For public

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

2nd appraisal committee A meeting
Chair: Jane Adam
Lead team: Rita Faria, Khalida Ismael and Richard Ballerand
ERG: School of Health and Related Research (ScHARR)
Technical team: Sarah Wilkes, Rufaro Kausi and Janet Robertson
Company: Merck Sharp and Dohme
April 2022

# Pembrolizumab combination not recommended

- Clinical trial evidence shows pembrolizumab combination increases overall and progression-free survival compared with paclitaxel but the long-term benefit is uncertain
  - Paclitaxel is mainly used in NHS, some patients receive docetaxel
- No direct evidence comparing pembrolizumab combination with atezolizumab combination
  - Company updated population to exclude atezolizumab combination as a comparator
- The company did not make a robust case for applying end of life criteria
  - Modelled overall survival estimates were different to estimates in TA639
- Cost-effectiveness estimates for pembrolizumab combination are higher than what NICE normally considers an acceptable use of NHS resources

# Recap from 1st meeting

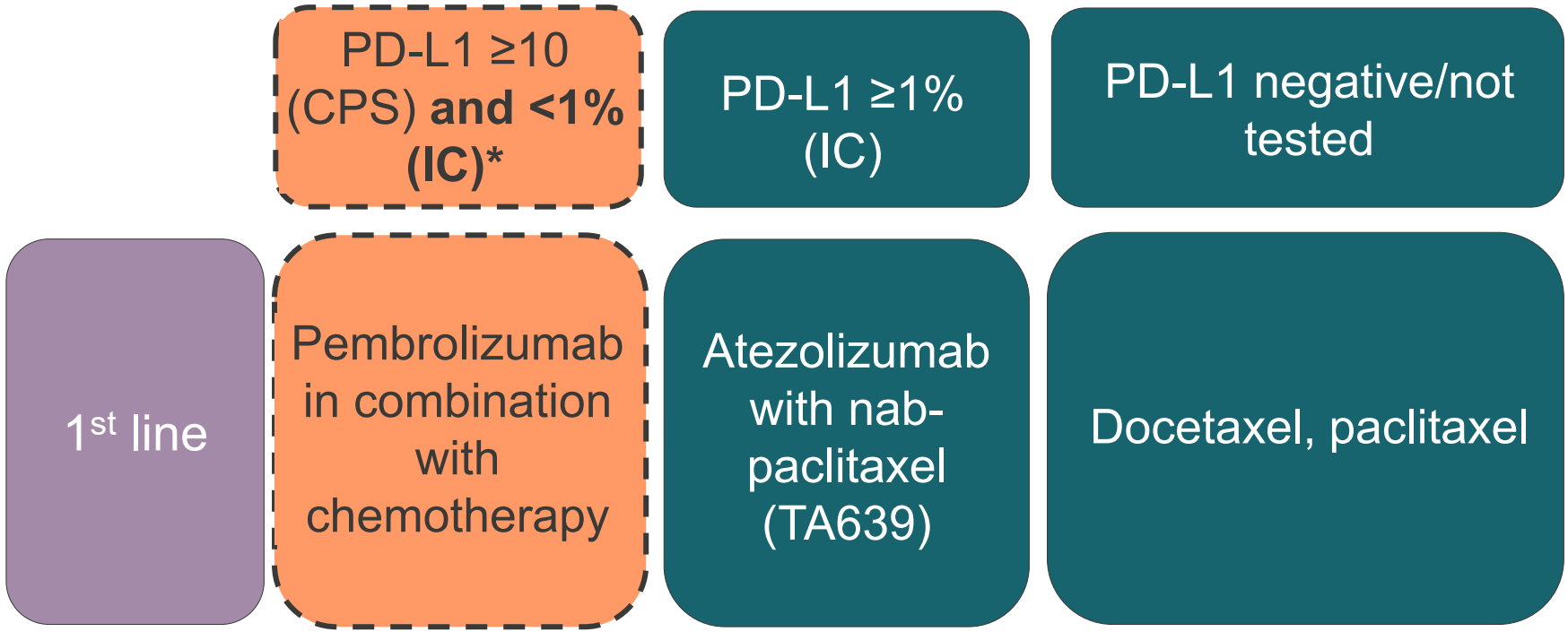
# Pembrolizumab (KEYTRUDA)

| | |
|---|---|
| **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.<br>Average drug acquisition cost per treatment for pembrolizumab is [redacted] at list price<br>Pembrolizumab has a PAS discount |



