

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

Technology appraisal guidance

Published: 1 July 2020

[www.nice.org.uk/guidance/ta639](https://www.nice.org.uk/guidance/ta639)

## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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# 1 Recommendations

- 1.1 Atezolizumab with nab-paclitaxel is recommended, within its marketing authorisation, for treating triple-negative, unresectable, locally advanced or metastatic breast cancer in adults whose tumours express PD-L1 at a level of 1% or more and who have not had previous chemotherapy for metastatic disease. It is recommended only if the company provides atezolizumab according to the [commercial arrangement](#).

## Why the committee made these recommendations

There are currently no targeted or immunotherapy treatments for triple-negative breast cancer. The only treatment option is chemotherapy, usually with taxane monotherapy. Atezolizumab is the first immunotherapy to be approved for PD-L1-positive, triple-negative advanced breast cancer. It is used in combination with the chemotherapy agent, nab-paclitaxel.

Clinical trial evidence shows that people having atezolizumab plus nab-paclitaxel live longer before their condition gets worse than people having placebo plus nab-paclitaxel. It also suggests that they live longer. There is no direct comparison of atezolizumab plus nab-paclitaxel with taxanes that are used in the NHS, such as weekly paclitaxel. However, it is reasonable to assume that nab-paclitaxel has a similar efficacy to weekly paclitaxel.

Atezolizumab plus nab-paclitaxel is considered to be a life-extending treatment at the end of life. The cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources. Therefore, atezolizumab with nab-paclitaxel is recommended.

## 2 Information about atezolizumab

### Marketing authorisation indication

- 2.1 Atezolizumab (Tecentriq, Roche) '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  $\geq$  1% and who have not received prior chemotherapy for metastatic disease'.

### Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics](#).

### Price

- 2.3 The list price for atezolizumab is £2,665.38 per 840 mg/14 ml vial (excluding VAT, BNF online accessed April 2020). The company has a [commercial arrangement](#), which makes atezolizumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

### 3 Committee discussion

The appraisal committee ([section 5](#)) considered evidence submitted by Roche, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the [committee papers](#) for full details of the evidence.

The appraisal committee was aware that 1 issue was resolved during the technical engagement stage, and agreed that:

- The company's assumption that patients in the progression-free and progressed disease health states have an oncology appointment at 6 months and then every 2 months underestimates health-resource use in the NHS.
- The ERG's assumption that patients in the NHS have a monthly oncology visit is more plausible and should be used for modelling health-resource use.

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, section 1.2), and took these into account in its decision making. It discussed the following issues (issues 1, 2, 3, 4, 5, 6 and 7), which were outstanding after the technical engagement stage.

## Clinical need and treatment pathway

### The burden of triple-negative advanced breast cancer is high

3.1 The patient expert explained that triple-negative advanced breast cancer is a devastating condition, and has a huge negative effect on the quality of life of patients and their families. Progression of the condition may be more aggressive than in other types of breast cancer, and the outcomes can be worse. The prognosis is extremely poor and average survival for advanced disease is 12 to 18 months. The condition often affects people of a younger age who may have young children and caring responsibilities, and who have to rely on family members and friends to take on their caring responsibilities. The patient expert emphasised that the burden of the disease on the family is high, both emotionally and financially. The committee understood these factors. It recognised both the poor prognosis and the disease burden in people with triple-negative advanced breast cancer.

## Limited treatment options are available

3.2 The clinical and patient experts explained that, unlike in hormone receptor-positive or human epidermal growth factor receptor 2 (HER2)-positive breast cancer, there are no specific targeted treatments for people with triple-negative advanced breast cancer. Currently, the only treatment option for people with triple-negative advanced breast cancer is chemotherapy, usually with a taxane. This has side effects including increased risk of infection, hair loss, sickness, nausea and fatigue. Atezolizumab is the first immunotherapy for PD-L1-positive, triple-negative breast cancer. It is also the first treatment to substantially improve outcomes for people with triple-negative breast cancer compared with taxane chemotherapy alone, so is considered to be a major breakthrough in managing the condition. The patient expert explained that the availability of a new treatment that increases progression-free survival compared with chemotherapy alone gives hope to people with the condition that they will be able to maintain a good quality life for as long as possible. The side effects of atezolizumab plus nab-paclitaxel are manageable and allow people to have a reasonably good quality of life. The patient expert also explained that atezolizumab plus nab-paclitaxel is available to some patients through the Early Access to Medicines Scheme, and that a negative recommendation would be devastating to patients and their families. The committee concluded that there is a very high unmet clinical need among people with triple-negative advanced breast cancer, and that the availability of a new immunotherapy is an important development in this condition.

