NICE National Institute for Health and Care Excellence

NICE guidance

Durvalumab for maintenance treatment of unresectable non-small-cell lung cancer after platinum-based chemoradiation

Technology appraisal guidance
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www.nice.org.uk/guidance/ta798

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 is 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.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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.

Contents

This guidance replaces TA578.

1 Recommendations

1.1 Durvalumab is recommended as an option for treating locally advanced unresectable non-small-cell lung cancer (NSCLC) in adults whose tumours express programmed cell death ligand 1 (PD-L1) on 1% or more of cells and whose disease has not progressed after platinum-based chemoradiation, only if:

- they have had concurrent platinum-based chemoradiation
- the company provides durvalumab according to the commercial arrangement.

Why the committee made these recommendations

This appraisal reviews the additional evidence collected as part of the Cancer Drugs Fund managed access agreement for durvalumab for treating locally advanced unresectable NSCLC in adults whose tumours express PD-L1 on 1% or more of cells and whose disease has not progressed following platinum-based chemoradiation (NICE technology appraisal guidance 578).

The new evidence includes longer term data from the PACIFIC clinical trial and from people having treatment in the NHS while this treatment was available in the Cancer Drugs Fund. It shows that people having durvalumab live longer than those who have standard care, defined as routine surveillance and an annual CT scan.

While a different modelling approach would have been preferred, the cost-effectiveness estimates for durvalumab were considered sufficiently plausible. They are within what NICE considers to be an acceptable use of NHS resources. So, durvalumab is recommended.

2 Information about durvalumab

Marketing authorisation indication

2.1 Durvalumab (Imfinzi, AstraZeneca) is 'indicated for the treatment of locally advanced, unresectable non-small-cell lung cancer (NSCLC) in adults whose tumours express programmed cell death ligand 1 (PD-L1) on 1% or more of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for durvalumab.

Price

2.3 Ths list price of durvalumab is £2,466 per 500 mg per 10-ml infusion vial (excluding VAT; BNF online, accessed April 2022).

2.4 The company has a commercial arrangement. 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 considered evidence submitted by AstraZeneca, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

This review looks at data collected in the Cancer Drugs Fund to address uncertainties identified during the original appraisal of durvalumab. Further information about the original appraisal is in the committee papers. As a condition of the Cancer Drugs Fund funding and the managed access arrangement, the company was required to collect updated efficacy data from the PACIFIC trial, comprising progression-free survival, overall survival and subsequent treatments. In addition, data was collected on durvalumab in the NHS through the Cancer Drugs Fund using the Systemic Anti-Cancer Therapy (SACT) dataset.

The appraisal committee recognised that there were remaining areas of uncertainty associated with the analyses presented (see the ERG report, pages 10 and 11). It discussed the following issues, and took them into account in its decision making:

- the generalisability of the PACIFIC trial to clinical practice, in terms of programmed cell death ligand 1 (PD-L1) status and dosing regimen
- the model structure used by the company
- the progression-free survival extrapolations in the durvalumab arm and their effect on modelled overall survival
- the duration of treatment effect for durvalumab
- subsequent treatments taken after durvalumab.

Clinical need

Durvalumab is a valued treatment option for people with locally advanced unresectable NSCLC

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 platinum-based chemoradiation. In the original appraisal, the committee agreed that these people would otherwise have standard care, and that this was the appropriate comparator. Standard care involves surveillance every 6 months for 2 years, and a volume chest CT scan at least every year. The committee was aware that locally advanced unresectable NSCLC is a distressing condition, and that treatment options are limited. It noted that people with unresectable NSCLC and their carers welcome treatments that improve symptoms and survival without negatively affecting quality of life. People having durvalumab value the survival benefit in a setting where overall survival is otherwise still low despite advances in chemotherapy and radiotherapy. The clinical experts advised that since its introduction in the Cancer Drugs Fund durvalumab has become standard care in this setting and has led to more people having concurrent chemoradiation when it is considered suitable. The committee considered that durvalumab is a valued treatment option among people with NSCLC and the clinicians who manage the condition.

