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NICE guidance on nivolumab with ipilimumab for untreated unresectable malignant pleural mesothelioma

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On Aug 17, 2022, the National Institute for Health and Care Excellence (NICE) published guidance recommending nivolumab plus ipilimumab as an option for treating previously untreated unresectable malignant pleural mesothelioma in adults with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, but only if the company, Bristol Myers Squibb, provides it according to the commercial arrangement.[1]

Nivolumab (Opdivo®), an antineoplastic human immunoglobulin G4 monoclonal antibody, binds to the programmed death-1 (PD-1) receptor and potentiates T-cell anti-tumour responses. Ipilimumab (Yervoy®) blocks T-lymphocyte antigen-4. Nivolumab plus ipilimumab, an immunotherapy, is indicated 'for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma' in addition to other indications.[2] Nivolumab and ipilimumab are administered intravenously 360 mg over 30 minutes every 3 weeks for nivolumab and 1 mg per kilogram over 30 minutes every 6 weeks for ipilimumab. Treatment continues until disease progresses or for up to 24 months.

Under NICE's single technology appraisal process, the company provided evidence on clinical and cost effectiveness[3], which an evidence review group (ERG), Kleijnen Systematic Reviews Ltd, critiqued. An independent committee comprised of clinicians, managers, statisticians, health economists and lay members held two public meetings; the company attended both meetings, while clinical and patient experts attended the first. The committee met again after it second meeting to discuss remaining uncertainties. The remit of the committee is to appraise how

effective a new treatment is compared with what the NHS currently offers, and to determine whether this reflects value given finite NHS resources.

Malignant pleural mesothelioma is an aggressive cancer. Most cases are associated with occupational exposure to asbestos; despite the UK banning asbestos in 1999, cases continue to rise. The most common histology is epithelioid; non-epithelioid tumours are less common, but more aggressive. Current UK treatment is platinum-doublet chemotherapy using pemetrexed with either cisplatin or carboplatin. The committee understood that the NICE scope included raltitrexed as a comparator, but the company excluded it, arguing that it is not used in the UK, and which experts confirmed. The committee concluded that the company's positioning of nivolumab plus ipilimumab as first-line treatment and an alternative to chemotherapy, the only relevant comparator, was appropriate.

The company presented interim data cuts at '2-years' (median follow-up 29.7 months) and '3-years' (median follow-up 43.1 months) for Checkmate 743, an ongoing, phase 3, randomised controlled, open-label multicentre trial with a primary outcome of overall survival.[4] The trial compared nivolumab 3 mg per kg every 2 weeks plus ipilimumab 1 mg per kg every 6 weeks with pemetrexed every 3 weeks and the 'investigator's choice' of adding either cisplatin or carboplatin. In the trial, either treatment would stop for disease progression or unacceptable toxicity, or for immunotherapy, after 2 years of treatment, and, for chemotherapy, after 6 cycles. The Cancer Drugs Fund clinical lead noted that the NHS would fund immunotherapy only up to 2 years. The trial included participants with an ECOG of 0 or 1 only. The committee concluded that for nivolumab, the trial's weight-based dosing and the licensed fixed dose are likely to have similar efficacy.

Randomisation to nivolumab plus ipilimumab was associated with longer overall survival than chemotherapy at both the 2-year (HR 0.74, 95% confidence interval [CI] 0.60 to 0.91) and 3-year follow up (HR 0.73, 95% CI 0.61 to 0.87). For progression free survival, a secondary endpoint, neither data cut showed a difference between treatments; the committee noted that the Kaplan–Meier curves by treatment allocation crossed. The company stated chemotherapy may exert an 'early but transient' effect compared with a 'delayed but durable' effect of

immunotherapy. The committee concluded that nivolumab plus ipilimumab reduces the risk of death compared with chemotherapy.

The company considered that nivolumab plus ipilimumab increases quality-adjusted life years (QALYs) compared with chemotherapy because people live longer with a higher quality of life assuming treatment delays disease progression. The company used a partitioned survival model with 3 health states: progression-free, progressed, and dead with a cycle length of 1 week and a horizon of 20 years. The ERG noted that the model predicted that a large proportion of life-years and progression-free years accrued in the immunotherapy arm after the trial, and for which no evidence exists. The committee was aware that other model structures would have the same uncertainties.

The company assumed non-proportional hazards for overall survival because the mechanism of immunotherapy and chemotherapy differ. To extrapolate overall survival beyond the trial data, it fitted parametric distributions to the treatments separately. It used data on chemotherapy from the Mesothelioma Avastin Cisplatin Pemetrexed Study, a randomised trial comparing bevacizumab plus chemotherapy with chemotherapy alone in people with newly-diagnosed pleural mesothelioma.[5] The committee noted that at the end of the modelled period, the log-logistic distribution, preferred by the company and the ERG, predicted better survival with immunotherapy than did other distributions, but also predicted better survival than observed in the trial. For chemotherapy, the company preferred a 1-knot spline normal model, and the ERG a log-logistic model for both treatments.

The committee noted a continuing survival benefit after stopping treatment, but considered it unclear how long it would last, and considered it reasonable to assume some waning of treatment effect. After the committee's second meeting, the company provided scenario analyses that assumed treatment effect waning after starting treatment at 5, 7, or 10 years, and with a duration of treatment effect waning of 5 or 10 years. All scenarios worsened the estimates of cost-effectiveness. Considering the uncertainties, the committee concluded that it is acceptable to assume that if immunotherapy stops at 2 years, the survival benefit would continue for 3 more years, when treatment waning would start.

For progression free survival, the committee considered it appropriate to use a generalised gamma distribution to extrapolate immunotherapy, and a log-logistic distribution for chemotherapy, acknowledging uncertainties.

The committee discussed the second-line treatment used in Checkmate 743. It noted that at 3 years, among the people randomised to first-line nivolumab plus ipilimumab, some received second-line immunotherapies, which does not reflect UK practice; it therefore considered it appropriate to adjust the trial results to reflect the UK. The company used four methods, including the inverse probability censoring weights which the company preferred, and the committee considered appropriate when assuming no unmeasured confounding.

In the committee meetings, the committee considered that the company's base case estimates of cost effectiveness across all histological subtypes were far too high to reflect a cost-effective treatment to the NHS given the price the company chose to charge for nivolumab plus ipilimumab. The committee then considered people with non-epithelioid disease; the committee was aware that there was a strong interaction between treatment and histology subtype. However, the most plausible cost-effectiveness estimates for non-epithelioid disease were also higher than the range considered a cost-effective use of NHS resources, even when consider end-of-life criteria.[6]

After committee discussion following the committee's second public meeting, NICE paused the appraisal in April 2022 for the company and NHS England to engage in commercial negotiations.[7] Following the conclusion of these discussions, the committee chair took chair's action[8] to approve the final appraisal document recommending the technology as an option. The committee had previously concluded that nivolumab plus ipilimumab meets end-of-life criteria, and the company's revised incremental cost effectiveness estimates (ICERs) with a new patient access scheme were now less than £50,000 per QALY gained across the whole population and likely reflected a cost-effective use of NHS resources.

The committee heard from the clinical lead of the Cancer Drug Fund that some people develop mesotheliomas in the pericardium or peritoneum and agreed that any guidance should extend to these individuals. NICE had no requests for appeal on this guidance. The NHS will make the treatment available within 3 months of its publication date in line with its legal obligation to fund treatments recommended by NICE's technology appraisals.

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