# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Final appraisal document

# Durvalumab for treating locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation

## 1 Recommendations

1.1 Durvalumab monotherapy is recommended for use within the Cancer Drugs Fund as an option for treating locally advanced unresectable non-small-cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on at least 1% of tumour cells and whose disease has not progressed after platinum-based chemoradiation only if:

- they have had concurrent platinum-based chemoradiation
- the conditions in the managed access agreement are followed.

1.2 This recommendation is not intended to affect treatment with durvalumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

### Why the committee made these recommendations

Locally advanced NSCLC that is unresectable is usually treated with platinum-based chemoradiation. After this there are no treatment options to delay or stop the disease progressing. Durvalumab is a possible treatment at this stage.



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The main evidence for durvalumab comes from a clinical trial (PACIFIC). This suggests that durvalumab is more effective than standard care in delaying disease progression after concurrent platinum-based chemoradiation (chemotherapy and radiation at the same time). But PACIFIC is ongoing, so there is not yet enough evidence about:

- how long the treatment effect of durvalumab lasts
- how many people taking durvalumab would live without their disease progressing.

Durvalumab has the potential to be cost effective compared with standard care, but more evidence from the ongoing trial is needed to address the uncertainties. Therefore, it is recommended for use in the Cancer Drugs Fund.

# 2 Information about durvalumab

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| **Marketing authorisation indication** | Durvalumab (Imfinzi, AstraZeneca) 'as monotherapy is indicated for the treatment of locally advanced, unresectable non-small-cell lung cancer in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation'. |
| **Dosage in the marketing authorisation** | 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks, until disease progression or unacceptable toxicity or a maximum of 12 months.<br>Continue treatment for patients who are clinically stable with initial evidence of disease progression until disease progression is confirmed.<br>Dose escalation or reduction is not recommended. Dose withholding or discontinuation may be needed based on individual safety and tolerability.<br>In the PACIFIC trial a small number of patients had retreatment with durvalumab if their disease progressed after 12 months of therapy. However, durvalumab does not have a marketing authorisation for treating progressed disease. Therefore its use for retreatment is off-label and is not covered by this guidance. |
| **Price** | £592.00 per 120 mg/2.4 ml vial, £2,466.00 per 500 mg/10 ml vial (British national formulary online, accessed February 2019).<br>The company has a commercial arrangement (managed access agreement including a commercial access agreement). This makes durvalumab 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 6) considered evidence submitted by AstraZeneca, 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 several issues were resolved during technical engagement, and agreed with the conclusions that:

- Standard care (which involves surveillance every 6 months for 2 years, and a volume chest CT scan at least every year) was the appropriate comparator for this appraisal.
- A generalised gamma extrapolation of progression-free survival in the standard care arm was acceptable although some uncertainty remains (issue 3, see technical report pages 11 to 18).
- An exponential extrapolation of post-progression survival for both treatment arms is clinically plausible (see technical report table 2, pages 29 to 30).
- Age-related utility decrements should be captured in the model (issue 4, see technical report pages 18 to 21).
- It was appropriate to model the distribution and costs of subsequent treatments in line with the PACIFIC trial (see technical report table 3, pages 31 and 32).
- Assuming vial sharing for durvalumab was not realistic (see technical report table 3, page 31).

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 2, pages 28 to 30), and took these into account in its decision making. It discussed the following issues, which were outstanding after technical engagement.

## *Clinical need*

### There is an unmet need for treatment options in this disease area

3.1 Locally advanced unresectable non-small-cell lung cancer (NSCLC) is a highly heterogeneous disease with complex symptoms. Durvalumab is indicated for use in people whose tumours express PD-L1 on at least 1% of tumour cells and whose disease has not progressed after chemoradiation. At this stage, durvalumab has the potential to be curative. The patient expert explained that locally advanced unresectable NSCLC is a distressing condition, and that treatment options were limited. They noted that patients and their carers would welcome new treatments that

improve symptoms and survival without negatively affecting quality of life. The clinical experts advised that people who cannot have surgery would have chemoradiation, and that durvalumab would be used to consolidate any effects of this. Currently there are no other treatment options for people whose disease has not progressed after chemoradiation. The committee accepted that there is an unmet need for treatment options for locally advanced unresectable NSCLC.

