NICE National Institute for Health and Care Excellence

NICE guidance

Durvalumab with gemcitabine and cisplatin for neoadjuvant treatment then alone for adjuvant treatment of muscle-invasive bladder cancer

Technology appraisal guidance
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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

1 Recommendation

1.1 Durvalumab can be used, within its marketing authorisation, as an option with gemcitabine and cisplatin for neoadjuvant treatment, and then alone for adjuvant treatment, of muscle-invasive bladder cancer in adults. Durvalumab can only be used if the company provides it according to the commercial arrangement.

What this means in practice

Durvalumab with gemcitabine and cisplatin for neoadjuvant treatment, then alone for adjuvant treatment, must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. It must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that it provides benefits and value for money, so it can be used routinely across the NHS in this population.

NICE has produced tools and resources to support the implementation of this guidance.

Why this recommendation was made

Usual treatment for muscle-invasive bladder cancer before surgery (neoadjuvant) is gemcitabine plus cisplatin. Usual treatment after surgery (adjuvant) is best supportive care. But if the cancer is at high risk of recurrence and the tumours express PD-L1 at a level of 1% or more, adjuvant nivolumab may be used.

Clinical trial evidence shows that risk of recurrence is lower with neoadjuvant durvalumab with gemcitabine plus cisplatin, then adjuvant durvalumab, than with neoadjuvant gemcitabine plus cisplatin alone. Adjuvant durvalumab has not been directly compared in a clinical trial with adjuvant nivolumab.

There are uncertainties in the economic model. But the most likely cost-effectiveness estimate is within the range that NICE considers an acceptable use of NHS resources. So, durvalumab can be used.

2 Information about durvalumab with gemcitabine and cisplatin

Marketing authorisation indication

2.1 Durvalumab (Imfinzi, AstraZeneca) with gemcitabine and cisplatin as neoadjuvant treatment then alone as adjuvant treatment after radical cystectomy is indicated for 'the treatment of adults with resectable muscle-invasive bladder cancer'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of durvalumab is £592.00 per 2.4-ml vial and £2,466.00 per 10-ml vial. The list price of cisplatin is £5.36 per 10-ml vial. The list price of gemcitabine varies by pack size and dose.

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.

Sustainability

2.5 For information, the Carbon Reduction Plan for UK carbon emissions is published on AstraZeneca's webpage on sustainability.

3 Discussion

This topic was done as a streamlined evaluation by the chair and a subset of committee members (from here, the lead team). The lead team considered evidence submitted by AstraZeneca, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence and NICE's technology appraisal and highly specialised technologies guidance manual for more information on streamlined evaluations.

Clinical effectiveness

Adjuvant nivolumab is a relevant comparator

3.1 NICE's technology appraisal guidance on nivolumab for adjuvant treatment of invasive urothelial cancer at high risk of recurrence (TA817) recommends adjuvant nivolumab for tumours that express PD-L1 at a level of 1% or more. The company did not consider adjuvant nivolumab a relevant comparator because of the small number of people having it in the NHS. But nivolumab is in routine commissioning in the NHS for this population and is used in clinical practice. NHS England indicated that about 5 to 10% of people would be eligible for adjuvant nivolumab after radical cystectomy. So, the lead team concluded that adjuvant nivolumab is a relevant comparator for this small subgroup of eligible people and should be included in the modelling.

Uncertainty in the indirect treatment comparison

3.2 The company did not do a standard indirect treatment comparison (ITC) of durvalumab as neoadjuvant and adjuvant treatment compared with adjuvant nivolumab. Standard ITC methods were not suitable for comparing the adjuvant phases of CheckMate-274 (a nivolumab trial) and NIAGARA (a durvalumab trial) because of differences in the control arms, the timing of randomisation and the inclusion criteria. So the company did a survival-time adjusted ITC. This approach simulated a scenario in which eligible people with high risk of recurrence and a

PD-L1 level of 1% or more in the control arm of NIAGARA had adjuvant nivolumab instead of no treatment. The company identified people in the control arm of NIAGARA who had had radical cystectomy and would have been eligible for nivolumab in the NHS. The company then adjusted treatment efficacy for this population using the hazard ratio of nivolumab compared with placebo from CheckMate-274. The EAG commented that the methodology applied in this approach is very similar to the recommended methods that are commonly used to account for treatment switching. But it cautioned that it was not aware of the methodology having been used in this way before and that its performance in this context has not been externally validated. So, the results from the ITC are uncertain. The EAG also explained that the assumption that the effect of adjuvant nivolumab is exchangeable across CheckMate-274 and NIAGARA relies on the populations being well matched. But the subgroup data from CheckMate-274 does not fully match the population of people with high-risk PD-L1 positive tumours from NIAGARA who had neoadjuvant chemotherapy, because only a small number of people in CheckMate-274 had this treatment. So, the EAG noted there may be possible bias in the adjusted survival times for the eligible population in NIAGARA. But the EAG explained that the company had compared the hazard ratios obtained from the adjusted analysis in eligible NIAGARA patients (adjuvant nivolumab compared with no adjuvant treatment) with the original hazard ratios from CheckMate-274 (nivolumab compared with placebo). It noted that all the hazard ratios from the adjusted analyses were more favourable to nivolumab than the hazard ratios estimated in CheckMate-274. This suggests that the company's analyses may be conservative, but this is uncertain. The EAG also noted that the company's ITC method created counterfactual survival times for all people in NIAGARA who fulfilled the criteria for adjuvant nivolumab. This survival time is considered confidential by the company so cannot be reported here. But it is higher than for the 5 to 10% eligible population estimated by NHS England. So, the adjustment may overestimate the additional benefit of nivolumab in the NHS population. The lead team considered the appropriateness of the company's approach to the ITC comparing perioperative durvalumab with adjuvant nivolumab. It agreed with the EAG that the company's survival-time adjusted approach is not commonly used but the method is robust. The lead team acknowledged the various risks of bias. But it concluded that the company's analysis is appropriate for decision making.

