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

Evidence Status Report: 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)

Report prepared by the All Wales Therapeutics and Toxicology Centre

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Key findings

Licence status
Nivolumab is not licensed as monotherapy for the first-line treatment of patients with metastatic or locally advanced and unresectable oesophageal and gastric cancer with deficient mismatch repair (dMMR) / high microsatellite instability (MSI-H); its use for this indication is off-label.

Clinical evidence
There are no clinical trials that have assessed the use of nivolumab as monotherapy in this setting. A study highlighting the efficacy of adding nivolumab treatment to chemotherapy as first-line treatment for advanced oesophageal and gastric cancer concluded that nivolumab with chemotherapy has superior overall survival and progression free survival benefit versus chemotherapy alone. There are post hoc data on the use of other PD-1 inhibitors (pembrolizumab) as monotherapy which demonstrates some antitumor activity. A meta-analysis of randomised controlled trials found a statistically significant improvement in survival and response for patients with MSI-H advanced gastric cancer who received anti-PD-1-based therapy. Clinicians in Wales have reported on three patients treated with nivolumab with positive results.

Safety
Safety data in this setting are lacking. Results from clinical efficacy trials of nivolumab used in combination with chemotherapy show that nivolumab was generally well tolerated.

Patient factors
Patients with dMMR/MSI-H tumours are reported to have a lower response rate with chemotherapy.

Cost effectiveness
There are no published studies on the cost effectiveness of nivolumab for this indication. AWTTC cost analyses identified that Nivolumab is associated with higher costs. AWTTC threshold analysis, with a limited cost perspective, identified that treatment with 24 cycles of nivolumab would require an improvement of at least [confidential data removed] QALYs to be cost-effective. There is insufficient evidence to support a robust case for cost-effectiveness.

Budget impact
The addition of nivolumab as first line treatment is estimated to increase the spend associated with this patient group in Wales between [confidential data removed] per year between 2024/7. This assumes nivolumab replaces standard chemotherapy for between 5 and 9 patients and uses median progression free

survival of 11.2 months from the KEYNOTE-062 clinical trial.

Impact on health and social care services
No additional impact is expected on existing services.

Innovation and/or advantages
Nivolumab offers an additional treatment option for this group. The aim of using this medicine for the indication described is to replace chemotherapy and reduce resultant chemotherapy toxicities.

Background

Nivolumab as monotherapy was previously available as part of the NG161 COVID-19 interim guidelines. Its indication on the Cancer Drugs Fund (CDF) was as an option to treat microsatellite instability-high (MSI-H) upper gastrointestinal cancers as an alternative to **first-line** chemotherapy[1]. Following the withdrawal of NG161, nivolumab was removed from the CDF for this indication and access to this treatment in Wales via this route was discontinued in March 2023. Clinicians indicate that for oesophageal or gastric tumours that are MSI-H or mismatch repair deficient (dMMR) patients have poorer outcomes and poorer response to chemotherapy. Experience has shown immunotherapy alone is associated with high response rates and excellent long-term outcomes. Clinicians in Wales consider there is an unmet need and have identified a cohort of patients who could benefit from this treatment, nivolumab was therefore considered suitable for assessment through the One Wales medicines process.

Target group

The indication under consideration is monotherapy for the first-line treatment of patients with metastatic or locally advanced and unresectable oesophageal and gastric cancer with dMMR/MSI-H.

Marketing authorisation date: Not applicable, off-label

Nivolumab is not licensed as first-line monotherapy for the treatment of patients with metastatic or locally advanced and unresectable oesophageal and gastric cancer with dMMR/MSI-H. [confidential data removed].

Nivolumab is currently licensed in the UK for use in a range of solid tumours including the following upper gastrointestinal cancers[2]:

- in combination with ipilimumab for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell programmed death-ligand 1 (PD-L1) expression ≥ 1%.

- in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%.

- as monotherapy for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy.

- as monotherapy for the adjuvant treatment of adult patients with completely resected oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.

- in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with human epidermal growth factor receptor 2 (HER2) -negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5.

Dosing information

The recommended dose as monotherapy is 240 mg every 2 weeks or 480 mg every 4 weeks administered intravenously over 30 minutes, depending upon the indication and population being treated[2]. Treatment with nivolumab is recommended until disease progression or unacceptable toxicity. For some indications treatment is capped up to 24 months in patients without disease progression[2].

Clinical background

Oesophageal cancer is a malignant tumour arising from cells lining the oesophagus (gullet), which is the muscular tube through which food passes from the throat to the stomach[3]. The two main types of oesophageal cancer are squamous cell carcinoma and adenocarcinoma. Cancers in the upper or middle part of the oesophagus are usually squamous cell carcinomas. Cancers in the lower oesophagus are usually adenocarcinomas[3]. Symptoms related to the cancer include dysphagia, nausea, indigestion, coughing, hoarse voice and fatigue[4].

Stomach cancer is a malignant tumour arising from cells in the stomach[5]. The most common type of stomach cancer is gastric or gastro-oesophageal junction adenocarcinoma, which affects about 95% of people with the disease[5]. Symptoms can be nonspecific and include heartburn, dysphagia, nausea, loss of appetite and stomach pain[6].

Survival rates for upper gastrointestinal cancers are improving and mortality rates have decreased by 9% in the UK in the last 10 years[7]. But survival remains poor due to late diagnosis as symptoms can be mistaken for more benign conditions. Around 17% of people diagnosed with oesophageal cancer and around a fifth (21%) of people diagnosed with stomach cancer in 2016 - 2020 in Wales are expected to survive their disease for 5 years or more[8]. For patients with stage 4 (metastatic) oesophageal or gastric cancer, 1-year survival rates are 22% and 18% respectively; patients are not expected to survive for 5 years or longer[8].

Nivolumab is a fully humanised IgG4 monoclonal antibody which targets the programmed cell death-1 receptor (PD-1) and blocks its interaction with programmed death ligands 1 and 2 (PD-L1 and PD-L2), to promote an anti-tumour immune response in T-cells[2]. The dMMR/MSI-H phenotypes found across upper gastrointestinal cancers are characterised by high tumour mutational burden and

high neoantigen load[9,10]. Increased neoantigen presentation can lead to higher tumour immunogenicity with increased populations of tumour-infiltrating lymphocytes and increased immune checkpoint expression[10]. These characteristics make these tumours more likely to respond to anti PD-1 therapy than those that are microsatellite stable[10].

Incidence/prevalence

Gastric cancer is the 17th most common cancer in the UK, accounting for 2% of all new cancer cases[11]. Oesophageal cancer is the 14th most common cancer in the UK, accounting for 2% of all new cancer cases[7]. Between 2018 and 2020 there were 2596 cases of oesophageal and gastric cancer in Wales, at diagnosis 1120 of these were stage 4 (metastatic), this gives an annual average of 373 cases. Clinical pathology experts inform us that in Wales 30% of gastric cancer tumours tested would be HER2 negative and have a PD-L1 CPS < 5 (approximately 112 patients annually), at which point they would be tested for dMMR/MSI. Approximately 4 – 8% of gastric and gastroesophageal junction cancers present with dMMR/MSI-H tumours[12], indicating between 5 and 9 newly diagnosed patients a year.