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

# Treatment pathway- New restricted population since ACM1




*Previously PD-L1 ≥10 (CPS). Note: At ACM1 it was agreed nab-paclitaxel, anthracycline based chemotherapy or gemcitabine with or without carboplatin were not standard NHS practice.

**Company are now seeking access for pembrolizumab combination only in patients whose tumours express CPS ≥10 and IC <1%.**

**Key**: **Current practice** | Under consideration

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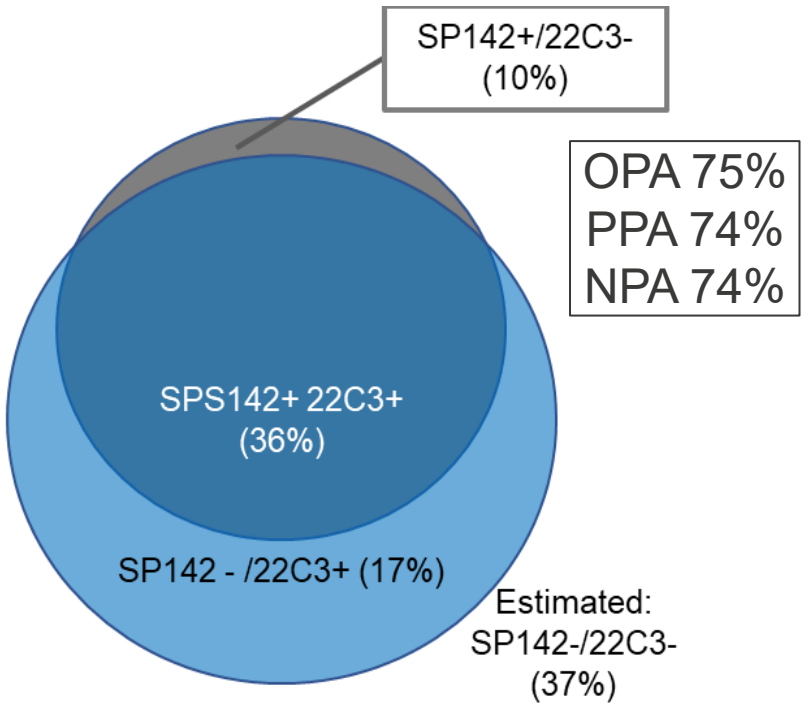
CPS: combined positive score; IC: immune cell staining.

# New restricted population

- Committee acknowledged an overlap between CPS and IC PD-L1 measurements
- Company are now seeking access for pembrolizumab combination only in patients whose tumours express CPS ≥10 and IC <1% (approx. 17% metastatic TNBC patients[1])
  - Atezolizumab is not a relevant comparator in CPS ≥10 and IC <1% population
  - Indirect treatment comparison only required for pembrolizumab and atezolizumab comparison
  - Both CPS and IC tests would need to be taken

**IC≥1% and CPS≥10**
(recreated from Rugo 2020[2])
n = 614




What is the reason for restricting the population?
Is committee satisfied with excluding atezolizumab as a comparator?



1. Rugo et al. 2021. J Natl Concer Inst.2. Rugo et al. 2020. Cancer Research. 80: p. PD1-07. Abbreviations: CPS: combined positive score; IC: immune cell staining; OPA: overall percentage agreement; PPA: positive percentage agreement; NPA: negative percentage agreement.

