NICE National Institute for Health and Care Excellence

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Atezolizumab in combination with nab-paclitaxel for untreated, locally advanced or metastatic, triple negative PD-L1-positive breast cancer

Lead team presentation

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Company: Roche

11th September 2019

Key issues: clinical

- What is the clinical need in this patient group?
- What is the committee's view on the available results from the IMpassion130 clinical trial?
- Are the results of the trial generalisable to UK clinical practice?
- Is PD-L1 testing feasible in the NHS? When and how would the test be carried out?
- Are weekly paclitaxel, and docetaxel the most relevant comparators, and is paclitaxel the key comparator?
- Nab-paclitaxel monotherapy (as used in the clinical trial) is not routinely used in the NHS, how does it compare with taxanes currently in use?

[redacted]

Atezolizumab with nab-paclitaxel

- **Atezolizumab** humanised PD-L1 monoclonal antibody involved in the blockade of immune suppression & reactivation of T-cells.
- **Nab-Paclitaxel:** a form of paclitaxel: blocks cell division and promotes cell death. Contains albumin to help transport paclitaxel through vessel walls. This is thought to increase the amount of paclitaxel in the area of the tumour.

Anticipated marketing authorisation (CHMP positive opinion)	Atezolizumab in combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease
Additional tests	Conditional on the presence of PD-L1 biomarker. Patients with previously untreated TNBC should be tested for PD-L1 expression by a validated test.
Administration and dosage	Atezolizumab and nab-paclitaxel given by intravenous injection. Dose of atezolizumab 840 mg, dose of nab-paclitaxel 100 mg/m^2. Atezolizumab given on days 1 and 15, and nab-paclitaxel on days 1, 8, and 15 of 28 day cycle Both atezolizumab and nab-paclitaxel are available with a simple discount patient access scheme. The size of the discount is commercial in confidence.

[redacted]

Treatment pathway - advanced triple negative breast cancer (TNBC)

Comparators defined in NICE final scope:

- Anthracycline based chemotherapy
- Single agent taxane chemotherapy regimens (docetaxel and paclitaxel)

[redacted]

Patient and carer perspectives

- Triple negative breast cancer is a hard-to-treat and often aggressive type of breast cancer. Its management remains one of the greatest areas of unmet need as current treatment options are limited to surgery, radiotherapy and chemotherapy
- The disease puts a lot of emotional as well as financial pressure on patients and their families. It often affects women of a younger age who may have young children, therefore maintaining a high quality of life for as long as possible is one of the most important outcomes for patients
- The delay in disease progression (2.5 months on average) observed in the clinical trial 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, and live a full life, which can improve the emotional wellbeing of patients and their families
- There are some increased side effects from this treatment option compared to nab-paclitaxel alone e.g. alopecia, nausea, cough, neutropenia, pyrexia and hypothyroidism. All side effects need to be monitored
- Frequent visits to hospital are needed - the benefits and risks of 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.

Clinical trial evidence – IMpassion130

Trial design	Phase III, randomised, double-blind, placebo plus nab-paclitaxel controlled study
Population	People with advanced triple negative breast cancer not previously treated for metastatic disease For this submission: A subgroup analysis of patients with PD-L1 expression ≥ 1% was presented. 41% of patients recruited had PD-L1 positive mTNBC (185/451 in the atezolizumab plus nab-paclitaxel arm and 184/451 in the placebo plus nab-paclitaxel arm) Baseline patient characteristics were well balanced between arms and between the PD-L1 subgroup and ITT population.
Primary endpoints	Progression-free survival: • Definitive analysis was conducted on 17 April 2018 in the ITT population and subgroup analysis of the PD-L1 population was also conducted • Second interim analysis was conducted in January 2019 in the PD-L1 positive population only Overall survival (no formal testing of OS was performed in the PD-L1 positive population because trial protocol indicates formal testing can only occur if OS is statistically significant in the ITT population first): • First interim analysis was conducted at the same time of the definitive PFS analysis, in the ITT population and PD-L1 subgroup • Second interim analysis was conducted in line with PFS analysis

[redacted]