Clinical evidence

Durvalumab lengthens progression-free survival and overall survival compared with standard care

3.2 The main clinical evidence for durvalumab came from a subgroup of people in an ongoing randomised controlled trial (PACIFIC). PACIFIC compared the efficacy and safety of durvalumab with standard care (placebo) in people with locally advanced unresectable NSCLC who had had at least 2 cycles of concurrent chemoradiation therapy. A cohort of people in PACIFIC whose cancers expressed

PD-L1 on 1% or more of tumour cells provided the evidence for this appraisal. Progression-free survival was statistically significantly longer in the durvalumab arm than the standard care arm. At the 5-year data cut, median progression-free survival was 24.9 months in the durvalumab arm and 5.5 months in the standard care arm. The hazard ratio was 0.47 (95% confidence interval [CI] 0.35 to 0.64). Durvalumab also lengthened overall survival compared with standard care in PACIFIC. Median overall survival in the durvalumab arm was 63.1 months while in the standard care arm it was 29.6 months. The hazard ratio for overall survival was 0.61 (95% CI 0.44 to 0.85). The data from the SACT dataset, which was collected while durvalumab was available on the Cancer Drugs Fund, supported the generalisability of the PACIFIC trial data to NHS practice. The overall survival rates from the SACT PD-L1 of 1% or more cohort (n=522) at 12 and 24 months were comparable to those in PACIFIC. The committee concluded that, for those people whose tumours express PD-L1 on 1% or more of cells, durvalumab lengthens progression-free and overall survival compared with standard care.

The PACIFIC trial is only generalisable to people who have had concurrent chemoradiation

3.3 The marketing authorisation for durvalumab is for people whose cancer has not progressed after platinum-based chemoradiation. There are 2 main types of chemoradiation, sequential and concurrent. The PACIFIC trial (see section 3.2) only recruited people who had 2 or more cycles of concurrent platinum-based chemoradiation, and explicitly excluded people who had had sequential chemoradiation. In the original appraisal, clinical experts explained that people who have concurrent chemoradiation may be in better health than those having sequential chemoradiation. Concurrent chemoradiation may also produce better outcomes than sequential chemoradiation. The original appraisal committee considered that, because the PACIFIC trial was not generalisable to those who had had sequential chemoradiation, the appraisal would be optimised to only those having had concurrent chemoradiation. The population in the company's submission for the current appraisal reflected this.

The PACIFIC trial is generalisable to NHS practice, despite some uncertainty around people whose tumours have unknown PD-L1

status

3.4 In the Cancer Drugs Fund, people could have durvalumab if their tumour PD-L1 status could not be determined despite a clear intent and reasonable attempt to do so. The clinical experts stated that it was not always possible to do lung cancer biopsies, either because the tumour is not accessible or there is not enough sample tissue available. This can lead to an inability to determine PD-L1 status. The company anticipated that the option of offering durvalumab to people whose tumours were PD-L1 unknown is likely to continue if durvalumab is recommended for routine commissioning. In the SACT cohort, 12% of people who had durvalumab had an unknown tumour PD-L1 status. The ERG explained that this population would have included some people whose tumours express PD-L1 on less than 1% of tumour cells (were PD-L1 negative). Because durvalumab is less efficacious in these people, there may be a reduction in the overall efficacy of durvalumab in clinical practice compared with the trial. This was because the PACIFIC cohort of interest (see section 3.2) did not include people whose tumour PD-L1 status was unknown. The clinical experts explained that the 12% PD-L1 unknown figure was slightly higher than their clinical experience but that it was plausible. A clinical expert also noted that, within the population whose tumours are PD-L1 unknown, the proportion of people whose tumours were actually PD-L1 negative would be around 25%. As such, the overall reduction in durvalumab efficacy was likely to be small. The committee noted that overall survival at 24 months was similar in the full SACT cohort (67%) and the SACT cohort when data from people with tumours with PD-L1 unknown status was removed (68%). This suggested that including the PD-L1 unknown population had a minimal effect on treatment outcomes. The committee noted that people whose tumour PD-L1 status was unknown were outside of the NICE scope for the appraisal. The possibility that these people would have durvalumab in clinical practice added some uncertainty to the generalisability of the PACIFIC trial. However, the committee concluded that any effect on the cost-effectiveness results was likely to be small.

The weight-based dose and fixed dose of durvalumab are likely to have similar efficacy

3.5 In the PACIFIC trial people had durvalumab at a dose of 10 mg per kg every

2 weeks. A second, fixed dosing regimen of 1,500 mg every 4 weeks has since been added to the marketing authorisation. In its submission the company stated that the fixed dose was now standard clinical practice in the UK, and it therefore incorporated it into its base-case economic model. The company cited a European Medicines Agency report which concluded there were no anticipated clinically significant differences in efficacy and safety between the 2 dosing regimens. However, the ERG questioned whether the fixed dose could lead to reduced efficacy in certain people. The clinical experts described how the switch to the 4-weekly fixed dose was widespread and had improved people's quality of life and helped increase chemotherapy day unit capacity. They noted that other immunotherapies had been switched from weight-based to fixed dosing with no apparent decrease in efficacy. The nominated deputy for the Cancer Drugs Fund clinical lead stated that it was likely that most of the SACT cohort would have had the fixed dose. The similar survival between the SACT dataset and the PACIFIC trial (in which people had a weight-based dose) therefore supported equivalency of the dosing regimens. The committee concluded that although it had not seen direct clinical-effectiveness evidence for the new dosing regimen, it was unlikely to have a large effect on the clinical and cost effectiveness of durvalumab.

