



# AWTTC

All Wales Therapeutics & Toxicology Centre  
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

**One Wales Medicines Assessment Group Recommendation:  
Nivolumab monotherapy as a first-line treatment for patients with  
metastatic or locally advanced and unresectable, deficient  
mismatch repair (dMMR) / high microsatellite instability (MSI-H)  
oesophageal and gastric cancer (OW28)**

## **ONE WALES INTERIM DECISION**

**Nivolumab monotherapy as a first-line treatment for patients with metastatic or locally advanced and unresectable, deficient mismatch repair (dMMR) / high microsatellite instability (MSI-H) oesophageal and gastric cancer.**

**Date of advice: Monday July 2024**

**The following One Wales Medicines Assessment Group (OWMAG) recommendation has been endorsed by the All Wales Medicines Strategy Group (AWMSG) and ratified by Welsh Government.**

It is the view of the One Wales Medicines Assessment Group (OWMAG) that nivolumab should not be supported within NHS Wales for monotherapy as a first-line treatment for patients with metastatic or locally advanced and unresectable, deficient mismatch repair (dMMR) / high microsatellite instability (MSI-H) oesophageal and gastric cancer.

Individual Patient Funding Request (IPFR) consideration remains appropriate for those patients who are likely to obtain significantly more clinical benefit from the intervention than would normally be expected at a reasonable value for money.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.

**One Wales advice promotes consistency of access across NHS Wales.**

**One Wales Medicine Assessment Group summary of decision rationale**

Medicine: **Nivolumab reassessment**  
 Indication: **As monotherapy for the first-line treatment of patients with metastatic or locally advanced and unresectable, deficient mismatch repair (dMMR) / high microsatellite instability (MSI-H) oesophageal and gastric cancer.**

Meeting date: **3 June 2024**

Criteria	OWMAG opinion
Clinical effectiveness	<p>OWMAG notes that there has been no direct clinical effectiveness data for using nivolumab as monotherapy in the first-line setting for the indication under consideration since the original report.</p> <p>The group acknowledge that based on the lack of direct clinical effectiveness data with nivolumab as monotherapy in the first-line setting, the report used data for use of PD-1 inhibitor pembrolizumab comparing the antitumor activity in first-line use.</p> <p>The majority of available clinical evidence is for pembrolizumab. OWMAG considers that pembrolizumab, as another PD-L1 inhibitor and therefore with the same mechanism of action, is a suitable proxy for nivolumab. The group recognise that the high tumour mutational burden of dMMR/MSI-H tumours make them more responsive to anti-PD-L1 therapy compared with microsatellite stable (MSS) tumours. The clinical effectiveness evidence included 4 studies investigating first line anti-PD-L1-based treatments of oesophageal, gastric or colorectal cancers which provide analyses of dMMR/MSI-H tumour response. Where results for dMMR/MSI-H tumours are available, results consistently demonstrate increased PFS and OS for treatment with anti-PD-L1 compared to chemotherapy-based regimens. The group overall concluded that treatment with an anti-PD-L1 medicine such as nivolumab confers improved clinical benefit for patients with dMMR/MSI-H tumours compared with standard of care.</p>
Cost-effectiveness	<p>There is no new cost-effectiveness evidence available for this treatment since the original report. The group acknowledged that clinical effectiveness, HRQoL and adverse event data may be considered to inform a more general value for the intervention. It was noted that not all parameters were able to be captured as part of the economic assessment and that there is uncertainty in the clinical effectiveness.</p>