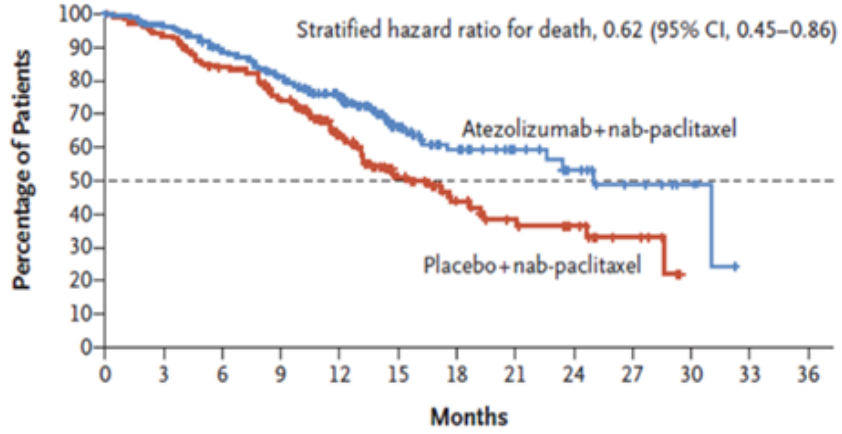
Results of 1st analysis (April 2018)

	PD-L1-positive		ITT	
	Atezolizumab + nabPx (n=185)	Placebo + nabPx (n=184)	Atezolizumab + nabPx (n=451)	Placebo + nabPx (n=451)
Definitive PFS analysis				
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
Hazard ratio (95% CI) p-value (log-rank)	0.62 (0.49–0.78) <0.0001		0.80 (0.69–0.92) 0.0025	
First interim OS analysis				
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
Hazard ratio (95% CI) p-value (log-rank)	0.62 (0.45–0.86) 0.0035		0.84 (0.69–1.02) 0.0840	

Overall Survival Kaplan-Meier curves
1st interim analysis (April 2018)

PD-L1–positive subpopulation

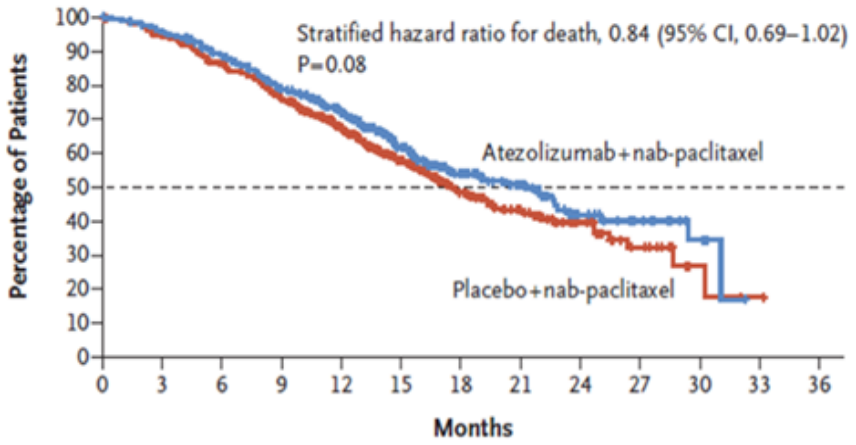
	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	64/185	25.0 (22.6–NE)	53.5 (42.3–64.6)
Placebo+Nab-Paclitaxel	88/184	15.5 (13.1–19.4)	36.6 (26.4–46.7)



No. at Risk													
Atezolizumab+ nab-paclitaxel	185	177	160	142	113	61	36	22	15	9	5	NE	NE
Placebo+ nab-paclitaxel	184	170	147	129	89	44	27	19	13	6	NE	NE	NE

Intent-to-treat population

	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	181/451	21.3 (17.3–23.4)	42.1 (34.3–49.9)
Placebo+Nab-Paclitaxel	208/451	17.6 (15.9–20.0)	39.7 (33.2–46.3)



No. at Risk													
Atezolizumab+ nab-paclitaxel	451	426	389	337	271	146	82	48	26	15	6	NE	NE
Placebo+ nab-paclitaxel	451	419	375	328	246	145	89	52	27	12	3	1	NE

Censored events are indicated with a + symbol.

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

[redacted]

Results of 2nd interim analysis (January 2019)

	PD-L1-positive	
	Atezolizumab + nabPx (n=185)	Placebo + nabPx (n=184)
PFS analysis		
% of patients with events	[redacted]	[redacted]
Median, months	[redacted]	[redacted]
Hazard ratio (95% CI) p-value (log-rank)	[redacted]	
OS analysis		
% of patients with events	[redacted]	[redacted]
Median, months	[redacted]	[redacted]
Hazard ratio (95% CI) p-value (log-rank)	[redacted]	

Company: The IMpassion130 data are relatively mature (with an 80% information fraction at the second interim analysis), and therefore the company believes that further data collection will not significantly reduce clinical uncertainty within this appraisal.