Current treatment options and relevant guidance

For many people with upper gastrointestinal cancer, curative surgery or chemoradiotherapy is not possible and treatment is palliative care[13]. This may include palliative radiotherapy or chemotherapy, inserting an oesophageal stent or simply providing appropriate supportive care[13].

For patients who have a performance status of 0 to 2, NICE recommend first-line palliative chemotherapy for locally advanced or metastatic oesophageal and gastric cancer which includes[13]:

- trastuzumab (in combination with cisplatin and capecitabine or 5-fluorouracil) as a treatment option for people with HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction
- doublet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin
- triplet treatment: 5-fluorouracil or capecitabine in combination with cisplatin or oxaliplatin plus epirubicin.

National Comprehensive Cancer Network (NCCN) guidelines recommend that patients with a performance status of 3 or more should be offered palliative or best supportive care only. First-line systemic therapy regimens with 2 cytotoxic drugs are preferred for patients with advanced disease because of their lower toxicity. The use of 3 cytotoxic drugs in a regimen should be reserved for medically fit patients with an excellent performance score and easy access to frequent toxicity evaluations[14].

Pembrolizumab in combination with platinum and fluoropyrimidine-based chemotherapy is recommended by NICE as an option for the treatment of untreated (first-line) metastatic oesophageal carcinoma in adults whose tumours express PD-L1 with CPS ≥10 (TA737[15]). Pembrolizumab as monotherapy is recommended as an option for MSI-H/dMMR unresectable or metastatic gastric, small intestine or biliary cancer that has progressed during or after one therapy (NICE TA914[16]).

Therefore, this assessment only considers nivolumab monotherapy in the first-line setting.

Nivolumab is currently recommended as an option by NICE in combination with platinum- and fluoropyrimidine-based chemotherapy for untreated (first-line) metastatic oesophageal squamous cell carcinoma in adults whose tumours express PD-L1 at a level of 1% or more. It is recommended only if pembrolizumab plus chemotherapy is not suitable (TA865[17]).

Nivolumab is also recommended by NICE in combination with chemotherapy for advanced gastric, gastro oesophageal junction or oesophageal adeno- or squamous cell carcinoma (TA857[18], TA865[17]) and as an adjuvant treatment of resected oesophageal or gastro-oesophageal junction cancer (TA746[3]).

The European Society for Medical Oncology (ESMO), NCCN and American Society of Clinical Oncology (ASCO) guidelines are in accordance with NICE guidance[3,14,18-21]. For advanced oesophageal squamous-cell carcinoma PD-L1 negative or <1%, ESMO recommends first line platinum-fluoropyrimidine neoadjuvant chemotherapy and second line nivolumab monotherapy[19].

The NCCN guidelines recommend that HER2 and PD-L1 testing should be performed in patients with documented or suspected metastatic adenocarcinoma and MSI or MMR testing in all newly diagnosed patients[14]. In terms of the testing pathway in Wales, patients who present with oesophageal and gastric adenocarcinoma will be tested for HER2 and PD-L1 CPS status[22]. Clinical experts have confirmed that if the cancer is HER2 positive, treatment would include trastuzumab. If HER2 negative but PD-L1 CPS ≥ 5, nivolumab or pembrolizumab (if CPS ≥10) in combination with chemotherapy would be the treatment choices. For those patients who are negative for HER2 and with CPS < 5, chemotherapy alone would be the standard treatment regimen. At this stage in the pathway patients are tested for dMMR/MSI status. Clinicians indicate that for CPS ≥ 5 tumours would not be routinely tested for dMMR/MSI status. This means that access to nivolumab for dMMR/MSI-H disease for patients with HER2 negative and PD-L1 CPS < 5 is not associated with additional monitoring outside of the normal testing pathway. It also indicates that the true comparator in this setting is chemotherapy alone. Patients who present with junctional or oesophageal squamous cell carcinoma follow a different pathway and are tested for PD-L1 CPS status only. For squamous cell carcinoma with a CPS ≥ 10, treatment is pembrolizumab, for CPS < 10 treatment option is determined by tumour proportion score[22].

Summary of evidence on clinical effectiveness

A literature search was conducted in November 2023 by the All Wales Therapeutics and Toxicology Centre (AWTTC) relating to nivolumab as monotherapy in upper gastrointestinal cancers with dMMR/MSI-H phenotypes. Pembrolizumab monotherapy was also searched as a proxy PD-1 inhibitor to extrapolate any relevant data. Searches were performed using Cochrane, Central Register of Controlled Trials, EMBASE, MEDLINE and TRIP database. The primary outcomes intended were overall survival (OS), progression-free survival (PFS), objective response rate (ORR), adverse events (AE), health related quality of life (HRQoL) and resource use. A literature search identified 109 records which were assessed for eligibility, with 83 excluded following removal of duplicates and screening of title and abstracts. Following eligibility screening, 5 publications were included in the report covering 3

clinical trials, one post hoc cohort study and a meta-analysis. The remaining records were excluded due to small patient numbers, incorrect cohort or unsuitable study design.

In May 2024, AWTTC performed an updated search using the same databases as above. A total of 871 records were identified, 649 following de-duplication. Following sifting on title and abstract, 21 remained for eligibility screening. No additional relevant references were identified.

A second literature search to include cancers (unspecified) with dMMR or MSI-H phenotypes identified a total of 147 records, following initial sift 20 reports were screened. This along with the original literature search was re-screened with broadened criteria to identify potential useful references for anti-PD-1 use as later line therapy or different cancer with the dMMR/MSI-H genotype. An additional 11 references have been included in this updated report.

Efficacy

No clinical trials were found looking at the use of nivolumab monotherapy in the first-line setting. One study comparing nivolumab with chemotherapy versus chemotherapy alone as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/oesophageal adenocarcinoma, is described below[23,24]. Due to no direct comparative clinical effectiveness data, two KEYNOTE studies evaluating pembrolizumab for upper gastrointestinal cancers have been used to extrapolate clinical efficacy data as a proxy for nivolumab[25-27].
A meta-analysis was also included which investigated anti-PD-1-based regimens versus chemotherapy and includes a sub analysis based on microsatellite status of the tumours[28].

Janjigian et al (2021) conducted a multicentre, randomised, open-label, phase 3 trial (CheckMate 649) to assess the efficacy and safety of nivolumab plus chemotherapy versus chemotherapy alone[23]. Eligible patients were all HER2 negative regardless of PD-L1 expression. Primary endpoints included overall survival (OS) or progression-free survival (PFS) in patients whose tumours had a PD-L1 CPS ≥ 5. Secondary endpoints were OS in patients with a PD-L1 CPS ≥ 1and in all randomly assigned patients (irrespective of PD-L1 status). Patients (n = 1581) were randomly assigned to nivolumab (360 mg every 3 weeks or 240 mg every 2 weeks) plus chemotherapy (XELOX [capecitabine and oxaliplatin] or FOLFOX [leucovorin, fluorouracil, and oxaliplatin]) (n = 789) versus chemotherapy alone (n = 792). A third arm of nivolumab plus ipilimumab was later closed and was not included in these results.

