusions on the level of any possible effect modification, and such an assumption was required in order to undertake any indirect comparisons for the purposes of this appraisal.

Furthermore, the piecewise exponential model is sensitive to the data in the tail and is uncertain when only a few events were observed after the last cut-point. In addition to this, the piecewise exponential model assumes the hazard rate in the tail to be constant. In the absence of longer follow up, this cannot be validated and may over-estimate the relative efficacy of atezolizumab in combination with nab-paclitaxel.

### B.2.9.4 Assessment of heterogeneity

A qualitative and quantitative assessment of the study heterogeneity was conducted.

In the qualitiative assessment, it was deemed that the trials were sufficiently homogenous to combine into the final connected networks. However, the small size of the evidence networks and the availability of single studies for direct comparisons within the final networks limited the ability to assess heterogeneity using meta-regression.

The quantitative approach to assessing and addressing heterogeneity (using fixed and random effects models) is provided in section B.2.9.1. Random effects models were utilised in the base case to account for heterogeneity, as it was considered the assumption of no heterogeneity in treatment effect was implausible. Further, the sensitivity analyses conducted allowed for up to approximately twice as large between-trial heterogeneity as the base case.

A comparison of ITC outcomes generated in the base case, and sensitivity analysis are similar (Table 23), demonstrating results are not sensitive to a change in the prior distribution for between-study heterogeneity in treatment effects, or a change to a fixed effects model.

**Table 23: Comparison of median hazard ratios (base case results vs. scenario analyses assessing heterogeneity)**

| | | OS | | PFS | | |
|---|---|---|---|---|---|---|
| **Cut point** | **Comparator** | **t<5months** | **5months≤t** | **0≤t<4 months** | **4 months ≤t< 7 months** | **7 months ≤t** |
| **Base case results (median Hazard ratio)** | **Paclitaxel** | 1.06 | 2.38 | 1.28 | 3.33 | 1.10 |
| **Alternative prior normal distribution for the between-study heterogeneity in treatment effects** | | 1.05 | 2.36 | 1.29 | 3.32 | 1.10 |
| **Fixed effects scenario analysis** | | 1.07 | 2.36 | 1.31 | 3.31 | 1.13 |
| **Base case results (median Hazard ratio)** | **Docetaxel** | 2.35 | 1.86 | 1.07 | 5.00 | 1.43 |
| **Alternative prior normal distribution for the between-study heterogeneity in treatment effects** | | 2.36 | 1.85 | 1.07 | 4.97 | 1.43 |
| **Fixed effects scenario analysis** | | 2.37 | 1.87 | 1.07 | 4.99 | 1.43 |

## *B.2.10 Adverse reactions*

- **Overall, the AE incidences were similar between the PD-L1–positive safety-evaluable subpopulation and the safety-evaluable population**

**Safety-evaluable population:**

- **AEs regardless of attribution occurred in 99.3% patients in the A + nabPx arm and 97.9% patients in the P + nabPx arm**
- **Fatal AEs occurred in 6 patients (1.3%) in the A + nabPx arm and 3 patients (0.7%) in the P + nabPx arm**
- **29 patients (6.4%) and 6 patients (1.4%) experienced AEs leading to discontinuation of atezolizumab or placebo respectively**
- **Serious AEs occurred in 103 patients (22.8%) in the A + nabPx arm and 80 patients (18.3%) in the P + nabPx arm**

**PD-L1–positive safety-evaluable population:**

- **AEs regardless of attribution occurred in 100% patients in the A + nabPx arm and 97.8% patients in the P + nabPx arm**
- **Fatal AEs occurred in 2 patients (1.1%) in the A + nabPx arm and 1 patient (0.6%) in the P + nabPx arm**
- **12 patients (6.5%) and 4 patients (2.2%) experienced AEs leading to discontinuation of atezolizumab or placebo respectively**
- **Serious AEs occurred in 42 patients (22.7%) in the A + nabPx arm and 31 patients (17.1%) in the P + nabPx arm**

Unless otherwise specified, safety data presented below originates from the Schmid et al. 2018 publication (13).

### B.2.10.1 Overview of safety data

The safety-evaluable population included 452 patients in the A + nabPx arm and 438 patients in the P + nabPx arm. Adverse events (AEs) regardless of attribution occurred in 99.3% patients in the A + nabPx arm and 97.9% patients in the P + nabPx arm (Table 24). Fatal AEs occurred in 6 patients (1.3%) in the A + nabPx arm and 3 patients (0.7%) in the P + nabPx arm (Table 24); 3 of the deaths in the A + nabPx arm (autoimmune hepatitis, mucosal inflammation/death, and septic shock, n = 1 each) and 1 in the P + nabPx arm (hepatic failure) were deemed treatment-related. AEs that led to withdrawal of any agent occurred in 15.9% of A + nabPx–treated patients and 8.2% of P + nabPx–treated patients. There were 29 patients (6.4%) and 6 patients (1.4%) who experienced AEs leading to discontinuation of atezolizumab or placebo respectively (Table 24). Serious AEs occurred in

103 patients (22.8%) in the A + nabPx arm and 80 patients (18.3%) in the P + nabPx arm (Table 24).

**Table 24: Overview of safety (safety-evaluation population)**

| | A + nabPx (n=452) | P + nabPx (n=438) |
|---|---|---|
| Total number of patients with at least one AE | 449 (99.3%) | 429 (97.9%) |
| Total number of deaths | 181 (40.0%) | 203 (46.3%) |
| **Total number of patients with at least one:** | | |
| Grade 5 AE | 6 ( 1.3%) | 3 ( 0.7%) |
| Treatment-related grade 5 AE | 3 ( 0.7%) | 1 ( 0.2%) |
| Grade 3–4 AEs | 220 (48.7%) | 185 (42.2%) |
| Treatment-related grade 3–4 AE | 179 (39.6%) | 132 (30.1%) |
| Serious AE regardless of attribution | 103 (22.8%) | 80 (18.3%) |
| Treatment-related serious AE | 56 (12.4%) | 32 ( 7.3%) |
| Treatment-related AE | 436 (96.5%) | 410 (93.6%) |
| AE leading to any treatment discontinuation | 72 (15.9%) | 36 ( 8.2%) |
| AE leading to atezolizumab/placebo discontinuation | 29 ( 6.4%) | 6 ( 1.4%) |
| AE leading to Nab-paclitaxel discontinuation | 72 (15.9%) | 36 ( 8.2%) |
| AE leading to any dose reduction or interruption | 212 (46.9%) | 177 (40.4%) |
| AE leading to dose interruption of atezolizumab/ placebo | 139 (30.8%) | 103 (23.5%) |
| AE leading to dose reduction or interruption of nab-paclitaxel | 195 (43.1%) | 172 (39.3%) |
| Any-grade AESIs | 259 (57.3%) | 183 (41.8%) |
| Grade 3–4 AESIs | 34 (7.5%) | 19 (4.3%) |

Investigator text for AEs is coded using MedDRA version 21.0. Percentages are based on n in the column headings. Multiple occurrences of the same AE in one individual are counted only once. Six patients in each arm were not treated, and 7 patients in the P+nabPx arm accidentally received A+nabPx and were evaluated in the A+nabPx safety population. Includes AEs with onset from first dose of study drug through the clinical cut-off.

AE: adverse event; AESI: AE of special interest

### B.2.10.2 Extent of exposure to study treatment

In the safety-evaluable population, the median duration of treatment with nab-paclitaxel and placebo/atezolizumab was similar between the treatment arms (Table 25). Overall, the addition of atezolizumab did not compromise the patient's ability to receive nab-paclitaxel.

**Table 25: Exposure to atezolizumab, placebo, and nab-paclitaxel and dose intensity (ITT population)**

| | Nab-paclitaxel exposure | Atezolizumab or placebo exposure |
|---|---|---|

| | A + nabPx (n = 452) | P + nabPx (n = 438) | A + nabPx (n = 452)* | P + nabPx (n = 438) |
|---|---|---|---|---|
| **Treatment Duration (wks)** | | | | |
| Mean (SD) | 27.6 (20.0) | 23.9 (18.5) | 31.6 (24.7) | 26.9 (21.9) |
| Median | 22.1 | 21.8 | 24.1 | 22.1 |
| Min–Max | 0–137 | 0–103 | 0–139 | 0–109 |
| **Patients with indicated treatment duration** | | | | |
| ≤8 weeks | 436 (96.5%) | 425 (97.0%) | 426 (94.2%) | 424 (96.8%) |
| ≤12 weeks | 387 (85.6%) | 338 (77.2) | 383 (84.7%) | 338 (77.2%) |
| ≤16 weeks | 361 (79.9%) | 316 (72.1%) | 355 (78.5%) | 316 (72.1%) |
| ≤6 months | 315 (69.7%) | 257 (58.7%) | 311 (68.8%) | 259 (59.1%) |
| ≤9 months | 181 (40.0%) | 145 (33.1%) | 215 (47.6%) | 170 (38.8%) |
| ≤12 months | 100 (22.1%) | 75 (17.1%) | 138 (30.5%) | 108 (24.7%) |
| ≤18 months | 53 (11.7%) | 44 (10.0%) | 89 (19.7%) | 63 (14.4%) |
| >18 months | 12 (2.7%) | 7 (1.6%) | 25 (5.5%) | 15 (3.4%) |
| **Dose Intensity (%)** | | | | |
| Mean (SD) | 87.7 (17.8) | 90.4 (15.1) | 95.8 (10.4) | NE |
| **Number of Cycles** | | | | |
| Median | 6 | 6 | 7 | 6 |
| Min–Max | 1–34 | 1–26 | 1–35 | 1–28 |
| **Total Cumulative Dose – mg/m$^2$ (nab-paclitaxel) or mg (atezolizumab or placebo)** | | | | |
| Mean (SD) | 1980 (1303.1) | 1764.4 (1238.3) | 13237.8 (9880.4) | 0 |

* Excludes placebo exposure for 13 patients in the A + nabPx arm.

A + nabPx: atezolizumab + nab-paclitaxel; P + nabPx: placebo + paclitaxel; SD: standard deviation

### B.2.10.3 Common adverse events: Adverse events by incidence

The most common AEs reported were similar across both arms (Table 26), with the most common event in both arms being alopecia. The incidence of nausea, cough, neutropenia, pyrexia, and hypothyroidism were ≥5% higher in the A + nabPx arm than in the P + nabPx arm. The rates of grade 3 or 4 AEs were 48.7% and 42.2% in the A + nabPx and P + nabPx arms, respectively, and the most common in both arms were neutropenia, decreased neutrophil count, peripheral neuropathy, fatigue, and anaemia.

**Table 26: Incidence of adverse events***

| Patients with indicated event | A + nabPx (n = 452) | | P + nabPx (n = 438) | |
|---|---|---|---|---|
| **No. (%)** | **Any Grade** | **Grade 3–4** | **Any Grade** | **Grade 3–4** |
| Alopecia | 255 (56.4) | 3 (0.7) | 252 (57.5) | 1 (0.2) |
| Fatigue | 211 (46.7) | 18 (4.0) | 196 (44.7) | 15 (3.4) |
| Nausea | 208 (46.0) | 5 (1.1) | 167 (38.1) | 8 (1.8) |
| Diarrhoea | 147 (32.5) | 6 (1.3) | 150 (34.2) | 9 (2.1) |

| | | | | |
|---|---|---|---|---|
| Anaemia | 125 (27.7) | 13 (2.9) | 115 (26.3) | 13 (3.0) |
| Constipation | 113 (25.0) | 3 (0.7) | 108 (24.7) | 1 (0.2) |
| Cough | 112 (24.8) | 0 | 83 (18.9) | 0 |
| Headache | 105 (23.2) | 2 (0.4) | 96 (21.9) | 4 (0.9) |
| Neuropathy peripheral | 98 (21.7) | 25 (5.5) | 97 (22.1) | 12 (2.7) |
| Neutropenia | 94 (20.8) | 37 (8.2) | 67 (15.3) | 36 (8.2) |
| Decreased appetite | 91 (20.1) | 3 (0.7) | 79 (18.0) | 3 (0.7) |
| Vomiting | 88 (19.5) | 4 (0.9) | 74 (16.9) | 5 (1.1) |
| Pyrexia | 85 (18.8) | 3 (0.7) | 47 (10.7) | 0 |
| Arthralgia | 81 (17.9) | 1 (0.2) | 70 (16.0) | 1 (0.2) |
| Rash | 78 (17.3) | 2 (0.4) | 72 (16.4) | 2 (0.5) |
| Dyspnoea | 72 (15.9) | 4 (0.9) | 64 (14.6) | 3 (0.7) |
| Peripheral sensory neuropathy | 72 (15.9) | 9 (2.0) | 52 (11.9) | 8 (1.8) |
| Peripheral oedema | 66 (14.6) | 1 (0.2) | 68 (15.5) | 6 (1.4) |
| Myalgia | 64 (14.2) | 2 (0.4) | 67 (15.3) | 3 (0.7) |
| Back pain | 69 (15.3) | 6 (1.3) | 58 (13.2) | 2 (0.5) |
| Dizziness | 63 (13.9) | 0 | 47 (10.7) | 0 |
| Dysgeusia | 62 (13.7) | 0 | 60 (13.7) | 0 |
| Hypothyroidism | 62 (13.7) | 0 | 15 (3.4) | 0 |
| Pruritus | 62 (13.7) | 0 | 45 (10.3) | 0 |
| Neutrophil count decreased | 57 (12.6) | 21 (4.6) | 48 (11.0) | 15 (3.4) |
| Asthenia | 56 (12.4) | 2 (0.4) | 50 (11.4) | 4 (0.9) |
| Urinary tract infection | 53 (11.7) | 4 (0.9) | 46 (10.5) | 2 (0.5) |
| Insomnia | 51 (11.3) | 0 | 51 (11.6) | 3 (0.7) |
| Pain in extremity | 49 (10.8) | 2 (0.4) | 43 (9.8) | 1 (0.2) |
| Nasopharyngitis | 49 (10.8) | 0 | 37 (8.4) | 0 |
| Upper respiratory tract infection | 48 (10.6) | 5 (1.1) | 40 (9.1) | 0 |
| Increased alanine aminotransferase | 47 (10.4) | 8 (1.8) | 40 (9.1) | 5 (1.1) |
| Abdominal pain | 46 (10.2) | 2 (0.4) | 53 (12.1) | 1 (0.2) |

A + nabPx: atezolizumab + nab-paclitaxel; P + nabPx: placebo + paclitaxel

* Evaluated in patients who received ≥1 dose of treatment. Adverse events listed are irrespective of treatment attribution, with events occurring at frequency ≥10% in either arm shown, along with corresponding frequencies of Grade 3 or 4 events. Grade 5 adverse events in the A + nabPx arm included mucosal inflammation and death (n = 1 each in 1 patient), autoimmune hepatitis, pneumonia, septic shock, aspiration, and pulmonary embolism (n = 1 each), and grade 5 adverse events in the P + nabPx arm include death not otherwise specified, hepatic failure, and acute myocardial infarction (n = 1 each).

### B.2.10.4 Treatment-related adverse events

Treatment-related AEs are reported in Table 27. AEs (any grade) considered by the investigator to be related to placebo/atezolizumab were reported in a lower proportion of patients in the P + nabPx arm (69.2%) compared with the A + nabPx arm (81.4%). The most common AEs considered related to placebo/atezolizumab (≥10% patients in A + nabPx arm) were (percentages are shown for A + nabPx and P + nabPx arms, respectively): fatigue

(27.9% vs 24.2%), nausea (18.0%), diarrhoea (17.3% vs. 17.4%), hypothyroidism (12.6% vs. 2.7% vs), anaemia (11.9% vs. 10.7%), and rash (10.0% vs. 11.3%). The frequency of grade 3 or 4 peripheral neuropathy was higher in the A + nabPx arm (25 patients [5.5%] vs. 12 patients [2.7%] in the P + nabPx arm).

AEs (any grade) considered by the investigator to be related to nab-paclitaxel were reported in similar proportions of patients in the A + nabPx and A + nabPx arms (95.1% vs. 92.9% respectively).

**Table 27: Adverse events related to any study treatment***

| Patients with indicated event no. (%) | A + nabPx (n = 452) | | P + nabPx (n = 438) | |
|---|---|---|---|---|
| | Any Grade | Grade 3–4 | Any Grade | Grade 3–4 |
| 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) |

* Includes all-grade adverse events related to treatment with either study drug occurring in ≥10% of patients in either arm and grade 3 or 4 treatment-related adverse events occurring in ≥2% of patients in either arm (with corresponding all-grade frequencies). Treatment-related Grade 5 events included atezolizumab-related autoimmune hepatitis, nab-paclitaxel–related mucosal inflammation, and nab-paclitaxel–related septic shock (n = 1 each in A + nabPx arm) and hepatic failure related to either agent (n =1 in P + nabPx arm).

A + nabPx: atezolizumab + nab-paclitaxel; P + nabPx: placebo + paclitaxel

### B.2.10.5 Adverse events of special interest for atezolizumab

Two hundred fifty-nine patients (57.3%) in the A + nabPx arm and 183 (41.8%) in the P + nabPx arm experienced an adverse event of special interest (AESI), which suggests there is potential immune-related aetiology (Table 24 and Table 28); grade 3 or 4 AESIs occurred in 34 patients (7.5%) in the A + nabPx arm and 19 patients (4.3%) in the P + nabPx arm. Only 2 grade 5 AESIs occurred (autoimmune hepatitis in the A + nabPx arm and hepatic failure in the P + nabPx arm). Immune-related hypothyroidism occurred at a higher frequency in the A + nabPx arm (17.3% vs. 4.3% in the P + nabPx arm); all events were grades 1 or 2, and none led to treatment discontinuation.

**Table 28: Adverse events of special interest**

| Patients with indicated event no. (%)* | A + nabPx (n = 452) | | P + nabPx (n = 438) | |
|---|---|---|---|---|
| | Any Grade | Grade 3–4 | Any Grade | Grade 3–4 |
| Important AESIs occurring in any patient† | | | | |
| All | 259 (57.3) | 34 (7.5) | 183 (41.8) | 19 (4.3) |
| Immune-related hepatitis (all) | 69 (15.3) | 23 (5.1) | 62 (14.2) | 13 (3.0) |
| Immune-related hepatitis (diagnosis) | 10 (2.2) | 6 (1.3) | 7 (1.6) | 1 (0.2) |
| Immune-related hepatitis (lab abnormalities) | 62 (13.7) | 17 (3.8) | 58 (13.2) | 12 (2.7) |
| Immune-related hypothyroidism | 78 (17.3) | 0 | 19 (4.3) | 0 |
| Immune-related hyperthyroidism | 20 (4.4) | 1 (0.2) | 6 (1.4) | 0 |
| Immune-related pneumonitis | 14 (3.1) | 1 (0.2) | 1 (0.2) | 0 |
| Immune-related meningoencephalitis | 5 (1.1) | 0 | 2 (0.5) | 0 |
| Immune-related colitis | 5 (1.1) | 1 (0.2) | 3 (0.7) | 1 (0.2) |
| Immune-related adrenal insufficiency | 4 (0.9) | 1 (0.2) | 0 | 0 |
| Immune-related pancreatitis | 2 (0.4) | 1 (0.2) | 0 | 0 |
| Immune-related diabetes mellitus | 1 (0.2) | 1 (0.2) | 2 (0.5) | 1 (0.2) |
| Immune-related nephritis | 1 (0.2) | 0 | 0 | 0 |
| Other AESIs occurring in ≥1% of patients in either arm‡ | | | | |
| Immune-related rash | 154 (34.1) | 4 (0.9) | 114 (26.0) | 2 (0.5) |
| Infusion-related reactions | 5 (1.1) | 0 | 5 (1.1) | 0 |

* A set of comprehensive definitions using standardised Medical Dictionary for Regulatory Activities queries. Sponsor-defined adverse event–grouped terms and high-level terms were used to identify AESIs by each medical concept.

† No events of Guillain-Barré syndrome, hypophysitis, myasthenia gravis or myocarditis were reported. One grade 5 event was observed in each arm (A + nabPx, autoimmune hepatitis; P + nabPx, hepatic failure).

‡ Additional AESIs occurring at <1% in either arm included: immune-related ocular inflammation, immune-related severe cutaneous reactions, autoimmune haemolytic anaemia, immune-related myositis, immune-related vasculitis, systemic immune activation.

AESI: adverse event of special interest

### B.2.10.6 PD-L1–positive SE population

Safety data were reviewed for PD-L1–positive patients in the safety-evaluable population (hereafter called the PD-L1–positive SE population) alongside the overall safety-evaluable population (29). Overall, the adverse event (AE) incidences were similar between the PD-L1–positive SE subpopulation and the safety-evaluable population. An overview of treatment duration and the median number of cycles is shown in Table 29.

AE (Table 30) and AESI (Table 31) data show a consistent pattern in the PD-L1–positive SE and overall safety-evaluable populations (29).

**Table 29: Overview of exposure in the PD-L1–positive population (29)**

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

A + nabPx: atezolizumab + nab-paclitaxel; P + nabPx: placebo + paclitaxel

**Table 30: Overview of AE incidence in the PD-L1–positive population (29)**

| | **A + nabPx (n=185)** | **P + nabPx (n=181)** |
|---|---|---|
| Total number of patients with at least one AE (any grade) | 185 (100) | 177 (97.8) |
| Total number of deaths | 63 (34.1) | 88 (48.6) |
| Total number of patients with at least one: | | |
| Grade 5 AE | 2 (1.1) | 1 (0.6) |
| Related Grade 5 AE | 1 (0.5) | 0 |
| Grade 3–4 AE | 95 (51.4) | 72 (39.8) |
| Related Grade 3–4 AE | 76 (41.1) | 49 (27.1) |
| SAE | 42 (22.7) | 31 (17.1) |
| 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 atezolizumab/placebo | 60 (32.4) | 38 (21.0) |

AE: adverse event; A + nabPx: atezolizumab + nab-paclitaxel; P + nabPx: placebo + paclitaxel

**Table 31: Overview of AESIs in the PD-L1–positive populations (29)**

| | **A + nabPx (n=185)** | **P + nabPx (n=181)** |
|---|---|---|
| Total number of patients with at least one AESI (any grade) | 105 (56.8) | 66 (36.5) |
| Total number of patients with at least one Grade 3–4 AESI | 10 (5.4) | 7 (3.9) |
| **Important AESIs 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 AESIs 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 |

AESI: adverse event of special interest; A + nabPx: atezolizumab + nab-paclitaxel; P + nabPx: placebo + paclitaxel

Taken together, these data describe a safety profile for A + nabPx consistent with the known toxic effects of each agent and no new adverse event signals were observed (13).

## *B.2.11 Ongoing studies*

IMpassion130 is ongoing and as per the statistical analysis plan, a final OS analysis is planned (100). Atezolizumab is currently also being evaluated in combination with other chemotherapy agents for mTNBC:

| | **IMpassion131 (NCT03125902)** | **IMpassion132 (NCT03371017)** |
|---|---|---|
| **Study design** | Phase III, multicentre, randomised, double-blind, placebo controlled study | Phase III, randomised, double-blind, placebo-controlled, multicentre study |
| **Population** | Previously untreated, inoperable locally advanced or metastatic, centrally confirmed TNBC | Early relapsing recurrent (inoperable locally advanced or metastatic) TNBC |
| **Intervention** | Atezolizumab + paclitaxel | Atezolizumab with gemcitabine and carboplatin OR with capecitabine |
| **Comparators** | Placebo + paclitaxel | Placebo with gemcitabine and carboplatin OR with capecitabine |

## *B.2.12 Innovation*

- **There is a clear unmet need for better treatments for mTNBC; with chemotherapy, median OS remains at best in the region of 18 months (1-3)**
- **Atezolizumab is the first targeted agent to demonstrate a survival benefit beyond chemotherapy in mTNBC, with a mOS of 25 months in the subset of PD-L1+ patients (13)**
- **In recognition of this significant advance, PIM designation was granted by the MHRA on 23rd November 2018**
- **Following this, MHRA approval for an EAMS was granted on 13th March 2019, meaning patients with PD-L1+ mTNBC now have access to treatment with atezolizumab and nab-paclitaxel**

Targeted therapies for HER2+ or ER+/PR+ breast cancer have significantly improved outcomes for patients over and above those achieved with chemotherapy (18). Without the same progress in TNBC, chemotherapy remains the standard of care, resulting in a clear divergence in outcomes between breast cancer subtypes (24).

**Table 32: Median OS for different breast cancer subtypes per year of diagnosis (24)**

| | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 |
|---|---|---|---|---|---|---|
| **HR+ HER2- (n=9908) OS median (95% CI)** | 43.7 (40.2–46.6) | 42.0 (38.9–44.6) | 40.9 (38.0–43.4) | 42.0 (39.26–45.04) | 44.5 (41.8–47.3) | 40.3 (37.8–ND) |
| **HER2+ (n=2861) OS median (95% CI)** | 38.67 (33.6–44.6) | 42.3 (38.3–50.8) | 40.1 (35.2–45.6) | 42.38 (36.5–49.8) | 51.1 (46.5–ND) | Median not reached |
| **TNBC (n=2317) OS median (95% CI)** | 15.1 (12.7–16.4) | 15.1 (13.0–17.4) | 14.7 (13.2–17.0) | 14.0 (11.4–15.9) | 13.9 (11.4–15.9) | 14.1 (12.5–15.5) |

CI: confidence interval; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; ND: not defined; OS: overall survival

Thus there is a clear unmet need for more effective therapies for patients with mTNBC (28, 101). Without more effective therapies, patient median OS will remain at ≤18 months (1, 13, 18, 24).

While other agents have demonstrated improved PFS in patients with mTNBC, these have not translated into survival advantages. A meta-analysis of a subgroup of 621 patients with mTNBC from three randomised trials of bevacizumab in combination with chemotherapy (E2100, AVADO, and RIBBON-1) demonstrated significantly longer PFS with the addition of bevacizumab compared with treatment with chemotherapy alone ($p<0.0001$) but no significant improvement in OS (102). Likewise with poly ADP ribose polymerase (PARP) inhibitors, including olaparib (103) and talazoparib (104), have yet to demonstrate a survival advantage in BRCA mutant HER2- mBC despite statistically significant improvements in PFS.

Patients in the PD-L1 subgroup of the IMpassion130 trial treated with A + nabPx achieved a median OS of 25 months (compared with 15.5 months in the P + nabPx arm, HR: 0.62; CI: 0.45–0.86; p-value not tested due to statistical hierarchy testing). In addition, HRQoL was maintained through the duration of the treatment period (29). The current median OS for patients with mTNBC treated with standard of care is ≤18 months (1, 13, 18). Thus, the survival advantage demonstrated for atezolizumab and nab-paclitaxel in the IMpassion130 trial represents the first improvement in survival in mTNBC in 20 years and is considered a significant step change for the management of this condition. This is reflected in recent changes to clinical guidelines: atezolizumab + nab-paclitaxel had an National Comprehensive Cancer Network (NCCN) category “2a preferred” recommendation 5 days

after FDA approval and also a "+" rating (second highest rating) in the German guidelines (105, 106).

The significance of the IMpassion130 trial results and the potential for atezolizumab plus nab-paclitaxel to address an unmet clinical need for patients is further underlined by the Promising Innovative Medicines (PIM) designation granted by the Medicines and Healthcare Products Regulatory Agency (MHRA) on [redacted]. Treatments are only eligible for PIM designation if they treat a life-threatening or seriously debilitating condition with a high unmet need, are likely to offer a major advantage over current methods used in the UK and adverse effects are likely to be outweighed by the benefits.

Following this, an application for the early access to medicines scheme (EAMS) for atezolizumab plus nab-paclitaxel for the first-line treatment of mTNBC submitted [redacted] was granted by the MHRA on 13th March 2019 (107). Thus, eligible patients with unresectable, locally advanced, or metastatic PD-L1–positive mTNBC now have access to treatment with atezolizumab and nab-paclitaxel in the UK.

## *B.2.13 Interpretation of clinical effectiveness and safety evidence*

- **IMpassion130 is the first phase III trial in several decades to demonstrate an improvement in OS in a subpopulation of 1L mTNBC (13).**
- **There was clear clinically meaningful PFS and OS benefit in treatment with atezolizumab plus nab-paclitaxel in the PD-L1–positive subpopulation, despite a lack of formal statistical testing of OS (13).**
- **In both the ITT and PD-L1–positive populations, patients' HRQoL, and physical, role, cognitive function was maintained for a similar duration of time in both the A + nabPx population and the P + nabPx arms (29)**
- **A + nabPx had a manageable safety profile, with no new AE signals observed (13)**

### B.2.13.1 IMpassion130

IMpassion130 is the first phase III trial of an anti–PD-L1/PD-1 antibody in patients with breast cancer, specifically 1L mTNBC. The addition of atezolizumab to a chemotherapy backbone of nab-paclitaxel demonstrated both a PFS and more importantly OS advantage in the PD-L1+ subgroup of patients (median OS of 25 months vs. 15.5 months in the P + nabPx arm, HR: 0.62; CI: 0.45–0.86; p-value not tested due to statistical hierarchy testing; median PFS 7.5 months A + nabPx vs. 5.0 months P + nabPx, stratified HR: 0.62; 95% CI: 0.49–0.78, p-value<0.001) (13). This is especially impactful given atezolizumab is the first

agent to increase survival in several decades. The safety profile of the combination was in keeping with that known for each agent individually and no new safety signals were observed (13). Furthermore, HRQoL was maintained for the period of study treatment (29).

IMpassion130 was designed to be an all-comers study with provision for analysis of the PD-L1+ subgroup, due to a robust scientific rationale and early clinical signal of benefit of PD-L1/PD-1 treatment in an un-selected population. While this study in fact confirmed the robustness of PD-L1+ as a biomarker for clinical activity of the atezolizumab plus nab-paclitaxel combination, the hierarchical statistical testing prevents testing of OS in the PD-L1+ subgroup until significance has been reached in the ITT. While statistical significance cannot be stated, the clear separation of the Kaplan-Meier (KM) curves and the improvement with a magnitude of >6 months can be considered meaningful not only to the clinicians who will be prescribing this treatment but more importantly to the patients being treated. This is also the case for the improvement in PFS of ~2.5 months in the PD-L1+ subgroup, which represents more time for patient to live before being told that their disease is getting worse.

Secondary endpoint results reinforce the potential for a positive impact of this treatment - a numerically higher ORR (58.9% vs. 42.6%), complete response rate (10.3% vs. 1.1%), and longer DOR was observed (8.5 months vs. 5.5 months) for A + nabPx compared with P + nabPx in the PD-L1+ population, supporting the positive results seen in the survival analyses. While the difference in rates between the arms did not reach the predefined threshold for statistical significance ($p<0.001$), these measures are important for communicating control of disease to patients (13).

Combination therapy with atezolizumab plus nab-paclitaxel had a safety profile that was consistent with the known toxic effects of each agent. Consistent with observations from other atezolizumab–chemotherapy combination trials, no new adverse-event signals were observed. The incidence of grade 3 or 4 adverse events of special interest, which suggests there is potential immune-related aetiology, was higher in the A + nabPx arm than in the P + nabPx arm (7.5% vs. 4.3%). Discontinuations of either agent were higher in the A + nabPx arm than in the P + nabPx arm; however, atezolizumab did not compromise the dose intensity of nab-paclitaxel (13). Overall, the AE incidences were similar between the PD-L1–positive SE subpopulation and the safety-evaluable population.

Due to the challenge of combining an immunotherapy with chemotherapy pre-medication, the chemotherapy backbone in the study is different to the comparators detailed in the scope

of this appraisal. These complications have made indirect treatment comparisons necessary where possible, which has not been the case for all comparators.

### B.2.13.2 Indirect treatment comparison

OS for atezolizumab in combination with nab-paclitaxel was statistically significantly better as compared with paclitaxel alone, and there was a clear trend for improved OS as compared with docetaxel. Similarly, there was a trend for improved PFS for atezolizumab in combination with nab-paclitaxel in comparison to both paclitaxel and docetaxel. All improvements are deemed clinically meaningful. However, it should be highlighted: proportional hazards were not met in a number of trials included in the indirect comparisons, and the matching-adjusted indirect comparisons (MAIC) methodology includes additional uncertainty beyond usual ITC methodology. As such, results should be interpreted with caution.

The safety profiles of comparator chemotherapy agents are well established and different agents have somewhat different profiles making comparisons difficult. While some events are acute and life threatening (e.g. febrile neutropenia) others have long lasting impact on quality of life (e.g. peripheral neuropathy). Cross-trial comparisons are challenging and AE prophylaxis, treatment and management may not be consistent between studies. That said, a comparison of Grade 3–5 AEs with an incidence of ≥2% across IMpassion130 and the comparator studies included in the indirect treatment comparison (E2100, LOTUS, MERIDIAN, AVADO and JapicCTI-09092; Table 53) shows that all adverse events occurred in a smaller proportion of enrolled patients in the A + nabPx arm of IMpassion130 than in the paclitaxel/docetaxel control arms of the other studies, with the exception of neutropenia and febrile neutropenia. The neutropenia rate was slightly higher for A + nabPx vs paclitaxel but both values were significantly less than doc (8.2% v 6% v 42%), while febrile neutropenia was numerically similar between agents (13% v 13% v 11% for A+nabPx, paclitaxel and docetaxel respectively).

It is clear that the body of available evidence supports a meaningful benefit of the combination of A + nabPx over existing single agent chemotherapy regimens. A benefit gained with a manageable toxicity profile for the combination in addition to maintenance of HRQoL, despite the use of an additional agent. This is all the more meaningful given the considerable unmet need for efficacious treatments in this breast cancer subpopulation which carries a dire prognosis.

End-of-Life criteria are considered to be met for A + nabPx in patients with metastatic TNBC – a population that has poorer prognosis than other metastatic breast cancer types. The justification for this patient population meeting the end-of-life criteria is provided below:

**Table 33: End-of-life criteria**

| Criterion | Data available | Reference in submission (section and page number) |
|---|---|---|
| The treatment is indicated for patients with a short life expectancy, normally less than 24 months | Estimates from literature and observational data for median overall survival for mTNBC consistently fall below 24 months, ranging, from to 10 to 21.3 months (1, 13, 18, 24, 32).<br><br>Of these estimates, the 21.3 months was an outlier (32); the authors recognise that their caseload may not reflect general population, not least because 7.5–12.9% of patients were treated with investigational approaches across the first 4 lines of treatment versus a general population proportion of 2-3%.<br><br>Estimates of mean life expectancy from the cost-effectiveness analysis are: 13.8 months (for patients treated with paclitaxel), and 14.3 months (for patients treated with docetaxel). | Section B.1.3.1, page 20<br><br>Economic model |
| There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment | If nab-paclitaxel is to be considered similar in efficacy to paclitaxel, the IMpassion130 trial demonstrated a median life extension of 9.5 months in the primary analysis.<br>Based upon the indirect comparison incorporated into the cost-effectiveness analysis, the mean life extension was 12.6 months (paclitaxel) and 11.6 months (docetaxel). Hence, the life extension is expected to be substantially greater than 3 months. | Section B.2.6.2, page 43<br><br>Economic model |

# B.3 Cost effectiveness

## *B.3.1 Published cost-effectiveness studies*

An SR was conducted to identify published cost-effectiveness studies for treatment of patients in the first line of metastatic TNBC. Cost-effectiveness modelling approaches were expected to be similar between metastatic TNBC vs. metastatic non-TNBC Breast cancer – and so, to ensure that all relevant publications were captured - the population of interest was kept broad and included adult patients with advanced or metastatic BC, regardless of line of therapy.

Detailed descriptions of the search strategy and extraction methods, as well as an overview of the identified studies are provided in Appendix G.

An overview of the identified studies is provided below. Descriptions of the eligibility (inclusion/exclusion) criteria, search strategy, extraction methods, results extracted from included publications and PRISMA flow are provided in Appendix G.

### B.3.1.1 Summary of identified studies and results

A total of 27 economic evaluations published as full reports/fully published were included in the SR. In addition, 23 abstracts were identified.

The majority of studies were cost-utility analyses (CUAs) reporting incremental costs per quality adjusted life year (QALY) gained (n=21). Four studies were cost-effectiveness analyses (CEAs) (108-111); outcomes reported across these studies included the cost per life year gained (LYG)/life year saved (LYS) and the cost per progression free month/year. Finally, two studies were cost-minimisation analyses (CMAs).

All 27 fully published economic evaluations considered populations of patients with advanced or metastatic breast cancer. No fully published economic evaluations were identified which specifically considered a population of patients with TNBC. Two abstracts identified considered a population of patients with TNBC. However, these concerned patients in the adjuvant (early) breast cancer setting and patients who had received ≥1 prior chemotherapy for advanced/ metastatic disease.

The most common approach to modelling was the Markov approach (n=14). Six studies utilised a four-state Markov model and included the following health states: (i) response (complete/partial); (ii) stable disease; (iii) progression; and (iv) death. One study included

incorporation of treatment complications alongside states for response and progression, and one study did not specify the health states considered in their Markov model. Three studies used a decision tree to model costs and health outcomes, and one study used a combined decision tree and Markov model. The type of model was not applicable to nine studies as they were trial-based analyses (n=7) or CMAs (n=2).

A summary of the included economic evaluations is provided in Table 34.

**Table 34: Summary list of fully published economic evaluations (N=27)**

| Study | Year | Summary of model | Patient population | QALYs (intervention, comparator) | Costs (currency) (intervention, comparator) | ICER (per QALY gained) |
|---|---|---|---|---|---|---|
| Alba et al (Spain) (112) | 2013 | Cost Utility Analysis<br>Markov model (PFS, PD, Death) | Female patients with MBC in whom first-line antitumour treatments, including anthracyclines, had failed, or in whom anthracyclines were not indicated | Total QALYs:<br>Nab-paclitaxel q3w: 0.80<br>sb-paclitaxel q3w: 0.64<br>sb-paclitaxel qw: 0.80 | Total costs:<br>Nab-paclitaxel q3w: €16,447<br>sb-paclitaxel q3w: €13,509<br>sb-paclitaxel qw: €17,158 | nab-paclitaxel q3w vs sb-paclitaxel q3w: €17,808 |
| Benedict et al (UK) (113) | 2009 | Cost Utility Analysis<br>Markov model (PFS, PD, Death) | Patients with MBC | Discounted total QALYs:<br>Docetaxel: 1.18<br>Pac3w: 0.85<br>Pac1w: 0.89<br>Nab-paclitaxel: 0.96 | Discounted total costs:<br>Docetaxel: £17,321<br>Pac3w: £13,301<br>Pac1w: £15,973<br>Nab-paclitaxel: £14,116 | Pac3w: £12,032<br>Pac1w: £4,583<br>Nab-paclitaxel: £14,694 |
| Brown et al (UK) (114) | 2001 | Cost Utility Analysis<br>Markov model (Response, stable disease, progressive disease, death) | Patients with anthracycline-resistant ABC | Total QALYs:<br>Docetaxel: 0.7347<br>Paclitaxel: 0.6485<br>Vinorelbine: 0.4822 | Total costs:<br>Docetaxel: £7,817<br>Paclitaxel: £7,645<br>Vinorelbine: £4,268 | Docetaxel vs paclitaxel: £1,995<br>Docetaxel vs vinorelbine: £14,055 |
| Brown et al (USA) (115) | 1998 | Cost Utility Analysis<br>Markov model (Complete/partial response, stable disease, progressive disease, death) | Patients with MBC | Total QALYs per patient:<br>Docetaxel: 0.8670<br>Paclitaxel: 0.6605 | Total costs per patient:<br>Docetaxel: $15,683<br>Paclitaxel: $13,904 | Docetaxel vs paclitaxel: $8,615 |
| Cooper et al (UK) (116) | 2003 | Cost Utility Analysis<br>Markov model (Response, stable disease, progressive | Patients with ABC | Mean incremental QALYs, docetaxel vs doxorubicin (95% CI):<br>Classical model (Monte Carlo): 0.047 (-0.110, | Mean incremental cost, docetaxel vs doxorubicin (95% CI):<br>Classical model (Monte Carlo): £5,250 (3,175, | NR |



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|---|---|---|---|---|---|---|
| | | disease, death) | | 0.194)<br>Bayesian model (MCMC): 0.040 (-0.198, 0.270)<br>Bayesian model (MCMC) with informative prior distributions: 0.036 (-0.201, 0.251) | 7,262)<br>Bayesian model (MCMC): £4,468 (1,317, 7,492)<br>Bayesian model (MCMC) with informative prior distributions: £4,438 (1,520, 7,336) | |
| Dedes et al (Switzerland) (117) | 2009 | Cost Utility Analysis<br>Markov model (Stable/responsive disease, progressive disease, death) | Patients with histologically or cytologically proven MBC | Total QALYs:<br>Bevacizumab + paclitaxel: 0.90<br>Paclitaxel alone: 0.69 | Total cost:<br>Bevacizumab + paclitaxel: €69,042<br>Paclitaxel alone: €28,673 | bevacizumab + paclitaxel vs paclitaxel alone: €189,427 |
| Dranitsaris et al (UK) (108) | 2010 | Trial based cost effectiveness analysis | Patients with MBC | NR | Mean cost per patient:<br>Nab-paclitaxel 100 mg/m2 qw: £15,396<br>Nab-paclitaxel 150 mg/m2 qw: £27,222<br>Nab-paclitaxel 300 mg/m2 q3w: £15,809<br>Docetaxel 100 mg/m2 q3w: £12,923 | NR |
| Dranitsaris et al (Canada) (118) | 2009 | Trial based cost utility analysis | Patients with MBC | Incremental QALYs vs paclitaxel:<br>Nab-paclitaxel: 0.20 (range 0.15-0.26)<br>Docetaxel: 0.016 (range -0.067-0.98) | Total cost per course:<br>Nab-paclitaxel: $15,105<br>Docetaxel: $15,268<br>Paclitaxel: $3,557 | Nab-paclitaxel: $56,800<br>Docetaxel: $739,600 |
| Frias et al (Spain) (119) | 2010 | Cost Utility Analysis<br>Markov model (No progression, progression, Death) | Patients with MBC | Total QALYs:<br>Docetaxel: 1.08<br>Paclitaxel: 0.84 | Total costs:<br>Docetaxel: €20,052.38<br>Paclitaxel: €19,981.51 | ICER, docetaxel vs paclitaxel:<br>€295.27 |
| Hutton et al (UK) (120) | 1996 | Cost Utility Analysis<br>Markov model | Patients with anthracycline- | Total QALYs per patient:<br>Paclitaxel: 0.5111 | Total cost per patient:<br>Paclitaxel: £8,013 | ICER/QALY, docetaxel vs |



 

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|---|---|---|---|---|---|---|
| | | (Response, stable disease, progressive disease, death) | resistant MBC | Docetaxel: 0.6016 | Docetaxel: £8,233 | paclitaxel: £2,431 |
| Launois et al (France) (121) | 1996 | Cost Utility Analysis<br>Markov model: health states unspecified (53 in total) | Patients with MBC | NR | Total costs:<br>Docetaxel: FF 250,400<br>Paclitaxel: FF 251,100<br>Vinorelbine: FF 257,200 | NR |
| Lazzaro et al (Italy) (122) | 2013 | Cost Utility Analysis<br>Markov model (PFS, PD, Death) | Patients with pretreated MBC | Total QALYs:<br>Nab-paclitaxel: 0.805<br>Conventional paclitaxel: 0.640 | Total costs:<br>Nab-paclitaxel: €14,564<br>Conventional paclitaxel: €12,058 | nab-paclitaxel vs conventional paclitaxel: €15,189 |
| Leung et al (Canada) (123) | 1999 | Cost Utility Analysis<br>Decision tree:<br>• Chance node 1: toxic death rate<br>• Chance node 2: treatment-limiting toxicity rate<br>• Chance node 3: response rate<br>• Discontinue treatment | Patients with anthracycline-resistant ABC | NR | Overall treatment cost:<br>Paclitaxel: $6,039<br>Docetaxel: $10,090<br>Vinorelbine: $3,259 | NR |
| Li et al (Netherlands) (124) | 2001 | Cost Utility Analysis<br>Decision tree:<br>• Chance node 1: neutropenia<br>• Chance node 2: hospitalisation | Patients with MBC | Total QALYs:<br>Paclitaxel: 0.35<br>Docetaxel: 0.34<br>Vinorelbine + mitomycin C: 0.43<br>Mitomycin + vinblastine: 0.29 | Total cost per patient:<br>Paclitaxel: $10,594<br>Docetaxel: $16,911<br>Vinorelbine + mitomycin C: $7,359<br>Mitomycin + vinblastine: $4,037 | ICER/QALY, comparator vs mitomycin + vinblastine:<br>Paclitaxel: $6,557<br>Docetaxel: $12,873<br>Vinorelbine + |



 

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|---|---|---|---|---|---|---|
| | | | | | | mitomycin C: $3,322 |
| Lopes et al (USA) (125) | 2013 | Cost Utility Analysis<br>Markov model (Response, progression, death) | Patients with previously treated MBC | Incremental QALYs, eribulin vs:<br>TPC: 0.119<br>Capecitabine: 0.119<br>Nab-paclitaxel: 0.119<br>Doxorubicin: 0.119<br>Ixabepilone: 0.119 | Total incremental cost, eribulin vs:<br>TPC: $25,458.86<br>Capecitabine: $19,923.30<br>Nab-paclitaxel: $15,457.40<br>Doxorubicin: $13,016.73<br>Ixabepilone: $9,150.44 | ICER/QALY, eribulin vs:<br>TPC: $213,742.01<br>Capecitabine: $167,267.64<br>Nab-paclitaxel: $129,773.83<br>Doxorubicin: $109,283.00<br>Ixabepilone: $76,823.29 |
| Maniadakis et al (Greece) (126) | 2009 | Trial based cost utility analysis | Patients with histologically proven MBC | NR | Total cost:<br>Group A (paclitaxel/carboplatin): €20,498<br>Group B (gemcitabine/docetaxel): €19,343<br>Group C (Q1W paclitaxel): €20,578 | ICER/QALY:<br>Group C vs group A: dominance<br>Group C vs group B: €3,596<br>Group A vs group B: €7,462 |
| Nerich et al (France) (127) | 2014 | Cost Minimisation Analysis | Patients with HER2+ MBC | NA | Mean total cost:<br>Trastuzumab plus docetaxel: €68,532<br>Trastuzumab plus paclitaxel: €66,296 | NA |
| Nerich et al (France) (128) | 2012 | Cost Minimisation Analysis | Patients with HER2- MBC | NA | Mean total cost:<br>Bevacizumab + docetaxel: €53,093<br>Bevacizumab + paclitaxel: €60,196 | NA |
| Poncet et al (France) (111) | 2008 | Trial based cost effectiveness | Patients with HER2+ MBC | NR | Overall care cost:<br>Trastuzumab + paclitaxel: | NR |



 

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|---|---|---|---|---|---|---|
| | | analysis | | | €33,271<br>Chemotherapy without trastuzumab: €11,291 | |
| Reed et al (USA) (129) | 2009 | Cost Utility Analysis<br>Decision tree:<br>• Response to treatment (complete/partial response, stable disease, progressive disease, undetermined)<br>• Discontinuation (toxicity, progression or death, other)<br>• Subsequent treatment (yes, no) | Patients with taxane-resistant MBC | Total QALYs:<br>Ixabepilone + capecitabine: 0.623<br>Capecitabine alone: 0.535 | Total undiscounted medical costs:<br>Ixabepilone + capecitabine: $60,900<br>Capecitabine alone: $30,000 | ICER, ixabepilone + capecitabine vs capecitabine alone:<br>ICER/QALY: $359,000 |
| Reefat et al (USA) (130) | 2013 | Cost Utility Analysis<br>Markov model (Response, progression, treatment complications, death) | Patients with HER2-MBC | Incremental QALYs, bevacizumab + paclitaxel vs paclitaxel alone: 0.369 | Incremental cost, bevacizumab + paclitaxel vs paclitaxel alone: $86,000 | ICER/QALY, bevacizumab + paclitaxel vs paclitaxel alone: $232,720.72 |
| Shiroiwa et al (Japan) (131) | 2017 | Trial based cost utility analysis | Patients with HER2-, hormone-resistant MBC | Total QALYs:<br>Taxane: 2.04<br>S-1: 2.11 | Total cost (JPY 1,000):<br>Taxane: ¥5,731<br>S-1: ¥5,307 | S-1 dominated taxanes |
| Takeda et al (UK) (132) | 2007 | Cost Utility Analysis<br>Markov model (Response, stable disease, | Patients with MBC who had relapsed post anthracycline-based chemotherapy | Total QALYs:<br>Gemcitabine + paclitaxel: 1.00<br>Paclitaxel: 0.83 | Total costs:<br>Gemcitabine + paclitaxel: £26,202 | ICER, gemcitabine + paclitaxel vs paclitaxel:<br>ICER/QALY: |



 

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|---|---|---|---|---|---|---|
| | | progressive disease, death) | | | Paclitaxel: £16,653 | £58,876 |
| Tremblay et al (South Korea) (133) | 2016 | Cost Utility Analysis<br>Markov model (Stable disease, progressive disease, death) | Patients with HER2-MBC | Total QALYs:<br>Eribulin: 1.18<br>Capecitabine + vinorelbine: 0.94 | Total costs:<br>Eribulin: ₩14,527,724<br>Capecitabine + vinorelbine: ₩10,465,673 | ICER, eribulin vs capecitabine + vinorelbine:<br>ICER/QALY: ₩16,898,483 (USD 14,800) |
| Van Kampen (The Netherlands) (134) | 2017 | Cost Utility Analysis<br>Markov model (PFS, PD, Death) | Patients with HER2-MBC | Total QALYs:<br>• Real-world scenario:<br>Bevacizumab-taxane: 1.778<br>Taxane monotherapy: 1.416<br>• Trial scenario:<br>Bevacizumab-taxane: 1.573<br>Taxane monotherapy: 1.384 | Total costs:<br>• Real-world scenario:<br>Bevacizumab-taxane: €125,496<br>Taxane monotherapy: €69,282<br>• Trial scenario:<br>Bevacizumab-taxane: €119,369<br>Taxane monotherapy: €66,619 | ICER/QALY, bevacizumab-taxane vs taxane monotherapy:<br>• Real-world scenario: €155,261<br>• Trial scenario: €278,711 |
| Verma et al (Canada) (109) | 2003 | Trial based cost effectiveness analysis | Patients with MBC | NR | Total costs:<br>Capecitabine/docetaxel: $13,659<br>Docetaxel: $12,833 | NR |
| Vu et al (Canada) (110) | 2008 | Trial based cost effectiveness analysis | Patients with MBC | NR | Total monthly cost:<br>Docetaxel: $2,221<br>Paclitaxel: $865 | NR |

ABC: advanced breast cancer; BC, advanced breast cancer; AUC, area under the curve; BC, breast cancer; BNF, British National Formulary; CEA, cost-effectiveness analysis; CMA, cost-minimisation analysis; CSR, clinical study report; CUA, cost-utility analysis; EQ-5D, European Quality of Life-5 Dimensions; HER2, human epidermal growth factor receptor 2; HUI3, Health Utilities Index 3; JPY: Japanese Yen; LYG, life year gained; LYS, life year saved; MBC, metastatic breast cancer; MIMS, Monthly Index of Medical Specialities; NA, not applicable; NHS, National Health Service; NR, not reported; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; q3w, three times weekly; QALY, quality adjusted life year; QOL, quality of life; qw, weekly; RCT, randomised controlled trial; SG, standard gamble; TTO, time trade off; UK, United Kingdom; US, United States.



## *B.3.2 Economic analysis*

- **Area Under the Curve (partitioned survival) model composed of 3-mutually exclusive health states: PFS, PD and death, was developed in Excel**
- **Model uses a time horizon of 15 years, considered sufficient to demonstrate all differences in costs and benefits**
- **The comparators included within the appraisal are paclitaxel (primary comparator) and docetaxel (secondary comparator). No robust RCT or observational evidence was identified to enable a comparison to anthracyclines**

The cost-effectiveness studies identified in section B.3.1 were used to inform the model structure of the economic analysis. As none of the identified literature directly appraised atezolizumab in combination nab-paclitaxel for the first-line treatment of adult patients with metastatic TNBC, a *de novo* economic model was built to inform decision making.

### B.3.2.1 Patient population

The *de novo* analysis assesses atezolizumab in combination with nab-paclitaxel for the first-line treatment of adult patients with metastatic TNBC who have PD-L1 positive status. This population is consistent with the appraisal final scope, Marketing Authorisation, and the study population of IMpassion130.

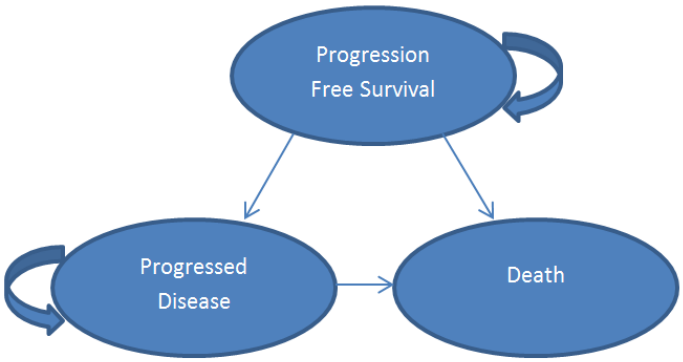
### B.3.2.2 Model structure

The economic evaluation was developed in Microsoft Excel and is an Area-Under-the-Curve (AUC; or 'partitioned survival') model. The AUC model was selected in order to reduce the number of assumptions required when assessing and extrapolating immature OS, and to allow for full use of the IMpassion130 data as opposed to alternative data sources where populations may not be equivalent.

The model is composed of 3-mutually exclusive health states, consistent with previous appraisals accepted by NICE for metastatic breast cancer (TA509, TA503, TA495): "progression-free survival (PFS)", "progressed disease (PD)" and "death". The resulting structure can be found in Figure 19.

**Figure 19: Area under the curve model structure**




The health economic model was developed to compare the cost-effectiveness of atezolizumab in combination with nab-paclitaxel versus the final scope comparators.

Due to a lack of advancements in TNBC, there is no clear standard of care for patients. Rather, a range of therapies are used (Section B.1). The final scope for this appraisal details the following regimens as key comparators:  paclitaxel (single agent), docetaxel (single agent) and anthracycline therapies.

As detailed in section B.1.3, paclitaxel is often the taxane of choice for 1L mTNBC. This is due to the favourable toxicity profile of weekly paclitaxel compared with 3-weekly docetaxel which increases tolerability and helps maintain QoL for patients with limited life expectancy (56). Docetaxel is often used in the curative eBC setting where the toxicities of treatment are offset by the aim of cure rather than palliation (UK Clinical expert opinion, (20)). Both in vitro and in vivo studies have demonstrated only partial cross-resistance between docetaxel and paclitaxel (57-59), increasing the likelihood of additional benefit from a different taxane agent i.e., paclitaxel. Furthermore, re-challenge with docetaxel (following use in eBC) may be unacceptable to some patients due to the extent of toxicities experienced, possibly coupled with a perception that the treatment was not effective if they relapse.

Eligibility for 1L metastatic TNBC patients for anthracyclines is limited: Approximately 80–85% of this population will have progressed to the metastatic setting from the eBC setting, where anthracyclines are a preferred treatment regimen. Re-challenge with anthracyclines is hindered by lifetime maximum cumulative dose (e.g. epirubicin (25)) and as such, patients treated in the eBC setting are unlikely to be eligible for re-challenge. As such, these regimens are rarely used within this setting. This is supported by observational data in

the UK, demonstrating 7.5% usage in 1L mTNBC (32); as well as the clinical trial literature (see B.2.9), with no RCT assessing anthracyclines meeting the inclusion criteria, and therefore able to be included within the NMA.

Given the limited real world usage, and the lack of robust trial evidence identified in the clinical SR to provide a comparison to anthracyclines, no clinical effectiveness comparisons can be made and subsequently, no cost effectiveness analyses could be generated for this comparison.

As such, for the purposes of this appraisal, paclitaxel is considered the primary comparator. Docetaxel is still incorporated in to the base case, despite its limited usage, but should be considered the secondary comparator.

The model inputs (efficacy, safety/tolerability) for the intervention arm were based on the results of the phase III IMpassion130 trial. Model inputs for paclitaxel and docetaxel are generated from the Indirect Treatment Comparison (ITC), as discussed in section B.2.9.

Results are reported in terms of cost per life years gained (LYG) and costs per quality adjusted life years (QALY) gained. This appropriately reflects the decision problem.

Within the AUC model, health states are based on the partitioning of the proportion of patients alive in a “PFS” state and “PD” state at discrete time points, based on the PFS and OS curve from IMpassion130, and the results of the ITC and observational data analyses, with the proportion of patients in the “PD” health state assumed to be the difference between the two. The health states in the model represent the stages of disease in metastatic TNBC.

All patients start in the PFS health state and remain in this health state until they progress. At progression, defined as per the Response Evaluation Criteria in Solid Tumours (RECIST) criteria, patients transition into PD health state or enter the absorbing health state of death. Patients in the PD health state stay in that health state until death. Patients cannot transition to an improved health state (back to PFS); a restriction that is consistent with previous economic modelling in oncology.

Due to the structural form of the model, patient transitions between the health states are not explicitly modelled. The partitioned survival approach allows for modelling of OS and PFS based on study-observed events, which is expected to accurately reflect disease progression and the long-term expected survival profile of patients treated with atezolizumab. However, the primary limitation of this approach is that as transitions are not

explicitly modelled, the model structure is rigid and does not allow exploratory or sensitivity analyses to be explored by changing the transition probability between different health states.

Costs and health-related utilities are allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle.

The economic model base case uses a time horizon of 15 years, which was considered to be sufficiently long enough to reflect all important differences in costs or outcomes between the technologies being compared. This takes into consideration: 1) prognosis of patients treated in this setting; 2) expected survival times following present NHS treatment in this setting and 3) the maximum plausible impact of improved outcomes following treatment with atezolizumab in combination with nab-paclitaxel. Scenario analyses are provided that consider both shorter and longer time horizons.

The model has been designed to use a weekly cycle, with the proportion of patients in each health state calculated each week. Transition between health states can occur at any time within the cycle. To account for the over or under estimation of transitions occurring at the beginning or end of the cycle, half-cycle corrections were applied to each time interval in the Markov trace sheets of the model. This is also consistent with previous NICE STAs in this disease area.

Table 35 details the main features of this economic analysis as compared with previous NICE appraisals in metastatic Breast Cancer. Appraisals reviewed have been confined to mBC due to the lack of development specifically for TNBC, and to within the last 5 years to ensure relevance.

**Table 35: Features of the economic analysis**

| Factor | TA509 | TA503 | TA495 | TA496 | This Appraisal (base case) | Justification |
|---|---|---|---|---|---|---|
| Time horizon | 25 years | 30 years | 40 years | 40 years | 15 years | This takes into consideration the known factors of: 1) prognosis of patients treated in this setting 2) expected survival times following present NHS treatment pathways and 3) the impact of outcomes improvement following treatment with atezolizumab with nab-paclitaxel. |
| Treatment waning | Not included | Not included | Not included | Not included | No waning | Not incorporated as the base case, in-line with previous HTAs in this disease area, and lack of sufficient data. However, explored as a scenario analysis to acknowledge the uncertainty regarding long term benefit. |
| Source of utilities | Lloyd et al 2006 | FALCON clinical trial, literature, prior NICE appraisals | PALOMA-2 clinical trial, literature | MONALEESA-2 and BOLERO-2 clinical trials, prior NICE Technology appraisals | EQ-5D-5L mapped to EQ-5D-3L from IMpassion130, literature | EQ-5D-5L was collected in the IMpassion130 phase III RCT. Following the NICE position statement on EQ-5D-5L, these figures were mapped to EQ-5D-3L, in-line with guidance in NICE reference case. Utilities derived from other types of advanced breast cancer (non-TNBC) would not be expected to be of a similarly poor-prognosis population to the present decision problem, hence the IMpassion130 utilities are most appropriate. |
| Source of costs | NHS reference costs<br>PSSRU<br>BNF | NHS reference costs<br>PSSRU<br>BNF | NHS reference costs<br>PSSRU<br>BNF | NHS reference costs<br>PSSRU<br>BNF | NHS reference costs<br>PSSRU<br>BNF/eMIMS<br>Published literature<br>Expert opinion input | Widely used and accepted sources of NHS resource use and costs, in-line with guidance in NICE reference case used. Accepted estimates taken from past technology appraisals used. |



### B.3.2.3 Intervention technology and comparators

The final scope intervention is atezolizumab in combination with nab-paclitaxel. For the purposes of this appraisal, the primary comparator is paclitaxel and the secondary comparator is docetaxel. Due to the lack of robust trial evidence identified in the clinical SR to provide a comparison to anthracyclines, no clinical effectiveness comparisons can be made and subsequently, no cost effectiveness analyses could be generated for this comparison.

## *B.3.3 Clinical parameters and variables*

- **Clinical data for atezolizumab in combination with nab-paclitaxel is sourced from the IMpassion130 trial. Comparator data is derived using the ITC (B.2.9)**
- **Extrapolation was required for the remaining patients who had not progressed, or died within the follow-up period of the trial**
- **NICE Decision Support Unit (DSU) guidance (Technical Support Document 14) was followed to identify base case parametric survival models for OS, PFS and TTOT using AIC/BIC statistical fit, visual inspection and clinical plausibility assessment**
- **The weibull distribution is utilised to extrapolate OS, providing a relatively conservative assessment of long term survival as compared to alternative distributions**
- **Given the maturity of PFS data, the unadjusted KM data followed by gompertz extrapolation was deemed the most appropriate**
- **Clinical expert opinion was sought to validate all extrapolations (20)**

### B.3.3.1 Incorporation of clinical data into the economic model

The primary source for clinical data in the economic model for the intervention is the phase III pivotal randomised controlled trial, IMpassion130, comparing atezolizumab in combination with nab-paclitaxel to nab-paclitaxel in combination with placebo. This study is the data source for the clinical outcomes (OS, PFS), adverse events and quality of life (utilities) for atezolizumab + nab-paclitaxel (the intervention).

Nab-paclitaxel is not licensed in the UK, nor is it NICE-recommended for the treatment of first line metastatic TNBC. Therefore, the comparator arm of the IMpassion130 trial is not directly relevant to the decision problem. To account for this, the primary data source for the comparator arms in the economic model is generated from the ITC (Section in B.2.9).

Extrapolation of atezolizumab OS, PFS and Time to Off Treatment (TTOT) from IMpassion130 was required, for the proportion of patients that had not progressed or died, within the follow-up period of IMpassion130.

NICE Decision Support Unit (DSU) guidance (Technical Support Document 14, (135)) was followed to identify base case parametric survival models for OS, PFS and TTOT. All parametric models were assessed against the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for statistical fit to the observed data. Curves were visually inspected and validated against relevant long term data sources available to help identify the most plausible survival model. Clinical expert opinion was also utilised to support the extrapolation approach taken.

Unless otherwise specified, the following section utilises the secondary analysis of the IMpassion130 clinical trial as the primary data source.

### B.3.3.2 OS extrapolation

#### *Intervention*

To determine which extrapolation was the most appropriate fit to the observed data, alternative distributions were mapped to the observed KM data from the trial through parameterisation. The following candidate distributions were assessed for goodness of fit using AIC, BIC and visual assessment: Exponential, Weibull, Log-normal, Gamma, Log-logistic, and Gompertz. When assessing the best statistical fit, a difference of five or more is generally considered important, thus when extrapolations have a narrow statistical margin between, visual inspection, and clinical plausibility becomes paramount.

Table 36 provides the AIC and BIC for the atezolizumab in combination with nab-paclitaxel arm. Most distributions are within five points, thus could be deemed similarly plausible. As statistical fit only assesses the available trial data, visual assessment is required to rule out any implausible distributions.

**Table 36: Summary of goodness of fit for OS – atezolizumab with nab-paclitaxel**

| | Overall Survival – goodness of fit statistics Atezolizumab + nabPaclitaxel | |
|---|---|---|
| **Parametric distribution** | **AIC** | **BIC** |
| Exponential | 862.3 (6) | 865.6 (3) |
| Weibull | 856.1 (1) | 862.6 (1) |
| Log-normal | 859.3 (4) | 865.7 (4 |
| Gamma | 857.6 (3) | 867.3 (6) |
| Log-logistic | 856.2 (2) | 862.7 (2) |

| | | |
|---|---|---|
| Gompertz | 859.3 (5) | 865.8 (5) |

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Based on the above, the Weibull, Log-logistic and Gamma are the best distributions by statistical fit. Next, all parametric distributions were assessed for visual fit to the Kaplan Meier data. Visual fit has been conducted against the primary analysis (Figure 20 and the second interim OS analysis (Figure 21 ).



**Figure 20: Visual fit of OS distributions to Primary Analysis KM data (atezolizumab + nab-paclitaxel)**

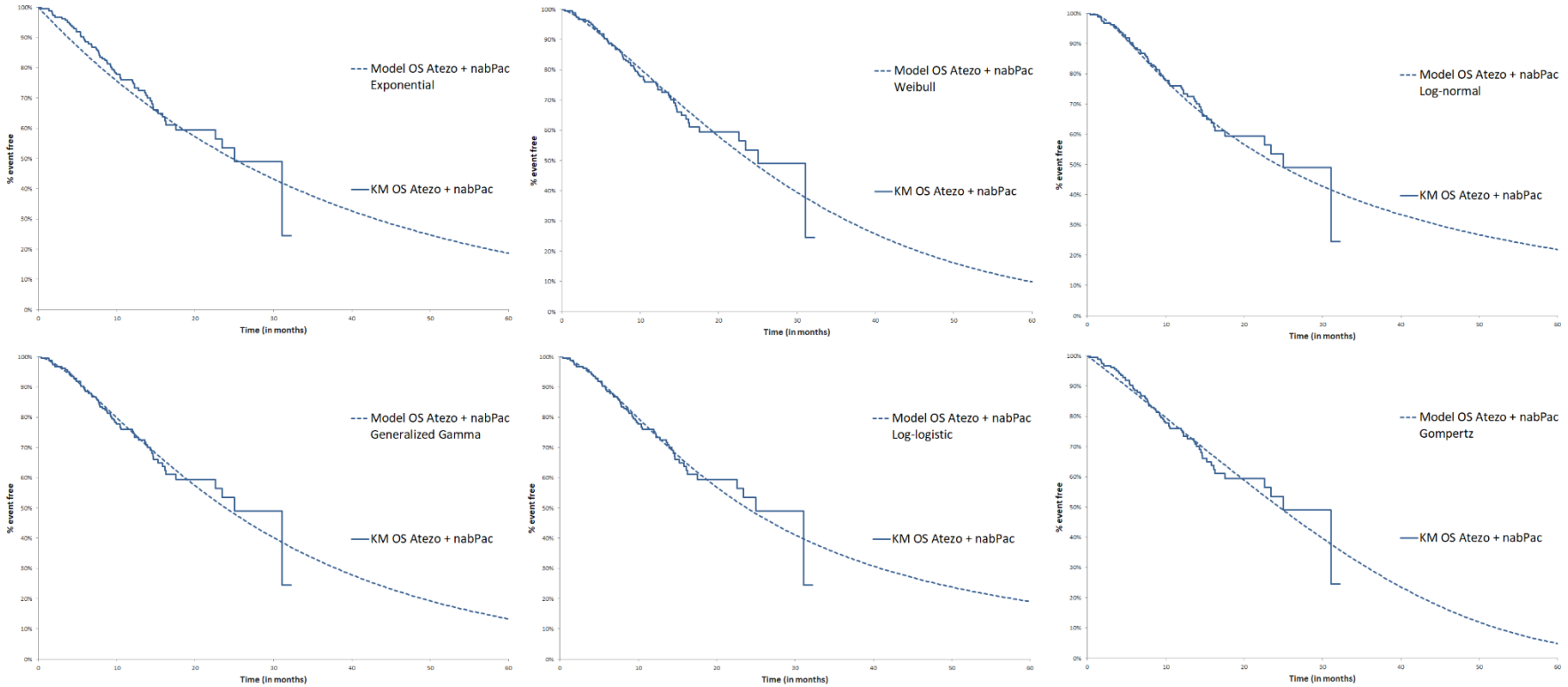




**Figure 21: Visual fit of OS distributions to second interim OS KM data (atezolizumab + nab-paclitaxel)**

As demonstrated, the exponential is not a good visual fit to the data, particularly due to underestimation of OS in the first 15months. The log-normal appears to overestimate survival towards the end of the KM data. The Gompertz is a generally poor fit across different stages of the KM: frequently over and underestimating survival. The Weibull, log-logistic and Gamma curves, similarly to AIC/BIC, appear as the best visual fits.

Next, the resulting tails of the distributions were assessed for their clinical plausibility. Table 37 provides a comparison of the proportion of patients expected to be alive at set time points up to 10 years between all parametric distributions, the IMpassion130 trial based survival, and clinical expert opinion (20).

**Table 37: Proportion of patients treated with atezolizumab and nab-paclitaxel alive at set time points based on parametric distributions, compared with IMpassion130 trial data**

| Analysis | | 12 months | 24 months | 30 months | 36 months | 48 months | 60 months | 72 months | 120 months |
|---|---|---|---|---|---|---|---|---|---|
| IMpassion130 (based upon primary analysis) | | 75% | 49% | 25% | - | - | - | - | - |
| IMpassion130 (based upon second interim OS analysis) | | [redacted] | [redacted] | [redacted] | [redacted] | - | - | - | - |
| Clinical expert opinion | | - | - | 37% | 30% | 13% | 8% | 4% | 0.2% |
| Parametric distributions | Exponential | 71.3% | 51.1% | 43.2% | 36.5% | 26.1% | 18.7% | 13.3% | 3.5% |
| | Weibull | 75.5% | 49.9% | 39.4% | 30.7% | 17.8% | 9.9% | 5.2% | 0.3% |
| | Log-normal | 72.6% | 50.4% | 42.8% | 36.8% | 28.0% | 21.9% | 17.5% | 8.5% |
| | Gamma | 74.8% | 49.8% | 40.1% | 32.3% | 20.8% | 13.4% | 8.6% | 1.5% |
| | Log logistic | 74.4% | 49.7% | 41.1% | 34.4% | 25.1% | 19.1% | 15.0% | 7.4% |
| | Gompertz | 75.2% | 50.8% | 39.6% | 29.5% | 13.9% | 4.9% | 1.1% | 0.0% |

AN, atezolizumab with nab-paclitaxel; PN, placebo with nab-paclitaxel

Comparing against results from set time points of the IMpassion130 trial, the exponential, log-normal and log-logistic can be ruled out on the basis of overestimation of survival at 36 months. This is further supported when comparing longer term outcomes to those anticipated by clinical experts, with the likes of the log-normal predicting 8.5% survival at 10 years, versus clinical expert opinion of 0.2%.

The remaining distributions are the weibull, gamma and gompertz. Gamma, although improved over exponential, log-normal and log-logistic, still appears to overestimate long term survival as compared to clinical expert opinion (for example, 13.4% alive at 5 years, as compared to an anticipated 8% from clinical expert opinion). As such, Gamma has also been excluded.

As gompertz has the second-to-worse fit of all the distributions, it was critiqued heavily for long-term plausibility. Across 12–24 months of the clinical trial, survival estimates appear to reflect the Impassion130 trial. At 30 months, there is an underestimation, but then between 36 and 48 months, it again appears to reflect clinical expert opinion of anticipated survival. Nevertheless, beyond this time point, it consistently and considerably underestimates likely survival of patients treated with atezolizumab in combination with nab-paclitaxel. This, in combination with the poor statistical fit, is clear rationale for its exclusion as an appropriate extrapolation.

Finally, the Weibull: in comparison against all other distributions, the clinical trial results of IMpassion130, and clinical expert opinion, this distribution is considered the most appropriate extrapolation, both in terms of best statistical fit to the data, and long-term clinical plausibility. Whilst the Weibull appears to mildly overestimate OS between 60 and 72 months (vs. clinician opinion), this is offset with the underestimation between 24 and 30 months, as compared with the IMpassion130 clinical trial (and associated discounting). In addition, it should be highlighted the extent of this overestimation is considerably less than the underestimation produced by the Gompertz.

Table 38 presents the resulting ranking of OS distributions based on AIC/BIC, visual fit and clinical plausibility of the Atezolizumab + nabPaclitaxel arm, as explored above.

**Table 38: Ranking of OS distributions based on AIC/BIC, visual fit and clinical plausibility for atezolizumab + nab- paclitaxel arm**

| Parametric distribution | AIC (rank) | BIC (rank) | Visual fit to KM | Clinical plausibility | Ranking |
|---|---|---|---|---|---|
| Exponential | 862.3 (6) | 865.6 (3) | × | × | 6 |
| Weibull | 856.1 (1) | 862.6 (1) | ✓ | ✓ | 1 |
| Log-normal | 859.3 (4) | 865.7 (4) | ~ | × | 5 |
| Gamma | 857.6 (3) | 867.3 (6) | ✓ | ~ | 2 |
| Log-logistic | 856.2 (2) | 862.7 (2) | ✓ | × | 4 |
| Gompertz | 859.3 (5) | 865.8 (5) | × | ~ | 3 |

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion, KM, Kaplan-Meier.

### *Comparators*

In order to implement comparator OS and PFS data, results of the piecewise exponential NMA were used.

The following section details the approach taken for the comparison to paclitaxel, the main comparator for the purpose of the NICE appraisal, and docetaxel, the secondary comparator. As detailed in section B.2.9, there was insufficient trial evidence to compare to anthracyclines.

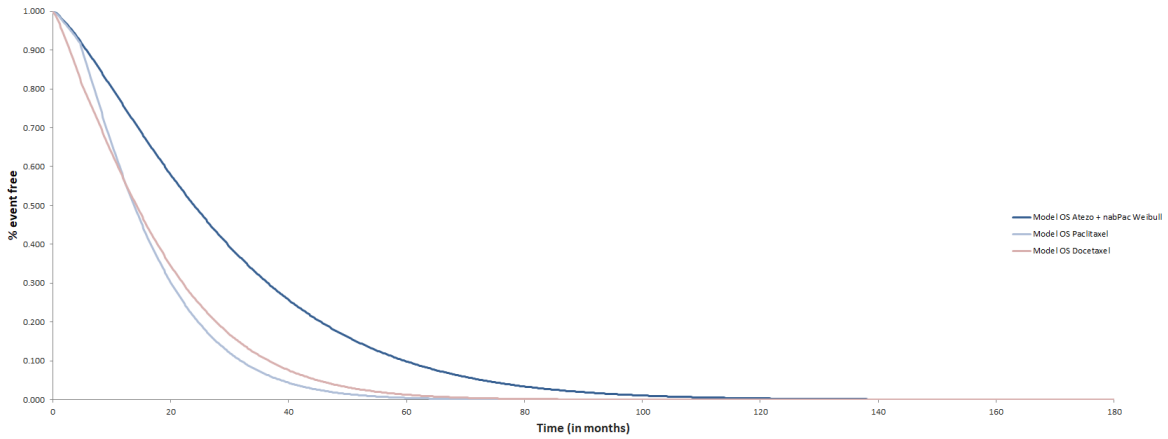
The results of the indirect comparisons were incorporated into the economic model in order to generate the extrapolation for the comparators. Comparator curves are constructed using the atezolizumab + nab paclitaxel extrapolation, and applying the time-dependant log hazard ratios over the span of the extrapolation.

As a result of this approach, the OS extrapolation distributions selected for the intervention arm (atezolizumab in combination with nab-paclitaxel) are the same selections as used for each of the paclitaxel and docetaxel comparisons.

Figure 22 demonstrates the resulting paclitaxel and docetaxel extrapolation, as compared with atezolizumab in combination with nab-paclitaxel.

**Figure 22: Resulting extrapolation of paclitaxel and docetaxel compared with atezolizumab + nab-paclitaxel**




In order to validate the resulting long term survival estimates for both paclitaxel and docetaxel, clinical expert opinion was sought.

As detailed in section B.1.3, clinical experts highlighted the more limited usage of docetaxel in clinical practice. This is due to the associated safety profile, and availability to re-challenge on patients from an eBC setting. Nevertheless, beyond these limitations, efficacy between docetaxel and paclitaxel were considered largely comparable.

This however, contrasts (to an extent) with the outcomes of the ITC. According to the ITC results, docetaxel has poorer survival as compared to paclitaxel for approximately the first 15 months after treatment initiation, but then outperforms paclitaxel beyond this time point. Given the method of ITC, it is difficult to determine if this is a limitation of the outputs, or representative of anticipated outcomes in the real world.

As further validation, observational data in the form of a RWD study was sought. In October 2018, a poster was presented at the European Society for Medical Oncology (ESMO) detailing the Comparative Effectiveness of nab-Paclitaxel vs Paclitaxel as First-Line Treatment of Triple-Negative Breast Cancer in US Clinical Practice. The findings from this analysis, was that “OS and time-to-next-treatment (TTNT) [considered a proxy to PFS in the real world setting] were similar between patients treated with nab-paclitaxel and those treated with paclitaxel, suggesting that the agents may be considered interchangeable as 1L treatments for mTNBC” (136). The associated OS KM can be found in Figure 23. This therefore suggests the placebo + nab-paclitaxel arm of the IMpassion130 trial could be utilised to validate at a minimum the anticipated survival for paclitaxel. However, it should be

highlighted, this evidence is conflicting with the ITC (see B.2.9 and **Figure 23**), where paclitaxel and docetaxel had approximately 4 months poorer median OS as compared to nab-paclitaxel. In addition, this data is derived from a US population, thus may not be comparable to UK clinical practice, thus should be interpreted with caution.