[redacted]

Issue 1: Generalisability

Background

- Company evidence: subgroup of the IMpassion130 trial: people with PD-L1 positive mTNBC.
- PD-L1 subgroup represents 41% of ITT population in both arms of the trial
- [redacted] with PD-L1 positive mTNBC were included from the UK
- 71.4%* of patients in the PD-L1 subgroup had been previously treated with anthracyclines
- 19.7%* of patients in the PD-L1 subgroup in the atezolizumab plus nab-paclitaxel arm and 23.1%* in the placebo and nab-paclitaxel arm had metastatic disease at presentation

* Data corrected at technical engagement

Stakeholder comments

- Clinical experts: population of IMpassion130 reflects the population who would be eligible for atezolizumab plus nab-paclitaxel in UK clinical practice

Technical team: The results of IMpassion130 are generalisable to UK clinical practice

[redacted]

Issue 2: PD-L1 testing

Background

- Proposed MA: people with metastatic TNBC with PD-L1 expression ≥1%
- PD-L1 testing not routine clinical practice in breast cancer, but is for non-small-cell lung cancer and urothelial carcinoma
- A specific test was used in the trial. Are currently used tests in the NHS comparable in breast cancer?
- The costs of testing have been incorporated in the economic model.

Stakeholder comments

- ERG and company: not problematic to include PD-L1 testing for people with TNBC
- Standard tests could be used but additional training/ resources needed
- Company supports use of SP142 test, as in trial, as the most specific assay to predict clinical benefit
- No new biopsy will be required, archival and fresh tumor tissue samples suitable
- Patient experts: timing of testing is key and should happen soon after diagnosis of metastatic TNBC and made available promptly after a positive NICE recommendation

Technical team: The introduction of PD-L1 testing is feasible in mTNBC

[redacted]

Issue 3: Appropriate comparators

Background

- Nab-paclitaxel (the form of paclitaxel used in the trial as comparator) is not routinely used in the UK in this population, and was not used at the licensed dose in the trial
- NICE final scope included anthracycline-based chemotherapy and docetaxel and paclitaxel as comparators
- Company did not present a comparison with anthracycline-based chemotherapy:
  - anthracyclines have a lifetime maximum cumulative dose, if used earlier in treatment, unlikely to be re-used for metastatic disease
  - no direct trial comparison evidence, and lack of robust trial data or real-world evidence to conduct an indirect comparison
- Company and ERG consider that the most relevant comparators in this setting are taxanes, mainly weekly paclitaxel, because of its more favourable toxicity profile.

Stakeholder comments

- Anthracycline-based chemotherapy regimens would rarely be used in this population because of previous use in the treatment pathway, therefore they are not a key comparator
- Only a few patients are treated with docetaxel in this setting, as it is not well tolerated.
- Weekly paclitaxel appears to be the most relevant comparator according to clinical experts.

[redacted]

Issue 4: Comparison with taxanes

Background

- No direct evidence compared atezolizumab plus nab-paclitaxel with weekly paclitaxel or 3-weekly docetaxel
- Studies relevant for an indirect comparison provide evidence on OS and/or PFS for docetaxel or weekly paclitaxel in mTNBC but these included no information about PD-L1 status of the patients in the trials
- The incidence of PD-L1 positivity is also unknown in this population
- Company assumed the results of the included studies could be generalised to the PD-L1 positive population, but it is unknown whether PD-L1 status has an impact on the effectiveness of those treatments
- Not all studies shared the same comparators, therefore the company presented a population adjusted indirect comparison (PAIC) to link the networks

[redacted]

Issue 4: Comparison with taxanes

Stakeholder comments

- Company provided additional information to address some of the potential limitations of the NMA
- Of 40 trials identified, 7 were included in OS analysis, 8 in PFS analysis. (Others excluded because did not include the relevant comparators, no triple negative information or not 1st line metastatic treatment)
- Baseline patient characteristics: age, ECOG status, prior taxane use, proportion of patients with liver metastases, visceral disease or bone metastases
  - based on these, company considers that the included trials were sufficiently homogeneous
- Trials started before PD-L1 status evaluable, but company view:
  - taxanes don't target the PD-L1 immune checkpoint - no rationale to assume that PD-L1 status is an effect modifier & no evidence that the relative effects of taxanes are impacted by PD-L1 status
  - however, IMpassion130 suggests a reduction in the absolute effect of nab-paclitaxel for the PD-L1 positive population (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) so it is plausible that the NMA overestimates outcomes for taxanes
- Wide credible intervals in the case of NMA results is not uncommon. Statistically non-significant result does not mean that there is no difference between groups or no effect of a treatment. 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.
- **NHSE**: very considerable heterogeneity in the populations and great uncertainty in the analysis

[redacted]

Issue 4: Comparison with taxanes

ERG's comments on company's response to technical engagement:

- The process of how studies were included or excluded from the NMA is now clear
- There are trials included in the NMA for which no information on baseline characteristics for the relevant patient population (mTNBC) is available.
- Other points raised by the ERG remain valid, and 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.
- 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 does not support the company position but rather points out that CrIs can be used for statistical inference as well as PSA.
- But statistically significant difference was not achieved for the comparison of nab-paclitaxel with paclitaxel or docetaxel, and therefore it is not appropriate to assume a difference in effectiveness.