In the latest analysis, the median follow-up was 47.4 months (interquartile range [IQR] 36.2-61.5) for nivolumab plus chemotherapy and 47.3 months (IQR 36.6-61.5) for chemotherapy alone. The median treatment duration was 6.8 months (IQR 0.1-57.7) with nivolumab plus chemotherapy and 4.9 months (IQR 0.0-55.2) with chemotherapy alone[23].

Nivolumab plus chemotherapy showed a significant improvement in OS in patients with a PD-L1 CPS ≥5 (HR [hazard ratio] 0.70 [95% confidence interval [CI] 0.61-0.81]) and all randomly assigned patients (0.79 [0.71-0.88]) versus chemotherapy alone in the stratified analysis[23]. At 36 months, 21% of patients who

received nivolumab plus chemotherapy were alive versus 10% of patients who received chemotherapy alone There was also clinically meaningful PFS benefit, improved and durable objective responses (see Table 1 and Appendix 1, Table A1, A2). There was a trend towards improved HRQoL with nivolumab plus chemotherapy, although this change was not clinically meaningful per the defined threshold[24]. There was no survival advantage in those patients with a CPS < 1 (see Appendix 1, Table A1, A2).

Microsatellite status
In patients with CPS ≥ 5 the median OS for patients with MSI-H tumours (n = 34) was 44.8 months with nivolumab plus chemotherapy versus 8.8 months with chemotherapy alone (unstratified HR for death 0.29 [95% CI 0.12-0.71]); for microsatellite stable tumours (n = 847), the median OS was 14.3 months versus 11.3 months respectively (unstratified HR 0.68 [95% CI 0.56 to 0.85]).

The median OS for all randomised patients with MSI-H tumours (n = 44) was 38.7 months with nivolumab plus chemotherapy versus 12.3 months with chemotherapy alone (unstratified HR for death 0.34 [95% CI 0.16–0.74]); for microsatellite stable tumours (n = 1,378) median OS was 13.8 months and 11.5 months respectively (unstratified HR for death 0.79 [95% CI 0.71–0.89]). Results were not reported for CPS scores <1[24].

Table 1. Three year follow up results from Checkmate 649 for all patients and for patients with PD-L1 CPS ≥ 5

Population	Nivolumab + chemotherapy	Chemotherapy alone	HR (95% CI)
Median overall survival (months)			
Overall (n = 1581)	13.7	11.6	0.79 (0.71 to 0.88)
PD-L1 CPS ≥5 (n = 955)	14.4	11.1	0.70 (0.61 to 0.81)
Median progression free survival (months)			
Overall (n = 1581)	7.7	6.9	0.79 (0.71 to 0.89)
PD-L1 CPS ≥5 (n = 955)	8.3	6.1	0.70 (0.60 to 0.81)
Objective response rate (%)			
Overall (n =1209)	58	46	NR
PD-L1 CPS ≥5 (n =768)	60	45	NR
CI: confidence interval; HR: hazard ratio; NR: not reached			

Pembrolizumab

Like nivolumab, the PD-1 inhibitor pembrolizumab is an immune checkpoint inhibitor with a similar mode of action by binding to the PD-1 receptor and blocks its interaction with ligands PD-L1 and PD-L2. Several published studies in various cancer sites have reported similar clinical effectiveness and survival benefit between nivolumab and pembrolizumab[29-31].

There is no direct clinical effectiveness data for nivolumab as monotherapy in the first-line setting however, pembrolizumab is being investigated in multiple KEYNOTE trials across different tumour types, either alone or as part of various combinations. Based on the lack of direct clinical effectiveness data with nivolumab as monotherapy in the first-line setting, we report on data for use of pembrolizumab monotherapy as proxy treatment.

Chao et al undertook a post hoc analysis based on MSI-H tumours of three pembrolizumab trials in gastric, or gastro-oesophageal junction cancer: phase 2 KEYNOTE-059 (third-line treatment or higher) single-arm trial and the phase 3 KEYNOTE-061 (second-line treatment) and KEYNOTE-062 (first-line treatment)[25]. In this analysis we concentrate on the first line results from KEYNOTE-062 as these are most relevant to the patient cohort under consideration[25].

KEYNOTE-062 compared the antitumor activity of first-line pembrolizumab, pembrolizumab plus chemotherapy, or chemotherapy alone in 763 patients with advanced gastric/gastroesophageal junction cancer and PD-1 CPS of 1 or greater[27]. The median follow-up was 29.4 (range 22.0-41.3) months. The study concluded that pembrolizumab monotherapy was noninferior, but not superior, to chemotherapy for OS in patients with CPS ≥ 1, but with fewer adverse events observed. HR for OS 0.91 (99.2% CI; 0.69-1.18) and HR for PFS 1.66 (95% CI; 1.37-2.01). When the CPS was 10 or greater, OS was higher with pembrolizumab monotherapy, 17.4 months compared with 10.8 months for chemotherapy alone, HR 0.69 (95% CI; 0.49-0.97). This was not statistically tested as superiority was not demonstrated. However, there was no significant difference in PFS, 2.9 months versus 6.1 months for pembrolizumab monotherapy and chemotherapy respectively, HR 1.10 (95% CI; 0.79-1.51), no p value was provided.

Microsatellite status

In exploratory analysis of patients with MSI-H tumours with PD-L1 CPS ≥ 1, response rates were better for pembrolizumab monotherapy than for chemotherapy alone (see Table 2)[25].

Table 2. Results from post hoc analysis of KEYNOTE-062 for all patients and for patients with MSI-H tumours, PD-L1 CPS ≥ 1[25]

	Pembrolizumab	Pembrolizumab plus chemotherapy	Chemotherapy
Overall results			
Total patients (No.)	256	257	250
ORR % (95%CI)	14.8 (10.7-19.8)	48.6 (42.4-54.9)	37.2 (31.2-43.5)
CR %	3.5	7.4	5.6
PR %	11.3	41.2	31.6
SD %	27.0	28.8	41.6
PD %	41.0	7.4	8.4
Median PFS, months (95% CI)	2.0 (1.5-2.8)	6.9 (5.8-7.3)	6.4 (5.7-7.1)
Median OS, months (95% CI)	10.6 (7.7-13.8)	12.5 (10.8-13.9)	11.1 (9.2-12.8)
Estimated OS % (95% CI)			
12 months	47 (41-53)	53 (47-59)	46 (39-52)
24 months	27 (21-32)	24 (19-30)	19 (15-24)
Results for MSI-H tumours			
Total patients (No.)	14	17	19
ORR % (95%CI)	57.1 (28.9-82.3)	64.7 (38.3-85.8)	36.8 (16.3-61.6)
CR %	7.1	35.3	10.5
PR %	50.0	29.4	26.3
SD %	21.4	17.6	42.1
PD %	14.3	0	10.5
PFS	11.2 (1.5-NR)	NR (3.6-NR)	6.6 (4.4-8.3)
OS	NR (10.7-NR)	NR (3.6-NR)	8.5 (5.3-20.8)
Estimated OS % (95% CI)			
12 months	79 (47-92)	71 (43-87)	47 (24-67)
24 months	71 (41-88)	65 (39-82)	26 (10-57)
CI: confidence interval; CR: complete response: MSI-H: microsatellite instability high; NR: not reached; ORR: objective response rate: OS: overall survival: PD: progressive disease: PFS: progression free survival; PR: partial response; SD: stable disease			

KEYNOTE-059 was a nonrandomised study that evaluated pembrolizumab treatment in HER2 negative, recurrent or metastatic gastric/gastroesophageal junction adenocarcinoma with PD-L1 positivity[26]. The study included two cohorts that received first line treatment of either pembrolizumab plus chemotherapy (cohort 2, n = 25) or pembrolizumab monotherapy (cohort 3, n = 31). One patient in cohort 3 had MSI-H tumours and achieved partial response, no patients in cohort 2 had MSI-H tumours. The median follow-up was 13.8 months (range 1.8 – 24.1). Cohorts 2 and 3 had a

complete response in one patient (4.0%) and two patients (6.5%) respectively. See Table 3.