**Figure 23: OS comparative effectiveness of nab-paclitaxel and paclitaxel in TNBC - RWD analysis by Luhn et al. (136)**

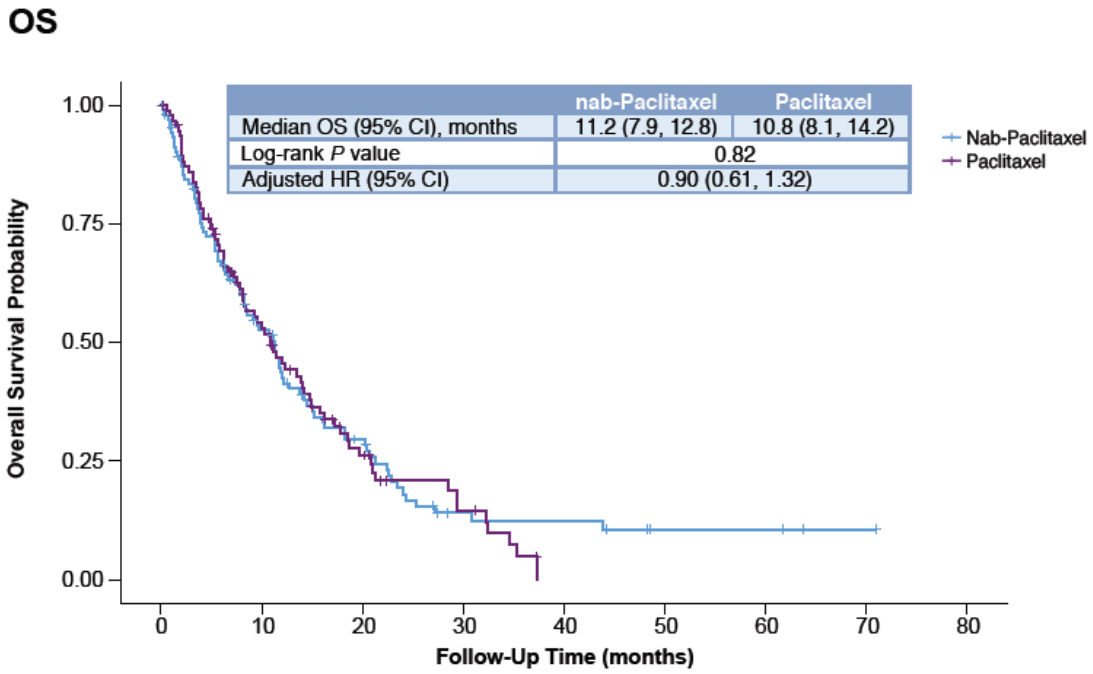



**Table 39: Nab-paclitaxel, paclitaxel and docetaxel outcomes from ITC**

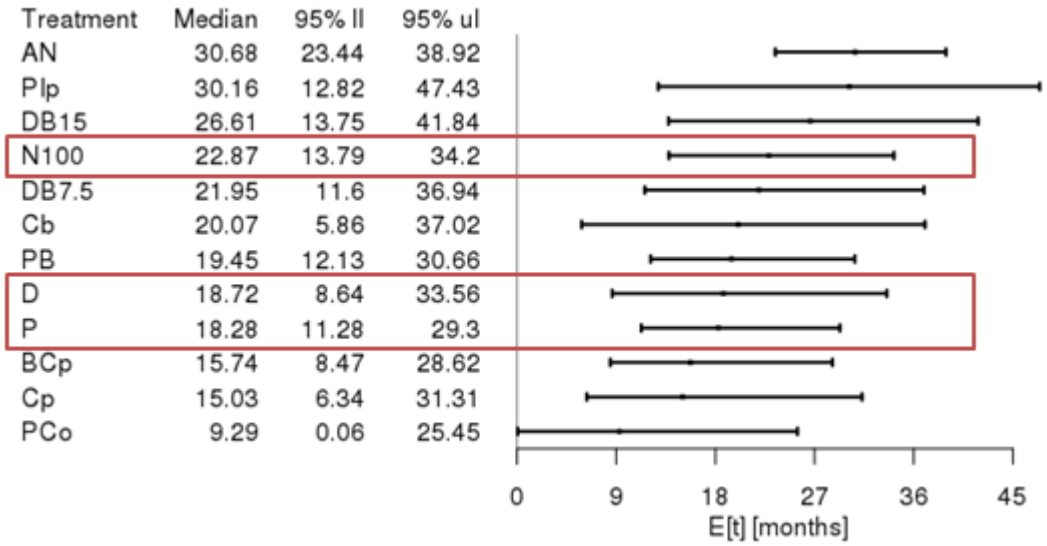




Table 40 and Table 41 compare the landmark survival estimates of the chosen extrapolation (Weibull) against the second and third ranked extrapolations (Gamma and Gompertz), with the IMpassion130 comparator arm and clinical expert opinion, for both paclitaxel and docetaxel.

As demonstrated, none of the top three distributions provide a good fit against the IMpassion130 comparator arm, or clinical expert opinion for paclitaxel, with all appearing to underestimate survival. Arguably, the gamma could be considered the best option, providing estimates closest to both the placebo + nab-paclitaxel arm of IMpassion130 and clinical expert opinion. All extrapolations are a better fit for docetaxel against clinical expert opinion, again with Gamma providing the closest estimates. However again do not fit the placebo + nab-paclitaxel arm of IMpassion130. Similar to the atezolizumab extrapolation, gompertz consistently underestimates survival the most for both paclitaxel and docetaxel. Whilst gamma appears to more favourably predict comparator survival, the distinct over-prediction it creates for atezolizumab is not out-weighed here, further supporting the conservative use of the Weibull distribution. Nevertheless, all three distributions are considered as part of the sensitivity analyses.

**Table 40: Comparison of landmark survival and clinical expert opinion (paclitaxel)**

| Analysis | 12 months | 24 months | 30 months | 36 months | 48 months | 60 months | 72 months | 120 months |
|---|---|---|---|---|---|---|---|---|
| IMpassion130 – Placebo + Nab-paclitaxel – primary analysis | 64.0% | 36.6% | | | | | | |
| IMpassion130 – Placebo + Nab-paclitaxel – 2nd interim OS analysis | [redacted] | [redacted] | [redacted] | | | | | |
| Paclitaxel and docetaxel Clinical expert opinion | - | - | 17% | 10% | 5% | 3% | 1% | 0% |
| Paclitaxel landmark survival from model (Base case – Weibull) | 57.8% | 21.2% | 12.1% | 6.6% | 1.8% | 0.4% | 0.1% | 0.0% |
| Paclitaxel landmark survival from model (second ranked distribution - Gamma) | 56.3% | 21.0% | 12.6% | 7.5% | 2.6% | 0.9% | 0.3% | 0.0% |
| Paclitaxel landmark survival from model (third ranked distribution - Gompertz) | 58.6% | 22.7% | 12.5% | 6.2% | 1.0% | 0.1% | 0.0% | 0.0% |

**Table 41: Comparison of landmark survival and clinical expert opinion (docetaxel)**

| Analysis | 12 months | 24 months | 30 months | 36 months | 48 months | 60 months | 72 months | 120 months |
|---|---|---|---|---|---|---|---|---|
| IMpassion130 – Placebo + Nab-paclitaxel – primary analysis | 64.0% | 36.6% | | | | | | |
| IMpassion130 – Placebo + Nab-paclitaxel – 2nd interim OS analysis | [redacted] | [redacted] | [redacted] | | | | | |
| Paclitaxel and docetaxel Clinical expert opinion | - | - | 17% | 10% | 5% | 3% | 1% | 0% |



| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Docetaxel landmark survival from model (Base case - Weibull) | 57.3% | 26.1% | 16.8% | 10.5% | 3.8% | 1.3% | 0.4% | 0.0% |
| Docetaxel landmark survival from model (second ranked distribution - Gamma) | 56.4% | 26% | 17.4% | 11.6% | 5.1% | 2.3% | 1.0% | 0.0% |
| Docetaxel landmark survival from model (third ranked distribution - Gompertz) | 56.3% | 26.8% | 16.8% | 9.7% | 2.4% | 0.3% | 0.0% | 0.0% |

### B.3.3.3 PFS extrapolation

***Intervention***

Similar to the approach taken to incorporate OS in to the economic model, alternative distributions were mapped to the observed KM PFS data from the trial. Parameterisation was used to define the most appropriate functional form for fit to the observed data, with candidate curves checked for clinical plausibility

As demonstrated in Table 42, the Log-Normal appears the best statistical fit to the KM, with Gamma and Log-Logistic being similarly plausible. The Gompertz and Exponential, have a much poorer fit (>15 points difference).

**Table 42: Summary of goodness of fit for PFS**

| | Overall Survival – goodness of fit statistics Atezolizumab + nabPaclitaxel | |
|---|---|---|
| **Parametric distribution** | **AIC** | **BIC** |
| Exponential | 1030.5 (5) | 1033.7 (4) |
| Weibull | 1029.9 (4) | 1036.3 (5) |
| Log-normal | 1012.0 (1) | 1018.4 (1) |
| Gamma | 1013.5 (2) | 1023.1 (3) |
| Log-logistic | 1015.5 (3) | 1021.9 (2) |
| Gompertz | 1032.2 (6) | 1038.6 (6) |

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Subsequently, all parametric distributions were assessed for visual fit to the Kaplan Meier data. The visual fit of each distribution to the KM of the primary analysis is provided in Figure 24 and the KM of the more recent second interim OS analysis is provided in Figure 25.

**Figure 24: Visual fit of PFS distributions to primary analysis KM data (atezolizumab + nab-paclitaxel)**

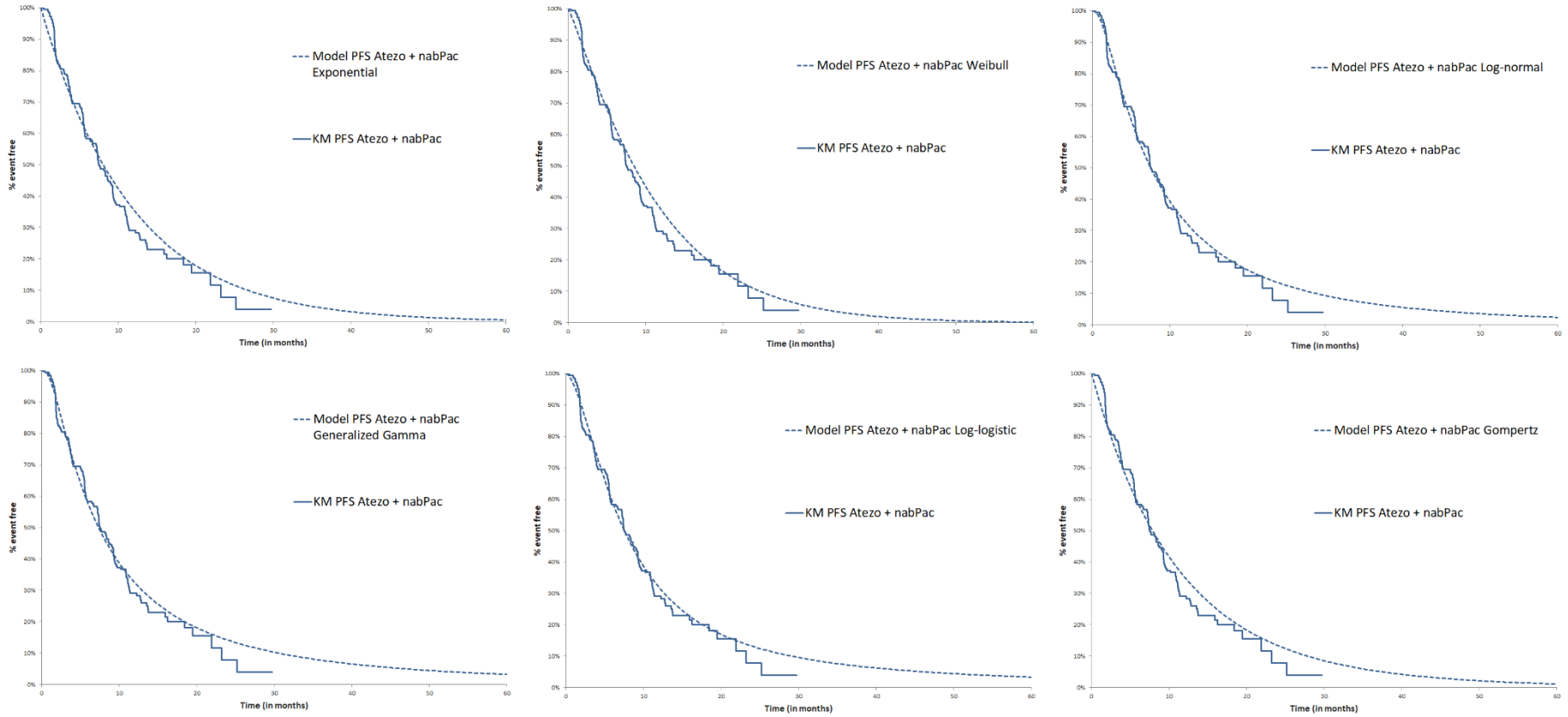




**Figure 25: Visual fit of PFS distributions to Visual fit of OS distributions to second interim OS KM data (atezolizumab + nab-paclitaxel)**



Weibull and gompertz appear to have a poor fit to the KM, with Gamma, Log-logistic and log-normal reflecting the AIC/BIC statistics providing the best visual fits.

Nevertheless, as per the OS assessment, clinical plausibility needed to be assessed. Figure 26 provides a visual assessment of the selected OS Weibull distribution compared with the potential PFS distribution selections. As demonstrated, the gamma, log-logistic, and more marginally, the log-normal distributions result in the PFS curve meeting, and subsequently being capped by the OS curve. This results in the clinically implausible scenario whereby PFS could, if uncapped, exceed OS. As such, these three distributions are ruled out on the basis of clinical plausibility.

The resulting curves (Exponential, Weibull and Gompertz) are then assessed against clinical expert opinion. As demonstrated in Table 43, whilst none of the landmark progression-free survival estimates accurately reflect clinical expert opinion, the gompertz provides the closest fit.

Nevertheless, as detailed above, gompertz provided the poorest fit to the data in statistical terms. To balance these considerations, the use of the unadjusted KM data followed by extrapolation was assessed. Given the maturity of the IMpassion130 PFS data, and precedence from recent NICE appraisals (137) it was deemed an appropriate approach. To reduce the uncertainty in the long term extrapolation, the starting point at which the parametric distribution is applied is based on consideration of the proportion of patients at risk using the IMpassion130 data. According to the Pocock criteria, the threshold used to implement the parameterised tail of KM data should not be greater than 20% (or less than 10%) of patients still at risk, and a mid-point of 15% was selected (138).

**Figure 26: Visual assessment of selected OS Weibull distribution compared with PFS distributions**

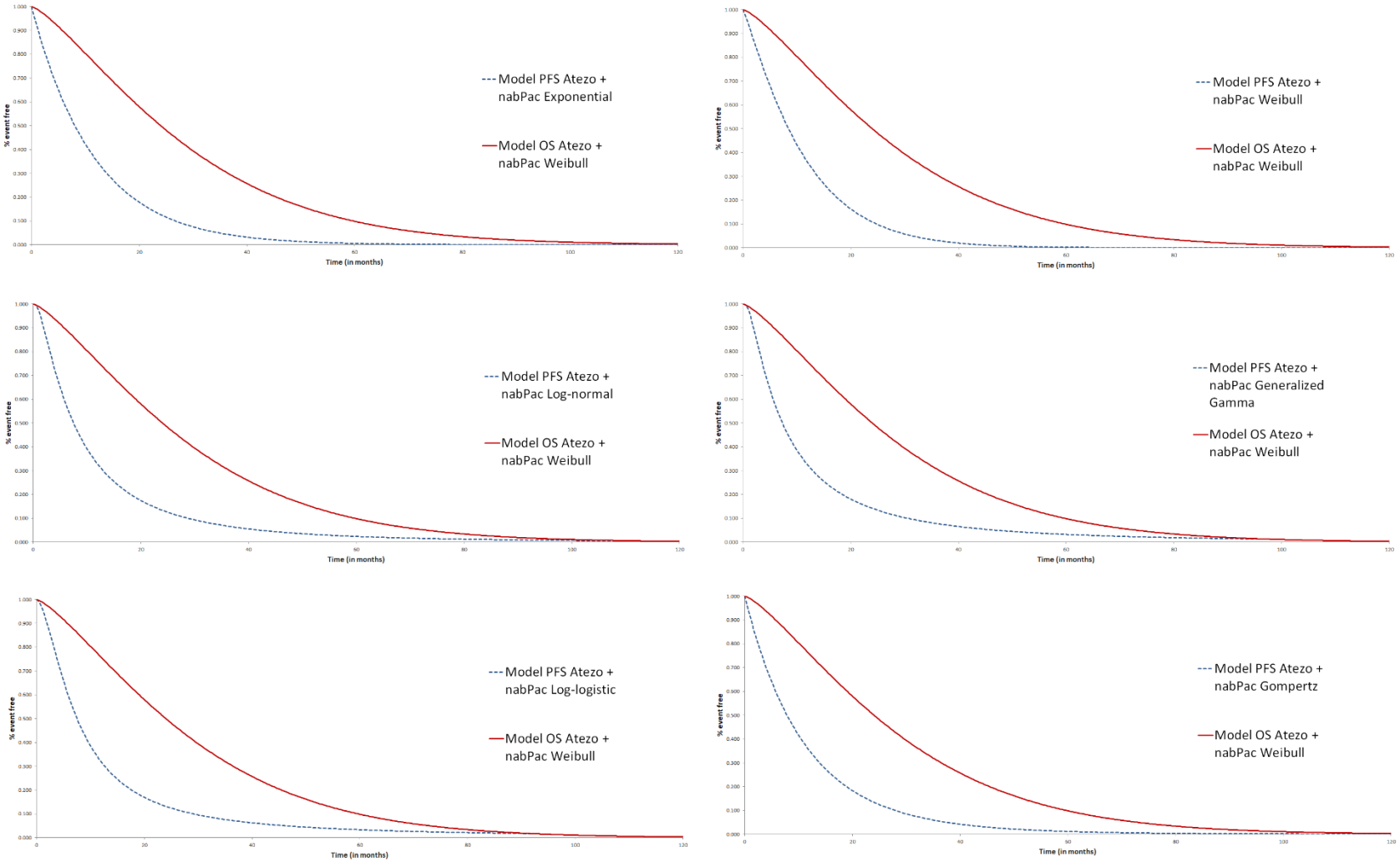




**Table 43: Proportion of patients treated with atezolizumab and nab-paclitaxel with PFS at set time points based on parametric distributions, compared with IMpassion130 trial data**

| PFS Analysis | | 12 months | 24 months | 30 months | 36 months | 42months | 48 months |
|---|---|---|---|---|---|---|---|
| IMpassion130 (based upon primary analysis) PFS | | 28% | 4% | - | - | - | - |
| IMpassion130 (based upon second interim OS analysis) PFS | | [redacted] | [redacted] | [redacted] | - | - | - |
| Clinical expert opinion | | - | - | 13% | 9% | 7% | 2% |
| Parametric distributions | Exponential | 35.3% | 12.6% | 7.5% | 4.5% | 2.7% | 1.6% |
| | Weibull | 35.6% | 10.8% | 5.8% | 3.1% | 1.6% | 0.8% |
| | Gompertz | 34.9% | 13.4% | 8.6% | 5.6% | 3.7% | 2.5% |

OS: overall survival; PFS: progression-free survival

Table 44 presents the resulting ranking of PFS distributions based on AIC/BIC, visual fit and clinical plausibility of the Atezolizumab + nabPaclitaxel arm. The resulting distribution selected was the KM data + Gompertz tail after 15% patients remained at risk.

**Table 44: Ranking of PFS distributions based on AIC/BIC, visual fit and clinical plausibility for atezolizumab + nab-paclitaxel arm**

| Parametric distribution | AIC (rank) | BIC (rank) | Visual fit to KM | Clinical plausibility | Ranking |
|---|---|---|---|---|---|
| Exponential | 1030.5 (5) | 1033.7 (4) | × | ~ | 2 |
| Weibull | 1029.9 (4) | 1036.3 (5) | × | ~ | 3 |
| Log-normal | 1012.0 (1) | 1018.4 (1) | ✓ | × | 4 |
| Gamma | 1013.5 (2) | 1023.1 (3) | ~ | × | 6 |
| Log-logistic | 1015.5 (3) | 1021.9 (2) | ✓ | × | 5 |
| Gompertz | 1032.2 (6) | 1038.6 (6) | × | ✓ | 1 |

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion, KM, Kaplan-Meier.

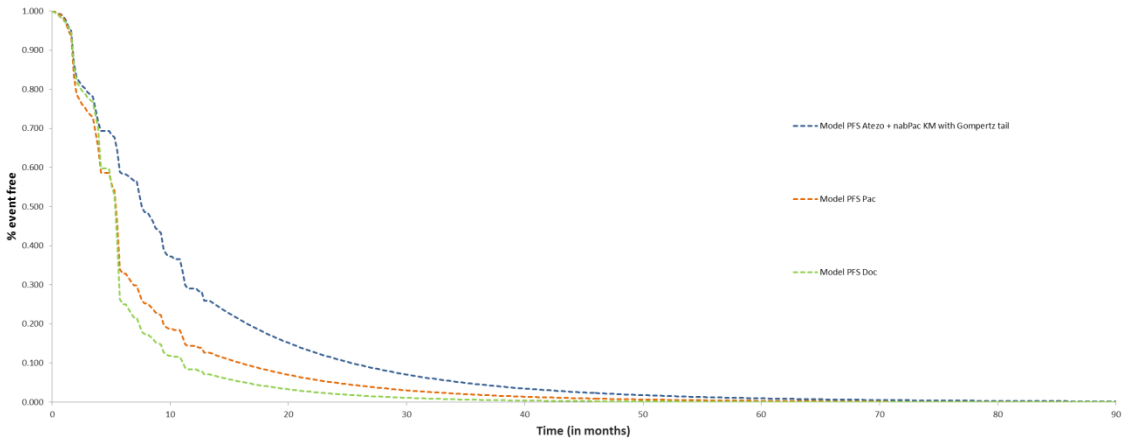
### *Comparators*

Similar to OS, the results of the indirect comparisons were incorporated into the economic model in order to generate the extrapolation for the comparators. Comparator curves were constructed using the atezolizumab + nab paclitaxel extrapolation, and applying the time-dependant log hazard ratios over the span of the extrapolation. As a result of the NMA, result, the PFS extrapolation distributions selected for the intervention arm (atezolizumab with nab-paclitaxel) are the same selections as used for each of the paclitaxel and docetaxel comparisons.

Figure 27 compares the selected PFS KM + Gompertz extrapolation to the NMA-based paclitaxel and docetaxel comparators.

**Figure 27: PFS curves of paclitaxel and docetaxel compared with atezolizumab + nab-paclitaxel**




In order to validate the resulting progression free survival estimates for both paclitaxel and docetaxel, clinical expert opinion was sought.

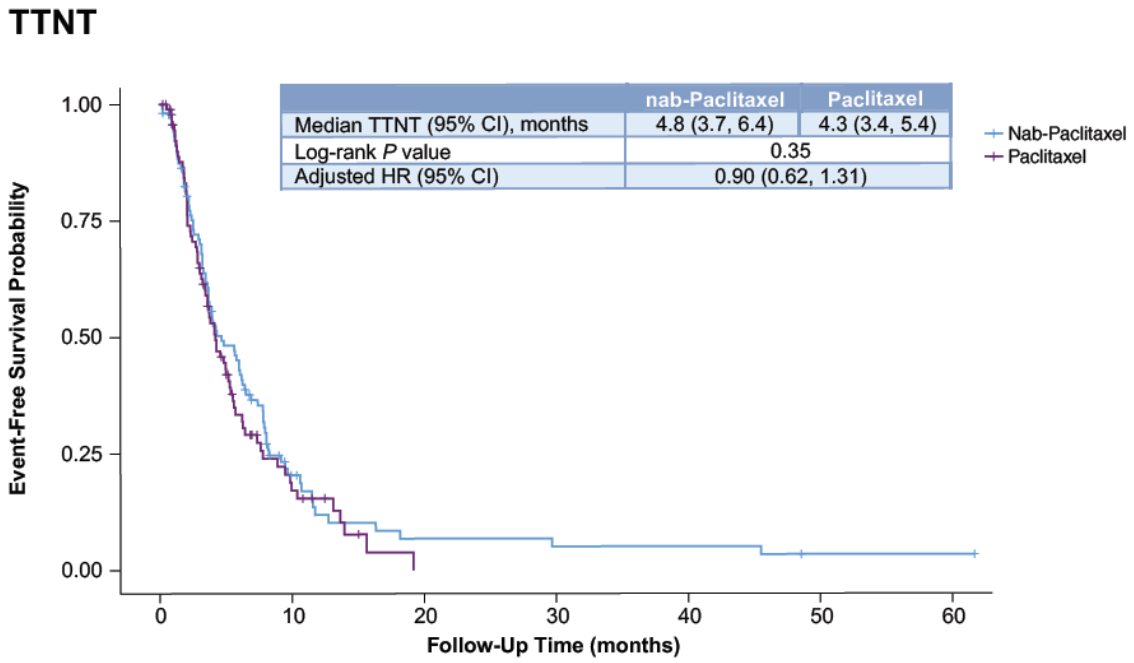
As described above, clinical experts highlighted the more limited usage of docetaxel in clinical practice. This is due to the associated safety profile, and availability to re-challenge on patients from an eBC setting. Nevertheless, beyond these limitations, efficacy between docetaxel and paclitaxel were considered largely comparable.

This is more consistent with the outcomes from the PFS ITC, than it was for OS. According to the ITC results, paclitaxel and docetaxel can be considered equivalent for approximately 7 months, with the curves then diverging and paclitaxel marginally outperforming docetaxel.

As further validation, following the RWD study presented at ESMO (136), demonstrating the comparability of nab-paclitaxel and paclitaxel in the 1L TNBC setting (see Figure 28 for TTNT (proxy to PFS in real world setting) comparison), the placebo + nab-paclitaxel arm of the IMpassion130 trial has been utilised to validate at a minimum, the anticipated progression free survival for paclitaxel. However, it should be highlighted, this evidence is from a US population, thus may not be comparable to UK clinical practice, thus should be interpreted with caution.

**Figure 28: PFS comparative effectiveness of nab-paclitaxel and paclitaxel in TNBC - RWD analysis by Luhn et al. (136)**




CI: confidence interval; HR: hazard ratio; TTNT: Time to next treatment

Table 45 and Table 46 compare the landmark survival estimates of the chosen extrapolation (KM+Gompertz) against the second and third ranked extrapolations (Exponential and Weibull), and clinical expert opinion, for both paclitaxel and docetaxel.

Similarly for OS, the predicted landmark survival for PFS is much lower on all extrapolations than what has been estimated by clinical experts, or as witnessed for the placebo + nab-paclitaxel arm of the IMpassion130 trial. Arguably, the gompertz selection provides the closest fit to the clinical expert opinion, however the exponential appears a better fit (at least for paclitaxel) to the IMpassion130 comparator arm. As with OS, all distributions are assessed as part of the sensitivity analysis. Ultimately, PFS is not a driver of cost-effectiveness for this appraisal.

**Table 45: Comparison of landmark PFS and clinical expert opinion (paclitaxel)**

| Analysis | 12 months | 24 months | 30 months | 36 months | 42 months | 48 months |
|---|---|---|---|---|---|---|
| IMpassion130 – Placebo + nab-paclitaxel – primary analysis | 16.4% | 5.6% | | | | |
| IMpassion130 – Placebo + nab-paclitaxel – 2nd interim OS analysis | [redacted] | [redacted] | [redacted] | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Paclitaxel and docetaxel – Clinical expert opinion | - | - | 4% | 4% | 2% | 0% |
| Paclitaxel landmark PFS from model (Base case – KM+Gompertz) | 14.3% | 4.9% | 3.0% | 1.9% | 1.2% | 0.8% |
| Paclitaxel landmark PFS from model (second ranked distribution - Exponential) | 17.1% | 5.4% | 3.1% | 1.7% | 1.0% | 0.6% |
| Paclitaxel landmark PFS from model (third ranked distribution - Weibull) | 17.3% | 4.6% | 2.3% | 1.1% | 0.6% | 0.3% |

KM: Kaplan-Meier; PFS: progression-free survival

**Table 46: Comparison of landmark PFS and clinical expert opinion (docetaxel)**

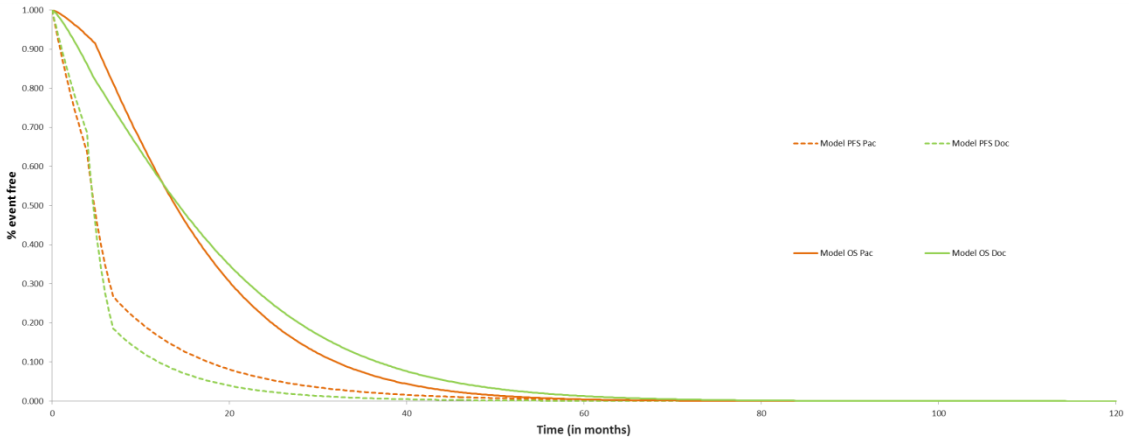
| Analysis | 12 months | 24 months | 30 months | 36 months | 42 months | 48 months |
|---|---|---|---|---|---|---|
| IMpassion130 – Placebo + Nab-paclitaxel – primary analysis | 16.4% | 5.6% | | | | |
| IMpassion130 – Placebo + Nab-paclitaxel – 2nd interim OS analysis | [redacted] | [redacted] | [redacted] | | | |
| Paclitaxel and docetaxel Clinical expert opinion | - | - | 4% | 4% | 2% | 0% |
| Docetaxel landmark PFS from model (Base case - KM+Gompertz) | 8.4% | 2.1% | 1.1% | 0.6% | 0.3% | 0.2% |
| Docetaxel landmark PFS from model (Exponential) | 10.3% | 2.3% | 1.1% | 0.5% | 0.3% | 0.1% |
| Docetaxel landmark PFS from model (third ranked distribution - Weibull) | 10.2% | 1.8% | 0.7% | 0.3% | 0.1% | 0% |

KM: Kaplan-Meier; PFS: progression-free survival

As a final assessment for clinical plausibility, the resulting PFS curves for paclitaxel and docetaxel, were assessed against the respective OS curves. As demonstrated in Figure 29, the resulting curves do not cross and thus can be deemed acceptable

**Figure 29: PFS vs OS of paclitaxel and docetaxel**




### B.3.3.4 TTOT extrapolation

***Intervention: atezolizumab with nab-paclitaxel (considered individually)***

To ensure all costs of treatment are captured accurately, atezolizumab and nab-paclitaxel are considered separately, as two TTOT curves.

The same approach to model selection has been utilised as described for OS and PFS.

Table 47 provides the AIC/BIC statistical fit for each of atezolizumab and nab-paclitaxel, within the intervention arm of the IMpassion130 trial.

**Table 47: Summary of goodness of fit for TTOT**

| | **TTOT – goodness of fit statistics atezolizumab (within atezolizumab with nab-paclitaxel)** | | **TTOT – goodness of fit statistics nab-paclitaxel (within atezolizumab with nab-paclitaxel)** | |
|---|---|---|---|---|
| Parametric distribution | AIC | BIC | AIC | BIC |
| Exponential | 1080.3 (3) | 1083.5 (3) | 1064.5 (4) | 1067.7 (4) |
| Weibull | 1081.6 (5) | 1088.0 (4) | 1060.9 (3) | 1067.3 (3) |
| Log-normal | 1096.5 (6) | 1102.9 (6) | 1066.1 (5) | 1072.5(5) |
| Gamma | 1080.8 (4) | 1090.5 (5) | 1055.3 (2) | 1065.0(2) |

| | | | | |
|---|---|---|---|---|
| Log-logistic | 1075.6 (1) | 1082.0 (1) | 1049.5 (1) | 1055.9(1) |
| Gompertz | 1077.0 (2) | 1083.4 (2) | 1066.5 (6) | 1072.9(6) |

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

As demonstrated, the best statistical fit for both atezolizumab and nab-paclitaxel TTOT is the Log-Logistic, with the Gompertz and Exponential similarly plausible for atezolizumab (within 5 points), and Gamma the second best fit for nab-paclitaxel (albeit, a meaningful difference in AIC/BIC).

Visual fit of the respective curves can be found in appendix N.

As with PFS and OS, clinical plausibility was assessed by comparing landmark estimates of time on treatment, with clinical trial data, and against the chosen PFS extrapolation (see Table 48 and Table 49).

**Table 48: TTOT (atezolizumab) based on parametric distributions, compared with IMpassion130 trial data and PFS**

| | | 12 months | 24 months | 30 months | 36 months | 42 months | 48 months |
|---|---|---|---|---|---|---|---|
| IMpassion130 (based upon primary analysis) TTOT | | 24% | 8% | - | - | - | - |
| IMpassion130 (based upon second interim OS analysis) TTOT | | [redacted] | [redacted] | [redacted] | - | - | - |
| Parametric distributions, atezolizumab PFS | KM + Gompertz | 29.1% | 11.1% | 7.0% | 4.6% | 3.0% | 2.0% |
| Parametric distributions, atezolizumab TTOT | Exponential | 29.1% | 9.0% | 5.0% | 2.8% | 1.5% | 0.8% |
| | Weibull | 29.1% | 9.8% | 5.7% | 3.3% | 2.0% | 1.1% |
| | Log-normal | 29.1% | 11.0% | 7.0% | 4.6% | 3.0% | 2.0% |
| | Gamma | 29.1% | 10.6% | 6.7% | 4.4% | 2.9% | 2.0% |
| | Log logistic | 28.0% | 11.0% | 7.0% | 4.6% | 3.0% | 2.0% |
| | Gompertz | 28.9% | 11.0% | 7.0% | 4.6% | 3.0% | 2.0% |

**Table 49: TTOT (nab-paclitaxel) based on parametric distributions, compared with IMpassion130 trial data and PFS**

| | | 12 months | 24 months | 30 months | 36 months | 42 months | 48 months |
|---|---|---|---|---|---|---|---|
| IMpassion130 (based upon primary analysis) TTOT | | 16% | 4% | | - | - | - |
| IMpassion130 (based upon second interim OS analysis) TTOT | | [redacted] | [redacted] | [redacted] | - | - | - |
| Parametric distributions, atezolizumab PFS | KM + Gompertz | 29.1% | 11.1% | 7.0% | 4.6% | 3.0% | 2.0% |
| Parametric distributions, atezolizumab TTOT | Exponential | 21.0% | 4.3% | 2.0% | 0.9% | 0.4% | 0.2% |
| | Weibull | 20.3% | 2.8% | 1.0% | 0.3% | 0.1% | 0.0% |
| | Log-normal | 20.3% | 6.5% | 4.2% | 2.9% | 2.0% | 1.5% |
| | Gamma | 19.2% | 3.7% | 1.8% | 0.9% | 0.4% | 0.2% |
| | Log logistic | 18.6% | 6.0% | 4.1% | 3.0% | 2.3% | 1.8% |
| | Gompertz | 21.0% | 4.3% | 2.0% | 0.9% | 0.4% | 0.2% |

It is anticipated the license for atezolizumab in combination with nab-paclitaxel will allow for treatment until disease progression or unacceptable toxicity. As such, it is anticipated TTOT should never exceed PFS. Further, based on the available data from the IMpassion130 trial to date, patients time on treatment is consistently considerably shorter than PFS, demonstrating earlier discontinuation due to adverse events. It can be assumed this will continue to be witnessed across the time horizon, validated through further data cuts of the trial.

This therefore enables the exclusion of a number of distributions for the atezolizumab arm, based on clinical plausibility: Log-normal, Gamma, Log logistic and Gompertz all meet, and are subsequently capped by PFS.

Similarly, the Log-normal and Log-logistic for the nab-paclitaxel arm come close to long term PFS (a difference of 0.5% and 0.2% respectively), despite time on treatment differing by approximately 10% throughout the duration of the IMpassion130 trial. As such, these have similarly been excluded based on clinical plausibility.

Given the remaining parametric distributions all had poorer statistical fit to the data (as per AIC/BIC), and given the maturity of the IMpassion130 trial, a similar approach to PFS extrapolation was taken, whereby the unadjusted KM data is used, followed by an extrapolated tail. Again, utilising the Pocock criteria, the starting point at which the parametric distribution is applied is based on 15% of the proportion of patients at risk using the IMpassion130 data.

Based on the best statistical fit of the remaining distributions, the KM + exponential tail is selected for atezolizumab TTOT, and the KM + gamma tail is selected for nab-paclitaxel TTOT. Alternative distributions are assessed as part of the scenario analyses.

### *Comparators*

TTOT are not available in the published literature for paclitaxel and docetaxel, therefore results of the piecewise exponential ITC, using PFS as a proxy were incorporated into the economic model. It is assumed treatment duration associated with both paclitaxel and docetaxel is equal to PFS, unless a treatment duration cap is in place.

### B.3.3.5 Clinical Expert opinion for validation of extrapolations

As detailed throughout section B.3.3, clinical expert opinion was sought to validate all extrapolations. This was conducted in two parts: initially, by seeking estimated landmark survival estimates, and then only subsequent to this, requesting visual validation of the resulting extrapolation selected. All information has been incorporated as data on file (20).

## *B.3.4 Measurement and valuation of health effects*

- **EQ-5D-5L was collected as part of the Impassion130 trial, and subsequently mapped to EQ-5D-3L using UK tariff and the van Hout algorithm**
- **Treatment was not a significant factor in the prediction of utility. Therefore, a consistent utility value for PFS and PD was used across treatment arms in the base case analyses – both were consistent with identified literature, and utilities used in prior NICE appraisals**
- **Adverse event disutilities were identified for all grade 3-5 AEs with an incidence of ≥2%, and applied in a scenario analysis**

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

Health-related quality of life was evaluated from the primary analysis of the IMpassion130 trial using the EuroQoL EQ-5D-5L and the European Organization 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. HRQoL utilities incorporated in the cost-effectiveness model were derived from this trial. Evaluation of HRQoL using EQ-5D-5L directly from patients is consistent with the NICE reference case. The approach taken was that of the current NICE position statement (139): EQ-5D-5L results were mapped to EQ-5D-3L, using the van Hout algorithm (140).

HRQoL was captured by assessing a multitude of covariates, to determine which can be considered accurate predictors of quality of life. As a result, utility values are applied in line with the model structure, with two distinct health states: PFS, and PD.

EQ-5D-5L questionnaires were completed at baseline (Cycle 1, Day 1), and then Day 1 of each 28-day subsequent cycle thereafter, at the treatment discontinuation visit, and during survival follow-up. Patients also completed EQ-5D-5L every 28 days for 1 year after treatment discontinuation. Quality of life estimates on progression-free and post-progression states have been collected.

### B.3.4.2 Mapping

Health related quality of life was evaluated in the IMpassion130 trial using the EuroQoL EQ-5D-5L. Following the NICE position paper on the EQ-5D-5L (139), the scores were mapped to the EQ-5D-3L using the Van Hout algorithm (140).

A mixed model linear regression was used, with subjects being a random factor. The fixed factor in the regression were the treatment arm and the pre- vs. post-progression indicator flag.

The regression analysis determined that age did not have an effect on the utility value generated and hence, age was omitted from the predictive equation. The assessment also sought to identify whether a loss of utility shortly before death could be observed in patients in the IMpassion130 trial. No such loss was of utility was observed.

Table 50 provides the resulting utility estimates.

**Table 50: Resulting EQ-5D-5L utility estimates, collected in IMpassion130**

| **Health state** | Health state | Utility value | 95% Confidence Intervals |
|---|---|---|---|
| **Progression free** | Both treatment arms | 0.726 | 0.706286, 0.746372 |
| | Atezolizumab with nab-paclitaxel | 0.741 | 0.710922, 0.770214 |
| | Placebo with nab-paclitaxel | 0.710 | 0.68372, 0.736419 |
| **Progressive disease** | Both treatment arms | 0.653 | 0.63075, 0.675221 |

Treatment was not a significant factor in the prediction of utility. Therefore, a consistent utility value for PFS and PD was used across treatment arms in the base case analyses. However, use of treatment-arm specific utility values are provided in a scenario analysis.

### B.3.4.3 Health-related quality-of-life studies

An SR was conducted to identify health related quality of life data in the first-line treatment of patients with advanced TNBC. However, to ensure all relevant data was captured, the population of the SR eligibility criteria was kept broader in the searches than the population of the decision problem - and so, included adult patients with advanced or metastatic TNBC or non-TNBC and, regardless of line of therapy.

Detailed descriptions of the search strategy, extraction methods and results are provided in Appendix H.

A total of 47 publications were identified which reported health state utility value (HSUVs) associated with patients with BC. Of these, 33 were presented as full publications and 14 were presented as conference abstracts. No studies were identified which specifically considered patients with TNBC.

Eighteen studies reported intervention-specific utilities. The treatment comparisons considered across the studies included:

- S-1 vs taxanes (n=4);
- Palliative care (no treatment comparison) (n=3);
- Palbociclib + letrozole vs placebo + letrozole (n=2);
- Palbociclib + fulvestrant vs placebo + fulvestrant (n=1)(141);
- Lapatinib + capecitabine vs capecitabine alone (n=1);
- Paclitaxel + carboplatin vs gemcitabine + docetaxel vs weekly paclitaxel (n=1);
- Nab-paclitaxel vs docetaxel vs paclitaxel (n=1);
- Tamoxifen vs anastrozole (n=1);
- Hormonal therapy vs chemotherapy (n=1);
- Cyclophosphamide/methotrexate/5-fluorouracil (5-FU) vs tamoxifen (n=1);
- Chemotherapy (docetaxel/paclitaxel) (no treatment comparison) (n=1);
- Surgery (mastectomy, breast-conserving surgery, radiation, and chemotherapy) (n=1).

Of the 47 included studies, seven met the requirements of the NICE reference case; that is, utilities were derived directly from patients using the preferred EQ-5D-3L, and health states were valued using UK societal preferences elicited using the direct TTO method. For 12 studies, it was unclear if the requirements of the NICE reference case were met. For the majority of these studies, this was due to a lack of reporting regarding the method of valuation (i.e. it was unclear if a UK tariff was used to value health states) (n=11). Further details of all studies included are provided in Appendix H.

Table 51 provides the results of the seven studies that met the NICE reference case.

Health state utility values reported in relevant recent NICE Technology Appraisals were additionally sought. The utility values reported in these appraisals are provided in Table 52.

**Table 51: Reported utility data of studies identified in the SR which meet the NICE reference case (N=7)**

| Study | Population details | Method of deriving HSUVs | Countries | Mean HSUVs | | |
|---|---|---|---|---|---|---|
| | | | | Pre-progression | Post-progression | Other |
| **Hagiwara, 2018 (142)** | Patients with histologically confirmed HER2- and endocrine-therapy resistant MBC | EQ-5D-3L | Japan | Not reported | Not reported | Reports disutility values associated with adverse events (but only for Grade 1-2 events, not Grade 3 to 5) |
| **Lidgren, 2007 (143)** | Outpatients with BC | 1) EQ-5D-3L<br>2) TTO | Sweden | Not reported | Not reported | Reports HSUV for early and metastatic BC but not by pre-progression and post-progression states |
| **Paracha, 2017 (144)** | Patients with HER2+ MBC who have failed on ≥2 regimens of HER2 directed therapy | EQ-5D-3L | UK | Not reported | -0.04 (disutility) | Reports disutility in 14 weeks prior to death only, AE hospitalisations (-0.06 (disutility)) |
| **Rautalin, 2018 (145)** | Patients with histologically confirmed BC | 1) EQ-5D-3L<br>2) 15D | Finland | Not reported | Not reported | Reports HSUV for early and metastatic BC but not by pre-progression and post-progression states |
| **Rugo, 2018 (80)** | Patients with treatment-naive postmenopausal women with ER+/HER2- MBC receiving first-line endocrine-based therapy | EQ-5D-3L | Multi-national (17 countries) | Not reported | Not reported | Reports HSUV for baseline and end of treatment but not by pre-progression and post-progression states |
| **Zhou, 2009 (146)** | Female patients with HER2+ ABC or MBC who had received prior therapy that included an anthracycline, a taxane, and | EQ-5D-3L | UK | Not reported | Not reported | Reports HSUV for baseline of treatment arms but not by pre-progression and post-progression states |



| | | | | | | |
|---|---|---|---|---|---|---|
| | trastuzumab | | | | | |
| **Crott and Briggs, 2010 (147)** | histologically or cytologically confirmed locally advanced or MBC, ≤3 prior chemotherapy regimens (including ≤2 for advanced and/or metastatic disease), including an anthracycline and a taxane. | HRQOL data from Study 301 using the EORTC-QLQ-C30 were mapped to EQ-5D derived utility scores using a regression algorithm | Multi-national | Stable disease, eribulin: 0.705<br>Stable disease, capecitabine: 0.697 | Progressed disease, eribulin: 0.679<br>Progressed disease, capecitabine: 0.679 | Not reported |

PFS, progression-free survival; PTD, Perjeta + Herceptin + docetaxel; TD, Herceptin + docetaxel; TP, Herceptin + paclitaxel.

**Table 52: Summary of utilities from identified relevant NICE appraisals**

| NICE TA | Study | Population details | Mean HSUVs | | |
|---|---|---|---|---|---|
| | | | Pre-progression | Post-progression | Other |
| TA509 (148) | Lloyd 2006 (149) | UK participants valuation of metastatic breast cancer states (standard gamble) | PTD (under docetaxel): 0.792<br>TD under docetaxel: 0.793<br>PTD (after docetaxel): 0.810<br>TD (after docetaxel): 0.802<br><br>(Above are ERG corrected values) | 0.535 | Peripheral neuropathy disutility (assumed as equivalent in lost QoL as "hand-foot syndrome": -0.12 |
| TA503 (150) | FALCON study 2016 | Oestrogen receptor-positive or progesterone receptor-positive, or both, locally advanced or metastatic breast | 0.7511 | 0.6913 | ALT increased: -0.050<br>Hypertension: -0.153<br>Pleural effusion: -0.371<br>Pain, bone: -0.069 Pain, other: -0.069<br>Dyspnoea: -0.05 |

| | | | | | |
|---|---|---|---|---|---|
| | | cancer | | | |
| TA495 (151) | PALOMA-2 trial for the pre-progression states, and from Lloyd et al (2006) for post-progression (149) | Oestrogen reception positive and HER2 negative recurrent or metastatic disease adenocarcinoma of breast | Not reported | 0.4492 | Febrile neutropenia (grade 3/4): -0.15<br>Diarrhoea and vomiting (grade 3/4): -0.103<br>Hand-foot syndrome (grade 3/4): -0.116<br>Stomatitis (grade 3/4): -0.151<br>Fatigue (grade 3/4): -0.115<br>Hair loss: -0.114<br><br>(Taken from Lloyd 2006) (149) |
| TA496 (152) | MONALEESA-2 to inform PFS1; the BOLERO-2 to inform PFS2; and the Lloyd et al. 2006 (149)value of 0.505 for the progression state. | Untreated Hormone receptor + HER2 negative locally advanced or metastatic breast cancer | PFS1 on treatment (Not reported)<br>PFS1 off treatment (Not reported)<br>PFS2 on treatment: 0.774 | 0.5052 | Decrement for chemotherapy: -0.113 |

### *Consistency of utilities from past NICE TAs and the literature with values derived from IMpassion130*

The progression free and progressed disease utilities values derived from IMpassion130 trial are similar to those reported in other NICE appraisals for mBC, and the one reference identified in the SR, reporting relevant health state utilities (147).

However, given the populations reported in the SR and previous NICE appraisals are not consistent with the population under consideration within this appraisal (1L mTNBC), it was deemed that the most appropriate source of HSUVs would be those derived from the IMpassion130 trial. EQ-5D-5L collected from the trial, then subsequently mapped to EQ-5D-3L allows most accurate representation of the patient population of the final scope.

The consistency of the IMpassion130 trial derived utilities with other published sources confirms these values can be deemed reflective and suitable for use within the appraisal.

### B.3.4.4 Adverse event disutilities

All grade ≥3 adverse events, with an incidence of ≥2% were sourced from the IMpassion130 clinical study for the intervention arm, and from key trials from the clinical SR for the comparator arms. This included E2100 (10, 11), LOTUS (86, 87), MERIDIAN for paclitaxel (12, 14, 15), and AVADO (16, 17) and JapicCTI-090921 for docetaxel (85).

Across trial sources, a total of 15 adverse events were captured, meeting the above criteria.

There are two approaches that could be taken regarding the inclusion of AE impacts on HRQoL:

1. The assumption that any disutility has already been incorporated in to the base case health state utilities through trial derived EQ-5D utilities, and incorporating an additional disutility could be considered double counting;

2. The assumption that averaged trial-derived utilities underestimate disutilities associated with adverse events, and therefore an additional disutility must be applied.

The base case analysis takes the former assumption (disutility has already been incorporated). However, for completeness, a scenario analysis is included, that contains quality of life decrements of adverse events.

For the scenario analysis, disutilities were sourced from published literature and previous NICE appraisals. See Table 53 for the complete list of AEs, and respective disutilities.

**Table 53: IMpassion130 adverse events included in the economic model (events occurring at Grade 3-5, affecting 2% or more of patients)**

| | Atezolizumab + nab-paclitaxel: n (%) | Paclitaxel, n (%) | Docetaxel n (%) | Disutility value (scenario analysis only) | Source of disutility value |
|---|---|---|---|---|---|
| **Anaemia** | - | 2 (3) | - | - | Assumed negligible |
| **Bone pain** | - | 1 (2) | - | -0.069 | TA503 (150) |
| **Venous thromboembolic event** | - | - | 7 (3) | - | Assumed negligible |
| **Diarrhoea** | - | - | 2 (2) | -0.103 | Lloyd 2006 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | (149) |
| **Fatigue** | 16 (3.4) * | 23(6) | - | -0.115 | TA495/Lloyd 2006 (149, 151) |
| **Febrile neutropenia** | 6 (13) | 30(13) | 26 (11) | -0.15 | Lloyd 2006 (149) |
| **Allergic reaction** | - | 9(3) | - | - | Assumed negligible |
| **Hypertension** | - | 12 (4) | - | -0.153 | TA503 (150) |
| **Infection** | - | 10(3) | - | - | Assumed negligible |
| **Leukopenia** | - | - | 90 (28) | - | Assumed negligible |
| **Nausea** | - | 1 (2) | - | -0.103 | Assumed the same as vomiting<br>Lloyd et al (149) |
| **Peripheral neuropathy** | 25 (5.5) * | 72(18) | - | -0.15 | Assumed same as Febrile Neutropenia |
| **Neutropenia** | 37 (8.2) * | 4 (6) | 138 (42) | -0.124 | TA423 (153) |
| **Edema** | - | - | 4 (2) | - | Assumed negligible |
| **Vomiting** | - | 7(2) | - | -0.103 | Lloyd 2006 (149) |

In the scenario analysis, the loss of QALYs per adverse event was calculated as the product of the utility decrement and the duration of the AE. Whilst Lloyd et al. 2006 does not meet the NICE reference case, it is the single most referenced literature for utilities in previous NICE appraisals in breast cancer (TA503 (150), TA509 (148), TA495 (151)). Lloyd et al does not specify assumed duration of events, as such, for simplicity purposes these have all been estimated as lasting 7 days (149). Resulting decrements are then applied to the first cycle of the model.

### B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

As HRQoL was collected using the EQ-5D-5L in the IMpassion130 (and then mapped to EQ-5D-3L), consistent with the NICE reference case, these values are utilised in the base case. This methodology is consistent with previous appraisals accepted by NICE for this disease

area, and other metastatic oncology indications. Utilities are applied to the model consistently over time, based on the health state a patient is in.

A summary of all utility values implemented in the cost-effectiveness analysis can be found in Table 54.

**Table 54: Summary of utility values for cost-effectiveness analysis**

| State | Utility value: mean (SE) | 95% CI | Reference in submission (section and page number) | Justification |
|---|---|---|---|---|
| **HS utilities – base case** | | | | |
| **Progression-free state** | 0.726 | 0.706 - 0.746 | B.3.4.1, page 127 | Utilities derived from IMpassion130 (PD-L1 positive patients only), relevant to the decision problem, are most desirable. |
| **Progressive disease** | 0.653 | 0.631 - 0.675 | B.3.4.1, page 127 | Utilities derived from IMpassion130 (PD-L1 positive patients only),, relevant to the decision problem, are most desirable. |
| **HS utilities – scenario analyses case** | | | | |
| **Progression-free state (Atezolizumab with nabPaclitaxel)** | 0.741 | 0.710922 - 0.770214 | B.3.4.1, page 127 | Utilities derived from IMpassion130 (PD-L1 positive patients only),, but use of treatment-arm specific utility for PF |
| **Progression-free state (placebo with nabPaclitaxel)** | 0.710 | 0.68372 - 0.736419 | B.3.4.1, page 127 | Utilities derived from IMpassion130 (PD-L1 positive patients only),, but use of treatment-arm specific utility for PF |
| **Progressive disease** | 0.653 | 0.63075- 0.675221 | B.3.4.1, page 127 | Utilities derived from IMpassion130 (PD-L1 positive patients only). Lower count of observations for PD, hence not split by treatment arm. |
| **AE disutilities (Scenario analysis only)** | | | | |

Company evidence document B submission for atezolizumab in combination with paclitaxel for untreated, locally advanced or metastatic, triple negative, PD-L1–positive breast cancer [ID1522].

| | | | | |
|---|---|---|---|---|
| **Bone pain** | -0.069 | - | B.3.4.4, page 133 | Grade 3-4 AEs with incidence of ≥2%, sourced from literature and past NICE appraisals |
| **Diarrhoea** | -0.103 | - | | |
| **Nausea** | -0.103 | - | | |
| **Hypertension** | -0.153 | - | | |
| **Peripheral neuropathy** | -0.15 | - | | |
| **Febrile neutropenia** | -0.15 | - | | |
| **Neutropenia** | -0.124 | - | | |
| **Vomiting** | -0.103 | - | | |
| **Fatigue** | -0.115 | - | | |
| **Peripheral neuropathy** | **-0.12** | **-** | | |

AE, Adverse event; CI, Confidence interval; HS, Health state; NICE, National institute for Health and Care Excellence; N/R, Not reported; PPS, post-progression survival, TKI, tyrosine-kinase inhibitor.

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

- **Acquisition, administration, supportive care and adverse event costs were sought from NHS reference costs, PSSRU, eMit and BNF**
- **Atezolizumab is subject to a PAS, which has been incorporated in the appraisal**
- **Nab-paclitaxel is also subject to a PAS, and has recently lost patent exclusivity, with a generic launching imminently. As such, the associated discount on nab-paclitaxel is critical to this appraisal, but cannot be incorporated in to base case results.**
- **A one-off cost associated with PD-L1 testing has been applied to the atezolizumab + nab-paclitaxel combination only, as PD-L1 testing is not currently routine in breast cancer**

An SR was conducted to identify relevant healthcare resource use/costs data from the UK NHS and/or PSS perspective. Given the lack of development in TNBC in recent years and lack of such data expected specifically in the advanced TNBC setting, resource use and costs associated with the management and treatment of adults with previously untreated metastatic breast cancer was sought. This population of the SR was broader than metastatic TNBC (in that it included metastatic non-TNBC). Detailed descriptions of the search strategy, search terms and abstraction methods are provided in Appendix I.

### B.3.5.1 Summary of identified studies and results

Four studies met the inclusion criteria. A summary of the 4 included studies identified in the SR is presented in Table 55, with full details provided in Appendix I.



**Table 55: Summary and results of identified studies (N=4)**

| Study | Patient population | Available cost/resource use data | Country and cost year | Evaluation/summary of costs | Suitability for cost-effectiveness analysis |
|---|---|---|---|---|---|
| Laudicella et al. 2016 (154) | Patients aged 18 years or older with a recorded diagnosis of breast cancer (C50) in the cancer registries of England between 1st January 2001 and 31st December 2010.<br><br>Individuals were excluded if they were less than 18 years of age, had a previous history of breast cancer, were male with breast cancer, or had died with improper death certificate registrations.<br><br>The final sample included 359,771 breast cancer patients, the total number of stage 3–4 patients was not reported (88.2% of 18–64 year olds and 83.5% of ≥65 year olds had stage 1–2 breast cancer). | Average incident costs per patient with stage 3–4 breast cancer (reported yearly for 3 years pre-diagnosis and 9 years post-diagnosis, and as a total over 9 years)<br><br>Five-year prevalence costs in patients with terminal breast cancer<br><br>Healthcare services accessed by patients with stage 3–4 breast cancer | England<br><br>Cost year: 2010 | Average incident costs for patients with stage 3–4 breast cancer are highest in the first year following diagnosis (£13,315 in 18–64 year olds, £8,804 in ≥65 year olds)<br><br>Five-year prevalence costs in terminal breast cancer were £38,173,000 in 18–64 year olds and £55,531,000 in ≥65 year olds<br><br>69.98% of 18–64 year olds and 42.37% of ≥65 year olds required surgery in the first 12 months following diagnosis | The analysis presented cost and resource use data for patients with stage 3–4 breast cancer, making this data suitable for a cost-effectiveness analysis of first-line treatment in locally advanced or metastatic breast cancer.<br><br>The study does not specify which sub-types of breast cancer were included, and data were collected between 1 January 2001 and 31 December 2010, meaning that these data might not be applicable to current clinical practice in TNBC specifically.<br><br>The costs are expressed from the perspective of the NHS, aligning with the NICE reference case. Costs are relevant to all stage 3 and 4 breast cancer patients, which is slightly broader than the population defined in the |



| Study | Patient population | Available cost/resource use data | Country and cost year | Evaluation/summary of costs | Suitability for cost-effectiveness analysis |
|---|---|---|---|---|---|
| | | | | | NICE scope (people with locally advanced or metastatic TNBC previously untreated in the advanced setting). |
| Luftner et al. 2014 (155) | Patients aged 18 years or older with bone metastases secondary to breast cancer and a life expectancy of at least 6 months.<br><br>Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2, and to have experienced at least one skeletal-related event (SRE) in the 97 days before signing informed consent or up to 7 days afterward.<br><br>Patients were excluded if they were enrolled in an investigational drug trial for treatment of bone metastases or prevention of SREs.<br><br>223 patients with a primary diagnosis of breast cancer who met the eligibility criteria were enrolled | Median duration of inpatient stay per SRE that required an inpatient stay<br>Proportion of vertebral fracture SREs requiring an inpatient stay<br>Proportion of outpatient visits for surgery to bone<br>Mean length of stay (in oncology wards/units) for radiation to bone<br>Mean number of outpatient visits required per SRE<br>Mean rates of external-beam radiation and intensity-modulated radiation therapy (IMRT) per SRE | United Kingdom<br>Cost year: NR | 28 of 45 UK patients were hospitalised due to SREs, with a mean length of stay of 12.9 days (median 8.0)<br>Mean number of outpatient visits required per SRE was 2.5 (SD 2.7) | The study presented resource use relating to SREs secondary to advanced breast cancer and most specific resource use data was presented as a pooled figure across the four included European sites. Therefore, this information is unlikely to be relevant in a cost-effectiveness analysis of TNBC in England.<br><br>It is unclear whether the resource use information is appropriate from an NHS/personal social services perspective. Additionally, the resources are relevant to patients with SREs |

| Study | Patient population | Available cost/resource use data | Country and cost year | Evaluation/summary of costs | Suitability for cost-effectiveness analysis |
|---|---|---|---|---|---|
| | across four European sites (Germany, Italy, Spain and the UK), including 45 patients from the UK. | | | | secondary to advanced breast cancer, which does not exactly match the NICE scope. |
| Majethia et al. 2014 (156) | Patients with any sub-type of third-line metastatic breast cancer (mBC) taking part in the phase III randomised controlled trial (RCT), EMBRACE. | Data from a phase III RCT of eribulin mesylate against Treatment of Physician's Choice (TPC) was used to source data for treatment-emergent adverse events (TEAEs) for third-line chemotherapy patients.<br>Treatment costs and hospitalisation costs for adverse events (AEs) observed in more than 2% patients that required treatment or hospitalisation<br>Monthly costs associated with treatment of TEAEs<br>Annual costs associated with treatment of TEAEs | United Kingdom<br>NHS reference costs 2012–2013 | Total annual costs associated with treatment of TEAEs were £2,605 in the eribulin arm and £2,738 in the TPC arm<br>The AEs associated with the highest treatment costs were anaemia (£1,101), febrile neutropenia (£549) and leukopenia (£273)<br>The AEs associated with the highest hospitalisation costs were neutropenia (£1,064), febrile neutropenia (£1,064) and asthenia/fatigue (£926) | The study presented the costs of TEAEs in patients receiving third-line treatment for mBC. The population included any sub-type of mBC, which may limit this study's applicability to a cost-effectiveness analysis in TNBC specifically. Additionally, as this analysis was based on a clinical trial, the results may not be applicable to wider UK clinical practice.<br><br>Cost information is derived from the BNF (which uses public list prices) and NHS reference costs, aligning with the NICE reference |

| Study | Patient population | Available cost/resource use data | Country and cost year | Evaluation/summary of costs | Suitability for cost-effectiveness analysis |
|---|---|---|---|---|---|
| | | | | | case. Reported costs are relevant to third-line mBC patients. This aligns with the NICE reference case, which stipulates that the time horizon for estimating cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared, and, therefore, includes subsequent lines of therapy. |
| Walsh et al. 2017 (157) | This study included data from 36,698 breast cancer patients, taken from a population-based, patient-level database, which combines data from the National Cancer Data Repository (NCDR), Hospital Episode Statistics (HES), and the National Schedules of Reference Costs (NSRC).<br><br>Patients were female and aged 18 or over with a recorded first diagnosis of breast cancer (C50) between 2006 and 2010, who died between 2006 and 2011. | End-of-life costs<br>Top Healthcare Resources Groups (HRGs) in the last 6 months of life for breast cancer patients<br>Top HRGs in the last month of life for breast cancer patients<br>Data was separated into average resource use from different quintiles (Q) of income distribution in England in order to assess differences in costs of care by socioeconomic status (SES). | England<br>Cost year 2010 (patients died between 2006 and 2011). | Mean total end-of-life costs for breast cancer patients ranged from £8,131 (Q5, highest SES quintile) to £9,307 (Q1, lowest SES quintile)<br>Top elective HRGs in the last month of life for breast cancer patients were Same Day Chemotherapy Admission, Malignant Breast Disorders W Intermediate CC, Malignant Breast Disorders W/O CC, Single Plasma Exchange, Leucophoresis or Red Cell Exchange W LOS 2 | Data were presented on cost and resource use for breast cancer patients at the end of life, this may not be directly applicable to the treatment of metastatic TNBC patients, as this assumes that all end-of-life patients have metastatic breast cancer.<br><br>The results were presented for breast cancer patients across five different SES quintiles and so may not be applicable to a cost- |

| Study | Patient population | Available cost/resource use data | Country and cost year | Evaluation/summary of costs | Suitability for cost-effectiveness analysis |
|---|---|---|---|---|---|
| | | | | days or less, and Chronic Kidney Disease W LOS 1 day or less associated W Renal Dialysis<br>Top emergency HRGs in the last month of life for breast cancer patients were Malignant Breast Disorders W Major CC, Malignant Breast Disorders W Intermediate CC, Lobar Atypical or Viral Pneumonia W Major CC, Pleural Effusion W Major CC, and Brain Tumours or Cerebral Cysts W CC | effectiveness analysis of TNBC patients in England more generally, unless the overall average across SES groups is calculated.<br>The costs are expressed from the perspective of the NHS, aligning with the NICE reference case. Reported costs are relevant end-of-life breast cancer patients. This aligns with the NICE reference case, which stipulates that the time horizon for estimating cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared, and, therefore, includes end-of-life treatment. |

aBC: advanced breast cancer; AE: adverse event; BC: breast cancer; BNF: British National Formulary; CC: complication or comorbidity; eBC: early breast cancer; ECOG: Eastern Cooperative Oncology Group; EG/PgR+: oestrogen/progesterone receptor positive; GBP: Great British Pound; GP: general practitioner; HES: Hospital Episode Statistics; HRG: Healthcare Resources Group; HRU: health resource utilisation; IMD: Index of Multiple Deprivation; IMRT: intensity-modulated radiation therapy; LOS: length of stay; NCDR: National Cancer Data Repository; mBC: metastatic breast cancer; NR: not reported; NSRC: National Schedules of Reference Costs; PPE: Palmar-Plantar Erythro-Dysesthesia; Q: quintile; RCT: randomised controlled trial; SD: standard deviation; SES: socioeconomic status; SR: systematic review; SRE: skeletal-related event; TEAE: treatment-emergent adverse event; TNBC: triple-negative breast cancer; TPC: treatment of physicians choice; W: with; W/O: without.



### B.3.5.2 Intervention and comparators' costs and resource use

#### *Drug acquisition costs – Intervention and comparators*

Drug acquisition costs used in the model for the initial treatments are presented in Table 56. Please note, all costs listed are at list price, however atezolizumab and nab-paclitaxel currently both have confidential patient access schemes. The confidential patient access scheme (PAS) discount for nab-paclitaxel is unknown to Roche Products Ltd., hence the list price is used in base case ICER estimates. A scenario analysis is provided that explores the impact of various levels of discount.

On 21st March 2019, The CJEU (Court of Justice of the European Union) issued its judgement that Celgene is not entitled to a Supplementary Protection Certificate (SPC) for Abraxane (158). As such, the EU patient for Abraxane expired 15th January, 2019. Further to this, in February 2019, a CHMP positive opinion was granted for a generic nab-paclitaxel ("Pazenir") (159). As such, it is important to highlight that a generic version of nab-paclitaxel (Abraxane) is anticipated to gain a Marketing Authorisation in May 2019, and thus is expected to be available in the NHS. As generics are almost always less costly than the "branded" versions of a drug, this would be expected to have a significant impact on this appraisal, by reducing the total cost of the combination of atezolizumab with nab-paclitaxel.

The dosing and schedule of the new technology and its comparators are as follows:

- **Atezolizumab in combination with nab-paclitaxel (intervention):** As per the SmPC, the recommended dose is 840 mg of atezolizumab by intravenous infusion on days 1 and 15, followed by 100 mg/m$^2$ nab-paclitaxel on days 1, 8 and 15 of each 28-day cycle.

- **Paclitaxel:** Whilst paclitaxel does not have a license for use in 1L TNBC as a monotherapy, clinical experts deem this as the most frequently used treatment. The most frequently used dosing regimen is 90 mg/m$^2$ every week. It is assumed that patients would receive 18 cycles (18 weeks) of paclitaxel monotherapy in the NHS. As detailed in earlier sections (B.1.3, B.2.9, B.3.2, B.3.3) paclitaxel is considered the most appropriate, and therefore, primary comparator in this appraisal.

- **Docetaxel:** As per the SmPC, the recommended dose is 100 mg/m$^2$ administered by intravenous infusion every 3 weeks. However, based on clinical expert opinion, 75

mg/m$^2$ is utilised in clinical practice, due to the toxicity profile. It is assumed that patients would receive 6 cycles (24 weeks) in the NHS.

In the costing of all regimens, the cheapest combination of vial sizes is taken for the base case, based on the appropriate body surface area (BSA) from the IMpassion130 trial. The base case assumes no vial wastage (i.e. full vial sharing).

In the circumstance where a full vial has not been used in an infusion, it could be assumed that the remaining product within the vial cannot be used, and is in effect, wasted. A scenario analysis is provided, where the full wastage of vials occurs.

**Table 56: Drug acquisition costs used in the cost-effectiveness model**

| Drug | Vial concentration | Cost per vial | Source |
|---|---|---|---|
| **Atezolizumab** | 840 mg | [redacted] | Proposed list price and net price |
| **Nab-paclitaxel** | 100 mg | £246.00 (list price) | BNF (list price, a confidential PAS exists) (160) |
| **Paclitaxel** | 30 mg / 8 ml | £3.41 | eMIT June 2018 (161) |
| | 100 mg / 16.7 ml | £7.35 | |
| | 150 mg / 25 ml | £10.48 | |
| | 300 mg / 50 ml | £22.82 | |
| **Docetaxel** | 20 mg / 1 ml | £5.75 | eMIT June 2018 (161) |
| | 80 mg / 4 ml | £11.95 | |
| | 160 mg / 8 ml | £30.82 | |

### *Drug acquisition costs – subsequent treatments*

The economic model includes costs and resource use of subsequent treatment for patients who have progressed on the new technology or comparator arms. From the primary analysis, at median follow up of 12.9 months, 23% of patients remained on treatment with atezolizumab, and 15% of patients remained on treatment with nab-paclitaxel in the intervention arm.

As a high proportion of patients in the clinical trial went on to receive treatments that are unlicensed, not recommended by NICE, or not generally used in clinical practice in the UK, it was not deemed appropriate to model subsequent therapies directly from the clinical trial.

Explicit modelling of second, third, and fourth treatments received (if any) has not been conducted, due to the complexity and additional uncertainty generated from such an

approach. Rather, a simpler approach to account for subsequent therapy costs was applied, in line with the approach taken in the NICE appraisal of palbociclib (TA495) (151). Within this appraisal, a one of cost of £1,200 per month was applied (£300 per weekly model cycle), which was deemed acceptable by the ERG and NICE committee. As such, the base case analysis uses this approach, and is applied for the remaining duration patients are alive.

To explore the sensitivity of this assumption, two scenario analyses are explored. Both required an adaptation of subsequent therapies from the IMpassion130 trial to better reflect UK clinical practice through the use of clinical expert opinion, NICE guidelines and market share data:

1. Applying subsequent therapies (adapted to UK clinical practice) separately per arm

2. Applying an average of subsequent therapies (adapted to UK clinical practice) across both arms

Table 57 details the resulting distribution of subsequent therapies and average treatment duration from the IMpassion130 trial, adapted to UK clinical practice, and utilised within the scenario analyses. It is assumed the subsequent therapies witnessed in the IMpassion130 trial for placebo + nab-paclitaxel (and subsequently adapted to UK clinical practice), are consistent with the subsequent therapies that would be utilised following treatment with paclitaxel or docetaxel.

**Table 57: Scenario analysis: Subsequent therapies from IMpassion130**

| Subsequent therapy | Atezolizumab + nab-paclitaxel | | | Placebo + nab-paclitaxel (utilised for paclitaxel and docetaxel comparators) | | |
|---|---|---|---|---|---|---|
| | N | % | Duration | N | % | Duration |
| Docetaxel | 1 | 1% | 22 | 8 | 4% | 128 |
| Vinorelbine | 6 | 3% | 77 | 7 | 4% | 123 |
| Eribulin | 12 | 6% | 56 | 15 | 8% | 143 |
| Gemcitabine | 24 | 13% | 128 | 24 | 13% | 75 |
| Carboplatin | 25 | 14% | 78 | 34 | 18% | 76 |
| Capecitabine | 41 | 22% | 83 | 37 | 20% | 124 |

Table 58 and Table 59 detail the drug acquisition costs, dose and frequency of administration for all pharmacological subsequent treatments for the scenario analyses.

**Table 58: Drug acquisition costs (subsequent treatments)**

| Drug | Dose/vial concentration | Pack size/vial volume | Cost per pack/vial | Source |
|---|---|---|---|---|
| **Docetaxel** | 20 mg/ml | 1 ml | £5.75 | eMIT June 2018 (161) |
| **Carboplatin** | 10 mg/ml | 5 ml | £3.07 | eMIT June 2018 (161) |
| | | 15 ml | £6.65 | |
| | | 45 ml | £17.03 | |
| | | 60 ml | £17.54 | |
| **Gemcitabine** | 1 g/10ml | 10 ml | £9.28 | eMIT June 2018 (161) |
| | | 20 ml | £16.01 | |
| **Capecitabine** | 150 mg | 60 mg | £4.83 | eMIT June 2018 (161) |
| | 500 mg | 120 mg | £43.82 | |
| **Eribulin** | 0.88 mg | 2 ml | £361 | BNF Sept 2018 (160) |
| | 1.32 mg | 3 ml | £541.50 | |
| **Vinorelbine** | 10 mg/ml | 1 ml | £14.14 | eMIT June 2018 (161) |
| | | 5 ml | £20.98 | |

**Table 59: Drug acquisition costs per week (subsequent treatments)**

| Drug | Total dose required per administration | Cost per administration per week | Frequency of administration | Drug cost per week |
|---|---|---|---|---|
| **Docetaxel** | 75 mg/m$^2$ | £58.13 | Every 3 weeks | £25.12 |
| **Carboplatin** | 400 mg/m$^2$ | £43.60 | Every 4 weeks | £42.62 |
| **Gemcitabine** | 1,250 mg/kg | £116.27 | Days 1 and 8 of a 21 days cycle | £20.13 |
| **Capecitabine** | 2,500 mg/m$^2$ | £0.00 | Daily for 2 weeks, followed by 1 week break | £3.17 |
| **Eribulin** | 1.23 mg/m$^2$ | £116.27 | Days 1 and 8 of a 21 days cycle | £875.65 |
| **Vinorelbine** | 30 mg/m$^2$ | £174.40 | Every week | £73.62 |

## *Drug administration costs*

### Intervention

In the Impassion130 trial, patients received atezolizumab at a dose of 840 mg, administered intravenously, on days 1 and 15 and received nab-paclitaxel at a dose of 100 mg per square meter of body-surface area, administered intravenously, on days 1, 8, and 15 of every 28-

day cycle. As such, in a 3-week period, patients would receive a combination of atezolizumab and nab-paclitaxel twice, and monotherapy nab-paclitaxel once.

In previous NICE appraisals for both atezolizumab (137, 162, 163) and nab-paclitaxel (164), a simple chemotherapy delivery was accepted as the appropriate administration cost. As such, this is the type of administration is applied on day 8, for monotherapy-nab paclitaxel (and monotherapy atezolizumab if patients discontinue nab-paclitaxel early). However, given the added complexities associated with administering a combination of atezolizumab and nab-paclitaxel on days 1 and 15, a complex chemotherapy delivery has been applied.

**Comparators**

- **Paclitaxel:** Whilst paclitaxel does not have a license for use in 1L TNBC as a monotherapy, clinical experts deem this as the most frequently used treatment. The most frequently used dosing regimen is 90 mg/m$^2$ every week, generally administered over a three-hour period. In addition, premedications are required ahead of infusion (see B.3.5.4). As such, a Complex Chemotherapy delivery has been applied.

- **Docetaxel:** As per the SmPC, the recommended dose is 100 mg/m$^2$ administered by intravenous infusion every 3 weeks. In previous NICE appraisals, a Simple Chemotherapy delivery has been utilised, as such the same is applied here.

**Table 60** provides the administration costs assumed for the intervention and comparators.

**Table 60: Drug administration costs: 1L treatments**

| Drug | Type of administration | NHS reference code | Cost per administration | Source |
|---|---|---|---|---|
| **Intervention** | | | | |
| **Atezolizumab + nab-paclitaxel (days 1 and 15)** | Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance | SB14Z | £336.55 | NHS reference costs 2017/2018 (165) |
| **Nab-paclitaxel monotherapy (day 8)** | Deliver Simple Parenteral Chemotherapy at First Attendance | SB12Z | £228.99 | NHS reference costs 2017/2018 (165) |

| | | | | |
|---|---|---|---|---|
| **Atezolizumab only (if nab-paclitaxel discontinued)** | Deliver Simple Parenteral Chemotherapy at First Attendance | SB12Z | £228.99 | NHS reference costs 2017/2018 (165) |
| **Nab-paclitaxel only (if atezolizumab discontinued)** | Deliver Simple Parenteral Chemotherapy at First Attendance | SB12Z | £228.99 | NHS reference costs 2017/2018 (165) |
| **Comparators** | | | | |
| **Paclitaxel** | Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance | SB14Z | £336.55 | NHS reference costs 2017/2018 (165) |
| **Docetaxel** | Deliver Simple Parenteral Chemotherapy at First Attendance | SB12Z | £228.99 | NHS reference costs 2017/2018 (165) |

N/A, Not applicable; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

### Subsequent therapies

In the base case analysis, it is assumed the cost per month of £1,200 also accounts for administration costs, as such, no further costing is applied.

For the scenario analyses, for simplicity purposes, all chemotherapy regimens (excluding capecitabine) have the same administration cost of Simple Parenteral Chemotherapy. As capecitabine is an oral treatment, only the cost of pharmacist time per administration is applied.

A full breakdown of administration costs for the scenario analyses of subsequent treatments applied in the model is given in Table 61.

**Table 61: Drug administration costs: subsequent treatments**

| Drug | Type of administration | | NHS reference code | Cost per administration | Source |
|---|---|---|---|---|---|
| **Docetaxel** | Deliver simple Parenteral Chemotherapy at first attendance | Outpatient setting | SB12Z | £228.99 | NHS reference costs 2017/2018 (165) |
| **Carboplatin** | | | | | |
| **Gemcitabine** | | | | | |
| **Eribulin** | | | | | |
| **Vinorelbine** | | | | | |

Company evidence document B submission for atezolizumab in combination with paclitaxel for untreated, locally advanced or metastatic, triple negative, PD-L1–positive breast cancer [ID1522].

| | | | | | |
|---|---|---|---|---|---|
| **Cisplatin** | | | | | |
| **Capecitabine** | 12 minutes pharmacist time every 4 weeks | Hospital pharmacist (band 6); cost per working hour | N/A | £44 per hour = £8.80 per administration | PSSRU 2018 (166) |

N/A, Not applicable; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

**PDL1 testing**

A PD-L1 test is expected to be used in the NHS, in line with the anticipated licenced indication. The cost of a PD-L1 test is £121.08. In clinical practice, this test would be administered once a patient had been determined to have TNBC. Based upon the IMpassion130 randomised trial proportion of patients enrolled, it is assumed that 41% of patients being treated in the first-line of the advanced setting of breast cancer would be PD-L1 positive. It is anticipated that a PD-L1 test would be a prerequisite for treatment. Hence, PD-L1 testing cost has been applied in the CE model as a one-off cost per patient identified to be PD-L1 positive of £295.32 applied at the point of treatment initiation with atezolizumab and nab-paclitaxel. This calculation is summarised in Table 62.

**Table 62: Cost of PD-L1 test implemented in model**

| Cost of PD-L1 test | % of patients expected to be PD-L1 positive, based upon IMpassion130 enrolment | Cost per patient tested | Cost of test per advanced TNBC patient treated with the new technology, assuming 41% of patients would be PD-L1 positive |
|---|---|---|---|
| **£121.08** | 41% | Calculated as: £121.08 x 100/41 | £295.32 |

### B.3.5.2 Health-state unit costs and resource use

Supportive care costs are applied for both PFS, and PD health states.

The types of resource and frequency of use are derived from the SR, previous technology appraisals and validated by UK clinicians. Unit costs were derived from NHS reference costs. Supportive care costs are applied as a “one-off” cost for the first model cycle of each of the progression free and progressed disease states associated with diagnosis costs. For the remaining cycles, a more general cost associated with more day-to-day supportive care is applied.

For the progressed disease state, subsequent treatment costs per cycle are also incurred. Details of these subsequent treatment costs are provided in section B.3.5.1.2.

Table 63: One-off diagnosis costs - PFS and PD details the one-off diagnosis costs for patients entering the progression free survival, and progressed disease health state (irrespective of treatment arm).

Resource use for progression free health state can be found in Table 64 and Table 65 describes the resource use in progressed disease. Unit costs are detailed in Table 66.

