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

Evidence Status Report
Dostarlimab (Jemperli®) for the treatment of locally advanced treatment-naïve stage II/III deficient mismatch repair (dMMR) / high microsatellite instability (MSI-H) rectal cancer (OW26)

Report prepared by the All Wales Therapeutics and Toxicology Centre June 2023

Key findings

Licence status
Dostarlimab (Jemperli®) is not licensed for treating locally advanced treatment-naïve stage II/III deficient mismatch repair (dMMR) / high microsatellite instability (MSI-H) rectal cancer; its use for this indication is off-label.

Clinical evidence
The clinical evidence for the use of dostarlimab in this setting comes from a single-group, prospective phase 2 study. A total of 23 patients have completed treatment with dostarlimab, with all 23 having a clinical complete response with no evidence of tumour on magnetic resonance imaging or endoscopic visualisation. At the time of publication, no patients had received chemoradiotherapy or undergone surgery, and no cases of progression or recurrence had been reported during follow-up (range, 0.0 – 36.3 months). It is acknowledged that longer follow-up is needed to assess the duration of response.

Safety
The safety of dostarlimab was found to be in line with previous literature, no new safety signals emerged with the use of dostarlimab in rectal cancer compared with its use in other indications.

Patient factors
This is a potential new option in the treatment pathway for stage II-III rectal cancer as an alternative to chemoradiotherapy and/or surgery with the potential for organ sparing. The current treatment approaches can cause substantial long-term sequelae that impacts quality of life. These include neuropathy, infertility, urinary, bowel and sexual dysfunction as well as secondary malignancy.

Cost effectiveness
There are no studies on the cost effectiveness of dostarlimab for this indication. There is literature to suggest that a 'watch and wait' approach may be more cost effective than surgery. However, there are inherent limitations with this approach and the suitability of this approach as a proxy for the treatment under consideration is uncertain.

Budget impact
The addition of dostarlimab as first line treatment is estimated to increase the spend associated with this patient group in Wales [commercial in confidence text removed] per year between 2023 and 2026. This assumes that dostarlimab replaces existing treatments which may include chemoradiotherapy and/or surgery

and associated costs of these treatments. It excludes future treatment costs associated with adverse events and consequences of surgical intervention.

Impact on health and social care services
Minimal increased use of existing services.

Innovation and/or advantages
Dostarlimab offers an additional treatment option for this group. The aim of using this medicine for the indication described is based on improving access to organ-sparing nonoperative treatments.

Background

The current treatment pathway for stage II/III rectal cancer is chemoradiotherapy/radiotherapy and/or surgery with/without adjuvant chemotherapy[1]. Mismatch repair deficient (dMMR) rectal cancer, which accounts for 5 to 10% of rectal adenocarcinomas, is relatively resistant to chemotherapy[2,3]. Recent evidence published for dostarlimab has shown complete clinical response for a small cohort of patients without the need for further treatment[4]. Clinicians in Wales have identified a cohort of people in Wales who would benefit from dostarlimab, representing a new clinical pathway for this group to preserve organ function. Dostarlimab was therefore considered suitable for assessment though the One Wales Medicines process.

Dostarlimab is a humanised monoclonal antibody that potentiates T-cell responses, including anti-tumour immuno responses through blockade of PD-1 binding to PD-L1 and PD-L2[5]. In colorectal cancer with high microsatellite instability (MSI-H) as is seen in dMMR cancer, tumours have an increased number of neoantigens. Increased neoantigen presentation can lead to higher tumour immunogenicity with increased populations of tumour-infiltrating lymphocytes and increased immune checkpoint expression. These characteristics make these tumours more likely to respond to anti-PD-1/L1 therapy than those that are microsatellite stable[6].

Target group

The indication under consideration is locally advanced treatment-naïve stage II/III dMMR / high microsatellite instability (MSI-H) rectal cancer.

Marketing authorisation date: Not applicable, off-label

Dostarlimab is not licensed for the treatment of locally advanced treatment-naïve stage II/III dMMR / MSI-H rectal cancer. Dostarlimab is licensed for the treatment of adult patients with dMMR/ MSI-H recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen[5].

Dostarlimab is recommended for use within the Cancer Drugs Fund as an option for treating advanced or recurrent endometrial cancer with MSI-H or dMMR in adults who have had platinum-based chemotherapy (NICE TA779)[7].