Table 3. Results from KEYNOTE-059[26]

Study & patient arm	Median overall survival (months)	Progression free survival (months)	Objective response rate (ITT)
KEYNOTE-059 cohort 2* Pembrolizumab plus chemotherapy	13.8 (95% CI 8.6-not estimable)	6.6 (95% CI 5.9-10.6)	60.0% (95% CI 39.0-79.0)
KEYNOTE-059 cohort 3** Pembrolizumab monotherapy	20.7 (95% CI 9.2-20.7)	3.3 (95% CI 2.0-6.0)	25.8% (95% CI 11.9-44.6%),
CI: confidence interval; CPS: combined positive score; HR: hazard ratio; ITT: intention-to-treat population; NR: not recorded *CPS ≥ 1 (n = 16 [64%]), CPS < 1 (n = 8 [32%]), CPS unknown (n = 1 [4%]) **CPS ≥ 1 (n =31 [100%])			

PD-1 inhibitors meta-analysis

Pietrantonio et al (2021) performed meta-analysis of randomised controlled trials (RCTs) investigating anti-PD-1-based regimens versus chemotherapy, with the aim of providing a more accurate estimate of the activity and efficacy of anti-PD-1-based regimens in patients with MSI-H advanced gastric cancer[28].Two studies were conducted in first-line therapy (KEYNOTE- 062 [pembrolizumab versus pembrolizumab plus chemotherapy versus chemotherapy; CheckMate 649 [nivolumab plus chemotherapy versus chemotherapy alone]). Another investigated anti-PD-1-based-therapy in maintenance (JAVELIN Gastric 100 [avelumab versus continued chemotherapy]) and (KEYNOTE-061 [pembrolizumab versus paclitaxel]) was conducted in second-line therapy. A total of 2545 patients with evaluable MSI status were included and 123 (4.8%) had MSI-H cancers. PFS and ORR were not reported for MSS tumours.

There was statistically significant evidence of improved survival and response in patients with MSI-H advanced gastric cancer who received anti-PD-1-based therapy compared with chemotherapy in the frame of RCTs. Significantly greater OS benefit was found in the subgroup with MSI-H tumours compared with the subgroup with MSS tumours. Firstline treatment with an anti-PD-1-based therapy was also significantly better than chemotherapy alone for OS in the MSI-H group than in the MSS sub-group. There were no comparisons made for microsatellite status with anti-PD-1 monotherapy, but OS was better with anti PD-1 monotherapy than chemotherapy alone for MSI-H tumours (see Table 4)[28].

Table 4. Results from Pietrantonio et al. meta-analysis[28]

	MSI-H		MSS		Interaction
	Number of studies/ subgroups	Relative Effect (95% CI)	Number of studies	Relative Effect (95% CI)	
OS with anti-PD-1-based regimens	5	HR 0.34*** (0.21-0.54)	3	HR 0.85*** (0.71-1.00)	p = 0.003
OS with first line anti-PD-1 based regimens	3	HR 0.33* (0.19-0.57)	2	HR 0.82 (0.64-1.05)	p = 0.003
OS with anti-PD-1 monotherapy	3	HR 0.32*** (0.17-0.63)		NR	
OS with anti-PD-1-based chemoimmunotherapy	2	HR 0.35** (0.18-0.69)			
PFS with anti-PD-1 regimens, any line	3	HR 0.57* (0.33-0.97)		NR	
Response (ORR) with anti-PD-1 regimens, any line	3	RR 1.76* (1.10-2.83)		NR	
CI: confidence interval; HR: hazard ratio; MSI-H: microsatellite instability-high MSS: Microsatellite Stability; NR: not recorded; OS: overall survival; ORR: overall response rate; PFS: progression free survival; RR: response rate *p ≤ 0.05, **p < 0.01, ***p < 0.001 compared to chemotherapy alone					

A study in colorectal cancer and a study of unspecified anti PD-L1 therapies in metastatic gastric cancer

In KEYNOTE-177 first-line pembrolizumab led to significantly longer PFS (median, 16.5 versus 8.2 months; HR, 0.60; 95% CI, 0.45 to 0.80; p = 0.0002) than chemotherapy for dMMR/MSI-H metastatic colorectal cancer, with fewer treatment-related adverse events. As of cut-off date, data on overall survival were immature[32]. This may be considered relevant to gastric patients as Mazzoli et al (2023) compared the efficacy of PD-1 blockade in dMMR/MSI-H metastatic gastric cancer versus dMMR/MSI-H metastatic colorectal cancer[33]. After adjusting for baseline prognostic characteristics, patients in the metastatic gastric cancer cohort did not show a statistically and clinically meaningful inferior PFS and OS compared to metastatic colorectal cancer patients, concluding the efficacy of immune checkpoint inhibitors appears similar in the two tumour types[33].

Randon et al retrospectively analysed 130 patients with dMMR/ MSI-H advanced gastric cancer receiving anti-PD-1 based therapies in various lines with the majority (89%) being monotherapy[34]. Thirty-two (25%) patients received ICIs in the first-line setting and 98 (75%) in later treatment lines. Which anti-PD-1 therapies had been administered were not specified. They observed 23 (22%) complete responses and 45 (44%) partial responses, with 22 (17%) reported as stable disease. ORR was 67% and disease control rate was 87%. They concluded that anti-PD-1 based therapies have a significant activity and efficacy in patients with microsatellite instability, advanced gastric cancer[34].

Real world data

AWTTC have data on three patients who have received or are receiving treatment with nivolumab first line for treatment of metastatic gastric or oesophageal cancer: [confidential data removed].

Safety

The clinical safety of nivolumab has been studied in patients as monotherapy across various tumour types (n = 4646) with minimum follow-up ranging from 2.3 to 28 months[2]. The majority of adverse reactions associated with nivolumab were mild to moderate, the most commonly reported (≥ 1 in 10 patients) were fatigue, musculoskeletal pain, diarrhoea, rash, cough, nausea, pruritus, decreased appetite, arthralgia, constipation, dyspnoea, abdominal pain, upper respiratory tract infection, pyrexia, headache, anaemia and vomiting. Immune-related adverse reactions affecting more than one body system can occur simultaneously, patients prescribed nivolumab are provided with a patient alert card[2].