**Table 63: One-off diagnosis costs - PFS and PD**

| Resource | Unit cost | Source |
|---|---|---|
| **Oncologist visit** | £136.25 | WF01A service code 800 Clinical Oncology (Previously Radiotherapy) Non- Admitted Face to Face Attendance, First, NHS Reference costs 2017/18. Similar approach to TA495, TA496. (151, 152, 165) |
| **CT scan** | £106.88 | RD24Z Computerised Tomography Scan of two areas, with contrast, NHS reference costs 2017/18 (165) |
| **Full blood count** | £2.51 | DAPS05 Haematology; NHS ref 2015-16, NHS reference costs 2017/18 (165) |
| **Total cost** | £245.64 | |

**Table 64: Resource use for PFS health state**

| Resource | No. required | Length | Unit cost | Cost per month | Cost per weekly model cycle | Source |
|---|---|---|---|---|---|---|
| **Oncologist visit** | 1 per 6 months | Unknown | £136.25 | £22.71 | £5.22 | WF01A service code 800 Clinical Oncology (Previously Radiotherapy) Non- Admitted Face to Face Attendance, First, NHS Reference costs 2017/18. Similar approach to TA495, TA496 (151, 152). |
| **GP visit (surgery)** | 1 per month | 9.22 minutes | £37.00 | £37.00 | £8.51 | PSSRU 2018 p127: 9.22 minute visit, with qualifications (£219). |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | including direct care staff costs. Similar approach to TA495, TA496 (151, 152). |
| **Clinical nurse specialist** | 1 per month | 1 hour | £74.00 | £74.00 | £17.02 | PSSRU 2018 p123: One hour of patient related work, band 6. Similar approach to TA495, TA496 (151, 152). |
| **Community nurse** | 1 per 4 months | 20 mins | £42.00 | £10.50 | £2.41 | PSSRU 2018 p125: One hour of patient-related work, with qualifications. Similar approach to TA495, TA496 (151, 152). |
| **Total cost per month** | £144.21 | | | | | |
| **Total cost per weekly cycle** | £33.16 | | | | | |

GP, general practitioner

**Table 65: Resource use for PD health state**

| Resource | No. required | Length | Unit cost | Cost per month | Cost per weekly model cycle | Source |
|---|---|---|---|---|---|---|
| **Oncologist visit** | 1 per 2 months | Unknown | £136.25 | £68.13 | £15.67 | WF01A service code 800 Clinical Oncology (Previously Radiotherapy) Non- Admitted Face to Face Attendance, First, NHS Reference costs 2017/18. Similar approach to TA495, TA496 (151, 152).. |
| **GP visit (surgery)** | 1 per month | 9.22 minutes | £37.00 | £37.00 | £8.51 | PSSRU 2018 p127: 9.22 minute visit, with qualifications (£219). including direct care staff costs. Similar approach to TA495, TA496 (151, 152).. |
| **Clinical nurse specialist** | 1 per month | 1 hour | £74.00 | £74.00 | £17.02 | PSSRU 2018 p123: One hour of patient related work, band 6. Similar approach to TA495, TA496 (151, 152).. |
| **Community nurse** | 1 per 2 months | 20 mins | £42.00 | £21.00 | £4.83 | PSSRU 2018 p125: One hour of patient-related work, with qualifications. Similar approach to TA495, TA496 (151, 152).. |
| **Total cost per month** | £200.13 | | | | | |
| **Total cost per weekly** | £46.02 | | | | | |



| | |
|---|---|
| **cycle** | |

GP, general practitioner

**Table 66: Unit costs (Progression-free and progressed disease health states)**

| Resource | Unit cost | Source |
|---|---|---|
| **Full blood count** | £2.51 | DAPS05 Haematology; NHS ref 2015-16, NHS reference costs 2017/18 (165, 167) |
| **CT scan** | £106.88 | RD24Z Computerised Tomography Scan of two areas, with contrast, NHS reference costs 2017/18 (165) |
| **Oncologist visit** | £127.63 | WF01A service code 800 Clinical Oncology (Previously Radiotherapy) Non- Admitted Face to Face Attendance, First, NHS Reference costs 2017/18 (165) |
| **GP visit (surgery)** | £37.00 | PSSRU 2018 p127: 9.22 minute visit, with qualifications (£219), including direct care staff costs. (166) |
| **Clinical nurse specialist** | £74.00 | PSSRU 2018 p123: One hour of patient related work, band 6. (166) |
| **Community nurse** | £42.00 | PSSRU 2018 p125: One hour of patient-related work, with qualifications (166) |

GP, general practitioner; PFS, progression-free survival; PD, progressive disease; PSSRU, Personal Social Services Research Unit.

An end of life/terminal care cost is applied to patients who enter the death state as a one off cost, in line with previous appraisals in metastatic Breast Cancer (151, 152, 168). The terminal care cost reflects the resource consumption in various care settings, and is weighted by the proportion of patients treated in each setting. This cost is assumed equal for all treatments. Resource use and costs are shown in Table 67. The total cost of end of life is £5,617.85.

**Table 67: Resource use for terminal care/end of life**

| Resource | Unit cost | % of patients in each setting | Source |
|---|---|---|---|
| **Hospital *and* Social Care (combined)** | £12,066 | 40 | Similar to Approach used in TA239, TA495, TA496. However, PSSRU 2018, Page 110, provides a new description of a unit cost: "Cost of hospital *and social care* services for cancer diagnostic group in the final year of life" (151, 152, 166, 168) |
| **Hospice** | £697.56 | 10 | Approach used in TA239, TA495, TA496 (151, 152, 168) |
| **Home** | £1,443.39 | 50 | Approach used in TA239, TA495, TA496 (151, 152, 168) |
| **Total cost** | £5,617.85 | | |

### B.3.5.3 Adverse reaction unit costs and resource use

All grade ≥3 adverse events, with an incidence of ≥2% were sourced from the IMpassion130 clinical study for the intervention arm, and from key trials from the clinical SR for the

comparator arms. This included E2100 (10, 11), LOTUS (86, 87), MERIDIAN for paclitaxel) (12, 14, 15), and AVADO (16, 17) and JapicCTI-090921 for docetaxel (85).

The proportion of patients experiencing AEs, and the unit costs associated with managing them (for the intervention and comparators) are provided in Table 69

The total cost of AEs for each intervention and comparator is applied as a once off cost at the first cycle of treatment only, hence it is assumed that the AE occurs at treatment initiation, only once across the time horizon of the economic model, and that this cost is only incurred in the first 7 days (cycle length 7 days). Whilst this is not reflective of the real world, such as approach has been taken in other NICE appraisals (169) and deemed acceptable.

The resulting cost of managing adverse events associated with each treatment regimen can be found in Table 68.

It should be noted, due to the level of missing information for the comparator arms, it is anticipated these costs are a conservative estimate.

**Table 68: Total costs per patient in the management of AEs, based on IMpassion130 (atezolizumab with nab-paclitaxel) and paclitaxel/docetaxel trials included in the SR of clinical evidence**

| Treatment | Atezolizumab+nab-paclitaxel | Paclitaxel | docetaxel |
|---|---|---|---|
| Cost of managing AEs, per patient | £113.99 | £210.75 | £246.10 |

**Table 69: Rates and costs of adverse events (occurring at Grade 3-4, in 2% or more of patients) applied for intervention and comparators (paclitaxel and docetaxel)**

| | Atezolizumab + nab-paclitaxel n (%) | Paclitaxel, n (%) | Docetaxel n (%) | Unit cost for adverse event | Unit Cost duration | Cost per week assumed (Applied as one-off) | Source of unit cost |
|---|---|---|---|---|---|---|---|
| **Anaemia** | 8 (2) | 2 (3) | Not reported | £1,748.10 | Per month | £402 | Majethia 2014 (156) |
| **Bone pain** | 2 (0.4) | 1 (2) | Not reported | £0.00 | - | - | Cost falls out-of-pocket, hence £0.00 cost to NHS |
| **Venous thromboembolic event** | 0(0) | Not reported | 7 (3) | £288.00 | Per episode | £288 | DZ09J Pulmonary Embolus with Interventions, with CC Score 9+, NON-ELECTIVE EXCESS BED DAYS NHS |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | reference costs 2017/2018 (165) |
| **Diarrhoea** | 6(1) | Not reported | 2 (2) | £0.00 | - | - | Cost falls out of pocket, and is not incurred to NHS |
| **Fatigue** | 16 (3.4) * | 23(6) | Not reported | £932.75 | Per month | £215 | Majethia 2014 (156) |
| **Febrile neutropenia** | 6 (13)* | 30(13) | 26 (11) | £1,612.55 | Per month | £371 | Majethia 2014 (156) |
| **Allergic reaction** | 1 (0.2) | 9(3) | Not reported | £438.00 | Per episode | £438 | WH05Z Allergy or Adverse Allergic Reaction, £438 (NHS reference costs 2017/2018) (165) |
| **Hypertension** | 0 (0) | 12 (4) | Not reported | £659.00 | Per episode | £659.00 | EB04Z Hypertension NHS reference costs 2017/2018 (165) |
| **Infection** | 0 (0) | 10(3) | Not reported | £1,612.55 | Per month | £371 | Majethia 2014(156) |
| **Leukopenia** | 8 (2) | Not reported | 90 (90) | £273.83 | Per month | £63 | Majethia 2014 (156) |
| **Nausea** | 4 | 1 (2) | Not reported | £568.33 | Per month | £131 | Majethia 2014 (156) |
| **Peripheral neuropathy** | 25 (5.5) * | 72(18) | Not reported | £874.80 | Per month | £201 | Majethia 2014 (156) |
| **Neutropenia** | 37 (8.2) * | 4 (6) | 138 (42) | £1,222.85 | Per month | £281 | Majethia 2014 (156) |
| **Oedema** | 0(0) | Not reported | 4 (4) | £544.00 | Per episode | £544 | WH10B Unspecified Oedema with CC Score 0-1, NHS reference costs, Unspecified Oedema with CC Score 0-1 |
| **Vomiting** | 2 (0.4) | 7(2) | Not reported | £568.33 | Per month | £131 | Majethia 2014 (156) |

### B.3.5.4 Miscellaneous unit costs and resource use

Both paclitaxel and docetaxel require premedication, as per the SmPC. Details are provided below in Table 70.

**Table 70: Premedication dosing**

| Premedication required for | Medicinal product | Dose | Administration prior to treatment | Source |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **Paclitaxel** | Dexamethasone | 20 mg oral | For oral administration: approximately 12 and 6 hours orf or i.v. administration: 30 to 60 minutes | Paclitaxel SmPC (27) |
| | Chlorpheniramine | 50 mg i.v. | 30 – 60 minutes | |
| | Cimetidine | 300 mg i.v. | 30 – 60 minutes | |
| **Docetaxel** | Dexamethasone | 16 mg oral per day for 3 days | 1 day | Docetaxel SmPC (170) |

Acquisition costs associated with premedications can be found in Table 71.

**Table 71: Acquisition costs of premedication**

| Product | Size | Pack cost | Source |
|---|---|---|---|
| **Dexamethasone** | 2 mg tablets, packsize 50 | £12.39 | eMit June 2018 (161) |
| **Chlorpheniramine** | 10 mg/1ml, packsize 5 | £22.50 | BNF Jan 2019 (160) |
| **Cimetidine** | 200 mg/5ml | £14.25 | |

Based on clinician descriptions of UK practice, it is assumed dexamethasone is always administered via the oral route (rather than IV infusion). No IV infusion administration cost is applied for the IV pre-medications (chlorpheniramine, cimetidine), as it is assumed that this resource use would occur on the same day as the IV infusion of the chemotherapy (as per National Tariff rules). However, an additional cost of clinical nurse specialist time is incorporated, to support with the administration.

The resulting costs of premedication for both paclitaxel and docetaxel can be found in Table 72.

**Table 72: Premedication total costs**

| Comparator | Premedication required | Total premedication dose (per administration) | Premedication cost | Administration cost | Sources | Total |
|---|---|---|---|---|---|---|
| **Docetaxel** | Dexamethasone | 48 mg | £5.95 | £8.80 | Table 52, 12 minutes pharmacist time for every administration, Hospital pharmacist (band 6); cost per working hour £44.00. Cost for 12 minutes: £8.80 | £14.74 |
| **Paclitaxel** | Dexamethasone | 20 mg | £2.48 | £8.80 | Table 52, 12 minutes pharmacist time for every administration, Hospital pharmacist (band 6); cost per working hour £44.00. Cost for 12 minutes: £8.80 | £11.28 |
| | Chlorpheniramine | 50 mg | £22.50 | £74.00 | Table 52, Clinical nurse specialist<br>PSSRU 2018 p123: One hour of patient related work, band 6. | £22.50 |
| | Cimetidine | 300 mg | £21.38 | | | £95.38 |

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

### B.3.6.1 Summary of base-case analysis inputs

**Table 73: Summary of variables applied in the economic model**

| Variable | Value (reference to appropriate table or figure in submission) | Measurement of uncertainty and distribution: CI (distribution) | Reference to section in submission |
|---|---|---|---|
| **General model parameters** | | | |
| Time horizon | 15 years | Fixed | B.3.6.2 |
| Discount rate - efficacy | 3.5% | Fixed | |
| Discount rate - costs | 3.5% | Fixed | |
| Full vial sharing | 100% | Fixed | |
| **Population parameters** | | | |
| Age | 53.59 | Fixed | B.3.6.2 |
| Body weight | 70.42 | Fixed | |
| Height | 161.21 | Fixed | |
| Body surface area | 1.74 | Fixed | |
| **Parametric curves** | | | |
| TTOT – atezolizumab | KM + Exponential | Multivariate normal | B.3.3.1 |
| TTOT – nab-paclitaxel | KM + Gamma | | |
| PFS - atezolizumab with nab-paclitaxel | KM+ Gompertz | | |
| OS - atezolizumab with nab-paclitaxel | Weibull | | |
| **Method of ITC** | | | |
| Piecewise exponential | | Fixed | B.2.9.1 |
| **Utilities – base case – IMpassion130** | | | |
| Progression free | 0.726 | Beta (0.706, 0.746) | B.3.4.1 |
| Progressive disease | 0.653 | Beta (0.631, 0.675) | |
| **Utilities – scenario analysis** | | | |
| Progression free (atezolizumab) | 0.741 | NA – scenario only | B.3.4.1 |
| Progression free (comparators) | 0.710 | | |
| Progressive disease | 0.653 | | |
| **Adverse event disutilities – scenario analysis** | | | |
| Bone pain | -0.069 | NA – scenario only | B.3.4.4 |
| Diarrhoea | -0.103 | | |
| Hypertension | -0.153 | | |
| Nausea | -0.103 | | |
| Vomiting | -0.103 | | |
| Peripheral neuropathy | -0.15 | | |
| Febrile neutropenia | -0.15 | | |

| | | | |
|---|---|---|---|
| Neutropenia | -0.124 | | |
| Fatigue | -0.115 | | |
| **Technology acquisition costs per pack (unit costs at list price)** | | | |
| Atezolizumab 840mg | [redacted] | Fixed | B.3.5.1.1 |
| Nab-paclitaxel | £246.00 | Fixed | |
| Paclitaxel - 100mg/16.7ml | £7.35 | Fixed | |
| Paclitaxel - 150mg/25ml | £10.48 | Fixed | |
| Paclitaxel - 300mg/50ml | £22.82 | Fixed | |
| Paclitaxel - 30mg/50ml | £3.41 | Fixed | |
| Docetaxel - 160mg/8ml | £30.82 | Fixed | |
| Docetaxel - 20mg/1ml | £5.75 | Fixed | |
| Docetaxel - 80mg/4ml | £11.95 | Fixed | |
| **Administration costs: Intervention and Comparator – per administration** | | | |
| **Admin cost, deliver complex chemotherapy, first attendance** | £336.55 | Normal | B.3.5.1.3 |
| **Admin cost, deliver simple chemotherapy, first attendance** | £228.99 | Normal | |
| **Subsequent therapies – per weekly model cycle** | | | |
| NICE TA495 cost for subsequent therapies (171) | £300 | Fixed Normal | B.3.5.1.3 |
| **Subsequent therapies – scenario analysis (individual arms)** | | | |
| Atezolizumab | £161 | NA – scenario only | B.3.5.1.3 |
| Comparators | £171 | | |
| **Subsequent therapies – scenario analysis (combined arms)** | | | |
| Atezolizumab | £166 | NA – scenario only | B.3.5.1.3 |
| Comparators | £166 | | |
| **Supportive care costs** | | | |
| PFS – one off cost for first model cycle | £245.64 | Normal | B.3.5.2 |
| PFS – cost for follow-on cycles | £33.16 | Normal | |
| PD – one off cost for first model cycle | £245.64 | Normal | |
| PD – cost for follow-on cycles | £46.02 | Normal | |
| **Terminal care cost** | | | |
| Terminal care cost | £5,617.85 | Fixed | B.3.5.2 |
| **Adverse event management costs** | | | |
| Atezolizumab | £113.99 | Normal | B.3.5.3 |
| Paclitaxel | £210.75 | Normal | |



| | | | |
|---|---|---|---|
| Docetaxel | £246.10 | Normal | |
| **Cost of PD-L1 test, assuming a patient is tested regardless of PD-L1 status** | | | |
| Cost of identifying a person with PD-L1 positive advanced TNBC | £121.08 | Fixed | B.3.5.1 |
| **Premedication costs** | | | |
| Paclitaxel | £129.16 | Fixed | B.3.5.4 |
| Docetaxel | £14.57 | | |

## B.3.6.2 Assumptions

**Table 74: Key assumptions used in the economic model (base case)**

| Area | Assumption | Justification |
|---|---|---|
| Time horizon | 15 years | The average age of patients in the model at the start is 53.60 (based upon the IMpassion130 trial). The 15-year model horizon is in line with NICE reference case, and also long enough to reflect the difference in costs and outcomes between the interventions being compared in this submission. |
| Comparators | Paclitaxel, docetaxel | Paclitaxel considered taxane of choice for 1L mTNBC. Docetaxel more limited usage due to toxicity, and availability for rechallenge from eBC setting. Anthracyclines listed in final scope, however only 20% patients eligible in clinical practice, and no robust evidence identified in SR in order to perform ITC |
| Clinical efficacy and safety | Efficacy and safety results for atezolizumab with nab-paclitaxel, seen in the IMpassion130 trial, are transferable to UK population | Expert clinical advice suggests the outcomes seen from the study are expected in UK patients, given the similarity of outcomes in the trial and observational data. |
| OS: atezolizumab with nab-paclitaxel | Weibull distribution | Best fit based upon: Highest ranking statistical fit (AIC/BIC), visual fit to KM and clinical plausibility. All but one alternative distributions provide significantly more favourable ICERs, as such, this can be considered a conservative approach |
| PFS: atezolizumab with nab-paclitaxel | KM + Gompertz | Best fit based upon: statistical fit (AIC/BIC), visual fit to KM and clinical plausibility |
| TTOT | Atezolizumab: KM + Exponential<br>Nab-paclitaxel: KM+ Gamma | Modelled separately to ensure all costs of treatment are captured accurately. Assumes there may be circumstances where a patient will discontinue one medicine before the other.<br>Distributions selected based on best fit by: statistical fit (AIC/BIC), visual fit to KM and clinical plausibility |
| Supportive care costs (in PFS and PD) | Resource use based upon NICE appraisals TA239, TA495, TA496 (152, 168, 172) | Based upon past NICE appraisals in the metastatic breast cancer setting (152, 168, 172) and validated by clinical experts. |

| | | |
|---|---|---|
| **Administration costs** | • Atezolizumab or nab-paclitaxel monotherapy: simple chemotherapy<br>• Atezolizumab + nab-paclitaxel: complex chemotherapy<br>• Paclitaxel: complex chemotherapy<br>• Docetaxel: simple chemotherapy | • In previous NICE appraisals for both atezolizumab (137, 162, 163) and nab-paclitaxel (164), a simple chemotherapy delivery was accepted as the appropriate administration cost<br>• A greater cost (complex chemotherapy) is required when administering a combination of atezolizumab and nab-paclitaxel to account for the added complexities<br>• Paclitaxel is administered over a 3 hour period, with pre-medications required ahead of infusion, as such complex chemotherapy applied<br>• Previous NICE appraisals considering docetaxel deemed simple chemotherapy as appropriate |
| End of life cost | End of Life costs approach as per previous appraisals but updated to reflection new PSSRU 2018 publication description of both hospital and social services costs. | Similar to approach used in TA239, TA495, TA496. However, updated unit costs from PSSRU 2018 which provides a new description of a unit cost ("Cost of hospital and social care services for cancer diagnostic group in the final year of life"). |
| Subsequent therapies | Fixed cost of £1,200 per month applied until a patient dies. | Consistent with the approach taken in TA495 |
| HRQoL | Based upon EQ-5D-5L collected within IMpassion130 trial | In line with NICE reference case and NICE position on EQ-5D-5L utilities generation, consistent approach with previous appraisals and validated by UK clinical experts |
| | Omission of AE disutilities in the base case analysis | The disutility associated with AEs was assumed to have been captured in the EQ-5D-5L responses in IMpassion130. |
| Safety: costs | Specified AEs incorporated into the CE model were those which occurred in 2% or more patients at Grade 3-5, across any of: IMpassion130 trial, paclitaxel or docetaxel trials, for a consistent approach across the intervention and comparators (paclitaxel and docetaxel). | Consistent with other NICE appraisals in the metastatic oncology space |
| Patient body weight, height and body surface area, for dosing calculations | Based upon IMpassion130 trial | IMpassion130 data are best available to describe the body surface area of patients, which then determines the dosing of nab-paclitaxel and comparators. |

## *B.3.7 Base-case results*

- **The base case ICER versus paclitaxel is £51,145 at atezolizumab PAS price (nab-paclitaxel list price)**
- **Only a small discount of 10% on the nab-paclitaxel list price is required for this combination to be deemed cost-effective versus the primary comparator, paclitaxel**
- **The base case ICER versus docetaxel is £63,859 at atezolizumab PAS price (nab-paclitaxel list price)**
- **Atezolizumab with nab-paclitaxel is associated with a clear clinical benefit over paclitaxel (1.05 LYs gained, [redacted] QALYs gained) and docetaxel (0.97 LYs gained, [redacted] QALYs gained)**
- **The main drivers of the economic analysis include the assumed nab-paclitaxel discount; the survival extrapolation chosen; the atezolizumab time on treatment extrapolation; and utility estimates**

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

Base-case results of the economic model are presented below.

As detailed in earlier sections (B.1.3, B.3.2) paclitaxel is often the taxane of choice for 1L mTNBC. This is due to the favourable toxicity profile of weekly paclitaxel compared with 3-weekly docetaxel which increases tolerability and helps maintain QoL for patients with limited life expectancy (56). Docetaxel is often used in the curative eBC setting where the toxicities of treatment are offset by the aim of cure rather than palliation (UK Clinical expert opinion, (20)). Both *in vitro* and *in vivo* studies have demonstrated only partial cross-resistance between docetaxel and paclitaxel (57-59), increasing the likelihood of additional benefit from a different taxane agent in later lines i.e., paclitaxel. Furthermore, re-challenge with docetaxel (following use in eBC) may be unacceptable to some patients due to the extent of toxicities experienced, possibly coupled with a perception that the treatment was not effective if they relapse. As such, paclitaxel is considered the primary comparator. Docetaxel is provided to support the final decision problem.

Atezolizumab in combination with nab-paclitaxel provided a QALY gain of [redacted], and a life-year gain of 2.43, at a total drug cost of [redacted], and total overall cost of [redacted] when accounting for the atezolizumab PAS price. Nab-paclitaxel is also subject to a PAS (with a generic due to launch imminently), which is not accounted for here.

### *Paclitaxel*

Paclitaxel provided a QALY gain of 0.93, and a life-year gain of 1.38, at a total cost of £16,489.

The resulting ICERs using the list prices of atezolizumab and nab-paclitaxel, versus paclitaxel are [redacted]. When incorporating the PAS for atezolizumab, the resulting ICER drops to £51,145.

However, it should be highlighted; nab-paclitaxel is also associated with a PAS at an unknown level of discount. As such, these ICERs are unable to account for this discount, and should be interpreted with caution.

In addition, as detailed in section B.3.5.1, it is important to highlight that a generic version of nab-paclitaxel (Abraxane) is anticipated to gain a Marketing Authorisation in May 2019, and thus is expected to be available in the NHS. As generics are almost always less costly than the “branded” versions of a drug, this would be expected to have a significant impact on this appraisal, by reducing the total cost of the combination of atezolizumab with nab-paclitaxel, thus further improving the ICER.

### *Docetaxel*

Docetaxel provided a QALY gain of 0.97, and a life-year gain of 1.47, at a total cost of £10,818.

The resulting ICERs using the list prices of atezolizumab and nab-paclitaxel, versus docetaxel are [redacted]. When incorporating the PAS for atezolizumab, the resulting ICER drops to £63,859. This figure does not account for the nab-paclitaxel PAS, so should be interpreted with caution.

Table 75 provides a summary of the base case results at PAS price. Table 76 provides the base case results at list price.

Base case results are then varied across different level of potential nab-paclitaxel discounts in Table 77 to account for, and demonstrate ICER levels based on the current PAS, and

future generic entry. As demonstrated, only a small discount of 10% on the nab-paclitaxel list price is required for this combination to be deemed cost-effective versus the primary comparator, paclitaxel.

**Table 75: Base-case results (PAS price)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incr. costs (£) | Incr. LYG | Incr. QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| Atezolizumab + nab-paclitaxel (list prices) | [redacted] | 2.43 | [redacted] | | | | |
| Paclitaxel | £16,489 | 1.38 | 0.93 | [redacted] | 1.05 | [redacted] | £51,145 |
| Docetaxel | £10,818 | 1.47 | 0.97 | [redacted] | 0.97 | [redacted] | £63,859 |

**Table 76: Base-case results (list price)**

| Technologies | Total costs (£) | Total LYG | Total QALYs | Incr. costs (£) | Incr. LYG | Incr. QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|---|
| Atezolizumab + nab-paclitaxel (list prices) | [redacted] | 2.43 | [redacted] | | | | |
| Paclitaxel | £16,489 | 1.38 | 0.93 | [redacted] | 1.05 | [redacted] | [redacted] |
| Docetaxel | £10,818 | 1.47 | 0.97 | [redacted] | 0.97 | [redacted] | [redacted] |

**Table 77: Base case results, varied by nab-paclitaxel discount**

| | Nab-paclitaxel discount | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% |
| ICER vs. paclitaxel | £49,496 | £47,846 | £46,197 | £44,548 | £42,898 | £41,249 | £39,599 | £37,950 | £36,301 |
| ICER vs. docetaxel | £62,099 | £60,340 | £58,580 | £56,821 | £55,061 | £53,302 | £51,542 | £49,783 | £48,023 |

## *B.3.8 Sensitivity analyses*

### B.3.8.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means, and sources used to estimate the parameters are detailed in section B.3.6.

Results of the PSA compared to deterministic results are presented in Table 78. The scatterplot in Figure 30 shows the iterations and the cost effectiveness acceptability curve is shown in Figure 31.

The analyses below are based on the PAS price of atezolizumab. Please see the confidential PAS Appendix (Appendix L) for PSA results at list price. Nab-paclitaxel is associated with a confidential PAS; thus analyses could not be conducted on this. Furthermore, a generic nab-paclitaxel is expected to launch during the NICE appraisal process and would need to be taken into consideration.

**Table 78: PSA results compared to base-case (with PAS)**

| | Costs | | QALYs | | ICERs | |
|---|---|---|---|---|---|---|
| | Base case | PSA | Base case | PSA | Base case | PSA |
| Atezolizumab with nab-paclitaxel | [redacted] | [redacted] | [redacted] | [redacted] | | |
| paclitaxel | £16,489 | £16,666 | 0.93 | 0.94 | £51,145 | £48,688 |
| docetaxel | £10,818 | £10,918 | 0.97 | 0.98 | £63,859 | £61,412 |

ICERs, incremental cost-effectiveness ratios; PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.

**Figure 30: PSA Scatterplot**

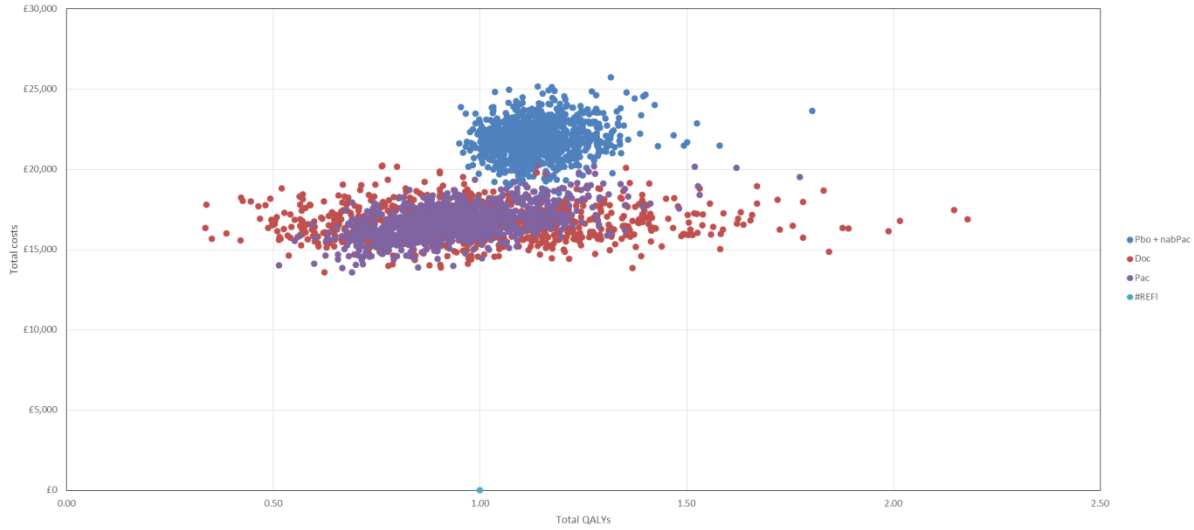
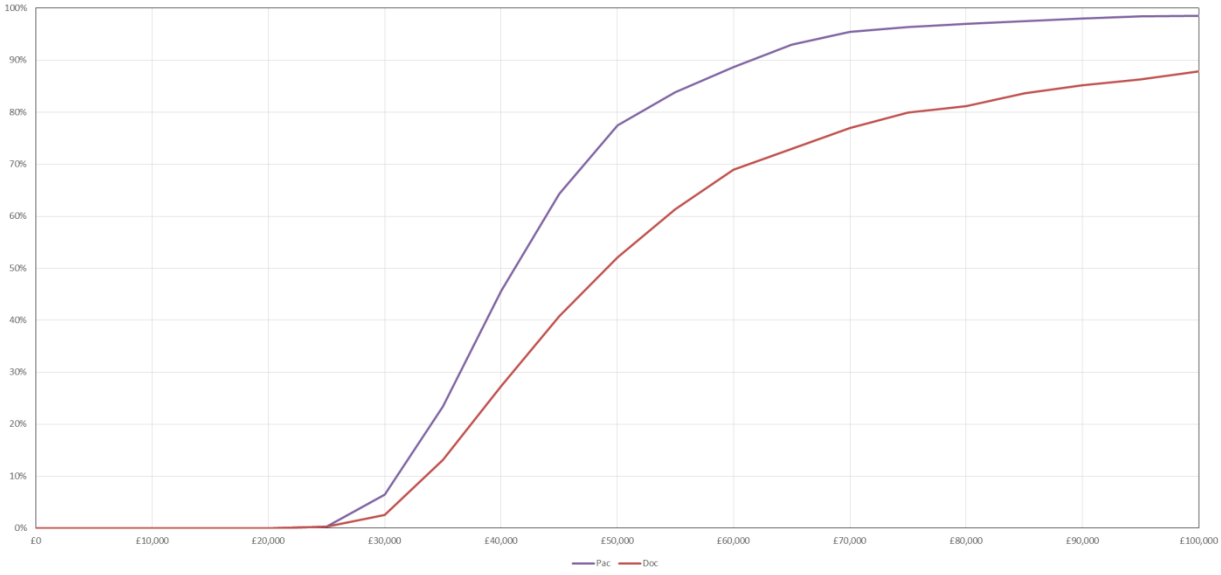


**Figure 31: CEAC - atezolizumab + nab-paclitaxel versus paclitaxel and docetaxel**




### B.3.8.2 Deterministic sensitivity analysis

The choice of parameters to include in univariate analysis was considered a-priori, and further informed by the results in section B.3.7, with focus on the parameters providing greatest impact on the percentage increment in costs or QALYs, thus having the greatest impact on the resulting ICER. The parameter values used in the analyses can be found in Table 79 below. Generally, the base case parameter values were varied across their 95% CI. Results of the analyses using the atezolizumab PAS price are displayed in Figure 32 and Figure 33.

For the results of the deterministic sensitivity analysis at list price, please see the confidential PAS Appendix (Appendix L).

**Table 79: Parameter values for univariate sensitivity analysis**

| Parameter | Base case value | Lower value | Higher value |
|---|---|---|---|
| Oncologist visit cost | £136.25 | £109.54 | £162.95 |
| Clinical nurse specialist cost | £74.00 | £59.50 | £88.50 |
| Community nurse cost | £42.00 | £33.77 | £50.23 |
| General practitioner visit (surgery) cost | £37.00 | £29.75 | £44.25 |
| Admin cost, deliver complex chemotherapy, first attendance | £336.55 | £270.59 | £402.51 |
| Admin cost, deliver simple | £228.99 | £184.11 | £273.87 |

| | | | |
|---|---|---|---|
| chemotherapy, first attendance | | | |
| Cost of diagnostic test (£) | £121.08 | £97.35 | £144.81 |
| End of life cost (£) | £5,617.85 | £4,516.77 | £6,718.93 |
| Utility PFS pooled | 0.73 | 0.57349 | 0.85582 |
| Utility PD | 0.65 | 0.52007 | 0.77479 |
| Time horizon | 15.00 | 12.06 | 17.94 |
| Discount rate (efficacy) | 0.035 | 0.01 | 0.06 |
| Discount rate (costs) | 0.035 | 0.01 | 0.06 |
| Adverse event management (atezo) | 113.99 | 91.65 | 136.33 |
| Adverse event management (nabpaclitaxel) | 128.64 | 103.42 | 153.85 |
| Adverse event management (paclitaxel) | 210.75 | 169.44 | 252.05 |
| Adverse event management (docetaxel) | 246.10 | 197.86 | 294.33 |
| Cost of subsequent therapies | £300.00 | £241.20 | £358.80 |
| PFS - one-off cost for first cycle | £245.64 | £197.49 | £293.78 |
| PFS - follow up cost | £33.16 | £26.66 | £39.67 |
| PD - one-off cost | £245.64 | £197.49 | £293.78 |
| PD - follow up cost | £46.02 | £37.00 | £55.04 |

AE, adverse event; PD, progressive disease; PFS, progression-free survival; PPS, post-progression survival

**Figure 32: Tornado diagram (versus paclitaxel)**

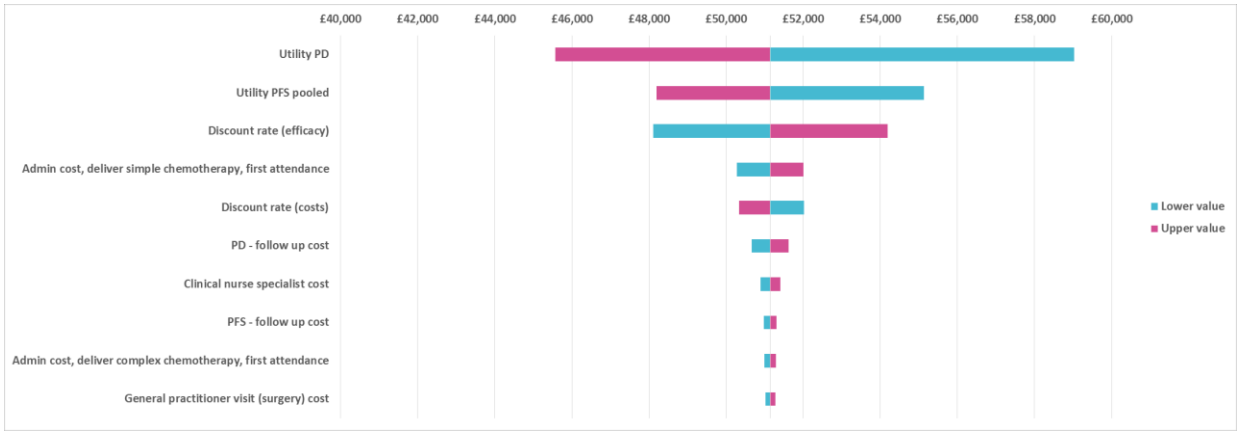
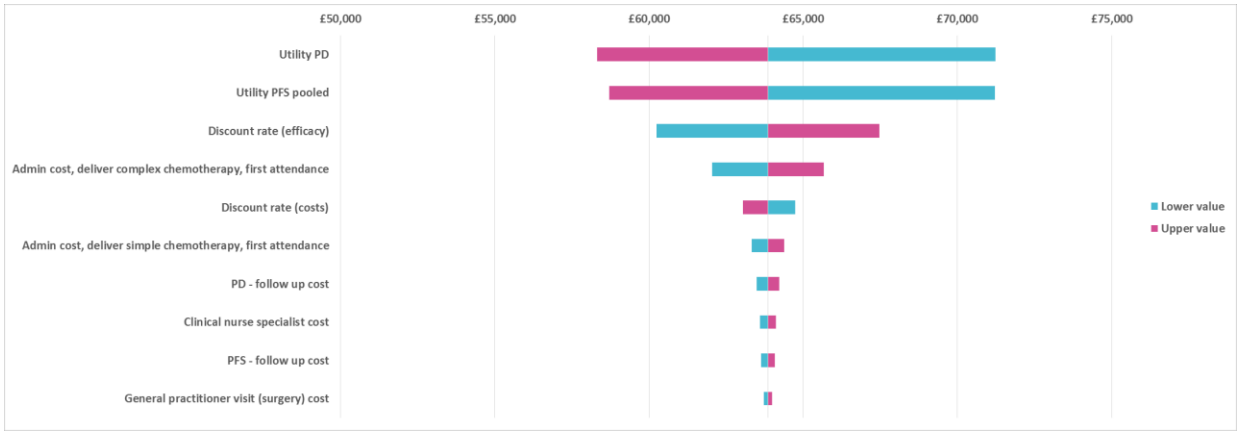



**Figure 33: Tornado diagram (versus docetaxel)**




### B.3.8.3 Scenario analysis

Scenario analyses were conducted to assess uncertainty around structural assumptions of the model. Atezolizumab PAS price results for the primary paclitaxel comparator are shown in Table 80. For scenario analyses for the docetaxel comparator, please see Appendix O. For list price results, please see the confidential PAS Appendix.

**Table 80: Scenario analyses versus paclitaxel – with PAS**

| | | Atezolizumab + nab-paclitaxel | | | Paclitaxel | | | |
|---|---|---|---|---|---|---|---|---|
| | Description | Total LYs | Total QALYs | Total costs | Total LYs | Total QALYs | Total costs | ICER |
| Base case | Base case | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | £51,145 |
| Nab-paclitaxel discount | 10% | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 49,496 |
| | 20% | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 47,846 |
| | 30% | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 46,197 |
| | 40% | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 44,548 |
| | 50% | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 42,898 |
| | 60% | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 41,249 |
| | 70% | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 39,599 |
| | 80% | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 37,950 |
| | 90% | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 36,301 |
| Alternative parametric extrapolations for OS | Exponential | 2.959 | [redacted] | [redacted] | 1.461 | 0.972 | 16,505 | 38,728 |
| | Weibull | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 51,145 |
| | Log-normal | 3.476 | [redacted] | [redacted] | 1.491 | 0.988 | 16,684 | 30,998 |
| | Gamma | 2.642 | [redacted] | [redacted] | 1.393 | 0.936 | 16,512 | 44,521 |
| | Log-logistic | 3.289 | [redacted] | [redacted] | 1.454 | 0.969 | 16,621 | 33,071 |
| | Gompertz | 2.238 | [redacted] | [redacted] | 1.378 | 0.928 | 16,427 | 60,492 |
| Alternative parametric | KM+ | 2.433 | [redacted] | [redacted] | 1.382 | 0.929 | 16,497 | 51,288 |

Company evidence document B submission for atezolizumab in combination with paclitaxel for untreated, locally advanced or metastatic, triple negative, PD-L1–positive breast cancer [ID1522].

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| extrapolations for PFS | Exponential | | | | | | | |
| | KM + Weibull | 2.433 | [redacted] | [redacted] | 1.382 | 0.928 | 16,508 | 51,350 |
| | KM +Log-normal | 2.433 | [redacted] | [redacted] | 1.382 | 0.931 | 16,479 | 50,809 |
| | KM + Gamma | 2.433 | [redacted] | [redacted] | 1.382 | 0.932 | 16,472 | 50,576 |
| | KM + Log-logistic | 2.433 | [redacted] | [redacted] | 1.382 | 0.932 | 16,474 | 50,549 |
| | KM + Gompertz | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 51,145 |
| Alternative parametric extrapolations for TTOT - atezolizumab | KM+ Exponential | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 51,145 |
| | KM + Weibull | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 51,841 |
| | KM +Log-normal | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 54,763 |
| | KM + Gamma | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 53,432 |
| | KM + Log-logistic | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 54,655 |
| | KM + Gompertz | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 54,411 |
| Alternative parametric extrapolations for TTOT – nab-paclitaxel | KM+ Exponential | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 51,208 |
| | KM + Weibull | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 50,500 |
| | KM +Log-normal | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 53,461 |
| | KM + Gamma | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 51,145 |
| | KM + Log-logistic | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 53,779 |



| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | KM + Gompertz | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 51,240 |
| Subsequent treatments | Estimates from TA495 | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 51,145 |
| | IMpassion130 | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,418 | 51,147 |
| | Average IMpassion130 | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,415 | 51,155 |
| Disutilities | Excluded | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 51,138 |
| | Included | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 51,145 |
| Utilities | Combined PFS | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 51,145 |
| | Treatment specific PFS | 2.433 | [redacted] | [redacted] | 1.382 | 0.920 | 16,489 | 49,392 |
| Vial sharing | Yes | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 51,145 |
| | No | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,585 | 54,522 |
| Time horizon | 10 years | 2.429 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 51,259 |
| | 20 years | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 51,144 |
| | 30 years | 2.433 | [redacted] | [redacted] | 1.382 | 0.930 | 16,489 | 51,144 |

AE, adverse event; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; LYs, life years; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; QALYs, quality-adjusted life years.B.3.8.4 Summary of sensitivity analyses results



### B.3.8.4 Summary of sensitivity analyses results

As seen in the probabilistic sensitivity analysis scatterplots, atezolizumab with nab-paclitaxel is associated with a clear clinical benefit over the majority of paclitaxel and docetaxel iterations. Further, the clinical benefit appears more certain, as opposed to the spread of iterations witnessed for paclitaxel and docetaxel. This clinical benefit is further validated in the one-way sensitivity analyses and scenario analyses whereby a change in the OS parametric distributions (for all, bar one) consistently has a favourable effect on the ICER.

The main drivers of the economic analysis include the assumed nab-paclitaxel discount; the survival extrapolation chosen; the atezolizumab time on treatment extrapolation; and utility estimates.

The results included above have been conducted on the PAS price of atezolizumab and the list price nab-paclitaxel. However, nab-paclitaxel is associated with a confidential PAS, hence the above reported ICER results do not accurately reflect the true cost-effectiveness estimates.

Furthermore, as detailed in B.3.5.1, it is important to highlight that a generic version of nab-paclitaxel (Abraxane) is anticipated to gain a Marketing Authorisation in May 2019, and thus is expected to be available in the NHS. As generics are almost always less costly than the "branded" versions of a drug, this would be expected to have a significant impact on this appraisal, by reducing the total cost of the combination of atezolizumab with nab-paclitaxel, and further improving the ICER.

## *B.3.9 Subgroup analysis*

No subgroup cost-effectiveness analyses were performed. The license for atezolizumab in combination with nab-paclitaxel is anticipated to be for patients with a PD-L1 positive biomarker result. As such, no analyses were conducted on restricted populations as compared to the anticipated indication.

## *B.3.10 Validation*

### B.3.10.1 Validation of cost-effectiveness analysis

Selection of the appropriate distributions has been driven by statistical fit to the data (AIC/BIC), visual fit to the KM and, importantly, clinical plausibility of the outcomes (derived

via oncologist input) – as described in guidance provided by the NICE Technical Decision Support Unit (Technical Support document 14).

All outcomes of the new technology and comparator arms of the economic model have been extensively compared to and validated against all available evidence for these products to assess the accuracy of the modelled survival (See Appendix J).

The economic model was constructed specifically from the UK-NHS perspective. The structure is consistent with other oncology models and previous mBC submissions to NICE and all costs are sourced from UK published literature. In addition, the model approach and inputs were validated by a number of UK clinical experts to ensure the model was reflective of clinical practice. This includes, but is not limited to: resource use; health state methodologies; OS projections and extrapolation techniques.

Internal quality control and validation of the model was conducted by an external consultancy. Cell by cell validation was conducted which included formula checking, cell references and all aspects of model functionality. A number of 'pressure tests' were conducted, including using extreme values. The results of the model using these values were then compared to expected outputs to assess functional accuracy.

### *B.3.11 Interpretation and conclusions of economic evidence*

This is the first economic evaluation focused on assessing the cost-effectiveness of atezolizumab in combination with nab-paclitaxel for the first-line treatment of patients with PD-L1 positive, locally advanced or metastatic TNBC.

The appraisal of this new technology is expected to meet the definitions laid out for meeting "End of Life criteria", which has been validated by trial, observational data and modelling sources.

The economic evaluation uses data from the IMpassion130 trial: A phase III open label RCT conducted in 246 centres in 41 countries, including the UK. The baseline characteristics of patients within the IMpassion130 trial have been validated by clinical experts and can be considered broadly representative of the UK population. The UK-NHS perspective has been taken throughout, with all costs from published UK sources.

Within clinical practice in the UK, there is no clear standard of care. However, in general, it is widely accepted that paclitaxel is the taxane of choice for treating this therapy area.

Docetaxel is associated with a greater toxicity profile, and is more limited in usage due to the rates of re-challenge from the early BC setting. As such, the primary comparator in this appraisal is paclitaxel. Docetaxel is presented to meet the decision problem, however should be considered secondary to paclitaxel. Due to lack of available evidence, no comparative effectiveness or cost effectiveness could be conducted versus anthracyclines.

Atezolizumab in combination with nab-paclitaxel generated 2.43 life-years, an increase of 1.05 as compared with paclitaxel (0.97 as compared with docetaxel).

Atezolizumab in combination with nab-paclitaxel provided an incremental gain of [redacted] QALYs compared to paclitaxel ([redacted] versus docetaxel). The utility differential is derived across both the PFS and PD health states, demonstrating atezolizumab in combination with nab-paclitaxel both lengthens, and improves the quality of life for patients living with such a devastating diagnosis.

The base-case ICER of atezolizumab in combination with nab-paclitaxel using the atezolizumab PAS price is £51,145 as compared to paclitaxel (£63,859 as compared to docetaxel). However, nab-paclitaxel is also subject to a PAS, which cannot be incorporated here, thus results should be interpreted with caution.

Extensive sensitivity and scenario analyses were conducted to test how robust the model results were to change in parameter values, and to consider alternative approaches or sources related to the estimation of QALYs, costs, and clinical inputs.

The model was particularly sensitive to assumptions of assumed nab-paclitaxel price. When applying the atezolizumab PAS, the ICER versus paclitaxel falls below the £50,000 threshold for End of Life medicines when a marginal discount of 10% is applied to nab-paclitaxel.

The key strengths associated with the cost-effectiveness analysis include:

- Relatively complete IMpassion130 trial data: PFS and TTOT are considered mature, with the second interim OS analysis also providing 80% OS events, allowing for an accurate capture (as much as possible) of clinical parameters within the submission.

- Systematic and robust approach taken to extrapolation of clinical parameters beyond available data to ensure approach taken is optimal reflection of OS, PFS and TTOT in the future.

- EQ-5D-5L utility values were derived from IMpassion130 data, and mapped to EQ-5D-3L using NICE-accepted methods, and the UK tariff.

- Resource utilisation and unit costs used in the analysis are reflective of UK clinical practice (NHS and PSS perspective) and were mostly derived from previous NICE appraisals

- Extensive sensitivity and scenario analyses were conducted to inform the uncertainty around key limitations, which helped understand which variables could potentially have a major impact on the cost-effectiveness results.

However, there are remaining limitations, including:

- There was no direct randomised controlled trial evidence for estimation of relative effects of atezolizumab in combination with nab-paclitaxel vs. each of the final scope comparators – necessitating indirect comparisons. Due to unconnected networks to paclitaxel and nab-paclitaxel, matching adjusted indirect comparisons were required. MAIC methodology is subject to its own limitations, which as a result are also reflected within the economic model once implemented. For more information, see section B.2.9.3.

- The indirect comparisons require updating with a second recent data cut from IMpassion130 trial (interim analysis of OS cut). These will be updated during the clarification questions process.

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## B.5 Appendices

Appendices are provided in a separate document (file name:

Appendices_ID1522_atezolizumab 1L mTNBC_29032019).



# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Single technology appraisal

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

## Company Responses to Clarification Questions

## May 2019

| File name | Version | Contains confidential information | Date |
|---|---|---|---|
| Company Responses to Clarification questions ID1522 [CIC] | V1 | Yes | 8 May 2019 |

# Section A: Clarification on effectiveness data

## *Impassion130 trial*

**A1.** Priority request: Please provide the following data for patients with PD-L1 ≥1% disease enrolled in the IMpassion130 trial:

a. Time between initial diagnosis of BC (mean, median and range) and Impassion130 trial randomisation

Table 1 provides the time between initial diagnosis of breast cancer (BC) (mean, median and range) and Impassion130 trial randomisation, for patients with programmed death-ligand 1 (PD-L1) ≥1% disease.

**Table 1: Time since initial diagnosis to randomisation (years) in PD-L1 positive population**

| | Atezolizumab + nab-paclitaxel (n=185) | Placebo + nab-paclitaxel (n=184) | Total (n=369) |
|---|---|---|---|
| n | 185 | 184 | 369 |
| Mean (SD) | 2.53 (2.86) | 2.53 (3.11) | 2.53 (2.98) |
| Median | 1.86 | 1.89 | 1.87 |
| Min–Max (range) | 0.0–16.1 | 0.0–23.0 | 0.0–23.0 |

b. Number of patients who, at initial diagnosis, presented with locally advanced or metastatic TNBC

Table 2 provides the initial diagnosis staging within the PD-L1 positive population (n=369) (Clinical Study Report Page 1479).

**Table 2: Initial diagnosis staging in the PD-L1 positive population**

| | Placebo + nab-paclitaxel (N=184) | Atezolizumab + nab-paclitaxel (N=185) | Total (N=369) |
|---|---|---|---|
| **n** | 182 | 183 | 365 |
| **STAGE 0** | 1 (0.5%) | 0 | 1 (0.3%) |
| **STAGE I** | 21 (11.5%) | 27 (14.8%) | 48 (13.2%) |

| | Placebo + nab-paclitaxel (N=184) | Atezolizumab + nab-paclitaxel (N=185) | Total (N=369) |
|---|---|---|---|
| **STAGE IIA** | 39 (21.4%) | 47 (25.7%) | 86 (23.6%) |
| **STAGE IIB** | 28 (15.4%) | 20 (10.9%) | 48 (13.2%) |
| **STAGE IIIA** | 26 (14.3%) | 25 (13.7%) | 51 (14.0%) |
| **STAGE IIIB** | 12 (6.6%) | 12 (6.6%) | 24 (6.6%) |
| **STAGE IIIC** | 13 (7.1%) | 16 (8.7%) | 29 (7.9%) |
| **STAGE IV** | 42 (23.1%) | 36 (19.7%) | 78 (21.4%) |

Furthermore, Table 3 provides additional information, on baseline disease characteristics in the PD-L1 positive population

**Table 3: Baseline disease characteristics in the PD-L1 positive population – split between locally advanced unresectable vs metastatic disease**

| | Placebo + nab-paclitaxel (N=184) | Atezolizumab + nab-paclitaxel (N=185) | Total (N=369) |
|---|---|---|---|
| **n** | 183 | 185 | 368 |
| **Locally advanced unresectable disease** | 24 (31.1%) | 23 (12.4%) | 47 (12.8%) |
| **Metastatic disease** | 159 (86.9%) | 162 (87.6%) | 321 (87.2%) |

c. Number of randomised UK patients

[redacted]

d. Number of patients with a positive BRCA test result

Forty-five patients had a BRCA 1/2 mutation in the PD-L1 IC+ population (1)

**A2. Priority request:** Please complete Table 1 and Table 2 below:

Please note: Information requested in Table 1 is provided in Table 4 and Table 5. Information requested in Table 2 is provided in Table 6 and Table 7.

One of the main criteria for inclusion in the study was: patients having no prior chemotherapy or targeted systemic therapy for inoperable locally advanced or

metastatic triple-negative breast cancer (TNBC). Thus, by definition, patients with recorded prior cancer therapy had an initial diagnosis other than metastatic TNBC.

At the time of study enrolment, the majority of patients in both treatment arms (63.0% atezolizumab + nab-paclitaxel vs 63.4% placebo + nab-paclitaxel) had received at least one prior cancer therapy. Overall, there were no notable differences between treatment arms with respect to the class and frequency of cancer therapies. The most commonly reported (≥20% patients in either arm) class of prior cancer therapies were (percentages are shown for atezolizumab + nab-paclitaxel and placebo + nab-paclitaxel, respectively): alkylating agents (56.1% in each arm), cytotoxic antibiotics (53.9% vs 53.7%), taxanes (51.2% vs 51.0%) and antimetabolites (20.0% vs 19.3%) (Clinical Study Report Page 96).

Table 4 and Table 5 (referring to Table 1 requested in the ERG Clarification question) are provided below.

Please note, the categories between Table 4 and Table 5 do differ, as per the following example: “Taxane only” (Table 4) represents patients that only received a taxane therapy; whereas “Taxanes” (Table 5) can include patients who received only a taxane *or* a taxane combined with another therapy(s).

**Table 4: Therapy prior to enrolment in the IMpassion130 trial (ITT population, excluding patients whose initial diagnosis was mTNBC)**

| | Number | Percentage |
|---|---|---|
| **Anthracycline only** | 92 | 10.1% |
| **Taxane only** | 68 | 7.5% |
| **Anthracycline and taxane** | 387 | 42.9% |
| **Other 1** | *See* Table 5 *below* | |
| **Other 2** | | |
| **etc** | | |

**Table 5: Prior cancer therapy, ITT population (Clinical Study Report Page 1514-1517)**

| | Total number of patients with at least one treatment | | |
|---|---|---|---|
| Treatment | Atezolizumab nab-paclitaxel (N=451) | Placebo nab-paclitaxel (N=451) | Total (N=902) |
| Total | 284 (63.0%) | 286 (63.4%) | 570 (63.2%) |
| ALKYLATING AGENTS | 253 (56.1%) | 253 (56.1%) | 506 (56.1%) |
| CYTOTOXIC ANTIBIOTICS | 243 (53.9%) | 242 (53.7%) | 485 (53.8%) |
| TAXANES | 231 (51.2%) | 230 (51.0%) | 461 (51.1%) |
| ANTIMETABOLITES | 90 (20.0%) | 87 (19.3%) | 177 (19.6%) |
| PLATINUM COMPOUNDS | 34 ( 7.5%) | 39 ( 8.6%) | 73 ( 8.1%) |
| AROMATASE INHIBITORS | 24 ( 5.3%) | 28 ( 6.2%) | 52 ( 5.8%) |
| ANTIESTROGENS | 16 ( 3.5%) | 26 ( 5.8%) | 42 ( 4.7%) |
| MONOCLONAL ANTIBODIES | 8 ( 1.8%) | 12 ( 2.7%) | 20 ( 2.2%) |
| ANTINEOPLASTIC AGENTS NEC | 4 ( 0.9%) | 2 ( 0.4%) | 6 ( 0.7%) |
| ANGIOGENESIS INHIBITORS | 1 ( 0.2%) | 4 ( 0.9%) | 5 ( 0.6%) |
| PITUITARY AND HYPOTHALAMIC HORMONES | 4 ( 0.9%) | 0 | 4 ( 0.4%) |
| PHARMACOTHERAPEUTIC CLASS(ES) NOT KNOWN | 2 ( 0.4%) | 1 ( 0.2%) | 3 ( 0.3%) |
| VINCA ALKALOIDS | 2 ( 0.4%) | 1 ( 0.2%) | 3 ( 0.3%) |
| GONADOTROPIN AND ANALOGUES | 0 | 2 ( 0.4%) | 2 ( 0.2%) |
| STEROIDS | 0 | 2 ( 0.4%) | 2 ( 0.2%) |
| TOPOISOMERASE INHIBITORS | 0 | 2 ( 0.4%) | 2 ( 0.2%) |
| ANTIANDROGENS | 0 | 1 ( 0.2%) | 1 ( 0.1%) |

| | Total number of patients with at least one treatment | | |
|---|---|---|---|
| **Treatment** | **Atezolizumab nab-paclitaxel (N=451)** | **Placebo nab-paclitaxel (N=451)** | **Total (N=902)** |
| BIGUANIDES | 1 ( 0.2%) | 0 | 1 ( 0.1%) |
| BONE MODULATING AGENTS | 1 ( 0.2%) | 0 | 1 ( 0.1%) |
| COLONY STIMULATING FACTORS | 0 | 1 ( 0.2%) | 1 ( 0.1%) |

Table 6 and Table 7 (referring to Table 2 requested in the ERG Clarification question) are provided below.

**Table 6: Therapy prior to enrolment in the IMpassion130 trial (patients with PD-L1 ≥1% disease, excluding patients whose initial diagnosis was mTNBC)**

| | Number | Percentage |
|---|---|---|
| Anthracycline only | 46 | 12.5% |
| Taxane only | 26 | 7.0% |
| Anthracycline and taxane | 162 | 43.9% |
| Other 1 | *See* Table 7 *below* | |
| Other 2 | | |
| etc. | | |

**Table 7: Prior cancer therapy, PD-L1 positive population**

| | Total number of patients with at least one treatment | | |
|---|---|---|---|
| **Treatment** | **Atezolizumab nab-paclitaxel (N=185)** | **Placebo nab-paclitaxel (N=184)** | **Total (N=369)** |
| Total | 125 (67.6%) | 117 (63.6%) | 242 (65.6%) |
| ALKYLATING AGENTS | 115 (62.2%) | 105 (57.1%) | 220 (59.6%) |
| CYTOTOXIC ANTIBIOTICS | 109 (58.9%) | 101 (54.9%) | 210 (56.9%) |
| TAXANES | 96 (51.9%) | 94 (51.1%) | 190 (51.5%) |
| ANTIMETABOLITES | 42 (22.7%) | 35 (19.0%) | 77 (20.9%) |

| | Total number of patients with at least one treatment | | |
|---|---|---|---|
| **Treatment** | **Atezolizumab nab-paclitaxel (N=185)** | **Placebo nab-paclitaxel (N=184)** | **Total (N=369)** |
| PLATINUM COMPOUNDS | 8 (4.3%) | 14 (7.6%) | 22 (6.0%) |
| AROMATASE INHIBITORS | 11 (5.9%) | 5 (2.7%) | 16 (4.3%) |
| ANTIESTROGENS | 5 (2.7%) | 5 (2.7%) | 10 (2.7%) |
| MONOCLONAL ANTIBODIES | 3 (1.6%) | 3 (1.6%) | 6 (1.6%) |
| ANTINEOPLASTIC AGENTS NEC | 2 (1.1%) | 0 | 2 (0.5%) |
| ANGIOGENESIS INHIBITORS | 0 | 2 (1.1%) | 2 (0.5%) |
| PITUITARY AND HYPOTHALAMIC HORMONES | 3 (1.6%) | 0 | 3 (0.8%) |
| PHARMACOTHERAPEUTIC CLASS(ES) NOT KNOWN | 2 (1.1%) | 0 | 2 (0.5%) |
| STEROIDS | 0 | 2 (1.1%) | 2 (0.5%) |

**A3.** When the protocol of the IMpassion130 trial was amended to add OS as a co-primary endpoint, the trial sample size was increased. Please provide details of the calculations undertaken to determine this revised sample size.

The timing of the two interim analyses and the final analysis for overall survival (OS) are dependent on the results of the definitive analysis of the co-primary endpoint progression-free survival (PFS) as well as the secondary endpoint objective response rate (ORR) as described in Appendix 1 (Figure 16), where the pre-specified boundaries for the different scenarios are also presented.

The final analysis will take place around 56 months after first patient in (FPI), when the approximate pre-planned number of deaths will have been observed, based on the following assumptions:

- Two-sided, stratified log-rank test at the 0.05 significance level (two-sided) in the intention-to-treat (ITT) population

- Approximately 88% power for OS in ITT population
- Median OS of 16 months in the placebo + nab-paclitaxel arm and 20.5 months in the atezolizumab + nab-paclitaxel arm (corresponding to a hazard ratio [HR] of 0.78) in the ITT population
- Assumption of proportionality
- 5% annual loss to follow-up for OS
- two interim analyses, at approximately 50% and 80% of the information fraction

Accrual is projected to occur over 26 months. On the basis of these assumptions, the required number of OS events in the ITT population is projected to occur in Month 56 (α = 0.05; Month 62 if α = 0.04).

If the null hypothesis of no difference of OS in the ITT population can be rejected, OS in the PD-L1–selected subgroup will be tested with the same α as OS in the ITT population.

Again assuming a PD-L1–selected rate of 40% and assuming a median OS of 16 months in the placebo + nab-paclitaxel arm and 22.5 months in the atezolizumab + nab-paclitaxel arm (corresponding to a HR of 0.71) in the PD-L1–selected subgroup, it is predicted that there will be about 251 (α = 0.05; 268 if α =0.04) OS events in this subgroup. This corresponds to a power of about 76%.

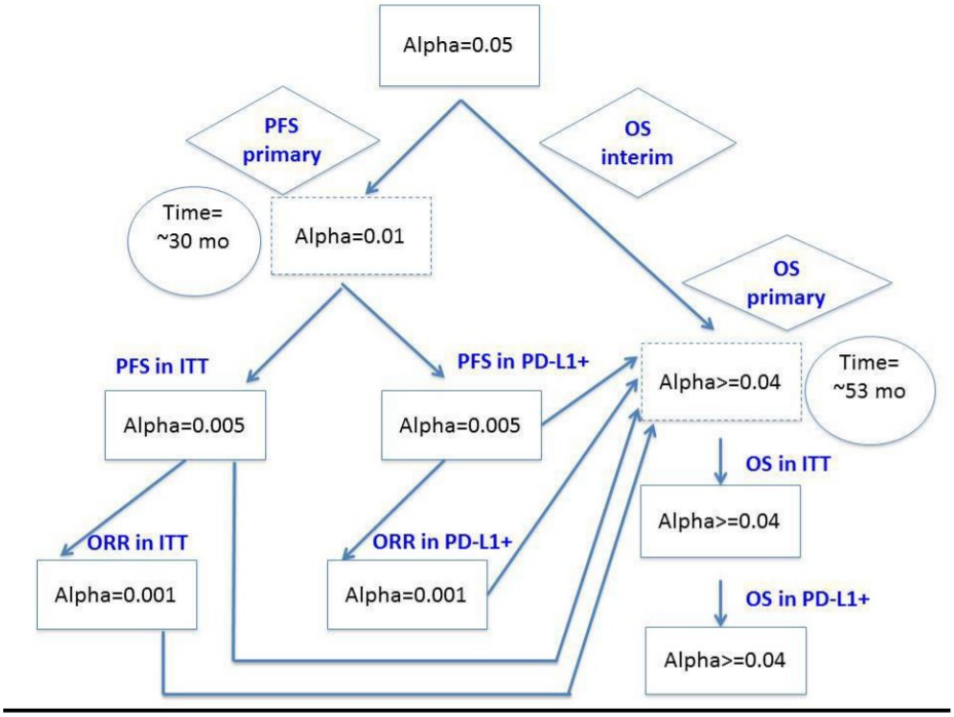
**A4.** In the Statistical Analysis Plan and the protocol of the Impassion130 trial, it is stated that OS would be tested with a significance level of between 0.04 and 0.05, depending on the PFS and OS results at the time of the definitive PFS analysis. Please clarify if the correct significance level for OS is provided in the CS (Table 6).

The Type I error (α) for this study was 0.05 (two-sided). Type I error was controlled for the following efficacy endpoints (Clinical Study Report Page 63-64):

- Co-primary efficacy endpoint of INV-PFS by RECIST v1.1 in ITT and PD-L1–positive subgroups.
- Co-primary efficacy endpoint of OS (ITT and PD-L1–positive subgroups)
- Secondary efficacy endpoint: Investigator-assessed ORR by RECIST v1.1 (measurable disease population)

Type I error was controlled by comparing these endpoints between treatment arms according to the following testing procedure (Figure 1)

**Figure 1: Overview of Type I error control**




At the time of the analysis of PFS, the co-primary endpoints of PFS and OS and the secondary endpoint of ORR were tested in the ITT population and in the PD-L1–positive subpopulation, as follows:

1. $\alpha$ (0.05) was allocated between PFS (0.01) and OS (0.04). The allocated Type I error for PFS was further allocated to PFS in the ITT (0.005) and PFS in the PD-L1–positive subgroup (0.005).

**Testing of PFS and ORR**

2. The null hypothesis of no difference in PFS between the two arms was tested using the stratified log-rank test in the ITT population and the PD-L1–positive subgroup with the allocated Type I error.
3. If one or both of the null hypotheses from the step above was rejected, ORR was compared between the two arms in the corresponding populations (one or both)

using the stratified Cochran–Mantel–Haenszel test using a Type I error of 0.001 for each, correspondingly.

**Testing of OS**

4. At the time of the analysis of PFS, an interim analysis of OS in the ITT (OS [ITT]) was performed. The interim analysis of OS (ITT) was performed regardless of the results of the analyses of PFS and ORR. The interim analysis boundary for statistical significance was determined based on the Lan–DeMets implementation of the O'Brien–Fleming use function according to the Type I error allocated to the comparison of OS (ITT). Allocation of the Type I error to the comparison of OS (ITT) depended on the outcome of the testing of PFS and ORR outlined in the Steps 1–3 above. Details for the different Type I error allocations to the OS (ITT) testing are provided in Table 3 (See Appendix A).
5. If hypothesis of no difference in OS in the ITT population was rejected, OS in the PD-L1–positive subgroup was compared by recycling the Type I error used for OS (ITT) testing.

PFS was significant in the ITT and PD-L1 positive population. ORR was not significant, neither in the ITT nor in the PD-L1 positive population. This means that 0.8% alpha could be reused for OS leading to an alpha of 4.8% for the final OS analysis.

**A5.** On page 37 of the CS, it is stated that, "the timing for the first clinical cut-off was chosen based on both the expected number of required events for the definitive PFS analysis and the first interim analysis of OS." However, only the required number of events for the PFS analysis (n=600) is provided.

a) Was there a pre-specified number of OS events that had to occur before the first clinical cut-off date?

The timing of the two interim analyses and the final analysis for OS were dependent on the results of the definitive analysis of the co-primary PFS endpoint as well as the secondary ORR endpoint, as described in Appendix 1 (Figure 16), where the pre-specified boundaries for the different scenarios are also presented.

There were a pre-specified number of OS events that had to occur before the first clinical cut-off date: 352 OS events were required. This was the maximum number of all the six possible scenarios.

b) What was the pre-specified number of OS events that had to occur before the second OS interim analysis could take place?

Based on the results of the primary PFS (and ORR) analysis the required number of OS events for the second OS interim analysis was 530 events.

c) What is the pre-specified number of OS events that must occur before the final OS analysis is performed?

Based on the results of the primary PFS (and ORR) analysis the required number of OS events for the final OS analysis is 662 events.

**A6.** In the IMpassion130 trial CSR (p98), it is stated that [redacted] This boundary does not appear to match the pre-specified boundary presented in the trial protocol (Appendix 9, pp145-146). Please clarify why the boundary [redacted] was used rather than the pre-specified boundary presented in the protocol.

The Independent Data Monitoring Committee (IDMC) meeting for efficacy was planned 3 months in advance, according to when 352 events should have happened. The cleaning of the data started thereafter. In the end, 389 OS events had occurred and the limits for the alpha spending were recalculated.

**A7.** In the CS (p62) it is stated that the proportional hazards (PH) assumption was assessed for both PFS and OS data from the IMpassion130 trial. Please clarify:

a) For OS, was the assessment carried out using data from the first or second interim analysis?

In the CS, for OS, the assessment has been carried out using data from *both* the first interim analysis (referred to as “primary analysis” in the Company submission (CS)) and the second interim analysis (second interim OS analysis, latest cut), as described in the CS (Section D.1.1.13., Pages 83 to 87).

b) For both PFS and OS, was the assessment carried out using data from the ITT or the PD-L1 +ve population?

For both PFS and OS, the assessment was carried out using data from the PD-L1 positive population only, as provided in the CS (Section D.1.1.13., Pages 83 to 87).

### *Network meta-analysis*

**A8.** MAIC methods can be used to "map" treatment effects observed in one population onto treatment effects that would be observed in another population. Please provide further information to explain why the real-world population was considered to be "too distinct from the IMpassion130 patient population" (CS, p52) for a MAIC of A+NabPx versus anthracyclines to be performed.

The systematic review of the clinical literature conducted for the CS (Document B Page 51) did not identify any randomised controlled trial data for patients treated with anthracyclines, for first line metastatic TNBC.

Consequently, as described in the CS (p52 of Document B and Appendix P), the potential use of observational data from patients treated with anthracyclines was explored to assess the feasibility of providing a comparison of atezolizumab and nab-paclitaxel versus anthracyclines. This was specifically an exploration of data previously collected within a single real-world database within the USA, which began with an assessment of the degree of homogeneity between the patient populations of the anthracycline treated patients from this database, and the patient population of the IMPassion130 trial.

Within this database, a cohort of metastatic TNBC (mTNBC) patients treated with anthracycline treatments (N=94) were identified. It was concluded that a comparison of atezolizumab and nab-paclitaxel versus anthracyclines (via a matching-adjusted indirect comparison [MAIC] or any other methods) would be inappropriate to conduct for the following reasons.

**Substantial differences exist between the patient baseline characteristics of anthracyclines treated patients in this database (N=94) and the IMpassion130 trial**

NICE Technical Support Document 18 recommends that prior to conduct of a MAIC "sufficient covariate overlap between the populations should be assessed".(2). In this assessment, Roche considered the covariate overlap to be insufficient as the baseline characteristics of patients using anthracyclines as first-line therapy in the real-world database differed from the PD-L1 positive patients in the IMpassion130 study to a degree that it was deemed infeasible to robustly and sufficiently adjust covariates in a multivariate analysis.

As provided in the CS (Appendix P), the IMpassion130 trial only included patients with a treatment-free interval of ≥12 months, compared with the anthracyclines cohort which included patients with ≤12 months (21%) or ≥12 months (79%). It is described in NICE Technical Support Document 18 that matching should only be conducted for a well *specified target population*. (Page 22, 23, 65)(2) In this circumstance, given the inclusion criteria of IMPassion130, this population is specifically the treatment-free interval ≥12 months cohort. As such, if a MAIC was to have been conducted, it would have been necessary to exclude the 20 (21%) patients with a treatment free interval of ≤12 months, to improve the cohort's homogeneity with the IMPassion130 trial population. This would have resulted in a very small starting sample size of 74 or fewer anthracyclines treated patients.

Furthermore, of patients treated with anthracyclines in the real-world database, a substantially greater proportion of patients had de novo (70%) vs recurrent disease (30%). In comparison, the Impassion130 trial PD-L1 positive patients had almost the reverse proportions – de novo (36%) vs recurrent (64%) disease. To adjust such a significant difference in demographics would further limit the available sample size for the real-world dataset.

Based upon the above assessment (treatment-free interval and disease type), Roche deemed the covariate overlap and homogeneity between the real-word data and Impassion130 trial to be insufficient to enable MAIC or other types of indirect comparison using these real-world data.

In addition, the following further limitations in using these anthracyclines real-world data were identified.

1. **Low relevance of specific anthracyclines treatments used in the cohort to UK practice:** The real-world database cohort contains data on patients treated in

the USA. It was identified that the specific anthracyclines treatments/regimens used significantly differ between the USA and UK.

For patients treated with anthracyclines in the real-world data analysis (N=94), Table 8 provides the split of specific anthracyclines treatments that were administered in this US cohort.

**Table 8: Split of anthracyclines treatments used in cohort identified (N=94)**

| Anthracyclines 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%) |

Anthracycline regimens differ between the US and UK, primarily around the specific anthracycline used. While doxorubicin was by far the most commonly used anthracycline in the US real-world data set (95%), epirubicin is more commonly used in the UK. In addition, inclusion of fluorouracil is more common in the UK than the US. Hence, the anthracycline regimens that patients in the US real-world data set received, do not reflect that of standard UK clinical practice.

2. **Small number of covariates:** Very few baseline characteristics were observable in the real-world database, for covariate adjustments – only age at diagnosis, stage at diagnosis, breast cancer type, time from initial to metastatic diagnosis, race, ECOG status and site of metastases could be used as covariates.

Because the IMpassion130 population was based on well defined, a priori inclusion/exclusion criteria, it was expected to be systematically different from patients in the real-world data base in terms of both observable and unobservable patient characteristics. Hence, it was not deemed this set of candidate variables were sufficiently large enough to carry out a matching adjustment. Prognostic and predictive baseline characteristics that are also determinants of treatment in a real-world setting are particularly important in the eventual outcomes observed. Given this small number of baseline characteristics, it was expected that covariate

adjustments would be biased and that unanchored comparisons would be inconsistent.

Furthermore, NICE TSD 18 states: “An unanchored MAIC or STC effectively assumes that absolute outcomes can be predicted from the covariates; that is, it assumes that all effect modifiers and prognostic factors are accounted for. This assumption is very strong, and largely considered impossible to meet. Failure of this assumption leads to an unknown amount of bias in the unanchored estimate”.(2) Due to the above, Roche is confident that this assumption will not be met as key covariates are missing.

3. **Missing data:** The real-world database for patients who had received anthracyclines had numerous missing values for key baseline characteristics (see Table 9). These key characteristics would be expected to be prognostic of outcomes in this treatment setting. The missing data that were most prohibitive of using these anthracyclines data for comparisons information were (Table 9): treatment history and subsequent treatments received (missing for the whole cohort), ECOG status (denoting fitness of patients, which influences treatment regimen received) missing in over half the cohort and also, missing data on the rate of progression from early TNBC to metastatic disease in the majority of the cohort (70%).

Given that these are all characteristics expected to be prognostic of outcomes and the large extent of missing data, usage of these data in comparisons had the potential to be highly biased and a multiple imputation method for these missing data was expected to lack validity.

**Table 9: Missing values of baseline characteristics available in the real-world data base for anthracyclines treated patients (N=94)**

| Variable | n (%) missing baseline characteristic information in cohort identified (N=94) |
|---|---|
| Treatment history | 94 (100%) |
| Subsequent treatments received (2L+ in metastatic setting) | 94 (100%) |
| Duration of time between progression from early TNBC to metastatic TNBC | 66 (70%) |
| ECOG status at 1L | 48 (51%) |
| Race | 5 (5%) |

| Variable | n (%) missing baseline characteristic information in cohort identified (N=94) |
|---|---|
| Stage at diagnosis | 4 (4%) |

If the alternative approach of no imputation was to have been used and only patients in the cohort with complete baseline characteristics were to be used in a comparison, either the number of matching variables or the sample size would have been further reduced which would have been prohibitive to conducting a valid covariate adjustment.

4. **Small sample size:** Even with prior adjustment to match the patient populations between the trials, the sample size of the real-world anthracyclines treated group (n=94) is not sufficiently large enough for a valid and robust MAIC or other comparison of atezolizumab and nab-paclitaxel to anthracyclines. The uncertainty around outcomes and covariates measured in a real-world setting is much larger than in a randomised controlled trial. Furthermore, while the sample sizes required for IMpassion130 were calculated *a priori* and PD-L1 status (PD-L1 positive vs PD-L1 negative) was stratified for in this trial, no sample size calculation was conducted *a priori* for collection and analysis of these real-world data on anthracyclines treated patients. Hence the generating robust analyses is much more unfavourable in the real-world dataset than the IMPassion130 trial.

**A9.** In the CS, it is stated that, “twenty-six trials, identified in the SR, were excluded from the NMA, based upon the NMA feasibility assessment.” Please provide a table detailing the reasons for excluding each of these 26 trials from the NMA.

The company submission contains an error: 27 unique trials were excluded based upon the network meta-analysis (NMA) feasibility assessment.

The 27 unique trials excluded (reported across 29 publications) are provided in Table 1, with their reasons for exclusion.