Extrapolation of immature overall-survival data

3.3 To inform long-term overall-survival extrapolations, the company decided that the hazard profiles were well-captured by standard parametric models. The EAG had concerns about the company's use of standard parametric modelling for the extrapolation of overall survival in its base case. The EAG commented that the choice of model for the overall-survival extrapolations had a large impact on cost-effectiveness. In the durvalumab arm, the company's choice of the Gompertz model closely aligned with the EAG's preferred flexible odds 1-knot model. But for the control arm, the EAG suggested that the company's preferred standard parametric log-logistic model substantially underestimates overall survival compared with the EAG's preferred flexible hazard 1-knot model. The company selected the log-logistic distribution for the control arm because 2 out of 4 clinical experts considered its long-term extrapolation to be most plausible, and the 10-year estimate aligned more closely with external literature sources. But the EAG commented that log-logistic was the fourth best-fitting distribution and also provided the lowest estimates of long-term overall survival out of the models considered. The EAG noted that the company's base-case model results in diverging hazards for the overall-survival extrapolation, implying that the hazard ratio is increasing with time before eventually converging because of the implementation of a general population mortality constraint. The EAG explained that there is no empirical evidence to suggest that the hazard is increasing over time. It stated that it was unclear why the company had originally disregarded flexible models for extrapolating overall survival when it had used flexible models for extrapolating event-free survival and metastasis-free survival, and the hazards for the 3 different outcomes appeared to be very similar. The EAG's preferred extrapolation, the hazard 1-knot model, appeared to fit the data better on visual inspection and produced similar curves to alternative parametric extrapolations (Gompertz or generalised gamma). The EAG noted that, in the company's model, a person is considered to be cured when they have no risk of recurrence, progression or cancer-related death and their only risk is all-cause mortality. In the company's base-case analysis, these criteria are reached much sooner in the durvalumab arm than in the control arm (the exact values are considered to be confidential by the company and cannot be reported here). Clinical advice to the EAG suggested that it was clinically plausible that a proportion of people with muscle-invasive bladder cancer could be considered to be cured if they have no disease recurrence after a significant period, but the

proportions are uncertain. The company provided a scenario that included the EAG's preference for the 1-knot spline odds distribution in the durvalumab arm but with a log-normal curve for the control arm. The company noted that the log-normal distribution was considered a plausible alternative by 1 of the 4 clinicians interviewed by the company. The lead team had concerns about whether the difference in effective cure time points between the durvalumab and control arms implied by the modelling was plausible. It noted that the gap between the effective cure time points between treatment arms was smaller with the EAG's preferred overall-survival extrapolations. The lead team accepted it is plausible that event-free survival translates into an overall-survival benefit. So, it agreed that the company's scenario using log-normal for the comparator allows more of a benefit to be captured in the model. The lead team concluded that the EAG's preference of using the 1-knot spline odds distribution for the perioperative durvalumab arm is appropriate.

Starting age of the modelled cohort

3.4 The starting age in the company's model came from NIAGARA, in which the mean age was 64.4 years. The EAG noted that NIAGARA recruited people from 168 sites in 22 countries across Europe, Asia-Pacific, North America and South America. But only 4 of these sites were in the UK, so the starting age may not be generalisable to people with muscle-invasive bladder cancer in the NHS. The EAG explained that the starting age used in the economic model has a large impact on the extrapolated overall-survival probabilities. This is because the hazard rate of overall survival is constrained to be at or above the age- and gender-matched all-cause general population risk of death. It explained that the impact of age is more pronounced in the perioperative durvalumab arm than in the control arm because the overall-survival hazard rates in the perioperative durvalumab arm approach the general population mortality earlier than in the control arm. The lead team noted that when the modelled starting age increases, the difference in survival between the 2 arms diminishes more rapidly after the point at which the hazards meet. This reduces the estimated life-year gains for the perioperative durvalumab arm compared with the control arm (the exact values are considered confidential by the company and cannot be reported here). The EAG explained that clinical advice it had received suggested that people eligible for neoadjuvant chemotherapy for muscle-invasive bladder cancer in the NHS are typically older