Is the company's NMA reliable for establishing the effectiveness of atezolizumab plus nab-paclitaxel compared with taxanes?

[redacted]

Key issues: clinical

- What is the clinical need in this patient group?
- What is the committee's view on the available results from the Impassion130 clinical trial?
- Are the results of the trial generalisable to UK clinical practice?
- Is PDL-1 testing feasible in the NHS? When and how would the test be carried out?
- Are weekly paclitaxel, and docetaxel the most relevant comparators, and is paclitaxel the key comparator?
- Nab-paclitaxel monotherapy (as used in the clinical trial) is not routinely used in the NHS, how does it compare with taxanes currently in use?

[redacted]

Key issues: cost effectiveness

- Which approach is most appropriate for comparing the effectiveness of atezolizumab plus nab-paclitaxel with weekly paclitaxel and docetaxel:
  - using the network meta-analysis (NMA) – are the results reliable and clinically plausible?
  - assuming that nab-paclitaxel (given in the control arm in the clinical trial) is equivalent to weekly paclitaxel and docetaxel and using data from the trial as a proxy for the effectiveness of atezolizumab plus nab-paclitaxel compared with taxanes?
- Duration of treatment effect:
  - in the trial people were treated until progression, would treatment benefits still be seen with atezolizumab plus nab-paclitaxel after treatment has stopped, or decline after a certain period from starting treatment?
  - is it appropriate to assume a waning effect in the absence of a stopping rule e.g. stopping at 2 years even if not progressed?
- In UK clinical practice, how long are people treated with weekly paclitaxel? Is there a maximum duration of treatment/number of cycles?
- Does atezolizumab plus nab-paclitaxel fulfil the criteria to be considered a ‘life-extending treatment at the end of life’?

[redacted]

Issue 5: Using nab-paclitaxel as a proxy for modelling the effectiveness of taxanes

Background: ERG presented a scenario analysis which assumed equal effectiveness of nab-paclitaxel, paclitaxel and docetaxel, instead of using the NMA results. Analysis used data from the placebo plus nab-paclitaxel arm of IMpassion130 as a proxy for the effectiveness of taxanes

	ICER (£/QALY gained)	
Comparator	Paclitaxel	Docetaxel
Company base case (using NMA results)	£63,347	£70,217
ERG scenario analysis (assuming equal effectiveness between nab-paclitaxel, paclitaxel and docetaxel)	£83,624	£96,824

Stakeholder comments

- Clinical experts: nab-paclitaxel is interchangeable with other taxanes and can be used as a proxy for modelling their effectiveness - delivers similar or slightly superior results as it is a slightly higher dose of paclitaxel
- NHSE: broadly similar efficacy in incurable breast cancer. Control arm of IMpassion130 reflects a randomised, unbiased and contemporaneous comparison, far more reliable than company's NMA using historical trial populations
- 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

[redacted]

Issue 5: Using nab-paclitaxel as a proxy for modelling the effectiveness of taxanes

Company's comments

- Assuming equivalence between nab-paclitaxel, docetaxel and paclitaxel is oversimplifying and overly conservative
- Results of licensing studies and other studies for nab-paclitaxel show a numerical advantage in outcomes over paclitaxel. Although dose of nab-paclitaxel was lower in IMpassion130 (100mg/m^2 weekly) than in the licensing study (260mg/m^2 3-weekly), literature review shows the doses achieve similar efficacy profiles
- This is consistent with the outcomes of the NMA, where nab-paclitaxel demonstrated a numerical but not statistically significant improvement compared with paclitaxel or docetaxel
  - non statistically significant difference does not mean no difference
- 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
  - ICER vs weekly paclitaxel increases by £21,956 if equivalence with nab-paclitaxel is assumed
- Nab-paclitaxel is not sufficiently similar to weekly paclitaxel and docetaxel for it to be reasonable to assume equivalence. Results of the PAIC reflect more robust evidence on relative effectiveness of atezolizumab plus nab-paclitaxel compared with taxanes

Is nab-paclitaxel sufficiently similar to weekly paclitaxel and docetaxel to assume equivalence and use data from IMpassion130 to model the effectiveness of taxanes?