## PD-L1 testing in triple-negative advanced breast cancer

### There would be no major barriers to introducing PD-L1 testing in people with triple-negative breast cancer

3.3 The marketing authorisation for atezolizumab specifies that it is indicated for the treatment of adults with unresectable, locally advanced or metastatic triple-negative breast cancer whose tumours have PD-L1 expression at a level of 1% or more and who have not had previous chemotherapy for metastatic disease. Currently PD-L1 testing is not part of routine clinical practice in triple-negative breast cancer. However, it is routinely carried out for people with other types of cancer such as non-small-cell lung cancer and urothelial carcinoma. The clinical experts and the Cancer Drugs Fund clinical lead explained that

introducing PD-L1 testing for people with triple-negative breast cancer would not be problematic, and that the currently used diagnostic tests could be used. Although additional training and resources would be needed, the testing would have a limited impact on the workflow in laboratories. The committee concluded that there would be no major barriers to introducing PD-L1 testing in people with triple-negative breast cancer.

## Appropriate comparators

### Weekly paclitaxel is the most relevant comparator

3.4 The final scope specified 2 groups of comparators: anthracycline-based chemotherapy and single-agent taxanes (docetaxel and paclitaxel). The company did not present evidence comparing atezolizumab plus nab-paclitaxel with anthracycline-based chemotherapy. It said this was because most people have anthracycline treatment for early breast cancer, and they are unlikely to be eligible for re-treatment at an advanced stage because anthracyclines have a lifetime maximum cumulative dose. The clinical experts explained that there is no standard of care in triple-negative advanced breast cancer but the most commonly used treatments are taxanes, particularly weekly paclitaxel. This is used because it has a more favourable toxicity profile than docetaxel so people are able tolerate treatment, and maintain a treatment response, for longer. The clinical experts agreed with the company that anthracycline-based chemotherapy regimens are not commonly used for advanced breast cancer. The committee concluded that weekly paclitaxel is the most relevant comparator.

### Nab-paclitaxel has similar efficacy to weekly paclitaxel and docetaxel

3.5 The clinical experts explained that nab-paclitaxel, which is the form of paclitaxel used in the trial in both the intervention and comparator arms (see [section 3.6](#)), is not routinely used in UK clinical practice. However, it is considered to be broadly equivalent to the taxanes currently in routine use and may be used when people develop hypersensitivity to the conventional formulations of paclitaxel or docetaxel. The clinical experts explained that nab-paclitaxel gives similar results compared with weekly paclitaxel, although it delivers a slightly higher dose of paclitaxel to the tissue because of its formulation. The licensing



studies for nab-paclitaxel showed no statistically significant difference in progression-free survival or overall survival between paclitaxel and nab-paclitaxel in patients having their first treatment for metastatic breast cancer. In terms of overall survival, 1 clinical expert expected there to be no difference in survival outcomes between weekly paclitaxel and nab-paclitaxel and the other expert considered that, if any difference exists at all, it would be marginal. The committee concluded that nab-paclitaxel and weekly paclitaxel have broadly similar efficacy in advanced breast cancer.

## Clinical trial evidence from IMpassion130

### The results of IMpassion130 are generalisable to UK clinical practice

3.6 IMpassion130 is a double-blind randomised clinical trial comparing atezolizumab plus nab-paclitaxel against placebo plus nab-paclitaxel in people with triple-negative advanced breast cancer who have not had previous treatment for metastatic disease. Nine treatment centres in the UK (44 patients) were included in the trial. The company presented a subgroup analysis of patients with PD-L1-positive (that is, PD-L1 expression level of 1% or more), triple-negative, advanced breast cancer. This subgroup represented 41% of the overall trial population. In the PD-L1-positive subgroup, 71% of patients had had previous treatment with anthracyclines and 21% of patients had metastatic disease at presentation. The clinical experts explained that these characteristics reflect the population who would be eligible for treatment with atezolizumab plus nab-paclitaxel in the NHS. The committee concluded that the PD-L1-positive subgroup of IMpassion130 is broadly generalisable to UK clinical practice.