# 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)<br>**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<br>• PFS based on RECIST 1.1<br>• OS |

*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; ROR: rate of response. All data based on final database lock 15 June 2021

# Clinical trial evidence – KEYNOTE-355

## *Overall survival (CPS≥10 and taxane population – 38.1% of ITT)*

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

**Committee's conclusions summary:**

- Pembrolizumab combination showed benefit compared with paclitaxel but the long-term benefit is uncertain
- Large proportion of people in the placebo arm had an overall survival of less than 24.0 months

Estimated CPS ≥10 and IC <1% population: 17% of ITT population (no trial data for this subgroup)

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

Is the trial data generalisable for the restricted population?
Does committee accept the CPS≥10 efficacy applies to restricted population?

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Source: Company response to TE, Table 1 and Figure 5. Company ACD response. CI: confidence interval; CPS: combined positive score. *Follow up updated due to typographical error by the company during TE.

# End-of-life criteria?

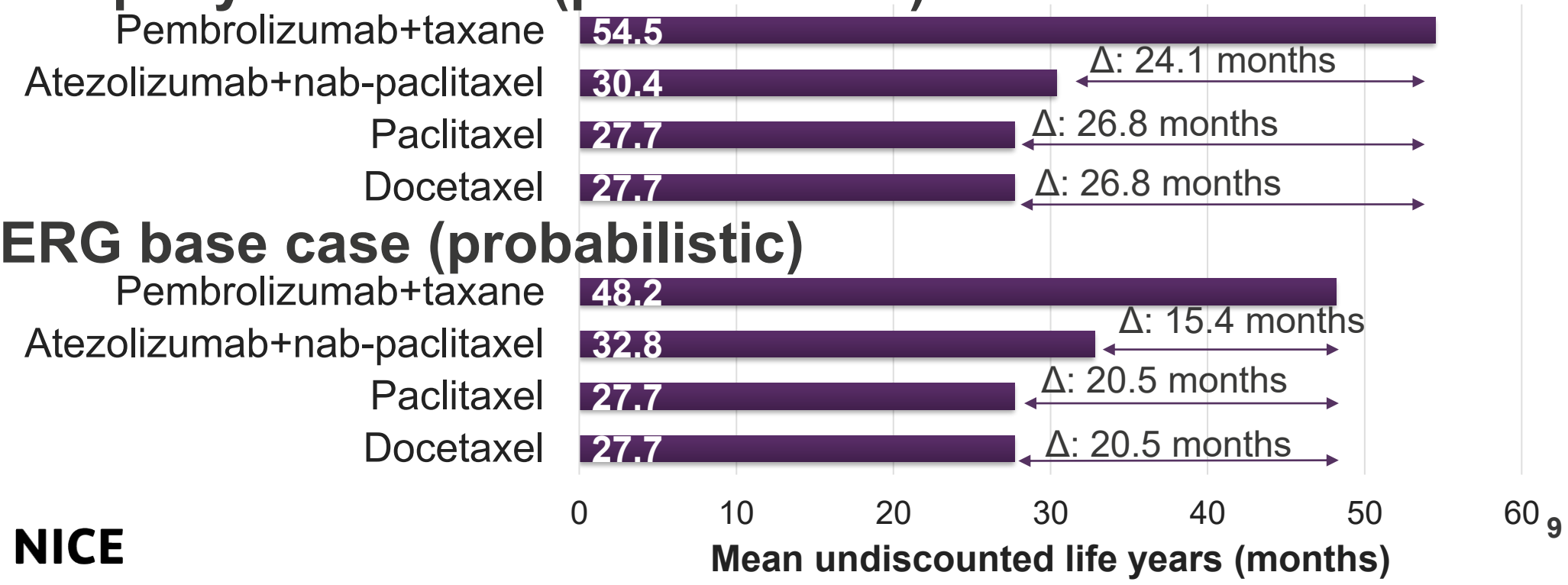
Criteria to be met:

1. Treatment indicated for patients with short life expectancy <24 months
2. Treatment offers extension to life, normally at least additional 3 months, compared to current NHS treatment

