NICE National Institute for Health and Care Excellence

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

Lead team presentation

1st appraisal committee A meeting
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February 2022

Key clinical issues

- What is current standard of care for this population?
- Are the CPS and IC PD-L1 measurements comparable?
- Is docetaxel an appropriate comparator?
- Is atezolizumab plus nab-paclitaxel the most appropriate comparator for some groups of people?
- Is the exclusion of the combination with gemcitabine appropriate since is was the most frequent combination in the trial?
- Does the NMA accurately calculate relative efficacy of atezolizumab?

Key:
Model driver; Unknown impact; Small/moderate impact

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CPS: combined positive score; IC: immune cell staining.

Background and decision problem

Pembrolizumab (KEYTRUDA)

Full marketing authorisation	KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple negative breast cancer (TNBC) in adults whose tumours express PD L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease
Dosage and administration	Pembrolizumab 200 mg IV on Day 1 of each 21-day cycle
Mechanism of action	Pembrolizumab is a monoclonal antibody (mAb) of the IgG4/kappa isotype designed to exert dual ligand blockade of the PD-1 pathway
Average list price per course of treatment	Pembrolizumab is £2,630 per 100mg vial, the cost of a single administration is £5,260. Average drug acquisition cost per treatment for pembrolizumab is [redacted] at list price Pembrolizumab has a PAS discount

AUC: area under the curve; CPS: combined positive score; IV: intravenous.

Disease background

- Over **46,100 people** were **diagnosed** with breast cancer and approximately **9,502 deaths** from breast cancer in England in 2017.[1]
- Approximately **15%** are **triple negative breast cancer** whereby the cancer cells test negative for oestrogen and progesterone receptors (hormone receptor negative) and human epidermal growth factor negative (HER2-negative).
- Diagnosed more frequently in **younger people** and people with **BRCA1 mutations** (gene that normally helps to suppress cell growth, which has mutation that may increase the risk of breast cancer)
- Triple negative breast cancer can be particularly **aggressive**, is **more likely to reoccur** than other breast cancers, and is associated with **poorer survival**.[2]
- Chemotherapy is the main treatment for advanced triple negative breast cancer. Patients would benefit from having an additional innovative treatment option – **high unmet need**

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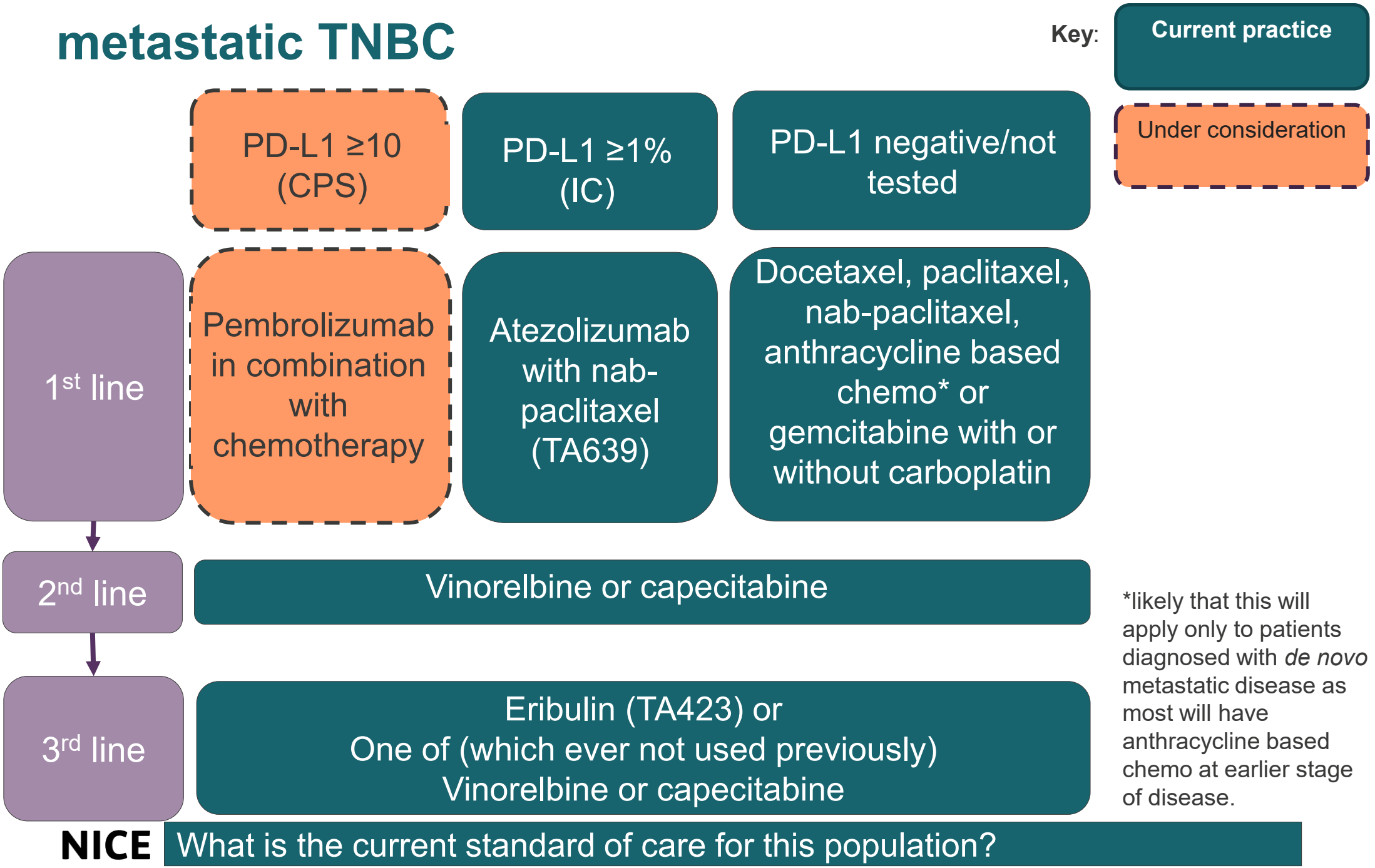
[1]ONS (2019) Cancer registration statistics;[3]Couch et al. (2015) J Clin Oncol 33(4):304-311.