than those in NIAGARA, with many people aged between 70 and 79 years. Data from NHS England suggested that NHS patients in the North East of England with resectable muscle-invasive bladder cancer who have neoadjuvant cisplatin-containing chemotherapy have a mean age of 66 years. The EAG noted that this is not dissimilar to the company's base-case starting age, but it is uncertain whether this data is generalisable to the whole of England and Wales. The EAG noted that in the absence of further nationwide information on age and sex distribution its preference would be to retain mean modelled age from NIAGARA. The lead team considered the different sources of data to inform the choice of starting age for the economic model. It agreed with the EAG's clinical expert that people eligible for neoadjuvant chemotherapy for muscle-invasive bladder cancer in the NHS are likely to be older than those in NIAGARA. It also agreed that the regional data from NHS England was likely to be generalisable to the wider NHS compared with those estimated from a global trial. The lead team concluded that a mean age of 66 was the most appropriate starting age for the economic model.

Risk of non-cancer-related death

3.5 The company did not model excess death risk. The EAG noted that people in NIAGARA had additional mortality risk factors other than muscle-invasive bladder cancer including smoking (23.7% smoke and 49.3% had stopped smoking) and comorbidities. The EAG explained that even after removing the risk of death from muscle-invasive bladder cancer, the overall risk of death for this population is likely to be higher than the general population mortality risk. Clinical advisers to the EAG confirmed that an increased non-cancer-related mortality risk for this population is clinically plausible. But it explained that the data from NIAGARA does provide some information about the extent of this increased risk because of these comorbidities. Of the 305 total deaths across the 2 arms, 199 were attributed to bladder cancer and 106 were attributed to non-cancer-related causes over a 5-year follow-up period. So, the 5-year probability of non-cancer-related death in NIAGARA is estimated to be 9.97%. This is higher than the corresponding 5-year age- and gender-adjusted mortality probability for the general population, which is 7.11%. The EAG calculated that the hazard ratio (increased death risk) would be 1.42 for people in NIAGARA compared with the general population (assuming an exponential model for simplicity). The EAG explained that it included this analysis as a scenario. The EAG acknowledged that

it's method of calculation is difficult to validate and is subject to uncertainty. The company noted that the hazard ratio drops to 1.23 for a model starting age of 66 years because of the higher general population mortality risk with older age. The lead team agreed with the EAG that it was difficult to know the extent to which the non-cancer-related deaths in NIAGARA were fully independent of the underlying condition itself or its associated treatments. It acknowledged that about a third of deaths in NIAGARA were unrelated to the underlying condition, which appears to be higher than might be expected. The lead team agreed that a hazard ratio should be used to account for the excess risk of death in the NIAGARA population compared with the general population. It noted that the evaluation committee for TA817 had applied a mortality rate of 1.1 to the long-term disease-free survival health state, but the source for this assumption was unclear. It agreed that an older model starting age should reflect a lower hazard ratio and that there is potential for a diminished hazard ratio over time. The lead team concluded that the standardised mortality ratio should be 1.23 for the first 5 years of the model and then 1.1.

Cost-effectiveness estimates

Acceptable ICER

3.6 NICE's technology appraisal and highly specialised technologies guidance manual notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The lead team noted that the analysis was associated with uncertainty, specifically that:

- much of the benefit for durvalumab compared with standard of care is from the extrapolated data beyond the trial period, and these extrapolations are uncertain
- the difference in the effective cure timepoints in each treatment arm is

uncertain

- there is uncertainty in the calculation of the excess mortality multiplier.

The lead team noted a high unmet need for treatments for muscle-invasive bladder cancer and that some assumptions, such as the comparison with nivolumab. may be conservative. So, it concluded that an acceptable ICER would be towards the upper end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Preferred assumptions

3.7 The preferred assumptions were to:

- include adjuvant nivolumab as a relevant comparator (see section 3.1)
- model overall survival using the odds 1-knot model for the neoadjuvant durvalumab arm, and the log-normal distribution for the control arm (see section 3.2)
- use a mean age of 66 years as the starting age in the economic model (see section 3.3)
- apply an excess mortality adjustment of 1.23 for the first 5 years and then 1.1 to account for excess non-cancer-related deaths in NIAGARA (see section 3.4).

Because of confidential commercial arrangements for durvalumab and some of the comparators, the exact cost-effectiveness results are confidential and cannot be reported here. Using the preferred assumptions, the probabilistic cost-effective estimates are within the range that NICE considers an acceptable use of NHS resources.

Other factors

Equality

3.8 The lead team did not identify any equality issues.

Conclusion

Recommendation

3.9 The cost-effectiveness estimate is within the range that NICE considers a cost-effective use of NHS resources. So, durvalumab with gemcitabine plus cisplatin can be used as neoadjuvant treatment, then alone as adjuvant treatment, for muscle-invasive bladder cancer.

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 integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days 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 cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England 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 guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

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 muscle-invasive bladder cancer and the healthcare professional responsible for their care thinks that durvalumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered as a streamlined evaluation by the lead team of committee D.

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

Chair

Paul Arundel
Chair, highly specialised technologies evaluation committee

NICE project team

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

Luke Cowie
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