**Table 10: Reasons for exclusion of N=27 unique trials (reported in 29 publications), based upon indirect comparisons feasibility assessment**

| | First Author | Citation | Trial name (if specified) | Trial interventions | Reason for exclusion |
|---|---|---|---|---|---|
| 1 | Awada, A | Annals of oncology. 2014;25(4):824-831. | NCT00448305 | Paclitaxel, endoTAG-1, Paclitaxel + endoTAG-1 | Trial connects into the network – however, the comparator(s) are not of interest as per the SLR "PICO" criteria, hence removed from network |
| 2 | Baselga J, G. P. | Journal of clinical oncology. 2013;31(20):2586-2592. | NCT00463788 | Cisplatin, cisplatin + cetuximab | Only 70% of patients were first-line (<80%) |
| 3 | Bergh, J. | Journal of clinical oncology. 2012;30(9):921-929. | Not reported | Sunitinib + docetaxel, docetaxel | Trial connects into the network – however, the comparator(s) are not of interest as per the SLR "PICO" criteria, hence removed from network |
| 4 | Brufsky A, | Clin Breast Cancer.2011;Aug;11(4):211-220 | Not reported | Bevacizumab + paclitaxel, Bevacizumab + paclitaxel + gemcitabine | Mixed BC study; only 28% TNBC; no TNBC subgroup data |
| 5 | Carey, L. A. | Journal of clinical oncology. 2012;30(21):2615-2623. | TBCRC 001 | Carboplatin + cetuximab, cetuximab | Only 46% of patients were first-line (<80%) |
| 6 | Clemens MR, G. O. | Breast cancer research and treatment. 2015;149(1):171-179. | NCT01038804 | Docetaxel, docetaxel + YM155 | Mixed BC study; only 25% TNBC; no TNBC subgroup data |
| 7 | Dieras V, C | Annals of oncology: official journal of the European | NCT01186991 | Placebo + bevacizumab + paclitaxel, onartuzumab + | Trial connects into the network – however, the |

| | First Author | Citation | Trial name (if specified) | Trial interventions | Reason for exclusion |
|---|---|---|---|---|---|
| | | society for medical oncology. 2015;26(9):1904-1910. | | placebo + paclitaxel, onartuzumab + bevacizumab + paclitaxel | comparator(s) are not of interest as per the SLR "PICO" criteria, hence removed from network |
| 8 | Dieras V, W | Breast (Edinburgh, Scotland). 2015;24(3):182-190. | NCT00511459 | Trebananib 3mg/kg + bevacizumab + paclitaxel, trebananib 10mg/kg + bevacizumab + paclitaxel, trebananib 10mg/kg + paclitaxel | Trial connects into the network – however, the comparator(s) are not of interest as per the SLR "PICO" criteria, hence removed from network |
| 9 | Fan, Y | Annals of oncology. 2013;24(5):1219-1225. | Not reported | Docetaxel + cisplatin, docetaxel + capecitabine | Does not connect within best-case scenario network. |
| 10 | Forero-Torres, A | Clinical cancer research. 2015;21(12):2722-2729. | TBCRC 019 | nab-paclitaxel, nab-paclitaxel + tigatuzumab | Trial connects into the network – however, the comparator(s) are not of interest as per the SLR "PICO" criteria, hence removed from network |
| 11 | Gradishar, W | European journal of cancer. 2013;49(2):312-322. | NU071B | Sorafenib + paclitaxel, placebo + paclitaxel | Trial connects into the network – however, the comparator(s) are not of interest as per the SLR "PICO" criteria, hence removed from network |
| 12 | Hu, X | The Lancet. 2015;Oncology. 16(4):436-446. | CBCSG006 | Gemcitabine + paclitaxel, cisplatin + gemcitabine | Does not connect within best-case scenario network. |

| | First Author | Citation | Trial name (if specified) | Trial interventions | Reason for exclusion |
|---|---|---|---|---|---|
| 13 | Kader, Y. A. | Breast cancer: targets and therapy. 2013;5:37-42. | Not reported | Bevacizumab + carboplatin + paclitaxel, carboplatin + docetaxel | Only 32% TNBC, no TNBC subgroup data |
| 14 | Kenjaeva, A. O. | Annals of oncology. 2015;3):iii7. | Not reported | Vinorelbine + cisplatin, vinorelbine + cisplatin + bevacizumab | Does not connect within best-case scenario network. |
| 15 | Luck HJ, L. K. | Breast cancer research and treatment. 2015;149(1):141-149. | TABEA | Paclitaxel/docetaxel + bevacizumab + capecitabine, paclitaxel/docetaxel + bevacizumab | Does not connect within best-case scenario network. |
| 16 | Mackey JR, R.-V. M. | Journal of clinical oncology. 2015;33(2):141-148. | Not reported | Docetaxel + ramucirumab, docetaxel + placebo | Mixed BC study; only 24% TNBC; no TNBC subgroup data |
| 17 | Martin, M. | Annals of oncology. 2017;28(2):313-320. | BELLE-4 | Paclitaxel + placebo, Paclitaxel + buparlisib | Mixed BC study; only 35.3% TNBC; no TNBC subgroup data |
| 18 | Martin, M. | Lancet oncology. 2011;12(4):369-76. | NCT00356681 | Bevacizumab, motesanib, placebo | Does not connect within best-case scenario network. |
| 19 | O'Shaughnessy, J | Journal of clinical oncology. 2014;32(34):3840-3847. | NCT00938652 | Gemcitabine + carboplatin, gemcitabine + carboplatin + iniparib | Same trial as O'Shaughnessy, J. 2011, below:<br>Does not connect within best-case scenario network. |

| | First Author | Citation | Trial name (if specified) | Trial interventions | Reason for exclusion |
|---|---|---|---|---|---|
| 20 | O'Shaughnessy, J. | New England journal of medicine. 2011;364(3):205-214. | NCT00938652 | Gemcitabine + carboplatin, gemcitabine + carboplatin + iniparib | Does not connect within best-case scenario network. |
| 21 | Park, I. H. | Cancer research and treatment. 2017;49(3):569-577. | NCT00876486 | Paclitaxel (polymeric micelle-formulated), paclitaxel (cremophor EL-based) | Does not connect within best-case scenario network. |
| 22 | Robert NJ, | Clin Breast Cancer.2011;Apr;11(2):82-92 | SUN 1094 | Sunitinib + paclitaxel, bevacizumab + paclitaxel | Mixed BC study; only 21% TNBC; no TNBC subgroup data |
| 23 | Rugo HS, | Breast Cancer Res Treat.2013;;139:411–9. | CA163-115 | Ixabepilone (Q3W) + bevacizumab, ixabepilone (QW) + bevacizumab, bevacizumab + paclitaxel | Mixed BC study; only 18% TNBC; no TNBC subgroup data |
| 24 | Schmid | J Clin Oncol.2018;Suppl; abstract 1007 | PAKT | AZD5363 + paclitaxel, paclitaxel | Trial connects into the network – however, the comparator(s) are not of interest as per the SLR “PICO” criteria, hence removed from network |
| 25 | Takashima T, M. H. | The Lancet. 2016;Oncology. 17(1):90-98. | SELECT BC | Docetaxel or paclitaxel, S-1 | Mixed BC study; only 20% TNBC; no TNBC subgroup data |
| 26 | Tredan O, C | Clinical breast cancer. 2015;15(1):8-15. | NCT00633464 | Ixabepilone, ixabepilone + cetuximab | Does not connect within best-case scenario network. |
| 27 | Yardley, D. A. | Annals of oncology. | tnAcity | nab-paclitaxel + | Does not connect within |

| | First Author | Citation | Trial name (if specified) | Trial interventions | Reason for exclusion |
|---|---|---|---|---|---|
| | | 2018;06:06. | | carboplatin, nab-paclitaxel + gemcitabine, gemcitabine + carboplatin | best-case scenario network. |
| 28 | Yardley, D. A. | Breast cancer research and treatment. 2015;154(1):89-97. | NCT00915603 | Bevacizumab + paclitaxel + placebo, bevacizumab + paclitaxel + everolimus | Mixed BC study; only 21% TNBC; no TNBC subgroup data |
| 29 | Zhang, J. | Annals of oncology. 2018;14:14. | CBCSG006 | Gemcitabine + paclitaxel, cisplatin + gemcitabine | Same trial as Hu, X 2015 above:<br>Does not connect within best-case scenario network. |

**Key:** BC, breast cancer; SLR, systematic literature review; TNBC, triple-negative breast cancer.

**A10.** A list of 13 studies that reported OS or PFS data that could be used to carry out indirect comparisons and that were included in the "final network" is provided in the CS (Table 12). This list includes the JapicCTI-090921 trial, the CARIN trial, and the EGF3001 trial; however, none of these three trials are included in the network (CS, Figure 9 and Figure 10). Please explain why these trials were not included in the network diagrams.

Table 12 (in CS, Document B) includes an error: the JapicCTI-090921 trial, the CARIN trial, and the EGF3001 trial were excluded from the final network, thus should not have been included Table 12.

While the publications included hazard ratios in the triple-negative breast cancer subgroup, there was insufficient information to re-create individual-level survival times for the triple-negative cases for use in the ITC.

The reasons for exclusion of these three trials are as follows:

- **JapicCTI-090921:** In the JapicCTI-090921 study, no OS or PFS Kaplan–Meier curves for triple-negative cases were published. Roche contacted "Taiho Pharma" and requested access to these Kaplan–Meier data, but they were unable to share these data. Furthermore, this was a small Phase II trial.
- **CARIN:** Although individual-level data from the CARIN study was provided by the external study group, it was not possible to replicate the publication of this trial, nor the clinical study report using these provided data. We thus could not include the data in a NMA using parametric survival models. Furthermore, this trial included treatment regimens that are not of interest to the decision problem (capecitabine and bevacizumab with vinorelbine versus capecitabine and bevacizumab without vinorelbine)
- **EGF30001:** The Kaplan–Meier PFS curves for triple-negative cases in the publication of the EGF30001 study results did not include the numbers at risk, which made the re-creation of individual-level event times from Kaplan–Meier data infeasible. No OS hazard ratio or Kaplan–Meier curves for triple-negative cases were published. Furthermore, this trial's only treatment arm of interest is paclitaxel

monotherapy and the other arm (paclitaxel with lapatinib) did not connect in the network.

Table 11 provides a summary of this assessment, highlighting that two of the three trials (CARIN and EGF30001) had no accessible or published OS data.

**Table 11: Inclusion of studies in the final networks**

| Study | PFS | | OS | | Comment |
|---|---|---|---|---|---|
| | HR | IPD | HR | IPD | |
| CARIN | P | × | × | × | • The PFS hazard ratio for triple-negative cases was obtained from the publication.<br>• Although individual-level data was transferred to Roche, the published PFS results could not be replicated, and the study was not used in any analyses using individual-level data.<br>• No OS hazard ratio for triple-negative cases was published. |
| EGF30001 | P | × | × | × | • The PFS hazard ratio for triple-negative cases was obtained from the publication.<br>• The Kaplan–Meier PFS curves for triple-negative cases did not include the numbers at risk, which made the re-creation of individual-level event times from Kaplan–Meier data infeasible.<br>• No OS hazard ratio or Kaplan–Meier curves for triple-negative cases were published. |

| Study | PFS | | OS | | Comment |
|---|---|---|---|---|---|
| | HR | IPD | HR | IPD | |
| JapicCTI-090921 | P | × | P | × | • The PFS hazard ratio for triple-negative cases was obtained from the publications.<br>• The OS hazard ratio for triple-negative cases was obtained from the publications. The confidence limits were not reported but were calculated using the reported p-values.<br>• No OS or PFS Kaplan–Meier curves for triple-negative cases were published. |
| **Abbreviations**: PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratio; IPD: Individual patient data. P: Data was obtained from the publication; R: Data was obtained from the Roche data base; E: Data was re-estimated using individual-level event times. | | | | | |

**A11.** In the appendices to the CS (p62), it is stated that, "a matching adjustment was performed to create an artificial atezolizumab with nab-paclitaxel arm in a comparison study."

a) When performing a MAIC, it is not necessary to have IPD data for the comparison study. Please clarify why data from the TNT, COLET, EGF3001, LOTUS, and JapicCTI-090921 trials were not used in the MAIC.

As described in the response to question A10, EGF3001 and JapicCTI-090921 were excluded from the final network due to insufficient data. Hence, the response below addresses why the TNT, COLET and LOTUS were not used in the base case indirect comparisons.

In the base case scenario, the E2100, MERIDIAN and AVADO studies were selected because they investigated paclitaxel and docetaxel and were available as individual

level data in the Roche database. However, it should be noted, TNT was utilised as a matching study in a scenario analysis only in the CS (Appendices Section D.1.1.10 Page 65, D.1.1.15 Pages 89 to 91).

Matching using individual-level data is substantially more robust than matching using summary statistics from a study publication because more covariates can be used and the full distributions and correlations of covariates in both studies are considered in the estimation of weights. The sample sizes of the COLET and LOTUS trials were very low. In the updated indirect comparisons using Impassion130 data from the second interim analysis (January 2019 cut) COLET and LOTUS were excluded from the network because they would only contribute to generation of evidence on the relative efficacy of unapproved therapies to paclitaxel. A scenario analysis excluding COLET and LOTUS in the NMA using Impassion130 data from the first interim analysis demonstrated that these two trials did not affect the estimates for the other treatments in the network. The results of this scenario analysis were provided in the CS (Section D.1.1.15 Page 91 and Page 93). Furthermore, the exclusion of COLET and LOTUS improved model convergence significantly.

b) As the company only included trials for which IPD were available in the network, it would have been possible to estimate treatment effect in the population of the IMpassion130 trial, rather than in the comparator trial populations. Please explain why the approach of estimating treatment effects in the comparator trial populations was taken.

The quality of a matching adjustment is considered superior when the larger group is matched to the smaller group because the pool of potential matches is larger. The number of PD-L1-positive triple-negative breast cancer cases in the atezolizumab + nab-paclitaxel arm was 185, which is much larger than the AVADO and MERIDIAN trials, for which individual-level data was available (Table 12). Given the low patient numbers available for some of the trials, estimating treatment effect in the population of the IMpassion130 trial, rather than in the comparator trial populations would be likely to lead to sample sizes too small to produce a stable estimate. Hence, the approach of

estimating treatment effects in the comparator trial populations was taken in the CS because it was expected to generate more valid and robust MAIC results.

**Table 12: Number of triple-negative cases in comparison studies for which individual-level data was available**

| Trial | Treatment arm | n |
|---|---|---|
| AVADO | Doc | 52 |
| AVADO | DocBev (15mg/kg) | 59 |
| AVADO | DocBev (7.5mg/kg) | 53 |
| COLET | Cobimetinib 60 Expansion | 47 |
| COLET | Placebo 60 Expansion | 43 |
| E2100 | PAC | 109 |
| E2100 | PAC/BV | 121 |
| IMpassion130 | Atezolizumab + nab-paclitaxel | 185 |
| IMpassion130 | Placebo + nab-paclitaxel | 184 |
| LOTUS | GDC-0068 | 62 |
| LOTUS | PLACEBO | 62 |
| MERIDIAN | PACLITAXEL + BEVACIZUMAB | 39 |
| MERIDIAN | PACLITAXEL + PLACEBO | 39 |
| RIBBON-1 | BEVACIZUMAB | 87 |
| RIBBON-1 | PLACEBO | 50 |
| TURANDOT | BevCap | 67 |
| TURANDOT | BevPac | 63 |

**A12.** There appear to be discrepancies between numbers reported in the main body of the CS and those reported in Appendix D.

a) In the CS (Table 13 and Table 14), the “effective sample size” for the paclitaxel arm of the E2100 trial is 230. The number of TNBC patients across all E2100 trial arms was 232, but it is not stated how many TNBC patients were in the

paclitaxel arm (Appendix D, Table 8). Please clarify why the effective sample size is 230.

The atezolizumab and nab-paclitaxel arm of IMpassion130 was matched to the entire triple-negative population of the comparison studies and not to single arms alone.

The objective of the matching adjustment was to create an artificial atezolizumab arm to represent the potential outcomes of patients in the comparison studies, as if they were treated with atezolizumab and nab-paclitaxel. If matching had been conducted to individual trial arms only, this would have discarded much data that improved the matching quality, by reducing uncertainty surrounding the baseline characteristics of patients in the comparison studies. The effective sample size reported for the comparison studies is the actual sample size because only patients in the atezolizumab and nab-paclitaxel arm were assigned weights to match the population to the comparison population.

The number of triple-negative cases per study arm in the E2100 trial are presented in the response to A11b (Table 12). In the E2100 trial, 230 triple-negative cases were randomised to a study treatment. The study publication (Miller et al., 2007) reported the number of eligible cases without describing the exact proportion of patients that had TNBC.(3) In the approach performed in the CS, the aim was to replicate the clinical study report for the E2100 trial, hence the effective sample size of 230 is used.

b) In the CS (Table 15 and Table 16), the “effective sample size” for the paclitaxel arm of the MERIDIAN trial is 78. Please clarify why the effective sample size is 78, when there were only 39 TNBC patients in the paclitaxel arm of the MERIDIAN trial (Appendix D, Table 8).

The number of triple-negative cases per study arm in the MERIDIAN study are presented in Table 12. The total sample size in the triple-negative subgroup of the MERIDIAN study was 78, and as described above, matching was not conducted to individual trial arms. Again, if matching was conducted to single trial arms only, this would have discarded much data that would have improved the matching quality.

c) In the CS (Table 17 and Table 18), the “effective sample size” for the docetaxel arm of the AVADO trial is 164. Please clarify why the effective sample size is 164 when there were only 43 TNBC patients in the docetaxel arm of the AVADO trial (Appendix D, Table 8).

The number of triple-negative cases per study arm in the AVADO study are presented in Table 12. The total sample size in the triple-negative subgroup of the AVADO study was 164, and as described above, matching was not conducted to individual trial arms. Again, if matching was conducted to individual trial arms only, this would have discarded much data that would have improved the matching quality.

**A13.** Please provide results of the updated MAICs that include data from the second interim OS analysis (data cut Jan 2019), for both OS and PFS. Please provide results for A+nabPx compared with paclitaxel and with docetaxel and for nabPx compared with paclitaxel and docetaxel.

The trials network informing the updated indirect comparisons analysis for OS and PFS remains the same as that in the CS (Document B, Table 12) - with the exception of the LOTUS and COLET studies, which were excluded from the updated analysis because they did not investigate currently approved or used treatments for metastatic triple-negative breast cancer, and would only contribute to generation of evidence on the relative efficacy of unapproved therapies to paclitaxel. Furthermore, the exclusion of COLET and LOTUS improved model convergence significantly. Furthermore, in response to clarification question B2, we provide two models, one containing each of a) and b) above.

## *Proportional hazards assessment*

The base case proportional hazards were re-assessed (for each of OS and PFS) using the “second interim OS analysis”. The diagnostic plots of the second interim OS analyses, for each of OS and PFS (of the PD-L1 positive population only) were examined. These are provided in Figure 2 and

Figure 3.

**Figure 2: IMpassion130 (WO29522) study second interim OS analysis (data cut Jan 2019)) – OS plot**

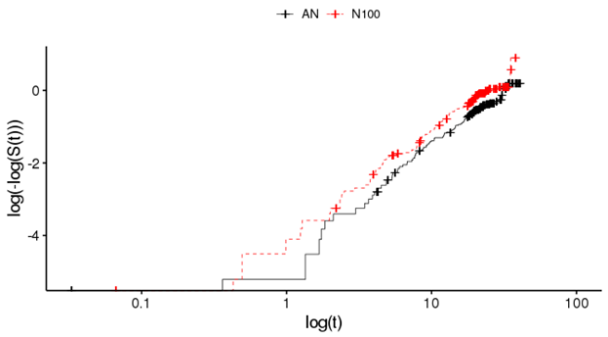
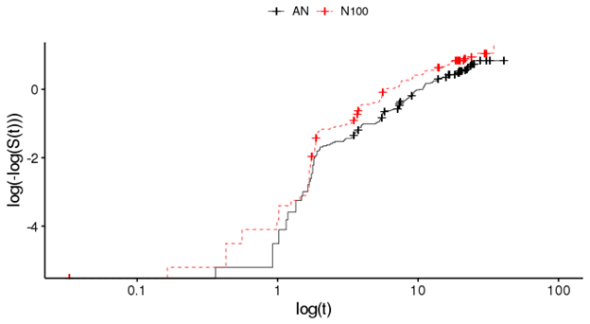



**Figure 3: IMpassion130 (WO29522) study (second interim OS analysis (Data cut Jan 2019)) – PFS plot**




As with the IMPassion130 primary analysis, the proportional hazards assumption for the IMPassion130 second interim OS analysis was marginally not met, nor was it met in multiple other studies. This indicated the need to consider more flexible methods of indirect comparisons.

## *Matching adjustments*

As conducted within the CS (Document B, Section B.2.9.1), three trials were used in the matching adjustments: E2100 and MERIDIAN (for a paclitaxel comparison) and AVADO (for docetaxel comparison).(3–9) Matching adjustments of the trials were performed

using the same methods as described in the CS (Document B, Section B.2.9.1). The same method of covariate balancing propensity score model was used for estimating the weights used in the matching of atezolizumab + nab paclitaxel patients to comparison studies.

The results of the baseline characteristics that were matched for the comparison with paclitaxel (E2100 and MERIDIAN trials) are provided in Table 13 to Table 16. The baseline characteristics that were matched for the comparison with docetaxel (AVADO trial) are provided in Table 17 and Table 18.

**Table 13: Weighted summary statistics of matching variables for matching to the E2100 (paclitaxel) trial – OS**

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

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

**Table 14: Weighted summary statistics of matching variables for matching to the E2100 (paclitaxel) trial – PFS**

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

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

**Table 15: Weighted summary statistics of matching variables for matching to the MERIDIAN trial – OS**

| | MERIDIAN | Atezolizumab + nab-paclitaxel | p | SMD |
|---|---|---|---|---|
| $n_{eff}$ (Effective sample size) | 78.00 | 95.08 | | |
| age | 54.83 (11.41) | 54.83 (13.50) | 1.000 | <0.001 |
| height | 160.88 (7.71) | 160.88 (8.49) | 1.000 | <0.001 |
| weight | 72.99 (18.04) | 72.99 (18.24) | 1.000 | <0.001 |
| BMI | 28.09 (6.11) | 28.09 (6.22) | 1.000 | <0.001 |
| regnaeu | 0.42 (0.50) | 0.42 (0.50) | 1.000 | <0.001 |

| | MERIDIAN | Atezolizumab + nab-paclitaxel | p | SMD |
|---|---|---|---|---|
| **Region: Asia** | 0.24 (0.43) | 0.24 (0.43) | 1.000 | <0.001 |
| **Race: White** | 0.56 (0.50) | 0.56 (0.50) | 1.000 | <0.001 |
| **Race: Black** | 0.14 (0.35) | 0.14 (0.35) | 1.000 | <0.001 |
| **Race: Asian** | 0.24 (0.43) | 0.24 (0.43) | 1.000 | <0.001 |
| **ECOG status 0** | 0.64 (0.48) | 0.64 (0.48) | 1.000 | <0.001 |
| **Number of disease sites** | 2.41 (1.13) | 2.41 (1.09) | 1.000 | <0.001 |
| **Sum of longest diameters 18mm** | 72.19 (57.05) | 72.19 (72.29) | 1.000 | <0.001 |
| **Bone metastases** | 0.26 (0.44) | 0.26 (0.44) | 1.000 | <0.001 |
| **Liver metastases** | 0.26 (0.44) | 0.26 (0.44) | 1.000 | <0.001 |
| **Lung metastases** | 0.47 (0.50) | 0.47 (0.50) | 1.000 | <0.001 |
| **Prior anthracycline therapy** | 0.50 (0.50) | 0.50 (0.50) | 1.000 | <0.001 |
| **Prior adjuvant taxane treatment** | 0.33 (0.47) | 0.33 (0.47) | 1.000 | <0.001 |
| **Systolic blood pressure** | 124.85 (13.52) | 124.85 (15.14) | 1.000 | <0.001 |
| **Body temperature** | 36.47 (0.40) | 36.47 (0.43) | 1.000 | <0.001 |
| **Key**: sd: Standard deviation; p: P-value from a Chi-square test; SMD: Standardised mean difference defined as the difference in means divided by the pooled standard deviation. | | | | |

**Table 16: Weighted summary statistics of matching variables for matching to the MERIDIAN trial - PFS**

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

| | MERIDIAN | Atezolizumab + nab-paclitaxel | p | SMD |
|---|---|---|---|---|
| **Race: White** | 0.56 (0.50) | 0.56 (0.50) | 1.000 | <0.001 |
| **Race: Black** | 0.14 (0.35) | 0.14 (0.35) | 1.000 | <0.001 |
| **Race: Asian** | 0.24 (0.43) | 0.24 (0.43) | 1.000 | <0.001 |
| **ECOG status 0** | 0.64 (0.48) | 0.64 (0.48) | 1.000 | <0.001 |
| **Number of disease sites** | 2.41 (1.13) | 2.41 (1.06) | 1.000 | <0.001 |
| **Sum of longest diameters 18mm** | 72.51 (52.49) | 72.51 (70.28) | 1.000 | <0.001 |
| **Time from met. diag. to rand.** | 0.27 (0.62) | 0.27 (0.29) | 1.000 | <0.001 |
| **Bone metastases** | 0.26 (0.44) | 0.26 (0.44) | 1.000 | <0.001 |
| **Liver metastases** | 0.26 (0.44) | 0.26 (0.44) | 1.000 | <0.001 |
| **Lung metastases** | 0.47 (0.50) | 0.47 (0.50) | 1.000 | <0.001 |
| **Prior anthracycline therapy** | 0.50 (0.50) | 0.50 (0.50) | 1.000 | <0.001 |
| **Prior adjuvant taxane treatment** | 0.33 (0.47) | 0.33 (0.47) | 1.000 | <0.001 |
| **Diastolic blood pressure** | 75.72 (10.51) | 75.72 (9.58) | 1.000 | <0.001 |
| **Body temperature** | 36.46 (0.40) | 36.46 (0.43) | 1.000 | <0.001 |

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

**Table 17: Weighted summary statistics of matching variables for matching to the AVADO trial – OS**

| | AVADO | Atezolizumab + nab-paclitaxel | p | SMD |
|---|---|---|---|---|
| **$n_{eff}$ (Effective sample size)** | 164.00 | 75.75 | | |
| **age** | 53.13 (11.21) | 53.13 (12.56) | 1.000 | <0.001 |
| **weight** | 67.50 (14.07) | 67.50 (13.90) | 1.000 | <0.001 |
| **Race: White** | 0.78 (0.42) | 0.78 (0.42) | 1.000 | <0.001 |
| **Race: Black** | 0.02 (0.13) | 0.02 (0.13) | 1.000 | <0.001 |

| | AVADO | Atezolizumab + nab-paclitaxel | p | SMD |
|---|---|---|---|---|
| **Race: Asian** | 0.15 (0.36) | 0.15 (0.36) | 1.000 | <0.001 |
| **ECOG status 0** | 0.59 (0.49) | 0.59 (0.49) | 1.000 | <0.001 |
| **Number of disease sites >3** | 0.51 (0.50) | 0.51 (0.50) | 1.000 | <0.001 |
| **Time from init. to met. diagnosis** | 38.36 (53.56) | 38.36 (47.96) | 1.000 | <0.001 |
| **Time from met. diag. to rand.** | 1.93 (4.16) | 1.93 (1.78) | 0.999 | <0.001 |
| **Liver metastases** | 0.30 (0.46) | 0.30 (0.46) | 1.000 | <0.001 |
| **Lung metastases** | 0.50 (0.50) | 0.50 (0.50) | 1.000 | <0.001 |
| **Prior anthracycline therapy** | 0.60 (0.49) | 0.60 (0.49) | 1.000 | <0.001 |
| **Prior adjuvant taxane treatment** | 0.24 (0.43) | 0.24 (0.43) | 1.000 | <0.001 |
| **BMI** | 26.05 (5.08) | 26.05 (4.96) | 1.000 | <0.001 |
| **Key:** sd: Standard deviation; p: P-value from a Chi-square test; SMD: Standardised mean difference defined as the difference in means divided by the pooled standard deviation. | | | | |

**Table 18: Weighted summary statistics of matching variables for matching to the AVADO trial – PFS**

| | AVADO | Atezolizumab + nab-paclitaxel | p | SMD |
|---|---|---|---|---|
| **$n_{eff}$ (Effective sample size)** | 164.00 | 69.78 | | |
| **age** | 53.13 (11.21) | 53.13 (12.66) | 1.000 | <0.001 |
| **Race: White** | 160.96 (7.93) | 160.96 (7.32) | 1.000 | <0.001 |
| **Race: Black** | 0.78 (0.42) | 0.78 (0.42) | 1.000 | <0.001 |
| **Race: Asian** | 0.02 (0.13) | 0.02 (0.13) | 1.000 | <0.001 |
| **ECOG status 0** | 0.15 (0.36) | 0.15 (0.36) | 1.000 | <0.001 |
| **Number of disease sites >3** | 0.59 (0.49) | 0.59 (0.49) | 1.000 | <0.001 |
| **Time from init. to met. diagnosis** | 0.51 (0.50) | 0.51 (0.50) | 1.000 | <0.001 |
| **Time from met. diag. to rand.** | 41.25 (58.04) | 41.25 (51.04) | 1.000 | <0.001 |

| | AVADO | Atezolizumab + nab-paclitaxel | p | SMD |
|---|---|---|---|---|
| **Liver metastases** | 1.91 (4.13) | 1.91 (1.75) | 0.999 | <0.001 |
| **Lung metastases** | 0.30 (0.46) | 0.30 (0.46) | 1.000 | <0.001 |
| **Prior anthracycline therapy** | 0.50 (0.50) | 0.50 (0.50) | 1.000 | <0.001 |
| **Prior adjuvant taxane treatment** | 0.60 (0.49) | 0.60 (0.49) | 1.000 | <0.001 |
| **Region: Asia** | 0.24 (0.43) | 0.24 (0.43) | 1.000 | <0.001 |
| **BMI** | 26.05 (5.08) | 26.05 (4.92) | 1.000 | <0.001 |
| **Key:** sd: Standard deviation; p: P-value from a Chi-square test; SMD: Standardised mean difference defined as the difference in means divided by the pooled standard deviation. | | | | |

For all comparison studies, the covariate balancing propensity score model achieved an almost perfect balance of covariate mean values at the cost of a low effective sample size.

### *Base case model selection*

Subsequently, model selection for OS and PFS was reassessed using the same approach in the CS (Document B, Section B.2.9.2). Following adjustment of the atezolizumab in combination with nab-paclitaxel arm, a set of candidate statistical models for OS and PFS were fitted. For OS and PFS, the statistical model for each outcome was selected from the set of candidate models based on evidence on the proportionality of hazard rates; the goodness of fit in a frequentist framework; the validity of extrapolations based on 12-month data; Bayesian model diagnostics; a comparison of extrapolated and observed survival curves and a comparison of the goodness of fit of fixed and random effects models. Please refer to the CS (Appendix D, Page 59) for further details of this approach.

For OS, the five best fitting models (Table 19) included three fractional polynomial models, and two piecewise exponential models, one with a cut-point of 5 months and one with cut points at 3 months with 6 months.

**Table 19: OS Akaike information criteria and Bayesian information criteria for frequentist discrete time models for overall survival, sorted by AIC**

| | Model | AIC | BIC |
|---|---|---|---|
| **A** | FP (Weibull, p1=0) | 1505.57 | 1647.17 |
| **B** | FP (2nd order, p1=0, p2=0) | 1506.32 | 1718.71 |
| **C** | FP (2nd order, p1=0, p2=1) | 1510.28 | 1722.67 |
| **D** | PWE (cutpoints at 5) | 1517.39 | 1658.98 |
| **E** | PWE (cutpoints at 3, 6) | 1517.55 | 1729.95 |

**Key:** AIC, Akaike information criteria p: Power, FP: Fractional Polynomial, PWE: piecewise exponential models.

In Table 19, the Akaike information criteria (AIC) was assessed as a first criteria, followed by the Bayesian information criterion (BIC). The differences in the AIC between the first-order fractional polynomial with power 0 (A) and the second order fractional polynomial models with powers of zero (B), and powers {0,1} (C) and between the piecewise exponential models with cut points 5 months (D) and 3, 6 months (E) were small.

In a comparison of extrapolations based on 12-month data and Kaplan–Meier curves, the two second order fractional polynomial models (B, C) demonstrated clear over- and under-predictions in the tails and high plateaus in 5-year extrapolations in the IMpassion130 study. Extrapolations from the first-order fractional polynomial model with power 0 (A) and the piecewise exponential models with cut-points at 5 months (D) and 3, 6 months (E) demonstrated a better fit of the tails compared with the other models and additionally, showed clear trends (convergence) towards zero in the IMpassion130 (WO29522) study over a 5-year horizon. Hence, based on extrapolations (based on 12-month data), the most appropriate three models were considered to be the first-order fractional polynomial model with power 0 (A) and the piecewise exponential models with cut-points 5 months (D) and 3, 6 months (E).

Subsequently, the Bayesian model diagnostic plots from a Bayesian random effects estimation were inspected for the above models. The first-order fractional polynomial

model with power 0 (A) showed slow convergence of running means and differences in total averages across chains for both study baselines means and treatment effects. The treatment effects exhibited serial correlation up to 50 iterations. By comparison, the piecewise exponential model with a cut-point at 5 months (B) showed the most stable running means of study baselines and treatment effects and converged to the same total average in all three chains.

Based upon the above assessment, the final base case model selected for OS was the piecewise exponential model with a cut points at 5 months (D).

For PFS, AIC and BIC was similarly assessed. The five best fitting models (Table 20) included four second order fractional polynomial models with powers {0, 0}, {0, 1} and {1, 1} (A, B, C), a first-order fractional polynomial model with power 0 (D) and a piecewise exponential model with cut-points at 2 and 4 months (E).

**Table 20: PFS Akaike information criteria and Bayesian information criteria for frequentist discrete time models for overall survival, sorted by AIC**

| | Model | AIC | BIC |
|---|---|---|---|
| **A** | FP (2nd order, p1=0, p2=0) | 1874.24 | 2124.19 |
| **B** | FP (2nd order, p1=0, p2=1) | 1897.85 | 2147.81 |
| **C** | FP (2nd order, p1=1, p2=1) | 1933.89 | 2183.84 |
| **D** | FP (Weibull, p1=0) | 2007.56 | 2174.2 |
| **E** | PWE (cutpoints at 2, 4) | 2009.66 | 2259.62 |

**Key:** AIC, Akaike information criteria; p: Power, FP: Fractional Polynomial, PWE: piecewise exponential models.

The difference in the AIC between the first-order fractional polynomial model with power 0 (D) and the piecewise exponential model with cut-points 2 and 4 months (E) was smaller than five, and hence the decision between these two models was informed by Bayesian model diagnostics and visual inspection of the extrapolated survival curves.

In a comparison of extrapolations based on 12-month data and Kaplan–Meier curves, the second order fractional polynomial models with powers {0, 1} (B) and {1, 1} (C) demonstrated clear overestimations of survival probabilities in the tails of some studies.

The within-study extrapolations of the second order fractional polynomial model with powers {0, 0} (A) demonstrated a good fit to the data but the extrapolations of survival probabilities for all treatments in the IMpassion130 study over a 5-year time horizon demonstrated plateaus at high levels which were interpreted as a sign of overfitting and deemed implausible in a population with metastatic breast cancer. Extrapolations from the first-order fractional polynomial model with power 0 (D) and the piecewise exponential model (E) with cut-points at 2 and 4 months fitted the data in the tails well and showed clear convergence towards zero in the IMpassion130 study over a 5-year horizon.

Based upon the extrapolations it was considered the first-order fractional polynomial model with power 0 (D) and the piecewise exponential model with cut-points 2, 4 months (E) were the best candidates for the base case model.

Subsequently, the Bayesian model diagnostic plots from a Bayesian random effects estimation were inspected for the above models. Although the plots suggested good convergence of the first-order fractional polynomial model with power 0 (D), the running means of many basic parameters were not stable towards the end of the simulation, and the averages often differed between the three chains. Furthermore, the autocorrelation plots showed significant correlation between iterations up to a time lag of 20 iterations. By comparison, the piecewise exponential model with cut-points 2, 4 months (E) demonstrated good convergence in all diagnostic plots and very little autocorrelation between stored iterations. The standard deviation of the random effects showed moderate serial correlation.

Based upon the above assessment, the final base case model selected for PFS was the piecewise exponential model with a cut points at 2 and 4 months (E).

Table 21 summarises the indirect comparisons base case selected (as utilised in the CS cost-effectiveness model submitted in response to question B2), based upon the primary analysis (previously provided in CS Appendix D) – additionally it provides a comparison to the base case selections based upon the second interim OS analysis. The model selection process led to a change of cut points for the PFS endpoint – from 4 and 7 months (in CS), to 2 and 4 months (in the present response results)(Table 21).

**Table 21: Base case model selection for indirect comparisons base case from primary analysis (CS), compared with Base case model selection based upon IMPassion130 Second interim OS analyses**

| | OS and PFS Base case model |
|---|---|
| **Primary analysis: Indirect Comparisons Base case (used in CS cost-effectiveness analysis)** | In the base case, a random effects piecewise exponential model was estimated with cutpoints at 5 months for OS, and 4 and 7 months for PFS. An informative prior normal distribution for the between-study heterogeneity in the treatment effects with mean -4.18 and variance 1.41^2 (OS) and mean -2.94 and variance 1.79^2 (PFS) was used (Turner et al.). The network included all studies from which OS/PFS data from TNBC cases was available either as digitised Kaplan–Meier curves or using individual-level data. The IMpassion130 (WO29522) study was connected to the network using matching adjustments to the E2100, MERIDIAN and AVADO studies. |
| **Second interim OS analyses: Indirect Comparisons Base case (used in cost-effectiveness analysis for ERG Clarification question B2)** | In the base case, a random effects piecewise exponential model was estimated with cutpoints at 5 months for OS, and 2 and 4 months for PFS. An informative prior normal distribution for the between-study heterogeneity in the treatment effects with mean -4.18 and variance 1.41^2 (OS) and mean -2.94 and variance 1.79^2 (PFS) was used (Turner et al. (69)). The network included all studies from which OS/PFS data from TNBC cases was available either as digitised Kaplan–Meier curves or using individual-level data. The IMpassion130 (WO29522) study was connected to the network using matching adjustments to the E2100, MERIDIAN and AVADO studies. |

## *Results of Second interim OS analysis-based indirect comparisons*

Results are provided for each of:

a) Atezolizumab and nab-paclitaxel as the reference treatment, compared with paclitaxel and docetaxel, and

b) Nab-paclitaxel (and placebo) as the reference treatment, compared with paclitaxel and docetaxel.

CSV (Excel) Files containing the posterior simulation traces for each of a) and b) are provided accompanying this response.

### Results: Atezolizumab and nab-paclitaxel as the reference treatment

The following base case results for atezolizumab and nab-paclitaxel (as the reference treatment), compared with paclitaxel and docetaxel, have been incorporated into our updated cost-effectiveness model, which is provided in our response to ERG Clarification Question B2. These are provided as hazard ratios for each “piece”.

### OS

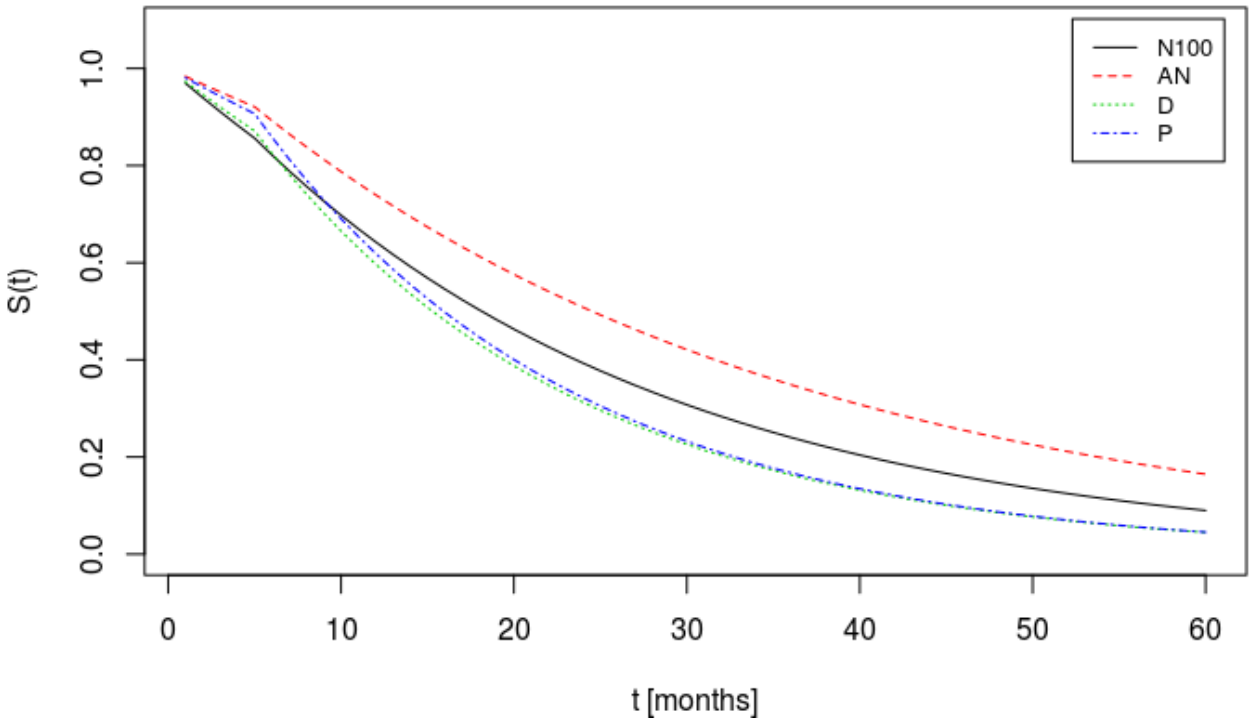
Table 22 provides the resulting HRs, by piece (0 to 5 months, greater than 5 months).

**Table 22: Overall survival hazard ratios of paclitaxel and docetaxel vs. atezolizumab + nab-paclitaxel, by piece**

| | t<5months | | | 5months≤t | | |
|---|---|---|---|---|---|---|
| | Hazard ratio (median) | 95% lower credible interval | 95% upper credible intervals | median | 95% lower credible interval | 95% upper credible intervals |
| P | 1.19 | 0.43 | 3.41 | 1.74 | 1.12 | 2.71 |
| D | 1.67 | 0.61 | 4.78 | 1.72 | 0.8 | 3.53 |
| P: Paclitaxel (80–90mg/m2 on Days 1, 8, and 15 of 28-day cycles), D: Docetaxel (100mg/m2 every 3 weeks). | | | | | | |

Extrapolations of survival probabilities in the IMpassion130 (WO29522) study over a 5-year time horizon using posterior median basic parameters produced pronounced differences in long-term survival between treatments (Figure 4). As demonstrated in, Figure 4 there is divergence of the survival curves from initiation versus docetaxel, and from 5 months versus paclitaxel.

**Figure 4: Overall survival probabilities extrapolated in the IMpassion130 (WO29522) study using posterior median basic parameters**

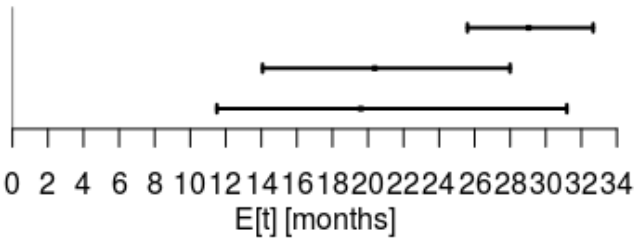



**Key:** AN: Atezolizumab (840mg on Days 1 and 15 of 28-day cycles) + nab-paclitaxel (100mg/m2 on Days 1, 8 and 15 of 28-day cycles), D: Docetaxel (100mg/m2 every 3 weeks), P: Paclitaxel (80–90mg/m2 on Days 1, 8, and 15 of 28-day cycles).

The posterior median restricted mean 5-year OS of atezolizumab and nab-paclitaxel demonstrated an improvement of OS by 8.62 months (vs paclitaxel) and 9.42 (vs docetaxel) (Figure 5 and Figure 6).

**Figure 5: Restricted mean overall survival times from extrapolations in the IMpassion130 study (Second interim OS analysis) over a 5-year time horizon**

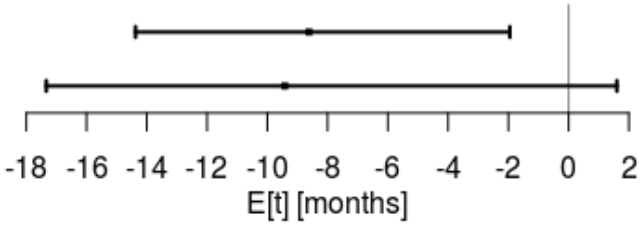
| Treatment | Median | 95% ll | 95% ul |
|---|---|---|---|
| AN | 29.04 | 25.59 | 32.67 |
| P | 20.38 | 14.07 | 27.99 |
| D | 19.6 | 11.5 | 31.19 |




**Key:** AN: Atezolizumab (840mg on Days 1 and 15 of 28-day cycles) + nab-paclitaxel (100mg/m2 on Days 1, 8 and 15 of 28-day cycles), D: Docetaxel (100mg/m2 every 3 weeks), P: Paclitaxel (80–90mg/m2 on Days 1, 8, and 15 of 28-day cycles).

**Figure 6: Differences to atezolizumab + nab-paclitaxel in restricted mean overall survival times from extrapolations in the IMpassion130 study (Second interim OS analysis) over a 5-year time horizon**

| Treatment | Median | 95% ll | 95% ul |
|---|---|---|---|
| P | -8.62 | -14.37 | -1.95 |
| D | -9.42 | -17.34 | 1.6 |




**Key:** D: Docetaxel (100mg/m2 every 3 weeks), P: Paclitaxel (80–90mg/m2 on Days 1, 8, and 15 of 28-day cycles).

## PFS

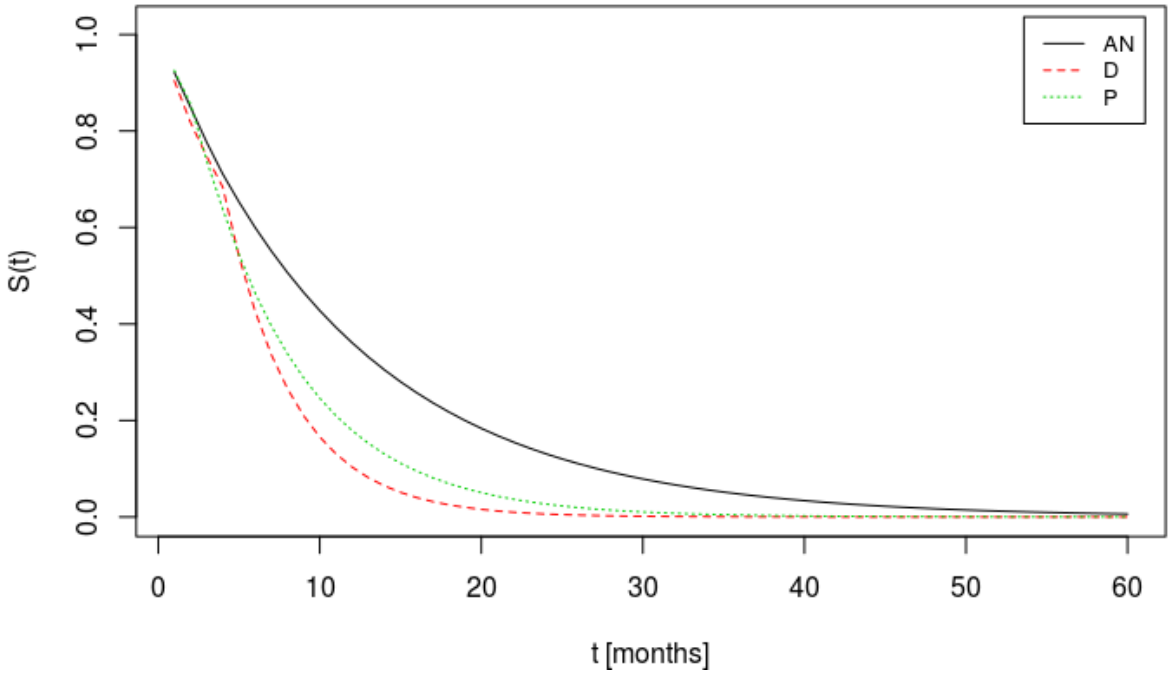
Table 23 provides the resulting HRs, by piece (0 to 2 months, 2 to 4 months, greater than 4 months).

**Table 23: PFS hazard ratios of paclitaxel and docetaxel vs. atezolizumab + nab-paclitaxel, by piece**

| | 0 months ≤t< 2months | | | 2 months ≤t< 4months | | | 4 months ≤t | | |
|---|---|---|---|---|---|---|---|---|---|
| | Hazard ratio (median) | 95% lower credible interval | 95% upper credible intervals | median | 95% lower credible interval | 95% upper credible intervals | median | 95% lower credible interval | 95% upper credible intervals |
| **P** | 0.95 | 0.42 | 2.09 | 1.65 | 0.82 | 3.27 | 1.88 | 1.10 | 3.11 |
| **D** | 1.23 | 0.44 | 3.48 | 1.01 | 0.31 | 3.07 | 2.79 | 1.30 | 6.03 |
| **Key:** P: Paclitaxel (80–90mg/m2 on Days 1, 8, and 15 of 28-day cycles), D: Docetaxel (100mg/m2 every 3 weeks). | | | | | | | | | |

Extrapolations of PFS in the IMpassion130 (WO29522) study over a 5-year time horizon using posterior median basic parameters produced pronounced differences in PFS between treatments Figure 7. As demonstrated in Figure 7, there is divergence of the survival curves from 4 months versus docetaxel, and from 2 months versus paclitaxel.

**Figure 7: PFS probabilities extrapolated in the IMpassion130 (WO29522) study using posterior median basic parameters**

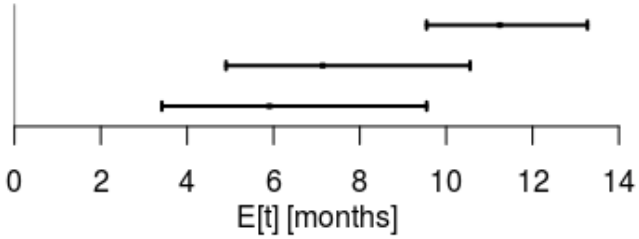



**Key:** AN: Atezolizumab (840mg on Days 1 and 15 of 28-day cycles) + nab-paclitaxel (100mg/m2 on Days 1, 8 and 15 of 28-day cycles), D: Docetaxel (100mg/m2 every 3 weeks), P: Paclitaxel (80–90mg/m2 on Days 1, 8, and 15 of 28-day cycles).

The posterior median restricted mean 5-year PFS of atezolizumab and nab-paclitaxel demonstrated an improvement of PFS by 4.08 months (vs paclitaxel) and 5.31 months (vs docetaxel) (Figure 8 and Figure 9).

**Figure 8: Restricted mean PFS times from extrapolations in the IMpassion130 study (Second interim OS analysis) over a 5-year time horizon**

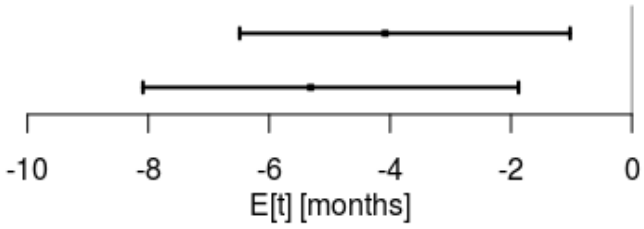
| Treatment | Median | 95% ll | 95% ul |
|---|---|---|---|
| AN | 11.24 | 9.55 | 13.27 |
| P | 7.14 | 4.9 | 10.55 |
| D | 5.91 | 3.42 | 9.55 |




**Key:** D: Docetaxel (100mg/m2 every 3 weeks), P: Paclitaxel (80–90mg/m2 on Days 1, 8, and 15 of 28-day cycles).

**Figure 9: Differences to atezolizumab + nab-paclitaxel in restricted mean PFS times from extrapolations in the IMpassion130 study (Second interim OS analysis) over a 5 -year time horizon**

| Treatment | Median | 95% ll | 95% ul |
|---|---|---|---|
| P | -4.08 | -6.49 | -1.02 |
| D | -5.31 | -8.09 | -1.88 |




**Key:** D: Docetaxel (100mg/m2 every 3 weeks), P: Paclitaxel (80–90mg/m2 on Days 1, 8, and 15 of 28-day cycles).

### Results: Nab-paclitaxel (and placebo) as the reference treatment

The following base case results for nab-paclitaxel (and placebo) as the reference treatment. These are provided as hazard ratios for each “piece”.

### OS

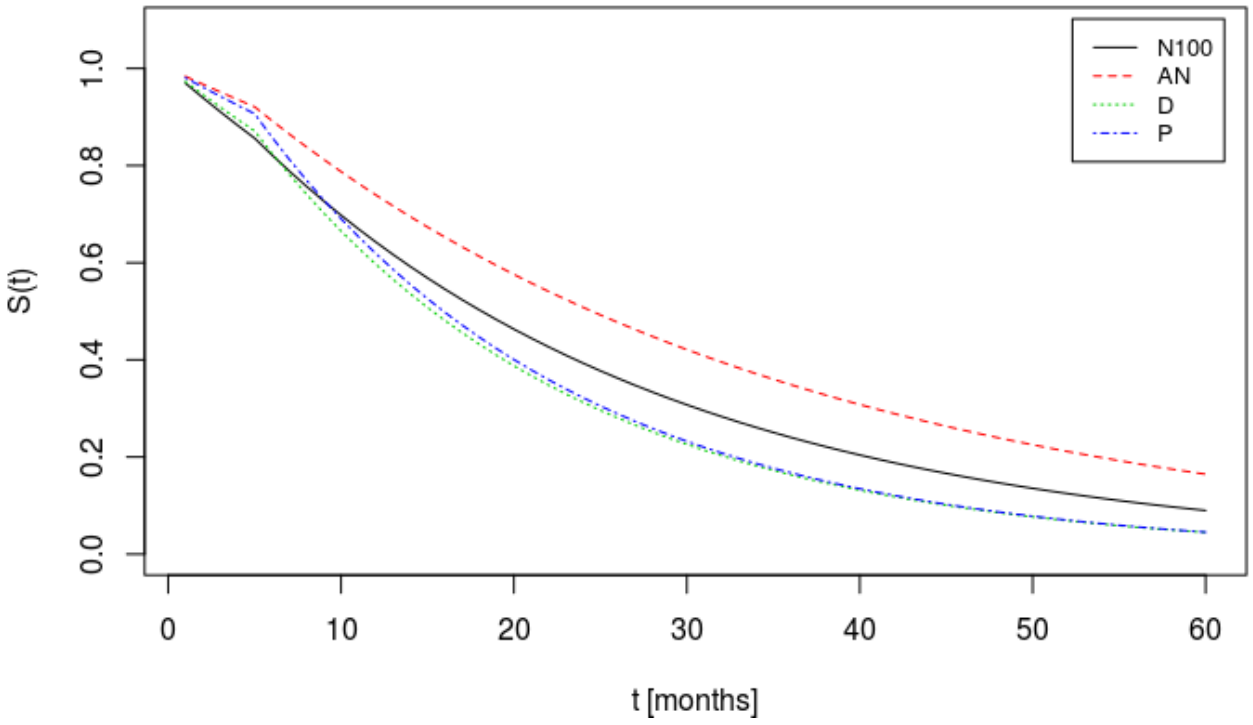
Table 24 provides the resulting HRs, by piece (0 to 5 months, greater than 5 months).

**Table 24: Overall survival hazard ratios of paclitaxel and docetaxel vs. nab-paclitaxel, by piece**

| | t<5months | | | 5months≤t | | |
|---|---|---|---|---|---|---|
| | **Hazard ratio (median)** | **95% lower credible interval** | **95% upper credible intervals** | **median** | **95% lower credible interval** | **95% upper credible intervals** |
| **P** | 0.63 | 0.18 | 2.2 | 1.33 | 0.72 | 2.46 |
| **D** | 0.89 | 0.25 | 3.14 | 1.32 | 0.56 | 3.00 |
| **AN** | 0.53 | 0.26 | 1.07 | 0.76 | 0.5 | 1.18 |
| **Key:** P: Paclitaxel (80–90mg/m2 on Days 1, 8, and 15 of 28-day cycles), D: Docetaxel (100mg/m2 every 3 weeks), AN: Atezolizumab (840mg on Days 1 and 15 of 28-day cycles) + nab-paclitaxel (100mg/m2 on Days 1, 8 and 15 of 28-day cycles). | | | | | | |

Extrapolations of survival probabilities over a 5-year time horizon are provided in Figure 10.

**Figure 10: Overall survival probabilities extrapolated in the IMpassion130 (WO29522) study using posterior median basic parameters**

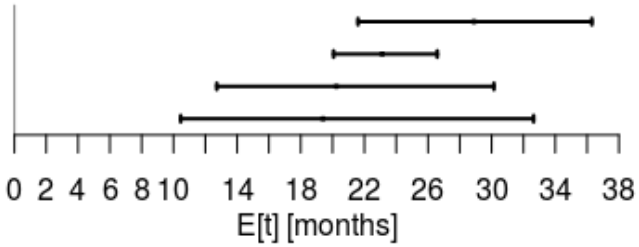



**Key:** N100: nab-paclitaxel (and placebo), D: Docetaxel (100mg/m2 every 3 weeks), P: Paclitaxel (80–90mg/m2 on Days 1, 8, and 15 of 28-day cycles), AN: Atezolizumab (840mg on Days 1 and 15 of 28-day cycles) + nab-paclitaxel (100mg/m2 on Days 1, 8 and 15 of 28-day cycles).

The posterior median restricted mean 5-year OS of nab-paclitaxel (and placebo) demonstrated an improvement of OS by 2.86 months (vs paclitaxel) and 3.74 months (vs docetaxel) (Figure 11 and Figure 12).

**Figure 11: Restricted mean overall survival times from extrapolations in the IMpassion130 study (Second interim OS analysis) over a 5-year time horizon**

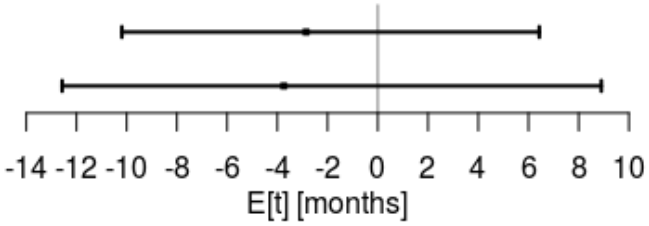
| Treatment | Median | 95% ll | 95% ul |
|---|---|---|---|
| AN | 28.89 | 21.6 | 36.3 |
| N100 | 23.12 | 20.06 | 26.58 |
| P | 20.24 | 12.72 | 30.14 |
| D | 19.4 | 10.45 | 32.64 |




**Key:** N100: nab-paclitaxel (and placebo), D: Docetaxel (100mg/m2 every 3 weeks), P: Paclitaxel (80–90mg/m2 on Days 1, 8, and 15 of 28-day cycles), AN: Atezolizumab (840mg on Days 1 and 15 of 28-day cycles) + nab-paclitaxel (100mg/m2 on Days 1, 8 and 15 of 28-day cycles).

**Figure 12: Differences to nab-paclitaxel in restricted mean overall survival times from extrapolations in the IMpassion130 study (Second interim OS analysis) over a 5-year time horizon**

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




**Key:** D: Docetaxel (100mg/m2 every 3 weeks), P: Paclitaxel (80–90mg/m2 on Days 1, 8, and 15 of 28-day cycles).

## PFS

Table 23 provides the resulting HRs, by piece (0 to 2 months, 2 to 4 months and greater than 4 months).

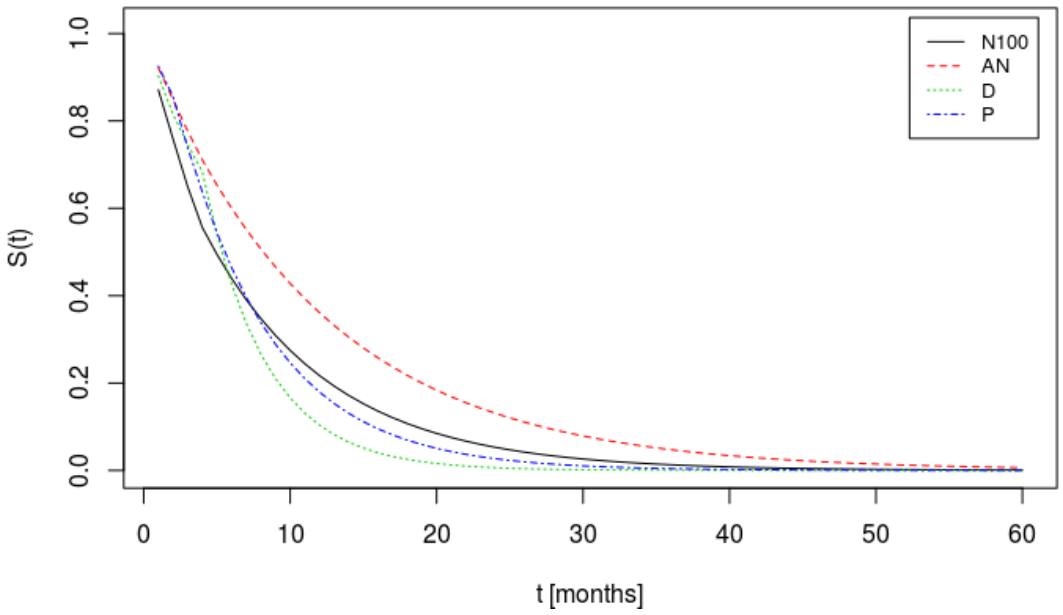
**Table 25: PFS hazard ratios of paclitaxel and docetaxel vs. nab-paclitaxel, by piece**

| | 0 months ≤t< 2months | | | 2months ≤t< 4months | | | 4months ≤t | | |
|---|---|---|---|---|---|---|---|---|---|
| | Hazard ratio (median) | 95% lower credible interval | 95% upper credible intervals | median | 95% lower credible interval | 95% upper credible intervals | 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 |

**Key:** P: Paclitaxel (80–90mg/m2 on Days 1, 8, and 15 of 28-day cycles), D: Docetaxel (100mg/m2 every 3 weeks), AN: Atezolizumab (840mg on Days 1 and 15 of 28-day cycles) + nab-paclitaxel (100mg/m2 on Days 1, 8 and 15 of 28-day cycles).

Extrapolations of PFS in the IMpassion130 trial over a 5-year time horizon using posterior median basic parameters produced pronounced differences in PFS between treatments (Figure 13).

**Figure 13: PFS probabilities extrapolated in the IMpassion130 (WO29522) study using posterior median basic parameters**

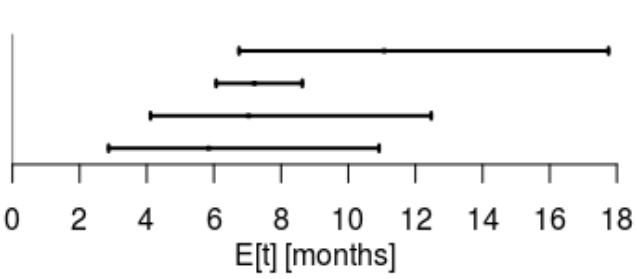



**Key:** N100: nab-paclitaxel (and placebo), D: Docetaxel (100mg/m2 every 3 weeks), P: Paclitaxel (80–90mg/m2 on Days 1, 8, and 15 of 28-day cycles).

The posterior median restricted mean 5-year PFS of nab-paclitaxel with placebo demonstrated an improvement of PFS by 0.18 months (vs paclitaxel) and 1.36 months (vs docetaxel) (Figure 14 and Figure 15).

**Figure 14: Restricted mean PFS times from extrapolations in the IMpassion130 study (Second interim OS analysis) over a 5-year time horizon**

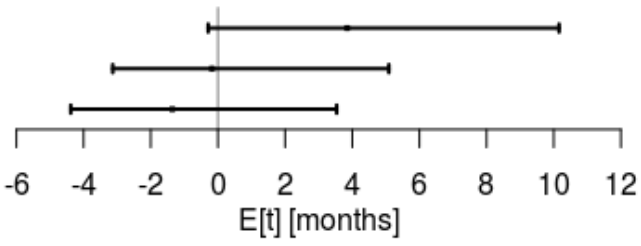
| Treatment | Median | 95% ll | 95% ul |
|---|---|---|---|
| AN | 11.07 | 6.75 | 17.75 |
| N100 | 7.21 | 6.07 | 8.63 |
| P | 7.03 | 4.11 | 12.47 |
| D | 5.84 | 2.86 | 10.92 |




**Key:** D: Docetaxel (100mg/m2 every 3 weeks), P: Paclitaxel (80–90mg/m2 on Days 1, 8, and 15 of 28-day cycles).

**Figure 15: Differences to nab-paclitaxel in restricted mean PFS times from extrapolations in the IMpassion130 study (Second interim OS analysis) over a 5 -year time horizon**

| 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 |




**Key:** D: Docetaxel (100mg/m2 every 3 weeks), P: Paclitaxel (80–90mg/m2 on Days 1, 8, and 15 of 28-day cycles).

## Reference treatment choice for implementation of the updated indirect comparisons in the cost-effectiveness model

Having completed the two requested updated indirect comparisons and considered the choice of reference treatment for the updated model base case, Roche would suggest use of nab-paclitaxel as the reference data. This is because, firstly, the Kaplan–Meier data are more mature for this treatment arm within IMpassion130. Secondly, the expected long-term survival profile of the relevant comparators are more similar to nab-paclitaxel than to atezolizumab + nab-paclitaxel, as included in the NMA (nab-paclitaxel, paclitaxel and docetaxel are all taxane-type chemotherapies). Hence two models have been provided, as requested in B2: One utilising the second interim analysis NMA with A+NPx as the reference treatment, and the second (which Roche supports as the new base case) utilising the second interim analysis NMA with P+NPx as the reference treatment.

## Section B: Clarification on cost-effectiveness data

**B1.** Priority request: Kaplan-Meier data. Please provide the Kaplan-Meier analyses listed in a to c below to the following specifications:

| | |
|---|---|
| Trial data set | IMpassion130 trial, January 2019 data cut |
| Format | Please present analysis outputs using the format of the sample table shown below |
| Population | PD-L1 population only |

a) Time to death from any cause (OS) Kaplan-Meier analysis for patients in the A+nabPx arm and P+nabPx arm of the trial

b) Time to investigator assessed progression (PFS) Kaplan-Meier analysis for patients in the A+nabPx arm and P+nabPx arm of the trial

c) Time to study treatment discontinuation (TTOT) Kaplan-Meier analysis for patients in the A+nabPx arm and P+nabPx arm of the trial.

Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

| Product-Limit Survival Estimates | | | | | | |
|---|---|---|---|---|---|---|
| **DAYS** | | **Survival** | **Failure** | **Survival Standard Error** | **Number Failed** | **Number Left** |
| **0.000** | | 1.0000 | 0 | 0 | 0 | 62 |
| **1.000** | | . | . | . | 1 | 61 |
| **1.000** | | 0.9677 | 0.0323 | 0.0224 | 2 | 60 |
| **3.000** | | 0.9516 | 0.0484 | 0.0273 | 3 | 59 |
| **7.000** | | 0.9355 | 0.0645 | 0.0312 | 4 | 58 |
| **8.000** | | . | . | . | 5 | 57 |
| **8.000** | | . | . | . | 6 | 56 |
| **8.000** | | 0.8871 | 0.1129 | 0.0402 | 7 | 55 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **10.000** | | 0.8710 | 0.1290 | 0.0426 | 8 | 54 |
| **SKIP…** | | …… | …… | …… | … | … |
| **389.000** | | 0.1010 | 0.8990 | 0.0417 | 52 | 5 |
| **411.000** | | 0.0808 | 0.9192 | 0.0379 | 53 | 4 |
| **467.000** | | 0.0606 | 0.9394 | 0.0334 | 54 | 3 |
| **587.000** | | 0.0404 | 0.9596 | 0.0277 | 55 | 2 |
| **991.000** | | 0.0202 | 0.9798 | 0.0199 | 56 | 1 |
| **999.000** | | 0 | 1.0000 | 0 | 57 | 0 |

The Kaplan–Meier analyses requested for B1 a), b) and c) have been provided as CSV (Excel) files accompanying this response.

**B2. Priority request:** Please provide a model populated with OS, PFS and TTOT data, and MAIC results, from the latest IMpassion130 trial data cut (January 2019). Please also provide instructions that would enable us to replicate the changes that were made to the model using the latest data.

As detailed in A13, two updated models have been provided (both ACIC), in line with our original submission:

1) **Model 1:** Containing indirect comparisons results of **Atezolizumab with nab-paclitaxel (as the reference treatment)** compared with paclitaxel and with docetaxel *and* updated KMs (OS, PFS, TTOT), using second data second interim OS analysis (data cut January 2019).
2) **Model 2:** Containing indirect comparisons results of Nab-paclitaxel (as the reference treatment) compared with paclitaxel and docetaxel and updated KMs (OS, PFS, TTOT), using second data second interim OS analysis (data cut January 2019). Roche supports this model be considered as the new base case (see further details below).

**Re-assessment of tails of survival curves required**

In the CS (Document B, Section B.3.3.2, B.3.3.3, B.3.3.4): statistical fit (AIC/BIC) and visual fit for OS, PFS and TTOT (for atezolizumab and nab-paclitaxel and nab-

paclitaxel monotherapy) was carried out based upon the second interim OS analysis (January 2019 data cut). However, please note, that, since the NMA has been updated to include data from the second interim OS analysis, a key next step is re-assessing the suitability of the survival curves for paclitaxel and docetaxel, in comparison to long-term estimates expected by clinical experts.

**Reference treatment choice**

As described in the response to question A13, Roche would suggest use of nab-paclitaxel as the reference data. This is because, firstly, the Kaplan–Meier data are more mature for this treatment arm within IMpassion130. Secondly, the expected long-term survival profile of the relevant comparators are more similar to nab-paclitaxel than to atezolizumab + nab-paclitaxel, as included in the NMA (nab-paclitaxel, paclitaxel and docetaxel are all taxane-type chemotherapies). Hence two models have been provided, as requested in B2: One utilising the second interim analysis NMA with A+NPx as the reference treatment, and the second (which Roche supports as the new base case) utilising the second interim analysis NMA with P+NPx as the reference treatment.

The instructions for implementing the data accompanying this response in each of Model 1 and Model 2 are provided in **Appendix 2.**

## Section C: Textual clarification and additional points

**C1.** Reference 20 in the CS is, 'Data on File. UK Clinical Expert Opinion. 2019'. Please provide this document.

This Data on file is provided separately to this responses document (File labelled Appendix 3 ACIC)

## References


1. 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-naïve, locally advanced or metastatic triple-negative breast cancer. 2018 San Antonio Breast Cancer Symposium. Publication Number: GS1-04
2. Phillippo, D.M., Ades, A.E., Dias, S., Palmer, S., Abrams, K.R., Welton, N.J. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE. 2016. Available from http://www.nicedsu.org.u
3. 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(26):2666-76.
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6. 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.
7. 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.

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# Appendices

# Appendix 1: Response to ERG question A3, Sample size calculations

### Figure 16: Interim and Final Analyses for Overall Survival, sample size calculations

| Different Scenarios of PFS and ORR Testing | Alpha Level | Analysis Timing | Time from 1st Patient Enrolled (months) | Information Fraction | No. of Events | Stopping Boundary in HR | Stopping Boundary in p-value |
|---|---|---|---|---|---|---|---|
| Both PFS and ORR are statistically significant in both IC1/2/3 and ITT | 0.05 | First interim | 30 | 53% | IC1/2/3: 133<br>AC: 347 | IC1/2/3: HR ≤ 0.608<br>AC: HR ≤ 0.735 | p-value ≤ 0.0041 |
| | | Second interim | 41 | 80% | IC1/2/3: 201<br>AC: 524 | IC1/2/3: HR ≤ 0.726<br>AC: HR ≤ 0.820 | p-value ≤ 0.0231 |
| | | Final | 56 | 100% | IC1/2/3: 251<br>AC: 655 | IC1/2/3: HR ≤ 0.774<br>AC: HR ≤ 0.853 | p-value ≤ 0.0425 |
| PFS is statistically significant in both IC1/2/3 and ITT; ORR is statistically significant in either IC1/2/3 or ITT, but not both | 0.049 | First interim | 30 | 53% | IC1/2/3: 134<br>AC: 349 | IC1/2/3: HR ≤ 0.608<br>AC: HR ≤ 0.735 | p-value ≤ 0.004 |
| | | Second interim | 41 | 80% | IC1/2/3: 202<br>AC: 526 | IC1/2/3: HR ≤ 0.725<br>AC: HR ≤ 0.820 | p-value ≤ 0.0225 |
| | | Final | 56 | 100% | IC1/2/3: 253<br>AC: 658 | IC1/2/3: HR ≤ 0.774<br>AC: HR ≤ 0.853 | p-value ≤ 0.0417 |
| PFS is statistically significant in both IC1/2/3 and ITT; ORR is not statistically significant in either IC1/2/3 or ITT | 0.048 | First interim | 30 | 53% | IC1/2/3: 135<br>AC: 351 | IC1/2/3: HR ≤ 0.609<br>AC: HR ≤ 0.735 | p-value ≤ 0.0039 |
| | | Second interim | 42 | 80% | IC1/2/3: 203<br>AC: 530 | IC1/2/3: HR ≤ 0.725<br>AC: HR ≤ 0.820 | p-value ≤ 0.0210 |
| | | Final | 57 | 100% | IC1/2/3: 254<br>AC: 662 | IC1/2/3: HR ≤ 0.774<br>AC: HR ≤ 0.853 | p-value ≤ 0.0408 |
| PFS is statistically significant in either IC1/2/3 or ITT, but not both, and the subsequent ORR is statistically significant | 0.045 | First interim | 30 | 52% | IC1/2/3: 135<br>AC: 350 | IC1/2/3: HR ≤ 0.602<br>AC: HR ≤ 0.729 | p-value ≤ 0.0031 |
| | | Second interim | 42 | 80% | IC1/2/3: 207<br>AC: 538 | IC1/2/3: HR ≤ 0.724<br>AC: HR ≤ 0.819 | p-value ≤ 0.0204 |
| | | Final | 59 | 100% | IC1/2/3: 259<br>AC: 673 | IC1/2/3: HR ≤ 0.773<br>AC: HR ≤ 0.852 | p-value ≤ 0.0384 |
| PFS is statistically significant in either IC1/2/3 or ITT, but not both ; ORR is not statistically significant | 0.044 | First interim | 30 | 52% | IC1/2/3: 136<br>AC: 352 | IC1/2/3: HR ≤ 0.601<br>AC: HR ≤ 0.729 | p-value ≤ 0.003 |
| | | Second interim | 43 | 80% | IC1/2/3: 209<br>AC: 542 | IC1/2/3: HR ≤ 0.725<br>AC: HR ≤ 0.819 | p-value ≤ 0.0200 |
| | | Final | 59 | 100% | IC1/2/3: 261<br>AC: 677 | IC1/2/3: HR ≤ 0.773<br>AC: HR ≤ 0.852 | p-value ≤ 0.0376 |
| PFS is not statistically significant in either IC1/2/3 or ITT | 0.04 | First interim | 30 | 50% | IC1/2/3: 134<br>AC: 347 | IC1/2/3: HR ≤ 0.586<br>AC: HR ≤ 0.718 | p-value ≤ 0.002 |
| | | Second interim | 44 | 80% | IC1/2/3: 214<br>AC: 554 | IC1/2/3: HR ≤ 0.723<br>AC: HR ≤ 0.818 | p-value ≤ 0.0179 |
| | | Final | 62 | 100% | IC1/2/3:268<br>AC: 693 | IC1/2/3: HR ≤ 0.772<br>AC: HR ≤ 0.851 | p-value ≤ 0.0344 |

AC=all-comer; HR=Hazard Ratio; IC=tumor-infiltrating immune cell; ITT=intent-to-treat; ORR=objective response rate; PFS=progression-free survival.

# Appendix 2: Instructions for implementation of updated indirect comparisons and updated KMs (OS, PFS, TTOT) into CS cost-effectiveness model

Two models have been provided (both ACIC), in line with our original submission:

**1) Model 1:** Containing indirect comparisons results of **Atezolizumab with nab-paclitaxel** (as the reference treatment) compared with paclitaxel and with docetaxel *and* updated KMs using second data second interim OS analysis (data cut January 2019).

**2) Model 2:** Containing indirect comparisons results of **Nab-paclitaxel** (as the reference treatment) compared with paclitaxel and docetaxel *and* updated KMs using second data second interim OS analysis (data cut January 2019).

Detailed instructions to implement these updated indirect comparisons data are as follows. Please additionally refer to the CSV/Excel files referenced below, containing traces by indirect comparisons “piece” accompanying this submission.

**Instructions: Implementation of NMA traces in CE model 1 (NMA using atezolizumab and nab-paclitaxel as the reference treatment)**

Please refer to the sheet in the Excel CE model named “NMA piece”. This sheet consists of two major parts: OS and PFS, for the comparators of paclitaxel and docetaxel. The user can change the posterior simulations, using updated NMA data, in columns AX to BO.

Please note that the indirect comparison cut points (in months) for PFS have changed based on re-assessment of model selection, using the January 2019 data cut (with the rationale described in the response to question A13). The OS indirect comparisons cut points have not changed (with the rationale described in the response to question A13).

**Implementation of updated OS indirect comparisons results**

The analysis has been generated in the form of posterior samples of the coefficients for each of the time intervals included in the analysis.

For OS, the files containing the posterior distribution (accompanying this response) are named:

- dtrace.os.bc.re.dtpwexph-p1.5 [ACIC]– posterior parameters for the first piece (0 to 5 months)
- dtrace.os.bc.re.dtpwexph-p2.5 [ACIC] – posterior parameters for the second piece (more than 5 months)

At this stage, based on the posterior results in Figure 17 and the cells in the model presented in Figure 18, these steps are required:

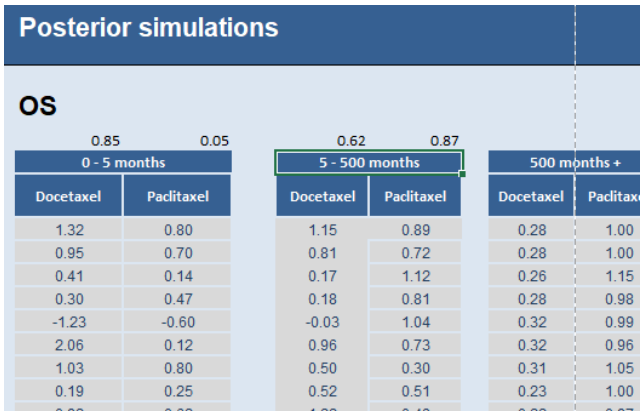
- dtrace.os.bc.re.dtpwexph-p1.5 [ACIC]
    - column F (D – Docetaxel) is copied and pasted in the AX column of the "NMA Piece" sheet of the CE model"
    - Column J (P – Paclitaxel) is copied and pasted in the AY column of the "NMA Piece" sheet of the CE model
- dtrace.os.bc.re.dtpwexph-p2.5 [ACIC]
    - column F (D – Docetaxel) is copied and pasted in the BA column of the "NMA Piece" sheet of the CE model"
    - Column J (P – Paclitaxel) is copied and pasted in the BB column of the "NMA Piece" sheet of the CE model

**Figure 17: Header of the dtrace.os.bc.re.dtpwexph-p1.5.csv file**

| A | B | C | D | E | F | G | H | I | J | K |
|---|---|---|---|---|---|---|---|---|---|---|
| | AN | BCp | Cb | Cp | D | DB15 | DB7.5 | N100 | P | PB |
| 1 | 0 | 0.626101 | 2.193377 | 0.678952 | 1.663842 | 1.184408 | 1.180495 | 0.854519 | 0.014022 | -0.48384 |
| 3 | 0 | 2.190111 | 0.573825 | 2.10926 | -0.15365 | -0.46541 | -1.23091 | 0.509328 | 1.79037 | 0.840339 |
| 5 | 0 | 1.792579 | 1.587715 | 1.943488 | 0.63538 | -0.13519 | -0.27577 | 0.939735 | 0.732844 | 0.60476 |
| 7 | 0 | 0.134472 | 1.589687 | 0.384375 | 0.720278 | 0.178862 | -0.17489 | 0.243566 | 0.355341 | 0.066953 |
| 9 | 0 | -0.08532 | 1.154437 | 0.788559 | 0.678095 | 0.185256 | -0.1677 | 0.677427 | 0.530904 | -0.22155 |
| 11 | 0 | -0.21124 | 0.766466 | -1.65338 | 0.804605 | -0.54209 | -0.36404 | 0.709345 | -0.32555 | -0.20485 |
| 13 | 0 | -1.0877 | 0.892195 | -1.837 | 0.445742 | -0.63741 | -0.92299 | 0.488083 | 0.536598 | -0.24407 |
| 15 | 0 | 0.309558 | 1.260705 | 1.326695 | 0.038153 | -0.01251 | -0.63292 | 1.237357 | 0.920563 | 0.284341 |
| 17 | 0 | 1.798713 | 2.663974 | 1.925398 | 1.427939 | 0.64847 | 0.494558 | 0.570635 | 1.065798 | 0.859782 |
| 19 | 0 | 0.709629 | 2.004351 | 1.927967 | 1.096049 | 0.626173 | 0.920573 | 1.074959 | -0.01541 | 0.661509 |
| 21 | 0 | 1.25675 | 2.123299 | 2.338662 | 1.556005 | 0.228834 | 0.8061 | 0.936872 | 0.973387 | 0.363373 |

These files contain posterior parameters for all the interventions included in the NMA. For our purposes, we use the data for Docetaxel and Paclitaxel only into the Cost-Effectiveness model (Figure 17).

**Figure 18: Cells in the cost-effectiveness model in which the posterior results can be included.**



Posterior simulations

OS

| 0.85 | 0.05 | 0.62 | 0.87 | | |
|---|---|---|---|---|---|
| 0 - 5 months | | 5 - 500 months | | 500 months + | |
| Docetaxel | Paclitaxel | Docetaxel | Paclitaxel | Docetaxel | Paclitax |
| 1.32 | 0.80 | 1.15 | 0.89 | 0.28 | 1.00 |
| 0.95 | 0.70 | 0.81 | 0.72 | 0.28 | 1.00 |
| 0.41 | 0.14 | 0.17 | 1.12 | 0.26 | 1.15 |
| 0.30 | 0.47 | 0.18 | 0.81 | 0.28 | 0.98 |
| -1.23 | -0.60 | -0.03 | 1.04 | 0.32 | 0.99 |
| 2.06 | 0.12 | 0.96 | 0.73 | 0.32 | 0.96 |
| 1.03 | 0.80 | 0.50 | 0.30 | 0.31 | 1.05 |
| 0.19 | 0.25 | 0.52 | 0.51 | 0.23 | 1.00 |

*A note on OS 500+months trace*

Please note, this trace is not in use as our base-case uses one cut point only. Hence, there is no usage of columns BD and BE.

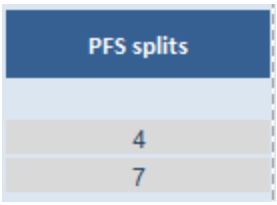
As the base-case indirect comparisons included one cut-off point only, there is no usage of using columns BD and BE, for potential addition of a further cut point. HJ19 and H20 similarly contains cells which have no present usage. Hence, columns BD and BE and cells HJ19 and H20 could be all left empty; but are kept unaltered in the CE model accompanying this response.