Treatment pathway- locally recurrent unresectable or metastatic TNBC



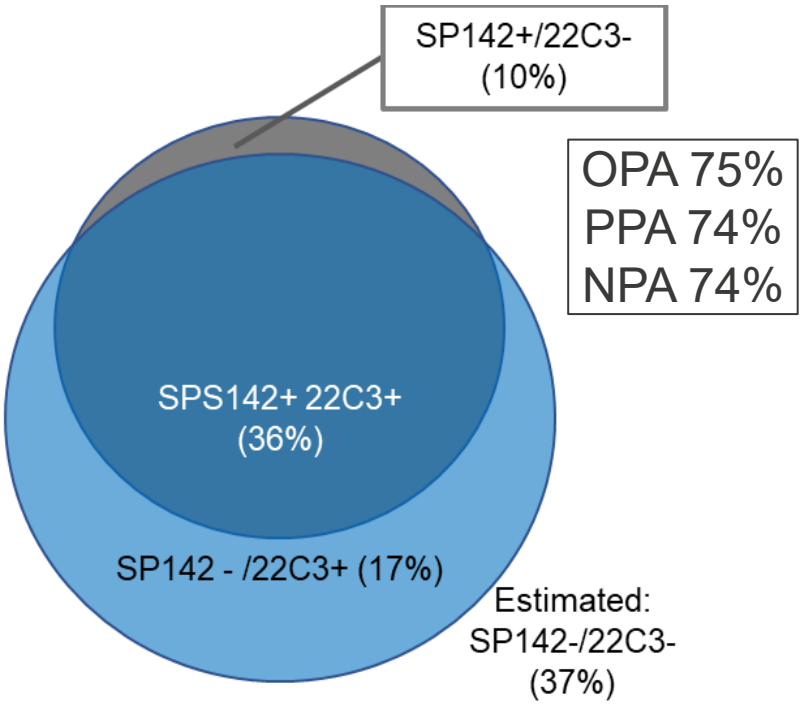
NICE What is the current standard of care for this population?

CPS: combined positive score; IC: immune cell staining.

PD-L1 measurement

PD-L1 measurement	Combined positive score (CPS)	IC
Expressed as	Whole number	Percentage (%)
Calculation of PD-L1 expression	see CPS calculation below	see IC calculation below
Threshold in licence for PD-L1 positivity	≥10	≥1%
Trial/assay (manufacturer)	KEYNOTE-355/22C3 pharmDX (Dako)	IMpassion130/ SP142 (Ventana)

IC≥1% and CPS≥10
(recreated from Rugo 2020)
n = 614



$$\text{CPS} = \frac{\text{Number of PD-L1 stained cells (tumour cells, lymphocytes, macrophages)}}{\text{Total number of viable tumour cells}} \times 100$$

$$\text{IC} = \frac{\text{Tumour area that is occupied by PD-L1 staining immunce cells of any intensity}}{\text{Total tumour area}}$$

Are the two PD-L1 measurements comparable?