### Atezolizumab plus nab-paclitaxel improves progression-free survival

3.7 The joint primary endpoints in IMpassion130 were progression-free survival and overall survival. The trial protocol specified that formal testing of statistical significance in the PD-L1-positive population could only occur if statistical significance was shown in the intention-to-treat population. For progression-free survival, at the first data cut in April 2018 (the definitive progression-free survival analysis), there was a statistically significant improvement with

atezolizumab plus nab-paclitaxel in both the intention-to-treat and the PD-L1-positive population. Median progression-free survival in the PD-L1-positive subgroup was 7.5 months in the atezolizumab plus nab-paclitaxel arm and 5.0 months in the placebo plus nab-paclitaxel arm (hazard ratio 0.62, 95% confidence interval 0.49 to 0.78). The committee concluded that atezolizumab plus nab-paclitaxel improves progression-free survival compared with placebo plus nab-paclitaxel.

## The evidence suggests that atezolizumab plus nab-paclitaxel increases overall survival in the PD-L1-positive subgroup

3.8 In the intention-to-treat population, the results for overall survival in the first interim analysis were not statistically significant, and formal testing of overall survival in the PD-L1-positive subgroup according to the trial protocol was not possible (see [section 3.7](#)). The company presented an informal analysis of overall survival in the PD-L1-positive subgroup. The median overall survival was 25.0 months compared with 15.5 months in the placebo plus nab-paclitaxel population (hazard ratio 0.62, 95% confidence interval 0.45 to 0.86). The company explained that the final analysis for overall survival is expected in 2020. However, because the data are already relatively mature, the company does not expect that this will substantially reduce the clinical uncertainty. The committee concluded that the data suggest that atezolizumab plus nab-paclitaxel increases overall survival in patients with triple-negative advanced breast cancer. However, it noted that the results were not from a formal analysis.

## Indirect comparison with taxanes

### The company's network meta-analysis is not reliable and lacks face validity

3.9 In the absence of a head-to-head trial comparing atezolizumab plus nab-paclitaxel against weekly paclitaxel or docetaxel, the company presented a type of network meta-analysis (NMA) known as a population-adjusted indirect comparison. This method is used to link studies in unconnected networks. There were 7 trials in the overall-survival analysis and 8 in the progression-free survival analysis. The committee heard from the ERG that the methods used in the NMA were broadly appropriate. However, the ERG had concerns about the

approach used to estimate the survival times, and the assumption that the results from patients with unknown PD-L1 disease status were generalisable to the subgroup with PD-L1-positive disease. It was also concerned about the limited data on baseline characteristics on which the matching of studies could be based. Also, the results of the NMA were associated with high uncertainty because the credible intervals around the point estimates of the hazard ratios were very wide. The ERG advised that the results should be interpreted with caution. This made it difficult for the committee to assess whether the effectiveness of the treatments is different. It discussed the methodology used in the NMA and the steps taken to adjust for heterogeneity in patient characteristics among the trials. It heard that the company adjusted for a number of variables including age, Eastern Cooperative Oncology Group (ECOG) status, previous taxane use, the time from initial diagnosis to metastatic disease and the proportion of patients with metastases in the liver, other viscera or bone. The clinical experts confirmed that these are key characteristics that determine treatment response in this patient population. However, the trials did not all report the same patient characteristics and therefore different variables were adjusted in each study. The proportion of de novo metastases is also an important determinant of response to further treatments and prognosis, but this was not included in the NMA. The committee heard from the company that, in order to connect trials together in the NMA, they created virtual trials using observational data-analysis techniques in which patients in one study were propensity-score matched to patients in another study. The committee noted the importance of having the relevant data on patient characteristics in order for the match to be appropriate and the resulting 'virtual study' to be unbiased. The committee discussed the face validity of the NMA results. The NMA predicted higher overall survival for docetaxel and paclitaxel compared with nab-paclitaxel in the first 5 months and then higher overall survival for nab-paclitaxel after 5 months. The clinical experts confirmed that paclitaxel and nab-paclitaxel are very similar, therefore such differences are unlikely. Using the results of the NMA, the cost-effectiveness model predicted much larger differences in overall survival between nab-paclitaxel and paclitaxel than those expected by the clinical experts. Also, using the results of the NMA, the cost-effectiveness model predicted better overall survival with docetaxel than with paclitaxel, which is contrary to the expectations of the clinical experts. The committee appreciated that the company's NMA incorporated the very limited evidence available to estimate the relative effectiveness of the treatments. However, it thought that there was considerable heterogeneity among the trials