Additionally, estimates are robust and assumptions in reference case and model are plausible and robust

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)



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

# 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 IC<1%** and have not received prior chemotherapy for metastatic disease. |
| **Intervention** | Pembrolizumab in combination with taxanes (paclitaxel or nab-paclitaxel)* |
| **Comparators** | Paclitaxel; docetaxel **(atezolizumab removed during consultation)** |
| **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

# Consultation responses

# ACD consultation responses:

**Received consultation responses from:**

- Company – MSD
- 1 patient organisation
  - Breast Cancer Now
- Web comments (n=1)

# Patient organisations, web comments and clinical expert

- Disappointment with preliminary recommendation
- Unmet need group of patients who may be ineligible for the atezolizumab combination
- Poor life expectancy of this group of patients and the urgent need for new effective treatments
- Importance of access to PD-L1 testing
- End of life criteria needs further discussion

"There is a strong argument that for patients who cannot receive a taxane, pembrolizumab addresses an unmet need and therefore should be made available"

"because triple negative breast cancer often affects younger patients, this disease is responsible for many decades of life lost. We therefore strongly argue that any treatment for metastatic triple negative breast cancer qualifies under the end of life criteria"

*"A patient told us "[…] different tests can pick up PDL1 differently which is why it's important that pembrolizumab and the test associated with it are made available alongside atezolizumab to ensure no patients are missed and that everyone has the chance to benefit from an effective immunotherapy"*

"As we still do not have accurate data on metastatic breast cancer, we cannot give an exact life expectancy for metastatic triple negative breast cancer, but we know that 12-18 months median is often quoted"

# Company ACD response summary

| Issue | Committee preferences | Company revised base case | Company additional analyses | ERG critique |
|---|---|---|---|---|
| Clinical evidence | Relevant comparators: docetaxel, paclitaxel and atezolizumab plus nab-paclitaxel | Yes* | Yes (alternative approach) | Some concerns |
| | Long term pembrolizumab benefit uncertain | No | Yes | Some concerns |
| Indirect treatment comparison | Unclear if pembrolizumab combination is more effective than atezolizumab combination | Yes* | No | No critique |
| Overall survival modelling | Exponential distribution for extrapolating overall survival better fitted the smoothed hazard plot | No | Yes (alternative extrapolations) | Disagree |
| TTD | Assuming time to treatment discontinuation (TTD) is the same for pembrolizumab and atezolizumab is over simplistic | Yes* | No | No critique |
| Treatment benefit duration | Duration of benefit for pembrolizumab should assume that the treatment effect wanes after stopping treatment | No | Yes (alternative waning rates) | Some concerns |
| End of life | Additional model validity analysis | No | Yes | Some concerns |
| | Exploration and justification of model estimates for end of life | No | Yes | Some concerns |



*Company removed atezolizumab as a comparator due to the repositioning of pembrolizumab only in patients whose tumours express IC <1% and CPS ≥10.

# Company removed Atezolizumab as comparator

**Committee conclusions:**

- Relevant comparators are paclitaxel, docetaxel and atezolizumab combination

**Company comments:**

- MSD is now seeking access for pembrolizumab combination only in patients whose tumours express IC <1% and CPS ≥10 so atezolizumab is no longer a relevant comparator
  - Approx. 17% metastatic TNBC patients eligible[1]
- High unmet need for those ineligible for atezolizumab

**ERG comments:**

- Company assumed efficacy data from the CPS ≥10 is generalisable to new positioning of pembrolizumab plus taxanes, which adds additional uncertainty
- Testing cost is likely underestimated in the company's model because both tests would be needed
  - Implied for every 1000 tests performed approx. 169 patients would be treated in the new positioning compared with approximately 381 in the original positioning, assuming that the CPS and IC were tested simultaneously

What is the reason for restricting the population?
Is committee satisfied with excluding atezolizumab as a comparator?
Are testing cost underestimated in the model?