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Rugo et al. 2020. Cancer Research. 80: p. PD1-07. Abbreviations: OPA: overall percentage agreement; PPA: positive percentage agreement; NPA: negative percentage agreement.

Patient and carer perspectives (Breast Cancer Now)

- Being diagnosed with metastatic breast cancer is extremely difficult to come to terms with both for patients and their family and friends. It affects patients' mental health and day-to-day activities

- Patients want treatment that will halt progression, extend life for as long as possible, have good safety profile and give them good quality of life

- There is unmet need for further treatments for people living with incurable triple negative secondary breast cancer

"It is scary. I am permanently scared about my future and what my family will have to deal with without me"

"How confused and scared I am all the time; even when I'm happy it's always there in the back of your mind"

"It totally and completely affects your life after diagnosis. Endless doctors' appointments can begin to wear you down in no time at all"

"My treatment goes on for as long as it works and this is my life now. Constant 'scanxiety', endless hospital appointments and the struggle with day to-day living that others either don't see or understand"

Decision problem

	Final scope issued by NICE	Evidence used in the model
Population	People with previously untreated locally recurrent inoperable or metastatic, triple negative breast cancer.	Adults with locally recurrent, unresectable or metastatic triple negative breast cancer whose tumours express PD L1 with a CPS≥ 10 and have not received prior chemotherapy for metastatic disease.
Intervention	Pembrolizumab (with chemotherapy)	Pembrolizumab in combination with taxanes (nab-paclitaxel or paclitaxel).
Comparators	• Anthracycline based chemotherapy • Single agent taxane chemotherapy regimens (docetaxel or paclitaxel) For people whose tumours have PD-L1 expression ≥1 • Atezolizumab in combination with nab-paclitaxel	• Paclitaxel • Docetaxel For people whose tumours express PD L1 CPS ≥10 (using the Dako PD-L1 IHC 22C3 pharmDx Assay) • Atezolizumab in combination with nab-paclitaxel
Outcomes	• overall survival (OS) • progression-free survival (PFS) • response rate (RR) • adverse effects of treatment (AEs) • health-related quality of life (HRQoL)	As per scope with the addition of: • Duration of response (DoR)

Inclusion of docetaxel and atezolizumab as comparators

Company

- Docetaxel is not a relevant comparator because it is used primarily at earlier stages of breast cancer and is associated with less favourable adverse event profile versus paclitaxel
- Included secondary analysis for docetaxel (assuming same efficacy as paclitaxel) because it was included within the final scope but fully incremental analysis not appropriate
- Atezolizumab included as secondary comparator

ERG

- Notes company's concerns but provided fully incremental ICERs and supplementary tables comparing to paclitaxel and atezolizumab separately for committee decision making
- ICERs more favourable against paclitaxel than docetaxel.
- Additional adverse events associated with docetaxel compared with paclitaxel have not been incorporated due to the assumption of equal health impact, which means pembrolizumab plus paclitaxel/nab-paclitaxel ICER compared to docetaxel may be unfavourable to pembrolizumab plus paclitaxel/nab-paclitaxel
- TA639 concluded that paclitaxel is most appropriate comparator and paclitaxel is most used

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Is docetaxel an appropriate comparator? Is atezolizumab plus nab-paclitaxel the most appropriate comparator for some groups of people?

Clinical effectiveness

Clinical trial evidence – KEYNOTE-355

Study design	Phase III, randomised (2:1 ratio), double-blind, placebo-controlled, active-comparator trial.
Population	Patients with previously untreated locally recurrent inoperable or metastatic triple negative breast cancer (protocol revision at interim analysis 2 to only include CPS ≥10)
Analysis populations	**Efficacy:** Intention-to-Treat Population (ITT) **Safety:** All Subjects as Treated (ASaT)
Intervention	Pembrolizumab in combination with chemotherapy (nab-paclitaxel, paclitaxel, gemcitabine/carboplatin*)
Comparator	Placebo in combination with chemotherapy (nab-paclitaxel, paclitaxel, gemcitabine/carboplatin*)
Outcomes	**Primary endpoint** • PFS based on RECIST 1.1 • OS **Key secondary endpoints** • ORR based on RECIST 1.1 • DCR based on RECIST 1.1 • ROR based on RECIST 1.1

*Gemcitabine/carboplatin not considered in this appraisal. Abbreviations: ASaT: all subjects as treated; DCR: disease control rate; DOR, duration of response; ITT: intention to treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours.