## *Clinical evidence*

### The evidence from PACIFIC is not generalisable to patients who have had sequential chemoradiation

3.2 The main clinical evidence came from a subgroup of patients in an ongoing randomised controlled trial (PACIFIC). PACIFIC compared the efficacy and safety of durvalumab with standard care in patients with locally advanced unresectable stage III NSCLC whose disease had not progressed after at least 2 cycles of concurrent platinum-based chemoradiation. Regulatory approval was granted for durvalumab to be used for a subgroup of patients whose tumours express PD-L1 on at least 1% of tumour cells. The inclusion criteria for PACIFIC limited the trial population to people who had had concurrent chemoradiation, and explicitly excluded people who had had sequential chemoradiation. The committee was aware that most patients in NHS clinical practice have sequential chemoradiation. The clinical experts explained that the population who have concurrent chemoradiation may be in better health than the population who have sequential chemoradiation. They also highlighted evidence that concurrent chemoradiation may produce better outcomes than sequential chemoradiation, and that adverse effects may differ between the groups. The committee considered that it had not seen any evidence of the efficacy or safety of durvalumab in the population who had had sequential chemoradiation. It concluded that evidence from the PACIFIC subgroup was not generalisable to a population who would have sequential chemoradiation.

### Progression-free survival in the placebo arm of PACIFIC is shorter than in the placebo arms of other trials for this condition

3.3 Median progression-free survival in the placebo arm of the PACIFIC subgroup was 5.6 months. The committee noted that this was substantially shorter than the median progression-free survival seen in the placebo arms of other trials in patients who have had concurrent chemoradiation. For example, median progression-free survival in the placebo arm of the RTOG-0617 trial of cetuximab was 10.7 months and in the placebo arm of the START trial of tecemotide was 11.4 months. The clinical experts confirmed that the progression-free survival in the placebo arm was lower than they would expect to see in clinical practice. The company explained that in these trials progression-free survival was measured from the start of chemoradiation, whereas in PACIFIC it was measured from the point of randomisation. The committee accepted this but considered that these differences did not fully explain the comparatively lower progression-free survival in the PACIFIC placebo arm. The committee considered that this might benefit the comparative effectiveness results in the durvalumab arm. The committee questioned whether the lower progression-free survival in the placebo arm of PACIFIC affected the generalisability of the evidence. The clinical experts explained that although progression-free survival was lower, overall survival was representative of survival in clinical practice. Based on the clinical expert advice, the committee concluded that the evidence from the PACIFIC subgroup was broadly generalisable to the population whose tumours express PD-L1 on at least 1% of tumour cells and whose disease has not progressed after at least 2 cycles of concurrent platinum-based chemoradiation.

### Durvalumab lengthens progression-free and overall survival compared with standard care but the size of the benefit in the long term is unclear

3.4 Progression-free survival was statistically significantly longer with durvalumab than with standard care in people with locally advanced unresectable stage III NSCLC whose disease had not progressed after at

least 2 cycles of concurrent platinum-based chemoradiation. At the latest data cut, median progression-free survival was 23.9 months in the durvalumab arm and 5.6 months in the standard care arm. The hazard ratio was 0.44 (95% confidence interval [CI] 0.31 to 0.63). Durvalumab also lengthened overall survival compared with standard care, producing a hazard ratio of 0.54 (95% CI 0.35 to 0.81). The committee was aware that evidence from PACIFIC was immature and that further data collection is planned, with final analyses expected in 2021. It considered that the immaturity of the data introduced substantial uncertainty because durvalumab's benefits are likely to build up over time (for example, through delaying disease progression). Based on the PACIFIC evidence, the committee concluded that durvalumab probably lengthens survival in people with locally advanced unresectable stage III NSCLC whose tumours express PD-L1 on at least 1% of tumour cells and whose disease has not progressed after at least 2 cycles of concurrent platinum-based chemoradiation.

## *Modelling of progression-free survival*

### A long-term treatment effect of durvalumab after stopping treatment is plausible but its duration is uncertain

3.5 The company's base case (updated after technical engagement) assumed a treatment effect duration of 5 years after starting treatment. The committee considered that because durvalumab is potentially curative a long-term treatment effect could be plausible. The clinical experts advised that duration of treatment effect was uncertain because the data are immature, but that experience with other immunotherapies showed that a 5-year duration of treatment effect was plausible. The committee recalled that in previous appraisals of immunotherapies for locally advanced or metastatic NSCLC, the preferred treatment effect duration was 3 to 5 years. However, the committee was aware that these appraisals were for advanced metastatic disease and typically featured a 2-year stopping rule, whereas durvalumab's marketing authorisation specified a 1-year

stopping rule. Because of this, the committee considered that the treatment effect duration for durvalumab may even be lower than assumed for other immunotherapies in previous appraisals. The committee, taking into account the clinical expert opinion, considered that assuming a 3 to 5-year treatment effect duration is plausible but concluded that durvalumab's long-term treatment effect after stopping treatment was highly uncertain.