In the most recent analysis of CheckMate 649 study (nivolumab plus chemotherapy vs chemotherapy alone), the most common treatment-related adverse events reported were nausea, diarrhoea, and peripheral neuropathy across both groups[24]. Grade 3–4 treatment-related adverse events occurred in 473 (60%) of 782 patients in the nivolumab plus chemotherapy group and 346 (45%) of 767 patients in the chemotherapy alone group. Any-grade treatment-related adverse events leading to discontinuation were reported in 331 (42%) patients in the nivolumab plus chemotherapy group and 198 (26%) patients in the chemotherapy alone group. Any grade serious treatment-related adverse events were reported in 176 (23%) of 782 patients given nivolumab plus chemotherapy (grade 3–4: 134 [17%] patients; grade 5: four [0.5%] patients). A total of 95 (12%) of 767 patients given chemotherapy (grade 3–4: 78 [10%] patients, no grade 5 events). There were 16 (2%) deaths in the nivolumab plus chemotherapy group, 12 of which were reported to be treatment related. There were four (1%) deaths in the chemotherapy alone group, all considered to be treatment related[23].

The safety of pembrolizumab as monotherapy in the two KEYNOTE studies indicated that pembrolizumab was better tolerated when used as monotherapy than in combination[35]. Grade ≥ 3 treatment related adverse events ranged from 60-73% for pembrolizumab plus chemotherapy versus 17-23% for pembrolizumab alone. Treatment discontinuations were also more common with combination treatment[26,27].

There were two treatment related deaths reported in the KEYNOTE-059 trial (acute kidney injury and pleural effusion)[26], and three reported treatment related deaths in the pembrolizumab monotherapy group in KEYNOTE-062 trial (cause not specified)[27].

Discussion

The current treatment pathway for patients who have oesophageal or gastric adenocarcinomas that are HER2 negative and with a PD-L1 CPS < 5 would be treatment with chemotherapy. The proposed place of nivolumab would be for a small cohort of patients within this category who have tumours that have tested positive for dMMR/MSI-H. AWTTC were unable to locate any clinical evidence of the use of nivolumab as monotherapy in this specific setting.

The genomic instability characteristic of dMMR/MSI-H tumours appears to be associated with chemoresistance, and the benefits of standard adjuvant or

neoadjuvant chemotherapy is uncertain[9]. It has been reported that whilst chemotherapy significantly improves prognosis for gastric cancer patients with microsatellite stable (MSS) tumours, significant benefit is less evident for the prognosis of gastric cancer patients with MSI-H tumours[36-38]. A study comparing response to fluorouracil-based adjuvant chemotherapy in dMMR and proficient mismatch repair (pMMR) stage II and III colorectal cancers found that adjuvant chemotherapy did not improve disease-free survival of dMMR cases compared with surgery alone[39]. Similarly, in a post hoc analysis of stage II-III gastric cancer trial, adjuvant chemotherapy did not improve disease free survival in patients with MSI-H tumours when compared to surgery alone. This was regardless of PD-L1 expression[36].

The main evidence for nivolumab as a first line treatment comes from CheckMate 649, but only when used in combination with chemotherapy. Versus chemotherapy alone, nivolumab plus chemotherapy improved OS and PFS. This improvement in survival benefit with nivolumab plus chemotherapy occurred regardless of microsatellite instability status, although the 3% of patients with MSI-H tumours had a greater reduction in the risk of death than those with MSS tumours. Although numbers are small and, further studies are needed to test these results. In an exploratory analysis, the unstratified HRs for OS with nivolumab plus chemotherapy versus chemotherapy alone in patients with a PD-L1 CPS < 1 (HR = 0.95 (95% CI 0.74–1.24 and < 5 (HR = 0.95 (0.80-1.12) were higher than in patients with a CPS ≥ 1, those with a CPS ≥ 5 and all randomly assigned patients; indicating a better response in those patients with a higher PD-L1 CPS status. Additionally, the majority (77%) of MSI-H tumours were associated with a CPS ≥ 5. This may have implications for the group under consideration who would have PD-L1 CPS < 5. This is also in accordance with the results from KEYNOTE-062 which found that median OS was longer for patients with a CPS ≥ 10 in the pembrolizumab monotherapy group compared with those with a CPS ≥ 1. There was no overall survival benefit using pembrolizumab monotherapy compared with chemotherapy alone and time to progression was shorter in the pembrolizumab monotherapy group.

Pembrolizumab has the same mechanism of action as nivolumab and pembrolizumab The KEYNOTE studies evaluating pembrolizumab have therefore been presented to provide clinical efficacy data for use of a PD-1 inhibitor as monotherapy in the first line setting for advanced oesophageal and gastric cancer. In the first line setting, 6.6% of patients in the KEYNOTE-062 trial had MSI-H tumours with exploratory analysis showing greater survival benefit of pembrolizumab monotherapy versus chemotherapy alone. Objective response rates were also higher with pembrolizumab monotherapy compared with chemotherapy, however, confidence intervals were fairly wide indicating increasing uncertainty. Patients on pembrolizumab with chemotherapy tended to have the better response of the three treatment groups in the MSI-H sub population. The limitation with these results as stated above is that all patients recruited in to the trial had a PD-L1 CPS ≥ 1 and the majority of MSI-H patients (64%) actually had a CPS of ≥ 10, unlike the cohort under consideration. In KEYNOTE-059, one patient who received first-line pembrolizumab monotherapy and had positive dMMR/MSI-H experienced a partial response to treatment[26]. No patients in the pembrolizumab monotherapy group had a CPS status of < 1. Overall adverse event rates were lower in the pembrolizumab monotherapy groups when compared to use in combination with chemotherapy.

In the meta-analysis by Pietrantonio et al (2021), the authors found that there was statistically significant evidence of improved survival and response in patients with

MSI-H advanced gastric cancer who received anti-PD-1-based therapy, with significantly greater OS benefit compared with the subgroup with MSS tumours[28]. The test for interaction between MSI status and treatment was possible only for OS, due to the lack of PFS and ORR data reported in the MSS subgroup. The analysis has a number of limitations as it did not look at individual patient level data and considered a broad range of treatment lines as well as both monotherapy and combination treatment with chemotherapy. There was also heterogeneity of trial populations in terms of CPS status which may affect its applicability to the group under consideration[28]. The retrospective study by Randon explored anti-PD-1 treatments in different lines of treatment for advanced dMMR/MSI-H gastric cancer demonstrating efficacy of this class of medicine in the treatment of gastric cancer with microsatellite instability[34].

Extrapolating to the first-line setting in other cancer sites, KEYNOTE-177 showed an advantage for dMMR/MSI-H metastatic colorectal cancers treated with pembrolizumab over treatment with chemotherapy. The study by Mazzoli et al suggests one could infer a similar advantage to metastatic gastric cancers, albeit this has not been peer reviewed.

Later line (third and above) nivolumab monotherapy demonstrated significant survival advantage over placebo in advanced gastric cancer in the ATTRACTION-2 clinical trial[40]. The DELIVER trial explored nivolumab monotherapy in the same patient group in the real-world setting; results confirmed efficacy in line with ATTRACTION-2 in routine clinical practice[41]. Sub-groups analyses were not provided for dMMR/MSI-H tumours.