All data based on final database lock 15 June 2021

KEYNOTE-355 trial - Baseline characteristics

Baseline characteristics of patients whose tumours express PD-L1 with a CPS≥10; Majority of data collected not included in economic model

Characteristic	Pembrolizumab + chemotherapy (n=220)	Placebo + chemotherapy (n=103)
Mean age, years	[redacted]	[redacted]
ECOG 0 or 1, n (%)	[redacted]	[redacted]
Disease status		
Metastatic, at presentation	[redacted]	[redacted]
Metastatic, recurrence	[redacted]	[redacted]
Locally recurrent, inoperable	[redacted]	[redacted]
Chemotherapy		
Nab-paclitaxel	61 (28)	36 (35)
Paclitaxel	33 (15)	11(11)
Gemcitabine/carboplatin (not considered in appraisal, although the majority received this combination in the trial)	125 (57)	56 (54)
Prior Treatment with Same Class Chemotherapy in the Neoadjuvant or Adjuvant Setting	46 (21)	19 (18)

Source: Company submission, Table 6. CPS: combined positive score; ECOG: Eastern Cooperative Oncology Group.

Exclusion of gemcitabine data in analysis

Company

- Clinical experts noted that the high gemcitabine/carboplatin use observed in KEYNOTE-355 would not be expected in the UK setting since it is primarily used in patients who relapse early and were previously treated with taxanes
- Market research confirms the very limited gemcitabine/carboplatin use in the UK as 1L mTNBC ([redacted] treatment prior to TA639)
- Did not include gemcitabine in analysis

ERG

- Characteristics were stratified in chemotherapy combinations therefore, randomisation was not broken when gemcitabine data was removed.
- Gemcitabine had better outcomes than paclitaxel and docetaxel leading to a less favourable HR compared with pembrolizumab combo

Clinical trial evidence – KEYNOTE-355

Progression-free survival based on BICR assessment per RECIST 1.1 (CPS≥10 and taxane population)

Median follow up (months):
Pembrolizumab arm: [redacted]
Placebo arm: [redacted]

	Pembrolizumab + taxane	Placebo + taxane
No. of events/ No. of patients	[redacted]	[redacted]
Hazard ratio (95% CI)		[redacted]

Source: Company response to TE, Table 2 and Figure 6. BICR: blinded independent central review; CI: confidence interval; CPS: combined positive score; RECIST, Response Evaluation Criteria in Solid Tumours.

Clinical trial evidence – KEYNOTE-355

Overall survival (CPS≥10 and taxane population)

Median follow up (months):
Pembrolizumab arm: [redacted]
Placebo arm: [redacted]

	Pembrolizumab + taxane	Placebo + taxane
No. of events/ No. of patients	61/96	39/47
Hazard ratio (95% CI)		0.54 (0.36, 0.82)

Source: Company response to TE, Table 1 and Figure 5. CI: confidence interval; CPS: combined positive score.

Clinical evidence – safety (*CPS≥10*)

Grade 3-5 adverse events with incidence ≥5% in one or more treatment groups; ASaT population*	Pembrolizumab + chemotherapy (n=219) %	Placebo + chemotherapy (n=103) %
with one or more adverse events	79.5	70.9
with no adverse events	20.5	29.1
Neutropenia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]

*Includes gemcitabine/ carboplatin data. ASaT all subjects as treated. Source: Company submission, Table 35.

Atezolizumab plus nab-paclitaxel: Indirect treatment comparison

- No head-to-head evidence for pembrolizumab combination therapy and atezolizumab plus nab-paclitaxel
- Differences between IMpassion130 and KEYNOTE-355 studies that affected the comparison, included:
  - Patient characteristics for IMpassion130 were only reported in PD-L1 IC ≥1%, not CPS ≥10
  - KEYNOTE-355 included treatment with both paclitaxel and nab-paclitaxel whereas IMpassion130 only included nab-paclitaxel

Studies included in the network meta-analysis

Author	Study	Population	Intervention	Comparator
Rugo et al 2020	IMpassion130	PD-L1 CPS ≥ 10	Atezolizumab + nab-paclitaxel	Placebo + Nab-paclitaxel
MSD (& Cortes et al 2020)	KEYNOTE-355*	PD-L1 CPS ≥ 10	Pembrolizumab + chemotherapy	Placebo + chemotherapy

* KEYNOTE-355 treatment effects used subsequently for the evidence synthesis are specific to the pembrolizumab + taxanes (paclitaxel + nab-paclitaxel) versus taxanes alone study sub-group to reduce heterogeneity.