**Implementation of updated PFS indirect comparisons results**

The model selection was re-assessed using the latest Impassion130 second OS interim analysis (latest data cut of January 2019). This led to a conclusion for the need for altered cut points from 4 and 7 months (in the CS) to 2 and 4 months in the present updated indirect comparisons.

Thus, as the first step, the user needs to change the time splits in cells AL19:AL20 in the CE model from 4 and 7 (used in CS, Figure 19) to 2 (in place of 4) and 4 (in place of 7), as the PFS splits.

**Figure 19: Time splits for PFS – analysis based on the primary analysis, April 2018.**



| PFS splits |
| --- |
| |
| 4 |
| 7 |

The files containing info on the posterior distributions for PFS (accompanying this response) are:

- dtrace.pfs.bc.re.dtpwexph-p1.2-4 [ACIC] - for 0 to 2 months
- dtrace.pfs.bc.re.dtpwexph-p2.2-4 [ACIC] - between 2 and 4 months
- dtrace.pfs.bc.re.dtpwexph-p3.2-4 [ACIC] - over 4 months

These files have similar headers to those shown in Figure 17. Thus, the user can focus only on the columns with results for D (Docetaxel) and P (Paclitaxel).

These steps are subsequently required:

- dtrace.pfs.bc.re.dtpwexph-p1.2-4 [ACIC]
    - column G (D – Docetaxel) is copied and pasted in the BH column of the "NMA Piece" sheet of the CE model"
    - Column L (P – Paclitaxel) is copied and pasted in the BI column of the "NMA Piece" sheet of the CE model
- dtrace.pfs.bc.re.dtpwexph-p2.2-4 [ACIC]
    - column G (D – Docetaxel) is copied and pasted in the BK column of the "NMA Piece" sheet of the CE model"
    - Column L (P – Paclitaxel) is copied and pasted in the BL column of the "NMA Piece" sheet of the CE model
- dtrace.pfs.bc.re.dtpwexph-p3.2-4 [ACIC]
    - column G (D – Docetaxel) is copied and pasted in the BN column of the "NMA Piece" sheet of the CE model"
    - Column L (P – Paclitaxel) is copied and pasted in the BO column of the "NMA Piece" sheet of the CE model

On completion of the above steps, the updated OS and PFS indirect comparisons have been incorporated into the CE model.

**Instructions: Implementation of NMA traces in CE model 2 (NMA using nab-paclitaxel as the reference treatment)**

To incorporate data for the posterior distributions for PFS and OS for the NMA results using nab-paclitaxel (N100) as the reference treatment, the user should refer to the following CSV files:

OS:

- dtrace.os.bc_n100.re.dtpwexph-p1.5 [ACIC] – posterior parameters for the first piece (0 to 5 months)
- dtrace.os.bc_n100.re.dtpwexph-p2.5 [ACIC] – posterior parameters for the second piece (more than 5 months)

PFS:

- dtrace.pfs.bc_n100.re.dtpwexph-p1.2-4 [ACIC] - for 0 to 2 months
- dtrace.pfs.bc_n100.re.dtpwexph-p2.2-4 [ACIC] - between 2 and 4 months
- dtrace.pfs.bc_n100.re.dtpwexph-p3.2-4 [ACIC] - over 4 months

These posterior traces are to be copied and pasted in the relevant cells for OS and PFS as described for Model 1 above.

When the base-case is set to Nab-Paclitaxel (N100), however, some additional steps are required. The anchor for both OS and PFS in the NMA piece sheet requires a change, as follows.

This is achieved by conducting the following steps in the NMA piece sheet:

- Cell C39: change from =INDEX(l_regimen_vec,1) to =INDEX(l_regimen_vec,2)
- Column from B42, copied down: replace column ='Atezo + nabPac'!D11 with ‘nabPac’!D11
- Column from C42, copied down: replace column ='Atezo + nabPac'!AT11 with ‘nabPac’!AN11
- Column from Z42, copied down: replace column ='Atezo + nabPac'!Z11 with ‘nabPac’!D11

- Column from AB42, copied down: replace column ='Atezo + nabPac'!Z11 with 'nabPac'!W11

**Instructions: Implementation of updated KMs of second interim OS analysis (January 2019 cut), for OS, PFS, TTOT, in both Model 1 and Model 2**

Accompanying this response are CSV (Excel) files of the KMs.

These updated second interim OS analysis (January 2019 cut) KM CSV (Excel) files are labelled as follows:

1. OS KMs:

- Atezolizumab and nab-paclitaxel: D_OS_ATEZO_[ACIC]
- Nab-paclitaxel: D_OS_NABPAC_[ACIC]

PFS KMs:

- Atezolizumab and nab-paclitaxel: D_PFS_ATEZO_[ACIC]
- Nab-paclitaxel: D_PFS_NABPAC_[ACIC]

TTOT KMs:

- Atezolizumab and nab-paclitaxel – atezolizumab: Atezolizumab and nab-paclitaxel – atezolizumab:
- Atezolizumab and nab-paclitaxel – nab-paclitaxel: D_TTOT_ATEZO_NABPAC_[ACIC]
- Nab-paclitaxel: D_TTOT_NABPAC_[ACIC]

These instructions are to be implemented in both Model 1 and Model 2, to ensure both models have incorporated the latest IMpassion130 KMs (January 2019 cut).

For TTOT KM - please refer to KM TTOT sheet:

1. Copy the cells from the provided TTOT CSV files into Columns AQ:BM, row 18 down.

2. Please note that cell AR:45 downwards denotes that ITT population (IC0 (PD-L1 negative) and IC123 (PD-L1 positive) data is also present.
3. Please insert the KMs only into the IC123 rows, representing the IC123 (PD-L1 positive) population

For OS and PFS:

1. Please refer to the KM OS and KM PFS sheets:
2. Repeat steps 1 to 3 above, except the column range is AE:AU for OS and PFS, rather than the AQ:BM for TTOT (above)

NICE National Institute for Health and Care Excellence

# Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

**Information on completing this submission**

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- Your response should not be longer than 10 pages.

| **About you** | |
|---|---|
| 1.Your name | [redacted] |

| | |
|---|---|
| 2. Name of organisation | Breast Cancer Now and Breast Cancer Care |
| 3. Job title or position | Policy team |
| 4a. Brief description of the organisation (including who funds it). How many members does it have? | Breast Cancer Now is the UK's largest breast cancer charity, dedicated to funding ground-breaking research into the disease. Our ambition is that by 2050, everyone who develops breast cancer will live. We're bringing together all those affected by the disease to improve the way we prevent, detect, treat and stop breast cancer. We're committed to working with the NHS and governments across the UK to ensure that breast cancer services are as good as they can be, and that breast cancer patients benefit from advances in research as quickly as possible. Our main sources of income are individual giving and corporate partnerships. In particular, in 2016/17 we received £2.7 million of income from Pfizer for our Catalyst programme, which provides grants for research. Further details about our income are set out in our annual report, which is available on our website at http://breastcancernow.org/about-us/what-we-do/annual-report-and-accounts Our work on access to drugs is independent of any funding we may receive from the pharmaceutical industry and is based on the evidence of the clinical effectiveness of drugs.<br><br>Breast Cancer Care is the only specialist UK-wide charity providing support for women, men, families and friends affected by breast cancer. Our free services include support over the phone with a nurse or someone who's been there, our welcoming online forums, reliable information and local group support. Every day, our care, support and information help thousands of people to find a way to live with, through and beyond breast cancer. We are funded by entirely by voluntary donations, this includes individual and corporate donations, corporate sponsorships, project grants and income generated from events.<br><br>**Breast Cancer Now and Breast Cancer Care will be merging on 1 April 2019.** |

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| 4b. Do you have any direct or indirect links with, or funding from, the tobacco industry? | No |
| 5. How did you gather information about the experiences of patients and carers to include in your submission? | Breast Cancer Now and Breast Cancer Care utilise their various networks of supporters to gather information about patient experience. |
| **Living with the condition** | |
| 6. What is it like to live with the condition? What do carers experience when caring for someone with the condition? | Locally advanced breast cancer is when the cancer spreads into the tissues around the breast. Metastatic (also known as advanced, secondary or stage 4) breast cancer is when cancer originating in the breast has spread to other parts of the body; most commonly the lungs, brain, bones or liver. There is no cure for metastatic breast cancer, so the aim of treatment is to extend the length of life and to improve quality of life for patients. A patient can be diagnosed with metastatic cancer initially, or they can develop the condition years after treatment for their primary breast cancer has ended.<br><br>Being diagnosed with locally advanced or metastatic breast cancer is extremely difficult to come to terms with both for patients and their family and friends and it can affect patients in different ways. Many people may feel upset and shocked or anxious, as well as angry and alone. These common feelings can have a huge impact on people's mental health. |

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| | As well as the huge emotional toll of living with metastatic breast cancer, patients often have to cope with numerous practical concerns, such as managing their day to day activities, including working, household responsibilities and travelling to and from hospital appointments.<br><br>Triple negative breast cancer is usually more aggressive and harder to treat than other types of breast cancer, resulting in poorer in outcomes. Therefore, it can be particularly upsetting and frightening to be diagnosed with this type of breast cancer. Treatment for triple negative breast cancer is currently limited to surgery, radiotherapy and chemotherapy and as a result patients may feel particularly anxious about the gruelling side effects often associated with chemotherapy and how it may impact on their day to day activities.<br><br>Patients are keen to find treatments that will halt progression and extend life for as long as possible. As patients' time is limited, people tell us that quality of life is just as important to take into account as length of life, as this enables them to spend quality time with their loved ones. Therefore, the type and severity of treatment side effects are also important for patients in their treatment decisions. |
| **Current treatment of the condition in the NHS** | |
| 7. What do patients or carers think of current treatments and care available on the NHS? | The treatment of triple negative breast cancer is particularly challenging and it is typically associated with an increased likelihood of disease progression, shorter progression free survival and poorer overall survival when compared to other types of breast cancer. There are currently no targeted therapies available for patients with metastatic triple negative breast cancer so chemotherapy remains the standard of care.<br><br>NICE guidelines recommend sequencing chemotherapy in this setting. There is the option of anthracyclines, however, for patients who have received this in the neo(adjuvant) setting, NICE recommends that systemic chemotherapy should be offered in the following sequence: 1) single agent docetaxel 2) single agent capecitabine or vinorelbine and 3) single agent capecitabine or vinorelbine (whichever was not used as second line treatment). Paclitaxel is another treatment option that is considered for this group of patients with this regimen generally better tolerated than docetaxel.<br><br>The side effects of chemotherapy can be particularly gruelling for patients. They can include nausea, |

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| | vomiting, hair loss and fatigue, although exact side effects can vary from person to person. With the side effects of chemotherapy affecting people both physically and emotionally, it can have a huge toll and impact on people's day to day lives and ability to continue with the activities that are important to them. |
| 8. Is there an unmet need for patients with this condition? | Yes. Around 15% of all breast cancers are triple negative, however, targeted and clinically-effective treatments for triple negative breast cancer remains one of the greatest areas of unmet need in breast cancer. Triple negative breast cancer is often more aggressive as well as harder-to-treat than other types of breast cancer, often resulting in poor survival outcomes. Treatment options for this patient group have remained mostly unchanged for a significant number of years.<br><br>One patient we spoke to who is currently being treated with atezolizumab said 'I knew my only other option was chemo that might at best give me months. My prognosis without [atezolizumab] is pretty poor but this gives me and my family hope and something to believe in.' |
| **Advantages of the technology** | |
| 9. What do patients or carers think are the advantages of the technology? | The main advantage of atezolizumab in combination with nab-paclitaxel is the improvement in progression free survival (PFS) for patients who express Programmed death-ligand 1 (PD-L1).<br><br>The IMpassion 130 trial demonstrated that this drug combination delayed the time until disease progression compared to nab-paclitaxel alone, with a median PFS of 7.5 months compared to 5.0 months in those patients with PDL1 expression.<br><br>In the context of a particularly difficult to treat breast cancer which currently has limited treatment options, this increase in PFS (an extra 2.5 months on average) is an important development. Crucially, it is of considerable significance to this group of patients and their family and friends.<br><br>We know that patients value this extra time, as delaying disease progression means more quality time to spend with their relatives and friends. Maintaining a high quality of life for as long as possible is currently the best outcome for this patient group. |

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| | Delaying progression can have a positive impact on patients' emotional wellbeing and mental health, as it may mean that the patient can continue doing the activities they enjoy.<br><br>Increasing the time until a patient's disease progresses is also likely to bring some comfort to their relatives and friends, as this is the best possible outcome for an incurable disease. This is in turn could help to reduce any stress the patient is experiencing as a result of worrying about any burden on their friends and family.<br><br>The patient we spoke to being who is currently being treated with atezolizumab said 'This doesn't just affect the patient. It gives hope to the whole family as its horrific watching someone slowly die before your eyes. I know my cancer is incurable however it could be much more manageable and give me a better quality of life.'<br><br>There have been no new treatment options for metastatic triple negative breast cancer for a significant number of years, and unlike other types of breast cancer, there are no targeted or personalised treatments. It is crucial that a range of treatment options are made available to this group of patients, that can better control the progression of their disease. |
| **Disadvantages of the technology** | |
| 10. What do patients or carers think are the disadvantages of the technology? | One of the main disadvantages of this technology is the side effects. Alopecia was the most common side effect experienced across both the atezolizumab-nab-paclitaxel and the placebo-nab-paclitaxel arms. Side effects such as nausea, cough, neutropenia, pyrexia and hypothyroidism were at least 5 percentage points more common in the atezolizumab and nab-paclitaxel group than in the placebo, nab-paclitaxel arm.<br><br>Side effects that were grade 3 or 4 were more common in the atezolizumab and nab-paclitaxel group, with the rate being 48.7% vs 42.4%. The most common side effects in these groups were neutropenia, decreased neurophil count, peripheral neuropathy, fatigue and anaemia. |

| | |
|---|---|
| | Furthermore, 57.3% of patients in the atezolizumab-nab-paclitaxel group had an adverse event of special interest, suggesting a potential immune-related cause, in comparison to 41.8% of those receiving placebo-nab-paclitaxel.<br><br>Every treatment for breast cancer has some side effects and each patient's situation will be different with side effects affecting some patients more than others. Patients' willingness to take treatments will vary, however, as long as all the side effects are clearly discussed with the patient, they will be able to make their own choice as to the level of risk they will be willing to take. Also some of the more common side effects outlined above are also associated with some of the current treatment options for this group of patients – chemotherapy.<br><br>The patient we spoke to who is currently being treated with atezolizumab said 'I appreciate the possible side effects and I wouldn't continue to take it if it made my quality of life so bad that it wasn't worth it, however it's the chance of a better quality of life and longer with those that I love that makes the chance of being offered it so priceless. I'd rather try it and it not work than feel my life slipping away with no hope.'<br><br>Patients would be required to travel regularly to hospital to receive this treatment, with both atezolizumab and nab-paclitaxel being administered intravenously by infusion. Patients would need to receive atezolizuamb on days 1 and 15 of a 28 day cycle and nab-paclitaxel on day 8 of the cycle. This requirement to travel can result in interruptions to a patient's day to day activities and prove burdensome,, however, any potential disruption caused by travelling to regular hospital appointments may be outweighed for patients by the increased progression free survival<br><br>The patient we spoke to makes weekly visits to the hospital and said that 'this becomes a regular, familiar and comforting routine and is not an issue to us, especially as it's giving hope.' |

| | |
|---|---|
| **Patient population** | |
| 11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why. | Not all patients with locally advanced or metastatic triple negative breast cancer will benefit from this treatment. It is only appropriate for those with a PD-L1 expression.<br>The marketing authorisation that has been submitted to the EMA for atezolizumab in combination with nab-paclitaxel is specifically for patients 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. Data shows that patients who expressed PD-L1 did better than those without this biomarker. |
| **Equality** | |
| 12. Are there any potential equality issues that should be taken into account when considering this condition and the technology? | None. |

| **Other issues** | |
|---|---|
| 13. Are there any other issues that you would like the committee to consider? | Not at this stage. |

**Key messages**

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Triple negative breast cancer is a harder-to-treat and often more aggressive type of breast cancer. Its management remains one of the greatest areas of unmet need and new treatment options are desperately needed.
- In the IMpassion 130 trial, atezolizumab in combination with nab-paclitaxel led to a longer progression free survival for patients with PD-L1, when compared to placebo and nab-paclitaxel (with a median PFS of 7.5 months, versus 5.0 months respectively).
- This delay in disease progression (an additional 2.5 months on average) is important as it enables patients to spend quality time with their friends and families, as well as increasing the likelihood of people being able to continue with their daily activities, which can improve the emotional wellbeing of both patients and their families.
- There are some increased side effects from this treatment option compared to nab-paclitaxel alone. It would also require frequent visits to hospital to receive the treatment. The benefits and risks of this treatment need to be clearly discussed with the patient to ensure they can make a decision that is right for them.
- Atezolizumab in combination with nab-paclitaxel could offer a much-needed new treatment option for patients with metastatic triple negative breast cancer.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

# Clinical expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

**Information on completing this expert statement**

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- Your response should not be longer than 13 pages.

| **About you** | |
|---|---|
| 1. Your name | **Andrew Wardley** |
| 2. Name of organisation | **The Christie** |
| 3. Job title or position | **Consultant and Honorary Professor in Breast Medical Oncology** |

| | |
|---|---|
| 4. Are you (please tick all that apply): | ☒ an employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ a specialist in the treatment of people with this condition?<br>☒ a specialist in the clinical evidence base for this condition or technology?<br>☐ other (please specify): |
| 5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☒ yes, I agree with it<br>☐ no, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☐ other (they didn't submit one, I don't know if they submitted one etc.) |
| 6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.) | ☒ yes |
| **The aim of treatment for this condition** | |

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| 7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.) | Improve progression free survival and overall survival for patients with metastatic triple negative breast cancer |
| 8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.) | An improvement of 2.8 months was seen in PFS for the first trial of trastuzumab in HER-2 positive breast cancer. The development of HER-2 targeting has been one of the most important advances in cancer treatment in the last 20 years<br>Atezolizumab produces a similar magnitude of benefit in this trial. This should be considered as a new targeted therapy in breast cancer. The improvement of 10 months in overall survival for the atezolizumab treated patients with PDL-1 expression represents a very meaningful improvement in what is considered the worst subtype of breast cancer (given the lack of effective treatments hitherto). |
| 9. In your view, is there an unmet need for patients and healthcare professionals in this condition? | Yes<br>The median overall survival for metastatic triple negative breast cancer is typically considered to be 12-13 months. The median overall survival of 15.5 months in the PDL-1 positive in the placebo–nab-paclitaxel group is slightly better than historical data and probably represents the population selected and maybe the improvement seen over years with better staging and earlier detection of metastatic breast cancer<br>The Kaplan–Meier analyses showed a median overall survival of 25.0 months in the PD-L1–positive subgroup atezolizumab–nab-paclitaxel group which would be an important and clinically meaningful improvement. It compares favorably with 25.1 vs. 20.3 months improvement seen with the first phase III trial of trastuzumab wit chemotherapy in metastatic breast cancer |

| What is the expected place of the technology in current practice? | |
|---|---|
| 10. How is the condition currently treated in the NHS? | The only treatment available currently for metastatic triple negative breast cancer is chemotherapy in various forms |
| • Are any clinical guidelines used in the treatment of the condition, and if so, which? | There are several guidelines NICE, ASCO, ESMO, NCCN |
| • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) | Well defined<br>Nuances about the sequence of chemotherapies |
| • What impact would the technology have on the current pathway of care? | Would replace chemotherapy alone for PDL-1 positive metastatic triple negative breast cancer as first line therapy |
| 11. Will the technology be used (or is it already used) in | Currently there is access through an EAMS program |

| | |
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| the same way as current care in NHS clinical practice? | |
| • How does healthcare resource use differ between the technology and current care? | Weekly paclitaxel and capecitabine probably represent the most commonly used chemotherapy as first line therapy<br>The addition of atezolizumab would impact on the systemic anti-cancer therapy services and the acute oncology services |
| • In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.) | Specialist services |
| • What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.) | The rate of increase of effective systemic anti-cancer therapy for all cancers places and increasing burden on the workforce and facilities required to supervise and deliver them<br>there is an urgent to address this problem |
| 12. Do you expect the technology to provide clinically meaningful benefits compared with current care? | Yes as above |
| • Do you expect the technology to increase | Yes as above |

| | |
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| length of life more than current care? | |
| • Do you expect the technology to increase health-related quality of life more than current care? | Yes<br>There are additional side-effects to be considered but in the context of metastatic triple negative breast cancer these are acceptable.<br>there was no difference in quality of life |
| 13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? | PDL-1 positive metastatic triple negative breast cancer |
| **The use of the technology** | |
| 14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant | Will be familiar to those already using PD1/PDL1 monoclonal antibodies for other cancers<br><br>Will be new to breast cancer only oncologist not involved in the trials of these agents<br><br>The biggest issue is the ongoing shortage of oncologists nurses and facility space to deliver all the systemic anti-cancer therapy required in England and Wales. Breast cancer represents 35% of systemic anti-cancer therapy activity |

| | |
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| treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.) | there is needs to be consideration of where treatment is given and who gives it and supervises care.<br><br>there has be no increase in Breast Medical Oncology consultant workforce at our trust to match the increase in demand |
| 15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing? | PDL-1 testing required |
| 16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? | |
| 17. Do you consider the technology to be innovative in | Yes first in class for metastatic breast cancer |

| | |
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| its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? | |
| • Is the technology a 'step-change' in the management of the condition? | Yes as described above |
| • Does the use of the technology address any particular unmet need of the patient population? | Yes the outlook for metastatic triple negative breast cancer is very poor at present |
| 18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life? | Immune related side-effects. These are treatable and do not affect all patients. On balance considering the nature of metastatic triple negative breast cancer these are acceptable |
| **Sources of evidence** | |

| | |
|---|---|
| 19. Do the clinical trials on the technology reflect current UK clinical practice? | The control arm nab-paclitaxel is not routinely used. The active agent paclitaxel is however. Another trial with weekly paclitaxel atezolizumab will shortly complete recruitment |
| • If not, how could the results be extrapolated to the UK setting? | |
| • What, in your view, are the most important outcomes, and were they measured in the trials? | PFS and OVERALL SURVIVAL which were both measured |
| • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? | |
| • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | The drug class and side-effects are well understood |
| 20. Are you aware of any relevant evidence that might | No |

| | |
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| not be found by a systematic review of the trial evidence? | |
| 21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA116] | Impassion 131 the weekly paclitaxel atezolizumab trial expected to report at end of year |
| 22. How do data on real-world experience compare with the trial data? | No real world data as yet in breast cancer |
| **Equality** | |
| 23a. Are there any potential equality issues that should be taken into account when considering this treatment? | No |

| | |
|---|---|
| 23b. Consider whether these issues are different from issues with current care and why. | |

**Key messages**

24. In up to 5 bullet points, please summarise the key messages of your statement.

- New targeted therapy
- Worst type of breast cancer with only chemotherapy at present
- Improved pfs and improved overall survival with clinically meaningful improvement
- Side-effects well understood and guidelines for management published
- Ever increasing demand on over-stretched systemic anti-cancer therapy services and workforce

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

**Your privacy**

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

# Clinical expert statement

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| **About you** | |
|---|---|
| 1. Your name | **Dr Mukesh B Mukesh** |
| 2. Name of organisation | **Colchester General Hospital**<br>**East Suffolk & North Essex NHS foundation Trust** |

| | |
|---|---|
| 3. Job title or position | **Consultant Clinical Oncologist** |
| 4. Are you (please tick all that apply): | ☐ an employee or representative of a healthcare professional organisation that represents clinicians?<br>☒ a specialist in the treatment of people with this condition?<br>☒ a specialist in the clinical evidence base for this condition or technology?<br>☐ other (please specify): |
| 5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☒ yes, I agree with it<br>☐ no, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☐ other (they didn't submit one, I don't know if they submitted one etc.) |
| 6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.) | ☐ yes |

| The aim of treatment for this condition | |
|---|---|
| 7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.) | The main aims of the treatment in metastatic Triple Negative Breast cancer (TNBC) are to stop disease progression and improve patients' quality of life. The treatment should have acceptable and manageable side effects. The treatment should also improve patient survival and/or proportion of patients living longer. |
| 8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.) | a. improvement in median progression free survival (PFS) and overall survival (OS)<br>b. Improvement in proportion of patients being alive 2 years and beyond. |
| 9. In your view, is there an unmet need for patients and healthcare professionals in this condition? | Yes, there is an unmet need for patients with metastatic TNBC. Newer drugs for ER positive and Her-2 positive patients have slowed disease progression, improved survival & Quality of life but no major breakthrough has been made before for managing metastatic TNBC. The average survival for patients with metastatic TNBC is extremely poor at 12-18 months. |
| **What is the expected place of the technology in current practice?** | |

| | |
|---|---|
| 10. How is the condition currently treated in the NHS? | There is no current standard of care for metastatic TNBC. Different chemotherapy agents have been used including weekly Paclitaxel, 3 weekly Docetaxel or Anthracycline. |
| • Are any clinical guidelines used in the treatment of the condition, and if so, which? | Both NCCN and ESMO guidelines confirm multiple lines of chemotherapy used for metastatic TNBC with no preferred chemotherapy regime used as first line treatment. |
| • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) | No standard of care with no consensus among colleagues in England |
| • What impact would the technology have on the current pathway of care? | Combination of Atezolizumab and Nab-Paclitaxel will become the standard 1st line treatment |
| 11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? | |

| | |
|---|---|
| • How does healthcare resource use differ between the technology and current care? | Currently Immunotherapy is not used for management of breast cancer, though Atezolizumab used in NHS for management of metastatic Lung cancer. Nab-Paclitaxel is also not routinely used in the NHS. |
| • In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.) | Secondary care/Specialist Cancer centres with experience in using Immunotherapy |
| • What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.) | Training of breast colleagues on potential complications of Atezolizumab and management of special immune mediated toxicities. |
| 12. Do you expect the technology to provide clinically meaningful benefits compared with current care? | |
| • Do you expect the technology to increase length of life more than current care? | Yes, based on the Impassion 130 data |

| | |
|---|---|
| • Do you expect the technology to increase health-related quality of life more than current care? | The technology will maintain the patient's QOL for longer |
| 13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population? | PD-L1 positive (≥ 1%) Triple negative Breast Cancer |
| **The use of the technology** | |
| 14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors | Immunotherapy drugs are already used in NHS hospitals for patients with lung cancer, Melanoma and Urothelial cancers. Chemotherapy units, Oncology wards and Acute Oncology staff are well trained to recognise and manage the uncommon Immunotherapy related toxicities. There are established guidelines to manage these side effects and it should not be challenging to use Atezolizumab for breast cancer patients. There would be general patient acceptance to this treatment as the prognosis otherwise is extremely poor. The technology in question has manageable and acceptable safety profile with no significant impact on Quality of life. |

| | |
|---|---|
| affecting patient acceptability or ease of use or additional tests or monitoring needed.) | a. Breast oncology professionals would need some initial support to recognise and manage Immune mediated side effects.<br><br>b. Timely PD-L1 testing would be important |
| 15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing? | a. Metastatic TNBC confirmed histologically<br><br>b. Patient tumour should be PD-L1 positive ≥1%<br><br>c. Patient PS should be 0-1<br><br>d. Treatment to continue till disease progression |
| 16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? | No |
| 17. Do you consider the technology to be innovative in its potential to make a | |

| | |
|---|---|
| significant and substantial impact on health-related benefits and how might it improve the way that current need is met? | |
| • Is the technology a 'step-change' in the management of the condition? | Yes, first drug to have shown positive results in metastatic TNBC |
| • Does the use of the technology address any particular unmet need of the patient population? | Yes, as mentioned before, poor outcome for patients with metastatic TNBC with no really progress in treatments. Atezolizumab offers the first treatment to significantly improve Progression free survival and overall all survival for patients with PD-L1 positive TNBC. |
| 18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life? | Most of the treatment related side effects are due to chemotherapy. The chances of developing specific immune mediated side effects are quite small. They are usually reversible and should not have a prolong impact on patients' quality of life. |
| **Sources of evidence** | |

| | |
|---|---|
| 19. Do the clinical trials on the technology reflect current UK clinical practice? | No, Nab-Paclitaxel is currently not reimbursed in the UK apart from patients who develop hypersensitivity to Paclitaxel and Docetaxel. |
| • If not, how could the results be extrapolated to the UK setting? | Gradishar et al. Phase III Trial of Nanoparticle Albumin-Bound Paclitaxel Compared With Polyethylated Castor Oil– Based Paclitaxel in Women With Breast Cancer reported in JCO 2005 greater efficacy and favourable safety profile of Nab-Paclitaxel over Paclitaxel.<br>The Nab-Paclitaxel does not require corticosteroid premedication. Corticosteroid pre-medication is immunosuppressive and can potentially affect Atezolizumab activity and hence combination of Nab-Paclitaxel and Atezolizumab may be favourable. |
| • What, in your view, are the most important outcomes, and were they measured in the trials? | Improvement in Progression Free Survival, Overall Survival and impact on Quality of Life. All these outcomes were measured in the Impassion 130 trial. |
| • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? | N.A |
| • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? | No |

| | |
|---|---|
| 20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence? | No |
| 21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA116] | The technology TA116 was looking at the use of Gemcitabine and Paclitaxel as an option of metastatic Breast cancer. The technology was not specific for patients with TNBC who have a worse outcome. |
| 22. How do data on real-world experience compare with the trial data? | N. A |
| **Equality** | |
| 23a. Are there any potential equality issues that should be taken into account when considering this treatment? | No |

| | |
|---|---|
| 23b. Consider whether these issues are different from issues with current care and why. | NA |

**Key messages**

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Unmet need for metastatic TNBC patients as current prognosis is very poor.
- No standard of care for 1st line treatment in metastatic TNBC based on NCCN or ESMO guidelines
- Combination of Nab-Paclitaxel and Atezolizumab first to show improvement in Progression Free Survival and Overall Survival in metastatic TNBC
- Nab-Paclitaxel and Atezolizumab most effective in patients with PD-L1 expression ≥ 1%
- Treatment related side effects are manageable with no significant impact on patients QOL

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

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……

NICE National Institute for Health and Care Excellence

## Patient expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

**Information on completing this expert statement**

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

| **About you** | |
|---|---|
| 1.Your name | **Holly Heath** |

| | |
|---|---|
| 2. Are you (please tick all that apply): | ☐ a patient with the condition?<br>☐ a carer of a patient with the condition?<br>☒ a patient organisation employee or volunteer?<br>☐ other (please specify): |
| 3. Name of your nominating organisation | Breast Cancer Care and Breast Cancer Now |
| 4. Did your nominating organisation submit a submission? | ☒ yes, they did<br>☐ no, they didn't<br>☐ I don't know |
| 5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission) | ☒ yes, I agree with it<br>☐ no, I disagree with it<br>☐ I agree with some of it, but disagree with some of it<br>☐ other (they didn't submit one, I don't know if they submitted one etc.) |

| | |
|---|---|
| 6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.) | ☒ yes |

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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.....

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.

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**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 |

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# 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.

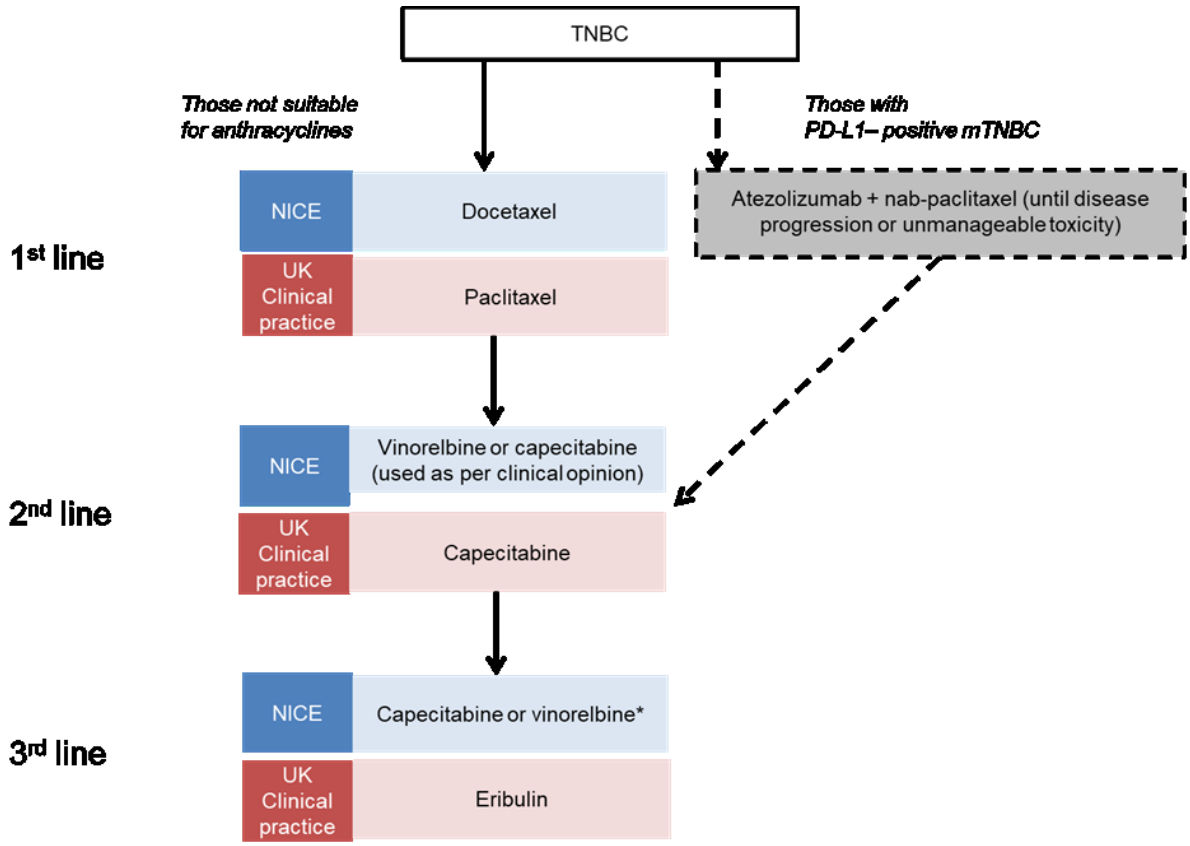


Figure 1 Proposed position of A+nabPx in the NHS treatment pathway

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<br>Parameter and specification | Comparison between the decision problem outlined in the NICE scope and addressed in the company submission |
|---|---|
| **Population**<br>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**<br>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**<br>• Anthracycline-based chemotherapy<br>• 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<br>The company carried out an indirect comparison of A+nabPx versus docetaxel and versus paclitaxel |
| **Outcomes**<br>• OS<br>• PFS<br>• RR<br>• AEs<br>• 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<br>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**<br>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY<br>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<br>Costs will be considered from an NHS and Personal Social Services perspective<br>The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account<br>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)<br>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<br>The costs have been calculated from the NHS perspective<br>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<br>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**<br>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<br>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)<br>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<br>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)<br>• 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<br>• The company performed an exploratory analysis of immune biomarker subgroups (CS, pp46-49); this analysis was pre-specified in the TSAP (p14)<br>• 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)<br>p-value (log-rank)[a] | | 0.62 (0.49 to 0.78)<br><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)<br>p-value (Cochran-Mantel-Haenszel)[d] | | 16.3% (5.7% to 26.9%)<br>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.

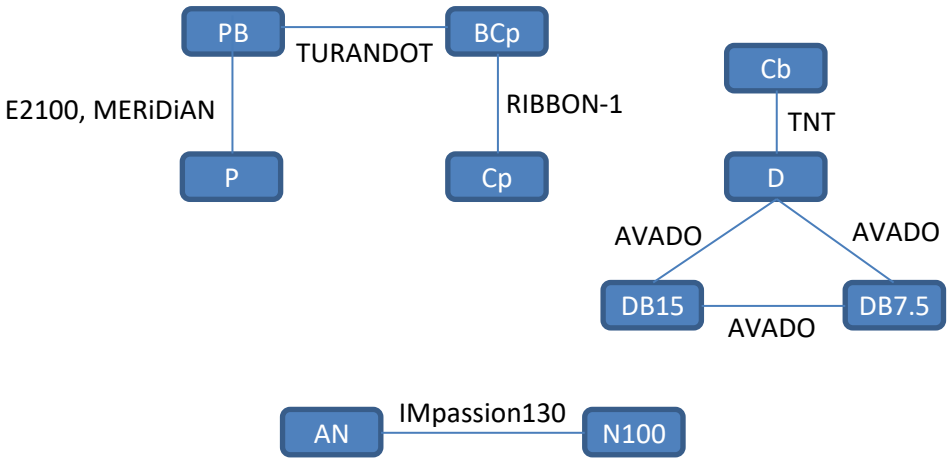


Figure 2 Network of trials for OS

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

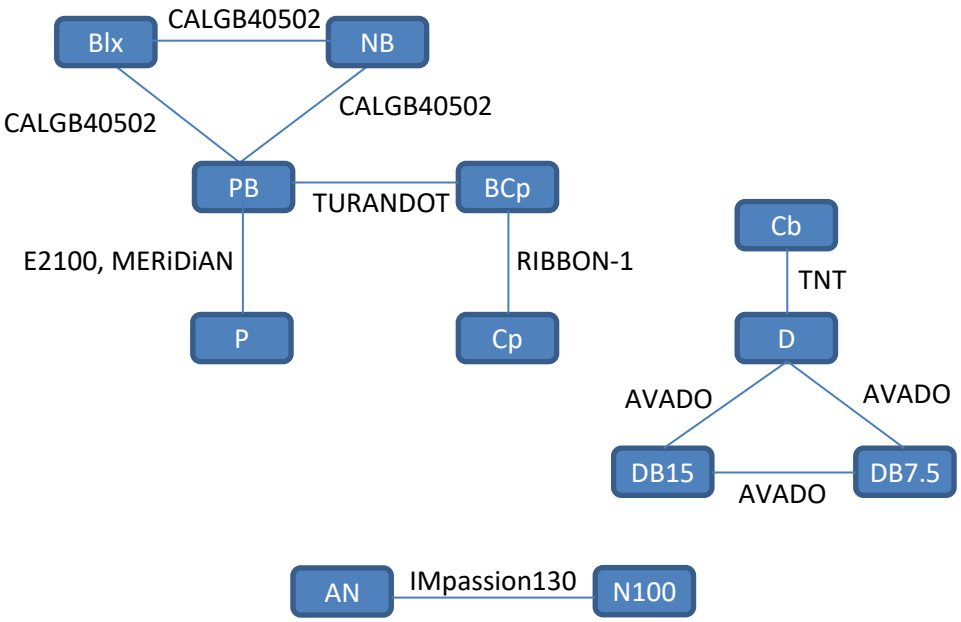


Figure 3 Network of trials for PFS

AN=atezolizumab+nab-paclitaxel; BCp=bevacizumab+capecitabine; BIx=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.

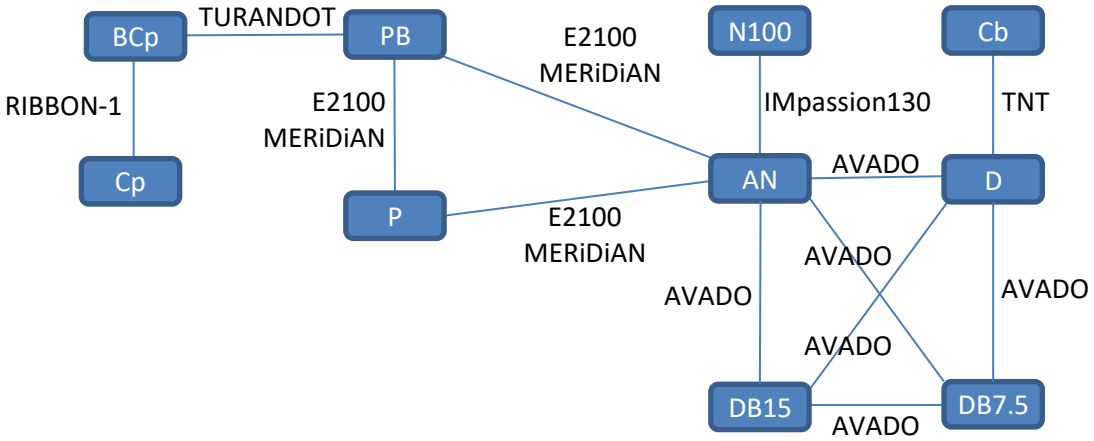


Figure 4 Final connected network for OS

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

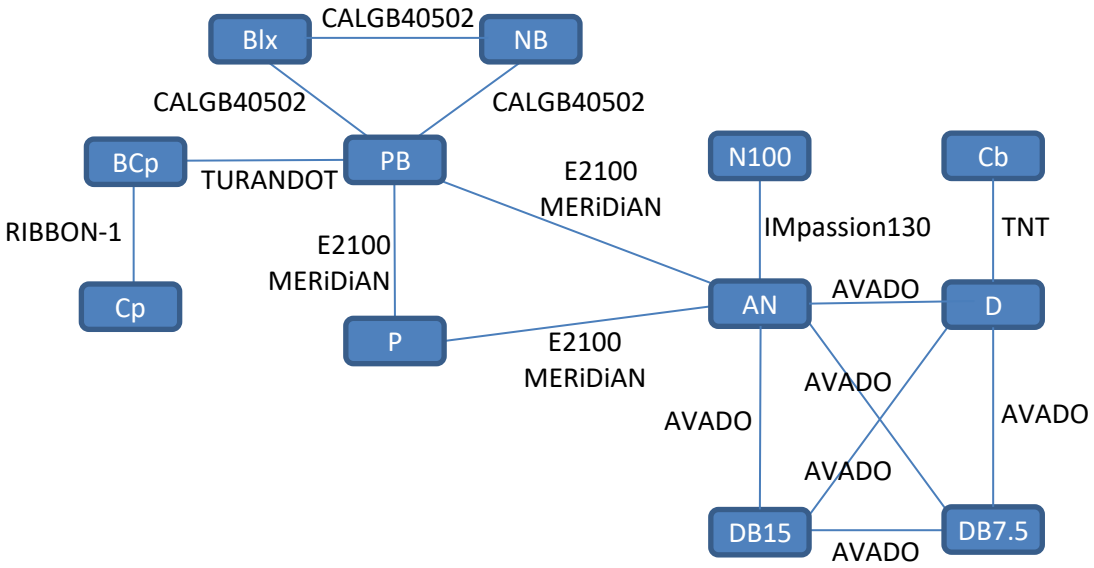


Figure 5 Final connected network for PFS

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.

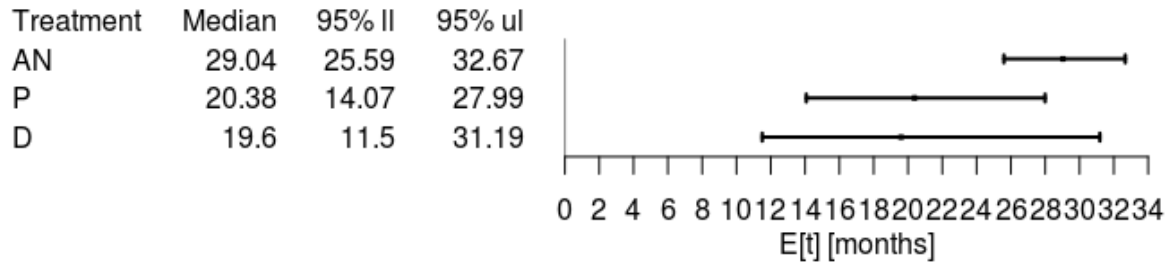


Figure 6 Restricted mean 5-year OS times based on extrapolations over a 5-year time horizon

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

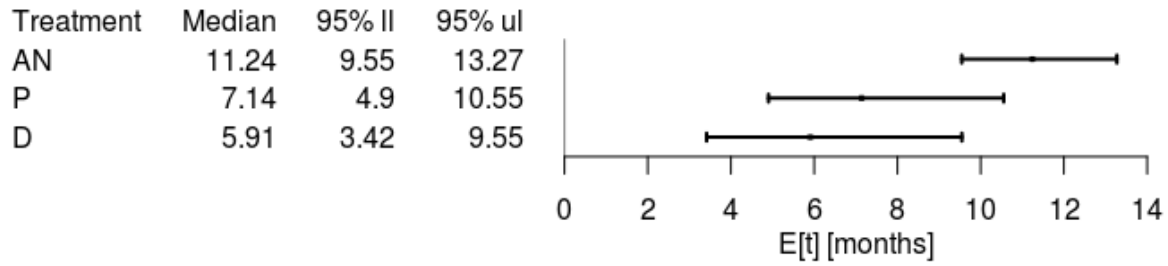


Figure 7 Restricted mean 5-year PFS times based on extrapolations over a 5-year time horizon

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

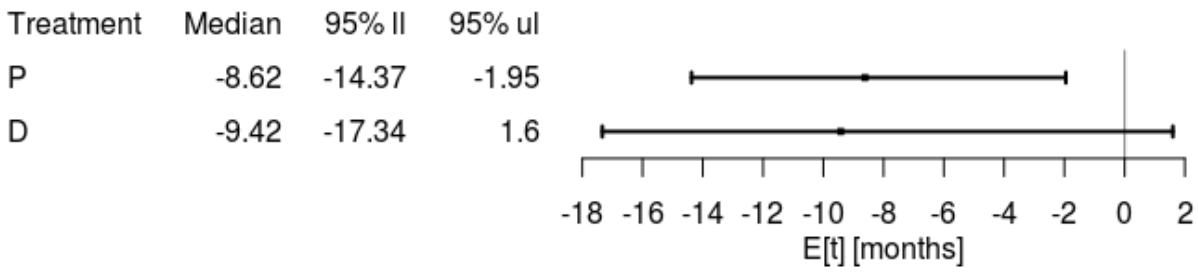


Figure 8 Differences between restricted mean OS times for paclitaxel and docetaxel versus A+nabPx

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

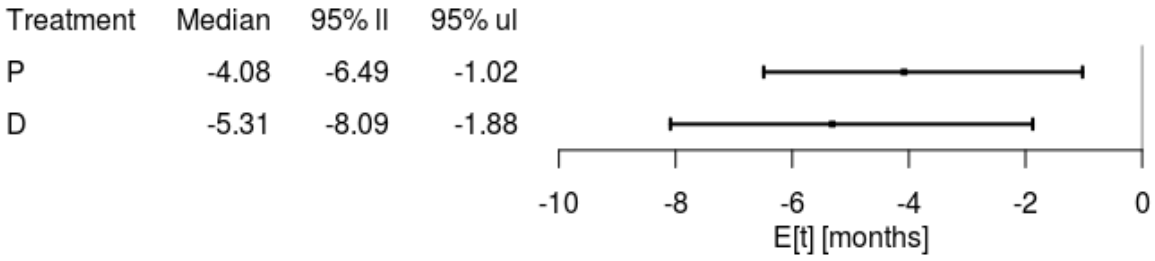


Figure 9 Differences between restricted mean PFS times for paclitaxel and docetaxel versus A+nabPx

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.

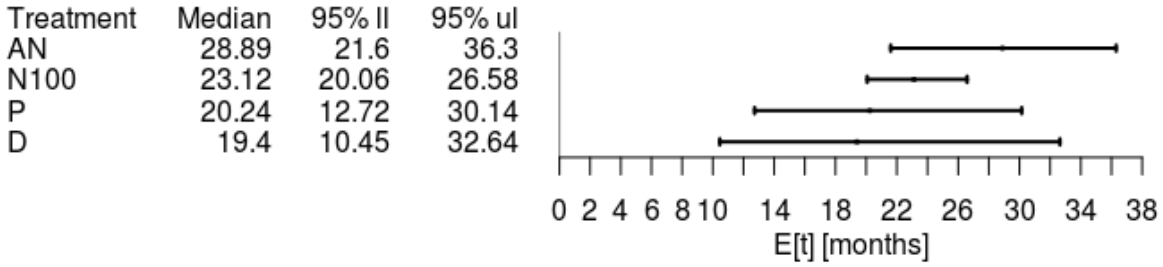


Figure 10 Restricted mean 5-year OS times based on extrapolations over a 5-year time horizon

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

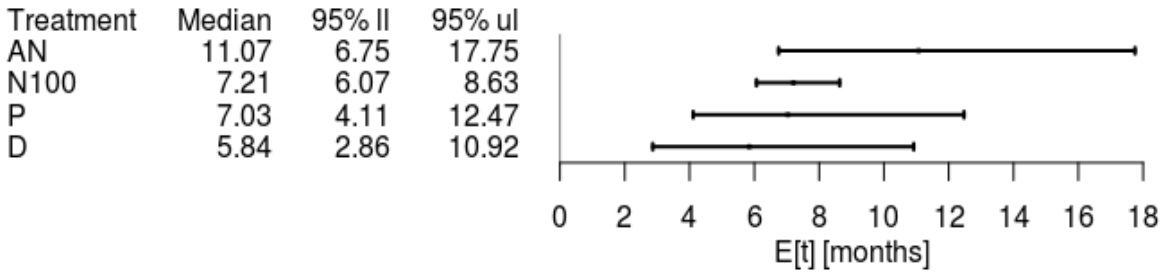


Figure 11 Restricted mean 5-year PFS times based on extrapolations over a 5-year time horizon

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 |

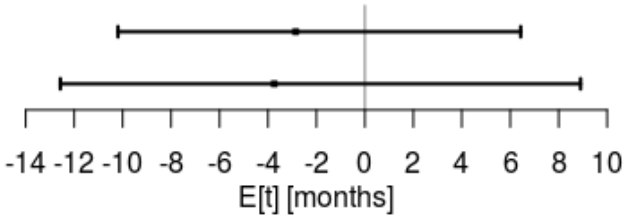


Figure 12 Differences between restricted mean OS times for paclitaxel and docetaxel versus nabPx

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 |

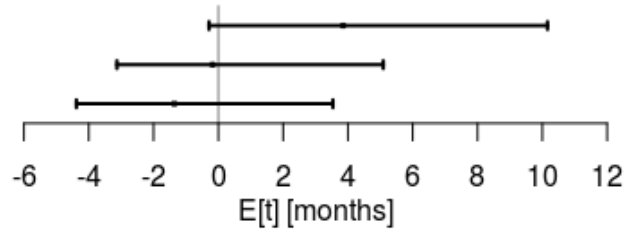


Figure 13 Differences between restricted mean PFS times for A+nabPx, paclitaxel and docetaxel versus nabPx

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<br><br>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<br>• Model type, structure, source of input parameters and assumptions<br>• Cost drivers as reported in sensitivity analyses |
| **Study design** | • Cost effectiveness analyses<br>• Cost utility analyses<br>• Cost minimisation analyses<br>• 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.

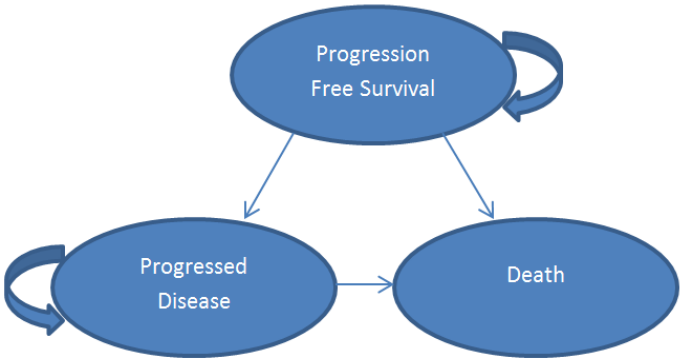


Figure 14 Structure of the company model

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

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

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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.

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# 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<br>$d_k \sim dnorm(0, 0.0001)$ … piece k |
| Fractional polynomials | $\begin{pmatrix}\mu_1\\ \mu_2\\ \mu_3\end{pmatrix} \sim dmnorm(\mathrm{M}, \Sigma)$<br><br>$\begin{pmatrix}d_1\\ d_2\\ d_3\end{pmatrix} \sim dmnorm(\mathrm{M}, \Sigma)$<br><br>$\mathrm{M} \sim \begin{matrix}0\\0\\0\end{matrix}$<br><br>$\Sigma \sim \begin{matrix}0.0001 & 0 & 0\\ 0 & 0.0001 & 0\\ 0 & 0 & 0.0001\end{matrix}$ |

Source: adapted from CS Appendix D, Table 11

Table 36 Informative priors for between study heterogeneity

| Endpoint | Base case | Sensitivity analyses |
|---|---|---|
| OS | $\tau^2 \sim dlnorm(-4.18, 1.41^{-2})$ | $\tau^2 \sim dlnorm(-4.18, 1.8^{-2})$<br>Log-normal with same median as main prior but 2x larger upper 95% quantile |
| PFS | $\tau^2 \sim dlnorm(-2.94, 1.79^{-2})$ | $\tau^2 \sim dlnorm(-2.94, 2.2^{-2})$<br>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<br>Age ≥18 years<br>ECOG PS 0 or 1<br>Previous chemotherapy for LR or metastatic disease not permitted | Docetaxel, 100 mg/m$^2$ on day 1<br>3-week cycles |
| | | | | Docetaxel, 100 mg/m$^2$ on day 1<br>Bevacizumab, 7.5 mg/kg on day 1<br>3-week cycles |
| | | | | Docetaxel, 100 mg/m$^2$ on day 1<br>Bevacizumab, 15.0 mg/kg on day 1<br>3-week cycles |
| CALGB40502[55] | Phase III, open-label RCT | USA | Stage IV or IIIC BC not amenable to local therapy<br>Age ≥18 years<br>ECOG PS 0 or 1<br>No prior chemotherapy for metastatic disease or prior treatment with bevacizumab was allowed | Paclitaxel, 90/m$^2$ on days 1, 8 and 15<br>Bevacizumab, 10mg/kg on days 1 and 15<br>28-day cycles |
| | | | | Nab-paclitaxel, 1500/m$^2$ on days 1, 8 and 15<br>Bevacizumab, 10mg/kg on days 1 and 15<br>28-day cycles |
| | | | | Ixabepilone, 16/m$^2$ on days 1, 8 and 15<br>Bevacizumab, 10mg/kg on days 1 and 15<br>28-day cycles |
| E2100[60] | Phase III, open-label RCT | US and Canada | MBC<br>Females<br>Age ≥18 years<br>ECOG PS 0 or 1<br>No prior cytotoxic therapy for MBC | Paclitaxel, 90/m$^2$ on days 1, 8 and 15<br>Bevacizumab, 10mg/kg on days 1 and 15<br>28-day cycles |
| | | | | Paclitaxel, 90mg/m$^2$ on day 1, 8 and 15<br>28-day cycles |
| IMpassion130 | Phase III, double-blind RCT | International (41 countries) | LA or metastatic TNBC<br>Age ≥18 years<br>ECOG PS 0 or 1<br>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<br>Atezolizumab, 840 mg (IV) on days 1 and 15<br>28 day cycles |
| | | | | Nab-paclitaxel 100 mg/m$^2$ (IV) on days 1, 8 and 15<br>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<br>ECOG PS ≤2<br>No previous chemotherapy for LR or metastatic disease permitted | 28-day cycles |
| | | | | Paclitaxel, 90/m$^2$ on days 1, 8 and 15<br>Bevacizumab, 10mg/kg on days 1 and 15<br>28-day cycles |
| RIBBON-1[69] | Phase III, double-blind RCT | International (22 countries) | LR or MBC<br>Age ≥18 years<br>ECOG PS 0 or 1<br>Previous chemotherapy for LR or metastatic disease not permitted | Capecitabine, 1000 mg/m2 bd on days 1 and 14<br>21-day cycle |
| | | | | Capecitabine, 1000 mg/m2 bd on days 1 and 14<br>Bevacizumab, 15mg/kg (IV) once every cycle<br>21-day cycle |
| TNT[73] | Phase III, open-label RCT | UK | TNBC or BRCA1 or BRCA2 mutation carrier with any ER, PgR, HER2 status<br>Females<br>Age ≥18 years<br>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<br>Females<br>Age ≥18 years<br>ECOG PS 0-2<br>No prior chemotherapy for LR or MBC | Paclitaxel, 90mg/m$^2$ on days 1, 8 and 15<br>Bevacizumab, 10mg/kg on days 1 and 15<br>28-day cycles |
| | | | | Capecitabine, 1000/m$^2$ bd on days 1-14<br>Bevacizumab, 10mg/kg on days 1 and 15<br>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'<br><br>Insert formula in cell BP11 =IF(AND('Cost Inputs'!$A$33=TRUE,E11>=18),0,INDEX(new_admin_cost,IF(MOD(E11+1,4)=0,4,MOD(E11+1,4)),4)*BL11*BN11)<br><br>Copy cell formula to range = BP11:BP1835<br><br>Insert formula in cell BQ11 =IF(E11>=18,0,'Dosing Calc'!$AM$8*BL11*BN11)<br><br>Copy cell formula to range = BQ11:BQ1835<br><br>Insert formula in cell BR11 =IF(E11=0,p_c_ae_com2,0)<br><br>Copy cell formula to range = BR11:BR1835 |
| R1 (**docetaxel**): setting efficacy of paclitaxel to be equal to nab-paclitaxel (by setting the costs of nab-paclitaxel to be the same as docetaxel) | In Sheets 'nappac'<br><br>Insert formula in cell BP11 = IF(E11>=18,0,IF(MOD(E11,3)=0,'Administration Cost'!$H$13,0)*BL11*BN11)<br><br>Copy cell formula to range = BP11:BP1835<br><br>Insert formula in cell BQ11 = IF(BP11=0,0,BL11*BN11*'Dosing Calc'!$AN$8)<br><br>Copy cell formula to range = BQ11:BQ1835<br><br>Insert formula in cell BR11 =IF(E11=0,p_c_ae_com3,0)<br><br>Copy cell formula to range = BR11:BR1835 |

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

# National Institute for Health and Care Excellence
# Centre for Health Technology Evaluation

## ERG report – factual accuracy check

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

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Friday 21 June 2019** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

## Issue 1 ERG preferences on duration of treatment effect and misinterpretation of NICE TA520 in the application of duration of treatment effect

| Description of problem | Description of proposed amendment | Justification for amendment | ERG Response |
|---|---|---|---|
| <u>Inappropriate application of treatment effect cap</u><br><br>Please see: Section 5.6.1, Limited Duration of Treatment effect, Page 88. paragraph 2.<br><br>Also, 3 or 5 year treatment duration cap is also mentioned at these places:<br><br>Section 1.8, paragraph 3, page 18.<br><br>Section 5.6.1, paragraph 6, page 88.<br><br>The ERG have provided scenarios that limited the duration of atezolizumab with nab-paclitaxel treatment effect to 3 or 5 years.<br><br>Firstly, there is no evidence to support any treatment effect cap: atezolizumab is a monoclonal antibody which activates an individual's immune system to exert its effects. This is a different mechanism of action to chemotherapy and therefore, there | Proposed amendment:<br><br>Amend statement "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 (Atezolizumab for treating locally advanced or metastatic NSCLC after chemotherapy)" (Page 88, Section 5.6.1, Limited Duration of Treatment effect, paragraphs 2)<br><br>to:<br><br>"Limiting the duration of treatment effect for A+nabPx to a maximum of 3 year's duration, post-treatment initiation, would be more pessimistic than the preferred assumptions supported by the NICE Appraisal Committee (AC) during TA520 and TA584 (Atezolizumab for treating locally advanced or metastatic NSCLC after chemotherapy), where the preference of the AC was that the duration of treatment effects was anticipated to last for up 3 years post-treatment *discontinuation*". | The ERG has missed one crucial detail in the interpretation of treatment effect caps within TA520 (2) and TA584 (3): a 2-year stopping rule was imposed so all patients (whether responding to therapy or not) had to come off treatment 2 years post-treatment initiation. Only upon treatment discontinuation (for all patients) was a treatment effect cap considered.<br><br>It has been agreed by the Committee in TA520, that it is plausible that the effects of atezolizumab would continue after stopping treatment:<br><br>"The company explained that atezolizumab's mechanism of action suggests that its effects on tumours would continue after treatment stopped." (1), and, "It (the AC) concluded that although it was biologically plausible for the treatment effect to continue after stopping treatment, the length of any continued effect was | The ERG statement is not factually inaccurate.<br><br>The approach taken in TA520 was to limit the duration of treatment effect to 5 years from the start of treatment. This approach was based on the understanding that as all patients stopped treatment at 2 years (and most patients stopped treatment much earlier than 2 years) the longest post-discontinuation treatment effect was somewhere between 3 years and 5 years. It is noted that the treatment effect equalised for both arms in the model 5 years after treatment commenced because it is impractical in a partitioned survival model to apply treatment waning from the times people stopped treatment.<br><br>To improve clarity, the wording in the ERG report has been changed to:<br><br>"Limiting the duration of treatment |

| | | | |
|---|---|---|---|
| is no rationale why treatment effect would stop and start as chemotherapy would. Further, the selection of 3 or 5 years is completely arbitrary, subjective and in contrast to the known efficacy profile of cancer immunotherapies whereby there is a proportion of patients who have long, durable responses.<br><br>The ERG provide the rationale that this was based upon the approach used in TA520 (1). However, the company would like to highlight that the ERG have misinterpreted the AC's preferred assumptions in TA520. | | uncertain." (1)<br><br>According to the preferred economic model approach (Model 2), at 3 years, the proportion of patients on treatment in the A+nabPx arm were: [redacted]% receiving A and [redacted]% receiving nabPx. Hence, it is implausible and inconsistent with previous committee conclusions that a treatment effect cap should be imposed whilst patients are still on and therefore benefiting from treatment.<br><br>If the ERG were to take a consistent approach to TA520 and TA584 and implement a 3 or 5 year treatment effect cap once all patients had discontinued treatment this should be implemented at 11.5 years and 13.5 years post-treatment initiation, respectively, as only at 8.5 years do all patients discontinue treatment. | effect for A+nabPx would be in line with the approach supported by the NICE Appraisal Committee (AC) during TA520 (Atezolizumab for treating locally advanced or metastatic NSCLC after chemotherapy) although it is noted that in TA520 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.<br><br>(Page 88, Section 5.6.1, Lifetime Duration of Treatment effect, paragraph 2), |
| <u>Rationale for applying a maximum treatment duration of 3 or 5 years, and potential for misinterpretation of rationale being consistent with TA520 and TA584</u><br><br>Please see: Page 17, Section 1.6, last paragraph. | Proposed amendment:<br><br>After the sentence: "The ERG considered scenarios that limited the duration of treatment effect to 3 and 5 years, noting that, in the IMpassion130 trial, only [redacted] of patients were still progression-free and receiving A+nabPx treatment at 3 years." (Page 17, Section 1.6, last paragraph.) | The ERG justify the use of a treatment cap (at 3 or 5 years) because only [redacted] of patients were still progression-free and receiving A+nabPx treatment at 3 years. However, this is inconsistent with the approach utilized by previous ACs for TA520 and TA584.<br><br>For consistency to TA520 and | Please see the above response as to how treatment waning was applied in TA520. Further, to take the company position described throughout 'Issue 1' would imply that people who stopped treatment early in the trial continue to get benefit from treatment for as long as other |

| | | | |
|---|---|---|---|
| The ERG's rationale for the time point of implementing a treatment effect cap is inconsistent with the AC's preferences in TA520 and TA584. | propose adding a sentence:<br>"The use of [redacted]% to define the point of expected duration of treatment effects is subjective and not in line with the AC's preferences in TA520 and TA584, where it was assumed that the treatment duration cap should be implemented after all patients discontinued treatment at 2 years | TA584, *all* patients (and not [redacted]%) should have discontinued treatment (and that was at 2 years in TA520 and TA584), before a treatment effect cap was implemented. | people on the trial remain on treatment. The ERG does not consider this plausible.<br>No change required. |
| <u>Statement that company has not submitted any evidence to support the effect of treatment duration</u><br>Please see: Section 1.9.2, Cost-effectiveness evidence, paragraph 3.<br>The ERG has misled the reader on what evidence has, or has not been provided by the company. | Proposed amendment:<br>Amend: "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 "<br>to:<br>"The company has assumed that, compared to paclitaxel or docetaxel, the effect of treatment with A+nabPx lasts for a lifetime. Whilst this lifetime treatment effect duration is unlikely, the long-term model outcomes (at various timepoints between 30 to 120 months) of A+nabPx described in the model were validated satisfactorily by input from 3 clinicians" | In Document B, Page 105, Table 37, summary (average) percentages of three clinician's expert opinions are provided at various time points between 30 to 120 months. This validates long-term OS outcomes of A+nabPx, which implicitly required clinical experts to reflect upon their anticipated duration of treatment effect. Expert opinion constitutes a form of evidence, featuring in the hierarchy of evidence (4). | The ERG paragraph is not factually inaccurate.<br>Clinical validation of model outputs at 30 months and 120 months is not evidence that treatment effect lasts a lifetime.<br>No change required. |

## Issue 2 Factual inaccuracies relating to the network meta-analysis (NMA)

| Description of problem | Description of proposed amendment | Justification for amendment | ERG response |
|---|---|---|---|
| <u>Inappropriate utilisation of, and conclusions from credible intervals in the NMA</u><br><br>Section 4.8.7, Paragraph 2, page 63<br><br>"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."<br><br>This implies that a lack of statistical significance from the NMA should necessarily be transferred to the modelled survival benefit. | Proposed amendment:<br><br>Following Section 4.8.7, Paragraph 2, page 63, to add the following text:<br><br>"However, statistical significance of hazard ratios per piece is not a necessary or sufficient condition for statistical significance of long-term survival benefits. First, the differences between treatments in different pieces can be the opposite sign and cancel each other out. Second, the uncertainty around hazard ratios depends on the widths of pieces which were chosen to fit the data best and thus can be quite small. Third, the variance of restricted mean survival times is a non-linear transformation of the sum of the variances of log-hazard ratios in different pieces and thus does not need to give the same result about statistical significance than the individual parameter estimates. It is accepted that via the alternative to ITCs, if using the P+Nabpx arm to represent paclitaxel and docetaxel OS, PFS and TTOT, there is a large difference between long term landmark survival (OS) derived from | Although results for the comparison of nab-paclitaxel to paclitaxel and docetaxel are not statistically significant, the analyses conducted do indicate some numerical improvements for nab-paclitaxel compared to paclitaxel and docetaxel for OS and for docetaxel in PFS.<br><br>Furthermore, the statement in Section 4.8.7, Paragraph 2, page 63 could be misleading or imbalanced, that a lack of statistical significance from the NMA should necessarily be transferred to the modelled survival benefit.<br><br>Although the credible intervals may be considered wide, the ITCs conducted are not powered to show significant differences between treatments - but assuming equality of these treatments allows no variability in the difference between nab-paclitaxel and paclitaxel/docetaxel which is possible based on these analyses. The use of ITCs does allow this to be captured, but also will allow the uncertainty in this estimate to be reflected.<br><br>The company does not deem statistical significance of hazard ratios in different time intervals a necessary or sufficient condition for assessing statistical significance of the survival benefit of | This is not a factual inaccuracy.<br><br>The ERG does not state, at any point, that the lack of statistical significance of hazard ratios per piece implies that there is no statistically significant long-term survival benefits. In fact, "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." (ERG report, p62).<br><br>The ERG considers that, when developing an economic model, if clinical results for a comparison of the effectiveness of two treatments are not statistically significant different, no difference should be modelled.<br><br>The fact that the OS results from the nabPx arm of the |

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| | the P+Nabpx arm compared with the long term outcomes expected by clinicians for paclitaxel and docetaxel, in this population, in clinical practice. This and any other discussion of ITC vs. P+Nabpx trial arm use warrants further exploration" | atezolizumab + nab-paclitaxel over comparison therapies. Statistical significance also depends on the width of pieces, and the hazard ratios of all pieces contribute to differences in long-term survival between therapies.<br><br>Wide credible intervals should be accounted for in the modelling through sensitivity analyses as opposed to assuming equivalence. The ERG's use of the nab-paclitaxel arm to represent paclitaxel and docetaxel efficacy causes a substantial OS benefit (at various long term survival landmarks) compared with that predicted by clinicians consulted by the company:<br><br>Even using the most conservative OS extrapolation of NabPx (Gomperz distribution), the landmark survival anticipated by the clinical experts for paclitaxel and docetaxel (Document B, Table 40, Page 111) at various timepoints between 30 and 120 months was substantially lower than that predicted by the model.<br><br>Utilising the P+nabPx clinical trial arm only exacerbates this over-estimation further - in a comparison of Gompertz landmark survival for P+nabpx vs. clinical expert opinion survival for paclitaxel/docetaxel: 30 months (30% vs. 17%), 36 months (25% vs. 10%), 48 months (17% vs. 5%), 60 months (13% vs. 3%), 72 months (10% vs, 1%), 120 months (5% vs. 0%)), | IMpassion130 trial do not reflect clinical opinion provided to the company about the expected duration of OS raises questions about the generalisability of the trial results to a UK patient population. The ERG highlights that OS for patients in the nabPx arm of the IMpassion130 trial was much longer than the duration expected by clinical experts and this may suggest that that OS trial result is over-optimistic.<br><br>No change required. |

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| | | demonstrating the ERG's preferred assumption is too optimistic for the comparator effectiveness.<br><br>Additionally, several aspects of the data of the ITC warrant further exploration of differences between paclitaxel, docetaxel and nab-paclitaxel:<br><br>• The docetaxel ITC demonstrated a shorter 5-year restricted mean survival times for both progression-free and overall survival, vs. paclitaxel, and this warrants further exploration.<br><br>• The objective response log-odds ratios versus atezolizumab were much smaller for P+Nabpx 100mg [redacted]) than for docetaxel [redacted]) and paclitaxel ([redacted]). (CS Appendices, Section D.1.4.2). Objective response is considered a meaningful surrogate outcome under chemotherapy.<br><br>• The ITC demonstrated that the 5-year restricted mean overall survival benefit of A+Nabpx over a pooled paclitaxel arm was not statistically significant while the overall survival benefit over paclitaxel in the base case was. This finding suggests that there is substantial heterogeneity between nab-paclitaxel and paclitaxel.<br><br>• Credible intervals can be applied to | |

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| | | the opposite direction, in that the current evidence from the ITC does not rule out an even larger indirect effect of Nabpx vs. paclitaxel. | |
| <u>Clarification on reason for CARIN study exclusion</u><br><br>Please see: Section 4.8.2, Assessment of proportional hazards, page 51 | Proposed amendment:<br>Change ""The JapicCTI-090921,63 CARIN,57 and EGF300162 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)"<br>to:<br>"The JapicCTI-090921,63 CARIN,57 and EGF300162 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 of the CARIN study (company response to the ERG clarification letter, question A10). The CARIN study did not investigate a comparator of interest to this appraisal (capecitabine/bevacizumab + vinorelbine and capecitabine/bevacizumab) and has not been carried out by the company but by an external study group that | The company would like to clarify that the study that had been excluded from the network because the publication could not be replicated was the CARIN study, which did not include a comparator of interest to this appraisal (capecitabine/bevacizumab + vinorelbine and capecitabine/bevacizumab) and had not been carried out by the company but by an external study group that provided individual-level data for this network meta-analysis. | This is not a factual inaccuracy.<br>No change required. |

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| | provided individual-level data for this network meta-analysis." | | |
| Clarification to ERG on company use of adjusted vs. unadjusted Impassion130 data<br><br>Please see Section 4.8.3, last paragraph, page 56:<br><br>"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). This wording suggests that the company extrapolated unadjusted A+nabPx data from the IMpassion130 trial (rather than adjusted A+nabPx data from the PAICs); however, the ERG considers it unlikely that this was the company's approach. 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."<br><br>We would like to provide some clarity here. | Proposed amendment:<br>Alter Section 4.8.3, last paragraph, page 56 and replace with ERG judgement based upon the following information:<br><br>Extrapolations of survival curves and calculations of the area under the curve in the IMpassion130 study were carried out using the functional form of the hazard rate g(·) (i.e. piecewise exponential) and the estimated basic parameters μ_IMpassion130 and d_i (t),i∈{1,…,n_treatments}<br><br>h_(i,IMpassion130) (t)=g(μ_IMpassion130,d_i (t)),<br><br>where μ_IMpassion130 is the reference study's study baseline parameter and d_i (t) is the time varying log-hazard ratio of treatment versus atezolizumab + nab-paclitaxel. The extrapolation was done in discrete time with interval widths of one month over a time horizon of 60 months. No half-cycle correction was applied as the hazard rate was by definition constant within each time interval. As stated in the company submission extrapolated | The ERG were provided with sufficient information to replicate and verify the extrapolations of survival curves and the restricted mean survival times using the reported median basic parameters in the piecewise exponential model. The ERG were also in possession of the posterior simulation traces for the log-hazard ratios of comparison treatments versus A+Nabpx and a request for the posterior simulations of the study baseline parameters at the clarification question stage would have allowed the ERG to replicate and verify the calculations of restricted mean 5-year survival times. Providing this information and making such an amendment will prevent the ERG from having to speculate on this issue. | The ERG has amended the paragraph to:<br><br>"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)." |

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| | survival curves were obtained using median basic parameters which were reported in the company submission. For the assessment of uncertainty around restricted mean 5-year progression-free and overall survival times the extrapolation and calculation of the area under the curve was done using the same methodology as described above but for each iteration of the posterior simulations to obtain 95% credible intervals of restricted mean 5-year survival times. | | |
| <u>Clarification to ERG on company methods for restricted mean 5-year survival times</u><br><br>Section 4.8.3, final paragraph, Page 56:<br><br>"Furthermore, it would not be possible to obtain restricted mean 5-year survival times for paclitaxel, docetaxel and nab-paclitaxel based on extrapolations of IMpassion130 trial data so it is unclear to the ERG how these restricted mean 5-year survival times for paclitaxel, docetaxel and nab-paclitaxel were obtained. Generally, the ERG considers the company's approach to obtaining estimates of restricted 5-year mean survival times to be unclear and is not able to determine | Proposed amendment:<br><br>Alter Section 4.8.3, final paragraph, Page 56 to reflect the ERG's judgement on the following further information:<br><br>The objective of the network meta-analysis was to assess potential outcomes in the (unweighted) IMpassion130 population under alternative treatments as this population informed the cost-effectiveness analysis, and the indirect comparison of costs and effects versus indirectly compared treatments was carried out in this population. Using the study baseline parameter of the IMpassion130 study and the log-hazard ratios of comparison treatments versus atezolizumab + nab-paclitaxel this | The company would have welcomed a clarification question about this topic to be raised, providing the company the opportunity to provide more detail about the calculations as well as the R code and posterior simulations for the calculation of restricted mean 5-year survival times. The calculations could have been replicated by the ERG using the reported basic parameters in the company submission or additional posterior simulations of the IMpassion130 study's baseline hazard requested at the clarification question stage. The company also believes that it was explained clearly in the company submission that extrapolations and calculations of the area under the curve were carried out for the IMpassion130 population. | The ERG has amended the paragraph to:<br><br>"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 |

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| whether appropriate methodology was used."<br><br>We have provided some further clarification | assessment of potential outcomes is possible. | | 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".<br><br>We have also amended the following text on p63 of the ERG report:<br><br>"the company's approach to obtaining estimates of restricted 5-year mean survival times was unclear and the ERG was unable to determine whether appropriate methodology had been used"<br><br>to:<br><br>"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 |

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| | | | 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",<br><br>We have also amended the following text on p65 of the ERG report:<br><br>"the ERG was unable to verify the methods the company used to obtain estimates of restricted 5-year mean survival times"<br><br>to:<br><br>"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"<br><br>We have also amended the following text on p14 of the ERG report:<br><br>"The ERG was unable to determine whether two important aspects of the company's methods, namely (i) |

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| | | | the approach to including and excluding studies from the NMAs and (ii) performing extrapolations to obtain estimates of restricted 5-year mean survival times, were appropriate."<br><br>to:<br><br>"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." |
| Section 4.8.4, paragraph 2, Page 56<br><br>"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 | Proposed amendment:<br><br>Alter Section 4.8.4, paragraph 2, Page 56 to reflect the ERG's judgement on the following further information:<br><br>"The company only used baseline characteristics of metastatic triple- | The company would have welcomed a clarification question regarding patient characteristics of the included populations. This would have given the company the opportunity to clarify this issue and provide more detailed information on patient's baseline characteristics. | This is not a factual inaccuracy.<br><br>The baseline characteristics are presented for the overall trial population rather than for the mTNBC subgroup, so the ERG's text is accurate. |

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| 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."<br><br>We have provided some further clarification | negative populations in the feasibility assessment. Studies were only included in the network meta-analysis if patients had metastatic breast cancer, and either more than 80% of intent-to-treat patients were triple-negative or data on triple-negative cases could be extracted from the Roche data base. Thus, patient characteristics that were assessed in the feasibility assessment were obtained from metastatic triple-negative populations, either from publications of studies that investigated metastatic triple-negative populations or from the subgroup extracted from the Roche data base." | | No change required. |
| <u>Contradicting statement in ERG report</u><br><br>Please see: Section 8.2.2, last paragraph, page 105<br><br>This statement contradicts an earlier statement in the ERG report and also, is not supported as the relevant information was provided in Document B. | Remove the following statement in Section 8.2.2, last paragraph, page 105:<br><br>"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; however, it is not clear whether the deviance information criterion was examined to inform this decision. No reference to the deviance information criterion is made in the company's explanation | In the response to the ERG Clarification letter, it is clearly highlighted that:<br><br>"Subsequently, model selection for OS and PFS was reassessed using the same approach in the CS (Document B, Section B.2.9.2, Page 61)." (ERG Clarification question response)<br><br>Further, within the company submission, deviance information criterion is detailed thoroughly as step within the model selection process: "Following adjustment of the atezolizumab in combination with nab- | The ERG has amended the paragraph to:<br><br>"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." |

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| | of the model selection process.” | paclitaxel arm, a set of candidate statistical models for OS and PFS were fitted. For OS and PFS, the statistical model for each outcome was selected from the set of candidate models based on evidence on the proportionality of hazard rates; the goodness of fit in a frequentist framework; the validity of extrapolations based on 12-month data; Bayesian model diagnostics; a comparison of extrapolated and observed survival curves and a comparison of the goodness of fit of fixed and random effects models.” (Document B, Section B.2.9.2, Page 61).”<br><br>As such, this statement is incorrect and misleading. | |
| <u>Consistency of information provided for comparison to docetaxel</u><br><br>Please see: Section 1.3, Indirect evidence, last paragraph, page 13:<br><br>The above reports improvements vs. paclitaxel for OS, but omits presenting the improvement for OS vs. docetaxel. | Proposed amendment:<br><br>Remove Section 1.3, Indirect evidence, last paragraph, page 13:<br><br>"However, the results suggested that treatment with A+nabPx improved OS versus paclitaxel ([redacted] and [redacted] months respectively), and that treatment with A+nabPx improved PFS versus both paclitaxel ([redacted] and [redacted] months respectively) and docetaxel ([redacted] and [redacted] months respectively).”<br><br>And replace with:<br><br>"However, the results suggested that treatment with A+nabPx improved OS versus paclitaxel ([redacted] vs. [redacted] | This statement refers to the differences between A+nabPx vs. each of paclitaxel and docetaxel. However, it omits presentation of the OS comparison with docetaxel<br><br>This amendment provides consistency of reporting of results, in comparisons vs. paclitaxel and vs. docetaxel. | This is not a factual inaccuracy.<br><br>The ERG has presented results where statistically significant improvements in OS/PFS were observed. There is no statistically significant evidence to suggest that treatment with A+nabPx improves OS in comparison to docetaxel.<br><br>No change required. |