Van der Velden et al have initiated an adaptive, precision oncology trial which identifies cohorts of patients with defined tumour types and molecular variants being treated with off-label anticancer medicines[42]. Two cohorts have completed accrual, the first being patients (n = 30) with MSI tumours (8 tumour types) treated with nivolumab (median 3rd line therapy; range 0–12). The rate of clinical benefit was 63% (3% complete response; 37% partial response; 23% stable disease) at ≥ 16 weeks. Median PFS was not reached after median follow-up of 16.5 months. The second cohort, pembrolizumab for MSS colorectal cancer, showed limited clinical benefit in stage 1 and was therefore closed. The authors concluded that these cohorts demonstrate the potential for the trial to identify subgroups of patients who may benefit from off-label treatments and prevent unnecessary treatment in other subgroups[43].

HRQoL was similar between the nivolumab and chemotherapy and chemotherapy alone arms, though due to the open-label study design of CheckMate 649, this might have potentially influenced patient responses. In KEYNOTE-062, HRQoL were similar between pembrolizumab monotherapy and chemotherapy alone, with only a longer time to deterioration regarding nausea/vomiting observed for pembrolizumab (HR, 0.61; 95% CI, 0.44-0.85; p = 0.003)[27,44].

In terms of adverse events, the available information suggests that nivolumab safety is consistent with the profile known for its pharmacological class and no new signals have been identified. Data available, although limited in size and long-term exposure, appear acceptable and suggest a tolerable profile, however there are no safety data available for the specific indication under consideration. Nivolumab monotherapy may be associated with primary and acquired resistance[45]. Combination therapy may overcome cancer resistance and boost efficacy; nivolumab has been combined with

various treatments including ipilimumab. Nevertheless, Checkmate 649 which included an arm comparing nivolumab and ipilimumab found OS did not meet the prespecified boundary for significance against chemotherapy alone whereas nivolumab plus chemotherapy demonstrated improvement in OS in patients with CPS > 1 compared with chemotherapy alone. In patients with MSI-H tumours, nivolumab and ipilimumab showed longer OS and higher ORR compared with chemotherapy alone[46].

Cost-effectiveness evidence

No studies were found for the cost-effectiveness of nivolumab for this indication.

The lack of cost-effectiveness evidence for the indication is not unexpected given the lack of clinical trial data for nivolumab monotherapy in the first-line treatment of patients with metastatic oesophageal and gastric cancer with dMMR)/MSI-H. Clinical effectiveness, HRQoL and adverse event data may be considered to inform a more general value for the intervention. Additionally, AWTTC has undertaken threshold analyses to determine how many QALY gains would be required for nivolumab to be considered relatively cost-effective.

Patients diagnosed with incurable oesophageal and gastric cancer have severely affected quality of life. In a study of newly diagnosed patients with oesophageal and gastric cancer, quality of life was significantly lower in patients with incurable oesophageal cancer than in those planned for curative treatment[47]. For patients planned for palliative treatment fatigue, pain and dyspnoea, body image and speech were all significantly worse when compared with those planned for curative treatment[47]. A literature review of the impact of gastric cancer treatment on quality of life in patients with gastric cancer reported on effects of systemic treatments[43]. The review reported on studies that show that systemic chemotherapy potentially improves quality of life beyond prolongation of OS. A choice-based analysis in patients with locally advanced or metastatic cancer reported the most important preference to be for low treatment toxicity followed by ability to self-care and an additional survival benefit of up to three months. It was also noted that reporting of HRQoL is limited in the majority of study reports[43].

HRQoL data was reported in the original analysis of the Checkmate 649 trial comparing nivolumab plus chemotherapy versus chemotherapy alone[23]. Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) total scores were reported for all randomly assigned patients and for patients with PD-L1 CPS ≥ 5. We report the results for all randomly assigned patients only. Baseline mean FACT-Ga total scores were similar between the nivolumab plus chemotherapy (126·6 [Standard deviation (SD), 28·3]) and chemotherapy alone groups (126·8 [SD, 26·8]), with an improvement from baseline in FACT-Ga total score at all on-treatment assessments. The least squares mean (LSM) difference between treatment groups favoured nivolumab plus chemotherapy versus chemotherapy alone (at timepoints with ≥ 50 patients in each group). However, this result was less than the minimally important difference of 15.1 points. Patients in the nivolumab plus chemotherapy group had decreased risk of symptom deterioration (e.g. nausea/vomiting) than the chemotherapy alone group while on treatment HR 0·77 [SD 0·63–0·95]. Three-year follow up results were similar, favouring the nivolumab plus chemotherapy group[24].

In KEYNOTE-062 HRQoL was measured in patients with a PD-L1 CPS of ≥ 1 who had received one dose or more of study drug and completed one or more HRQoL

questionnaire (European Organisation for the Research and Treatment of Cancer [EORTC], 30-question quality-of-life [QLQ-C30], EORTC 22-question quality-of-life gastric-cancer-specific module [QLQ-STO22])[44]. The HRQoL population comprised 252 patients from the pembrolizumab monotherapy arm and 243 from the chemotherapy arm. There was no difference between the two groups in LSM change in global health status/quality of life (GHS/QoL) from baseline to week 18 (-0.16; 95% CI 5.01 to 4.69; p = 0.948). LSM change for most subscales showed worsening in both groups. Time to deterioration (TTD) in the GHS/QoL were similar between arms, as were the TTD for appetite loss and pain. Longer TTD was observed for pembrolizumab versus chemotherapy for nausea/vomiting group (HR, 0.61; 95% CI, 0.44 to 0.85; p = 0.003) which aligns with the increased incidence of nausea and vomiting treatment-related AEs from chemotherapy in the primary analysis. With the exception of longer TTD for nausea/vomiting in the pembrolizumab group overall HRQoL was similar for both treatments. HRQoL was not stratified by microsatellite stability status[44].

Comparative clinical efficacy and safety data are described in the previous section. It is not possible to infer potential quality adjusted life-year (QALY) gains or added value for nivolumab over standard chemotherapy based on available evidence. Minimal gains in clinical effectiveness and a reduction in treatment-related adverse events may be associated with nivolumab monotherapy treatment compared with chemotherapy but it is not possible to estimate if these gains could be considered cost-effective.

To inform threshold analyses, a consideration is required as to whether nivolumab monotherapy as a first-line treatment for the specified patient population meets the QALY shortfall criteria set by the AWMSG policy on appraising medicines for severe conditions (Table 5).