Source: Company submission, Table 23

Relative efficacy hazard ratios (fixed-effects*)

NMA comparison (KEYNOTE-355 PD-L1/ IMpassion130-PD-L1 expression subgroup)	HR (95% CI)
Overall survival	
Pembrolizumab + paclitaxel/nab-paclitaxel vs. atezolizumab + nab-paclitaxel **(base case)**	[redacted]
Pembrolizumab + nab-paclitaxel vs. atezolizumab + nab-paclitaxel	[redacted]
Progression-free survival (KN-355 INV-assessed PFS)	
Pembrolizumab + paclitaxel/nab-paclitaxel vs. atezolizumab + nab-paclitaxel **(base case)**	[redacted]
Pembrolizumab + nab-paclitaxel vs. atezolizumab + nab-paclitaxel	[redacted]
Progression-free survival (KN-355 BICR-assessed PFS)	
Pembrolizumab + paclitaxel/nab-paclitaxel vs. atezolizumab + nab-paclitaxel	[redacted]
Pembrolizumab + nab-paclitaxel vs. atezolizumab + nab-paclitaxel	[redacted]

*ERG preferred random effects but these were not provided after technical engagement.
Gemcitabine/carboplatin not included in NMA. Source: Company response to TE, Tables 3 and 4

Relative efficacy of pembrolizumab plus paclitaxel/nab-paclitaxel versus atezolizumab plus nab-paclitaxel

Company

- Company acknowledge there are limitations with NMA due to differences in trials
- Prefer fixed-effects model - between study heterogeneity could not be estimated because only one study connected each treatment in the network
- ERG scenario assuming equal efficacy overly simplistic and creates inappropriate assumption of transferability between KEYNOTE-355 and IMpassion130

ERG

- NMA shows favourable midpoint estimates for pembrolizumab plus paclitaxel / nab-paclitaxel but with wide credible intervals including unity
- Given heterogeneity in studies, a random effects model would be preferable – unlikely to influence point estimate but will increase credible intervals and therefore probabilistic ICER. Company did not update random effects NMA with latest data cut so ERG could not include random effects in preferred analysis.
- Explored scenario where efficacy of atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel / nab-paclitaxel are assumed equal

NICE Does the NMA accurately calculate relative efficacy of atezolizumab?

Key clinical issues

- What is current standard of care for this population?
- Are the CPS and IC PD-L1 measurements comparable?
- Is docetaxel an appropriate comparator?
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Key:
Model driver; Unknown impact; Small/moderate impact

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CPS: combined positive score; IC: immune cell staining.

Cost-effectiveness

Key cost issues

- Does pembrolizumab meet the end of life criteria?
- Which survival curve is most appropriate for modelling OS?
- Should the TTD for atezolizumab combination be the same as pembrolizumab+paclitaxel/nab-paclitaxel or should the HR for PFS be applied to the pembrolizumab+paclitaxel/nab-paclitaxel TTD?
- How long should the benefit of pembrolizumab be after it is stopped?
- Should vial sharing be included for IV drugs?
- Is the 'time-to-death' or 'health state' approach more appropriate for estimating utilities?

Key:
Model driver; Unknown impact; Small/moderate impact

Company's model

Model type	Partitioned survival model (progression-free survival, post-progression survival and death)
Population	Adults with locally recurrent, unresectable or metastatic triple negative breast cancer whose tumours express PD L1 with a CPS≥ 10 and have not received prior chemotherapy for metastatic disease.
Intervention	Pembrolizumab in combination with taxanes (paclitaxel or nab-paclitaxel)*
Comparators	Paclitaxel; docetaxel; atezolizumab in combination with nab-paclitaxel
Time horizon	35 years
Model cycle	7 days (half-cycle correction applied)
Discount rates	3.5% for both health and cost outcomes
Treatment waning	Not included
Treatment duration	Lifetime
Utility values	EQ-5D-3L utilities collected alongside KEYNOTE-355
Costs	NHS reference costs; PSSRU; BNF; MIMS; eMIT; Published literature
Price year	2019/20
Perspective	NHS and Personal Social Services

*all analyses use taxane data only from clinical trial. eMIT: Drugs and pharmaceutical electronic market information tool; BNF: British National Formulary; CPS: combined positive score; MIMS: Monthly Index of Medical Specialities; PSSRU: Personal Social Services Research Unit.