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| | months respectively) and versus docetaxel ([redacted] months). Treatment with A+nabPx improved PFS versus both paclitaxel ([redacted] vs. [redacted] months respectively) and docetaxel ([redacted] months)." | | |
| <u>Further information to clarify surrounding reasons for exclusion of studies from the NMA</u><br><br>Section 4.8.2, paragraph 4, page 50<br><br>"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."<br><br>We have provided some further clarification. | Proposed amendment:<br>If the ERG is satisfied with the justification provided, removal of Section 4.8.2, paragraph 4, page 50 and replacement with:<br><br>"The text in Section D.1.1.6 of the CS Appendices provides *potential* reasons for exclusions rather than specific details of causes of eventual exclusions. The specific reasons for exclusion were highlighted in Table 10 of the Clarification Question responses and follow the conditions of the Flowchart in Figure 2 of Section D.1.1.6 (and are covered in the potential reasons highlighted)" | As presented in the PRISMA flow diagram (Figure 1, page 20) of Appendix D of the company submission, 43 studies were excluded because of differences in populations, study designs, the proportion of triple-negative cases and the proportion of patients receiving first-line therapy.<br><br>The clarification letter to the ERG included a table giving reasons for inclusion and exclusion of studies in the feasibility assessment from the 54 studies that had met the inclusion criteria of the systematic literature review. The feasibility assessment also considered study design, treatments and patient characteristics but no study was excluded based on these criteria at the feasibility assessment stage. The flow chart (Figure 2, Section D.1.1.6, Appendices) and corresponding text in Appendix D.1.1.6 of the Company submission appendices does correspond with the Table 10 of the Clarification question responses. | This is not a factual inaccuracy.<br><br>Based on the information provided in the CS (Section B.2.9.7) and the clarification response (Table 10), it was not possible to determine whether the company's approach to including/excluding studies was appropriate.<br><br>No change required. |
| <u>Further information to clarify</u> | Proposed amendment: | As described in the responses to the ERG | This is not a factual inaccuracy. |

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| surrounding how 27 trials were excluded<br><br>Please see: Section 4.8.2, paragraph 3, page 50<br><br>A full explanation is provided on how and why the included trials stayed the same. | Removal of statement<br>"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)" | Clarification questions, the company submission contained an error: 27 unique trials (reported across 29 publications) were actually excluded based upon the network meta-analysis (NMA) feasibility assessment, and not 26 unique trials as described in the CS.<br><br>A change of 26 to 27 does not change or create discrepancies in the PRISMA flow diagram reported in Appendix D of the CS and the reasons for this are as follows:<br><br>In the Clinical SLR, 54 publications reporting 39 unique trials were included based on the searches (Appendix D: Table 3). Subsequently, 13 unique trials, including Impassion130, were eventually included in indirect comparisons, following the feasibility assessment. This led to reporting of 26 trials (39 minus 13) being described as excluded, based upon feasibility assessment.<br><br>It was in error believed that the 39 unique trials included IMpassion130, when in fact, this list does not include IMpassion130 (Appendix D: Table 3). When IMpassion130 is included, this totals 40 unique trials included in the feasibility assessment. Subsequently, 27 unique trials were excluded, leading to the 13 unique trials used in the indirect comparisons.<br><br>As this error occurs after (“downstream” to) | Based on the information provided in the CS (Section B.2.9.7) and the clarification response (Table 10), it was not possible to determine the exact number of trials that were included in the SLR, and the numbers of trials that were subsequently included and excluded from the NMAs.<br><br>No change required. |

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| | | the PRISMA flow systematic searches, there are no PRISMA flow diagram discrepancies. | |

## Issue 3 IMPassion130 trial data clarifications required

| Description of problem | Description of proposed amendment | Justification for amendment | ERG Response |
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| <u>Presentation of OS primary analysis results, when this data cut has been superseded by the second interim OS (later) data cut</u><br><br>The ERG report on several occasions refers to the percentage of patients who have died in IMpassion130 at the primary analysis, instead of referring to the results of the second interim analysis. The ERG deems primary analysis data to be immature, however a later data cut has been provided. This difference is acknowledged in one part of the report (Section 4.5.2 Overall Survival, paragraph 2, Page 42) – but not in specific other instances. | For each of the ERG report sentences below:<br><br>1) "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." (Section 1.4, Paragraph 5, Page 14)<br><br>2) "The OS results presented are immature, with only 34.6% of patients in the A+nabPx arm and 47.8% of patients in the P+nabPx arm having died at the time of this analysis." (Section 1.9.2, Paragraph 2, Page 18)<br><br>3) "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." (Section 4.5.2, Paragraph 1, page 42) | As the second interim OS analysis was provided in full and fully incorporated into the NMA and cost-effectiveness model, this is now to be the basis of decision making and is more mature than the primary analysis. | <u>Sentence 1</u><br><br>This is not a factual inaccuracy.<br><br>The ERG report sentence (1) is referring to the immaturity of the data at the time of the first interim analysis: "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 |

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| | Replace with the following sentence:<br><br>"In the second interim analysis results of Impassion130 [redacted], presented by the company, [redacted]% of patients in the A+nabPx arm and [redacted]% of patients in the P+nabPx arm had died at the time of this analysis". | | the time of this analysis."<br>No change required.<br><u>Sentence 2</u><br>This is a factual inaccuracy<br>We have removed ERG report sentence 2).<br><u>Sentence 3</u><br>This is not a factual inaccuracy<br>The ERG report sentence (3) is referring to the immaturity of the data at the time of the first interim analysis: "At the time of the first interim OS analysis (data cut-off date: 17th April 2018),…, 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."<br>No change required. |
| <u>Emphasis on adverse events for A+nabPx, without reference to the adverse events profile of the comparator therapies (paclitaxel and docetaxel)</u> | Proposed amendment:<br>Provide a supplementary sentence at the end of these 3 occasions:<br>1) Section 1.3, Direct evidence, paragraph 3, page 12. | This is an imbalanced statement - in that the comparators of paclitaxel and docetaxel require can required even more management, as | This not a factual inaccuracy.<br>No change required. |

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| Section 1.3, Direct evidence, paragraph 3, page 12.<br><br>"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."<br><br>This is similarly referenced again in 2 other sections:<br><br>Section 1.9.2, Clinical evidence, paragraph 7 (last paragraph), page 19 and<br><br>Section 4.9, Direct evidence, bullet point 7, page 64.<br><br>These 3 statements reference AEs of atezolizumab, without a balanced reference to the comparators AEs | 2) Section 1.9.2, Clinical evidence, paragraph 7 (last paragraph), page 19<br><br>3) Section 4.9, Direct evidence, bullet point 7, page 64.<br><br>The supplementary sentence to add to the end of each of these 3 occasions is proposed as follows:<br><br>“However, adverse events resulting from paclitaxel and docetaxel are also known to carry noteworthy healthcare resource use. Indeed, the company’s cost-effectiveness model provides the costs per patient for managing adverse events in their model for AEs occurring at Grade 3-4, in 2% or more of patients. It was calculated that these adverse event management costs per patient treated were: £113.99 (A+nabPx), £210.75 (paclitaxel) and £246.10 (docetaxel).” | evidenced in the cost-effectiveness model submitted.<br><br>In the submitted cost-effectiveness analysis, the costs of AEs occurring at Grade 3-4, in 2% or more of patients were calculated. It was calculated that these adverse event costs per patient treated were: £113.99 (A+nabPx), £210.75 (paclitaxel) and £246.10 (docetaxel). Hence, the healthcare resource use of managing AEs due to the comparator drugs is expected to be substantially greater. | |
| <u>Clarification on patient population source of Impassion130 utility values</u> | Proposed amendment:<br><br>Remove statement and replace with: “Utility values were derived from the PD-L1+ population” | Utility data presented in the CS Document B, as stated in Table 54, were derived from the PD-L1 positive population only of | This is a factual inaccuracy.<br><br>The ERG has amended the text as suggested by the |

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| Section 4.7, Paragraph 3, page 47<br>"It is unclear to the ERG whether the utility data in Table 11 are derived from the ITT population or from the PD-L1+ population of the IMpassion130 trial. "<br>The company confirms that utility data in were derived from the PD-L1 positive population, as stated in the CS (Document B). | | the IMpassion130 trial. | company. |

## Issue 4 Textual clarifications

| Description of problem | Description of proposed amendment | Justification for amendment | ERG Response |
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| <u>Description of final scope population</u><br>Section 1.2, Population, first paragraph, page 9:<br>"The population described in the final scope issued by NICE is people with untreated, locally advanced or metastatic, triple negative PD-L1+ breast cancer. "<br>This description is not fully aligned to the final scope and could be misinterpreted (6). | Change Section 1.2, Population, first paragraph, first sentence, page 9 to:<br>“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” (6) | The verbatim Final scope population is (6):<br>“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”<br>This description of the final scope population described in the ERG report could cause confusion around the patient population under appraisal. Specifically, it could be interpreted that the ERG mean that | This is a factual inaccuracy.<br>The ERG has amended Section 1.2 and Table 2 of the ERG report to:<br>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 |

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| | | the population of the scope are patients who have never received *any* chemotherapy (or radiotherapy or other therapy) for TNBC, whether at the "early stage" or "metastatic/advanced/late" stage of TNBC. This is not accurate as the appraisal concerns patients who have not received prior *chemotherapy for metastatic* advanced/late *disease only*. | |
| <u>Text inconsistency in the ERG report in assumptions underlying ERG scenario of 3 years duration of treatment effect</u><br><br>Please see Section 1.6, last paragraph, Page 17,<br><br>And Section 5.6, Lifetime duration of treatment effect, 3rd last paragraph:<br><br>There is inconsistency in these reported these values and in addition, it is necessary to use values from the latest analyses submitted to the ERG during the Clarification Questions stage, as the latest point of reference. | Proposed amendment:<br><br>Either, update all references to [redacted]% of patient or provide information on how this value was derived. | We are unclear of how the value of [redacted]% has been calculated.<br><br>According to the preferred economic model approach (Model 2), at 3 years, the proportion of patients on treatment in the A+nabPx arm were: [redacted]% receiving A and [redacted]% receiving nabPx; and the proportion of patients progression-free were [redacted]%.<br><br>We would encourage the ERG to either update all references of this number, or provide more clarity on how [redacted]% was derived. | This is not a factual inaccuracy.<br><br>The [redacted]% is taken from Cell BR165 (the cycle where the year counter turns to "3.0" on the sheet "Atezo+nabpac" in the company model.<br><br>No change is required |
| <u>Inconclusive whether the new technology is cost-effective at the £50,000 per QALY ICER threshold</u> | Proposed amendment:<br><br>Replace both of these statements with:<br><br>"At present it is not possible to conclude as to whether the new technology is cost-effective at | The ICERs presented in the ERG report reflect the PAS price of atezolizumab and list price of nab-paclitaxel. Hence all ICERs | This is not a factual inaccuracy.<br><br>However, for clarity, the ERG has amended Sections 1.1 |

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| Section 1.10, last paragraph page 20<br><br>"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. ".<br><br>This is repeated in Section 5.8, paragraph 1:<br><br>"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."<br><br>It is not possible to conclude whether the combination meets the £50,000 threshold without the known PAS price of nab-paclitaxel (the ICERs reflect list price of nab-paclitaxel) | the £50,000 per QALY gained threshold, as all results reported in this ERG report reflect the PAS price of atezolizumab, but the list price of nab-paclitaxel. A generic nab-paclitaxel version (Pazenir) has recently gained a marketing authorisation (May 2019) therefore the cost-effectiveness incorporating this is unknown." (7) | presented will be an overestimate.<br><br>Furthermore, a generic of nab-paclitaxel (Pazenir) has recently gained a marketing authorization (7). As generics are usually less expensive than the branded version of the drug (e.g. Abraxane), the price of Pazenir in the NHS must be known to be able to make a judgement on whether the new technology is cost-effective at the £50,000 per QALY threshold. | and 5.8 of the ERG report by adding the following text:<br><br>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. |
| <u>Presentation of Figures from Model 1, when the ERG-stated preference is for Model 2 (following ERG Clarification</u> | Proposed amendment: Replace Figures 15, 16 and 19 with Figures taken from Model 2. The amended figures are provided from Model 2 as follows. Please use CIC marking of the figures: | ERG has highlighted a preference for Model 2 in the updated base case, therefore the figures in the report should be updated to reflect this. | This is not a factual inaccuracy.<br><br>The ERG does not have a |

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| questions).<br><br>The ERG report provides 3 figures of data (Figures 15, 16 and 19) that are not derived from “Model 2“ (submitted during the ERG Clarification questions) – yet the ERG describe that their preference is for Model 2 for their updated base case. | Figure 1 OS in the economic model (Model 2) for treatment with atezolizumab plus nab-paclitaxel, paclitaxel and docetaxel<br><br>  <br><br>Figure 2 PFS in the economic model (Model 2) for treatment with A+nabPx, paclitaxel and docetaxel<br><br>Figure 3 Scatter plot of the cost effectiveness of treatment with A+nabPx versus paclitaxel and docetaxel (1,000 iterations)(Model 2) | If Figures 15, 16 or 19 are transferred to the technical engagement, this could confuse and also misinform on 1) Relative survival of docetaxel and paclitaxel (Figure 15), 2) relative PFS for each of docetaxel and paclitaxel (Figure 16) and 3) reflect incremental costs accurately (Figure 19), as well as not fully reflect the latest data cut of Impassion130. | preference for Model 2. In the company response to the clarification letter it is stated that the company preference is for Model 2 to be considered as the base case and so the ERG amendments were applied to Model 2.<br><br>The results in Figures 15, 16 and 17 are those generated by the original company model and presented in the CS.<br><br>No change required. |

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| Inaccurate numerical value in Table 6<br><br>Section 4.5, Table 6<br><br>Inaccuracy of a numerical value reported | Required amendment:<br><br>In Table 6, change p-value reported: Change "0.62 (0.49 to 0.78), *<0.0001*" to "0.62 (0.49 to 0.78), *<0.001*" | There is an error in this reported value. | This is a factual inaccuracy included in the CS.<br><br>The reported p-value (*<0.0001)* was taken directly from the CS.<br><br>The ERG has changed the value in Table 6 of the ERG report to *<0.001*. |
| Inaccurate numerical value in Table 4<br><br>Section 4.3.2, Table 6<br><br>Inaccuracy of a numerical value reported | Required amendment:<br>In Table 4, change anthracyclines percentage reported: Change "109 (58)" to "109 (58.9)" | There is an error in this reported value. | This is factual inaccuracy.<br><br>The ERG has changed "109 (58)" to "109 (58.9)" in Table 4 of the ERG report. |
| Presentation of numerical values from initial submission, when the present ERG-stated preference is for Model 2 (following ERG Clarification questions)<br><br>Section 1.7 paragraph 2, page 17:<br><br>"The estimates generated by the company model are that median | Proposed amendment:<br><br>Change of Section 1.7 paragraph 2, page 17 to following:<br><br>"The estimates generated by the company model are that median life expectancy is [redacted] months for patients treated with paclitaxel and [redacted] 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 | If the ERG preference is now for Model 2 (following Clarification questions), the most recent estimate values should be used. The values provided are taken from Values based on "Model 2 ACIC" and are (column J "Pac" and "Docetaxel" sheets): Median life expectancy: 16.6 months for paclitaxel 15.9 months for docetaxel. Mean extension to life of ("Results table" sheet; L29:M29): 10.0 months compared to paclitaxel | This is not a factual inaccuracy.<br><br>The ERG does not have a preference for Model 2. In the company response to the clarification letter it is stated that the company preference is for Model 2 to be considered as the base case.<br><br>The results presented in Section 1.7 are those |

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| life expectancy is [redacted] months for patients treated with paclitaxel and [redacted] 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 [redacted] months and [redacted] months respectively."<br><br>The values referred to here refer to the initial submission, accompanying Document B. Following ERG Clarification questions, the ERG describe a preference for Model 2. | [redacted] months and [redacted] months respectively." | 10.3 months compared to docetaxel | generated by the original company model and presented in the CS.<br><br>No change required. |

## References


1. National Institute for Health and Care Excellence. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy - Committee discussion [TA520] 2018 [Date Accessed 21st June 2019]. Available from: https://www.nice.org.uk/guidance/ta584/chapter/3-Committee-discussion#duration-of-treatment-benefit-after-progression.
2. National Institute for Health and Care Excellence. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy [TA520] 2018 [Date Accessed 30th January 2019]. Available from: https://www.nice.org.uk/guidance/ta520.
3. National Institute for Health and Care Excellence. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer [TA584] 2019 [Date Accessed 21st June 2019]. Available from: https://www.nice.org.uk/guidance/ta584/chapter/3-Committee-discussion#duration-of-treatment-benefit-after-progression.
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5. Luhn P, Chui S, Hsieh A, Yi J, Mecke A, Bajaj P, et al., editors. 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.

6. National Institute for Health and Care Excellence. Atezolizumab for untreated, locally advanced or metastatic, triple negative, PD-L1 positive breast cancer - Final scope 2019 [Date Accessed 21st June 2019]. Available from: https://www.nice.org.uk/guidance/gid-ta10433/documents/final-scope.
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NICE National Institute for Health and Care Excellence

# Technical engagement response form

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

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm, Monday 12 August 2019**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

**Notes on completing this form**

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

**We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.**

**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

## About you

| | |
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| **Your name** | [redacted] |
| **Organisation name – stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank) | **Roche Products Ltd** |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **-** |

## Questions for engagement

| **Issue 1: Generalisability of the trial results** | |
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| a) Do the characteristics of the overall trial population and PD-L1 positive subgroup of Impassion130 reflect those of people who would be eligible for atezolizumab plus nab-paclitaxel in the UK clinical setting? | Roche Products Ltd. ("Roche") agrees with the NICE Technical team preliminary scientific judgement and rationale. The characteristics from the IMpassion130 trial for the overall trial population and PD-L1 positive subgroup broadly reflects the population who would be eligible for treatment with atezolizumab plus nab-paclitaxel, in the UK clinical setting. This is reflected in the ERG Report, where the ERG was satisfied that the patients recruited into the IMpassion130 trial are generally representative of patients with metastatic triple negative breast cancer (mTNBC) who are treated in the NHS (ERG Report, Section 1.4, p.14).<br>Roche acknowledges that the patient characteristics from large, globally recruited, Phase III studies will reflect differences in treatment practices. That said, the baseline characteristics of patients within the IMpassion130 trial have been validated by clinical experts (NICE Submission Document B p.166) and are balanced between both trial arms.(1)<br>Clinical experts confirmed that the IMpassion130 trial eligibility criteria were consistent with the population that they see and treat in the UK, the study recruited well in the UK and the recruiting centres were representative of the types of treatment centres in the UK. These clinical expert opinions are reflected within the ERG report (ERG Report, Section 4.3.1, p.36). |

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| b) Fewer people in the trial had been previously treated with anthracyclines compared with UK clinical practice and a higher proportion had newly diagnosed metastatic disease. How would these differences be expected to affect the generalisability of the trial results? | Roche agrees with the NICE Technical team preliminary scientific judgement and rationale. The characteristics from the IMpassion130 study trial for the overall trial population and PD-L1 positive subgroup broadly reflects the population who would be eligible for treatment with atezolizumab plus nab-paclitaxel, in the UK clinical setting.<br><br>Roche has identified a calculation error in the previously submitted data to the ERG, whereby the proportion of patients pre-treated with anthracyclines is 71.4% within the PD-L1 subgroup of the IMpassion130 trial. Furthermore, the proportion of patients in the PD-L1 population with newly diagnosed metastatic disease (at initial diagnosis) in the IMpassion130 study is 19.7% in the atezolizumab plus nab-paclitaxel arm and 23.1% in the placebo plus nab-paclitaxel arm, which is similar to that seen in a UK setting. The IMpassion130 trial is, in fact, similar to that seen in the UK clinical setting. We uncovered these revised numbers during a review of the past ID1522 ERG Clarification question responses provided on this issue. The updated patient characteristics tables are provided in **Appendix 1.** |
| Issue 2: PD-L1 testing | |
| a) Would the introduction of PD-L1 testing in the mTNBC population be feasible? | Introduction of PD-L1 testing in the mTNBC population is feasible, as demonstrated by the Early Access to Medicines Scheme (EAMS).(2)<br>Roche agrees with the NICE Technical Team preliminary scientific judgement and rationale that PD-L1 testing is already routine practice in some cancer types where immunotherapies have been introduced.<br>Currently PD-L1 expression is not part of routine testing in breast cancer within the UK. However, diagnostic testing for HER2 (via immunohistochemistry [IHC] and fluorescence in situ hybridisation [FISH]) and oestrogen and progesterone receptors (via IHC) is well established, and therefore an additional IHC test in breast cancer is expected to have a limited impact on workflow in hospitals.<br>In addition, clinical expert opinion provided to Roche has confirmed that the introduction of PD-L1 testing in the mTNBC population will be feasible as PD-L1 IHC assays are routinely carried out for patients with other tumour types such as advanced non-small-cell lung carcinoma (NSCLC) and metastatic urothelial carcinoma (mUC). Scaling up testing to include patients with mTNBC should not be problematic. These clinical expert opinions are also reflected within the ERG report (ERG Report, Section 1.2, p.9) and were confirmed verbally by clinical experts during the Technical Engagement Teleconference.<br>Finally, Roche has been able to experience first hand the feasibility of implementing PD-L1 testing for this indication through the IMpassion130-associated EAMS. During this scheme, NHS Pathology laboratories have already been |

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| | conducting an IHC test to establish the TNBC status of the patient. Since the EAMS was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) on the 13th March, more than 140 patients have been PD-L1 tested, as of the 5th August 2019. |
| b) What challenges would PD-L1 testing introduce to current clinical practice? Will it require a new biopsy? | PD-L1 testing in this population carries minimal challenges and, consistent with the IMpassion130 trial protocol (provided accompanying the company submission and updated clinical study report (CSR) provided with this response document), should not require a new biopsy.<br>As per the IMpassion130 trial protocol, the status of immune-mediated, tumour type-related, and other exploratory biomarkers (including but not limited to T-cell markers) for PD-L1 was evaluated in both archival and fresh tumour tissue samples of enrolled patients, therefore a new biopsy is not required.(3) This was confirmed by a clinical expert during the Technical Engagement teleconference where the clinical expert expressed that an archival biopsy is sufficient, particularly when considering the speed of relapse, and requirement to treat rapidly in these patients.<br>Roche agrees with the clinical advice to the ERG that scaling up PD-L1 testing to include patients with mTNBC should not be problematic (ERG Report, Section 1.2, p.9). The PD-L1 test can be conducted on existing tumour samples (assuming sufficient tissue is available). It can be carried out at sites currently conducting IHC testing following pathologist training to score the test. |
| c) Would the currently used tests in the NHS be used for testing people with breast cancer or will a specific test be required? | Roche anticipates at the approximate time point of the EMA Marketing Authorisation being granted ([redacted] the expanded use of the CE-Marked VENTANA PD-L1 (SP142) assay (test) for assessing PD-L1 status in TNBC will be launched. The only validated test in TNBC currently available for PD-L1 on immune cells ≥1% is SP142. This is the same assay used for testing the PD-L1 status in urothelial carcinoma (UC), and is already in use in some UK centres for this purpose and for the TNBC EAMS. Roche recommends patients with TNBC be tested for PD-L1 on immune cells ≥1%. Roche is investing actively in training of pathologists and set up of testing with SP142, following the established pathway for new immunohistochemistry test implementation in breast cancer that was successfully done previously with HER2 testing.<br><br>**Rationale for use of SP142 test**<br><br>**Tumour infiltrating immune cells**<br>PD-L1 is expressed in many tumour types, although its localisation and predictive value can vary. For instance, using the VENTANA PD-L1 (SP142) assay in NSCLC, PD-L1 is often expressed on both tumour cells (TCs) and immune cells (ICs), whereas in UC or TNBC tumours, expression tends to be more prevalent on ICs.(4) The VENTANA PD-L1 (SP142) assay was developed specifically for atezolizumab to optimise the staining of ICs for the detection of the |

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| | presence or absence of PD-L1. An amplification detection system was incorporated to visually enhance the assessment of PD-L1 on immune cells in particular.(5)<br><br>**IMpassion130**<br>Additional exploratory biomarker analysis evaluating PD-L1 expression on tumour cells, stromal tumour-infiltrating immune cells and cytotoxic T cells concluded that PD-L1 expression on ICs covering ≥1% of the tumour area based on the SP142 assay was the best predictor of clinical benefit in the IMpassion130 trial.(6, 7)<br><br>**FDA approval**<br>VENTANA PD-L1 (SP142) is an FDA approved companion diagnostic for TNBC. It is also FDA approved as the complementary diagnostic in metastatic NSCLC and as the companion diagnostic for Tecentriq® (atezolizumab) in mUC (5)(8).<br><br>[redacted] |
| d) What is the reason for the selection of ≥1% as a threshold in the trial? | PD-L1 expression on tumour infiltrating immune cells covering ≥1% of the tumour area based on the SP142 assay was the best predictor of clinical benefit in the IMpassion130 trial.<br>The IMpassion130 clinical trial was stratified and randomised according to PD-L1 expression in tumour infiltrating immune cells as a percentage of tumour area: < 1% (IC0) vs ≥ 1% (IC1/2/3), using the VENTANA SP142 assay. The other stratification factors were presence of liver metastases and prior taxane exposure.<br>Twenty-seven percent of patients were “PD-L1 positive low” (IC1: IC ≥ 1% and < 5%), and 14% were “PD-L1 positive high” (IC2/3: IC ≥ 5%).<br>The scoring criteria for SP142 with a 1% cut off in IMpassion130, predicted that 41% patients stained positive (IC1/2/3) for PD-L1, which was predictive for clinical benefit (Figure 1). In mTNBC, additional exploratory biomarker analysis evaluating PD-L1 expression on tumour cells, stromal tumour-infiltrating immune cells and cytotoxic T cells concluded |

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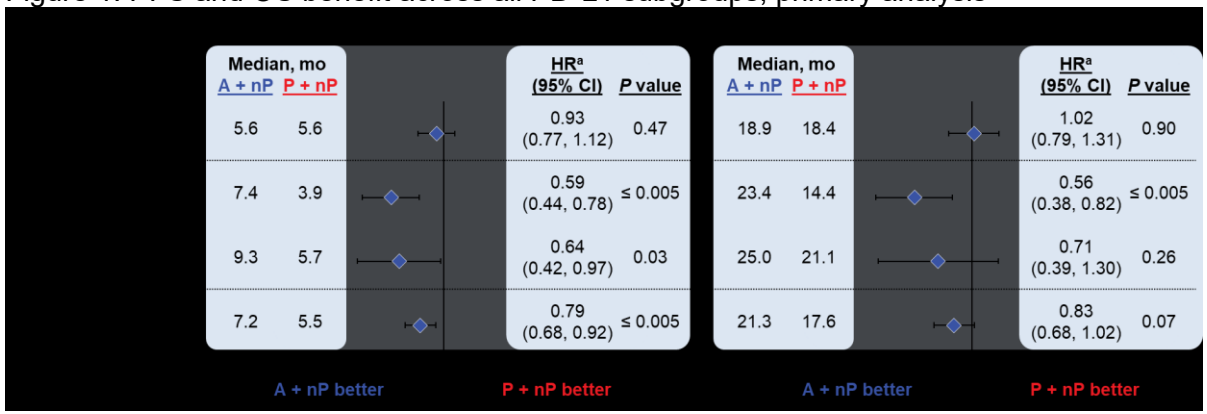
| | that PD-L1 expression on IC covering ≥1% of the tumour area based on the SP142 assay was the best predictor of clinical benefit in the IMPassion130 trial.<br>A forest plot reporting OS and PFS outcomes based upon IC cut off was provided in the company submission (Appendices, Appendix E, Section E.1.3 Exploratory analysis, Figure 21) – this is provided in Figure 1.<br><br>Figure 1: PFS and OS benefit across all PD-L1 subgroups, primary analysis<br>  |
| Issue 3: Appropriate comparators | |
| a) Are weekly paclitaxel and docetaxel the most relevant comparators?<br>- Which one is most commonly used? | Paclitaxel is the most relevant comparator for this appraisal. Roche agrees with the NICE Technical team preliminary scientific judgement and rationale that weekly paclitaxel appears to be the most relevant comparator according to clinical experts. This is also reflected in clinical advice to the ERG 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 (ERG Report, Section 2.2, p.24).<br><br>In the absence of a robust multi-centre UK real world data set, Roche understands from UK clinical experts that paclitaxel is the taxane of choice for first-line treatment of mTNBC (ID1522 ERG Clarification Question responses, Appendix 1, 2019). This is due to the favourable toxicity profile of weekly paclitaxel compared with 3-weekly docetaxel which helps maintain quality of life for patients with limited life expectancy.(9) Docetaxel is often used in the curative |

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| | early breast cancer (eBC) setting where the toxicities of treatment are offset by the aim of cure rather than palliation (ID1522 ERG Clarification Question responses, Appendix 1, 2019).<br><br>Both in vitro and in vivo studies have demonstrated only partial cross-resistance between docetaxel and paclitaxel(10-12), increasing the likelihood of additional benefit from a different taxane agent i.e., paclitaxel. Furthermore, re-challenge with docetaxel (following use in eBC) 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 if they have subsequently relapsed.<br><br>A retrospective audit of patients with advanced breast cancer treated at the Mount Vernon Cancer Centre found that only 5/29 patients with HER2-/unknown advanced breast cancer previously treated in the neoadjuvant/adjuvant setting received single-agent docetaxel as first-line therapy for their advanced disease as per the NICE guidelines.(13) Across all HER2- patients that were treated with first line chemotherapy (n=49) and only 3 received docetaxel.<br>Hence the incremental cost-effectiveness ratios (ICERs) versus paclitaxel should be the basis for decision making. |
| b) Do experts agree that anthracycline-based chemotherapy is not a relevant comparator in the metastatic setting? | Anthracycline-based chemotherapy is rarely used in the mTNBC setting. Roche agrees with the NICE Technical team preliminary scientific judgement and rationale that anthracycline-based chemotherapy regimens would be rarely used in this population, and therefore it is not a key comparator.<br><br>This opinion is also reflected in the clinical advice to the NICE Technical Team and the ERG (Technical Engagement Report p. 6, p.9 and ERG report p.10):<br>• Anthracyclines are generally used in the eBC setting and not very often for metastatic disease<br>• Most patients with mTNBC have relapsed following treatment for eBC<br>• Most NHS patients treated for eBC who subsequently develop metastatic disease would have previously been treated with a sequential regimen of anthracyclines and taxanes and have received a maximum lifetime dose<br>• Patients with de novo mTNBC are offered anthracyclines as a first-line treatment, if appropriate<br><br>In the IMpassion130 trial, 71.4% (n=208/291) of PD-L1 positive patients (excluding de novo metastatic patients) had received prior anthracycline treatment. This supports the UK clinical expert advice that the majority of patients in an early TNBC setting would have been treated with an anthracycline (see Table 4 in **Appendix 1**). |

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| | As per the data presented within the company submission (NICE Submission Document B, p.20–21), eligibility for first-line mTNBC patients to be treated with anthracyclines is limited in clinical practice. Approximately 80–85% of this population will have progressed to the metastatic setting from the eBC setting, where anthracycline-based treatment regimens are preferred. This is seen on an international level in the IMpassion130 trial, where approximately 80% of the population progressed from the eBC setting (see Table 1 in **Appendix 1**).<br><br>Re-challenge with anthracyclines is hindered by lifetime maximum cumulative dose (e.g. epirubicin(14)) and as such, patients treated in the eBC setting are unlikely to be eligible for re-challenge. Therefore, these regimens are rarely used within this setting. This is supported by a retrospective analysis of patients with mTNBC treated at the Royal Marsden NHS Foundation Trust. Despite 14% of patients in this analysis presenting with de novo metastatic disease, only 7.5% received an anthracycline-based regimen.(15) |
| Issue 4: Comparison with taxanes | |
| a) Are the methods and results of the company's network meta-analysis plausible to establish comparative effectiveness data for atezolizumab plus nab-paclitaxel compared with taxanes? | Roche sought, in line with the appraisal Final Scope, to provide evidence of relative effects for atezolizumab + nab-paclitaxel in comparison to paclitaxel, docetaxel and anthracyclines. Given the lack of direct evidence available, Roche considered that carrying out a network meta-analysis (NMA) to obtain indirect evidence was the most appropriate way of enabling these comparisons.<br><br>Roche acknowledges the feedback provided in the Technical Engagement report and the feedback heard at the Technical Engagement Call regarding the potential limitations of the network meta-analysis (NMA); however, we believe that the NMA is the most appropriate way to compare atezolizumab + nab-paclitaxel with the UK standard of care. We address the concerns about the NMA raised during Technical Engagement, below.<br><br>Following a SLR, Roche identified an unconnected network of evidence relating to atezolizumab + nab-paclitaxel and taxanes. To connect this network, Roche carried out population-adjusted indirect comparisons (PAIC) using all trials in the network that investigated either paclitaxel or docetaxel (AVADO (docetaxel), E2100 (paclitaxel), MERiDiAN (paclitaxel)). Roche carried out the NMA in accordance with the recommendations provided in NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE (16, 17). Specifically, Roche used patient level data to conduct a covariate balancing propensity score model (18, 19), matching the larger study group to the smaller to increase robustness, i.e. matching the A+NabPx arm to the entire comparison studies' triple-negative population, creating a virtual atezolizumab + nab-paclitaxel arm (or placebo + nab-paclitaxel arm |

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| | in the updated analyses provided during clarification questions) for each of the comparator studies. The atezolizumab + nab-paclitaxel arm from the IMpassion130 and the virtual atezolizumab + nap-paclitaxel for each comparator study then allow the network to be connected. As the proportional hazards assumption was not met in IMpassion130, nor numerous trials considered for inclusion in the NMA, piecewise exponential and fractional polynomial models were assessed. In model selection, the Akaike information criteria (AIC) and Bayesian information criteria (BIC) of a broad range of models and cut points were assessed. The five best fitting models were then assessed via a model selection process which assessed visual fit, plausibility and model diagnostics leading to the selection of the piecewise exponential for OS and PFS, with its specified cut points. Hence, an empirical approach was taken for selection of the base case model. Full clarification of the methods is provided in Appendix 4 (part 4, NMA feasibility assessment conducted and rationales for NMA model selection).<br><br>The four potential limitations of the NMA that Roche would like to address are:<br>1. Insufficient information regarding the inclusion and exclusion criteria for studies assessed for (N=40 trials) and included in the NMA<br>2. Baseline characteristics assessment for trials included in the NMA<br>3. Unknown PD-L1 status of patients for trials included in NMA, except for Impassion130<br>4. The confidence intervals around the hazard ratios for the NMA results were wide<br><br>The question on methods is addressed in this response (associated with limitations 1-2 above), and the question regarding the results (limitation 3-4 above) is incorporated in to question 4b.<br><br>**Insufficient information regarding the inclusion and exclusion criteria for studies assessed for (N=40 trials) and included in the NMA.**<br>The appearance of discrepancy in trial numbers included in the clinical SLR to final inclusion in the base case NMA is fully clarified in this response. The SLR of clinical data included 39 unique trials. This did not include the IMpassion130 trial, hence a total of 40 unique trials were included in the NMA feasibility assessment. Appendix 4, part 4, NMA feasibility assessment conducted and rationales for NMA model selection, provides further details of this feasibility assessment. Appendix 4 additionally provides the reasons for inclusion/exclusion of each of the individual 40 trials from the NMA, leading to the inclusion of N=7 trials (OS analysis) and N=8 trials (PFS analysis) (Appendix 4 part 1, clarification of trials included and excluded from the NMA, and rationales). Predominantly, this was because comparators |

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| | were not of interest as per the SLR PICO criteria; because the population were <80% first-line; or the trial studied a mixed BC population with a lack of TNBC subgroup data.<br><br>**Baseline characteristics assessment for trials included in the NMA.**<br>The baseline characteristics of trials were assessed for the degree of homogeneity. The details of this assessment are provided in Appendix 4 part 2, baseline characteristics of trials considered for use in the NMA. The assessment considered patient characteristics of: age, ECOG status, prior taxanes receipt, proportion of patients with liver metastases, proportion of patients with visceral disease, proportion of patients with bone metastases. From this assessment, it was deemed that the trials for inclusion in the NMA were sufficiently homogeneous. Furthermore, for the trials used in the PAIC (AVADO, MERIDIAN, E2100), summary statistics within each studies' triple-negative population of candidate covariates for matching have been provided in Appendix 4 part 3, summary statistics of candidate covariates for matching. It was deemed that there was sufficient homogeneity of the N=7 trials (OS analysis) and N=8 trials (PFS analysis) to carry out an NMA using these trials.<br><br>We hope the additional evidence and justifications provided will ease some concerns relating to the methodology of the NMA, which in turn, could validate the outcomes of the ITC and support its use in this appraisal. |
| b) Are the results of the NMA clinically plausible given the limitations highlighted by the ERG? In particular that the inclusion criteria of the trials were different from IMpassion130 and included people with unknown PD-L1 status? | Roche acknowledges the feedback in the Technical Engagement report and the feedback heard at the Technical Engagement Call regarding the potential limitations of the NMA, however we believe the results of the NMA are clinically plausible and appropriate in order to compare atezolizumab + nab-paclitaxel to the UK standard of care.<br><br>This response addresses limitations 3-4 highlighted by the ERG (as detailed in question 4.a) with regards to the clinical plausibility of the NMA results.<br><br>Clinical plausibility of the NMA results should also be considered in the context of the impact these results have when implemented in the economic model, versus interpreting the NMA results in isolation. This is captured in response to Issue 5.<br><br>**Unknown PD-L1 positive patients for trials included in NMA, except for IMpassion130**<br>With the exception of IMpassion130, PD-L1 status was not collected in any of the trials included in the NMA. The comparators included in this appraisal are chemotherapy taxanes which have been used in clinical practice for many |

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| | years, prior to the scientific advancement of PD-L1 expression. As PD-L1 was not a validated biomarker at the time of the studies, it is not feasible to collect evidence on PD-L1 expression from the trials included in the NMA.<br><br>Nevertheless, as taxanes do not target the PD-L1 immune checkpoints, there is no mechanistic rationale for PD-L1 status to be an effect modifier of chemotherapy. Hence, there is no evidence to suggest that the *relative effects* of nab-paclitaxel, paclitaxel and docetaxel are impacted by a selection of PD-L1-positive subpopulation.<br><br>There is, however, limited evidence which may allow us to draw conclusions on the level of any possible absolute effect modification for nab-paclitaxel (or other taxanes), based on the IMpassion130 trial, and therefore the resulting direction of effects that could be expected on the NMA.<br><br>As demonstrated in Figure 1 in question 2.d, and Schmid et al. 2018(1), median OS and PFS for P+NabPx is numerically higher in the ITT population (17.6 months, 5.5 months respectively) than the PD-L1 positive population (15.5 months, 5.0 months respectively). This suggests there is a reduction in the *absolute effects* on nab-paclitaxel for the PD-L1 positive population, as opposed to the ITT population.<br><br>As the paclitaxel and docetaxel trials included in the NMA are expected to contain a mixture of PD-L1 positive and negative patients (i.e. the equivalent to the ITT in IMpassion130), it is plausible the NMA has, in fact, overestimated the OS and PFS absolute effects of these treatments. If the trials had been PD-L1 positive populations only, one could anticipate a similar direction of effects as witnessed in the P+NabPx arm of the IMpassion130 trial i.e. that the OS and PFS outcomes of paclitaxel and docetaxel would be worse than the NMA currently predicts.<br><br>**The confidence intervals around the Hazard ratios for the NMA results were wide.**<br>The 95% credible intervals of hazard ratios and 5-year restricted mean survival times are accepted as wide. Indirect Treatment Comparisons are not powered to detect statistical significance; therefore, uncertainty is not uncommon. Nevertheless, Roche believe this is an insufficient rationale for disregarding the results:<br>• Appropriate use of statistical significances and p-values: Roche note that a statistically non-significant result does not prove the null hypothesis that there is no difference between groups or no effect of a treatment on some measured outcome. Indeed, this is supported by a recent article, Amrehein et al. 2019 (20). The authors carried out an analysis of 791 articles across 5 journals and found that 51% of articles mistakenly assumed that non-significance of results means no effect, and the authors caution around this interpretation. Roche believe that a |

reliance on thresholds of statistical significance, as in this case, can be misleading. As detailed in Altman et al. 1995 (21), "absence of evidence is not evidence of absence".

- Accounting for uncertainty in Bayesian indirect comparisons: Hazard ratios and 5-year restricted mean survival times point estimates are a representation of the likely result. However, the uncertainty surrounding point estimates (through the confidence interval) is reflected in the probabilistic sensitivity analysis used within the cost-effectiveness analysis. This approach is supported by the NICE Decision Support Unit guidance: “simulation from a Bayesian posterior distribution supplies both statistical estimation and inference, and a platform for probabilistic decision making under uncertainty” (22).

Finally, Roche made a conscious decision to reduce bias at the potential cost of higher variance, because bias cannot be quantified and reported while variance of the estimates can be reported and incorporated in the probabilistic analysis (PSA) of the cost-effectiveness analysis. Hence, these wider resulting confidence intervals came with the benefit of reducing bias in the NMA results point estimates.

We hope the additional evidence and justifications provided will ease some concerns relating to the clinical plausibility of the results of the NMA, which in turn, could support its use in this appraisal.

Issue 5: Using nab-paclitaxel as a proxy for modelling the effectiveness of taxanes

a) Is nab-paclitaxel sufficiently similar to weekly paclitaxel and docetaxel for it to be reasonable to assume equivalence between these treatments and use trial data from IMpassion130 as a proxy for the effectiveness of atezolizumab plus nab-paclitaxel compared with taxanes?

Roche recognises the appeal of making a simplifying assumption and assuming equivalence of these regimens to be able to utilise the comparator arm of the IMpassion130 trial as the best available, contemporaneous evidence. However, it is critical to highlight that such an assumption could be considered overly conservative and therefore has the potential to adversely impact the cost-effectiveness of atezolizumab plus nab-paclitaxel, and therefore impact access to this innovative medicine.

Table 1 details the outcomes from the licensing studies for nab-paclitaxel, as compared to paclitaxel. As demonstrated, nab-paclitaxel consistently demonstrates a pronounced numerical advantage in outcomes over paclitaxel.(23, 24)

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

| Efficacy variable | Abraxane (260 mg/m$^2$) | Solvent-based paclitaxel (175 mg/m$^2$) | p-value |
|---|---|---|---|
| *Response rate [95% CI] (%)* | | | |

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| > 1st-line therapy | 26.5 [18.98, 34.05] (n = 132) | 13.2 [7.54, 18.93] (n = 136) | 0.006[a] |
| **Median time to disease progression [95% CI] (weeks)* | | | |
| > 1st-line therapy | 20.9 [15.7, 25.9] (n = 131) | 16.1 [15.0, 19.3] (n = 135) | 0.011[b] |
| **Median progression free survival [95% CI] (weeks)* | | | |
| > 1st-line therapy | 20.6 [15.6, 25.9] (n = 131) | 16.1 [15.0, 18.3] (n = 135) | 0.010[b] |
| **Survival [95% CI] (weeks)* | | | |
| > 1st-line therapy | 56.4 [45.1, 76.9] (n = 131) | 46.7 [39.0, 55.3] (n = 136) | 0.020[b] |

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

While we acknowledge that the 100mg/m$^2$ weekly dosing schedule for nab-paclitaxel as per the IMpassion130 trial was slightly lower than the dose used in the licensing studies for nab-paclitaxel (260mg/m$^2$ three-weekly – see Table 2), a review of the literature has identified evidence that these doses achieve similar efficacy profiles, alongside improved tolerability (23, 25, 26). As such, the results from the licensing studies can be considered broadly reflective of the outcomes utilising the IMpassion130 dosing schedule.

This can also be supported by the same literature the ERG have previously highlighted, demonstrating the alternative interpretations that can be drawn:

- Liu et al. 2017 (27): whilst none of the studies included in the meta-analysis (n=4) were double blind trials, when assessing the difference between taxanes and nab-paclitaxel only in the first-line setting, as opposed to combining first line and second line data as the ERG have, Liu identified an OS HR of 1.21 (1.00-1.48, p=0.05), indicating a statistically significant difference between taxanes and nab-paclitaxel. Similarly, one- and two-year survival of first line patients indicates reduced results of taxanes versus nab-paclitaxel, with a HR of 1.08 (0.79-1.47) and 1.20 (0.98-1.47) respectively.
- Tamura et al. 2017 (28): whilst only small patient numbers (n=36), in the TNBC population, median OS was 27.1 months (95% CI: 18.1–not reached) in the nab-paclitaxel treatment group, and 19.3 months (95% CI: 14.1–26.0) in the docetaxel treatment group (HR: 0.56, P = 0.121). Even in the broader population, the median OS for nab-paclitaxel and docetaxel was 42.4 months (95% CI: 32.4–not reached) and 34.0 months (95% CI: 27.6–40.0) (HR: 0.78, *P* = 0.190).

- A US observational (real-world) study, Luhn et al.(29) demonstrated a HR of 0.9 (95% CI: 0.61, 1.32) between nab-paclitaxel and paclitaxel.

We believe that the results from the licensing study for nab-paclitaxel, in addition to other published literature using similar dosing regimens to IMpassion130, demonstrate pronounced numerical improvements of nab-paclitaxel over other taxanes, and that consequently, a clinical advantage of nab-paclitaxel over paclitaxel cannot be ruled out.

This is consistent with the outcomes of the Indirect Treatment Comparison, whereby nab-paclitaxel was demonstrated to be numerically, although not statistically significantly, better than paclitaxel and docetaxel.

For additional context, when the ITC results are incorporated in to the economic model, this accounts for a difference of 0.197 Life Years between nab-paclitaxel and paclitaxel, a marginal difference which equates to a drastic, and disadvantageous impact on the ICER (Table 2).

**Table 2: Comparison of ICERs resulting from use of NMA vs P+NabPx IMpassion130 arm**

| **Model used** | **ICER[1] vs paclitaxel (£ cost/QALY)** - pre-Roche amendment to paclitaxel treatment costs | **ICER[1] vs paclitaxel (£ cost/QALY)** - post-Roche amendment to paclitaxel treatment costs |
|---|---|---|
| Use of NMA paclitaxel outcomes | £63,339 | £50,629 |
| Use of P+NabPx Impassion130 (As a proxy for paclitaxel) | £85,295 | £72,579 |
| **Difference in ICERs generated** | +£21,956 | £21,950 |

1 atezolizumab PAS price and nab-paclitaxel list price ICERs reported. Assumed no waning of A+NabPx effect.

As discussed in response to 4.b, a statistically non-significant result does not prove the null hypothesis that there is no difference between groups or no effect of a treatment on some measured outcome. Instead, in statistical analyses (as

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| | described in DSU guidance 2) (22), the uncertainty surrounding point estimates (through the confidence interval) are reflected in the probabilistic sensitivity analysis used within the cost-effectiveness analysis.<br><br>As such, while recognising the limitations of the ITC but noting the robust methodology employed (see response to question 4a), Roche believes nab-paclitaxel is not sufficiently similar to weekly paclitaxel and three-weekly docetaxel for it to be reasonable to assume equivalence, and in fact the outcomes of the ITC in terms of Life Year gains are more reflective of the body of evidence suggesting a direction of travel of better outcomes for nab-paclitaxel. |
| Issue 6: Duration of treatment effect | |
| a) Would treatment benefits with atezolizumab plus nab-paclitaxel after treatment has stopped be maintained for the remaining lifetime of patients or would benefits decline after a certain period of time? | There is no clinical evidence to either support or refute any treatment effect assumption beyond the trial data, though it should be highlighted that the magnitude of benefit of atezolizumab + nab-paclitaxel is greater in Overall Survival than that demonstrated in Progression Free Survival (delta of 7 months and 2.2 months, respectively), which could identify a post-treatment discontinuation effect modification (see section B.2.6 and Appendix J from the company submission). This improvement in post progression survival is not uncommon either within some breast cancer or immune-oncology trials. Therefore, Roche did not consider a waning effect to be appropriate for atezolizumab in this indication.<br><br>Duration of treatment effect is an area of uncertainty for immunotherapies, and has arisen as a discussion item in many past appraisals (TA428, TA483, TA484, TA520, TA584). Interestingly, however, the same is not true for targeted therapies in metastatic breast cancer, whereby treatment effect caps have not been explored despite differential magnitudes of benefit seen between PFS and OS (TA458, TA496, TA495, TA563, TA509) (Table 3).<br><br>As such, in the absence of any clear evidence supporting or refuting a treatment effect cap, we acknowledge the precedent set in past appraisals and deem this to be a key consideration when answering this question.<br><br>Table 3 demonstrates the previous committee preferred assumptions regarding waning of treatment effects. We implore the committee to consider the detrimental impact of implementing more conservative assumptions than those used in other appraisals to date. |

**Table 3: Past examples of immunotherapy appraisals preference by the NICE committee on time point of waning of treatment effects**

| NICE Technology Appraisal (TA) number | Indication | NICE committee preferred assumption regarding assumptions on treatment waning |
|---|---|---|
| TA458 | HER2-positive advanced breast cancer after trastuzumab and a taxane | No treatment effect cap considered |
| TA496 | Previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer | No treatment effect cap considered |
| TA495 | Previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer | No treatment effect cap considered |
| TA563 | Previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer | No treatment effect cap considered |
| TA509 | HER2-positive breast cancer | No treatment effect cap considered |
| TA428 | PD-L1-positive non-small-cell lung cancer after chemotherapy | The Committee was not explicit on the duration of treatment effect that was most appropriate. However, it is observed from with-PAS ICERs published, that pembrolizumab would only have been cost-effective if waning was assumed to occur at 10 years (or longer) after treatment initiation. |

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| | TA520 | Locally advanced or metastatic non-small-cell lung cancer after chemotherapy | The ERG looked to cap the duration of treatment effect of atezolizumab at 3 years, however due to the model structure it was acknowledged that if duration of treatment effect for atezolizumab is actually 3 years, then, in the model, setting the duration of treatment effect to 3 years would mean the duration of treatment effect of atezolizumab would be 2.5 years for a patient who stopped treatment after 6 months, but zero for a patient who is still on treatment at 3 years. As such, the duration of treatment effect was set to 5 years to account for the 8% of patients still predicted to be on treatment at 2 years.<br><br>As such, atezolizumab effects were assumed to last for 5 years from treatment initiation |
| | TA483 | Previously treated squamous non-small-cell lung cancer | Nivolumab effects assumed to last for 5 years from treatment initiation |
| | TA484 | Previously treated non-squamous non-small-cell lung cancer | Nivolumab effects assumed to last for 5 years from treatment initiation |
| | TA584 | Metastatic non-squamous non-small-cell lung cancer | Atezolizumab effects assumed to last for 5 years from treatment initiation |
| | GID-TA10400 [Appraisal in progress] | Untreated extensive-stage small-cell lung cancer | Atezolizumab effects assumed to last for 5 years from treatment initiation |
| b) If waning effect is likely to occur, until which timepoint would treatment | As detailed in our response to a), there is no clinical evidence to either support or refute any treatment effect assumption beyond the trial data, though it should be highlighted that the magnitude of benefit of atezolizumab + nab-paclitaxel is greater in Overall Survival than that demonstrated in Progression Free Survival (delta of 7 months and 2.2 months, respectively), which could identify a post-treatment discontinuation effect modification (see section B.2.6 and Appendix J | | |

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| effect be maintained? | from the company submission). This improvement in post progression survival is not uncommon either within breast cancer or immune-oncology trials. Therefore, Roche did not consider a waning effect to be appropriate for atezolizumab in this indication.<br><br>Nevertheless, in the absence of any clear evidence supporting or refuting a treatment effect cap, we acknowledge the precedent set in past appraisals and deem this to be a key consideration when answering this question. In addition, clinical plausibility of the resulting Overall Survival extrapolations should be validated.<br><br>Table 3 demonstrates the previous committee preferred assumptions regarding waning of treatment effects. As demonstrated, a 5-year treatment effect cap from treatment initiation has become the standard precedent for immune-oncology indications.<br><br>TA520 reviewed this assumption in detail: while the ERG preference was to implement a 3-year treatment effect cap, there was an acknowledgement that due to the structural limitations of the economic model, "the duration of treatment effect to 3 years would mean the duration of treatment effect of atezolizumab would be 2.5 years for a patient who stopped treatment after 6 months, but zero for a patient who is still on treatment at 3 years" As such, "as 8.5% of patients are predicted by the company's TTD extrapolation to be receiving atezolizumab at 2 years … setting the company model duration of treatment effect to 5 years rather than 3 years probably produces more accurate ICERs per QALY gained". This appraisal is equivocally paralleled, with 10.7% of patients still on atezolizumab treatment at 2 years – further justification for a consistent approach.<br><br>Interestingly however, the same is not true for targeted therapies in metastatic breast cancer, whereby treatment effect caps have not been discussed. In these appraisals, similar to the trial data for atezolizumab, differential magnitudes of benefit have been seen between PFS and OS (TA458, TA496, TA495, TA563, TA509).<br><br>When assessing the impact of such assumptions of treatment effect on the resulting Overall Survival estimates, visual representation of curves is useful. A comparison of OS for A+NabPx vs P+NabPx is provided in Figure 2. |

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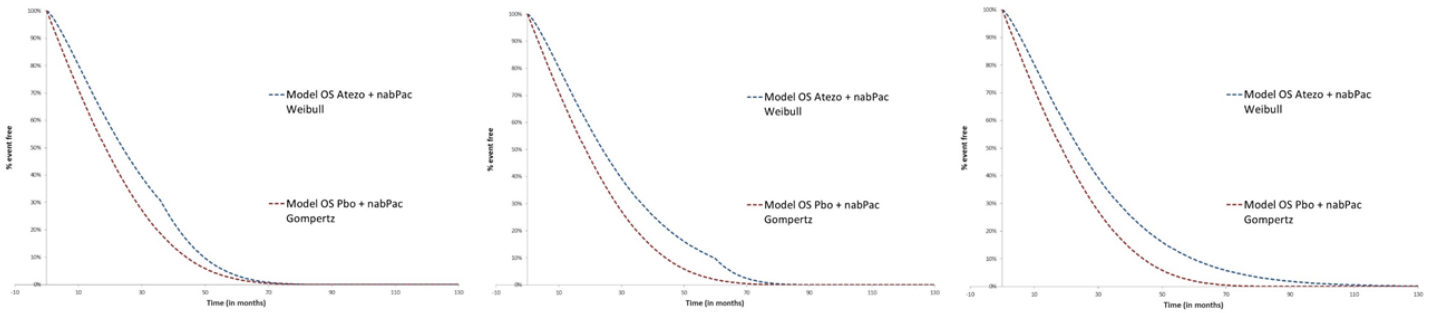
| | **Figure 2: Modelled OS for A+NabPx vs P+NabPx assuming treatment cap from initiation: 3 years, 5 years and lifetime (no waning)**<br>  <br><br>3 years duration of A+NabPx effects<br>5 years duration of A+NabPx effects<br>No waning of A+NabPx effects<br><br>When the duration of treatment effect is assumed to be 3 years from treatment initiation, the resulting drop in OS for patients treated with atezolizumab is larger than Roche (or clinical experts consulted with by Roche – see OS extrapolation validation, B.3.3.2 in company submission) anticipate for an immune-oncological therapy, with OS of atezolizumab + nab-paclitaxel meeting the OS of nab-paclitaxel at 70 months. Given the important clinical advancement this combination has demonstrated in the IMpassion130 trial for patients, Roche do not consider this scenario to be clinically plausible.<br><br>Roche is willing to accept a 5-year treatment effect cap from treatment initiation, in line with precedent set in prior appraisals. However, we implore the committee to consider the detrimental impact of implementing more conservative and clinically implausible assumptions than have been concluded as acceptable in other appraisals to date. |
| c) Is it appropriate to assume a waning effect in the absence of a stopping rule? | Roche acknowledge stopping rules have been implemented in other immune-oncology appraisals, however this is a separate consideration to waning effect assumptions: the two issues are mutually exclusive and have no bearing on one another, either for this appraisal, or when treatment effect caps had been determined in past appraisals (please see Table 3 and TA520 description in response to question 6.b)<br><br>Given the important clinical benefit demonstrated in the IMpassion130 trial, the small PDL1-positive TNBC population (approximately 6% of the total metastatic breast cancer population), and Roche's commitment to demonstrate atezolizumab + nab-paclitaxel in the full licensed indication as a cost-effective use of NHS resources, we do not believe a |

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| | stopping rule is necessary for this indication. Roche's preference would be to allow clinical experts to treat patients until they deem no additional benefit is being derived. This would be consistent with the clinical trial protocol and license, and will allow patients to clinically benefit as long as possible in this area of high unmet need.<br><br>As detailed in our response to question 6.b, Roche is willing to accept a 5-year treatment effect cap from treatment initiation, in line with precedent set in prior appraisals. However, we implore the committee to consider the detrimental impact of implementing more conservative and clinically implausible assumptions than have been concluded as acceptable in other appraisals to date. |
| Issue 7: Health state costs | |
| a) Do the company's estimates on the frequency of oncologist visits reflect UK clinical practice or are the ERG's estimates more plausible? | Roche gained clinical expert opinion to source and validate all NHS resource use/costs implemented in the cost-effectiveness model. Roche accept that of these NHS costs data inputs, the number of oncology visits applied in the progressed disease and progression free states underestimated NHS practice resource use and that the model should be updated to oncologist visits every month, as opposed to every 2 months. |
| Issue 8: End of life criteria | |
| a) Does atezolizumab plus nab-paclitaxel fulfil the criteria to be considered a 'life-extending treatment at the end of life'? | As per the NICE Technical Team "preliminary scientific judgement and rationale", Roche agrees that all scenario analyses presented by the company and ERG demonstrate that the end-of-life criteria are met: A+NabPx provides more than 3 months extension of life, and the population under consideration would usually have a life expectancy of less than 24 months. |
| Issue 9: Cancer Drugs Fund | |
| a) Would additional data collection in the Cancer Drugs Fund reduce the uncertainty? And<br>b) Is the technology a good candidate for use | Given the high unmet need in this patient population, Roche are committed to ongoing patient access, following the closure of the EAMS.<br>The IMpassion130 data are relatively mature (with an 80% information fraction at the second interim analysis), and therefore further data collection is not anticipated to significantly reduce clinical uncertainty within this appraisal. Roche are working with NHS England to agree a commercial access agreement which will enable A+NabPx to be deemed a |

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| in the Cancer Drugs Fund? | cost-effectiveness use of NHS resources, through baseline funding. However, if necessary, Roche are open to exploring all avenues to enable access. |
| Additional evidence submitted by Roche, approved by NICE | |
| Costs of weekly paclitaxel (including administration costs) can be incurred for greater than 18 weeks | On 24th July, Roche requested to submit additional evidence to NICE detailing the duration and costs of paclitaxel receipt in the NHS. This request was approved by NICE on 25th July.<br>Roche have misinterpreted how paclitaxel may be administered in the NHS, specifically in the implementation of the duration of paclitaxel (comparator) treatment and the associated administration costs. The cost-effectiveness model currently specifies that a maximum of 18 weekly cycles of paclitaxel treatment would be received by a patient in this treatment setting in the NHS. However, clinician feedback to Roche is that there is no definitive treatment cap associated with weekly paclitaxel in the NHS, as there is with docetaxel. Roche had previously misinterpreted clinical opinion received prior to our submission on the mean number of weekly paclitaxel cycles (approximately 18-19 cycles), implemented as a maximum number of cycles, thus impacting the drug and administration costs of paclitaxel. The resulting ICERs (A+NabPx vs. paclitaxel) from correction of this misinterpretation are provided **Error! Reference source not found.**, and ICERs varying the nab-paclitaxel discount from list price are provided in **Error! Reference source not found.**<br><br>**Table 4: ICERs resulting with 18 weeks paclitaxel cost cap, compared with 18 weeks cost cap removed** |

| Model | ICER of A+NabPx vs paclitaxel - assuming a maximum 18 cycles/weeks of paclitaxel treatment costs[1] | ICER of A+NabPx vs paclitaxel – removal of cap of maximum of 18 cycles/weeks of paclitaxel costs[1] |
|---|---|---|
| **Company base case model** | £63,339/QALY | £50,629/QALY |
| **ERG base case model** | £85,295/QALY | £72,579/QALY |

[1]ICERs presented at based upon PAS of atezolizumab and list price of nab-paclitaxel

**Table 5: ICERs when varying the Abraxane discount from list price with removal of cap of maximum of 18 weeks of paclitaxel costs**

| Model | Percentage discount from Abraxane (nab-paclitaxel) list price, with resulting ICER (cost (£)/QALY) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | List price | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% | 100% |
| **Company base case model** | 50,629 | 48,633 | 46,637 | 44,641 | 42,645 | 40,649 | 38,653 | 36,656 | 34,660 | 32,664 | 30,668 |
| **ERG base case model** | 72,579 | 69,983 | 67,388 | 64,793 | 62,197 | 59,602 | 57,006 | 54,411 | 51,815 | 49,220 | 46,624 |

There is a substantial impact on the ICER when removing the treatment cap to allow the accrual of treatment and administration costs for paclitaxel in line with current clinical practice. Roche's view is that this model correction should be applied to all ICERs generated for the remainder of the appraisal.

Please see **Appendix 3** for further information on this.

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# Appendices to Company Response to Technical Engagement

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

## Appendix 1: IMpassion130 PD-L1 Population Disease Characteristics

Based upon a further assessment of the IMpassion130 patient characteristics provided in response to the ERG Clarification questions, Roche have identified that the percentage of patients pre-treated with anthracyclines (71.4%) and the percentage of patients with newly diagnosed metastatic disease (21.4%) in the PD-L1 sub group of the IMpassion130 trial are representative of UK clinical practice. However, irrespective of the proportions accounted for within the Impassion130 trial or clinical practice, the forest plot within the IMpassion130 trial shows the treatment effect was consistent across the majority of the clinically relevant sub groups in question.(1)

The responses and further details of this technical engagement question have been split into two sections in response to the key limitations highlighted in the technical report:

1) Higher proportion in the IMpassion130 trial had newly diagnosed metastatic disease

2) Fewer people in the IMpassion130 trial had been previously treated with anthracyclines compared with UK clinical practice

#### 1) Higher proportion had newly diagnosed metastatic disease

Roche has further analysed the data provided to the ERG in response to this clarification question: *"Number of patients who, at initial diagnosis, presented with locally advanced or metastatic TNBC"*. Two sets of data were provided to the ERG in response to this question (Table 1 and Table 2).

**Table 1. Initial diagnosis staging in the PD-L1 population from the Clinical Study Report, split by TNM staging**

| | Placebo + nab-paclitaxel (N=184) | Atezolizumab + nab-paclitaxel (N=185) | Total (N=369) |
|---|---|---|---|
| **n** | **182** | **183** | **365** |
| **STAGE 0** | **1 (0.5%)** | **0** | **1 (0.3%)** |
| **STAGE I** | **21 (11.5%)** | **27 (14.8%)** | **48 (13.2%)** |
| **STAGE IIA** | **39 (21.4%)** | **47 (25.7%)** | **86 (23.6%)** |
| **STAGE IIB** | **28 (15.4%)** | **20 (10.9%)** | **48 (13.2%)** |
| **STAGE IIIA** | **26 (14.3%)** | **25 (13.7%)** | **51 (14.0%)** |
| **STAGE IIIB** | **12 (6.6%)** | **12 (6.6%)** | **24 (6.6%)** |
| **STAGE IIIC** | **13 (7.1%)** | **16 (8.7%)** | **29 (7.9%)** |
| **STAGE IV** | **42 (23.1%)** | **36 (19.7%)** | **78 (21.4%)** |
| **Source:** IMpassion130 Clinical Study Report (CSR) p. 1479 | | | |

**Table 2. Baseline disease characteristics in the PD-L1 positive population, split between locally advanced unresectable and metastatic disease (2)**

| | Placebo + nab-paclitaxel (N=184) | Atezolizumab + nab-paclitaxel (N=185) | Total (N=369) |
|---|---|---|---|
| **n** | **183** | **185** | **368** |
| **Locally advanced unresectable disease** | **24 (31.1%)** | **23 (12.4%)** | **47 (12.8%)** |
| **Metastatic disease** | **159 (86.9%)** | **162 (87.6%)** | **321 (87.2%)** |
| **Source:** IMpassion130 Clinical Study Report (CSR) p. 1479 | | | |

The proportion of patients in the PD-L1 population with newly diagnosed metastatic disease (at initial diagnosis) in the IMpassion130 study is highlighted in Table 1, 19.7% in the atezolizumab plus nab-paclitaxel arm and 23.1% in the placebo plus nab-paclitaxel arm. The higher numbers highlighted by ERG's experts in the ERG report are based on Table 1, which shows the disease characteristics at baseline (staging of the disease at study entry) as opposed to initial diagnosis.

As detailed in Company Evidence Submission Document B, a retrospective analysis of patients with metastatic TNBC treated at the Royal Marsden NHS Foundation Trust found that 14% of patients in this analysis presented with *de novo* metastatic disease (Company Submission, Document B, Section B.1.3.2, p.223)(2). The results in Table 1 are therefore comparable to what would be expected in UK clinical practice.

**2) Fewer patients in the trial previously treated with anthracyclines**

The ERG requested Roche Products Ltd. to populate the following table during the clarification question stage: Therapy prior to enrolment in the IMpassion130 trial (patients with PD-L1 ≥1% disease, excluding patients whose initial diagnosis was mTNBC)

| | Number | Percentage |
|---|---|---|
| **Anthracycline only** | | |
| **Taxane only** | | |
| **Anthracycline and taxane** | | |
| **Other 1** | | |
| **Other 2** | | |
| **etc.** | | |

The information provided to the ERG by Roche Products Ltd. is shown in Table 3 below. Please note that there was an error in the calculations applied (percentage column) and Roche wish to correct the data provided. The highlighted percentages in Table 3 were calculated by Roche Products Ltd. as a percentage of the total PD-L1 patient population of n=369. Roche Products Ltd. had calculated these percentages without excluding patients whose initial diagnosis was mTNBC (hence would not have been pre-treated at all).

**Table 3. Roche Products Ltd. response to ERG question: Therapy prior to enrolment in the IMpassion130 trial (patients with PD-L1 ≥1% disease, excluding patients whose initial diagnosis was mTNBC), provided in ERG Clarification Questions Company response**

| | Number | Percentage |
|---|---|---|
| **Anthracycline only** | [redacted] | [redacted]% |
| **Taxane only** | [redacted] | [redacted]% |
| **Anthracycline and taxane** | [redacted] | [redacted]% |
| **Other 1** | **See Table 4 below** | |
| **Other 2** | | |
| **etc.** | | |

When excluding patients whose initial diagnosis was mTNBC (by subtracting n=78 as per Table 1), the revised percentage of patients pre-treated with anthracyclines (whether alone or in combination with a taxane) is = 71.4% (see Table 4).

**Table 4. Therapy prior to enrolment in the IMpassion130 trial (patients with PD-L1 ≥1% disease, including and excluding patients whose initial diagnosis was mTNBC)**

| | Number | Percentage (**including** mTNBC patients at initial diagnosis n=369) | Percentage **(excluding mTNBC patients at initial diagnosis n=291)** |
|---|---|---|---|
| **Anthracycline Only** | [redacted] | [redacted]% | [redacted]% |
| **Taxane Only** | [redacted] | [redacted]% | [redacted]% |
| **Anthracycline and Taxane** | [redacted] | [redacted]% | [redacted]% |
| **Total Anthracycline Pre-Treatment** | [redacted] | [redacted]% | [redacted]% |
| **Total Taxane Pre-Treatment** | [redacted] | [redacted]% | [redacted]% |

Clinical advice to the ERG supports the Roche Products Ltd. assessment that most patients (80% to 85%) with mTNBC will have progressed from the neoadjuvant or adjuvant setting where treatment with anthracyclines is the standard of care (ERG Report, Section 2.2, p.23). In the IMpassion130 trial, 71.4% of PD-L1 patients (excluding mTNBC patients at initial diagnosis) had received prior anthracycline treatment and 64.6% of PD-L1 patients had received prior taxane treatment (Table 4).

In line with the NICE "Technical Team preliminary scientific judgement and rationale" the IMpassion130 clinical trial broadly reflects the population who would be eligible for treatment with atezolizumab plus nab-paclitaxel in the NHS.

# Appendix 3

## *Additional Evidence: Removal of 18 week treatment cap for paclitaxel, in line with NHS Clinical Practice usage of paclitaxel (correction of costs data misinterpretation in model)*

A misinterpretation in the implementation of paclitaxel costs in the cost-effectiveness model requires correction.

Roche has communicated to NICE the necessity to submit the following "Additional Evidence" on 24th July 2019. The approval for submitting this additional evidence was granted by NICE on 25th July 2019.

To correct this misinterpretation, please "Uncheck" the single "Limit to 18 cycles" tick box (click once on the tick box) in the "Cost Inputs" sheet contained in Cells I33, J33 and K33. This would subsequently allow paclitaxel costs to accrue as reflected in NHS clinical practice, and in line with either P+NabPx TTOT (ERG base case model) or paclitaxel PFS derived from the NMA (Company base case model).

The resulting impact on the Company base case and ERG base case models can be found in the main response document, and the impact when varying the nab-paclitaxel discount can be found in Table 5.

**Table 5: ICER calculations based upon varying the Abraxane discount from list price with removal of cap of maximum of 18 weeks of paclitaxel costs**

| Model | Percentage discount from Abraxane (nab-paclitaxel) list price, with resulting ICER (cost (£)/QALY) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | List price | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% | 100% |
| Company base case model | 50,629 | 48,633 | 46,637 | 44,641 | 42,645 | 40,649 | 38,653 | 36,656 | 34,660 | 32,664 | 30,668 |
| ERG base case model | 72,579 | 69,983 | 67,388 | 64,793 | 62,197 | 59,602 | 57,006 | 54,411 | 51,815 | 49,220 | 46,624 |

## References

1. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. The New England journal of medicine. 2018;379(22):2108-21.
2. 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 (Edinburgh, Scotland). 2018;40:60-6.

**Appendix 2 (document 7c)**

**This document is confidential and has been redacted.**

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# Appendices to Company Response to Technical Engagement

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

## Appendix 4: Further information on Clinical SLR, NMA feasibility assessment and NMA

The following Appendix provides information requested at the Technical Engagement call, as well as clarifications on areas of the ERG critique of the NMA.

### *1. Clarification of trials included and excluded from the NMA, and rationales*

The SLR of Clinical data yielded 39 unique included trials (reported across 54 publications). This list of included trials in the CS (Appendices, Section D.1.1.5 Results, Table 3, Page 29) did not include the pivotal Phase III IMpassion130 trial – hence the total number of included trials for NMA assessment was 40 trials. Of these 40 trials, based on feasibility assessment, at the second interim OS analysis (NMA updated using latest data cut during ERG Clarification questions), 7 trials were included in the base case network for OS and 8 trials were included in the base case network for PFS. The rationales as to why trials were included or excluded from the NMA are provided in Table 1.