The company's economic model

The company's state transition approach is not preferred, but is acceptable for decision making

3.6 The company's economic model used the same approach as in the original appraisal. It was a state transition model with 3 health states: progression-free disease, progressed disease and death. Health-state occupancy over time was informed by transition probabilities which were calculated from extrapolations of progression-free survival, time to progression and post-progression survival data from the PACIFIC trial. Progression-free survival and time to progression were extrapolated separately for each arm. The distribution used for progression-free survival in each arm was also used for time to progression. Post-progression survival was extrapolated from pooled data from both arms. The ERG in the original appraisal raised concerns that extrapolation of post-progression survival added uncertainty because it was based on a small sample size made up of those

whose disease progressed early, and who may have different survival to those whose disease progressed later. The ERG in the current appraisal had requested that a partitioned survival model be provided by the company to allow assessment of any potential bias in the state transition model. It considered that without this the company had not fully explored the most appropriate method to model the survival outcomes from PACIFIC. The company responded that a partitioned survival model would have had significant limitations because all standard parametric extrapolations of progression-free survival and overall survival crossed. This meant that, under that modelling approach, more people would be progression-free than were alive, which is not possible. The company therefore did not provide the partitioned survival model as requested. The committee considered that a partitioned survival model would have been preferable for consistency with previous appraisals, and because it would have allowed overall survival to be modelled directly from the trial data. It considered that the crossing of progression-free survival and overall survival curves suggested that more flexible parametric models should have been explored by the company. However, the committee concluded that, in the absence of preferable alternative approaches, the state transition model was acceptable for decision making.

The durvalumab survival extrapolations are only plausible when treatment effect waning is applied

3.7 The company selected a generalised gamma distribution to extrapolate progression-free survival and, by extension, time to progression in the durvalumab arm. It also submitted a scenario using the Gompertz distribution. The ERG stated that the generalised gamma distribution in the durvalumab arm resulted in modelled overall survival being higher than the PACIFIC trial at 5 years. At the same time, the company's generalised gamma distribution for progression-free survival and time to progression in the standard care arm underestimated overall survival compared with PACIFIC at 5 years. However, the ERG explained that none of the alternative standard parametric distributions provided better internal consistency with the PACIFIC data for the standard care arm. The committee was concerned that the company's base-case model overestimated the survival benefit of durvalumab. For the durvalumab arm, it considered that the Gompertz distribution, while providing a relatively good fit to the PACIFIC trial

data, generated implausible long-term progression-free survival estimates. Finally, it considered that the other standard parametric distributions tested by the company underestimated progression-free survival compared with the PACIFIC trial. The committee therefore concluded that all the progression-free survival distributions tested by the company for durvalumab either did not fit the PACIFIC data well, or resulted in implausible long-term predictions. In the absence of alternatives, it concluded that it would consider all scenarios thought to be potentially plausible by the company and ERG (generalised gamma, Gompertz and log-normal) during decision making, with treatment effect waning assumptions applied (see section 3.8).

It is appropriate to consider both 3- and 5-year waning scenarios because the true effect is likely between them

3.8 The company had not modelled any additional treatment effect waning, defined as the convergence of the risk of disease progression or death in the durvalumab arm with that of the standard care arm, in its base case. It stated that any treatment effect waning was already captured by its chosen extrapolations, because these were based on the 5-year data from PACIFIC. The clinical experts explained that for people with locally advanced NSCLC, most disease progression happens before 3 years and that progression is very unlikely after 5 years. The clinical experts noted that they had limited experience with people who were 5 years on from starting durvalumab treatment. However, they felt that the risk of disease progression or death would likely not be different at 5 years between somebody who had had durvalumab and somebody who had not had it. The ERG considered that there would be a waning of treatment effect by 3 years for progression-free survival and 5 years for overall survival, and that this was not captured by the generalised gamma distribution. It noted that if this distribution was used, additional treatment effect waning should be modelled. The company pointed out that the estimate of relative effectiveness towards the end of the trial was uncertain due to the small number of remaining patients. It also provided scenario analyses with treatment effect waning at 7.5 and 10 years after starting treatment for the generalised gamma distribution. The ERG's 2 preferred base cases were the generalised gamma extrapolation with treatment effect waning at 3 and 5 years after starting treatment respectively, stating that the true effect was probably somewhere in between. The committee understood that other