	<p>Overall, there was no difference in total quality of life scores between treatment arms in the studies Checkmate 649 and Keynote 062 included within the evidence report. However, in the two Keynote trials adverse events of grade 3 or greater were more likely to occur in the chemotherapy-based treatment groups when compared to anti-PD-1 monotherapy.</p> <p>OWMAG considered the severity modifier of 1.2 to be appropriate based on a proportional QALY shortfall of between 0.85 and 0.95. The base case was taken from utility estimates for people with stage IV oesophageal cancer compared to the general population without the condition. Mortality within the general population was sourced from pooled life tables and overall survival data for this patient cohort was taken from Checkmate 649.</p> <p>Based on the evidence presented the group agreed that a £20,000 per QALY cost-effectiveness threshold was appropriate.</p> <p>OWMAG consider that the expected clinical benefit is highly unlikely to result in the [confidential data removed] gain required for nivolumab to be cost effective in the context of the 1.2* multiplier and a £20,000 per QALY threshold, for this indication.</p> <p>On consideration of these factors OWMAG consider it is unlikely that nivolumab would be considered cost-effective when compared to standard treatments.</p>
Budget impact	<p>OWMAG considers the clinical estimate of patient numbers to be reasonable, acknowledging that this is only an estimate and numbers may be lower in year one dependent upon uptake.</p> <p>The group considers the use of the median progression free survival for MSI-H patients from the KEYNOTE-062 study to be a reasonable estimate for treatment duration in the base case.</p> <p>Monitoring costs may be higher with nivolumab due to longer treatment duration when compared to standard of care.</p> <p>The group noted that the budget impact assumed no treatment discontinuations for either nivolumab or chemotherapy.</p> <p>Whilst frequency of adverse events may be lower with nivolumab than chemotherapy there are a lack of direct data to support this. There was uncertainty around the</p>

	<p>respective costs of treating adverse events arising from chemotherapy compared to nivolumab.</p> <p>Whilst acknowledging the absence of costs for treatment of adverse events and discontinuations, OWMAG consider the base case presented to be a reasonable estimate of the expected budget impact.</p>
Resource use	<p>OWMAG note that treatment with nivolumab is likely to be longer than with chemotherapy and associated resource use higher.</p> <p>The group were undecided if nivolumab monotherapy is likely to be associated with lower resource use for management of adverse events than chemotherapy.</p> <p>The group note that monitoring may be more intensive for patients on chemotherapy. The longer treatment for nivolumab may result in cumulative greater monitoring.</p> <p>Given that the population eligible for this treatment is small, the potential impact on the service is considered to be low. There are mechanisms in place for testing for microsatellite status for patients who are HER2 negative and have a CPS of less than 5.</p> <p>The group consider any potential additional resource use to be acceptable.</p>
Other factors	<p>OWMAG acknowledge that nivolumab may offer an alternative monotherapy treatment as a first-line treatment for patients with metastatic deficient mismatch repair (dMMR) / high microsatellite instability (MSI-H) oesophageal and gastric cancer. Tumours with dMMR/MSI-H status are less likely to respond to chemotherapy compared to tumours that are microsatellite stable. This patient group would not currently be eligible for combination treatment with a PD-L1 inhibitor and chemotherapy based on their CPS scores.</p> <p>The group understand that the prognosis for this patient group is poor and treatment is expected to be in a palliative care situation. Nivolumab may offer a life-extending option when compared to standard chemotherapy. Nivolumab can be given once a month, resulting in fewer appointments compared to chemotherapy administered every three weeks.</p> <p>OWMAG acknowledge that access to testing for MMR/MSI status varies between Health Boards. This may result in a delay to treatment depending on which test is available locally. However, this would not affect access to treatment.</p>

Final recommendation	OWMAG does not recommend the use of nivolumab monotherapy as a first-line treatment for patients with metastatic deficient mismatch repair (dMMR) / high microsatellite instability (MSI-H) oesophageal and gastric cancer.
Summary of rationale	<p>OWMAG acknowledge that there is a lack of direct clinical data for the use of nivolumab for this indication. They consider that the evidence presented overall for PDL-1 inhibitors as monotherapy demonstrates improved overall survival and progression-free survival. Given that the mechanism of action for the use of PDI-1 inhibitors to treat dMMR/MSI-H tumours is a class effect the lack of direct data for nivolumab are not considered to be of significant concern. However, the group acknowledge the considerable uncertainty as to the magnitude of effect and feel that the QALY gain required to make nivolumab cost effective at a willingness to pay threshold of £20,000 is implausible. OWMAG felt unable to recommend the use of nivolumab as the cost was not considered to demonstrate value for money for the NHS.</p> <p>Individual Patient Funding Request (IPFR) consideration remains appropriate for those patients who are likely to obtain significantly more clinical benefit from the intervention than would normally be expected at a reasonable value for money.</p>