[redacted]

Issue 5: Using nab-paclitaxel as a proxy for modelling the effectiveness of taxanes

ERG's comments on company's response to technical engagement:

- There is no compelling evidence to suggest that nab-paclitaxel provides higher OS benefit compared with paclitaxel, however it is also not supported by the evidence that the two agents can be considered equivalent
- ERG believes that the assumption of equivalence is better supported by the available evidence than is the magnitude of the improvement with nab-paclitaxel
- ERG found evidence that suggests that weekly paclitaxel has higher OS benefit than a 3-weekly paclitaxel regimen, which is used in most of the trials included in the NMA. The only study in the NMA that used weekly paclitaxel (Luhn et al.) suggested that weekly paclitaxel and weekly nab-paclitaxel could be considered interchangeable as first line treatment for mTNBC

[redacted]

Issue 6: Duration of treatment effect

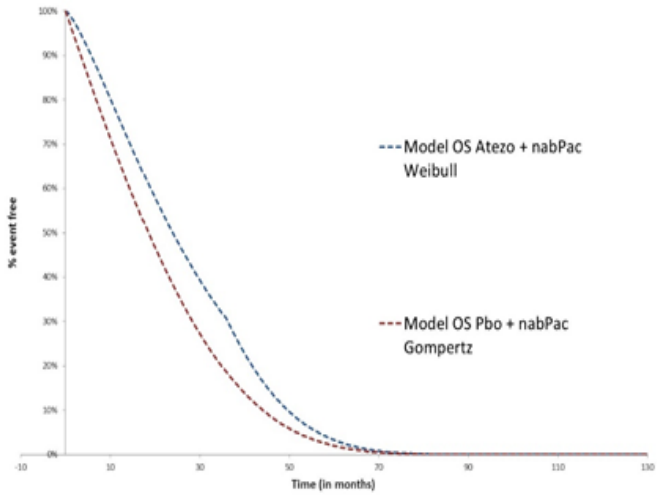
Background

- In IMpassion130 treatment continued until disease progression or unacceptable toxicity, median duration of treatment 26.4 weeks in atezolizumab arm and 16.1 weeks in placebo arm.
- In the trial median OS benefit exceeded median PFS benefit in the PD-L1 positive subgroup (9.5 vs 2.5 months, 1st interim analysis). Although no formal testing of OS was performed.
- Company assumed that some benefit would be maintained for a life-time horizon (15 years), which ERG considered implausible
- In other appraisals of immunotherapies, a treatment waning effect has been assumed alongside a treatment stopping rule (normally 2 years). Reason for stopping treatment at 2 years, before disease progression, based on 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 there is concern among clinicians about the use of immunotherapies beyond 2 years
- ERG: scenario analyses where it limited duration of treatment effect to 3 or 5 years from staring treatment (with treatment until progression and no stopping rule applied)

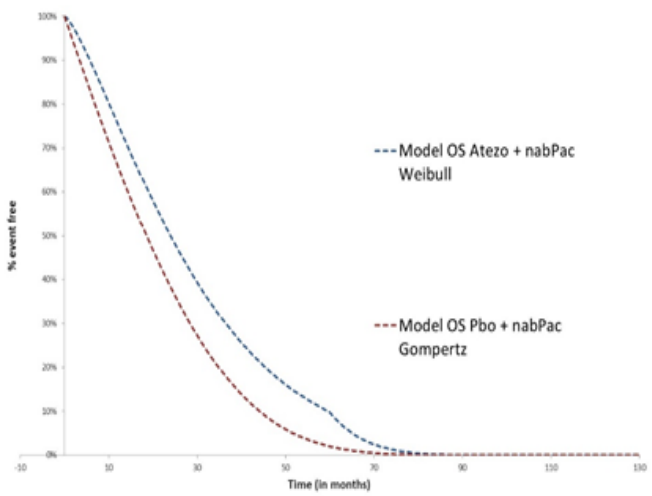
Comparator	Duration of treatment effect		
	3 years	5 years	Lifetime (company base case)
Paclitaxel	£82,686	£69,444	£63,347
Docetaxel	£90,015	£76,544	£70,217

[redacted]