**More mature data on progression-free survival are needed to inform long-term model predictions**

3.6 In its base case, the company used a generalised gamma extrapolation of progression-free survival in the durvalumab arm. This extrapolation predicted that 46%, 40% and 26% of patients would not have progressed disease at 3, 5 and 10 years respectively. The company explored cure rate models in scenario analyses (based on the assumption that an underlying proportion of patients are cured after treatment, or that patients who do not have progressed disease after 5 or 10 years are considered cured). Clinical experts advised the committee that durvalumab was a potentially curative treatment. They explained that with standard care, they would consider people who were not having treatment and did not have progressed disease at 5 years to have a low risk of future progression. However, they highlighted that in some patients, durvalumab might delay disease progression rather than curing the disease. Because of this, they could not be certain about the risk of future progression in people who had had durvalumab and whose disease had not progressed at 5 years. The ERG advised that cure rate models need mature data to model survival robustly. The committee agreed that the PACIFIC data were too immature for a cure model to be robust. It also considered that there was uncertainty in all extrapolations because of the immaturity of the data and the small number of patients at the end of the Kaplan–Meier curve. Based on statistical assessment of fit and external validity, the ERG preferred a log-normal extrapolation. The log-normal extrapolation predicted that 38%, 27% and 17% of patients would not have progressed

disease at 3, 5 and 10 years respectively. The committee noted that the predictions from the generalised gamma extrapolation were slightly higher than those from clinical expert opinion in the company's response to technical engagement. The clinical experts advised that both the generalised gamma and log-normal extrapolations could be plausible, but that the log-normal appeared to be a better fit based on their clinical opinion. The committee considered that there was substantial uncertainty about durvalumab's effect on progression-free survival in the long term (see section 3.4). The committee concluded that it preferred the log-normal extrapolation based on the clinical expert and ERG advice. However, because there were no long-term trial data it accepted a scenario analysis using the generalised gamma extrapolation.

**It is acceptable to prevent the risk of progression in the durvalumab arm from exceeding the risk in the standard care arm**

3.7 The committee was aware that with some progression-free survival extrapolations, varying the treatment effect duration in the model led to results that would not be expected (that is, a shorter treatment effect duration improved cost effectiveness). In response to technical engagement, the company proposed capping the underlying hazard functions of the distributions. This prevented the risk of progression in the durvalumab arm exceeding the risk of progression in the standard care arm. The ERG considered that this adjustment adequately addressed the unexpected results and included the adjustment in its preferred assumptions. The company highlighted that with a log-normal progression-free survival extrapolation of durvalumab and a generalised gamma extrapolation of standard care, the hazard cap would limit the modelled treatment effect duration to 39 months. The committee considered that this duration fell within the 3 to 5-year range it had accepted in previous appraisals (see section 3.5). The committee concluded that it was acceptable to apply the hazard cap to prevent the risk of progression in the durvalumab arm exceeding the risk in the

standard care arm when using the log-normal and generalised gamma distributions.

### *Utility values*

**It is acceptable to use utility values from PACIFIC for the progression-free and progressed disease health states**

3.8 In its base case, the company derived health state utility values from health questionnaire (EQ-5D-5L) data collected in PACIFIC (mapping these to EQ-5D-3L values in line with NICE's position statement on the use of the EQ-5D-5L valuation set). The company modelled progressed disease using a utility value of 0.67, derived from a study by Chouaid et al. (2013). The committee noted that the utility value for the progression-free health state (0.81) was slightly higher than the utility value for the general population (0.80 for people aged 55 to 64). The clinical experts explained that the PACIFIC trial population was likely to include patients who are in better health, and that in stage III disease it was realistic that the utility value could be similar to the general population (although not higher). The committee concluded that it was acceptable to use the utility value from PACIFIC for the progression-free health state. For consistency in the economic model, the committee considered that it was appropriate to also use the utility value from PACIFIC for the progressed disease health state (noting that this did not have a large effect on the decision-making incremental cost-effectiveness ratios [ICERs]).

**It is appropriate to model adverse events using a treatment-related decrement, but this decrement would not apply indefinitely**

3.9 In its report, the ERG noted that the incidence of adverse events in PACIFIC differed between treatment arms. One of the ERG's preferred assumptions was to apply a treatment-related decrement to the utility value (calculated by including treatment as a covariate in the mixed-effects model of the EQ-5D data). In response to technical engagement, the company updated its base case to apply a treatment-related

decrement. The committee considered that this was an appropriate method for capturing adverse events. However, it considered that it was unlikely that health state utility values would differ between treatment arms in the long term. It concluded that it was appropriate to model adverse events using a treatment-related decrement, but this decrement would not apply indefinitely.