recent appraisals of fixed-duration immunotherapies in NSCLC had assumed treatment effect durations lasting between 3 and 5 years after stopping treatment. It noted that the ERG's 3-year waning base case produced overall survival estimates which matched the PACIFIC data well, while the 5-year waning base case was more in keeping with previous appraisals and the clinical expert feedback. The committee concluded that both 3- and 5-year treatment effect waning scenarios, applied to the generalised gamma, Gompertz and log-normal progression-free survival distributions (see section 3.7), were appropriate for decision making.

Subsequent treatment assumptions should be based on the PACIFIC data to align costs and effects in the model

3.9 The company modelled subsequent treatments based on their distribution and duration in the PACIFIC trial. Some of the people in the PACIFIC trial had immunotherapy after stopping durvalumab, which would not currently happen in the NHS. The ERG was concerned that this could bias the model in favour of durvalumab. The company position was that people in the durvalumab arm had less subsequent immunotherapy, and for a shorter time, than those in the standard care arm. This meant that any such effect would be minimised. The company also cited treatment switching analyses, using a rank preserving structural failure time model and modified 2-stage method. These showed that, among people in PACIFIC with any tumour PD-L1 status, removing the effect of subsequent immunotherapy from the durvalumab arm did not affect the hazard ratio substantially. The company therefore stated that including the costs of subsequent immunotherapies was conservative, and submitted a scenario analysis showing that removing these costs greatly lowered the incremental cost-effectiveness ratio (ICER) for durvalumab. The nominated deputy to the Cancer Drugs Fund clinical lead explained that, if durvalumab was recommended in this indication, NHS England would likely offer some flexibility for people who have completed a course of durvalumab without disease progression to then have further immunotherapies if their lung cancer recurred. This would depend on how soon disease progression occurred after completing a course of durvalumab. The clinical experts welcomed NHS England's position on subsequent immunotherapy treatment for some people. The committee noted this but considered that there was uncertainty about subsequent immunotherapy usage after durvalumab in the

future. It concluded that subsequent treatment assumptions should be based on the data from the PACIFIC trial so that the data on costs and effects were aligned in the model.

Cost-effectiveness estimate

The most plausible ICERs for durvalumab are likely within the range considered to be a cost-effective use of NHS resources

3.10 The company's base-case ICER was generated using the generalised gamma distribution to extrapolate progression-free survival and time to progression in the durvalumab arm and was considerably lower than £20,000 per quality-adjusted life year (QALY) gained. Because there are confidential discounts for some of the subsequent treatments, the exact ICERs cannot be reported here. The committee considered scenarios with the following assumptions:

- The generalised gamma, Gompertz and log-normal distributions for extrapolating progression-free survival and time to progression in the durvalumab arm (see section 3.7)
- A treatment effect lasting 3 and 5 years after starting treatment (see section 3.8).

  The ICERs for all of the scenarios were between £20,000 and £30,000 per QALY gained, within the upper end of the range NICE normally considers a cost-effective use of NHS resources.

Other factors

3.11 No equality or social value judgement issues were identified.

3.12 NICE's advice about life-extending treatments for people with a short life expectancy did not apply.

3.13 Durvalumab is not innovative because all benefits of the technology are captured in the QALYs.

Conclusion

Durvalumab is recommended for routine commissioning for people with locally advanced unresectable NSCLC which has PD-L1 of 1% or more

3.14 New evidence was considered from the PACIFIC trial and the Cancer Drugs Fund SACT data. The committee recognised that there was residual uncertainty in the ICERs, stemming largely from the state transition model structure that the company used. However, taking this uncertainty into account, it considered that all estimates of cost effectiveness for durvalumab compared with standard care generated by the model, were below what is considered to be a cost-effective use of NHS resources. Durvalumab is therefore recommended as an option for treating locally advanced unresectable NSCLC in adults whose tumours express PD-L1 on 1% or more of cells and whose disease has not progressed after platinum-based chemoradiation, only if they have had concurrent platinum-based chemoradiation.

4 Implementation

4.1 Section 7 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 locally advanced unresectable non-small-cell lung cancer 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.

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 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.

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