Source: Company submission, Table 1, 42 and 75. Company response to clarification, Section D

Does pembrolizumab meet the end-of-life criteria?

- Both criteria must be met:
    1. Treatment is indicated for patients with a short life expectancy, normally less than 24 months
    2. Sufficient evidence to indicate that treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment
- In addition, committee should be satisfied that:
    - estimates are robust
    - assumptions used in the reference case economic modelling are plausible, objective and robust

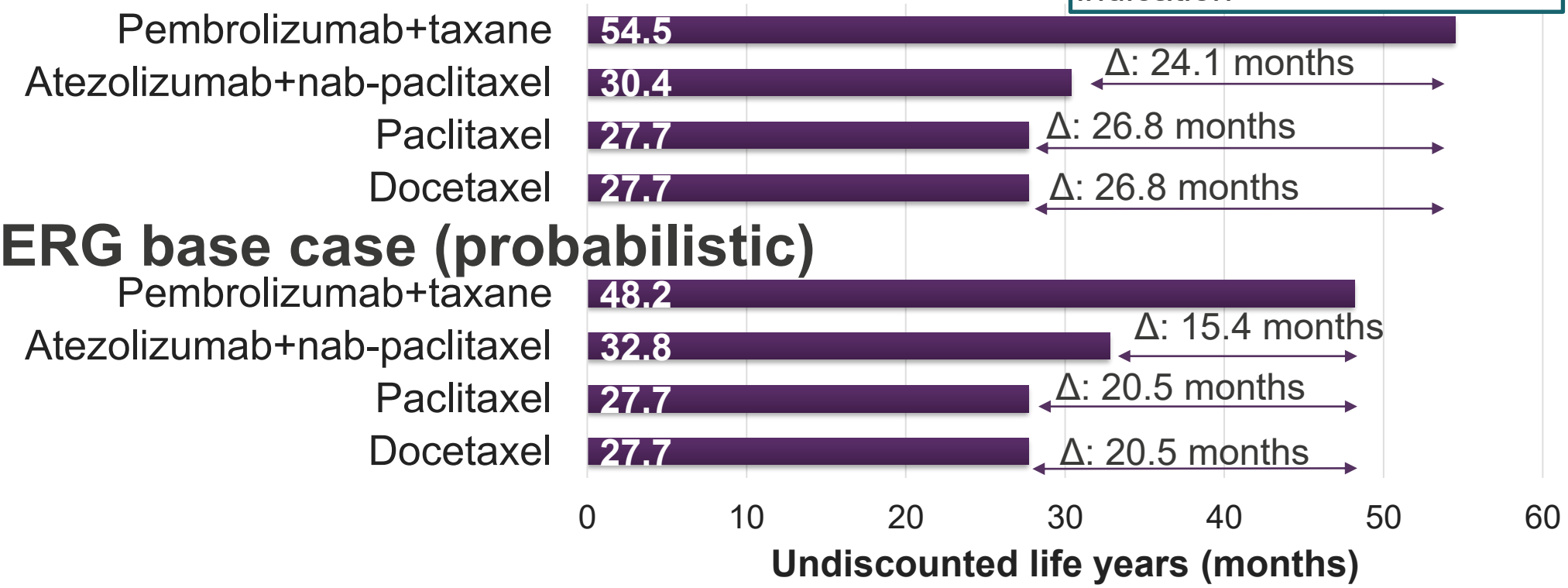
ERG

- Extension of life appears to be met; short life criterion may not be met.

End of life criteria

Committee agreed end of life criteria were met for atezolizumab+nab-paclitaxel (TA639) in the same indication

Company base case (probabilistic)



ERG base case (probabilistic)

Overall survival at 24 months	Company base case	ERG-preferred	KEYNOTE-355
Pembrolizumab plus paclitaxel/nab-paclitaxel	[redacted]	[redacted]	[redacted]
Atezolizumab plus nab-paclitaxel	[redacted]	[redacted]	[redacted]
Paclitaxel/docetaxel	[redacted]	[redacted]	[redacted]
Nab-paclitaxel/paclitaxel (placebo trial arm)	[redacted]	[redacted]	[redacted]

Source: ERG report post-TE, Table 3, 4, 5 and 6

Extrapolation of overall survival (OS)

Company

- Most appropriate curves based on goodness of fit statistics (AIC/BIC), clinical plausibility of long term extrapolations, and validity of long term projections are:
  - **Log-normal** for pembrolizumab plus paclitaxel / nab-paclitaxel
  - Log-logistic for paclitaxel
- Exponential is based on constant hazards which is an overly simplistic assumption

ERG

- ERG agree company choice appears plausible but prefer:
  - **Exponential** distribution for pembrolizumab plus paclitaxel / nab-paclitaxel
  - Log-logistic distribution for paclitaxel
- ERG preference increases ICER
- Difference in BIC between exponential and log-normal distributions does not show meaningful difference in fitting observed data, but smoothed hazard shows no turning point, whereas best-fitting log-normal distribution had reached its turning point within the first year

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Is log-normal or exponential most appropriate to extrapolate OS for pembrolizumab combination?