# Paclitaxel and docetaxel usage

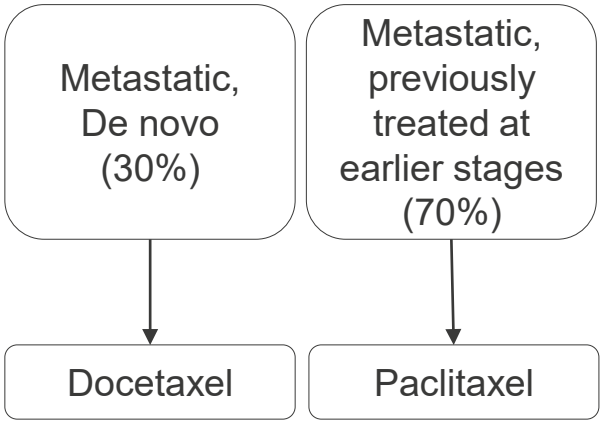
**Company comments:**

- Docetaxel used to treat earlier stages of disease, with exception of de novo metastatic patients (31.6% de novo metastatic in KEYNOTE-355)
- Including docetaxel in analysis disadvantages pembrolizumab because efficacy of paclitaxel assumed equal to docetaxel
  - Docetaxel has worse adverse event profile and potentially shorter treatment response
- Present blended ICER using 70:30 paclitaxel to docetaxel ratio
  - Pessimistic upper cost-effectiveness estimate because docetaxel model limitations

**ERG comments:**

- Prefer full incremental analyses rather than blended ICERs because this can improve the efficient allocation of resources
- Prefer toxicity and potentially shorter docetaxel treatment response explicitly included within the model

70:30 ratio based on KEYNOTE-355




**Clinical opinion (ACM1):**

- Capacity issues faced during COVID resulted in increased docetaxel utilisation - likely to remain post-COVID-19 due capacity benefit

Is a 70:30 ratio of paclitaxel to docetaxel use reasonable and does it have face validity clinically?
Are the company's assumptions around docetaxel reasonable?
Is a full incremental analyses preferable to blended ICER approach?

# Model validity

**Committee conclusions:**

- Life expectancy estimates in TA639 around half projected in pembrolizumab model for virtually identical population - committee questioned validity of the company's pembrolizumab model results and whether suitable for decision making
- Company should further explore validity of economic model outputs, particularly life-expectancy estimates

**Company comments:**

- TA639 trial design, population differences and alternative assumptions explain differences
- Validated modelled survival using real world evidence - clinical experts consulted to identify most generalisable sources
  - Taxanes primarily validated using Battisti et al - UK audit reporting OS over 11 year
  - Deluche et al. excluded as too optimistic
- Median OS ranged from 14.3 months (Battisti DFI within 12 months) to 21.3 months (Battisti DFI after 12 months)
- 2 year % survivorship ranged from 12.1% (Battisti DFI within 12 months) to 36.58% (Battisti DFI after 12 months)
- Model predicts accurately short to medium term taxane OS projections as well as longer term OS estimates for up to 12 years for which RWE is available

# Long term model validations vs RWE

| Source & Overall Survival | Years | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0.5 | 1 | 1.5 | 2 | 3 | 5 | 8 | 10 | 20 |
| Aly 2018 | 76.95% | 51.17% | 37.95% | 28.73% | 17.72% | - | - | - | - |
| Battisi 2018 (DFI after 12 months) | 89.88% | 69.82% | 57.22% | 36.58% | 22.66% | 13.51% | 3.49% | 3.49% | - |
| Battisi 2018 (DFI within 12 months) | 74.39% | 37.70% | 18.40% | 12.11% | 6.01% | 5.86% | - | - | - |
| Deluche 2020 (HR-/HER2-) | 81.07% | 59.85% | 43.22% | 33.25% | 20.72% | 11.76% | 6.91% | 6.65% | - |
| Modelled OS: Taxane (log-logistic) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Observed OS: Taxane | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Source: Company ACD, Figure 4 and Table 10