Table 1: Rationales for inclusion or exclusion of trials from second interim OS analysis-based base case NMA, following assessment of N=40 trials.

| | First author | Citation | Trial name (if specified) | Trial interventions | Included or excluded from base case NMA? | Reason for inclusion or exclusion |
|---|---|---|---|---|---|---|
| 1 | Awada, A | Annals of oncology. 2014;25(4):824-831. | NCT00448305 | Paclitaxel, endoTAG-1, Paclitaxel + endoTAG-1 | Excluded | Trial connects into the network – however, the comparator(s) are not of interest as per the SLR "PICO" criteria, hence removed from network |
| 2 | Baselga J, G. P. | Journal of clinical oncology. 2013;31(20):2586-2592. | NCT00463788 | Cisplatin, cisplatin + cetuximab | Excluded | Only 70% of patients were first-line (<80%) |
| 3 | Bergh, J. | Journal of clinical oncology. 2012;30(9):921-929. | Not reported | Sunitinib + docetaxel, docetaxel | Excluded | Trial connects into the network – however, the comparator(s) are not of interest as per the SLR "PICO" criteria, hence removed from network |
| 4 | Brufsky A, | Clin Breast Cancer.2011;Aug;11(4):211-220 | Not reported | Bevacizumab + paclitaxel, Bevacizumab + paclitaxel + gemcitabine | Excluded | Mixed BC study; only 28% TNBC; no TNBC subgroup data |
| 5 | Carey, L. A. | Journal of clinical oncology. 2012;30(21):2615-2623. | TBCRC 001 | Carboplatin + cetuximab, cetuximab | Excluded | Only 46% of patients were first-line (<80%) |

| | First author | Citation | Trial name (if specified) | Trial interventions | Included or excluded from base case NMA? | Reason for inclusion or exclusion |
|---|---|---|---|---|---|---|
| 6 | Clemens MR, G. O. | Breast cancer research and treatment. 2015;149(1):171-179. | NCT01038804 | Docetaxel, docetaxel + YM155 | Excluded | Mixed BC study; only 25% TNBC; no TNBC subgroup data |
| 7 | Dieras V, C | Annals of oncology: official journal of the European society for medical oncology. 2015;26(9):1904-1910. | NCT01186991 | Placebo + bevacizumab + paclitaxel, onartuzumab + placebo + paclitaxel, onartuzumab + bevacizumab + paclitaxel | Excluded | Trial connects into the network – however, the comparator(s) are not of interest as per the SLR "PICO" criteria, hence removed from network |
| 8 | Dieras V, W | Breast (Edinburgh, Scotland). 2015;24(3):182-190. | NCT00511459 | Trebananib 3mg/kg + bevacizumab + paclitaxel, trebananib 10mg/kg + bevacizumab + paclitaxel, trebananib 10mg/kg + paclitaxel | Excluded | Trial connects into the network – however, the comparator(s) are not of interest as per the SLR "PICO" criteria, hence removed from network |
| 9 | Fan, Y | Annals of oncology. 2013;24(5):1219-1225. | Not reported | Docetaxel + cisplatin, docetaxel + capecitabine | Excluded | Does not connect within best-case scenario network. |

| | First author | Citation | Trial name (if specified) | Trial interventions | Included or excluded from base case NMA? | Reason for inclusion or exclusion |
|---|---|---|---|---|---|---|
| 10 | Forero-Torres, A | Clinical cancer research. 2015;21(12):2722-2729. | TBCRC 019 | nab-paclitaxel, nab-paclitaxel + tigatuzumab | Excluded | Trial connects into the network – however, the comparator(s) are not of interest as per the SLR "PICO" criteria, hence removed from network |
| 11 | Gradishar, W | European journal of cancer. 2013;49(2):312-322. | NU071B | Sorafenib + paclitaxel, placebo + paclitaxel | Excluded | Trial connects into the network – however, the comparator(s) are not of interest as per the SLR "PICO" criteria, hence removed from network |
| 12 | Hu, X | The Lancet. 2015;Oncology. 16(4):436-446. | CBCSG006 | Gemcitabine + paclitaxel, cisplatin + gemcitabine | Excluded | Does not connect within best-case scenario network. |
| 13 | Kader, Y. A. | Breast cancer: targets and therapy. 2013;5:37-42. | Not reported | Bevacizumab + carboplatin + paclitaxel, carboplatin + docetaxel | Excluded | Only 32% TNBC, no TNBC subgroup data |

| | First author | Citation | Trial name (if specified) | Trial interventions | Included or excluded from base case NMA? | Reason for inclusion or exclusion |
|---|---|---|---|---|---|---|
| 14 | Kenjaeva, A. O. | Annals of oncology. 2015;3):iii7. | Not reported | Vinorelbine + cisplatin, vinorelbine + cisplatin + bevacizumab | Excluded | Does not connect within best-case scenario network. |
| 15 | Luck HJ, L. K. | Breast cancer research and treatment. 2015;149(1):141-149. | TABEA | Paclitaxel/docetaxel + bevacizumab + capecitabine, paclitaxel/docetaxel + bevacizumab | Excluded | Does not connect within best-case scenario network. |
| 16 | Mackey JR, R.-V. M. | Journal of clinical oncology. 2015;33(2):141-148. | Not reported | Docetaxel + ramucirumab, docetaxel + placebo | Excluded | Mixed BC study; only 24% TNBC; no TNBC subgroup data |
| 17 | Martin, M. | Annals of oncology. 2017;28(2):313-320. | BELLE-4 | Paclitaxel + placebo, Paclitaxel + buparlisib | Excluded | Mixed BC study; only 35.3% TNBC; no TNBC subgroup data |
| 18 | Martin, M. | Lancet oncology. 2011;12(4):369-76. | NCT00356681 | Bevacizumab, motesanib, placebo | Excluded | Does not connect within best-case scenario network. |
| 19 | O'Shaughnessy, J. | New England journal of medicine. 2011;364(3):205-214. | NCT00938652 | Gemcitabine + carboplatin, gemcitabine + carboplatin + iniparib | Excluded | Does not connect within best-case scenario network. |

| | First author | Citation | Trial name (if specified) | Trial interventions | Included or excluded from base case NMA? | Reason for inclusion or exclusion |
|---|---|---|---|---|---|---|
| 20 | Park, I. H. | Cancer research and treatment. 2017;49(3):569-577. | NCT00876486 | Paclitaxel (polymeric micelle-formulated), paclitaxel (cremophor EL-based) | Excluded | Does not connect within best-case scenario network. |
| 21 | Robert NJ, | Clin Breast Cancer.2011;Apr;11(2):82-92 | SUN 1094 | Sunitinib + paclitaxel, bevacizumab + paclitaxel | Excluded | Mixed BC study; only 21% TNBC; no TNBC subgroup data |
| 22 | Rugo HS, | Breast Cancer Res Treat.2013;;139:411–9. | CA163-115 | Ixabepilone (Q3W) + bevacizumab, ixabepilone (QW) + bevacizumab, bevacizumab + paclitaxel | Excluded | Mixed BC study; only 18% TNBC; no TNBC subgroup data |
| 23 | Schmid | J Clin Oncol.2018;Suppl; abstract 1007 | PAKT | AZD5363 + paclitaxel, paclitaxel | Excluded | Trial connects into the network – however, the comparator(s) are not of interest as per the SLR “PICO” criteria, hence removed from network |
| 24 | Takashima T, M. H. | The Lancet. 2016;Oncology. 17(1):90-98. | SELECT BC | Docetaxel or paclitaxel, S-1 | Excluded | Mixed BC study; only 20% TNBC; no TNBC subgroup data |

| | First author | Citation | Trial name (if specified) | Trial interventions | Included or excluded from base case NMA? | Reason for inclusion or exclusion |
|---|---|---|---|---|---|---|
| 25 | Tredan O, C | Clinical breast cancer. 2015;15(1):8-15. | NCT00633464 | Ixabepilone, ixabepilone + cetuximab | Excluded | Does not connect within best-case scenario network. |
| 26 | Yardley, D. A. | Annals of oncology. 2018;06:06. | tnAcity | nab-paclitaxel + carboplatin, nab-paclitaxel + gemcitabine, gemcitabine + carboplatin | Excluded | Does not connect within best-case scenario network. |
| 27 | Yardley, D. A. | Breast cancer research and treatment. 2015;154(1):89-97. | NCT00915603 | Bevacizumab + paclitaxel + placebo, bevacizumab + paclitaxel + everolimus | Excluded | Mixed BC study; only 21% TNBC; no TNBC subgroup data |

| | First author | Citation | Trial name (if specified) | Trial interventions | Included or excluded from base case NMA? | Reason for inclusion or exclusion |
|---|---|---|---|---|---|---|
| 28 | Kim, S.B. | Lancet oncology. 2017;18(10):1360-1372. | LOTUS | Paclitaxel + placebo, Paclitaxel + ipatasertib | Excluded | Excluded at second interim OS analysis. Did not investigate currently approved or used treatments for metastatic triple-negative breast cancer, and would only contribute to generation of evidence on the relative efficacy of unapproved therapies to paclitaxel. Furthermore, the exclusion of LOTUS improved model convergence significantly. |

| | First author | Citation | Trial name (if specified) | Trial interventions | Included or excluded from base case NMA? | Reason for inclusion or exclusion |
|---|---|---|---|---|---|---|
| 29 | Brufsky, A. | Cancer research. Conference: San Antonio Breast Cancer Symposium, SABCS. 2017;78(4 Supplement 1). | COLET | Cobimetinib to paclitaxel, Placebo + paclitaxel | Excluded | Excluded at second interim OS analysis. Did not investigate currently approved or used treatments for metastatic triple-negative breast cancer, and would only contribute to generation of evidence on the relative efficacy of unapproved therapies to paclitaxel. Furthermore, the exclusion of COLET improved model convergence significantly. |

| | First author | Citation | Trial name (if specified) | Trial interventions | Included or excluded from base case NMA? | Reason for inclusion or exclusion |
|---|---|---|---|---|---|---|
| 30 | Tamura K, I. K. | Cancer science. 2017;108(5):987-994. | JapicCTI-090921 | Docetaxel, Nab-paclitaxel | Excluded | In the JapicCTI-090921 study, no OS or PFS Kaplan–Meier curves for triple-negative cases were published. Roche contacted “Taiho Pharma” and requested access to these Kaplan–Meier data, but they were unable to share these data. Furthermore, this was a small Phase II trial. |

| | First author | Citation | Trial name (if specified) | Trial interventions | Included or excluded from base case NMA? | Reason for inclusion or exclusion |
|---|---|---|---|---|---|---|
| 31 | Welt, A. | Breast cancer research and treatment. 2016;156(1):97-107. | CARIN | Capecitabine + bevacizumab, Capecitabine + bevacizumab + vinorelbine | Excluded | Although individual-level data from the CARIN study was provided by the external study group, it was not possible to replicate the publication of this trial, nor the clinical study report using these provided data. We thus could not include the data in an NMA using parametric survival models. Furthermore, this trial included treatment regimens that are not of interest to the decision problem (capecitabine and bevacizumab with vinorelbine versus capecitabine and bevacizumab without vinorelbine) |

| | First author | Citation | Trial name (if specified) | Trial interventions | Included or excluded from base case NMA? | Reason for inclusion or exclusion |
|---|---|---|---|---|---|---|
| 32 | Finn, R.S. | Journal of clinical oncology. 2008;26(34):5544-52. | EGF30001 | Paclitaxel + lapatinib, Paclitaxel + placebo | Excluded | The Kaplan–Meier PFS curves for triple-negative cases in the publication of the EGF30001 study results did not include the numbers at risk, which made the re-creation of individual-level event times from Kaplan–Meier data infeasible. No OS hazard ratio or Kaplan–Meier curves for triple-negative cases were published. Furthermore, this trial's only treatment arm of interest is paclitaxel monotherapy and the other arm (paclitaxel with lapatinib) did not connect in the network. |

| | First author | Citation | Trial name (if specified) | Trial interventions | Included or excluded from base case NMA? | Reason for inclusion or exclusion |
|---|---|---|---|---|---|---|
| 33 | Pivot, X | Eur J Cancer. 2011;47(16):2387-95. | AVADO | Docetaxel + placebo, Bevacizumab 7.5 mg/kg + docetaxel, Bevacizumab 15 mg/kg + docetaxel | Included | Not excludable in systematic feasibility assessment. Contained at a minimum OS or PFS data that could be used in an NMA. Contributed to networks of comparisons of interest (to paclitaxel and docetaxel). |
| 34 | Gray, R | Journal of clinical oncology: 2009;27(30):4966-72. | E2100 | Paclitaxel, Bevacizumab + paclitaxel | Included | Not excludable in systematic feasibility assessment. Contained at a minimum OS or PFS data that could be used in an NMA. Contributed to networks of comparisons of interest (to paclitaxel and docetaxel). |

| | First author | Citation | Trial name (if specified) | Trial interventions | Included or excluded from base case NMA? | Reason for inclusion or exclusion |
|---|---|---|---|---|---|---|
| 35 | Miles, D. | European journal of cancer. 2017;70:146-155. | MERIDIAN | Paclitaxel, Bevacizumab + paclitaxel | Included | Not excludable in systematic feasibility assessment. Contained at a minimum OS or PFS data that could be used in an NMA. Contributed to networks of comparisons of interest (to paclitaxel and docetaxel). |
| 36 | Robert, NJ. D. | Journal of clinical oncology. 2011;29(10):1252-1260. | RIBBON-1 | Capecitabine + placebo, Capecitabine + bevacizumab | Included | Not excludable in systematic feasibility assessmentContained at a minimum OS or PFS data that could be used in an NMA. Contributed to networks of comparisons of interest (to paclitaxel and docetaxel). Contributed to networks of comparisons of interest (to paclitaxel and docetaxel). |

| | First author | Citation | Trial name (if specified) | Trial interventions | Included or excluded from base case NMA? | Reason for inclusion or exclusion |
|---|---|---|---|---|---|---|
| 37 | Zielinski, C | The Lancet Oncology. 2016;17(9):1230-1239. | TURNADOT | Bevacizumab + paclitaxel, Capecitabine + bevacizumab | Included | Not excludable in systematic feasibility assessment. Contained at a minimum OS or PFS data that could be used in an NMA. Contributed to networks of comparisons of interest (to paclitaxel and docetaxel). |
| 38 | Tutt A, T. H. | Nature medicine. 2018;24(5):628-637. | TNT | Carboplatin, docetaxel | Included | Not excludable in systematic feasibility assessment. Contained at a minimum OS or PFS data that could be used in an NMA. Contributed to networks of comparisons of interest (to paclitaxel and docetaxel). |

| | First author | Citation | Trial name (if specified) | Trial interventions | Included or excluded from base case NMA? | Reason for inclusion or exclusion |
|---|---|---|---|---|---|---|
| 39 | Rugo, H.S. | J Clin Oncol.2015;Jul 20;33(21):2361-9 | CALGB40502 | Bevacizumab + Nab-paclitaxel, Bevacizumab + Ixabepilone | Included | Not excludable in systematic feasibility assessment. Contained at a minimum OS or PFS data that could be used in an NMA. Contributed to networks of comparisons of interest (to paclitaxel and docetaxel). |
| 40 | Schmid, P. | N Engl J Med. 2018 Nov 29;379(22):2108-2121. | Impassion130 | Atezolizumab + nab-paclitaxel, placebo + nab-paclitaxel | Included | Roche sponsored trial forming basis of present NICE appraisal. Contained at a minimum OS or PFS data that could be used in an NMA. Contributed to networks of comparisons of interest (to paclitaxel and docetaxel). |

**Key:** BC, breast cancer; SLR, systematic literature review; TNBC, triple-negative breast cancer.

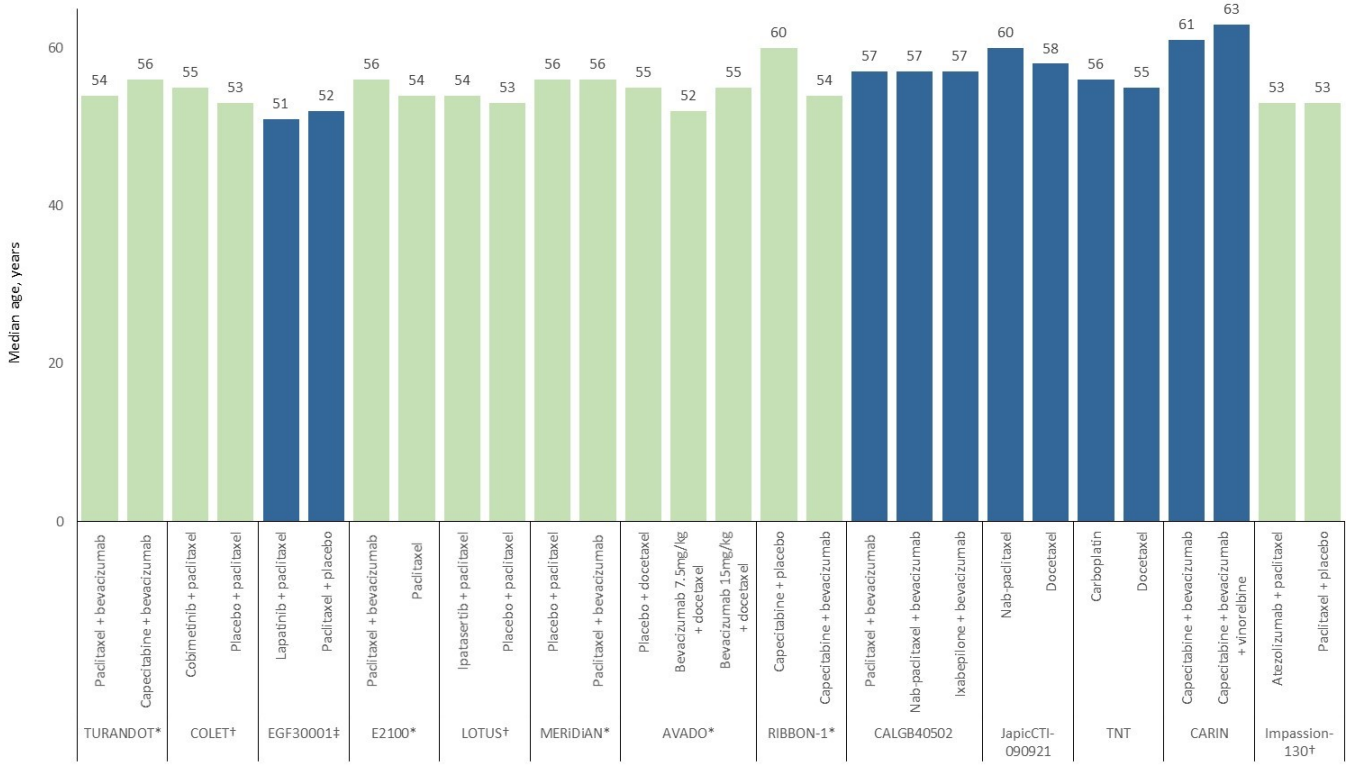
## 2. *Baseline characteristics of trials considered for use in the NMA*

The assessment of baseline characteristics was conducted as part of the feasibility assessment of all potential trials for the NMA to evaluate the homogeneity of evidence. These assessments are presented below. Based upon the assessment, the trials included in the NMA were deemed to be sufficiently homogenous to support indirect comparisons.

It is important to highlight, the ERG report concluded “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”. Roche have now provided the additional information below, thus do not anticipate this conclusion to change.

**Error! Reference source not found.** describes the median age of patients enrolled across the included trials. The between-trial ages of patients were broadly similar (highly homogenous for age). There was an outlier trial for age (CARIN), however, this study was excluded in the base case network for reasons described in the ERG Clarification question responses (Question A10 response, Page 22).

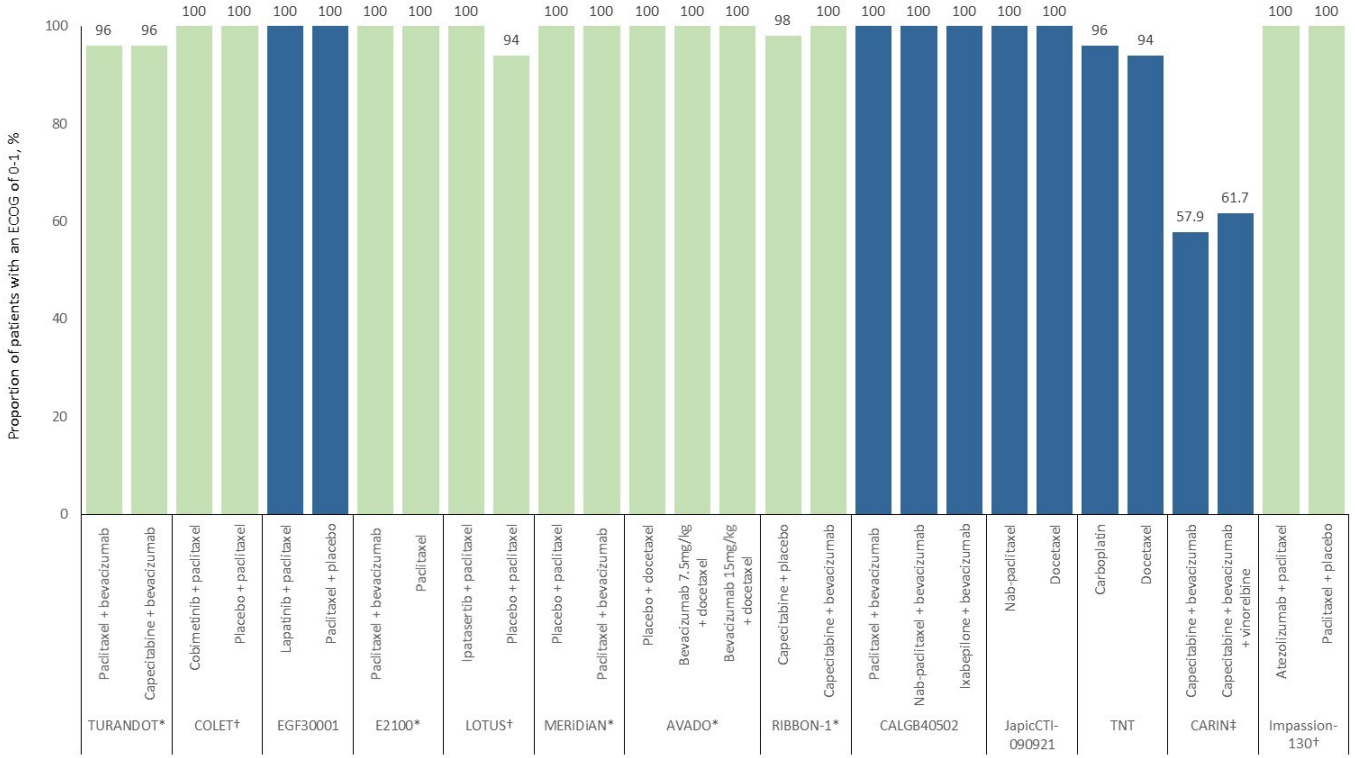
**Figure 1: Age of patients in trials considered for inclusion in the NMA (second interim OS analysis based NMA)**




Green bars represent studies that enrolled exclusively TNBC populations or identify where the data are provided for a TNBC subgroup only. Blue bars represent studies enrolling broader breast cancer populations that include a TNBC subgroup, but the baseline data were only available for the total trial population.*Baseline values reported for the TNBC subgroup. †Study conducted in TNBC population. ‡mean values

**Error! Reference source not found.** presents the proportion of patients enrolled with ECOG status 0 or 1. The between-trial ECOG status 0/1 proportions were very similar. There was an outlier trial for ECOG status (CARIN), however, this was excluded in the base case network for reasons described in the ERG Clarification question responses (Question A10 response, Page 22) and Appendix 2.

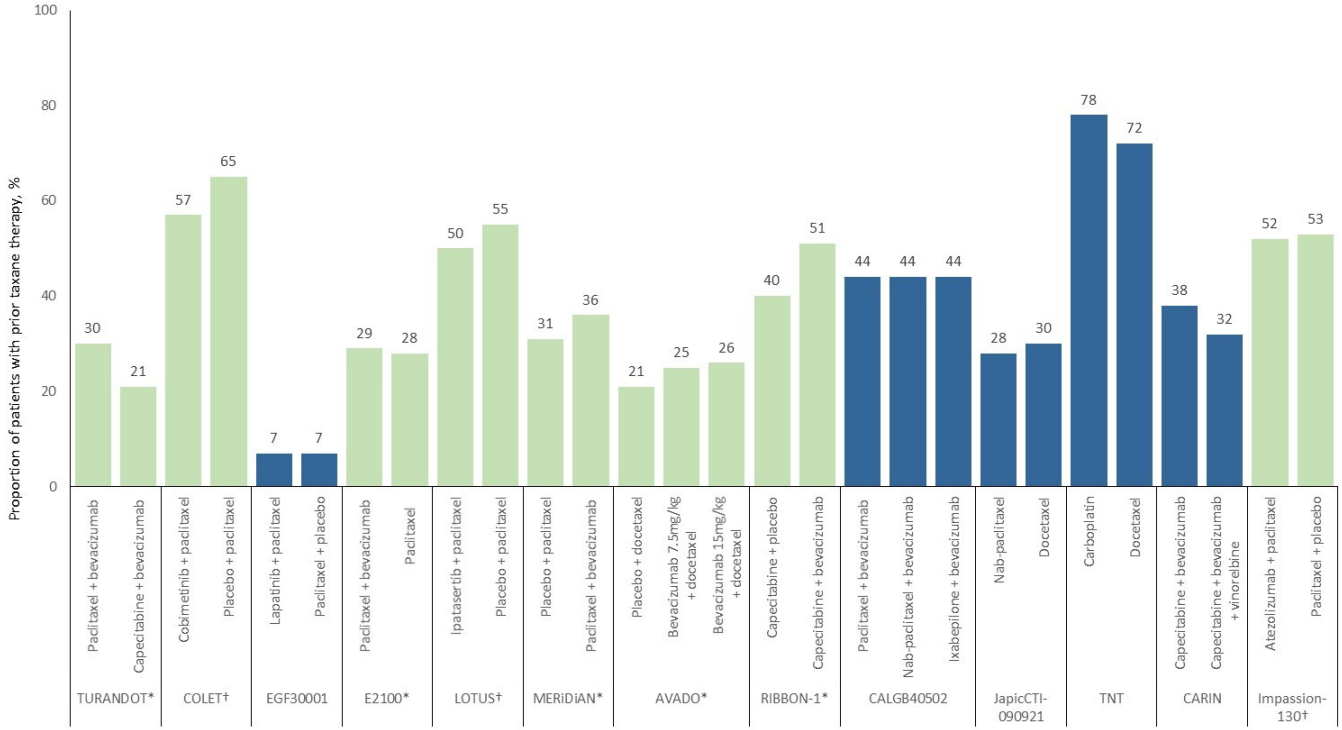
**Figure 2: Proportion of patients with an ECOG PS 0-1 in trials considered for inclusion in the NMA (second interim OS analysis based NMA)**



Green bars represent studies that enrolled exclusively TNBC populations or identify where the data are provided for a TNBC subgroup only. Blue bars represent studies enrolling broader breast cancer populations that include a TNBC subgroup, but the baseline data were only available for the total trial population.*Baseline values reported for the TNBC subgroup. †Study conducted in TNBC population. ‡Data for ECOG PS 0 available only (proportion of patients with an ECOG PS 1-2 also reported but only ECOG PS of 0 considered in the graph).

**Error! Reference source not found.** presents prior taxane therapies received by the populations across the trials considered for NMA inclusion. Use of taxanes across the neoadjuvant and adjuvant settings were inconsistently reported. It is accepted that there was some heterogeneity in the trials considered for inclusion in the second interim OS analysis-based NMA. However, the level of heterogeneity was considered acceptable for use in the NMA, with random effects used to account for this.

**Figure 3: Proportion of patients that had received prior taxane in trials considered for inclusion in the NMA (second interim OS analysis based NMA)**

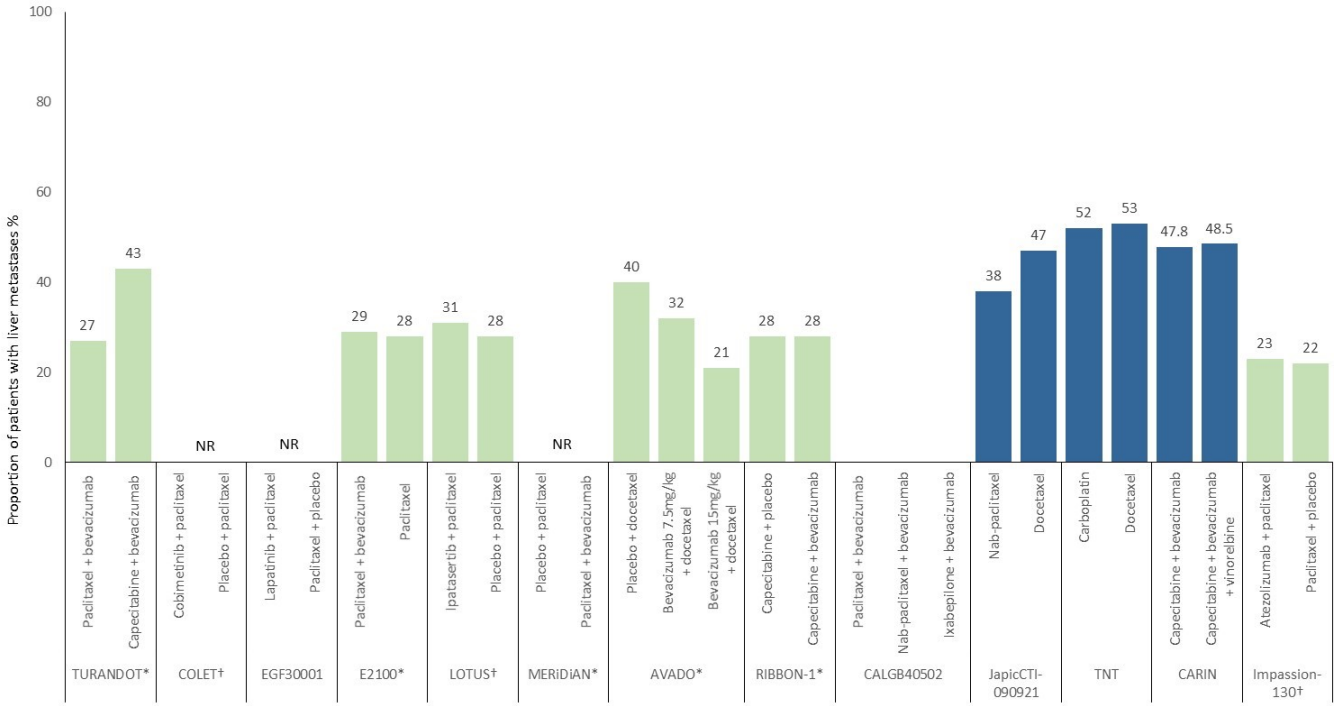



Green bars represent studies that enrolled exclusively TNBC populations or identify where the data are provided for a TNBC subgroup only. Blue bars represent studies enrolling broader breast cancer populations that include a TNBC subgroup, but the baseline data were only available for the total trial population.*Baseline values reported for the TNBC subgroup. †Study conducted in TNBC population

**Error! Reference source not found.** presents the proportion of patients with liver metastases across the trials considered for NMA inclusion. The TNT trial was the main outlier, with CARIN also indicating a difference. CARIN was excluded in the base case network for reasons described in the ERG Clarification question responses (Question A10 response, Page 22), and the level of heterogeneity associated with TNT was considered acceptable for use in the NMA (with random effects used to account for this).

It is worth noting that given the structure of the network, TNT will impact on the comparisons to regimens involving docetaxel and carboplatin, which are not considered the main comparators in this appraisal (the TNT trial will not impact on the comparisons of atezolizumab + nab-paclitaxel to the other regimens). The impact of matching to TNT instead of AVADO was assessed as part of the sensitivity analyses (provided in the company submission). This resulted in a considerably shorter restricted 5-year survival for both PFS and OS under docetaxel. As such, the PAIC utilised in this appraisal was deemed more conservative.

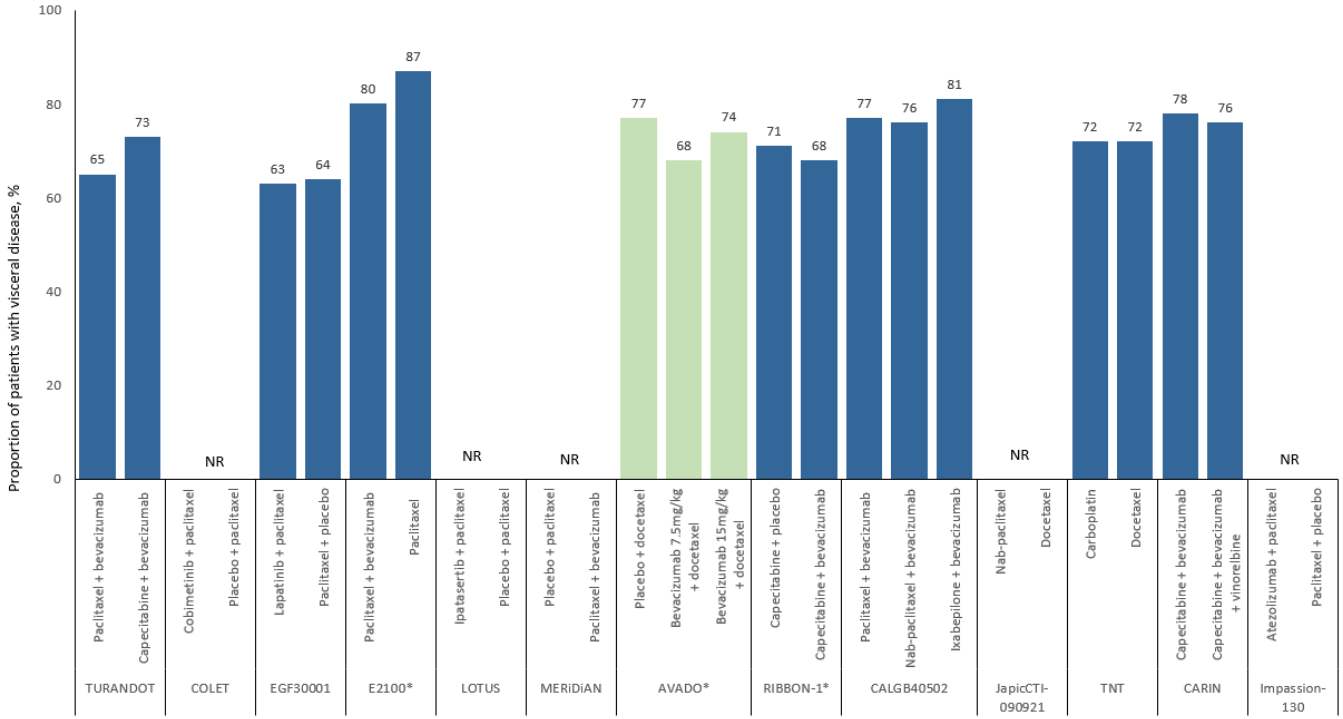
**Figure 4: Proportion of patients with liver metastases in the population of each trial considered for inclusion in the NMA (second interim OS analysis based NMA)**




Green bars represent studies that enrolled exclusively TNBC populations or identify where the data are provided for a TNBC subgroup only. Blue bars represent studies enrolling broader breast cancer populations that include a TNBC subgroup, but the baseline data were only available for the total trial population.*Baseline values reported for the TNBC subgroup. †Study conducted in TNBC population

**Error! Reference source not found.** presents the proportion of patients with visceral disease, across the trials considered for NMA inclusion. Where reported, the proportions were broadly similar across the trials.

**Figure 5: Proportion of patients with visceral disease in the population of each trial considered for inclusion in the NMA (second interim OS analysis based NMA)**

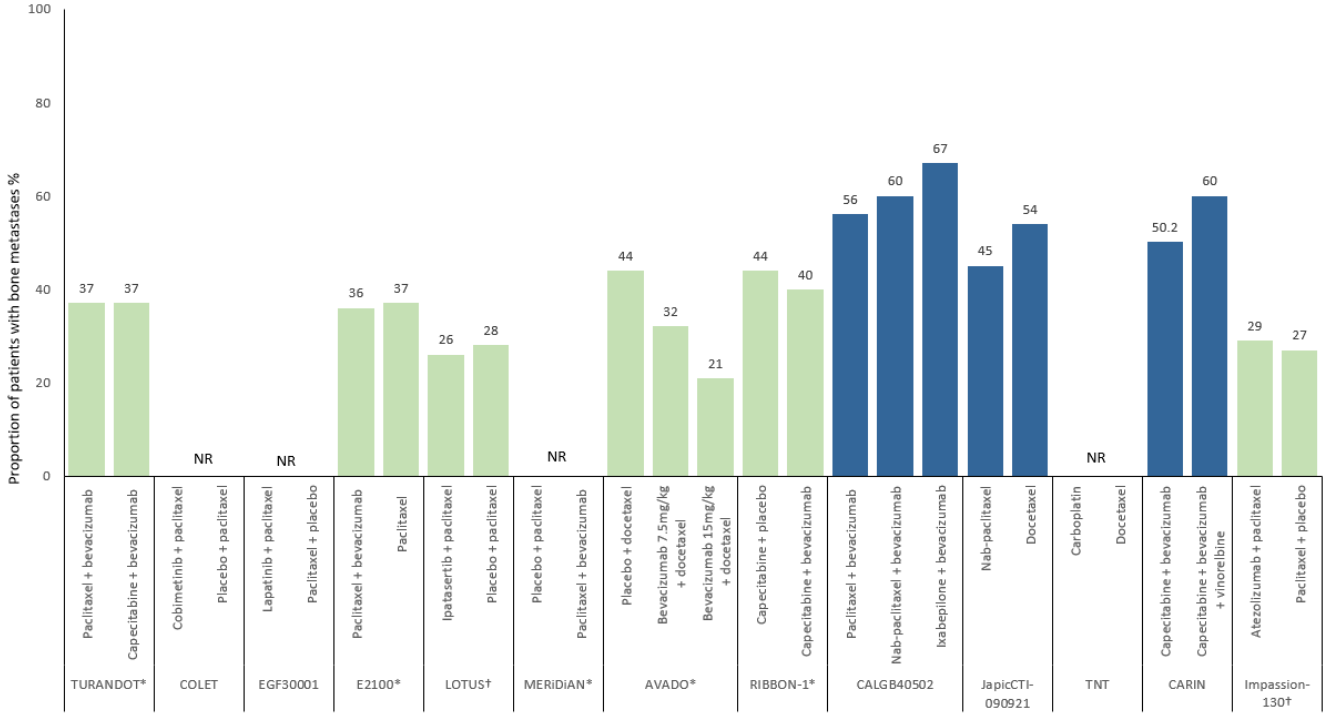



Green bars represent studies that enrolled exclusively TNBC populations or identify where the data are provided for a TNBC subgroup only. Blue bars represent studies enrolling broader breast cancer populations that include a TNBC subgroup, but the baseline data were only available for the total trial population.*Baseline values reported for the TNBC subgroup. †Study conducted in TNBC population

**Error! Reference source not found.** presents the proportion of patients with bone metastases across the trials considered for NMA inclusion. The TNT, JapicCTI-090921 and CARIN trials were the main outliers. JapicCTI-090921 and CARIN were excluded in the base case network for reasons described in the ERG Clarification question responses (Question A10 response, Page 22), and the level of heterogeneity associated with TNT was considered acceptable for use in the NMA (with random effects used to account for this).

It is worth noting that given the structure of the network, TNT will impact on the comparisons to regimens involving docetaxel and carboplatin, which are not considered the main comparators in this appraisal (the TNT trial will not impact on the comparisons of atezolizumab + nab-paclitaxel to the other regimens). The impact of matching to TNT instead of AVADO was assessed as part of the sensitivity analyses (provided in the company submission). This resulted in a considerably shorter restricted 5-year survival for both PFS and OS under docetaxel. As such, the PAIC utilised in this appraisal was deemed more conservative.

**Figure 6: Proportion of patients with bone metastases in the population of each trial considered for inclusion in the NMA (second interim OS analysis based NMA)**




Green bars represent studies that enrolled exclusively TNBC populations or identify where the data are provided for a TNBC subgroup only. Blue bars represent studies enrolling broader breast cancer populations that include a TNBC subgroup, but the baseline data were only available for the total trial population.*Baseline values reported for the TNBC subgroup. †Study conducted in TNBC population

### 3. *Summary statistics of candidate covariates for matching*

The summary statistics of candidate covariates for matching are provided in **Error! Reference source not found.** (E2100 trial), **Error! Reference source not found.** (MERIDIAN trial) and **Error! Reference source not found.** (AVADO trial).

The comparison of the summary statistics in the weighted A+NabPx group from IMpassion130 and the unweighted comparison studies' triple-negative populations demonstrated that the covariate balancing propensity score model achieved almost perfect balance in covariate means and reasonably similar standard deviations. The improvements in covariate balance compared to generalised linear models can come at the cost of lower effective sample size and higher uncertainty around the estimates. Roche made the conscious decision to reduce bias at the potential cost of higher variance, because bias cannot be quantified and reported while variance of the estimates can be reported and incorporated in the probabilistic analysis (PSA) of the cost-effectiveness analysis. The summary statistics of candidate covariates for matching are provided in this Appendix, below.

**Table 2: Summary statistics of all candidate covariates for matching to the E2100 trial**

| | Variable description | Value range | E2100 Mean (sd) | Atezolizumab + nab-paclitaxel Mean (sd) | p | SMD |
|---|---|---|---|---|---|---|
| N | Number of patients | | 230.00 | 185.00 | | |
| age | Age | [years] | 54.69 (11.59) | 53.66 (12.91) | 0.398 | 0.084 |
| regnoam | Region: North America | (0, 1) | 1.00 (0.00) | 0.26 (0.44) | <0.001 | 2.350 |
| racewhite | Race: White | (0, 1) | 0.74 (0.44) | 0.68 (0.47) | 0.160 | 0.139 |
| raceblack | Race: Black | (0, 1) | 0.13 (0.34) | 0.05 (0.22) | 0.003 | 0.289 |
| raceasian | Race: Asian | (0, 1) | 0.01 (0.09) | 0.21 (0.41) | <0.001 | 0.669 |
| time2met | Time from init. to met. diagnosis | [years] | 3.49 (3.74) | 2.35 (2.85) | <0.001 | 0.343 |
| time2rand | Time from met. diag. to rand. | [years] | 0.33 (0.93) | 0.19 (0.20) | 0.028 | 0.206 |
| dismet | Metastatic disease | (0, 1) | 0.97 (0.18) | 0.88 (0.33) | 0.001 | 0.335 |
| nsite | Number of disease sites | $Z$ | 2.47 (1.17) | 2.49 (1.23) | 0.822 | 0.022 |
| metbone | Bone metastases | (0, 1) | 0.37 (0.48) | 0.28 (0.45) | 0.051 | 0.192 |
| metliver | Liver metastases | (0, 1) | 0.28 (0.45) | 0.22 (0.42) | 0.154 | 0.140 |
| metlung | Lung metastases | (0, 1) | 0.53 (0.50) | 0.49 (0.50) | 0.424 | 0.079 |
| metskin | Skin metastases | (0, 1) | 0.05 (0.21) | 0.04 (0.20) | 0.824 | 0.022 |
| prianth | Prior anthracycline treatment | (0, 1) | 0.57 (0.50) | 0.59 (0.49) | 0.624 | 0.048 |
| pritax | Prior adjuvant taxane treatment | (0, 1) | 0.28 (0.45) | 0.52 (0.50) | <0.001 | 0.496 |

*Legend: sd: Standard deviation; p: P-value from a Chi-square test; SMD: Standardized mean difference defined as the difference in means divided by the pooled standard deviation. Z: Integer*

**Table 3: Summary statistics of all candidate covariates for matching to the MERIDIAN trial**

| | Variable description | Value range | MERIDIAN Mean (sd) | Atezolizumab + nab-paclitaxel Mean (sd) | p | SMD |
|---|---|---|---|---|---|---|
| N | Number of patients | | 78.00 | 185.00 | | |
| age | Age | [years] | 54.83 (11.41) | 53.66 (12.91) | 0.465 | 0.096 |
| height | Body height | [cm] | 160.88 (7.71) | 161.14 (7.72) | 0.801 | 0.034 |
| weight | Body weight | [kg] | 72.99 (18.04) | 70.69 (17.29) | 0.340 | 0.130 |
| bmi | Body mass index | $R_{\geq 0}$ | 28.09 (6.11) | 27.20 (6.26) | 0.284 | 0.144 |
| regnaeu | Region: North America & Europe | (0, 1) | 0.42 (0.50) | 0.64 (0.48) | 0.001 | 0.439 |
| regasia | Region: Asia | (0, 1) | 0.24 (0.43) | 0.18 (0.39) | 0.292 | 0.146 |
| racewhite | Race: White | (0, 1) | 0.56 (0.50) | 0.68 (0.47) | 0.093 | 0.230 |
| raceblack | Race: Black | (0, 1) | 0.14 (0.35) | 0.05 (0.22) | 0.031 | 0.318 |
| raceasian | Race: Asian | (0, 1) | 0.24 (0.43) | 0.21 (0.41) | 0.506 | 0.091 |
| ecog0 | ECOG = 0 | (0, 1) | 0.64 (0.48) | 0.58 (0.50) | 0.341 | 0.128 |
| nsite | Number of disease sites | $Z$ | 2.41 (1.13) | 2.49 (1.23) | 0.603 | 0.069 |
| sld | Sum of longest diameters[a] | [mm] | 72.51 (52.49) | 65.01 (53.72) | 0.294 | 0.141 |
| time2rand | Time from met. diag. to rand. | [years] | 0.27 (0.62) | 0.19 (0.20) | 0.247 | 0.181 |
| metbone | Bone metastases | (0, 1) | 0.26 (0.44) | 0.28 (0.45) | 0.747 | 0.043 |
| metliver | Liver metastases | (0, 1) | 0.26 (0.44) | 0.22 (0.42) | 0.552 | 0.081 |
| metlung | Lung metastases | (0, 1) | 0.47 (0.50) | 0.49 (0.50) | 0.858 | 0.024 |
| metmed | Mediastinum metastases | (0, 1) | 0.04 (0.19) | 0.15 (0.36) | 0.001 | 0.391 |
| metskin | Skin metastases | (0, 1) | 0.05 (0.22) | 0.04 (0.20) | 0.784 | 0.038 |

[a] In both studies, up to 5 target lesions, i.e. the lesions with the longest diameters, were considered for the calculation of the sum of longest diameters.

| | Variable description | Value range | MERIDIAN Mean (sd) | Atezolizumab + nab-paclitaxel Mean (sd) | p | SMD |
|---|---|---|---|---|---|---|
| N | Number of patients | | 78.00 | 185.00 | | |
| prianth | Prior anthracycline therapy | (0, 1) | 0.50 (0.50) | 0.59 (0.49) | 0.188 | 0.179 |
| pritax | Prior adjuvant taxane treatment | (0, 1) | 0.33 (0.47) | 0.52 (0.50) | 0.005 | 0.380 |
| diabp | Diastolic blood pressure | [mmHg] | 75.72 (10.51) | 76.43 (10.15) | 0.611 | 0.069 |
| sysbp | Systolic blood pressure | [mmHg] | 124.85 (13.52) | 126.01 (16.35) | 0.552 | 0.077 |
| pulse | Pulse rate | [r/min] | 82.76 (14.64) | 81.08 (12.56) | 0.377 | 0.123 |
| resp | Respiratory rate | [r/min] | 17.05 (2.55) | 17.24 (2.64) | 0.581 | 0.074 |
| temp | Body temperature | [C°] | 36.46 (0.40) | 36.52 (0.38) | 0.297 | 0.143 |
| ecgabn | Abnormal electrocardiography | | 0.33 (0.47) | 0.36 (0.48) | 0.716 | 0.049 |

*Legend: sd: Standard deviation; p: P-value from a Chi-square test; SMD: Standardized mean difference defined as the difference in means divided by the pooled standard deviation. Z: Integer*

**Table 4: Summary statistics of all candidate covariates for matching to the AVADO trial**

| | Variable description | Value range | AVADO Mean (sd) | Atezolizumab + nab-paclitaxel Mean (sd) | P | SMD |
|---|---|---|---|---|---|---|
| n | | | 164.00 | 185.00 | | |
| age | Age | [years] | 53.13 (11.21) | 53.66 (12.91) | 0.684 | 0.043 |
| height | Body height | [cm] | 160.96 (7.93) | 161.15 (7.66) | 0.824 | 0.024 |
| weight | Body weight | [kg] | 67.50 (14.07) | 70.83 (17.27) | 0.049 | 0.211 |
| bmi | Body mass index | $R_{\geq 0}$ | 26.05 (5.08) | 27.24 (6.24) | 0.050 | 0.210 |
| regasia | Region:Asia | (0, 1) | 0.14 (0.35) | 0.18 (0.39) | 0.270 | 0.118 |
| racewhite | Race: White | (0, 1) | 0.78 (0.42) | 0.68 (0.47) | 0.028 | 0.237 |
| raceblack | Race: Black | (0, 1) | 0.02 (0.13) | 0.05 (0.22) | 0.111 | 0.169 |
| raceasian | Race: Asian | (0, 1) | 0.15 (0.36) | 0.21 (0.41) | 0.197 | 0.138 |
| ecog0 | ECOG status 0 | (0, 1) | 0.59 (0.49) | 0.58 (0.50) | 0.895 | 0.014 |
| nsite3 | Number of disease sites >3 | (0, 1) | 0.51 (0.50) | 0.46 (0.50) | 0.386 | 0.093 |
| time2met | Time from init. to met. diagnosis | [years] | 41.25 (58.04) | 28.16 (34.25) | 0.012 | 0.275 |
| time2rand | Time from met. diag. to rand. | [years] | 1.91 (4.13) | 2.28 (2.39) | 0.320 | 0.108 |
| metliver | Liver metastases | (0, 1) | 0.30 (0.46) | 0.22 (0.42) | 0.079 | 0.189 |
| metlung | Lung metastases | (0, 1) | 0.50 (0.50) | 0.49 (0.50) | 0.802 | 0.027 |
| prianth | Prior anthracycline therapy | (0, 1) | 0.60 (0.49) | 0.59 (0.49) | 0.874 | 0.017 |
| priadjrad | Prior adjuvant radiotherapy | (0, 1) | 0.59 (0.49) | 0.57 (0.50) | 0.816 | 0.025 |
| pritax | Prior adjuvant taxane treatment | (0, 1) | 0.24 (0.43) | 0.52 (0.50) | <0.001 | 0.604 |

*Legend: sd: Standard deviation; p: P-value from a Chi-square test; SMD: Standardized mean difference defined as the difference in means divided by the pooled standard deviation. Z: Integer*

## 4. *NMA feasibility assessment conducted and rationales for NMA model selection*

As described above, a total of 8 studies were included in the base case network for PFS and 7 studies were included in the base case network for OS (Table 1).

**Table 5: Final base case network of trials following the second interim OS analysis, for PFS and OS**

| **Trials included in *base case* network of Impasson130 second interim OS analysis** | |
|---|---|
| **OS (N=7 trials)[1]** | **PFS (N=8 trials) [1]** |
| Impassion130 | Impassion130 |
| AVADO | AVADO |
| E2100 | E2100 |
| MERIDIAN | MERIDIAN |
| RIBBON-1 | RIBBON-1 |
| TURNADOT | TURNADOT |
| TNT | TNT |
| - | CALGB40502 |

[1]Following the CS NMA, which utilised the Impassion130 primary analysis, an updated NMA, based on the Impssion130 second interim OS analysis was conducted. This was submitted in the responses to the ERG Clarification Questions. Two further trials were excluded in the updated NMA (second interim OS analysis data cut-based NMA). These were the LOTUS and COLET studies: which were excluded from the NMA because they did not investigate currently approved or used treatments for metastatic triple-negative breast cancer, and would only contribute to generation of evidence on the relative efficacy of unapproved therapies to paclitaxel. Furthermore, the exclusion of COLET and LOTUS improved model convergence significantly.

Roche selected and specified the Bayesian models for the analysis of time-to-event outcomes in a pre-specified manner using a broad set of tests and model diagnostics without knowledge of the results. Candidate models included the normal likelihood model using published log-hazard ratios, discrete time first and second order fractional polynomial models and discrete time piecewise exponential models using aggregate event rates per period of time obtained from individual-level survival times.(1)

Roche rejected the normal likelihood model using published log-hazard ratios because the proportional hazards assumption was deemed to be violated in multiple studies included in the analysis. The piecewise exponential model was favoured over first and second order fractional polynomial models based on the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) in a frequentist framework, the validity of long-term extrapolations, Bayesian model diagnostics and a comparison of observed Kaplan-Meier curves and extrapolated survival probabilities. Following this primary analysis-based NMA assessment, this assessment was re-performed for the second interim OS analysis and is provided in the response A13 to ERG Clarification Questions (ERG Clarification Questions, A13, Page 28 to 39).

The random effects model was selected as the base case model because the Deviance Information Criterion (DIC) of the random effects model was smaller or not more than 5 points larger than the DIC of the fixed effects model(2) and the random effects assumption was deemed more realistic in the context of a network meta-analysis.(3) Cut-points of the piecewise exponential model were selected from a broad set of candidate sets based on the AIC and BIC in a frequentist framework. Roche also carried out an extensive set of sensitivity analyses to assess the robustness of the analyses and to identify important sources of uncertainty.

Piecewise exponential models are very flexible models, suitable for use in cases where the proportional hazards assumption is violated. Piecewise exponential models rely on less restrictive assumptions about the shape of parametric survival functions than standard parametric survival models and are less prone to overfitting and implausible extrapolations than fractional polynomial models. Another important strength is that the cut-points of the NMA can be selected in an empirical manner. Piecewise exponential models are also recommended in the NICE DSU Technical Support Document 14(4) for the analysis of time-to-event outcomes in situations when the proportional hazards assumption is violated.

Because the networks were unconnected, Roche used an unanchored population adjusted indirect comparison (PAIC) to create virtual connections, following the recommendations outlined within NICE DSU Technical Support Document 18.(5) Roche carried out the PAIC in the base case using all three trials in the network that investigated either paclitaxel or docetaxel (AVADO, E2100, MERiDiAN trials). The TNT trial was only used in the PAIC for a scenario analysis. However, the TNT was used in the overall base case NMA (which included the base case PAIC).

Roche extended the standard approach recommended in the NICE DSU Technical Support Document 18(5) to improve the robustness of the indirect comparisons:

- Roche used individual-level data in the base case NMA from the three Roche supported HER2-negative trials (AVADO, E2100, MERIDIAN trials) that investigated paclitaxel and docetaxel. The use of individual-level data allowed:
    - Consideration of the full distributions for the patient characteristic data in Impassion130 and the comparison studies

- Inclusion of all covariates that were available in the final analysis data sets of both IMpassion130 and the comparison studies, and not just the variables that were presented in the baseline characteristics tables of the study publications.
- More detailed assessment of the similarity (homogeneity) of the study populations and the assessment towards achieving balance after weighting individual patients.
- Matching of the larger group to the smaller group, i.e. the A+NabPx arm to the entire comparison studies' triple-negative population, which is superior to matching a smaller to the larger group, (i.e. superior to matching the paclitaxel and docetaxel arms of comparison studies to the entire IMpassion130 study population.)

Roche used a covariate balancing propensity score model(6, 7) instead of the standard generalised linear model for the estimation of weights. The covariate balancing propensity score model employs a generalised method of moments approach to find the weights that best fulfil the specified moment conditions. Unlike generalised linear models, the covariate balancing propensity score model does not rely on a well specified model, and it has been shown to dramatically improve balance and fit compared to weighting methods previously reported in the literature.(7)

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NICE National Institute for Health and Care Excellence

# Technical engagement response form

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

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

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Deadline for comments: **5pm, Monday 12 August 2019**

Thank you for your time.

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- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

**We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.**

**Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.**

## About you

| | |
|---|---|
| **Your name** | [redacted] |
| **Organisation name – stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank) | Breast Cancer Care and Breast Cancer Now |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | N/A |

## Questions for engagement

| **Issue 1: Generalisability of the trial results** |
| --- |

| | |
|---|---|
| a) Do the characteristics of the overall trial population and PD-L1 positive subgroup of Impassion130 reflect those of people who would be eligible for atezolizumab plus nab-paclitaxel in the UK clinical setting? | |
| b) Fewer people in the trial had been previously treated with anthracyclines compared with UK clinical practice and a higher proportion had newly diagnosed metastatic disease. How would these differences be expected to affect the generalisability of the trial results? | |
| **Issue 2: PD-L1 testing** | |
| a) Would the introduction of PD-L1 testing in the mTNBC population be feasible? | |
| b) What challenges would PD-L1 testing introduce to current clinical practice? Will it require a new biopsy? | If atezolizumab with nab-paclitaxel is recommended for use, timely PD-L1 testing in the pathway for patients with triple negative breast cancer would be essential in order to identify those suitable for this treatment option. Routine use of this test would need to be adopted quickly into practice. Whilst PD-L1 testing is in place for other cancers, this will be new to some of the breast cancer workforce and it will be important to ensure any support and training required is put in place promptly. |
| c) Would the currently used tests in the NHS be used for testing people with breast cancer or will a specific test be required? | |
| d) What is the reason for the selection of ≥1% as a threshold in the trial? | |

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| **Issue 3: Appropriate comparators** | |
| a) Are weekly paclitaxel and docetaxel the most relevant comparators?<br>- Which one is most commonly used? | Chemotherapy options include anthracycline based chemotherapy or single agent taxanes – docetaxel and paclitaxel. However, if anthracyclines have been used in the early breast cancer setting – generally docetaxel or paclitaxel would be considered. Clinical experts will be best placed to advise regarding whether paclitaxel or docetaxel is most commonly used in practice. . |
| b) Do experts agree that anthracycline-based chemotherapy is not a relevant comparator in the metastatic setting? | |
| **Issue 4: Comparison with taxanes** | |
| a) Are the methods and results of the company's network meta-analysis plausible to establish comparative effectiveness data for atezolizumab plus nab-paclitaxel compared with taxanes? | |
| b) Are the results of the NMA clinically plausible given the limitations highlighted by the ERG? In particular that the inclusion criteria of the trials were different from IMpassion130 and included people with unknown PD-L1 status? | |
| **Issue 5: Using nab-paclitaxel as a proxy for modelling the effectiveness of taxanes** | |
| a) Is nab-paclitaxel sufficiently similar to weekly paclitaxel and docetaxel for it to be reasonable to assume equivalence between these treatments and use trial data from IMpassion130 as a proxy for | |

| | |
|---|---|
| the effectiveness of atezolizumab plus nab-paclitaxel compared with taxanes? | |
| **Issue 6: Duration of treatment effect** | |
| a) Would treatment benefits with atezolizumab plus nab-paclitaxel after treatment has stopped be maintained for the remaining lifetime of patients or would benefits decline after a certain period of time? | |
| b) If waning effect is likely to occur, until which timepoint would treatment effect be maintained? | |
| c) Is it appropriate to assume a waning effect in the absence of a stopping rule? | |
| **Issue 7: Health state costs** | |
| a) Do the company's estimates on the frequency of oncologist visits reflect UK clinical practice or are the ERG's estimates more plausible? | |
| **Issue 8: End of life criteria** | |
| a) Does atezolizumab plus nab-paclitaxel fulfil the criteria to be considered a 'life-extending treatment at the end of life'? | Yes, we agree with the ERG and the company's scenarios which outline that atezolizumab with nab-paclitaxel fulfils the end of life criteria. |
| **Issue 9: Cancer Drugs Fund** | |
| a) Would additional data collection in the Cancer Drugs Fund reduce the uncertainty? | |

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| b) Is the technology a good candidate for use in the Cancer Drugs Fund? | If this treatment is not recommended for routine use, we would urge Roche, NICE and NHS England to work together to explore all possibilities for ensuring this treatment can reach patients, including considering how the Cancer Drugs Fund may facilitate useful additional data collection. |

NICE National Institute for Health and Care Excellence

# Technical engagement response form

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## About you

| | |
|---|---|
| **Your name** | [redacted] |
| **Organisation name – stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank) | **NHS England and NHS Improvement** |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **None** |

## Questions for engagement

| **Issue 1: Generalisability of the trial results** |
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| | |
|---|---|
| a) Do the characteristics of the overall trial population and PD-L1 positive subgroup of Impassion130 reflect those of people who would be eligible for atezolizumab plus nab-paclitaxel in the UK clinical setting? | Although anthracycline-based therapies are the recommended 1st line treatment options for anthracycline-naïve patients with locally advanced/metastatic TNBC and 43% of patients in the PD-L1 subgroup were anthracycline-naïve in the Impassion 130 study, NHS England and NHS Improvement (NHS E & NHS I) nevertheless regard the treatment design of the Impassion 130 trial of taxane plus atezolizumab versus taxane plus placebo as being appropriate to clinical practice in England. This is because most patients in England have had neoadjuvant/adjuvant anthracyclines prior to disease relapse and in those who are anthracycline-naïve at the time of diagnosis of incurable breast cancer, many of these are currently treated with 1st line taxanes, particularly paclitaxel.<br><br>Nab-paclitaxel is considered to be broadly equivalent to paclitaxel and docetaxel in terms of efficacy in the palliative treatment of breast cancer.<br><br>NHS & NHS I therefore consider the results of the PD-L1 subgroup of the Impassion 130 trial to be generalizable to the NHS. |
| b) Fewer people in the trial had been previously treated with anthracyclines compared with UK clinical practice and a higher proportion had newly diagnosed metastatic disease. How would these differences be expected to affect the generalisability of the trial results? | See above. |
| Issue 2: PD-L1 testing | |

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| a) Would the introduction of PD-L1 testing in the mTNBC population be feasible? | PD-L1 testing is already in widespread use in England, particularly in patients with non small cell lung cancer but not currently in patients with breast cancer. Although a specific PD-L1 diagnostic test was used in the Impassion 130 study, this will not be the case in England.<br><br>If atezolizumab is recommended for use by NICE, NHS E & NHS I would expect to commission the testing of PD-L1 at the time of diagnosis of incurable breast cancer, rather than at the time of diagnosis of early breast cancer. Although the incidence of TNBC is 15-20%, Roche has indicated in its submission that 25% of breast cancer deaths are in TNBC patients as a consequence of the generally more aggressive nature of TNBC. Thus about one quarter of patients with breast cancer would be eligible for testing at the time of diagnosis of incurable breast cancer although those patients who are unfit for any chemotherapy would not require testing.<br><br>Provided that the costs of testing of at least 20% of all locally advanced/metastatic breast cancer patients are fully included in the economic modelling, NHS E & NHS I expect the testing of PD-L1 to be readily and quickly implemented if NICE recommends atezolizumab in this indication. |
| b) What challenges would PD-L1 testing introduce to current clinical practice? Will it require a new biopsy? | Whilst a new biopsy is done in some patients at relapse after a previous diagnosis of early breast cancer, NHS E & NHS I do not regard a second biopsy as being necessary. |
| c) Would the currently used tests in the NHS be used for testing people with breast cancer or will a specific test be required? | Currently used PD-L1 diagnostic tests will be used. NHS E & NHS I would not support the use of a specific diagnostic test from one company (the trial used a Ventana test, NHS E & NHS I noting that Ventana is a Roche company). |
| d) What is the reason for the selection of ≥1% as a threshold in the trial? | The definition of PD-L1 positivity as being ≥1% is one that is used widely in cancer and has been done so in non small cell lung cancer for several years. This definition is therefore widely used and accepted. |
| Issue 3: Appropriate comparators | |

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| a) Are weekly paclitaxel and docetaxel the most relevant comparators?<br>- Which one is most commonly used? | Taxane therapy is the most reasonable comparator to use (see above) and weekly paclitaxel is the most commonly used taxane regimen for the palliation of incurable breast cancer. |
| b) Do experts agree that anthracycline-based chemotherapy is not a relevant comparator in the metastatic setting? | Yes. See above. |
| Issue 4: Comparison with taxanes | |
| a) Are the methods and results of the company's network meta-analysis plausible to establish comparative effectiveness data for atezolizumab plus nab-paclitaxel compared with taxanes? | NHS E and NHS I regard there to be very considerable heterogeneity in the populations with which atezolizumab plus nab-paclitaxel in the Impassion 130 trial is being compared ie with historical studies of paclitaxel and docetaxel. There is a great paucity of PD-L1 data in the (older) studies of the efficacy of pacilitaxel and docetaxel monotherapies.<br>NHS E & NHS I also note that in this indirect comparison in which piece-wise exponential analysis is used, the hazard ratios seem to be very labile according to which time period is chosen for comparison. In addition, there appear to be very significant differences in the hazard ratios for progression free survival according to time points in the analyses of paclitaxel and docetaxel.<br>NHS E & NHS I therefore regard there to be great uncertainties in the company's network meta-analyses for the comparison of atezolizumab plus nab-paclitaxel versus paclitaxel and docetaxel monotherapies. NHS E & NHS I note the very considerable effect that this uncertainty has on the ICER. |

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| b) Are the results of the NMA clinically plausible given the limitations highlighted by the ERG? In particular that the inclusion criteria of the trials were different from IMpassion130 and included people with unknown PD-L1 status? | See above. |
| Issue 5: Using nab-paclitaxel as a proxy for modelling the effectiveness of taxanes | |
| a) Is nab-paclitaxel sufficiently similar to weekly paclitaxel and docetaxel for it to be reasonable to assume equivalence between these treatments and use trial data from IMpassion130 as a proxy for the effectiveness of atezolizumab plus nab-paclitaxel compared with taxanes? | Nab-paclitaxel is only commissioned in England in those patients who have severe hypersensitivity reactions to paclitaxel and docetaxel. NHS E & NHS I consider that the efficacy of nab-paclitaxel and paclitaxel and docetaxel are broadly similar in incurable breast cancer. In view of this, NHS E & NHS I conclude that this appraisal should use the control arm of Impassion 130 as the proxy for the efficacy of paclitaxel and docetaxel monotherapies as this reflects a randomised, balanced, unbiased and contemporaneous comparison which is far more reliable than the company's indirect comparisons using historical trial populations..<br><br>NHS E & NHS I note that Impassion 131 is a trial of atezolizumab plus weekly paclitaxel versus weekly paclitaxel and that this has completed recruitment. This is a comparison which will best illustrate how effective atezolizumab is when added to the main taxane choice in England. |
| Issue 6: Duration of treatment effect | |
| a) Would treatment benefits with atezolizumab plus nab-paclitaxel after treatment has stopped be maintained for the remaining lifetime of patients or would benefits decline after a certain period of time? | NHS E & NHS I note that the ERG has supplied analyses of 3 and 5 year treatment waning effects for the atezolizumab treatment arm. Impassion 130 did not have a stopping rule and hence patients will be potentially treated until disease progression. NHS E and NHS I therefore do not understand why a treatment waning effect has been applied in the absence of a stopping rule either in the design of the trial or as a plan by the company to limit the duration of treatment to a fixed time. |
| b) If waning effect is likely to occur, until which timepoint would treatment effect be maintained? | See above. |

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| c) Is it appropriate to assume a waning effect in the absence of a stopping rule? | See above. |
| Issue 7: Health state costs | |
| a) Do the company's estimates on the frequency of oncologist visits reflect UK clinical practice or are the ERG's estimates more plausible? | The company economic model uses the assumption that the frequency of oncology review only starts at 2-monthly intervals after an initial period of 6 months of active treatment. NHS E & NHS I regards this as totally incorrect. Patients will be monitored closely, particularly in the early months of treatment in order to assess whether the treatment is working and for monitoring of the toxicities of atezolizumab in combination with chemotherapy. |
| Issue 8: End of life criteria | |
| a) Does atezolizumab plus nab-paclitaxel fulfil the criteria to be considered a 'life-extending treatment at the end of life'? | NHS E and I regard the only robust overall survival data to be used for the assessment of the EOL criteria is the control arm data of placebo plus nab-paclitaxel in the Impassion 130 study. Such data still results in the NICE EOL criteria being satisfied. |
| Issue 9: Cancer Drugs Fund | |
| a) Would additional data collection in the Cancer Drugs Fund reduce the uncertainty? | NHS E & NHS I note that a final data analysis is planned. So far there is no sign of a potential tail on the progression free and overall survival curves, although few patients are at risk beyond 2 years in the current analyses. The anti-PD-L1 immunotherapies in other diseases and at the times of initial NICE appraisal (eg non small cell lung cancer, melanoma) had apparent plateauing on the progression-free and overall survival curves which, in some cases of mature follow-up, have been shown to be real and sustained . It could be that further follow-up of the Impassion 130 study could answer this question as to whether there are very long term benefits (or not) of atezolizumab in TNBC. NHS E & NHS I note that long term overall survival was not a key driver of the ICER in the model. |
| b) Is the technology a good candidate for use in the Cancer Drugs Fund? | As the major uncertainty in this appraisal is the network meta-analysis which the company has considered necessary to provide the comparison of the atezolizumab plus nab-paclitaxel arm of |

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| | Impassion 130 with the monotherapies of paclitaxel/docetaxel, the CDF could be an option whilst Impassion 131 matures as this latter trial is a direct comparison of the effect of atezolizumab on the taxane most used in England. Given that the addition of atezolizumab to taxane chemotherapy (at least with nab-paclitaxel) offers a noteworthy clinically significant overall survival advantage in patients with PD-L1 positive TNBC and new data will resolve the uncertainty created by the indirect comparison used in this appraisal by the company, NHS E & NHS I would regard the CDF option as one that is worth considering if the Technology Appraisal Committee would not otherwise recommend atezolizumab in this indication and the Committee concludes that there is a plausibly cost effective ICER at the time of appraisal.. |

Other points that NHS E & NHS I would wish to make:

1. In keeping with the likely marketing authorisation and if this indication is recommended by NICE, NHS E & NHS I would wish to commission the use of atezolizumab plus nab-paclitaxel only as 1st line systemic therapy of patients with PD-L1 positive unresectable locally advanced or metastatic TNBC who are of ECOG performance status 0 or 1.

2. Atezolizumab is innovative in this indication as it provides a noteworthy and clinically relevant improvement in survival. Nevertheless, NHS E & NHS I regard that the benefits of atezolizumab in this indication have been incorporated into the health economic modelling.

3. NHS E & NHS I note that 41% of patients in Impassion 130 were PD-LI positive. Despite the company's submission stating that 25% of breast cancer deaths occur in TNBC patients (and therefore there are over 1800 deaths per year in TNBC patients), the company has estimated that 7 patients will be treated in year 1 following a NICE recommendation for atezolizumab plus nab-paclitaxel, 40 patients in year 2, 68 patients in year 3 and 117 patients in year 4. These figures are nonsense, especially as Roche has been keen to impress on NHS England how rapid the EAMS uptake of atezolizumab has been in this indication. Another reason as to why these uptake figures are wrong is that there will be very many fit patients who will be keen to avail themselves of the benefits of atzolizumab in this indication. A further reason is that uptake will be far faster than Roche suggests: rapid uptake has been shown in breast cancer for neoadjuvant pertuzumab for example where uptake was fast and over time measured in months, not years.

4. The company submission mentions that generic nab-paclitaxel will soon be available. NHS E & NHS I have enquired as to the likelihood of this and have concluded that a generic formulation of nab-paclitaxel is unlikely to be marketed in England in the foreseeable future.

NICE National Institute for Health and Care Excellence

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## About you

| | |
|---|---|
| **Your name** | [redacted] |
| **Organisation name – stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank) | **Pfizer** |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **N/A** |

## Questions for engagement

| **Issue 1: Generalisability of the trial results** |
| --- |

| | |
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| a) Do the characteristics of the overall trial population and PD-L1 positive subgroup of Impassion130 reflect those of people who would be eligible for atezolizumab plus nab-paclitaxel in the UK clinical setting? | |
| b) Fewer people in the trial had been previously treated with anthracyclines compared with UK clinical practice and a higher proportion had newly diagnosed metastatic disease. How would these differences be expected to affect the generalisability of the trial results? | |
| Issue 2: PD-L1 testing | |
| a) Would the introduction of PD-L1 testing in the mTNBC population be feasible? | |
| b) What challenges would PD-L1 testing introduce to current clinical practice? Will it require a new biopsy? | |
| c) Would the currently used tests in the NHS be used for testing people with breast cancer or will a specific test be required? | |
| d) What is the reason for the selection of ≥1% as a threshold in the trial? | |
| Issue 3: Appropriate comparators | |
| a) Are weekly paclitaxel and docetaxel the most relevant comparators? | The population in the final NICE scope is given as “People with locally advanced or metastatic, triple negative breast cancer whose tumours have PD-L1 expression ≥1% and have not received |

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| - Which one is most commonly used? | prior chemotherapy for metastatic disease." Unfortunately, the anticipated indication for atezolizumab + Nab-paclitaxel is redacted and it is unclear whether the BRCA+ sub-population is included in this appraisal. If the BRCA+ TNBC population is under consideration, then carboplatin should also be included as a comparator, as recommended in ESMO and NICE guidelines - unless atezolizumab is only to be considered for patients post carboplatin. |
| b) Do experts agree that anthracycline-based chemotherapy is not a relevant comparator in the metastatic setting? | |
| Issue 4: Comparison with taxanes | |
| a) Are the methods and results of the company's network meta-analysis plausible to establish comparative effectiveness data for atezolizumab plus nab-paclitaxel compared with taxanes? | |
| b) Are the results of the NMA clinically plausible given the limitations highlighted by the ERG? In particular that the inclusion criteria of the trials were different from IMpassion130 and included people with unknown PD-L1 status? | |
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| a) Does atezolizumab plus nab-paclitaxel fulfil the criteria to be considered a 'life-extending treatment at the end of life'? | |
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| a) Would additional data collection in the Cancer Drugs Fund reduce the uncertainty? | |

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| b) Is the technology a good candidate for use in the Cancer Drugs Fund? | |

NICE National Institute for Health and Care Excellence

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## About you

| | |
|---|---|
| **Your name** | [redacted] |
| **Organisation name – stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank) | **Roche Products Ltd** |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | **-** |

## Questions for engagement

| **Issue 1: Generalisability of the trial results** | |
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| a) Do the characteristics of the overall trial population and PD-L1 positive subgroup of Impassion130 reflect those of people who would be eligible for atezolizumab plus nab-paclitaxel in the UK clinical setting? | Roche Products Ltd. ("Roche") agrees with the NICE Technical team preliminary scientific judgement and rationale. The characteristics from the IMpassion130 trial for the overall trial population and PD-L1 positive subgroup broadly reflects the population who would be eligible for treatment with atezolizumab plus nab-paclitaxel, in the UK clinical setting. This is reflected in the ERG Report, where the ERG was satisfied that the patients recruited into the IMpassion130 trial are generally representative of patients with metastatic triple negative breast cancer (mTNBC) who are treated in the NHS (ERG Report, Section 1.4, p.14).<br>Roche acknowledges that the patient characteristics from large, globally recruited, Phase III studies will reflect differences in treatment practices. That said, the baseline characteristics of patients within the IMpassion130 trial have been validated by clinical experts (NICE Submission Document B p.166) and are balanced between both trial arms.(1)<br>Clinical experts confirmed that the IMpassion130 trial eligibility criteria were consistent with the population that they see and treat in the UK, the study recruited well in the UK and the recruiting centres were representative of the types of treatment centres in the UK. These clinical expert opinions are reflected within the ERG report (ERG Report, Section 4.3.1, p.36). |

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| b) Fewer people in the trial had been previously treated with anthracyclines compared with UK clinical practice and a higher proportion had newly diagnosed metastatic disease. How would these differences be expected to affect the generalisability of the trial results? | Roche agrees with the NICE Technical team preliminary scientific judgement and rationale. The characteristics from the IMpassion130 study trial for the overall trial population and PD-L1 positive subgroup broadly reflects the population who would be eligible for treatment with atezolizumab plus nab-paclitaxel, in the UK clinical setting.<br><br>Roche has identified a calculation error in the previously submitted data to the ERG, whereby the proportion of patients pre-treated with anthracyclines is 71.4% within the PD-L1 subgroup of the IMpassion130 trial. Furthermore, the proportion of patients in the PD-L1 population with newly diagnosed metastatic disease (at initial diagnosis) in the IMpassion130 study is 19.7% in the atezolizumab plus nab-paclitaxel arm and 23.1% in the placebo plus nab-paclitaxel arm, which is similar to that seen in a UK setting. The IMpassion130 trial is, in fact, similar to that seen in the UK clinical setting. We uncovered these revised numbers during a review of the past ID1522 ERG Clarification question responses provided on this issue. The updated patient characteristics tables are provided in **Appendix 1.** |
| ERG comment | This was discussed during the Technical Engagement Call, the ERG has no further comments. Thank you for providing extra information. |
| Issue 2: PD-L1 testing | |
| a) Would the introduction of PD-L1 testing in the mTNBC population be feasible? | Introduction of PD-L1 testing in the mTNBC population is feasible, as demonstrated by the Early Access to Medicines Scheme (EAMS).(2)<br>Roche agrees with the NICE Technical Team preliminary scientific judgement and rationale that PD-L1 testing is already routine practice in some cancer types where immunotherapies have been introduced.<br>Currently PD-L1 expression is not part of routine testing in breast cancer within the UK. However, diagnostic testing for HER2 (via immunohistochemistry [IHC] and fluorescence in situ hybridisation [FISH]) and oestrogen and progesterone receptors (via IHC) is well established, and therefore an additional IHC test in breast cancer is expected to have a limited impact on workflow in hospitals.<br>In addition, clinical expert opinion provided to Roche has confirmed that the introduction of PD-L1 testing in the mTNBC population will be feasible as PD-L1 IHC assays are routinely carried out for patients with other tumour types such as advanced non-small-cell lung carcinoma (NSCLC) and metastatic urothelial carcinoma (mUC). Scaling up testing to include patients with mTNBC should not be problematic. These clinical expert opinions are also reflected within the ERG report (ERG Report, Section 1.2, p.9) and were confirmed verbally by clinical experts during the Technical Engagement Teleconference. |

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| | Finally, Roche has been able to experience first hand the feasibility of implementing PD-L1 testing for this indication through the IMpassion130-associated EAMS. During this scheme, NHS Pathology laboratories have already been conducting an IHC test to establish the TNBC status of the patient. Since the EAMS was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) on the 13th March, more than 140 patients have been PD-L1 tested, as of the 5th August 2019. |
| b) What challenges would PD-L1 testing introduce to current clinical practice? Will it require a new biopsy? | PD-L1 testing in this population carries minimal challenges and, consistent with the IMpassion130 trial protocol (provided accompanying the company submission and updated clinical study report (CSR) provided with this response document), should not require a new biopsy.<br>As per the IMpassion130 trial protocol, the status of immune-mediated, tumour type-related, and other exploratory biomarkers (including but not limited to T-cell markers) for PD-L1 was evaluated in both archival and fresh tumour tissue samples of enrolled patients, therefore a new biopsy is not required.(3) This was confirmed by a clinical expert during the Technical Engagement teleconference where the clinical expert expressed that an archival biopsy is sufficient, particularly when considering the speed of relapse, and requirement to treat rapidly in these patients.<br>Roche agrees with the clinical advice to the ERG that scaling up PD-L1 testing to include patients with mTNBC should not be problematic (ERG Report, Section 1.2, p.9). The PD-L1 test can be conducted on existing tumour samples (assuming sufficient tissue is available). It can be carried out at sites currently conducting IHC testing following pathologist training to score the test. |
| c) Would the currently used tests in the NHS be used for testing people with breast cancer or will a specific test be required? | Roche anticipates at the approximate time point of the EMA Marketing Authorisation being granted ([redacted]), the expanded use of the CE-Marked VENTANA PD-L1 (SP142) assay (test) for assessing PD-L1 status in TNBC will be launched. The only validated test in TNBC currently available for PD-L1 on immune cells ≥1% is SP142. This is the same assay used for testing the PD-L1 status in urothelial carcinoma (UC), and is already in use in some UK centres for this purpose and for the TNBC EAMS. Roche recommends patients with TNBC be tested for PD-L1 on immune cells ≥1%. Roche is investing actively in training of pathologists and set up of testing with SP142, following the established pathway for new immunohistochemistry test implementation in breast cancer that was successfully done previously with HER2 testing.<br><br>**Rationale for use of SP142 test**<br><br>**Tumour infiltrating immune cells**<br>PD-L1 is expressed in many tumour types, although its localisation and predictive value can vary. For instance, using the VENTANA PD-L1 (SP142) assay in NSCLC, PD-L1 is often expressed on both tumour cells (TCs) and immune cells (ICs), whereas in UC or TNBC tumours, expression tends to be more prevalent on ICs.(4) The VENTANA PD-L1 |

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| | (SP142) assay was developed specifically for atezolizumab to optimise the staining of ICs for the detection of the presence or absence of PD-L1. An amplification detection system was incorporated to visually enhance the assessment of PD-L1 on immune cells in particular.(5)<br><br>**IMpassion130**<br>Additional exploratory biomarker analysis evaluating PD-L1 expression on tumour cells, stromal tumour-infiltrating immune cells and cytotoxic T cells concluded that PD-L1 expression on ICs covering ≥1% of the tumour area based on the SP142 assay was the best predictor of clinical benefit in the IMpassion130 trial.(6, 7)<br><br>**FDA approval**<br>VENTANA PD-L1 (SP142) is an FDA approved companion diagnostic for TNBC. It is also FDA approved as the complementary diagnostic in metastatic NSCLC and as the companion diagnostic for Tecentriq® (atezolizumab) in mUC (5)(8).<br><br>**Concordance data**<br>[redacted] |
| d) What is the reason for the selection of ≥1% as a threshold in the trial? | PD-L1 expression on tumour infiltrating immune cells covering ≥1% of the tumour area based on the SP142 assay was the best predictor of clinical benefit in the IMpassion130 trial.<br>The IMpassion130 clinical trial was stratified and randomised according to PD-L1 expression in tumour infiltrating immune cells as a percentage of tumour area: < 1% (IC0) vs ≥ 1% (IC1/2/3), using the VENTANA SP142 assay. The other stratification factors were presence of liver metastases and prior taxane exposure.<br>Twenty-seven percent of patients were “PD-L1 positive low” (IC1: IC ≥ 1% and < 5%), and 14% were “PD-L1 positive high” (IC2/3: IC ≥ 5%). |

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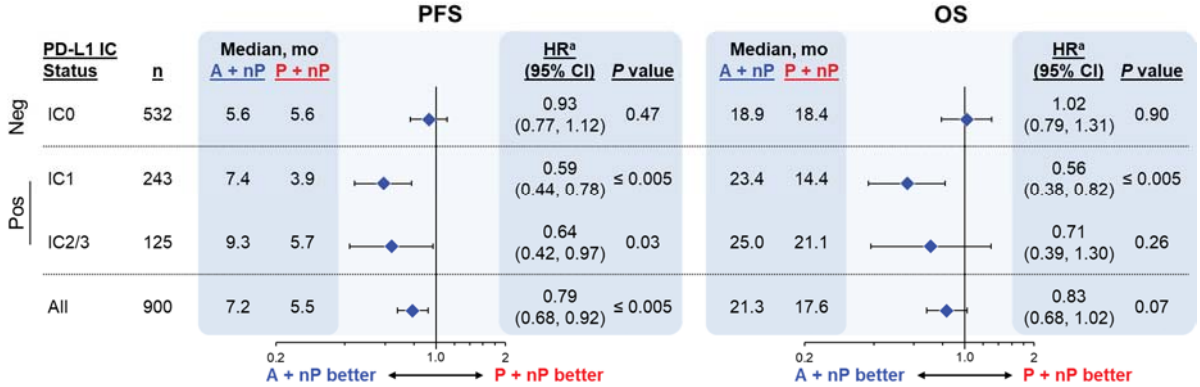
| | The scoring criteria for SP142 with a 1% cut off in IMpassion130, predicted that 41% patients stained positive (IC1/2/3) for PD-L1, which was predictive for clinical benefit (Figure 1). In mTNBC, additional exploratory biomarker analysis evaluating PD-L1 expression on tumour cells, stromal tumour-infiltrating immune cells and cytotoxic T cells concluded that PD-L1 expression on IC covering ≥1% of the tumour area based on the SP142 assay was the best predictor of clinical benefit in the IMPassion130 trial.<br>A forest plot reporting OS and PFS outcomes based upon IC cut off was provided in the company submission (Appendices, Appendix E, Section E.1.3 Exploratory analysis, Figure 21) – this is provided in Figure 1.<br><br>Figure 1: PFS and OS benefit across all PD-L1 subgroups, primary analysis<br>  |
| ERG comment | This was discussed during the Technical Engagement Call, the ERG has no further comments. |
| Issue 3: Appropriate comparators | |
| a) Are weekly paclitaxel and docetaxel the most relevant comparators?<br>- Which one is most commonly used? | Paclitaxel is the most relevant comparator for this appraisal. Roche agrees with the NICE Technical team preliminary scientific judgement and rationale that weekly paclitaxel appears to be the most relevant comparator according to clinical experts. This is also reflected in clinical advice to the ERG 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 (ERG Report, Section 2.2, p.24). |

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| | In the absence of a robust multi-centre UK real world data set, Roche understands from UK clinical experts that paclitaxel is the taxane of choice for first-line treatment of mTNBC (ID1522 ERG Clarification Question responses, Appendix 1, 2019). This is due to the favourable toxicity profile of weekly paclitaxel compared with 3-weekly docetaxel which helps maintain quality of life for patients with limited life expectancy.(9) Docetaxel is often used in the curative early breast cancer (eBC) setting where the toxicities of treatment are offset by the aim of cure rather than palliation (ID1522 ERG Clarification Question responses, Appendix 1, 2019).<br><br>Both in vitro and in vivo studies have demonstrated only partial cross-resistance between docetaxel and paclitaxel(10-12), increasing the likelihood of additional benefit from a different taxane agent i.e., paclitaxel. Furthermore, re-challenge with docetaxel (following use in eBC) 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 if they have subsequently relapsed.<br><br>A retrospective audit of patients with advanced breast cancer treated at the Mount Vernon Cancer Centre found that only 5/29 patients with HER2-/unknown advanced breast cancer previously treated in the neoadjuvant/adjuvant setting received single-agent docetaxel as first-line therapy for their advanced disease as per the NICE guidelines.(13) Across all HER2- patients that were treated with first line chemotherapy (n=49) and only 3 received docetaxel.<br>Hence the incremental cost-effectiveness ratios (ICERs) versus paclitaxel should be the basis for decision making. |
| b) Do experts agree that anthracycline-based chemotherapy is not a relevant comparator in the metastatic setting? | Anthracycline-based chemotherapy is rarely used in the mTNBC setting. Roche agrees with the NICE Technical team preliminary scientific judgement and rationale that anthracycline-based chemotherapy regimens would be rarely used in this population, and therefore it is not a key comparator.<br><br>This opinion is also reflected in the clinical advice to the NICE Technical Team and the ERG (Technical Engagement Report p. 6, p.9 and ERG report p.10):<br>• Anthracyclines are generally used in the eBC setting and not very often for metastatic disease<br>• Most patients with mTNBC have relapsed following treatment for eBC<br>• Most NHS patients treated for eBC who subsequently develop metastatic disease would have previously been treated with a sequential regimen of anthracyclines and taxanes and have received a maximum lifetime dose<br>• Patients with de novo mTNBC are offered anthracyclines as a first-line treatment, if appropriate |