AIC: Akaike information criterion; BIC: Bayesian Information Criteria

Hazard plot for death for pembrolizumab plus taxanes

Source: ERG report post-TE, figure 10.

Overall survival: pembrolizumab plus paclitaxel/nab-paclitaxel

Source: Adapted from ERG report post-TE, Figure 1

Treatment discontinuation for atezolizumab plus nab-paclitaxel

Company

- Assumed atezolizumab plus nab-paclitaxel time to treatment discontinuation (TTD) equals TTD for pembrolizumab + nab-paclitaxel
- Disagrees with applying the hazard ratio (HR) of PFS from the network meta-analysis to the TTD model of pembrolizumab +taxanes from KEYNOTE-355 – likely to bias against pembrolizumab+taxanes because nab-paclitaxel is better tolerated than paclitaxel and based on comparisons to IMpassion130 study

ERG

- Prefer to apply HR between atezolizumab plus nab-paclitaxel and pembrolizumab plus paclitaxel / nab-paclitaxel for PFS to the pembrolizumab plus paclitaxel / nab-paclitaxel TTD - better than company arbitrarily assuming HR of 1.
- ERG preference increases ICER

TTD survival functions for atezolizumab plus nab-paclitaxel

- Which approach best estimates TTD for atezolizumab combination?

Source: ERG report post-TE, Figure 12

Inclusion of vial sharing for intravenous drugs

Company

- Assumed vial sharing exists for intravenous drugs, with the exception of pembrolizumab and atezolizumab
- Understands that to maximise value in clinical care setting, vial sharing is routine for chemotherapies which are not flat dosed (nab-paclitaxel, paclitaxel and subsequent chemotherapies).

ERG

- Clinical advice to ERG suggests vial sharing would not happen
- Prefer removal of all assumptions related to vial sharing for all drugs
- ERG preference increases ICER

Stopping rules and treatment duration

Combination	Stopping rule
Pembrolizumab	Pembrolizumab will be administered for a maximum of 35 cycles (~24 months). Chemotherapy treatment may continue beyond this point if patient continues to receive benefit. This assumption is in line with the KEYNOTE355 clinical trial.
Atezolizumab	No stopping rule. Atezolizumab + nab-paclitaxel time on treatment has been assumed to extend beyond 2 years for atezolizumab + nab-paclitaxel and is set equal to PFS to projections for this comparison. IMpassion130 trial did not include an atezolizumab maximum treatment duration.

TA639: Committee noted in **previous appraisals** in which a **treatment duration cap** was considered, a **treatment stopping rule was applied**. The **marketing authorisation for atezolizumab recommends that treatment should be continued until disease progression or unacceptable toxicity**…treatment-effect duration is an area of uncertainty. However, in the absence of evidence, the committee concluded that incorporating an arbitrary treatment waning effect was not appropriate. IMpassion130: 6% still on atezolizumab at 3 years.

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Treatment with pembrolizumab is up to 2 years. How long should the duration of benefit for pembrolizumab be after it is stopped?

Source: Company submission Document B, Table 75

Long-term benefits of pembrolizumab plus paclitaxel/nab-paclitaxel

Company

- Assumes treatment benefit applies throughout the time horizon despite max duration for pembrolizumab treatment being two years.
- Unique mode of action of pembrolizumab means that patients continue to experience benefit beyond pembrolizumab cessation as demonstrated by KEYNOTE-355 - No evidence of treatment waning
- 'Prior precedent' justification weak, in absence of any data indicating loss of treatment effect
- TA639 considered treatment effect waning for atezolizumab inappropriate
- Scenario: gradual waning adjustments using data from SEER

ERG

- Company approach creates possibility that 2 patients alive at year 7 on third-line treatment have different hazards of death dependent on initial treatment - not plausible
- Based on previous TAs, prefer 5 year treatment benefit
- ERG preference increases ICER
- KEYNOTE-335 consistent with ERG approach that no waning over initial 5 years. No data available beyond [redacted]
- No stopping rule in TA639, discussion about whether the treatment would lose efficacy over time rather than longer-term residual benefit
- Subsequent treatment use (original data cut - [redacted]% 2nd line, [redacted]% 3rd line, [redacted]% 4th line*) indicates pembrolizumab not sufficiently efficacious in large proportion of people - implausible relative survival benefit maintained many years after treatment cessation, and subsequent treatments