# Robust case for EoL not made at ACM1 (1)

**Company comments:**

- Explored median, mean and 2-year survivorship across this submission and from TA639
  - Median survival demonstrates high level of consistency in modelled short-term predictions
- ERG report TA639 estimates 19.2 months for paclitaxel (company preferred assumptions) to 21.5 months (ERG preferred assumptions)
  - Consistent with lower estimate of mean life months alive from this submission using alternative and worse fitting parametric distributions to the taxane arm (range of life months; [redacted] to 27.09)
- This submission employs longer time horizon which may skew mean further
  - 15-year time horizon results in a mean life expectancy for taxanes of [redacted] months
- Performance differences between nab-paclitaxel and paclitaxel in KEYNOTE-355 - If paclitaxel selected as comparator (company base-case) mean expected survival is [redacted]
- Mean survivorship of 27.07 months should be considered an upper estimate of mean survival for this very aggressive type of cancer

# Robust case for EoL not made at ACM1 (2)

**ERG comments:**

- Company exponential distribution scenario for taxane OS weakened as hazards appear to show clear turning point (see hazard plot below)
- Company provides life expectancy from TA639 ERG report for patients treated with taxanes - ERG prefers to use NICE FAD, which reports median overall survival of 25.0 months for patients receiving atezolizumab and 15.4 months for patients receiving nab-paclitaxel and agreeing that the end-of-life criteria are met. No reference to mean life expectancy was made in the FAD for TA639
- ERG unclear why a 15 year time horizon would be supported
- ERG cautions that the longer life expectancy shown in KEYNOTE-355 may be due to studies recruiting healthier patients, which may mean that the incremental QALYs are greater in KEYNOTE-355 than would be observed in clinical practice, which if treatment durations were similar would increase the ICER

Source: ERG critique of company ACD response, Figure 4

# Direct comparison of modelled and observed outcomes for chemotherapies

| Study | | Mean (months) | Median (months) | % alive at 24 months |
|---|---|---|---|---|
| **KEYNOTE-355 Taxanes** | Observed | NA | [redacted] | [redacted] |
| | Modelled (ERG/company base case - log-logistic) | [redacted] | [redacted] | [redacted] |
| | Modelled (scenario - exponential) | [redacted] | [redacted] | [redacted] |
| **IMpassion130 nab-paclitaxel** | Observed | N/A | 17.9± | 36.65%≠ |
| | Modelled | 1.6 LYs or 19.2 months updated to 1.797 LYs or 21.5 months[3≠] | 13.8 to 14.3 updated to 18.6 - 21.6 by ERG[3] | Paclitaxel[1]: 21% to 22.7% Docetaxel[2:] 26% to 26.8% |

**Notes: extracted from TA639 Committee Documents: [1]; Table 40 CS, [2]; Table 41 CS, [3]; Table 33 ERG (we assume LY estimates are undiscounted). ± Medians extracted from latest IM-130 publication by Emens et al 2020; PD-L1 +ve, ≠ 2Y OS extracted from earlier IMpassion-130 publication by Schmid et al 2019; PD-L1 +ve.**

Source: Company ACD response, Table 5

# Clinical trial evidence – KEYNOTE-355

## *Overall survival (CPS≥10 and taxane population – 38.1% of ITT)*

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

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Source: Company response to TE, Table 3, 4, 5, 6 and Figure 5. Company ACD response. CI: confidence interval; CPS: combined positive score. *Follow up updated due to typographical error by the company during TE.