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| | In the IMpassion130 trial, 71.4% (n=208/291) of PD-L1 positive patients (excluding de novo metastatic patients) had received prior anthracycline treatment. This supports the UK clinical expert advice that the majority of patients in an early TNBC setting would have been treated with an anthracycline (see Table 4 in **Appendix 1**).<br><br>As per the data presented within the company submission (NICE Submission Document B, p.20–21), eligibility for first-line mTNBC patients to be treated with anthracyclines is limited in clinical practice. Approximately 80–85% of this population will have progressed to the metastatic setting from the eBC setting, where anthracycline-based treatment regimens are preferred. This is seen on an international level in the IMpassion130 trial, where approximately 80% of the population progressed from the eBC setting (see Table 1 in **Appendix 1**).<br><br>Re-challenge with anthracyclines is hindered by lifetime maximum cumulative dose (e.g. epirubicin(14)) and as such, patients treated in the eBC setting are unlikely to be eligible for re-challenge. Therefore, these regimens are rarely used within this setting. This is supported by a retrospective analysis of patients with mTNBC treated at the Royal Marsden NHS Foundation Trust. Despite 14% of patients in this analysis presenting with de novo metastatic disease, only 7.5% received an anthracycline-based regimen.(15) |
| ERG comment | This was discussed during the Technical Engagement Call, the ERG has no further comments. Thank you for providing extra information. |
| Issue 4: Comparison with taxanes | |
| a) Are the methods and results of the company's network meta-analysis plausible to establish comparative effectiveness data for atezolizumab plus nab-paclitaxel compared with taxanes? | Roche sought, in line with the appraisal Final Scope, to provide evidence of relative effects for atezolizumab + nab-paclitaxel in comparison to paclitaxel, docetaxel and anthracyclines. Given the lack of direct evidence available, Roche considered that carrying out a network meta-analysis (NMA) to obtain indirect evidence was the most appropriate way of enabling these comparisons.<br><br>Roche acknowledges the feedback provided in the Technical Engagement report and the feedback heard at the Technical Engagement Call regarding the potential limitations of the network meta-analysis (NMA); however, we believe that the NMA is the most appropriate way to compare atezolizumab + nab-paclitaxel with the UK standard of care. We address the concerns about the NMA raised during Technical Engagement, below. |

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| | Following a SLR, Roche identified an unconnected network of evidence relating to atezolizumab + nab-paclitaxel and taxanes. To connect this network, Roche carried out population-adjusted indirect comparisons (PAIC) using all trials in the network that investigated either paclitaxel or docetaxel (AVADO (docetaxel), E2100 (paclitaxel), MERiDiAN (paclitaxel)). Roche carried out the NMA in accordance with the recommendations provided in NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE (16, 17). Specifically, Roche used patient level data to conduct a covariate balancing propensity score model (18, 19), matching the larger study group to the smaller to increase robustness, i.e. matching the A+NabPx arm to the entire comparison studies' triple-negative population, creating a virtual atezolizumab + nab-paclitaxel arm (or placebo + nab-paclitaxel arm in the updated analyses provided during clarification questions) for each of the comparator studies. The atezolizumab + nab-paclitaxel arm from the IMpassion130 and the virtual atezolizumab + nap-paclitaxel for each comparator study then allow the network to be connected. As the proportional hazards assumption was not met in IMpassion130, nor numerous trials considered for inclusion in the NMA, piecewise exponential and fractional polynomial models were assessed. In model selection, the Akaike information criteria (AIC) and Bayesian information criteria (BIC) of a broad range of models and cut points were assessed. The five best fitting models were then assessed via a model selection process which assessed visual fit, plausibility and model diagnostics leading to the selection of the piecewise exponential for OS and PFS, with its specified cut points. Hence, an empirical approach was taken for selection of the base case model. Full clarification of the methods is provided in Appendix 4 (part 4, NMA feasibility assessment conducted and rationales for NMA model selection).<br><br>The four potential limitations of the NMA that Roche would like to address are:<br>1. Insufficient information regarding the inclusion and exclusion criteria for studies assessed for (N=40 trials) and included in the NMA<br>2. Baseline characteristics assessment for trials included in the NMA<br>3. Unknown PD-L1 status of patients for trials included in NMA, except for Impassion130<br>4. The confidence intervals around the hazard ratios for the NMA results were wide<br><br>The question on methods is addressed in this response (associated with limitations 1-2 above), and the question regarding the results (limitation 3-4 above) is incorporated in to question 4b.<br><br>**Insufficient information regarding the inclusion and exclusion criteria for studies assessed for (N=40 trials) and included in the NMA.** |

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| | The appearance of discrepancy in trial numbers included in the clinical SLR to final inclusion in the base case NMA is fully clarified in this response. The SLR of clinical data included 39 unique trials. This did not include the IMpassion130 trial, hence a total of 40 unique trials were included in the NMA feasibility assessment. Appendix 4, part 4, NMA feasibility assessment conducted and rationales for NMA model selection, provides further details of this feasibility assessment. Appendix 4 additionally provides the reasons for inclusion/exclusion of each of the individual 40 trials from the NMA, leading to the inclusion of N=7 trials (OS analysis) and N=8 trials (PFS analysis) (Appendix 4 part 1, clarification of trials included and excluded from the NMA, and rationales). Predominantly, this was because comparators were not of interest as per the SLR PICO criteria; because the population were <80% first-line; or the trial studied a mixed BC population with a lack of TNBC subgroup data.<br><br>**Baseline characteristics assessment for trials included in the NMA.**<br>The baseline characteristics of trials were assessed for the degree of homogeneity. The details of this assessment are provided in Appendix 4 part 2, baseline characteristics of trials considered for use in the NMA. The assessment considered patient characteristics of: age, ECOG status, prior taxanes receipt, proportion of patients with liver metastases, proportion of patients with visceral disease, proportion of patients with bone metastases. From this assessment, it was deemed that the trials for inclusion in the NMA were sufficiently homogeneous. Furthermore, for the trials used in the PAIC (AVADO, MERIDIAN, E2100), summary statistics within each studies' triple-negative population of candidate covariates for matching have been provided in Appendix 4 part 3, summary statistics of candidate covariates for matching. It was deemed that there was sufficient homogeneity of the N=7 trials (OS analysis) and N=8 trials (PFS analysis) to carry out an NMA using these trials.<br><br>We hope the additional evidence and justifications provided will ease some concerns relating to the methodology of the NMA, which in turn, could validate the outcomes of the ITC and support its use in this appraisal. |
| b) Are the results of the NMA clinically plausible given the limitations highlighted by the ERG? In particular that the inclusion criteria of the trials were different from IMpassion130 and included people | Roche acknowledges the feedback in the Technical Engagement report and the feedback heard at the Technical Engagement Call regarding the potential limitations of the NMA, however we believe the results of the NMA are clinically plausible and appropriate in order to compare atezolizumab + nab-paclitaxel to the UK standard of care. |

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| with unknown PD-L1 status? | This response addresses limitations 3-4 highlighted by the ERG (as detailed in question 4.a) with regards to the clinical plausibility of the NMA results.<br><br>Clinical plausibility of the NMA results should also be considered in the context of the impact these results have when implemented in the economic model, versus interpreting the NMA results in isolation. This is captured in response to Issue 5.<br><br>**Unknown PD-L1 positive patients for trials included in NMA, except for IMpassion130**<br>With the exception of IMpassion130, PD-L1 status was not collected in any of the trials included in the NMA. The comparators included in this appraisal are chemotherapy taxanes which have been used in clinical practice for many years, prior to the scientific advancement of PD-L1 expression. As PD-L1 was not a validated biomarker at the time of the studies, it is not feasible to collect evidence on PD-L1 expression from the trials included in the NMA.<br><br>Nevertheless, as taxanes do not target the PD-L1 immune checkpoints, there is no mechanistic rationale for PD-L1 status to be an effect modifier of chemotherapy. Hence, there is no evidence to suggest that the *relative effects* of nab-paclitaxel, paclitaxel and docetaxel are impacted by a selection of PD-L1-positive subpopulation.<br><br>There is, however, limited evidence which may allow us to draw conclusions on the level of any possible absolute effect modification for nab-paclitaxel (or other taxanes), based on the IMpassion130 trial, and therefore the resulting direction of effects that could be expected on the NMA.<br><br>As demonstrated in Figure 1 in question 2.d, and Schmid et al. 2018(1), median OS and PFS for P+NabPx is numerically higher in the ITT population (17.6 months, 5.5 months respectively) than the PD-L1 positive population (15.5 months, 5.0 months respectively). This suggests there is a reduction in the *absolute effects* on nab-paclitaxel for the PD-L1 positive population, as opposed to the ITT population.<br><br>As the paclitaxel and docetaxel trials included in the NMA are expected to contain a mixture of PD-L1 positive and negative patients (i.e. the equivalent to the ITT in IMpassion130), it is plausible the NMA has, in fact, overestimated the OS and PFS absolute effects of these treatments. If the trials had been PD-L1 positive populations only, one could |

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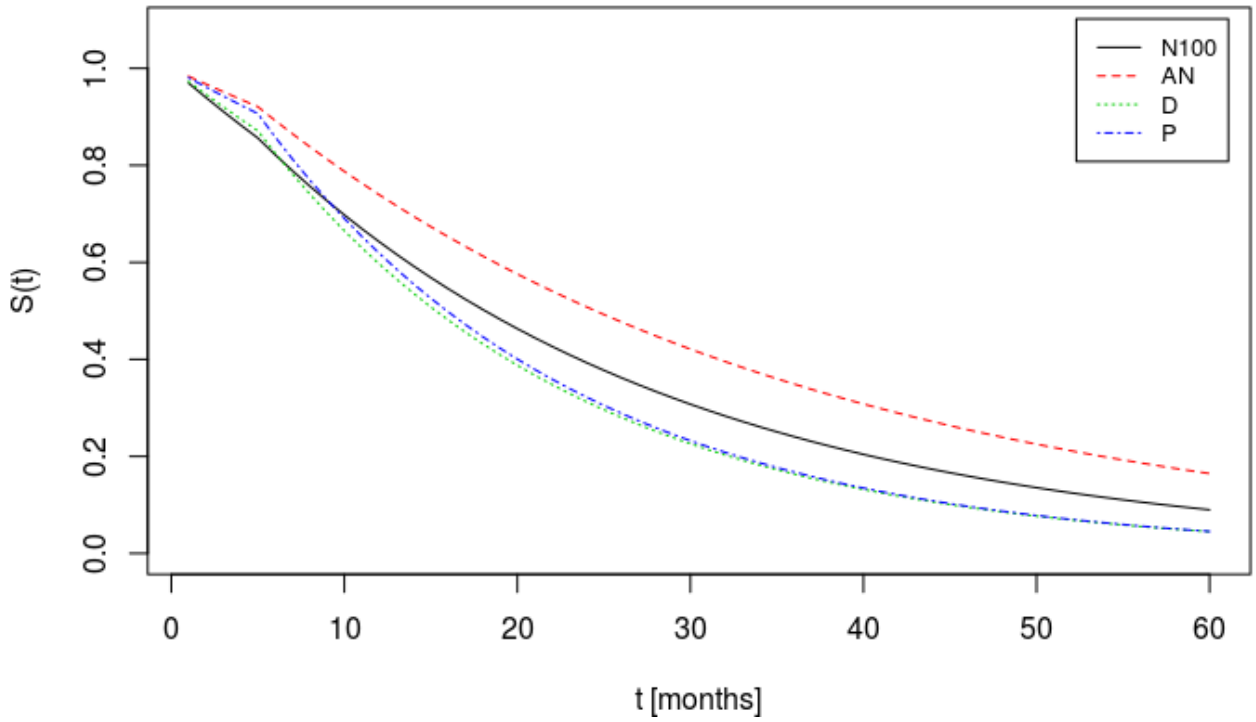
| | anticipate a similar direction of effects as witnessed in the P+NabPx arm of the IMpassion130 trial i.e. that the OS and PFS outcomes of paclitaxel and docetaxel would be worse than the NMA currently predicts.<br><br>**The confidence intervals around the Hazard ratios for the NMA results were wide.**<br>The 95% credible intervals of hazard ratios and 5-year restricted mean survival times are accepted as wide. Indirect Treatment Comparisons are not powered to detect statistical significance; therefore, uncertainty is not uncommon. Nevertheless, Roche believe this is an insufficient rationale for disregarding the results:<br>• Appropriate use of statistical significances and p-values: Roche note that a statistically non-significant result does not prove the null hypothesis that there is no difference between groups or no effect of a treatment on some measured outcome. Indeed, this is supported by a recent article, Amrehein et al. 2019 (20). The authors carried out an analysis of 791 articles across 5 journals and found that 51% of articles mistakenly assumed that non-significance of results means no effect, and the authors caution around this interpretation. Roche believe that a reliance on thresholds of statistical significance, as in this case, can be misleading. As detailed in Altman et al. 1995 (21), "absence of evidence is not evidence of absence".<br>• Accounting for uncertainty in Bayesian indirect comparisons: Hazard ratios and 5-year restricted mean survival times point estimates are a representation of the likely result. However, the uncertainty surrounding point estimates (through the confidence interval) is reflected in the probabilistic sensitivity analysis used within the cost-effectiveness analysis. This approach is supported by the NICE Decision Support Unit guidance: “simulation from a Bayesian posterior distribution supplies both statistical estimation and inference, and a platform for probabilistic decision making under uncertainty” (22).<br><br>Finally, Roche made a conscious decision to reduce bias at the potential cost of higher variance, because bias cannot be quantified and reported while variance of the estimates can be reported and incorporated in the probabilistic analysis (PSA) of the cost-effectiveness analysis. Hence, these wider resulting confidence intervals came with the benefit of reducing bias in the NMA results point estimates.<br>We hope the additional evidence and justifications provided will ease some concerns relating to the clinical plausibility of the results of the NMA, which in turn, could support its use in this appraisal. |
| ERG comment | Thank you for the additional information regarding the methods and evidence sources used in the NMAs. The ERG considers that the new information is helpful but does not solve all of the previously described methodological problems. The process of how studies were included and excluded from the NMAs is now clear. However, there are trials included in the NMAs for which no information on baseline characteristics for the relevant patient population (mTNBC patients) is available, so a comprehensive evaluation of comparability of patient populations included in the NMAs is still not possible. |

All other issues raised in the ERG report concerning the company's NMAs remain valid, and the ERG therefore still has reservations about the reliability of results generated by the NMAs; these issues are highlighted by the hazard ratios from the NMAs which suggest that patients have higher OS in the first 5 months with paclitaxel and docetaxel but higher OS with nab-paclitaxel from month 5 onwards (shown in Figure 1 below from the companies clarification responses).

**Figure 1: Overall survival probabilities extrapolated in the IMpassion130 (WO29522) study using posterior median basic parameters**




**Key:** N100: nab-paclitaxel (and placebo), D: Docetaxel (100mg/m2 every 3 weeks), P: Paclitaxel (80–90mg/m2 on Days 1, 8, and 15 of 28-day cycles), AN: Atezolizumab (840mg on Days 1 and 15 of 28-day cycles) + nab-paclitaxel (100mg/m2 on Days 1, 8 and 15 of 28-day cycles)

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| | Wide credible intervals<br>Credible intervals (CrIs) provide a measure of certainty around results. In this case, the CrIs are very wide, which means that there is considerable uncertainty around the central estimates. This makes it difficult to judge whether the effectiveness of the three treatments (nab-paclitaxel, paclitaxel and docetaxel) are different and, if effectiveness does differ, the magnitude of that difference. If the magnitude of the CrIs is ignored, then the purpose of the calculation is questionable. The DSU guidance quoted does not support the company position but rather points out that CrIs can be used for statistical inference as well as PSA.<br>The purpose of statistical significance testing is to remove bias from the interpretation of statistical results (central estimates) by introducing an objective, albeit arbitrary, boundary points outside which the interpreter can be satisfied that the balance of evidence points to a real effect. This threshold has been met (for OS) for the comparison of the effectiveness of atezolizumab+nab-paclitaxel versus nab-paclitaxel, but not for the comparison of nab-paclitaxel versus paclitaxel. When this threshold has not been met, the ERG considers it inappropriate to model a difference as if it had been met. |
| Issue 5: Using nab-paclitaxel as a proxy for modelling the effectiveness of taxanes | |
| a) Is nab-paclitaxel sufficiently similar to weekly paclitaxel and docetaxel for it to be reasonable to assume equivalence between these treatments and use trial data from IMpassion130 as a proxy for the effectiveness of atezolizumab plus nab-paclitaxel | Roche recognises the appeal of making a simplifying assumption and assuming equivalence of these regimens to be able to utilise the comparator arm of the IMpassion130 trial as the best available, contemporaneous evidence. However, it is critical to highlight that such an assumption could be considered overly conservative and therefore has the potential to adversely impact the cost-effectiveness of atezolizumab plus nab-paclitaxel, and therefore impact access to this innovative medicine.<br><br>Table 1 details the outcomes from the licensing studies for nab-paclitaxel, as compared to paclitaxel. As demonstrated, nab-paclitaxel consistently demonstrates a pronounced numerical advantage in outcomes over paclitaxel.(23, 24)<br><br>**Table 1: Results for overall response rate, median time to disease progression, and progression-free survival as assessed by the investigator**<br><br>Efficacy variable \| Abraxane \| Solvent-based paclitaxel \| p-value |

compared with taxanes?

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

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

While we acknowledge that the 100mg/m$^2$ weekly dosing schedule for nab-paclitaxel as per the IMpassion130 trial was slightly lower than the dose used in the licensing studies for nab-paclitaxel (260mg/m$^2$ three-weekly – see Table 2), a review of the literature has identified evidence that these doses achieve similar efficacy profiles, alongside improved tolerability (23, 25, 26). As such, the results from the licensing studies can be considered broadly reflective of the outcomes utilising the IMpassion130 dosing schedule.

This can also be supported by the same literature the ERG have previously highlighted, demonstrating the alternative interpretations that can be drawn:

- Liu et al. 2017 (27): whilst none of the studies included in the meta-analysis (n=4) were double blind trials, when assessing the difference between taxanes and nab-paclitaxel only in the first-line setting, as opposed to combining first line and second line data as the ERG have, Liu identified an OS HR of 1.21 (1.00-1.48, p=0.05), indicating a statistically significant difference between taxanes and nab-paclitaxel. Similarly, one- and two-year survival of first line patients indicates reduced results of taxanes versus nab-paclitaxel, with a HR of 1.08 (0.79-1.47) and 1.20 (0.98-1.47) respectively.
- Tamura et al. 2017 (28): whilst only small patient numbers (n=36), in the TNBC population, median OS was 27.1 months (95% CI: 18.1–not reached) in the nab-paclitaxel treatment group, and 19.3 months (95% CI: 14.1–26.0) in the docetaxel treatment group (HR: 0.56, P = 0.121). Even in the broader population, the median OS for nab-

paclitaxel and docetaxel was 42.4 months (95% CI: 32.4–not reached) and 34.0 months (95% CI: 27.6–40.0) (HR: 0.78, *P* = 0.190).

- A US observational (real-world) study, Luhn et al.(29) demonstrated a HR of 0.9 (95% CI: 0.61, 1.32) between nab-paclitaxel and paclitaxel.

We believe that the results from the licensing study for nab-paclitaxel, in addition to other published literature using similar dosing regimens to IMpassion130, demonstrate pronounced numerical improvements of nab-paclitaxel over other taxanes, and that consequently, a clinical advantage of nab-paclitaxel over paclitaxel cannot be ruled out.

This is consistent with the outcomes of the Indirect Treatment Comparison, whereby nab-paclitaxel was demonstrated to be numerically, although not statistically significantly, better than paclitaxel and docetaxel.

For additional context, when the ITC results are incorporated in to the economic model, this accounts for a difference of 0.197 Life Years between nab-paclitaxel and paclitaxel, a marginal difference which equates to a drastic, and disadvantageous impact on the ICER (Table 2).

**Table 2: Comparison of ICERs resulting from use of NMA vs P+NabPx IMpassion130 arm**

| **Model used** | **ICER[1] vs paclitaxel (£ cost/QALY)** - pre-Roche amendment to paclitaxel treatment costs | **ICER[1] vs paclitaxel (£ cost/QALY)** - post-Roche amendment to paclitaxel treatment costs |
|---|---|---|
| Use of NMA paclitaxel outcomes | £63,339 | £50,629 |
| Use of P+NabPx Impassion130 (As a proxy for paclitaxel) | £85,295 | £72,579 |
| **Difference in ICERs generated** | +£21,956 | £21,950 |

1 atezolizumab PAS price and nab-paclitaxel list price ICERs reported. Assumed no waning of A+NabPx effect.

As discussed in response to 4.b, a statistically non-significant result does not prove the null hypothesis that there is no difference between groups or no effect of a treatment on some measured outcome. Instead, in statistical analyses (as

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| | described in DSU guidance 2) (22), the uncertainty surrounding point estimates (through the confidence interval) are reflected in the probabilistic sensitivity analysis used within the cost-effectiveness analysis.<br><br>As such, while recognising the limitations of the ITC but noting the robust methodology employed (see response to question 4a), Roche believes nab-paclitaxel is not sufficiently similar to weekly paclitaxel and three-weekly docetaxel for it to be reasonable to assume equivalence, and in fact the outcomes of the ITC in terms of Life Year gains are more reflective of the body of evidence suggesting a direction of travel of better outcomes for nab-paclitaxel. |
| ERG comment | The ERG re-iterates that there is no compelling evidence to suggest that, in terms of OS, treatment with nab-paclitaxel will result in a different OS outcome from treatment with paclitaxel. The ERG, therefore, considers that, for the purposes of modelling, the OS associated with the two treatments can be treated as equivalent. The ERG has not stated that the available evidence has proved that the effectiveness of the two treatments is equivalent; this would be a misinterpretation of the evidence.<br>The ERG considers that, for the purposes of economic modelling, neither assuming nab-paclitaxel is equivalent to paclitaxel nor implementing the result from the company's NMA is ideal. However, the ERG also considers that the assumption of equivalence is better supported by the available evidence than is the magnitude of the improvement with nab-paclitaxel suggested by the company NMA.<br>Corrected ICERs per QALY gained: without having access to more information than is presented in Table 4, the ERG cannot comment on the reliability of the corrected ICERs per QALY gained.<br>The ERG notes that weekly paclitaxel, the regimen modelled by the company, has been shown to have higher OS than a 3-weekly paclitaxel regimen in a meta-analysis (Mauri D, Kamposioras K, Tsali L, Bristianou M, Valachis A, Karathanasi I, Georgiou C, Polyzos NP. Overall survival benefit for weekly vs 3-weekly taxanes regimens in advanced breast cancer: A meta-analysis; Cancer Treat Rev. 2010 Feb;36(1):69-74. doi: 10.1016/j.ctrv.2009.10.006. Epub 2009 Nov 27. Review.). The only study in which the regimen was weekly paclitaxel was the study by Luhn which concluded that weekly paclitaxel and weekly nab-paclitaxel could be considered to be 'interchangeable as 1L treatments for mTNBC'. |
| Issue 6: Duration of treatment effect | |
| a) Would treatment benefits with atezolizumab plus nab-paclitaxel after treatment has | There is no clinical evidence to either support or refute any treatment effect assumption beyond the trial data, though it should be highlighted that the magnitude of benefit of atezolizumab + nab-paclitaxel is greater in Overall Survival than that demonstrated in Progression Free Survival (delta of 7 months and 2.2 months, respectively), which could identify a post-treatment discontinuation effect modification (see section B.2.6 and Appendix J from the company submission). This |

stopped be maintained for the remaining lifetime of patients or would benefits decline after a certain period of time?

improvement in post progression survival is not uncommon either within some breast cancer or immune-oncology trials. Therefore, Roche did not consider a waning effect to be appropriate for atezolizumab in this indication.

Duration of treatment effect is an area of uncertainty for immunotherapies, and has arisen as a discussion item in many past appraisals (TA428, TA483, TA484, TA520, TA584). Interestingly, however, the same is not true for targeted therapies in metastatic breast cancer, whereby treatment effect caps have not been explored despite differential magnitudes of benefit seen between PFS and OS (TA458, TA496, TA495, TA563, TA509) (Table 3).

As such, in the absence of any clear evidence supporting or refuting a treatment effect cap, we acknowledge the precedent set in past appraisals and deem this to be a key consideration when answering this question.

Table 3 demonstrates the previous committee preferred assumptions regarding waning of treatment effects. We implore the committee to consider the detrimental impact of implementing more conservative assumptions than those used in other appraisals to date.

**Table 3: Past examples of immunotherapy appraisals preference by the NICE committee on time point of waning of treatment effects**

| NICE Technology Appraisal (TA) number | Indication | NICE committee preferred assumption regarding assumptions on treatment waning |
|---|---|---|
| TA458 | HER2-positive advanced breast cancer after trastuzumab and a taxane | No treatment effect cap considered |
| TA496 | Previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer | No treatment effect cap considered |
| TA495 | Previously untreated, hormone receptor-positive, HER2-negative, | No treatment effect cap considered |

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| | locally advanced or metastatic breast cancer | | |
| TA563 | Previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer | No treatment effect cap considered | |
| TA509 | HER2-positive breast cancer | No treatment effect cap considered | |
| TA428 | PD-L1-positive non-small-cell lung cancer after chemotherapy | The Committee was not explicit on the duration of treatment effect that was most appropriate. However, it is observed from with-PAS ICERs published, that pembrolizumab would only have been cost-effective if waning was assumed to occur at 10 years (or longer) after treatment initiation. | |
| TA520 | Locally advanced or metastatic non-small-cell lung cancer after chemotherapy | The ERG looked to cap the duration of treatment effect of atezolizumab at 3 years, however due to the model structure it was acknowledged that if duration of treatment effect for atezolizumab is actually 3 years, then, in the model, setting the duration of treatment effect to 3 years would mean the duration of treatment effect of atezolizumab would be 2.5 years for a patient who stopped treatment after 6 months, but zero for a patient who is still on treatment at 3 years. As such, the duration of treatment effect was set to 5 years to account for the 8% of patients still predicted to be on treatment at 2 years.<br><br>As such, atezolizumab effects were assumed to last for 5 years from treatment initiation | |

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| | <table><tr><td>TA483</td><td>Previously treated squamous non-small-cell lung cancer</td><td>Nivolumab effects assumed to last for 5 years from treatment initiation</td></tr><tr><td>TA484</td><td>Previously treated non-squamous non-small-cell lung cancer</td><td>Nivolumab effects assumed to last for 5 years from treatment initiation</td></tr><tr><td>TA584</td><td>Metastatic non-squamous non-small-cell lung cancer</td><td>Atezolizumab effects assumed to last for 5 years from treatment initiation</td></tr><tr><td>GID-TA10400 [Appraisal in progress]</td><td>Untreated extensive-stage small-cell lung cancer</td><td>Atezolizumab effects assumed to last for 5 years from treatment initiation</td></tr></table> |
| b) If waning effect is likely to occur, until which timepoint would treatment effect be maintained? | As detailed in our response to a), there is no clinical evidence to either support or refute any treatment effect assumption beyond the trial data, though it should be highlighted that the magnitude of benefit of atezolizumab + nab-paclitaxel is greater in Overall Survival than that demonstrated in Progression Free Survival (delta of 7 months and 2.2 months, respectively), which could identify a post-treatment discontinuation effect modification (see section B.2.6 and Appendix J from the company submission). This improvement in post progression survival is not uncommon either within breast cancer or immune-oncology trials. Therefore, Roche did not consider a waning effect to be appropriate for atezolizumab in this indication.<br><br>Nevertheless, in the absence of any clear evidence supporting or refuting a treatment effect cap, we acknowledge the precedent set in past appraisals and deem this to be a key consideration when answering this question. In addition, clinical plausibility of the resulting Overall Survival extrapolations should be validated.<br><br>Table 3 demonstrates the previous committee preferred assumptions regarding waning of treatment effects. As demonstrated, a 5-year treatment effect cap from treatment initiation has become the standard precedent for immune-oncology indications.<br><br>TA520 reviewed this assumption in detail: while the ERG preference was to implement a 3-year treatment effect cap, there was an acknowledgement that due to the structural limitations of the economic model, “the duration of treatment effect to 3 years would mean the duration of treatment effect of atezolizumab would be 2.5 years for a patient who stopped treatment after 6 months, but zero for a patient who is still on treatment at 3 years” As such, “as 8.5% of patients |

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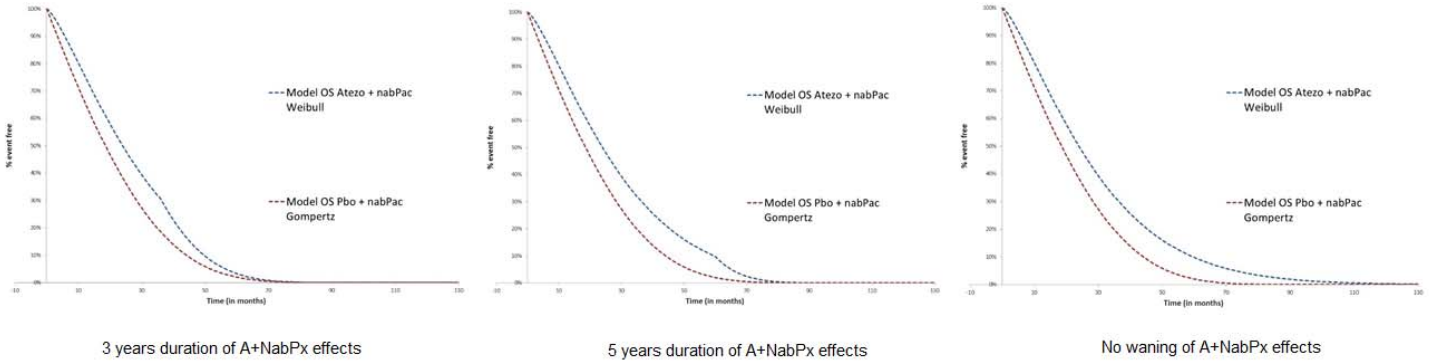
| | are predicted by the company's TTD extrapolation to be receiving atezolizumab at 2 years … setting the company model duration of treatment effect to 5 years rather than 3 years probably produces more accurate ICERs per QALY gained". This appraisal is equivocally paralleled, with 10.7% of patients still on atezolizumab treatment at 2 years – further justification for a consistent approach.<br><br>Interestingly however, the same is not true for targeted therapies in metastatic breast cancer, whereby treatment effect caps have not been discussed. In these appraisals, similar to the trial data for atezolizumab, differential magnitudes of benefit have been seen between PFS and OS (TA458, TA496, TA495, TA563, TA509).<br><br>When assessing the impact of such assumptions of treatment effect on the resulting Overall Survival estimates, visual representation of curves is useful. A comparison of OS for A+NabPx vs P+NabPx is provided in Figure 2.<br><br>**Figure 2: Modelled OS for A+NabPx vs P+NabPx assuming treatment cap from initiation: 3 years, 5 years and lifetime (no waning)**<br><br>  <br><br>When the duration of treatment effect is assumed to be 3 years from treatment initiation, the resulting drop in OS for patients treated with atezolizumab is larger than Roche (or clinical experts consulted with by Roche – see OS extrapolation validation, B.3.3.2 in company submission) anticipate for an immune-oncological therapy, with OS of atezolizumab + nab-paclitaxel meeting the OS of nab-paclitaxel at 70 months. Given the important clinical advancement |

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| | this combination has demonstrated in the IMpassion130 trial for patients, Roche do not consider this scenario to be clinically plausible.<br><br>Roche is willing to accept a 5-year treatment effect cap from treatment initiation, in line with precedent set in prior appraisals. However, we implore the committee to consider the detrimental impact of implementing more conservative and clinically implausible assumptions than have been concluded as acceptable in other appraisals to date. |
| c) Is it appropriate to assume a waning effect in the absence of a stopping rule? | Roche acknowledge stopping rules have been implemented in other immune-oncology appraisals, however this is a separate consideration to waning effect assumptions: the two issues are mutually exclusive and have no bearing on one another, either for this appraisal, or when treatment effect caps had been determined in past appraisals (please see Table 3 and TA520 description in response to question 6.b)<br><br>Given the important clinical benefit demonstrated in the IMpassion130 trial, the small PDL1-positive TNBC population (approximately 6% of the total metastatic breast cancer population), and Roche's commitment to demonstrate atezolizumab + nab-paclitaxel in the full licensed indication as a cost-effective use of NHS resources, we do not believe a stopping rule is necessary for this indication. Roche's preference would be to allow clinical experts to treat patients until they deem no additional benefit is being derived. This would be consistent with the clinical trial protocol and license, and will allow patients to clinically benefit as long as possible in this area of high unmet need.<br><br>As detailed in our response to question 6.b, Roche is willing to accept a 5-year treatment effect cap from treatment initiation, in line with precedent set in prior appraisals. However, we implore the committee to consider the detrimental impact of implementing more conservative and clinically implausible assumptions than have been concluded as acceptable in other appraisals to date. |
| ERG comment | This was discussed during the Technical Engagement Call. As stated by the company, there is no evidence to accept or refute any treatment effect assumption beyond the trial data. |
| Issue 7: Health state costs | |
| a) Do the company's estimates on the frequency of oncologist visits reflect UK clinical practice or are the | Roche gained clinical expert opinion to source and validate all NHS resource use/costs implemented in the cost-effectiveness model. Roche accept that of these NHS costs data inputs, the number of oncology visits applied in the progressed disease and progression free states underestimated NHS practice resource use and that the model should be updated to oncologist visits every month, as opposed to every 2 months. |

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| ERG's estimates more plausible? | |
| ERG comment | This was discussed during the Technical Engagement Call, the ERG has no further comments. |
| Issue 8: End of life criteria | |
| a) Does atezolizumab plus nab-paclitaxel fulfil the criteria to be considered a 'life-extending treatment at the end of life'? | As per the NICE Technical Team "preliminary scientific judgement and rationale", Roche agrees that all scenario analyses presented by the company and ERG demonstrate that the end-of-life criteria are met: A+NabPx provides more than 3 months extension of life, and the population under consideration would usually have a life expectancy of less than 24 months. |
| ERG comment | This was discussed during the Technical Engagement Call, the ERG has no further comments. |
| Issue 9: Cancer Drugs Fund | |
| a) Would additional data collection in the Cancer Drugs Fund reduce the uncertainty? And<br>b) Is the technology a good candidate for use in the Cancer Drugs Fund? | Given the high unmet need in this patient population, Roche are committed to ongoing patient access, following the closure of the EAMS.<br>The IMpassion130 data are relatively mature (with an 80% information fraction at the second interim analysis), and therefore further data collection is not anticipated to significantly reduce clinical uncertainty within this appraisal. Roche are working with NHS England to agree a commercial access agreement which will enable A+NabPx to be deemed a cost-effectiveness use of NHS resources, through baseline funding. However, if necessary, Roche are open to exploring all avenues to enable access. |
| ERG comment | The ERG has no further comments. |
| Additional evidence submitted by Roche, approved by NICE | |
| Costs of weekly paclitaxel (including administration costs) can be incurred for greater than 18 weeks | On 24th July, Roche requested to submit additional evidence to NICE detailing the duration and costs of paclitaxel receipt in the NHS. This request was approved by NICE on 25th July.<br>Roche have misinterpreted how paclitaxel may be administered in the NHS, specifically in the implementation of the duration of paclitaxel (comparator) treatment and the associated administration costs. The cost-effectiveness model currently specifies that a maximum of 18 weekly cycles of paclitaxel treatment would be received by a patient in this treatment setting in the NHS. However, clinician feedback to Roche is that there is no definitive treatment cap associated with weekly paclitaxel in the NHS, as there is with docetaxel. Roche had previously misinterpreted clinical |

opinion received prior to our submission on the mean number of weekly paclitaxel cycles (approximately 18-19 cycles), implemented as a maximum number of cycles, thus impacting the drug and administration costs of paclitaxel. The resulting ICERs (A+NabPx vs. paclitaxel) from correction of this misinterpretation are provided **Error! Reference source not found.**, and ICERs varying the nab-paclitaxel discount from list price are provided in **Error! Reference source not found.**.

**Table 4: ICERs resulting with 18 weeks paclitaxel cost cap, compared with 18 weeks cost cap removed**

| Model | ICER of A+NabPx vs paclitaxel - assuming a maximum 18 cycles/weeks of paclitaxel treatment costs[1] | ICER of A+NabPx vs paclitaxel – removal of cap of maximum of 18 cycles/weeks of paclitaxel costs[1] |
|---|---|---|
| **Company base case model** | £63,339/QALY | £50,629/QALY |
| **ERG base case model** | £85,295/QALY | £72,579/QALY |

[1]ICERs presented at based upon PAS of atezolizumab and list price of nab-paclitaxel

**Table 5: ICERs when varying the Abraxane discount from list price with removal of cap of maximum of 18 weeks of paclitaxel costs**

| Model | Percentage discount from Abraxane (nab-paclitaxel) list price, with resulting ICER (cost (£)/QALY) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | List price | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% | 100% |
| **Company base case model** | 50,629 | 48,633 | 46,637 | 44,641 | 42,645 | 40,649 | 38,653 | 36,656 | 34,660 | 32,664 | 30,668 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **ERG base case model** | 72,579 | 69,983 | 67,388 | 64,793 | 62,197 | 59,602 | 57,006 | 54,411 | 51,815 | 49,220 | 46,624 |

There is a substantial impact on the ICER when removing the treatment cap to allow the accrual of treatment and administration costs for paclitaxel in line with current clinical practice. Roche's view is that this model correction should be applied to all ICERs generated for the remainder of the appraisal.

Please see **Appendix 3** for further information on this.

**ERG comment**

The ERG has not had access to the updated company model which includes the company's revised approach to costing paclitaxel treatment. In the company model, submitted to the ERG at the start of the appraisal process, if treatment with paclitaxel was not stopped after six cycles (i.e., there was no cap), then treatment was projected to continue such that 22.5% of patients would still be on treatment at 9 months, 14.3% at 1 year, 5.2% at 2 years, and 0.3% at 5 years.

There is no national guidance that recommends when treatment with weekly paclitaxel (i.e., a weekly infusion for three consecutive weeks followed by a week without infusion) should be stopped. Published local guidance suggests that treatment duration should generally be for a maximum of six cycles of 28 days (i.e., for 6 months). However, weekly treatment with paclitaxel can be extended if there is no progression, the treatment is well tolerated and there are no alternative maintenance therapies available. Clinical advice to the ERG is that extension of weekly treatment with paclitaxel beyond 6 months was unusual and had never been beyond10 months.

The ERG estimates that if no patients went beyond 10 monthly of weekly paclitaxel (30 infusions) then this would decrease the ICER per QALY gained for the comparison of treatment with for atezolizumab+nabpaclitaxel versus paclitaxel by approximately £3,000 to £4,000, not the £13,000 suggested by the company.

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# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Technical report

# Atezolizumab in combination with nab-paclitaxel for untreated, locally advanced or metastatic, triple negative PD-L1-positive breast cancer

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- a commentary on the evidence received and written statements
- technical judgements of the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the key evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.



Issue date: September 2019

# 1. Summary of the technical report

After technical engagement the technical team has collated the comments received and, if relevant, updated the judgement made by the technical team and rationale.

1.1 In summary, the technical team considered the following:

- The IMpassion130 trial and whether its results for the PD-L1 subgroup are generalisable to UK clinical practice.
- Introducing PD-L1 testing in patients with metastatic triple negative breast cancer (mTNBC) in the future is plausible and does not have huge potential barriers.
- The appropriate comparators to compare atezolizumab plus nab-paclitaxel in mTNBC are weekly paclitaxel and docetaxel.
- The ERG's estimates on the frequency of oncologist visits, once monthly, reflect UK clinical practice.
- Atezolizumab plus-nab paclitaxel meets the end of life criteria.

1.2 The technical team recognised that the following uncertainties would remain in the analyses and were not resolved during technical engagement and require further discussion by the appraisal committee:

- The network meta-analysis conducted by the company for establishing comparative effectiveness data for the comparison of atezolizumab plus nab-paclitaxel with taxanes is associated with several limitations. The committee will have to discuss if the company's NMA is reliable for establishing the effectiveness of atezolizumab plus nab-paclitaxel compared with taxanes.
- The evidence base for supporting better effectiveness with nab-paclitaxel, compared with other taxanes is weak and does not show statistically significant difference in effectiveness. The committee will need to discuss if using data from the placebo plus nab-paclitaxel arm

of IMpassion130 as a proxy for the effectiveness of other taxanes is a plausible assumption.

- It is not known if there is a prolonged benefit of treatment with atezolizumab plus nab-paclitaxel after treatment has stopped and whether it is appropriate to assume a waning effect

1.3 The cost-effectiveness results include a commercial arrangement (patient access scheme) for atezolizumab.

1.4 The NICE technical team do not have a preferred set of assumptions using the current company's model and therefore it cannot specify the most plausible incremental cost-effectiveness ratio (ICER). However, the technical team believes that it is plausible that the ICER could be over £85,000 per QALY gained, when atezolizumab plus nab-paclitaxel is compared with paclitaxel and over £98,000 per QALY gained when compared with docetaxel. These estimates do not include the commercial arrangement for nab-paclitaxel, because that is confidential and cannot be reported here. Estimates that include these commercial arrangements would be lower than those reported above.

1.5 Based on the modelling assumptions, the intervention is likely to meet the end-of-life criteria (see issue 8).

1.6 The company has not submitted a proposal for the Cancer Drugs Fund and no ongoing data collection is planned (see issue 9).

1.7 Innovation: Atezolizumab plus nab-paclitaxel is the first treatment that is likely to demonstrate a survival benefit compared with chemotherapy.

1.8 No equality issues were identified by the company, consultees and their nominated clinical experts and patient experts.

# 2. Key issues for consideration

## *Issue 1 – Generalisability of the trial results*

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| **Background/description of issue** | Clinical evidence presented by the company comes from the IMpassion130 trial, which included patients with untreated metastatic triple negative breast cancer (mTNBC). The proposed marketing authorisation for atezolizumab plus nab-paclitaxel specifies that only patients with PD-L1 expression ≥1% will be eligible for this treatment. The company presented results of a subgroup analysis which included people with PD-L1 positive TNBC. Nearly all patients in this subgroup had metastatic disease and there were [redacted] included from the UK.<br>In response to technical engagement the company updated some of the figures from IMpassion130 because it identified some errors in the previously reported data. The proportion of patients previously treated with anthracyclines was 71.4% within the PD-L1 subgroup of the IMpassion130 trial and not 57% as previously reported.<br>The percentage of patients with newly diagnosed metastatic disease at initial diagnosis was 19.7% in the atezolizumab plus nab-paclitaxel arm and 23.1% in the placebo plus nab-paclitaxel arm. The percentage previously reported in the company's clarification response indicated the percentage of patients with metastatic disease at study entry.<br>The population of interest is normally treated with a sequence of anthracyclines and taxanes in UK clinical practice. The comparator treatment in Impassion130, nab-paclitaxel, is not a standard treatment in the UK. Clinical advice to the NICE technical team is that nab-paclitaxel has a different mode of delivery and is only used in the UK if patients are not eligible for other taxanes (because it has a better toxicity profile). Clinical experts believe it is interchangeable with other taxanes and would be expected to deliver similar or slightly superior results as it is a slightly higher dose of paclitaxel. |
| **Why this issue is important** | The generalisability of the clinical trial evidence to UK clinical practice is an important consideration for decision making. It introduces uncertainty into the clinical and cost effectiveness evidence if the population of the trial dissimilar to the population who is likely to be eligible for the treatment in the UK. |

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| **Questions for engagement** | a) Do the characteristics of the overall trial population and PD-L1 positive subgroup of IMpassion130 reflect those of people who would be eligible for atezolizumab plus nab-paclitaxel in the UK clinical setting? |
| **Technical team preliminary scientific judgement and rationale** | The population of the IMpassion130 clinical trial broadly reflects the population who would be eligible for treatment with atezolizumab plus nab-paclitaxel in the NHS. Nab-paclitaxel is not a standard treatment in the NHS for this indication but would be expected to yield similar or slightly superior results to taxanes used for this indication. |
| **Summary of comments** | The company agrees with the technical team's preliminary judgement that the population of the IMpassion130 trial reflects the population who would be eligible for treatment with atezolizumab plus nab-paclitaxel in the NHS. Patient characteristics from large, international clinical trials will always reflect differences in treatment practices, however the baseline characteristics of patients within the IMpassion130 trial have been validated by clinical experts and it was confirmed that the population reflects people in UK clinical practice.<br>Clinical experts at the technical engagement teleconference confirmed that the population of IMpassion130 reflects the population who would be eligible for atezolizumab plus nab-paclitaxel in UK clinical practice.<br>NHS England also regards the treatment design of the Impassion 130 trial of taxane plus atezolizumab versus taxane plus placebo as being appropriate to clinical practice in England and the results being generalisable for UK clinical practice. |
| **Technical team judgement after engagement** | The technical team's judgement did not change after engagement. The population of the IMpassion130 clinical trial broadly reflects the population who would be eligible for treatment with atezolizumab plus nab-paclitaxel in the NHS and therefore the results of the trial and the results of the subgroup analysis for the PD-L1 positive subgroup are generalisable to UK clinical practice. |

## *Issue 2 –PD-L1 testing*

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| **Background/description of issue** | The proposed marketing authorisation for atezolizumab plus nab-paclitaxel specifies that only patients with metastatic TNBC with PD-L1 expression ≥1% would be eligible for treatment. Currently PD-L1 testing is not part of routine clinical practice in this population, however it is routinely carried out for patients with other types of cancer (non-small-cell lung cancer, melanoma). The ERG and the company are on the opinion that it would not be problematic to scale up and extend testing for people with breast cancer.<br>Clinical experts have also highlighted that a specific test was used in the trial, and it will need to be decided whether the currently used tests in the NHS are feasible for testing people with breast cancer. |
| **Why this issue is important** | Introducing PD-L1 testing for breast cancer might require training and additional funding from the NHS. |
| **Questions for engagement** | a) Would the introduction of PD-L1 testing in the mTNBC population be feasible?<br>b) What challenges would PD-L1 testing introduce to current clinical practice? Will it require a new biopsy?<br>c) Would the currently used tests in the NHS be used for testing people with breast cancer or will a specific test be required?<br>d) What is the reason for the selection of ≥1% as a threshold in the trial? |
| **Technical team preliminary scientific judgement and rationale** | PD-L1 testing is already routine practice in some cancer types where immunotherapies have been introduced. Atezolizumab plus nab-paclitaxel is the first immunotherapy that targets mTNBC with PD-L1 mutation, therefore additional resources and training will be needed to introduce the test in this population. In the economic model the company applied a one-off cost to account for the costs of testing. |
| **Summary of comments** | **Company**: the introduction of PD-L1 testing in the mTNBC population is feasible as it was demonstrated during the MHRA granted Early Access to Medicines Scheme (EAMS) period, during which 140 patients have been tested for PD-L1 status.<br>Currently PD-L1 testing is not part of routine testing in breast cancer, however diagnostic testing for HER2 and oestrogen and progesterone receptors is well established. Therefore, introducing an additional immunohistochemistry test in breast cancer is expected to have a limited impact on |

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| | workflow in hospitals. Given that PD-L1 testing is routinely carried out in patients with other tumor types, introducing it in patients with mTNBC should not be problematic. It can be carried out at sites currently conducting IHC testing following pathologist training to score the test.<br>For PD-L1 testing, both archival and fresh tumor tissue samples are suitable, therefore new biopsy will not be needed.<br>A specific test used in the trial, Ventana SP142, which is currently the only validated test for testing PD-L1 expression in TNBC. It is expected to be launched by the receival of the marketing authorization of atezolizumab plus nab paclitaxel for PD-L1 positive mTNBC. The company supports the use of this specific test, because this is the most specific assay to predict clinical benefit.<br>The 1% threshold for measuring PD-L1 positivity was chosen because PD-L1 expression on tumour infiltrating immune cells covering ≥1% of the tumour area based on the SP142 assay was the best predictor of clinical benefit.<br>**NHS England** confirmed that PD-L1 testing is already part of routine practice in disease areas like non-small-cell lung cancer, but not in breast cancer. In case atezolizumab gets recommended NHS England would expect to commission the testing of PD-L1 at the time of diagnosis of incurable breast cancer. The implementation would be ready and quick. The currently used PD-L1 diagnostic tests will be sufficient to use, no specific diagnostic test (e.g. SP142) is needed to be used. About one quarter of patients with breast cancer would be eligible for testing at the time of diagnosis of incurable breast cancer although those patients who are unfit for any chemotherapy would not require testing. Using a threshold of 1% for determining PD-L1 positivity is widely used and accepted.<br>The **patient experts** emphasized that testing would need to be adopted quickly and that it will be important to ensure any support and training required is put in place promptly. |
| **Technical team judgement after engagement** | Based on the comments received at technical engagement the technical team believes that the introduction of PD-L1 testing is feasible in mTNBC. |

## *Issue 3 –Appropriate comparators*

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| **Background/description of issue** | The clinical trial, IMpassion130 compared atezolizumab plus nab-paclitaxel with placebo plus nab-paclitaxel. The final scope specified two groups of comparators, anthracycline based chemotherapy and singe agent taxane chemotherapy regiments (docetaxel and paclitaxel).<br>The company did not present evidence to compare atezolizumab plus nab-paclitaxel with anthracycline-based chemotherapy, for two reasons:<br>• 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,<br>• the literature search did not identify direct evidence, and there is also a lack of robust trial data or real-world evidence to conduct an indirect comparison.<br>The ERG could not find any relevant evidence for this comparison either and, based on clinical advice, agrees with the company that anthracyclines are only used in a small percentage of patients in this population. Clinical advice to the NICE technical team has also highlighted that anthracyclines are generally used in the early breast cancer setting and not very often for metastatic disease.<br>Both the company and the ERG thinks, based on clinical advice that the most relevant comparators in this setting are single agent taxanes, more specifically paclitaxel, because of the more favorable toxicity profile.<br>Preliminary clinical opinion to the NICE technical team also suggests that weekly paclitaxel is the most relevant comparator in this population. |
| **Why this issue is important** | Anthracycline-based chemotherapy is a comparator specified in the final scope issued by NICE and may be used for treating mTNBC in UK clinical practice.<br>Other comparators specified in the scope are taxanes (paclitaxel and docetaxel) and preliminary clinical advice to the NICE technical team suggests that weekly paclitaxel is the most relevant comparator in this population. |
| **Questions for engagement** | a) Are weekly paclitaxel and docetaxel the most relevant comparators?<br>- Which one is most commonly used? |

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| | b) Do experts agree that anthracycline-based chemotherapy is not a relevant comparator in the metastatic setting? |
| **Technical team preliminary scientific judgement and rationale** | Preliminary clinical advice to the NICE technical team suggests that anthracycline-based chemotherapy regimens would be rarely used in this population, and therefore it is not a key comparator. Weekly paclitaxel appears to be the most relevant comparator according to clinical experts. |
| **Summary of comments** | **Company**: Agrees with the NICE Technical team preliminary scientific judgement and rationale that weekly paclitaxel is the most relevant comparator, based on clinical expert opinion. This is due to the favourable toxicity profile of weekly paclitaxel compared with 3-weekly docetaxel which helps maintain quality of life for patients with limited life expectancy. Docetaxel is often used in the curative early breast cancer setting, which might prevent patients wanting to take docetaxel again in the advanced setting. On the other hand studies have demonstrated only partial cross-resistance between docetaxel and paclitaxel, increasing the likelihood of additional benefit from a different taxane agent, that is paclitaxel.<br>In the IMpassion130 trial, 71.4% (n=208/291) of PD-L1 positive patients (excluding de novo metastatic patients) had received prior anthracycline treatment. This supports the UK clinical expert advice that the majority of patients in an early TNBC setting would have been treated with an anthracycline, which seems to be in line with UK clinical practice, and supports the argument that only a limited percentage of patients would be eligible for anthracyclines treatment in the metastatic TNBC setting. This is also supported by a retrospective analysis of patients with mTNBC treated at the Royal Marsden NHS Foundation Trust. Despite 14% of patients in this analysis presenting with de novo metastatic disease, only 7.5% received an anthracycline-based regimen.<br>Re-challenge with anthracyclines is hindered by lifetime maximum cumulative dose,<br>**NHS England**: Taxane therapy is the most reasonable comparator to use and weekly paclitaxel is the most commonly used taxane regimen for the palliation of incurable breast cancer. This is because most patients in England have had neoadjuvant/adjuvant anthracyclines prior to disease relapse and in those who are anthracycline-naïve at the time of diagnosis of incurable breast cancer, many of these are currently treated with 1st line taxanes, particularly paclitaxel. |

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| | **Patient organisation**: Chemotherapy options include anthracycline based chemotherapy or single agent taxanes – docetaxel and paclitaxel. However, if anthracyclines have been used in the early breast cancer setting – generally docetaxel or paclitaxel would be considered<br>**Comparator company**: it is unclear if the population in the final NICE scope includes the BRCA-positive sub-population or not. If the BRCA-positive TNBC population is under consideration, then carboplatin should also be included as a comparator. |
| **Technical team judgement after engagement** | The technical team's judgement did not change after technical engagement and it was confirmed by stakeholders during technical engagement that weekly paclitaxel appears to be the most relevant comparator.<br>People with a BRCA mutation were not considered as a subgroup and carboplatin was not included as a comparator. |

## *Issue 4 – Comparison with taxanes*

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| **Background/description of issue** | **The company's** systematic literature review did not identify any direct evidence that compared atezolizumab plus nab-paclitaxel with taxanes in PD-L1 positive mTNBC. However, it identified studies relevant for an indirect comparison to generate evidence for comparative effectiveness. These studies provided evidence on overall survival and/or progression-free survival for docetaxel and paclitaxel in the mTNBC population. The network was not connected, because not all studies shared the same comparators, therefore the company conducted a population adjusted indirect comparison, which methodology is usually used to link studies in unconnected networks. Then it applied a covariate balancing propensity score model to adjust survival data from the atezolizumab plus nab-paclitaxel arm of IMpassion130. These propensity score models reflect the likelihood of each patient to be enrolled in each comparator trial.<br>The company used discrete time models to summarise treatment effects across the networks, because the proportional hazard assumption was violated in multiple studies and these models do not require the assumption of proportional hazards. The final models were estimated in a Bayesian framework and random effects models were used for both OS and PFS. The company then presented the results in terms of hazard ratios. For overall survival, a piecewise exponential model |

with 5 months cut-off point was used in the base-case, whereas for progression-free survival, a piecewise exponential model with 2- and 4-months cut-off points up to 5 years was used. The treatment effect of atezolizumab plus nab-paclitaxel versus each comparator in the comparator trial population is identical to the treatment effect observed in the IMpassion130 trial population. In its final base case analysis (at clarification stage the company updated its network meta-analysis) it used placebo plus nab-paclitaxel as reference treatment in the network. The median HR applied for paclitaxel and docetaxel compared with nab-paclitaxel, by piece are shown in the tables below.

| | Overall survival | | Progression-free survival | | |
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| Cut-off point | t<5months | 5months≤t | 0 months ≤t< 2months | 2months ≤t< 4months | 4months ≤t |
| Paclitaxel | 0.63 | 1.33 | 0.56 | 0.95 | 1.35 |
| Docetaxel | 0.89 | 1.32 | 0.74 | 0.57 | 2 |
| Atezolizumab plus nab-paclitaxel | 0.53 | 0.76 | 0.59 | 0.57 | 0.72 |

**The ERG** was unable to validate the results of the network meta-analysis conducted by the company due to insufficient information regarding the inclusion and exclusion criteria for studies in the NMA and on baseline patient characteristics of the studies. It also warned that the confidence intervals around the HRs are wide, which indicates high uncertainty in the results. The ERG also highlighted that the company assumed that the results reflected effectiveness in a population with PD-L1 positive disease, however apart from IMpassion130, no information was available about PD-L1 status and it is unknown whether PD-L1 status has an impact on the effectiveness of other treatments. Because of these limitations, the ERG cautions that the NMA results should be interpreted with caution and may not be sufficiently robust to use in the model.

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| **Why this issue is important** | Uncertainties in the results of the network meta-analysis introduce uncertainty in the clinical and cost-effectiveness evidence and have high impact on the ICER (also see Issue 5). |
| **Questions for engagement** | a) Are the methods and results of the company's network meta-analysis plausible to establish |

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| | comparative effectiveness data for atezolizumab plus nab-paclitaxel compared with taxanes?<br>b) Are the results of the NMA clinically plausible given the limitations highlighted by the ERG? In particular that the inclusion criteria of the trials were different from IMpassion130 and included people with unknown PD-L1 status? |
| **Technical team preliminary scientific judgement and rationale** | The NMA has several limitations and the results may not be sufficiently robust to use in the model. |
| **Summary of comments** | **Company**: Acknowledged the limitations of the NMA, however thought that in order to establish comparative effectiveness evidence for comparing atezolizumab plus nab-paclitaxel with standard of practice in the UK the most appropriate method was to conduct an NMA.<br>Therefore the company provided additional information to address some of the criticism of the ERG and gave more explanation on the potential limitations of the NMA.<br>In response to the ERG's critique regarding the inclusion and exclusion criteria the company explained that of 40 trials identified, 7 were included in OS analysis, 8 in PFS analysis. The other trials were excluded for the following reasons:<br>• they did not include the relevant comparators,<br>• less than 80% of the trial population was first-line metastatic TNBC; or<br>• the trial included a mixed BC population with a lack of TNBC subgroup data.<br>The baseline patient characteristics assessment of the trials included age, ECOG status, prior taxane use, proportion of patients with liver metastases, visceral disease or bone metastases.<br>Comparing the trials based on these categories, the company considers that the included trials were sufficiently homogeneous.<br>In response to the question that the trials In the NMA did not include information on PD-L1 status, the company explained that these trials normally started before PD-L1 status was evaluable, and on the other hand taxanes do not target the PD-L1 immune checkpoint, therefore there is no rationale to assume that PD-L1 status is an effect modifier and there is no evidence that the relative effects of taxanes are impacted by PD-L1 status. However, the company thinks that the IMpassion130 trial suggests a reduction in the absolute effect of nab-paclitaxel for the PD-L1 positive population |

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| | (median PFS and OS: 5 months and 15.5 months) vs the ITT population (median PFS and OS: 5.5 months and 17.6 months) and that it is plausible that the NMA overestimates outcomes for taxanes.<br>With regards to the wide credible intervals of the results of the NMA, the company explained that in the case of NMA results it is not uncommon to see wide credible intervals. The company decided to reduce bias at the potential cost of higher variance, because bias cannot be quantified and reported while variance of the estimates can be reported and incorporated in the probabilistic analysis (PSA) of the cost-effectiveness analysis. Hence, these wider resulting confidence intervals came with the benefit of reducing bias in the NMA results point estimates.<br>Also the company emphasises that a statistically non-significant result does not mean that there is no difference between groups or no effect of a treatment.<br>NICE Decision Support Unit guidance also states, that "simulation from a Bayesian posterior distribution supplies both statistical estimation and inference, and a platform for probabilistic decision making under uncertainty". Therefore, hazard ratios and 5-year restricted mean survival times point estimates are a representation of the likely result. However, the uncertainty surrounding point estimates (through the confidence interval) is reflected in the probabilistic sensitivity analysis used within the cost-effectiveness analysis.<br>**The ERG** in response to the company's comments said that the additional information was helpful but did not solve all the previously discussed methodological issues.<br>The process of how studies were included or excluded from the NMA is now clear. However there are trials included in the NMA for which no information on baseline characteristics for the relevant patient population (mTNBC) was available. Therefore the other points raised by the ERG remain valid, and the ERG still has reservations about the reliability of the results. The HRs for example suggest that patients have higher OS in the first 5 months with paclitaxel and docetaxel and then higher OS with nab-paclitaxel from 5 months onwards. Moreover, in this case credible intervals (CrIs) around the HRs are very wide, which indicates considerable uncertainty around the results and makes it difficult to assess whether the effectiveness of the 3 treatments (nab-paclitaxel, paclitaxel and docetaxel) is different. The DSU guidance quoted by the company does not support the company position but rather points out that CrIs can be used for statistical inference as well as PSA. But since statistically significant difference was not achieved for the comparison of nab-paclitaxel with paclitaxel or docetaxel, it is not appropriate to assume a difference in effectiveness. |

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| | **NHS England** emphasised that there is very considerable heterogeneity in the populations and great uncertainty in the analysis. The hazard ratios seem to be very labile according to which time period is chosen for comparison. In addition, there appear to be very significant differences in the hazard ratios for progression free survival according to time points in the analyses of paclitaxel and docetaxel. This uncertainty also has a high impact on the ICER. |
| **Technical team judgement after engagement** | The technical team's judgement did not change after engagement, the comments did not clarify all of the uncertainties, but suggest that the NMA has several limitations and the results may not be sufficiently robust to use in the model |

## *Issue 5 – Using nab-paclitaxel as a proxy for modelling the effectiveness of taxanes*

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| **Background/description of issue** | In the absence of any evidence of difference between nab-paclitaxel, paclitaxel and docetaxel in OS and PFS outcomes, the ERG presented results of a scenario analysis which assumed equal effectiveness between these treatments, and used data from the placebo plus nab-paclitaxel arm of IMpassion130 to compare taxanes with atezolizumab plus nab-paclitaxel.<br>These changes increased the incremental cost-effectiveness ratio (ICER) from £63,347 per QALY gained (company base case) to £83,624 per QALY gained for atezolizumab plus nab-paclitaxel compared with paclitaxel. For the comparison with docetaxel, the ICER increased from £70,217 per QALY gained to £96,824 per QALY gained.<br>**Clinical expert advice** to the NICE technical team is that nab-paclitaxel is interchangeable with, and can be used as a proxy for, other taxanes used in clinical practice in the UK (mainly weekly paclitaxel, docetaxel is used less frequently). Experts believe it would be expected to deliver similar or slightly superior results as it is a slightly higher dose of paclitaxel. A study (IMpassion131) comparing atezolizumab plus paclitaxel with weekly paclitaxel is underway and some results are expected within a year. |
| **Why this issue is important** | Assuming equal effectiveness between nab-paclitaxel, paclitaxel and docetaxel and using the placebo plus nab-paclitaxel arm of the IMpassion130 trial have a high impact on the ICER. |
| **Questions for engagement** | a) Is nab-paclitaxel sufficiently similar to weekly paclitaxel and docetaxel for it to be reasonable to assume equivalence between these treatments and use trial data from IMpassion130 as a |

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| | proxy for the effectiveness of atezolizumab plus nab-paclitaxel compared with taxanes? |
| **Technical team preliminary scientific judgement and rationale** | Advice from clinical experts is that nab-paclitaxel would be expected to deliver similar or slightly superior results to other taxanes. Therefore, the technical team considers that it may be more appropriate to use data from the placebo plus nab-paclitaxel arm of IMpassion130 as a proxy for the effectiveness of other taxanes. |
| **Summary of comments** | **Company**: Understands that the purpose of using nab-paclitaxel as a proxy is to find a simplified approach compared with the NMA, which is associated with uncertainties. However it argues that assuming equivalence between nab-paclitaxel, docetaxel and paclitaxel is oversimplifying and overly conservative.<br>Results of licensing studies and other studies for nab-paclitaxel shown a non-statistically significant advantage in outcomes (PFS, OS, response rate, time to disease progression) over paclitaxel. Although the dose of nab-paclitaxel was lower in IMpassion130 (100mg/m2 weekly) than in the licensing study (260mg/m2 3-weekly). Results of a literature review show that these doses however achieve similar efficacy profiles.<br>The company believes that the results from the licensing study for nab-paclitaxel, in addition to other published literature using similar dosing regimens to IMpassion130, demonstrate a clinical advantage of nab-paclitaxel over paclitaxel cannot be ruled out.<br>This is consistent with the outcomes of the NMA, where nab-paclitaxel demonstrated a non-statistically significant improvement compared with paclitaxel or docetaxel.<br>Using the NMA results in the model generates a difference of 0.197 life years between nab-paclitaxel and paclitaxel, a marginal difference which has a drastic impact on the ICER.<br>And the ICER compared with weekly paclitaxel increases by £21,956 if equivalence with nab-paclitaxel is assumed.<br>As discussed under Issue 4, the company argues that non-significant results do not mean that there is no difference between groups or no effect of a treatment on some measured outcome.<br>The company does not beleive that nab-paclitaxel is sufficiently similar to weekly paclitaxel and three-weekly docetaxel for it to be reasonable to assume equivalence. It argues that the results of the PAIC reflect more robust evidence on relative effectiveness of atezolizumab plus nab-paclitaxel compared with taxanes<br>**The ERG** in their critique of the company's response to technical engagement reiterated that there |

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| | was no compelling evidence that suggests that treatment with nab-paclitaxel will result in a different OS outcome from treatment with paclitaxel.<br>Therefore the ERG considers that, for the purpose of modelling, the OS associated with the two treatments can be treated equivalent. The ERG has not stated that the available evidence has proved that the effectiveness of the two treatments is equivalent; this would be a misinterpretation of the evidence. However, the ERG also considers that the assumption of equivalence is better supported by the available evidence than is the magnitude of the improvement with nab-paclitaxel suggested by the company NMA.<br>The ERG also noted that weekly paclitaxel, the regimen modelled by the company, has been shown to have higher OS than a 3-weekly paclitaxel regimen in a meta-analysis (Mauri et al. 2010).<br>**Clinical experts** at the technical engagement teleconference also confirmed that nab-paclitaxel is interchangeable with other taxanes and can be used as a proxy for modelling their effectiveness, because according to their clinical opinion it delivers similar or slightly superior results as it is a slightly higher dose of paclitaxel.<br>**NHS England**: nab-paclitaxel has broadly similar efficacy to paclitaxel and docetaxel in incurable breast cancer. Therefore the control arm of IMpassion130 reflects a randomised, unbiased and contemporaneous comparison, far more reliable than company's NMA using historical trial populations.<br>The IMpassion131 trial comparing atezolizumab plus weekly paclitaxel with weekly paclitaxel is underway and will show how effective atezolizumab is when added to the main taxane choice |
| **Technical team judgement after engagement** | The technical team considers that it may be appropriate to use data from the placebo plus nab-paclitaxel arm of IMpassion130 as a proxy for the effectiveness of other taxanes. However, this issue remains unresolved after technical engagement and will be discussed by the appraisal committee. |

## *Issue 6 – Duration of treatment effect*

<table>
<tr><td>Background/description of issue</td><td>In the IMpassion130 trial according to the trial protocol treatment was continued until disease progression or unacceptable toxicity. The median duration of treatment was 26.4 weeks in the atezolizumab arm and 16.1 weeks in the placebo arm. The company assumed that treatment effect would be maintained for a life-time horizon (assumed to be 15 years), which meant that the mortality rate for patients treated with A+nabPx is lower than the mortality rate for patients treated with docetaxel or paclitaxel. The company did not present any scenario analyses with waning of treatment effect. However, in another appraisal for atezolizumab for treating non-small-cell lung cancer (NSCLC), a treatment waning effect was assumed (TA520, published 2018), alongside a 2 year stopping rule. The reason for stopping treatment after 2 years, before disease progression was that clinical experience of immunotherapies in other indications (nivolumab and pembrolizumab for previously treated NSCLC) suggests that significant treatment-related toxicities may occur while the disease is still responding and that there is growing concern among clinicians about the use of immunotherapies beyond 2 years.<br><br>In order to test these assumptions, the ERG provided scenario analyses which limited the treatment effects to 3 or 5 years, but without applying a stopping rule. The ERG warned however that given the lack of evidence on long term treatment effect, any time point from which waning is assumed is arbitrary. After the 3- or 5-year time points risk of event was assumed to be the same in both arms of the model.
<table>
<tr><td rowspan="2">Comparator</td><td colspan="3">Duration of treatment effect</td></tr>
<tr><td>3 years</td><td>5 years</td><td>Lifetime (company’s base case)</td></tr>
<tr><td>Paclitaxel</td><td>£82,686</td><td>£69,444</td><td>£63,347</td></tr>
<tr><td>Docetaxel</td><td>£90,015</td><td>£76,544</td><td>£70,217</td></tr>
</table>
</td></tr>
<tr><td>Why this issue is important</td><td>Changing the assumptions around the duration of the treatment effect has a high impact on the ICER.</td></tr>
<tr><td>Questions for engagement</td><td>a) Would treatment benefits with atezolizumab plus nab-paclitaxel after treatment has stopped be maintained for the remaining lifetime of patients or would benefits decline after a certain period of time?</td></tr>
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| | b) If waning effect is likely to occur, until which timepoint would treatment effect be maintained?<br>c) Is it appropriate to assume a waning effect in the absence of a stopping rule? |
| **Technical team preliminary scientific judgement and rationale** | It is not known whether there is a prolonged benefit of treatment with atezolizumab plus nab-paclitaxel after treatment has stopped. However, the company's approach may be optimistic as there is a lack of evidence to support the company's assumption of a lifetime treatment effect. |
| **Summary of comments** | **Company**: There is no clinical evidence to either support or refute any treatment effect assumption beyond the trial data, The benefit of atezolizumab + nab-paclitaxel is greater in OS than in PFS ([redacted] difference, respectively), which could indicate continued benefit after treatment discontinuation. This improvement in post progression survival is not uncommon in breast cancer or in other immune-oncology trials and therefore the company does not think that assuming a waning effect is appropriate.<br>Duration of treatment effect is an area of uncertainty for immunotherapies and has come up in many appraisals. However in appraisals of targeted therapies for metastatic breast cancer, treatment waning effect has not been explored despite differential magnitudes of benefit between PFS and OS.<br>The company also presented a table with a list of appraisals where treatment effect cap was assumed. Based on their findings assuming a 5-year treatment effect cap is a standard assumption in appraisals for immuno-oncology drugs and was also considered plausible in a previous appraisal for atezolizumab (TA520). It accepts that assuming a 5-year treatment effect cap is a plausible assumption to apply. However it highlights that assuming a treatment waning starting at 3 years after treatment initiation, 6% of patients who were still on treatment in the clinical trial will experience no further benefits.<br>On the other hand when the duration of treatment effect is assumed to be 3 years from treatment initiation, the resulting drop in OS for patients treated with atezolizumab is larger than anticipated for an immune-oncological therapy. The OS of atezolizumab plus nab-paclitaxel meets the OS of nab-paclitaxel only at 70 months. Given the important clinical advancement atezolizumab plus nab- |

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| | paclitaxel has demonstrated in the IMpassion130 trial for patients, the company does not consider this scenario to be clinically plausible.<br>The company also acknowledged that treatment stopping rules have been considered in the case of other immune-oncology appraisals, however this is a separate issue to treatment waning effect.<br>Applying a stopping rule in the case of atezolizumab plus nab-paclitaxel is not feasible clinically or for cost-effectiveness reasons. On the other hand the proposed marketing authorisation outlines that treatment should be continued until disease progression.<br>NHS England does not understand why a treatment waning effect has been applied in absence of a stopping rule. Therefore it does not consider it to be a plausible assumption. |
| **Technical team judgement after engagement** | It is not known whether there is a prolonged benefit of treatment with atezolizumab plus nab-paclitaxel after treatment has stopped. However, the company's approach may be optimistic as there is a lack of evidence to support the company's assumption of a lifetime treatment effect. Therefore based on comments received after technical engagement a 5 year treatment effect cap seems to be a plausible scenario. This issue remains unresolved and will be discussed further by the appraisal committee. |

## *Issue 7 – Health state costs*

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| **Background/description of issue** | The company assumed that both in the progression-free and progressed disease health state, patients would have an appointment with and oncologist at 6 months and then every 2 months. The ERG's clinical experts advised that these assumptions underestimate health resource use in the NHS because patients in the NHS have an appointment every month.<br>Therefore, the ERG presented the results of a scenario analysis, where these assumptions have been updated and health state costs have been increased to reflect more frequent oncologist visits.<br>These changes increase the ICER for atezolizumab plus nab-paclitaxel compared with both paclitaxel and docetaxel. |

| Health state costs (weekly) | Company base case | ERG scenario analysis |
|---|---|---|

| | | | |
|---|---|---|---|
| | | assumption | |
| | Progression free disease | £33.16 | £59.28 |
| | Progressed disease | £46.02 | £61.69 |
| | ICERs calculated using the above weekly health state costs | | |
| | ICER versus paclitaxel | £63,347 | £64,969 |
| | ICER versus docetaxel | £70,217 | £71,864 |
| **Why this issue is important** | Changes around the assumptions on health state cost affect the ICER. | | |
| **Questions for engagement** | a) Do the company's estimates on the frequency of oncologist visits reflect UK clinical practice or are the ERG's estimates more plausible? | | |
| **Technical team preliminary scientific judgement and rationale** | Based on clinical advice to the ERG, the company appears to have underestimated health resource use. However, this appears to have only a modest effect on the ICERs. | | |
| **Summary of comments** | Company sought further advice from clinical experts and agrees with the ERG's changes to the health state costs.<br>Clinical experts at the technical engagement teleconference confirmed that patients with mTNBC would have an appointment with an oncologist at least once in every 4 weeks, therefore the ERG's estimates are more plausible and should be used in the analyses. | | |
| **Technical team judgement after engagement** | The ERG's estimates were more plausible for modelling health resource use in the different health states of the model. | | |

## *Issue 8 – End of life criteria*

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| **Background/description of issue** | The company has put forward the case to demonstrate that atezolizumab plus nab-paclitaxel meets the end of life criteria, which are:<br>• Life expectancy with standard of care treatments for the target population is under 24 months<br>• The increase in life expectancy with the technology being appraised is at least 3 months. |

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| | The company's model estimates that life expectancy in the paclitaxel arm is 13.8 months and in the docetaxel arm is 14.3 months. Compared with paclitaxel, atezolizumab plus nab-paclitaxel offers a median extension to life of 12.6 months. Compared with docetaxel, atezolizumab plus nab-paclitaxel offers a median extension to life of 11.6 months.<br>The ERG first scenario analysis results suggest that when using data from the placebo arm of the IMpassion130 trial, treatment with paclitaxel or docetaxel offers a median life expectancy of 18.6 months and a mean life expectancy of 21.6 months.<br>In the scenario when the duration of effect of treatment with atezolizumab plus nab-paclitaxel is limited to 3 years, results show that atezolizumab plus nab-paclitaxel offers a mean 5.3 months extension to life when compared with treatment with paclitaxel, and a mean 4.8 months extension to life when compared with treatment with docetaxel.<br>Therefore, the ERG agrees with the company that atezolizumab plus nab-paclitaxel meets the end of life criteria. |
| **Why this issue is important** | According to the Guide to the methods of technology appraisal, if a technology fulfils the criteria to be considered a 'life-extending treatment at the end of life' the committee will consider the impact of giving a greater weight to QALYs achieved in the later stages of terminal disease, with a maximum weight of 1.7. This increases the upper end of the range normally accepted as cost-effective use of NHS resources to £50,000 per QALY gained. |
| **Questions for engagement** | a) Does atezolizumab plus nab-paclitaxel fulfil the criteria to be considered a 'life-extending treatment at the end of life'? |
| **Technical team preliminary scientific judgement and rationale** | According to all scenario analysis presented by the company and the ERG atezolizumab plus nab-paclitaxel offers more than 3 months extension to life in a population that has a life expectancy of less than 24 months. Therefore the NICE technical team is satisfied that atezolizumab plus nab-paclitaxel meets the end of life criteria. |
| **Summary of comments** | Company agrees that all scenario analyses presented by the company and ERG demonstrate that the end-of-life criteria are met.<br>Patient and clinical experts also consider that atezolizumab plus nab-paclitaxel meets end of life criteria. |

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| | NHS England regards the only robust overall survival data to be used for the assessment of the EOL criteria is the control arm data of placebo plus nab-paclitaxel in the Impassion 130 study. But these results still suggest that end of life criteria are met. |
| **Technical team judgement after engagement** | The technical team's judgement did not change after engagement, the NICE technical team is satisfied that atezolizumab plus nab-paclitaxel meets the end of life criteria. |

## *Issue 9 – Cancer Drugs Fund*

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| **Background/description of issue** | The available data comes from the IMpassion130 trial, which compared atezolizumab plus nab-paclitaxel with placebo plus nab-paclitaxel. Evidence on the relative effectiveness of atezolizumab plus nab-paclitaxel compared with weekly paclitaxel, which seems to be the most relevant comparator, according to preliminary clinical advice to the NICE technical team, is only available from an indirect comparison. The ERG highlighted several limitations of the network meta analysis, which introduces uncertainty in the evidence base. |
| **Why this issue is important** | If atezolizumab plus nab-paclitaxel is not recommended for routine use, but the committee thinks that there is plausible potential for atezolizumab plus nab-paclitaxel to be cost effective, the committee could recommend it for use in the Cancer Drugs Fund while additional data are collected that address the uncertainties in the evidence base. |
| **Questions for engagement** | a) Would additional data collection in the Cancer Drugs Fund reduce the uncertainty?<br>b) Is the technology a good candidate for use in the Cancer Drugs Fund? |
| **Technical team preliminary scientific judgement and rationale** | The main uncertainty is about the relative effectiveness of atezolizumab plus nab-paclitaxel compared with taxanes. Additional data collection within the Cancer Drugs Fund would not reduce the uncertainty, because no data on comparator treatments would be collected. Also, the company did not present a case for consideration of atezolizumab plus nab-paclitaxel as a suitable candidate for inclusion in the Cancer Drugs Fund. |
| **Summary of comments** | The company is committed to ensure ongoing patient access for atezolizumab plus nab-paclitaxel after the termination of the Early Access to Medicines Scheme (EAMS).<br>The IMpassion130 data are relatively mature (with an 80% information fraction at the second interim |

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| | analysis), and therefore further data collection is not anticipated to significantly reduce clinical uncertainty within this appraisal.<br>The company is working with NHS England to agree a commercial access agreement which will enable atezolizumab plus nab-paclitaxel through routine commissioning however they are open to consider Cancer Drugs Fund to enable patient access. |
| **Technical team judgement after engagement** | The company did not put forward a case for demonstrating that atezolizumab plus nab-paclitaxel is a good candidate for the Cancer Drugs Fund and also highlighted that further data collection does not seem to reduce clinical uncertainties. |

# 3. Issues for information

**Table 1: Other issues for information**

| Issue | Comments |
|---|---|
| **Innovation** | Currently there is no targeted treatment option available for people with PD-L1 positive mTNBC and there is a high unmet need. The currently available treatment options are sequential chemotherapy treatments. Atezolizumab plus nab-paclitaxel is the first treatment that is likely to demonstrate a survival benefit compared with chemotherapy. The results of the IMpassion130 trial show promising overall survival results for atezolizumab plus nab-paclitaxel compared with placebo plus nab-paclitaxel<br>The company considers atezolizumab plus nab-paclitaxel to be innovative. However, the technical team considers that all relevant benefits associated with the drug are adequately captured in the model. |
| **Equality considerations** | No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts. |

**Table 2: Cost-effectiveness results**

| Scenario | Comparison with paclitaxel | Comparison with docetaxel |
|---|---|---|
| **Company base case** | **£63,347** | **£70,217** |
| ERG scenario analysis 1: Using nab-paclitaxel as a proxy for taxanes | £83,624 | £96,824 |
| ERG scenario analysis 2: Revised PFS and PD health state costs | £64,969 | £71,864 |
| ERG scenario analysis 3:<br>3-year duration of treatment effect | £82,686 | £90,015 |
| ERG scenario analysis 4:<br>5-year duration of treatment effect | £69,444 | £76,544 |
| **Combining ERG scenario 1 and 2** | **£85,306** | **£98,506** |
| **Combining ERG scenario 1, 2 and 4** | **£96,298** | **£111,297** |

**Table 3: Additional evidence submitted at technical engagement**

The company believes it has misinterpreted how paclitaxel is administered in the NHS, and incorrectly assumed a maximum of 18 weeks/cycles duration of treatment. Therefore in response to technical engagement, company presented results without this treatment duration cap applied. The impact of this change to the cost-effectiveness results is shown in the table below.

| **Assumption** | **ICER of atezolizumab plus nab-paclitaxel assuming a maximum 18 cycles/weeks of paclitaxel treatment** [1] | **ICER of atezolizumab plus nab-paclitaxel removing a cap of maximum of 18 cycles/weeks of paclitaxel treatment** [1] |
|---|---|---|
| Company base case model | £63,347/QALY | £50,629/QALY |
| Combining ERG scenario 1 and 2 | £85,306/QALY | £72,579/QALY |
| [1] ICERs include the PAS for atezolizumab and list price for nab-paclitaxel | | |

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