Uncertainty related to the most appropriate way to estimate utility

Company

- Adopted two methods for estimating utility:
  - Time-to-death approach (base case)
  - Health state based approach (scenario)
- Does not have preference on approach but believe time-to death more appropriate based on aggressiveness of triple negative breast cancer and acceptance of this approach for other recent HTA submissions in other disease areas

ERG

- Both methods have limitations, neither approach overcomes main limitation that collected data has been heavily censored, either at the point of progression, or at treatment discontinuation
- ERG has no preference for either method but provides exploratory analysis using both methods noting health-state approach consistently has higher ICERs than the time-to-death approach
- Company did not report how many recent HTA submissions estimated utility based on health state approach and thus the relative frequency of the time-to-death approach is unknown

Utility estimates from time-to-death approach and health-state approach

Utilities for base case	Utility value: mean (SE)	95% CI
Base case: Time-to-Death approach (pooled across treatment arms)		
≥ 360 days left	[redacted]	[redacted]
< 360 but ≥180 days	[redacted]	[redacted]
< 180 but ≥ 90 days	[redacted]	[redacted]
<90 days but ≥ 30 days	[redacted]	[redacted]
< 30 days left	[redacted]	[redacted]
Adverse event (AE) disutility	NA: Implicitly accounted for	
Alternative sensitivity analysis: Utilities by progression status (pooled)		
PFS utility pooled	[redacted]	[redacted]
PPS utility pooled	[redacted]	[redacted]
AE related disutility	[redacted]	
AE adverse: event, CI: Confidence Interval, SE; Standard Error		

TA639: 0.73 for progression-free survival and 0.65 for progressed disease

NICE Is the 'time-to-death' or 'health-state' approach more appropriate for estimating utilities?

Source: Company submission Document B, Table 56

Key assumptions in company and ERG analyses after TE

Parameter	Base case	
	Company	ERG
OS: pembrolizumab combination	Log-normal	Exponential
OS: taxanes	Log-logistic	Log-logistic
PFS: pembrolizumab combination	KM 9W* + Weibull	Weibull
PFS: taxanes	KM 9W* + Log-logistic	Log-logistic
TTD: pembrolizumab combination	Log-normal	Log-logistic
TTD: taxanes	Log-logistic	Log-normal
TTD: atezolizumab combination	TTD assumed equal to pembro+ TTD	PFS HR applied to pembro+ TTD model
Treatment benefit duration for pembrolizumab	Lifetime	5 years
Vial sharing**	✓	✗
Random effects	✗	✗ ***
Clinical efficacy equivalence assumed between atezolizumab and pembrolizumab	✗	✗

ERG note the model is not overly sensitivity to PFS distribution, and that TTD distributions were based on best fitting based on BIC

*Used observed KM function up to 9 weeks, **for all IV drugs except for pembrolizumab and atezolizumab, ***ERG were not able to use random effects after TE, all ICERs include fixed effects. HR: hazard ratio; pembro+: pembrolizumab plus paclitaxel/nab-paclitaxel; KM: Kaplan-Meier; PFS: progression-free survival; OS: overall survival; TTD: time to treatment discontinuation. Source: ERG report, Table 36; Company updated base case at TE

Key cost issues

- Does pembrolizumab meet the end of life criteria?
- Which survival curve is most appropriate for modelling OS?
- Should the TTD for atezolizumab combination be the same as pembrolizumab+paclitaxel/nab-paclitaxel or should the HR for PFS be applied to the pembrolizumab+paclitaxel/nab-paclitaxel TTD?
- How long should the benefit of pembrolizumab be after it is stopped?
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Innovation and Equality

Innovation:

- Until recently there has been limited treatment options for those patients with triple negative breast cancer compared with those with other types of breast cancer
- Pembrolizumab, when combined with chemotherapy, [redacted] for triple negative breast cancer patients whose tumours express PD-L1 CPS ≥10, with an acceptable tolerability profile

Equality issues:

- Use of pembrolizumab is not expected to raise any equality issues.

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential discounts

Due to an error identified after technical engagement, results in the ERG technical report underestimate LYG, QALYs and costs in the atezolizumab arm, though conclusions remain the same