# Appeal panel comments on end of life

**Appeal panel ID3735:**

- *"unreasonable to state that life-expectancy was not "normally less than 24 months", even if the mean life expectancy was greater than 24 months, …if the significant majority, in the modelled cohort had died prior to 24 months"*
- *"The panel understood the concern about using means in one context and medians in another, but the end of life criteria are a stand-alone test that have to be considered on their own terms"*
- *The panel also agreed that "normally" allowed a committee a discretion to apply end of life criteria even if it felt on some measures of life expectancy might be somewhat over 24 months. Even if it had been correct to use the mean as the main driver of a decision in this case, given that the median and clinical expert opinion was all significantly below 24 months, and the mean was not substantially above 24 months, this was a case where that discretion would have needed to have been discussed"*

Is the committee confident the model accurately estimates overall survival?
Is the short life expectancy criteria met for taxanes?

# Overall survival extrapolations

**Committee conclusions:**

- Exponential distribution for extrapolating overall survival better fitted smoothed hazard plot

**Company comments:**

- Exponential function is highly conservative – prefer log-normal
- Cautioned against over-interpreting smooth hazard plots in isolation during parametric model selection
  - lack of turning point could be due to the method used to generate the “smoothed” hazard plots, or small sample size
  - NICE DSU 14 - Goodness-of-fit should not be measured by the hazard plots but instead be evaluated versus the survival curves
- Overly simplistic to assume a constant hazard for an IO agent given prior experience in treating solid tumors with IO therapies
- Leads to overly pessimistic OS predictions over time based upon clinical opinion and long-term validity of OS projections versus real world evidence data for taxanes alone

**ERG:**

- Constant hazard in keeping with observed hazards from KEYNOTE-355
- Lack of observed turning point could be because not a turning point in true distribution
- Use of external information can be informative in choosing distributions to fit immature data, but should not override observed data unless there are strong prior beliefs
- ERG maintains exponential appears most appropriate distribution for OS, but is possible that hazard of death could decrease as data mature

# Log-normal vs. exponential overall survival

| Source & Overall Survival- | Years | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0.5 | 1 | 1.5 | 2 | 3 | 5 | 8 | 10 | 20 |
| Company experts | - | - | - | - | - | [redacted] | [redacted] | [redacted] | - |
| Modelled OS: Pembro + taxane (exponential) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Modelled OS: Pembro + taxane (log-normal) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Observed OS: Pembro + taxane | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Source: Company ACD response, Figure 2, Table 9 and 10.

# Hazard plot for death for pembrolizumab plus taxanes

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



Source: ERG report post-TE, figure 10.

# Treatment benefit duration

**Committee conclusions:**

- The duration of benefit for pembrolizumab combination should include an assumption that the treatment effect wanes after stopping treatment

**Company comments:**

- KEYNOTE-355 does not show evidence of treatment effect waning for pembrolizumab + taxanes during the follow up period which is approx. [redacted] in taxane arm (follow-up from randomisation to database-cut off)
- Continued treatment benefit consistently observed across number of tumours whereby small subset of patients experiences long term survival benefit
- Two scenarios:
  - Abrupt treatment effect stop at specific time point (implies HR = 1 for OS from that time point onwards (not clinically plausible; similar to the preferences of Committee C)
  - Constant hazard rate after 4 years across both treatment arms which results in gradual treatment waning adjustments being made from that timepoint onwards using 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
- Subsequent KEYNOTE-355 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 treatment
- SEER not generalisable and scenario lacks face validity - decreased ICER compared to no waning

*The company has not provided in their TE response updated data on subsequent treatments based on the FA data-cut (15th June 2021);.SEER: Surveillance, Epidemiology and End Results program

# 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.

Will the risk of progression diminish with time? Is there a turning point? How long should the duration of benefit for pembrolizumab be after it is stopped?

Source: Company submission Document B, Table 75

# Equalities and innovation re-cap

**Committee's conclusions:**

- **Equalities:**
  - Use of pembrolizumab not expected to pose any equality issues.
- **Innovation:**
  - Pembrolizumab combination provides benefit for triple-negative breast cancer in people whose tumours express PD-L1 with a CPS of 10 or more
  - Health-related quality of life gains had been captured in the QALY calculations

**Consultation comments:**

- Black women are nearly three times more likely to be diagnosed with TNBC than white women

# Cost-effectiveness results

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