NICE guidance on nivolumab with ipilimumab for untreated advanced renal cell carcinoma

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On May 15, 2019, the National Institute for Health and Care Excellence (NICE) published guidance[1] recommending nivolumab with ipilimumab within the Cancer Drugs Fund as an option for treating adults with untreated advanced renal cell carcinoma that is intermediate risk or poor risk, as defined by the International Metastatic Renal Cell Carcinoma Database Consortium. Nivolumab with ipilimumab is recommended only if Bristol-Myers Squibb follows the managed access agreement for nivolumab with ipilimumab.

NICE appraised nivolumab with ipilimumab as a single technology appraisal. Bristol-Myers Squibb submitted clinical and cost-effectiveness evidence, which an evidence review group, the Liverpool Reviews and Implementation Group, critiqued. An independent appraisal committee of health professionals, academics, lay members, and industry representatives met three times to consider the evidence and to develop the guidance. Because of the anticipated marketing authorisation date, the committee first met in May, 2018. The European Medicines Agency (EMA) did not grant the marketing authorisation until November, 2018, so the second and third committee meetings were delayed until January and February, 2019; the first two meetings were held in public.

Nivolumab with ipilimumab (both manufactured by Bristol-Myers Squibb) has a marketing authorisation for "the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma". Both treatments are given intravenously.

The committee recognised that the marketing authorisation limits treatment to intermediate-risk and poor-risk disease. The committee heard from clinicians that although they do not use prognostic scores in practice, they routinely collect all components of the scores.

The committee knew that people with untreated advanced renal cell carcinoma in the UK National Health Service (NHS) could be offered one of four NICE-recommended oral tyrosine kinase inhibitors: cabozantinib,[2] pazopanib,[3] sunitinib,[4] or tivozanib.[5] NICE's scope[6] for this appraisal did not include cabozantinib and tivozanib, which, at scoping, were not used in NHS practice. The committee concluded that the relevant comparators were pazopanib and sunitinib.

Bristol-Myers Squibb submitted as evidence CheckMate 214, an open-label, randomised, controlled trial, comparing nivolumab with ipilimumab to sunitinib. The company indirectly compared nivolumab plus ipilimumab with pazopanib, but the committee recalled that in previous appraisals it considered pazopanib and sunitinib to be equally effective, and that an indirect treatment comparison was not needed.

The trial's co-primary endpoints were overall survival and progression-free survival, amended by the company to include overall response. In its original submission, the company presented data from an interim analysis (August, 2017), reflecting a median follow-up of 25 months. In response to consultation, the company provided confidential updated results (August, 2018). The company focused on the subgroup with a prognostic risk score that was intermediate or poor, which the company stated had adequate power to detect outcomes.

In the analysis (August, 2017), nivolumab with ipilimumab compared with sunitinib improved progression-free survival and overall survival of people with intermediate-risk or poor-risk disease. The committee was aware that the trial stopped early, and that trials stopped early for benefit can overestimate relative benefit. It noted the immature data, with a median follow-up of 25·2 months, and with only a third of people randomised to nivolumab with ipilimumab having died—a value lower than the company included in its statistical analysis plan (50%). The committee recognised that the company amended the trial protocol to allow people randomly assigned to sunitinib to switch to nivolumab with ipilimumab on disease progression, but that the company did not adjust for this in analyses from August, 2018. The committee concluded that the later (compared with the earlier) data reduced uncertainty, that crossover probably worsened the apparent treatment effect, and that the data remained too immature to establish the long-term effect.

The company considered that nivolumab plus ipilimumab would cure some people, basing this on durable response, which it defined as achieving a complete or partial response in CheckMate 214 by August, 2017. The committee was concerned that the company had not defined durable response in the protocol, instead defining it at the analysis stage; clinicians do not use durable response in the NHS; the company had not presented validated evidence associating durable response and overall survival; and that the company assumed that the treatment would cure 15% of patients randomly assigned to it, which the committee considered implausible because less than 15% of patients were still on treatment at the end of follow-up. The committee agreed that the analysis using durable response was

inappropriate for modelling long-term survival or cure rate.

The company assumed that, after 5 years of treatment, people stop treatment, even if they continue to benefit. The committee recognised that the company assumed that people who stop continue to benefit as if they had never stopped treatment. The company modelled time-to-stopping treatment independently from an immunological response, which the committee considered would underestimate treatment costs for patients who responded. The committee concluded that it is not appropriate to include a stopping rule.

The company estimated quality of life using utility values from EuroQol 5 dimensions, 3 levels from CheckMate 14. The company assumed that people's utility differs by treatment, and by whether or not they were on treatment, but not by whether or not their disease had progressed. The committee agreed that quality of life should reflect disease progression.

The committee considered which treatments trial participants used as second line and concluded that they do not reflect NHS clinical practice. The committee would have preferred to see results from an analysis that included both the costs and the clinical benefits of treatments used as second line and beyond in the NHS, but had not been presented with this finding.

To estimate parameters beyond the end of the trial, the company extrapolated survival outcomes (August, 2018, data cutoff) by fitting parametric curves to the observed data (a log-normal distribution for overall survival, cubic spline for progression-free survival, and gamma for time-to-stopping treatment). The evidence review group preferred using piecewise modelling, specifically, Kaplan-Meier data from the trial followed by an exponential curve starting from the point at which the cumulative hazard plots showed a constant hazard rate. The committee considered both approaches.

The committee addressed the estimated cost-effectiveness, noting that the incremental cost-effectiveness ratios exceeded the lower end of the range of £20 000–30 000 per quality-adjusted life-year gained, and having concluded that that the treatment did not meet the criteria for routine NHS commissioning, it considered if it could recommend treatment as part of a managed access agreement. The committee agreed that nivolumab with ipilimumab had potential to be cost-effective either at a lower price or by lessening the clinical uncertainty about overall survival by collecting longer-term data and addressing the issues in the modelling. The committee agreed that the uncertainty emanated primarily from extrapolating overall survival. The committee understood that the company planned another analysis of CheckMate 214 for August, 2019, and then yearly to 2021, which would provide 6-year data on overall survival. The committee discussed two other sources of data that would accrue if treatment were available to NHS patients through the Cancer Drugs Fund.[7] The first source of data was NHS England's systemic anticancer therapy (SACT) database: the committee agreed that it would provide information on people with intermediate-risk and poor-risk renal cell carcinoma in clinical practice, would document NHS treatments offered after nivolumab with ipilimumab, and would better define frequency of death and treatment duration early in therapy. Second, the company explained that the EMA requires it to set up a randomised trial including people with poor-risk or intermediate-risk disease to evaluate whether the effectiveness of nivolumab with ipilimumab compared with nivolumab alone justifies the additional toxicity of ipilimumab. The committee noted that the trial could contribute information about treatment duration, frequency of early deaths, and time to progression, but was unlikely to reduce the uncertainty about long-term effectiveness.

The company proposed a commercial arrangement that would make nivolumab with ipilimumab available at discount while in the Cancer Drugs Fund. The committee was satisfied that the proposed price compensates for the uncertainty relating to survival and recommended the treatment within the Cancer Drugs Fund.

We declare no competing interests.

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