One Wales Medicine Assessment Group summary of decision rationale

Medicine: **nivolumab plus ipilimumab (OPDIVO® plus YERVOY®)**

Indication: **neoadjuvant treatment of patients with resectable macroscopic stage III melanoma with ≥1 pathologically proven lymph node metastasis and up to 3 in-transit metastases (OW35)**

Meeting date: **9 February 2026**

Criteria	OWMAG opinion
Clinical effectiveness and safety	OWMAG noted that the NHS Wales Cancer Network Immunotherapy Group had identified an unmet clinical need for a neoadjuvant treatment option for resectable macroscopic stage III melanoma with ≥1 pathologically proven lymph node metastasis and up to 3 in-transit metastases in NHS Wales. Currently, treatment for resectable stage III melanoma in NHS Wales is surgery, followed by adjuvant therapy with either sub-cutaneous (SC) nivolumab every 4 weeks for 13 cycles, IV pembrolizumab every 6 weeks for 9 cycles, or oral dabrafenib plus trametinib daily for 13 x 4-week cycles. The intervention under request is nivolumab IV plus ipilimumab IV every 3 weeks for 2 cycles, followed by surgery. For those patients who have a major pathological response to the neoadjuvant treatment, adjuvant treatment would not be required post-surgery. OWMAG considered the evidence provided by the pivotal NADINA study, which is deemed the most relevant source of evidence pertinent to the assessment. The group noted the favourable event-free survival, pathological response rates and estimated 12-month recurrence-free survival rates in patients who received neoadjuvant nivolumab plus ipilimumab in the NADINA study. The group acknowledged the treatment-sparing potential of neoadjuvant nivolumab plus ipilimumab, as 59% of patients who received this treatment in the NADINA study achieved a major pathological response and did not require adjuvant treatment. OWMAG considered updated data from the NADINA study, presented at conference, which was shared by a clinical expert. They reported that the event free survival (EFS) was 20% higher in the neoadjuvant group versus the adjuvant group, suggesting that the benefits of neoadjuvant treatment are greater than those patients who would have otherwise received adjuvant treatment in accordance with current standard of care (SOC).

	The group also noted the supporting clinical trials that provide evidence to supplement the NADINA study. OWMAG acknowledged that, although neoadjuvant nivolumab plus ipilimumab is not currently surgery-sparing, a supporting study suggests that it may be feasible for surgery to be safely omitted in patients achieving a major pathological response to neoadjuvant treatment in the future. OWMAG noted that the comparative evidence provided by the NADINA study is limited to one NHS Wales SOC treatment regimen. Due to the similar efficacy and safety profiles of the SOC treatment regimens, the group felt that the study's findings were generalisable to NHS Wales. OWMAG considered the safety profile of neoadjuvant nivolumab plus ipilimumab. The most frequently reported severe adverse effects were acknowledged, which were raised aspartate aminotransferase, raised alanine aminotransferase, diarrhoea, adrenal insufficiency, and colitis. These were comparable to the expected safety profile for the medicines. OWMAG concluded that the pathological response, EFS, and RFS rates reported in the NADINA and supporting studies suggests that neoadjuvant nivolumab plus ipilimumab is a clinically effective treatment for stage III melanoma. The consistency between the safety findings in the clinical studies and SmPC suggests that the off-label use of nivolumab plus ipilimumab is a tolerable treatment regimen.
Cost-effectiveness	OWMAG did not consider the cost-effectiveness of the treatment, as no cost-effectiveness evidence was identified in the literature and AWTTC did not conduct a cost-effectiveness analysis. OWMAG consider that the likely costs associated with using nivolumab plus ipilimumab for this indication would be reasonable in considering the potential benefit gained from this intervention. Noting that this regimen is cost saving when compared to SOC.
Budget impact / economic evaluation	OWMAG considered the estimated patient numbers provided by clinicians to be reasonable. The addition of neoadjuvant nivolumab plus ipilimumab is anticipated to decrease the spend associated with this patient group in Wales. This is based on an estimated uptake of 41 patients receiving treatment per year and assumes full displacement of comparator adjuvant