that may not have been appropriately taken into account, given the limitations of the data. It also noted the poor face validity of the results. For these reasons, the committee concluded that there was great uncertainty in the NMA, and that the results were not robust and lacked face validity.

## Cost effectiveness

### Data from the nab-paclitaxel arm of IMpassion130 are appropriate for modelling the effectiveness of weekly paclitaxel

3.10 The company submitted a 3-state partitioned survival model to estimate the cost effectiveness of atezolizumab plus nab-paclitaxel compared against weekly paclitaxel or docetaxel. The approach used to model the relative effectiveness of these treatments was a key driver of the model results. The company used the results of its NMA to model the differences in effectiveness. However, because of the limitations of the NMA and the high uncertainty in the results (see [section 3.9](#)), the ERG did not consider the results of the NMA to be robust enough to use in the economic model. Because there was no clear evidence of a difference between nab-paclitaxel, paclitaxel and docetaxel in terms of overall survival and progression-free survival, the ERG presented the results of a scenario analysis that assumed equal effectiveness between these treatments. It used data from the placebo plus nab-paclitaxel arm of IMpassion130 as a proxy for the effectiveness of other taxane regimens. The committee considered which approach was more appropriate. It recalled its previous conclusions that the results of the NMA were not reliable and lacked face validity (see [section 3.9](#)), and the feedback from clinical experts that nab-paclitaxel and weekly paclitaxel have broadly similar efficacy (see [section 3.5](#)). The company argued that this assumption was overly conservative and oversimplified the evidence. It also highlighted that using the NMA predicted a 0.197-year difference in life years between nab-paclitaxel and paclitaxel (which it believed to be a marginal difference) but has a big impact on the incremental cost-effectiveness ratio (ICER). The committee did not consider that the 10.27-week life year gain predicted by the model was a trivial difference. It accepted that using data from the placebo plus nab-paclitaxel arm of IMpassion130 as a proxy for the effectiveness of weekly paclitaxel was not a perfect approach. However, it considered a randomised, unbiased and contemporaneous comparison to be more reliable than the NMA, which was based on heterogenous and historical trial populations and associated with high

uncertainty. The committee therefore concluded that the ERG's approach, using the control arm of IMpassion130 as a proxy for the effectiveness of weekly paclitaxel, was preferable.

## Treatment-effect duration

### Assuming a treatment waning effect is not appropriate

3.11 In IMpassion130, treatment was continued until disease progression or unacceptable toxicity. The median treatment duration was 26.4 weeks in the atezolizumab arm and 16.1 weeks in the placebo arm. The company assumed that a treatment benefit would be maintained for a lifetime horizon (assumed to be 15 years). The ERG considered that this assumption was implausible. It presented a scenario analysis in which it limited the treatment effect to 3 or 5 years from the start of treatment. However, the ERG acknowledged that there was a lack of evidence on the long-term treatment effect and these were arbitrary time points. The company explained that applying a 3-year treatment benefit cap meant that patients still on treatment at 3 years (6% in the clinical trial) would experience no further benefit, which it did not consider to be clinically plausible. The committee noted that, in previous NICE appraisals in which a treatment duration cap was considered, a treatment stopping rule was applied in the analyses. However, the marketing authorisation for atezolizumab recommends that treatment should be continued until disease progression or unacceptable toxicity. The committee acknowledged that 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.