Table 5. Severity modifier considerations for One Wales (OWMAG)/AWMSG

AWMSG criteria for applying a severity modifier weight	*Nivolumab* considerations
AWMSG can: • apply a QALY weight of 1 if the medicine is indicated for patients with a condition associated with an absolute QALY shortfall < 12 and/or a proportional QALY shortfall < 0.85. • apply a QALY weight of 1.2 if the medicine is indicated for patients with a condition associated with an absolute QALY shortfall ranging between 12 and 18 and/or a proportional QALY shortfall ranging between 0.85 and 0.95. • apply a QALY weight of 1.7 if the medicine is indicated for patients with a condition associated with an absolute QALY shortfall >18 and/or a proportional QALY shortfall ≥ 0.95.	A standard approach was used to compare the expected total QALY estimates for patients being treated with chemotherapy and the expected QALYs general population without the condition[48]. The general population expected total QALY estimates are a function of age and the percentage of females in the population, these are informed by the Checkmate 649 trial cohort as 62 and 28% respectively[23]. Mortality within the general population is sourced from pooled life tables, this is used in conjunction with age and sex based QoL to offer overall QALYs.[49,50]. Expected QALYs for people with oesophageal and gastric cancer were identified using a targeted literature approach. Utility estimates for people with Stage IV oesophageal cancer were used in the base case[51]. The EQ-5D score of 0.72 is used in conjunction with the Checkmate 649 trial overall survival figure of 11.1 months to offer a QALY estimate of 0.67[23,51]. An annual discount rate of 3.5% has been used to calculate QALY shortfall estimates. AWTTC considers the most plausible absolute QALY loss to be around 11.28 with a proportional QALY shortfall of 0.94 (intervention QALY estimate 0.67 compared to absence of disease of 11.95, representing a 94% reduction in expected QALYs). Given this proportional shortfall estimate, a QALY weight of 1.2 is applicable for the evaluation of nivolumab as monotherapy as a first-line treatment in the target population. A plausible alternative quality of life figure of 0.742 was calculated by weighting the QoL figures for stage IV oesophageal cancer by the 28% female population from Checkmate 649[23,52]. This approach was used to assess the robustness of the QALY shortfall finding to the QoL estimate, the appropriate modifier remained the same.
QALY: quality-adjusted life-year	

An AWTTC cost analysis includes the costs of first line cancer treatments procurement and administration costs. Dosing is informed by the KEYNOTE-062 study, nivolumab standard dose of 240 mg every 2 weeks by intravenous infusion. Acquisition costs for nivolumab are [confidential data removed] for a 240 mg vial, excluding VAT (which includes a confidential discount). Delivery costs of intravenous cancer treatments are derived from NHS reference costs, they consist of outpatient chemotherapy delivery (SB12Z and SB15Z). Evidence from the KEYNOTE-062 study showed a PFS of 11.2 months, this duration is used to calculate overall treatment costs. Intervention costs equate to [confidential data removed] (medicine acquisition [confidential data removed] + administration £7,716).

The acquisition cost of chemotherapy (oxaliplatin 130mg/m^2 every 3 weeks and capecitabine 625 mg/m^2 twice daily every 3 weeks for 6 cycles is [confidential data removed] excluding VAT (which includes a confidential discount). An average body surface area of 1.8 m^2 was used to calculate capecitabine dose which was rounded to the nearest 500 mg. Total chemotherapy costs amount to [confidential data removed]. Nivolumab is associated with a net cost of [confidential data removed].

Using this net cost AWTTC conducted a threshold analysis to estimate the minimum required QALY gain required for nivolumab to be deemed cost-effective. The [confidential data removed]net cost is combined with a cost-effectiveness threshold

of £20,000 per QALY. The threshold of £20,000 is chosen due to the high level of uncertainty inherent in the clinical and cost effectiveness data. When a severity modifier QALY multiplier of 1.2 is applied, a required QALY gain of [confidential data removed] is needed for cost effectiveness. Currently, there is no clinical evidence suggesting that nivolumab is associated with QALY gains of this magnitude.

The licence indication for nivolumab lists the maximum duration of treatment to be 24 months. Costs associated with a 24-month treatment delivery of 240 mg nivolumab every 2 weeks by intravenous infusion equate to [confidential data removed]. The comparator cost is the same as the threshold analysis above, 6 cycles of platinum fluoropyrimidine combination therapy costing [confidential data removed]. The net cost of nivolumab is [confidential data removed]. Using a cost-effectiveness threshold of £20,000 per QALY in combination with the severity modifier QALY multiplier of 1.2 results in a required QALY gain of [confidential data removed] for cost-effectiveness.

Cost Effectiveness evidence issues

- There are no appropriate cost effectiveness studies for this intervention.
- Considered costs are limited to intervention and administration costs, the cost impact of adverse events and ongoing healthcare resource use are not included as there is insufficient supporting evidence. Total costs are likely to be underestimated for nivolumab and the comparator.
- Overall survival in the QALY shortfall calculation uses median overall survival instead of mean overall survival to calculate expected QALYs, this add to the uncertainty.
- The QoL estimates reflect figures reported by people with stage IV oesophageal and gastric cancer as opposed the target subset population.
- Procurement and administration costs are based on a median PFS duration figure as opposed to a mean PFS, this may bias the calculation.
- The cost model assumes complete treatment adherence, potential biasing the costs upwards.
- Due to limitations with the clinical and cost data, the hypothetical threshold may be misleading. Extension to overall survival is likely to incur healthcare costs and be associated with changes in QoL over that duration. The point estimate approach for expected QALYs required is unable to vary account for these factors, however, the QALY gain required is likely to remain implausible.

Budget Impact

The budget impact used the nivolumab standard dose of 240 mg every 2 weeks by intravenous infusion. An alternative regimen would be 480mg every 4 weeks by intravenous infusion. Post-hoc data taken from the KEYNOTE-062 study in 14 patients (with MSI-H tumours and PD-L1 ≥ 1) who received pembrolizumab for first line treatment of gastric or gastroesophageal junction cancer showed a PFS of 11.2 months. This period is taken as an estimate of the average time of nivolumab monotherapy treatment in the base case[25].

Clinical expert opinion is that 21 patients with PD-L1 CPS < 5 would be tested for dMMR/MSI-H each year and of these five to nine people would test positive and therefore be eligible for nivolumab monotherapy in place of chemotherapy. The cost of a 240 mg vial, excluding VAT, is [confidential data removed] (which includes a confidential discount), the acquisition cost to treat one patient for 11.2 months is [confidential data removed] including VAT. The acquisition cost of chemotherapy (oxaliplatin 130mg/m^2 every 3 weeks and capecitabine 625 mg/m^2 twice daily every 3 weeks for 6 cycles is [confidential data removed] (including VAT). An average body surface area of 1.8 m^2 was used to calculate capecitabine dose which was rounded to the nearest 500 mg. Administration costs for delivering nivolumab and chemotherapy were taken from the National Schedule of NHS Costs 2021-22[53]. Table 7 shows the budget impact for a range between five and nine patients to reflect the eligible patient numbers estimated to receive nivolumab monotherapy in place of chemotherapy. The cumulative three-year cost is between [confidential data removed]. Monitoring costs are not included.

Table 7: Estimated patient numbers and cost

	Year 1	Year 2	Year 3
Number of patients with MSI-H/dMMR tumours*	5 to 9	5 to 9	5 to 9
Scenario without nivolumab			
Range of costs without nivolumab (all patients treated with chemotherapy)†	¶¶	¶¶	¶¶
Scenario with nivolumab			
Costs with MSI-H/dMMR positive patients treated with nivolumab†	¶¶	¶¶	¶¶
Budget impact	¶¶	¶¶	¶¶

*Range based on lowest and highest incidence estimate
†Medicine acquisition cost plus administration costs from National Schedule of NHS Costs 2021-22
¶¶ confidential data removed

An alternative scenario was generated over a two-year time horizon in which patients received nivolumab for different time periods. The proportions of patients receiving nivolumab therapy were; 50 % for 6 months, 25% for 18 months and 25% for 24 months. The total cost per patient for 6 months, 18 months and for 24 months treatment is estimated to be [confidential data removed] and [confidential data removed] respectively. The budget impact for this scenario is given in Table 8. Costs are presented for 8 new patients starting treatment with nivolumab each year, the annual budget impact in this scenario would remain stable from Year 2 onwards.