	treatment. This took in to account an estimate of the proportion of patients currently receiving each of the adjuvant treatments in Wales, the proportion of patients who would not obtain a major pathological response and would require adjuvant treatment, grade 3 or higher adverse events treatment costs as reported across the NADINA and relevant adjuvant clinical studies, monitoring costs and administration costs. Uncertainty around the number of patients that currently receive each NHS Wales SOC treatment regimen, and who are estimated to receive neoadjuvant nivolumab plus ipilimumab, was acknowledged by OWMAG. OWMAG raised uncertainties around the approach underpinning the budget impact. OWMAG noted that long-term treatment costs are not accounted for, and the adverse event costs are associated with uncertainties. OWMAG noted that variation in the types of adverse events, their severity, and management could increase or decrease the budget impact. However, these factors were deemed to be unlikely to make a material difference on the clear cost benefit in removing the need for adjuvant treatment in those patients who had a major pathological response. Also there is emerging evidence that patients who receive neoadjuvant treatment respond better longer term and therefore are less likely to accrue longer term treatment costs. Whilst understanding the limitations presented, OWMAG consider that the budget impact provides a reasonable estimate of the associated costs to NHS Wales. Recognising that this regimen would be cost saving when compared to SOC, OWMAG consider nivolumab plus ipilimumab to be a reasonable use of NHS resources.
Resource use	OWMAG recognises that neoadjuvant treatment with nivolumab plus ipilimumab requires additional resources compared to SOC treatment, including a baseline electrocardiogram, an additional Computerised Tomography (CT) scan prior to surgery, and additional pathology reporting post-surgery. Due to the higher rates of severe adverse events that are associated with the neoadjuvant treatment, OWMAG recognised that there may be a greater rate of hospital admissions compared to SOC treatment, resulting in higher resource use in the short term. However, the group agreed that the neoadjuvant treatment may reduce the longer-term burden of adverse events associated with adjuvant

	treatment in patients who achieve a major pathological response, which would reduce resource use. The group acknowledge that, despite the additional resource requirements associated with neoadjuvant treatment in the short term, the potential to avoid adjuvant treatment in approximate 59% patients would reduce the number of clinic appointments required in the long term. The group discussed the potential surgery-sparing effects of the treatment, which would further reduce the resource burden in the longer term. OWMAG acknowledge that alignment between surgical and oncology multi-disciplinary teams would be essential to ensure that surgery is performed in a timely manner. OWMAG noted that this will be more challenging in north Wales as the surgery takes place in England.
Other factors	There are currently no UK-licenced neoadjuvant treatment options for this indication. In Scotland, the National Cancer Medicines Advisory Group support the off-label use of nivolumab in combination with ipilimumab for the neoadjuvant treatment of resectable stage III melanoma. Therefore, the treatment is available to eligible patients in Scotland. OMWAG were informed by the Melanoma Focus representative that neoadjuvant nivolumab plus ipilimumab is also available to eligible patients in Northern Ireland. From an international standpoint, the European Society for Medical Oncology, the American Society of Clinical Oncology, The National Comprehensive Cancer Network®, and the European Association of Dermato-Oncology recommend both neoadjuvant treatment (followed by adjuvant treatment where required) and resection followed by adjuvant treatment for patients with resectable stage III melanoma.
Final recommendation	OWMAG recommends the use of nivolumab plus ipilimumab for neoadjuvant treatment of patients with resectable macroscopic stage III melanoma with ≥1 pathologically proven lymph node metastasis and up to 3 in-transit metastases. This recommendation is subject to the development of appropriate start/stop criteria.
Summary of rationale	OWMAG recognise that there is a clinical need for a neoadjuvant treatment option for this indication in Wales, particularly as there are currently no UK-licenced treatments available. OWMAG concluded that, based on

	the evidence provided by the NADINA study, the treatment is likely to reduce the treatment burden for patients, particularly for those achieving a major pathological response. OWMAG acknowledged that a lower treatment burden benefits both the patient, and NHS Wales due to lower medicine acquisition, medicine administration, and healthcare resource costs. The group consider the budget impact presented to demonstrate a reasonable use of NHS resources. The review after 12 months will provide the number of patients who have received this treatment in Wales and more evidence on whether this is an effective treatment for this patient population.

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