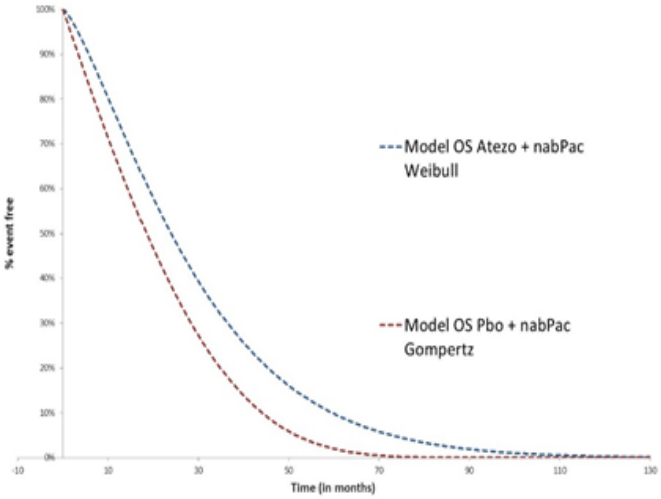
Modelled OS for Atezolizumab + nab-paclitaxel vs placebo + nab-paclitaxel assuming treatment cap from initiation: 3 years, 5 years and lifetime (no waning)



3 years duration of A+NabPx effects



5 years duration of A+NabPx effects



No waning of A+NabPx effects

Source: Figure 3 from company's response to technical engagement

[redacted]

Issue 6: Duration of treatment effect

Stakeholder comments

- **Company**: according to ERG's scenario, if treatment waning starts at 3 years after treatment initiation, those who are still on treatment after 3 years (6%) experience no further benefits
- The benefit of atezolizumab + nab-paclitaxel is greater in OS than in PFS ([redacted]) months 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 may indicate that a waning effect is not appropriate
- 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
- Company: 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)
- Company willing to accept a 5-year treatment effect cap from treatment initiation in line with previous appraisals
- Considering a treatment stopping rule is not feasible clinically or for cost-effectiveness reasons. [redacted]
- NHSE: not clear why a treatment waning effect has been applied in absence of a stopping rule

Is it appropriate to assume a waning effect?

[redacted]

Issue 8: End of life criteria

Background

- Company case
  - Life expectancy with standard of care treatments for the target population is under 24 months
  - The increase in life expectancy with the technology being appraised is at least 3 months.
- Company's model estimates that life expectancy is 13.8 months with paclitaxel, and 14.3 months with docetaxel.
- Compared with paclitaxel, atezolizumab plus nab-paclitaxel offers a median extension to life of 12.6 months. Compared with docetaxel, the median extension to life is 11.6 months.
- According to the ERG's scenario analyses, atezolizumab plus nab-paclitaxel meets the end of life criteria

Stakeholder comments

Stakeholders agree that atezolizumab plus nab-paclitaxel meets end of life criteria

All scenario analysis presented by the company and ERG suggest that 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

NICE technical team is satisfied that atezolizumab plus nab-paclitaxel meets the end of life criteria

[redacted]

Issues resolved during technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
7	Health state costs: The company assumed that in the progression-free and progressed disease health states, patients would have an appointment with an oncologist at 6 months and then every 2 months. Clinical advice to the ERG suggested that the frequency of oncologist visits is once a month regardless of health state	Clinical experts confirmed that patients with mTNBC would have an appointment with an oncologist once every 4 weeks. Company agrees that the model should be updated to reflect clinical expert opinion.	The ERG's assumption reflects UK clinical practice.	No

[redacted]

Additional evidence – duration of treatment with paclitaxel

- Company believes it has misinterpreted how paclitaxel is administered in the NHS, and incorrectly assumed a maximum of 18 weeks/cycles duration of treatment.
- In response to technical engagement, company presented results without this treatment duration cap applied, which decreased the ICER.

Assumption	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	£63,347/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.

*Health state costs were not updated in the company's results.

[redacted]

ERG critique of additional evidence

- There is no national guidance that recommends when weekly paclitaxel treatment should be stopped
- Local guidance suggests that treatment should continued for a maximum of 6 cycles of 28 days (i.e. for 6 months), however treatment can be extended if needed
- Clinical advice to the ERG suggests that extension beyond 6 months is unusual and never continues beyond 10 months
- The ERG estimates that if no patients continued taking weekly paclitaxel after 10 months, this would reduce the ICER by approx. £3,000-4,000 per QALY gained, but not by £13,000 as suggested by the company
- No updated model was submitted by the company, therefore the ERG could not check the correctness of their scenario analysis

[redacted]

Cost effectiveness results

- The estimates below do not include the commercial arrangement for nab-paclitaxel, because that is confidential. Estimates that include these commercial arrangements would be lower than those reported.