## *Cost-effectiveness estimate*

**The most plausible ICERs for durvalumab are uncertain and not clearly within the range considered to be a cost-effective use of NHS resources**

3.10 The committee recalled its preferred modelling assumptions:

- Treatment effect duration of 3 to 5 years (see section 3.5).
- Log-normal extrapolation of progression-free survival in the durvalumab arm and a scenario using the generalised gamma extrapolation (see section 3.6).
- Generalised gamma extrapolation of progression-free survival in the standard care arm (an issue that was resolved during technical engagement).
- Cap on hazards so that the risk of progression in the durvalumab arm does not exceed the risk of progression in the standard care arm (see section 3.7).
- Trial-based utility values with a treatment-related decrement and age-related decrement applied (see sections 3.8 and 3.9).

Using the log-normal extrapolation of progression-free survival in the durvalumab arm, the ICER (recalculated by the ERG to include the confidential commercial arrangements for durvalumab and the subsequent treatments) was higher than £30,000 per quality-adjusted life year (QALY) gained. Using the generalised gamma extrapolation, the ICER was below £30,000 per QALY gained.

## *End of life*

**Durvalumab does not meet the short life expectancy criterion, and therefore does not meet the end-of-life criteria**

3.11 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. Based on evidence from PACIFIC and predictions from the economic model (using its preferred assumptions), the committee concluded that durvalumab was likely to extend life by over 3 months and therefore met the extension-to-life criterion. The company presented evidence from real world data sources, indicating that median overall survival in the population was less than 24 months. The committee noted that it had not been presented with mean overall survival for these studies, which it considered to be relevant because of the proportion of patients predicted to be progression-free after 10 years. It also noted that the PACIFIC data did not show that life expectancy in the population was less than 24 months. The mean and median overall survival predicted by the economic model (using the committee's preferred assumptions) was higher than 24 months. The committee considered that it had accepted data from PACIFIC to inform its decisions throughout the appraisal, and that it was appropriate to base its decision on life expectancy on the trial data. The committee concluded that durvalumab did not meet the short life expectancy criterion, and therefore did not meet the end-of-life criteria.

## *Other factors*

3.12 No relevant equality issues were identified.

3.13 Durvalumab may be innovative. However, all relevant benefits of the technology are captured in the QALY.

## *Conclusion*

### Durvalumab is not recommended for routine use in the NHS

3.14 The committee recognised that there was a high level of uncertainty in the clinical evidence supporting the appraisal. Because of this, it was unable to conclude that the most plausible ICER fell within range usually considered to be a cost-effective use of NHS resources. Also, durvalumab does not meet NICE's end-of-life criteria. Because of this, the committee concluded that durvalumab could not be recommended for routine use based on what NICE normally considers an acceptable use of NHS resources.

### Durvalumab is recommended for use in the Cancer Drugs Fund

3.15 Having concluded that durvalumab could not be recommended for routine use, the committee then considered if it could be recommended for treating locally advanced unresectable NSCLC (in adults whose tumours express PD-L1 on at least 1% of tumour cells and whose disease has not progressed after concurrent platinum-based chemoradiation) within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The committee was aware that the company had expressed an interest in durvalumab being considered for funding through the Cancer Drugs Fund. It was also aware that PACIFIC was ongoing, and that more data would be available. It agreed that:

- Further data on progression-free survival and overall survival would inform decisions about whether treatment with durvalumab improves cure rates in the disease.
- Further data on progression-free survival would likely reduce uncertainty about the treatment effect duration.
- Further data on progression-free survival would inform the choice of progression-free survival extrapolation.

The committee recalled its conclusion that the current cost-effectiveness results were very uncertain, but some scenarios were within the range considered a cost-effective use of NHS resources. It agreed that with longer follow-up data from PACIFIC on progression-free survival, durvalumab has the potential to be cost effective. The committee concluded that durvalumab met the criteria to be considered for inclusion in the Cancer Drugs Fund. It recommended durvalumab for use within the Cancer Drugs Fund as an option for adults with locally advanced unresectable NSCLC whose tumours express PD-L1 on at least 1% of tumour cells and whose disease has not progressed after concurrent platinum-based chemoradiation, if the conditions in the managed access agreement are followed.

# 4 Implementation

4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has locally advanced unresectable non-small-cell lung cancer that expresses PD-L1 on at least 1% of tumour cells and the disease has not progressed after concurrent platinum-based chemoradiation, and the doctor responsible for their care thinks that durvalumab is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it

within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

# 5 Review of guidance

5.1 The data collection period is expected to end in September 2021, when the final analyses from PACIFIC are expected to be available. The process for exiting the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start.

5.2 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the standard timelines described in NICE's Cancer Drugs Fund methods guide (addendum).

Gary McVeigh
Chair, appraisal committee
March 2019

# 6 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 D.

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), a technical adviser and a project manager.

**Lucy Beggs**
Technical lead

**Victoria Kelly**
Technical adviser

**Gemma Barnacle**
Project manager

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