Table 8. Scenario with patients treated with nivolumab for different time periods.

	Year 1	Year 2
Patients with MSI-H tumours treated with nivolumab (%)	8	12
Costs without nivolumab (all patients treated with chemotherapy)	¶¶	¶¶
Costs with MSI-H positive patients treated with nivolumab	¶¶	¶¶
Budget impact	¶¶	¶¶
¶¶ confidential data removed		

Budget impact issues

- All cost estimates assume that patient numbers remain constant.
- A full 6 cycles of chemotherapy and 100% compliance for both medicines is assumed. In KEYNOTE-062, 3.9% of pembrolizumab monotherapy and 18% of the chemotherapy patients discontinued treatment due to adverse events[27].
- The average treatment time period used for nivolumab (11.2 months) in the base case is subject to uncertainty because it is taken from data for a small number of patients treated with a different medicine (i.e. pembrolizumab). However, the magnitude of this time scale is consistent with use in the palliative setting.
- The alternative regimen of 480 mg every 4 weeks has not been included in the main budget impact estimates. Due to fewer administration costs this would cost [confidential data removed] per patient for 11.2 months of treatment and would equate to a budget impact of between [confidential data removed] and [confidential data removed] for 5 to 9 patients annually.
- The budget impact is most sensitive to patient numbers due to the medicine acquisition cost of nivolumab compared to chemotherapy.
- The longest time scale of treatment used in the alternative scenario is 24 months. The mean PFS reported for MSI-H patients treated with pembrolizumab was 11.2 months. For patients with PD-L1 CPS < 1 treated with nivolumab plus chemotherapy, it was 8.7 months in KEYNOTE-062 and Checkmate 649 respectively. In the scenario analysis the 25% of patients receiving treatment for 2 years may therefore be an over estimate.
- No monitoring costs were included in the analysis. It is anticipated that treatment with nivolumab would require less intensive monitoring than chemotherapy however tests for thyroid function and cortisol levels would be required in addition to standard blood monitoring tests. Nivolumab treatment is expected to have a longer duration so cumulative treatment-related monitoring may be greater for this medicine.
- Costs associated with adverse effects have not been included, there is no direct comparative safety data for nivolumab monotherapy versus

chemotherapy. In the KEYNOTE-062 clinical trial adverse events of grade 3 and above occurred in 16.9% of pembrolizumab monotherapy patients compared to 69.3% of chemotherapy patients[27]. A systematic review with network meta-analysis reported that nivolumab has higher incidences of all-grade and grade 3 adverse events compared with pembrolizumab[54]. It is unlikely, however that the adverse effect profile for nivolumab would be unfavourable compared with chemotherapy.

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Appendix 1. Additional results

Table A1. Checkmate 649 results from original subgroup analysis by PD-L1 CPS[23,55]

Population	Nivolumab + chemotherapy	Chemotherapy alone	Unstratified HR (95% CI)	Interactive p value*
Median overall survival (months)				
Overall (n = 1581)	13.8	11.6	0.79 (0.70-0.89)	NR
PD-L1 CPS < 1 (n = 265)	13.1	12.5	0.92 (0.70-1.23)	NS
PD-L1 CPS ≥1 (n = 1296)	14.0	11.3	0.76 (0.67-0.87)	0.2041
PD-L1 CPS <5 (n = 606)	12.4	12.3	0.94 (0.78-1.13)	NS
PD-L1 CPS ≥5 (n = 955)	14.4	11.1	0.70 (0.60-0.81)	0.0107*
Median progression free survival (months)				
Overall (n = 1581)	7.7	6.9	0.77 (0.68-0.87)	NR
PD-L1 CPS < 1 (n = 265)	8.7	8.1	0.93 (0.69-1.26)	NS
PD-L1 CPS ≥ 1 (n = 1296)	7.5	6.9	0.75 (0.65-0.85)	0.1391*
PD-L1 CPS < 5 (n = 606)	7.5	8.2	0.93 (0.76-1.12)	NS
PD-L1 CPS ≥ 5 (n = 955)	7.7	6.1	0.69 (0.59-0.80)	0.0073*
Objective response rate (%)				
Overall (n = 1211)	58	46	12 (6-17.5)	NR
PD-L1 CPS < 1 (n = 178)	51	41	9 (-5 to 23)	NR
PD-L1 CPS ≥ 1 (n = 1019)	60	46	13 (7 – 19)	NR
PD-L1 CPS < 5 (n = 428)	55	46	9 (-0.6 – 18)	NR
PD-L1 CPS ≥ 5 (n = 769)	60	45	15 (7.5 – 21)	NR

CI: confidence interval; HR: hazard ratio; NR: not recorded; NS: not significant
*Significance level for interactive p value was predefined at 0.2
The median follow-up for OS in the original analysis was 13.1 months (interquartile range [IQR] 6.7 19.1) for nivolumab plus chemotherapy and 11.1 months (IQR 5.8 16.1) for chemotherapy alone. The median treatment duration was 6.8 months (IQR 3.7 13.3) with nivolumab plus chemotherapy and 4.9 months (IQR 2.5 8.4) with chemotherapy alone.

Table A2 Checkmate 649 results from subgroup analysis by PD-L1 CPS: Three year follow up[24].

Population	Nivolumab + chemotherapy	Chemotherapy alone	Unstratified HR (95% CI)	Comment
Median overall survival (months)				
Overall (n = 1581)	13.8	11.6	0.79 (0.70-0.89)	Favours combination
PD-L1 CPS < 1 (n = 265)	13.1	12.5	0.95 (0.74-1.24)	NS
PD-L1 CPS ≥1 (n = 1297)	13.8	11.3	0.75 (0.66-1.124)	Favours combination
PD-L1 CPS <5 (n = 607)	12.4	12.3	0.95 (0.80-1.12)	NS
PD-L1 CPS ≥5 (n = 955)	14.4	11.1	0.69 (0.60-0.79)	Favours combination
Objective response rate (%)				
Overall (n = 1209)	58	46	12 (6-17.7)	NR
PD-L1 CPS < 1 (n = 179)	51	41	10 (-4.7 to 23.8)	NS
PD-L1 CPS ≥ 1 (n = 1016)	60	46	13 (7 – 19.2)	Favours combination
PD-L1 CPS < 5 (n = 427)	56	46	9 (-0.4 – 18.3)	NS
PD-L1 CPS ≥ 5 (n = 768)	60	45	15 (7.6 – 21.5)	Favours combination

CI: confidence interval; HR: hazard ratio; NS: not significant

P values not reported for 3-year follow up.
PFS not reported for all CPS sub-groups for 3-year follow up.