## Treatment duration with paclitaxel

### Data on time to stopping treatment from the control arm of IMpassion130 may be more relevant for decision making

3.12 The company submitted additional evidence during technical engagement. This was because it considered that it had misinterpreted how weekly paclitaxel is administered in the NHS and had incorrectly assumed a maximum of 18 weeks or cycles of treatment. In its updated base-case model, it removed this treatment cap and assumed that patients have paclitaxel until disease

progression. This reduced the ICER. The ERG commented that it had been given clinical advice suggesting that treatment beyond 6 months is unusual and that it does not exceed 10 months. Applying a 10-month treatment cap in the model also decreased the ICER but had a more modest effect than the company's scenario. The clinical experts explained that there is variation in the duration of paclitaxel treatment in the NHS. In the past, it was common for treatment to continue for a fixed period. But now, patients are more likely to have paclitaxel until disease progression or unacceptable toxicity. They explained that, to extend the treatment period, side effects are often managed by dose reductions and dose 'holidays', so assuming full dosage for all patients until disease progression was not realistic. However, the committee also heard from the clinical experts that assuming an 18-cycle cut-off point would be arbitrary and not supported by evidence. Their experience is that most chemotherapies stop working after 10 months. However, because there are no effective alternative treatments in this condition, it is common practice to continue treatment until there is evidence of no further benefit. The committee accepted that an 18-cycle treatment cap does not reflect clinical practice in the NHS. However, it considered that the company's revised analysis, which assumed all patients on paclitaxel would have it at the full dose until disease progression, was not reliable because it did not account for dose reductions, or for variation in practice in the NHS. The committee concluded that the company's updated analysis overestimated average treatment duration with weekly paclitaxel and the associated costs. It suggested that, in the absence of robust real-world evidence, the treatment duration of weekly paclitaxel may have best been informed by the treatment duration in the nab-paclitaxel control arm of IMpassion130 (see [section 3.10](#)). The committee concluded that average treatment duration with weekly paclitaxel was uncertain and would have best been informed by data on time to stopping treatment from the control arm of IMpassion130.

## Cost-effectiveness estimate

### The company's updated commercial arrangement reduced the ICER

- 3.13 Following consultation, the company updated its commercial arrangement and submitted an updated analysis that incorporated the committee's preferred assumptions (see [section 3.10](#) and [section 3.12](#)). The ICER is not reported here

to protect the confidentiality of the commercial arrangement. The committee noted that the commercial arrangement reduces the ICER for atezolizumab plus nab-paclitaxel compared with weekly paclitaxel. However, it remains above the range normally considered cost effective (that is, £20,000 to £30,000 per quality-adjusted life year [QALY] gained) for technologies that are not given special consideration as life-extending treatments for people with a short life expectancy.

## End of life

### End-of-life criteria are met

- 3.14 The committee considered the advice about life-extending treatments for people with a short life expectancy in [NICE's guide to the methods of technology appraisal](#). It considered that all scenario analyses presented by the company and the ERG indicated 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. Therefore, it concluded that atezolizumab plus nab-paclitaxel fulfils the end-of-life criteria.

## Other factors

- 3.15 The company and clinical experts considered atezolizumab plus nab-paclitaxel to be innovative, and a major breakthrough in managing triple-negative breast cancer. It is the first treatment to substantially improve outcomes compared with chemotherapy in this population. However, the committee considered that all relevant benefits associated with the drug were adequately captured in the model.

## Conclusion

### Atezolizumab plus nab-paclitaxel is recommended for PD-L1-positive, triple-negative advanced breast cancer

- 3.16 Clinical trial evidence has shown that atezolizumab plus nab-paclitaxel increases progression-free survival and suggests it could increase overall survival compared with placebo plus nab-paclitaxel. When the updated commercial offer and the greater weight assigned to QALYs at the end of life are

taken into account, the ICER is acceptable. Therefore, atezolizumab plus nab-paclitaxel is recommended for PD-L1-positive, triple-negative advanced breast cancer.



## 4 Implementation

- 4.1 [Section 7\(6\) of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 [Chapter 2 of Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – a new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The [NHS England and NHS Improvement Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that if a patient has triple-negative, unresectable, locally advanced or metastatic breast cancer with tumour PD-L1 expression of 1% or more and no previous chemotherapy for metastatic disease, and the doctor responsible for their care thinks that atezolizumab with nab-paclitaxel is the right treatment, it should be available for use, in line with NICE's recommendations.

## 5 Appraisal committee members and NICE project team

### Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee A](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), technical advisers and a project manager.

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ISBN: 978-1-4731-3798-1

## Accreditation