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: 3-year duration of treatment effect	£82,686	£90,015
ERG scenario analysis 4: 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 3	£122,745	£142,072
Combining ERG scenario 1, 2 and 4	**£96,298**	**£111,297**
Company updated base case: Removing the duration of treatment cap for paclitaxel + updated HS costs	**£52,260***	**£71,864***

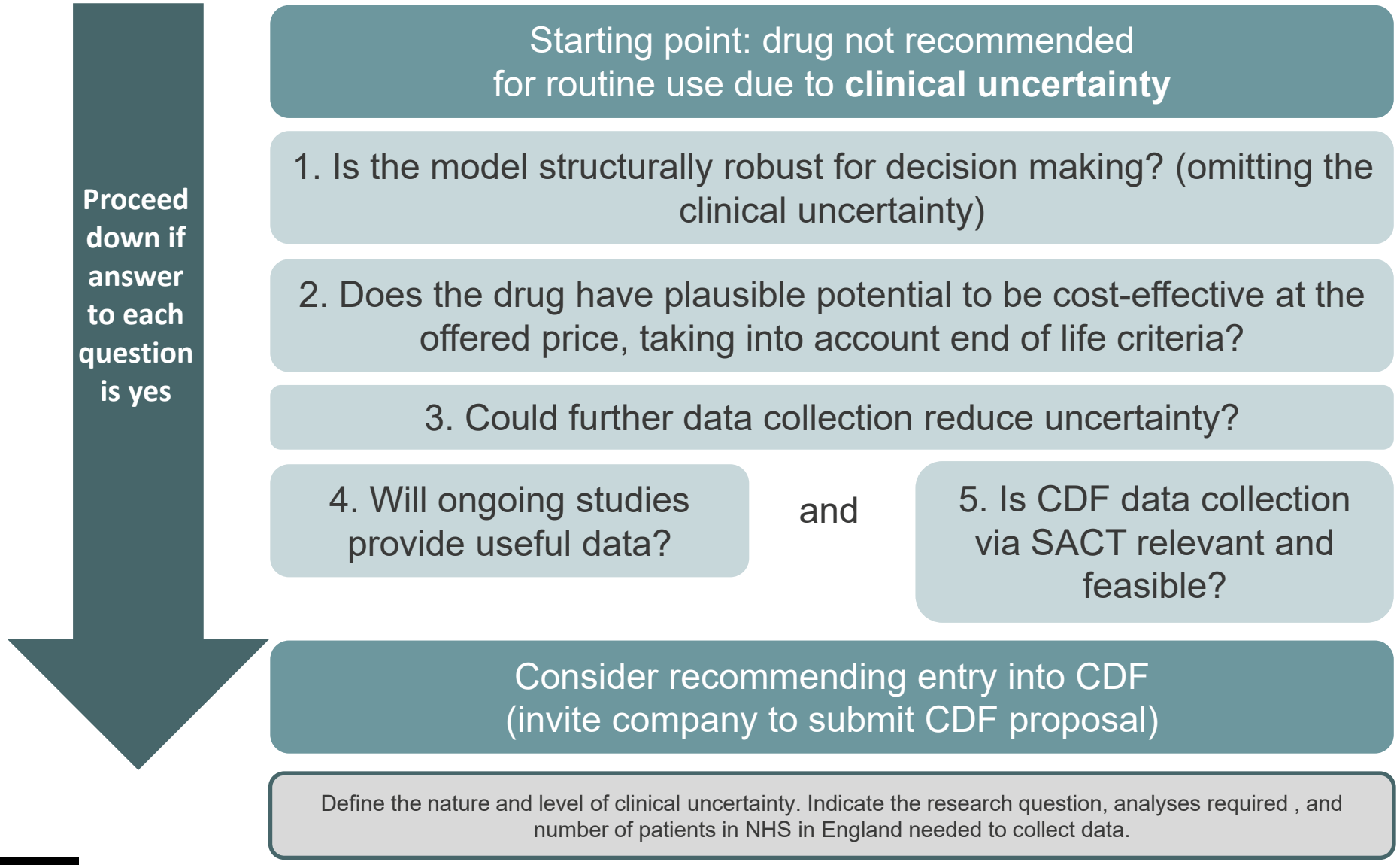
* Figures calculated by NICE technical team and ERG, based on model 2 submitted by the company at clarification response stage

Key issues: cost effectiveness

- Which approach is most appropriate for comparing the effectiveness of atezolizumab plus nab-paclitaxel with weekly paclitaxel and docetaxel:
  - using the network meta-analysis (NMA) – are the results reliable and clinically plausible?
  - assuming that nab-paclitaxel (given in the control arm in the clinical trial) is equivalent to weekly paclitaxel and docetaxel and using data from the trial as a proxy for the effectiveness of atezolizumab plus nab-paclitaxel compared with taxanes?
- Duration of treatment effect:
  - In the trial people were treated until progression, would treatment benefits still be seen with atezolizumab plus nab-paclitaxel after treatment has stopped, or decline after a certain period from starting treatment?
  - is it appropriate to assume a waning effect in the absence of a stopping rule e.g. stopping at 2 years even if not progressed?
- In UK clinical practice, how long are people treated with weekly paclitaxel? Is there a maximum duration of treatment/number of cycles?
- Does atezolizumab plus nab-paclitaxel fulfil the criteria to be considered a ‘life-extending treatment at the end of life’?

[redacted]

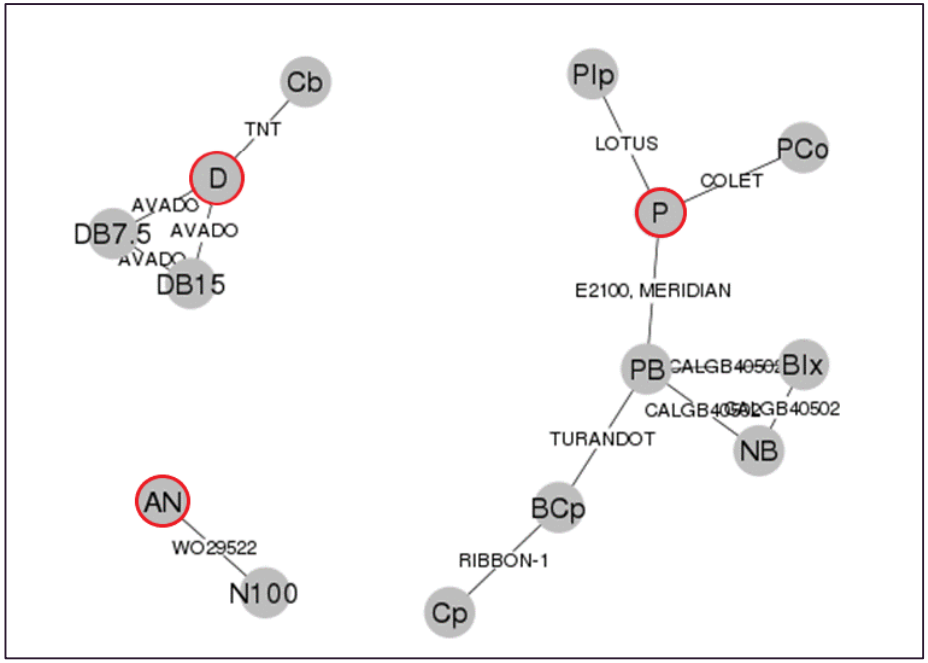
Committee decision making: CDF recommendation criteria



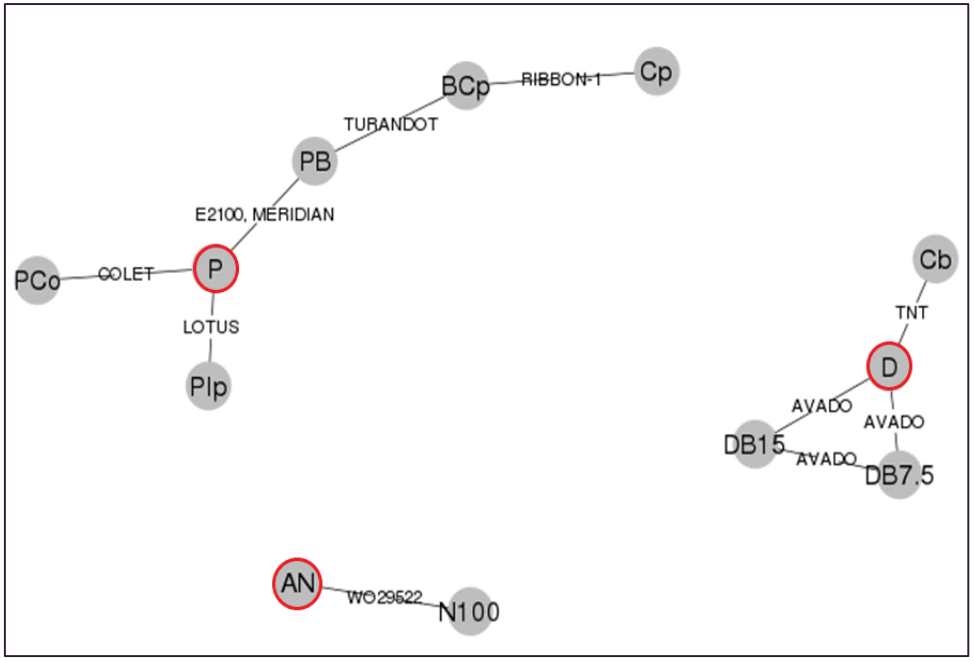
Backup slide

Issue 4: Comparison with taxanes

Network of trials for PFS



Network of trials for OS



Abbreviations in the networks:

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