Pembrolizumab, another PD-1 inhibitor, was recommended by NICE in 2021 as an option for untreated metastatic colorectal cancer with MSI-H or dMMR in adults (TA 709)[8].

Dosing information

The recommended dose as monotherapy for rectal cancer is 500 mg dostarlimab by intravenous infusion every 3 weeks for 9 cycles (6 months), as per planned phase II study AZUR-1[9]. This differs to the recommended licensed indication (endometrial cancer) dose as monotherapy of 500 mg dostarlimab every 3 weeks for 4 cycles followed by 1000 mg every 6 weeks for all cycles thereafter, continued until disease progression or unacceptable toxicity[5].

Clinical background

Although the colon and rectum are distinct from one another, colorectal cancers (CRCs) are often grouped together in epidemiological and clinical research[10,11]. CRC is the third most common cancer in the Western World, and approximately 30% of all CRC tumours develop in the rectum[12].

By definition, rectal cancer is a tumour arising within 15 cm of the anal verge[10]. Although rectal cancer is histologically similar to cancers occurring at other sites in the colon, blood supply, lymphatic drainage and nervous innervation are specific in rectal cancer due to the anatomical confinements of the bony pelvis and result in rectal cancer being considered a distinct entity. This distinction is relevant with regards to the invasive growth pattern, surgical approach, as well as treatment outcomes[10].

The mismatch repair (MMR) pathway corrects DNA replication errors that lead to incorporation of the wrong nucleotide as well as nucleotide insertions/deletions. MMR deficiency (dMMR) causes accumulation of mutations and can lead to a high microsatellite instability (MSI-H) phenotype[13]. Germline mutations in MMR genes are associated with Lynch syndrome, a form of inherited dMMR that accounts for 2% to 4% of CRC. The majority of dMMR/MSI-H rectal cancers are associated with Lynch syndrome[13]. Clinical experts indicate that they reflex test all CRC patients for MMR or MSI and this has also now been added to the single cancer pathway[14].

Incidence/prevalence

Rectal cancer accounts for 27.3% of all cases of CRC and 2.7% of all rectal cancers are dMMR[15,16]. In 2019, there was an estimated 124 Stage II and 318 stage III cases of rectal cancer in Wales[17], and using a prevalence of 2.7%, it is estimated that 12 of these will be dMMR/MSI-H rectal cancers.

Clinicians consulted by AWTTC estimate that between 15 and 20 people in Wales per year would be likely to be eligible to receive dostarlimab in this setting.

Current treatment options and relevant guidance

The National Institute for Health and Care Excellence (NICE) has published guidelines which covers managing colorectal (bowel) cancer in people aged 18 and over (NG151)[1]. The European Society for Medical Oncology (ESMO) have also published rectal cancer clinical practice guidelines for diagnosis, treatment and follow-up[18]. Other guidelines include The National Comprehensive Cancer Network® (NCCN®) clinical practice guidelines in oncology and the Onkopedia guidelines

Rectal Cancer: Recommendations from the society for diagnosis and therapy of haematological and oncological diseases[19,20].

The standard of care for patients with locally advanced stage II or III rectal cancer has traditionally been trimodal, including (chemo)radiotherapy, surgery (total mesorectal excision [TME]) and adjuvant chemotherapy based on histology[1,19]. There is evidence to suggest that dMMR CRCs are less sensitive to chemotherapy than MMR proficient (pMMR) tumours and this can therefore alter the treatment choice for this patient group[2,21]. Seligmann (2020) reported significantly decreased response to neoadjuvant chemotherapy in dMMR versus pMMR colon cancer, with only 7% of patients with dMMR disease experiencing moderate or greater histological regression versus 23% of patients with pMMR tumours[21]. Similarly, Cercek et al. (2020) reported 29% of patients with dMMR rectal tumours experiencing disease progression during neoadjuvant chemotherapy treatment versus 0% of patients with pMMR tumours[2].

A large proportion of patients (up to 50% in some studies) fail to complete planned adjuvant chemotherapy after chemoradiation and subsequent surgery[22]. This led to the concept of total neoadjuvant therapy (TNT), whereby the additional chemotherapy is delivered prior to surgery[22]. This trend has recently been enhanced by the successful trials RAPIDO and PRODIGE 23, which demonstrated a doubling of pCR with TNT as compared with standard neoadjuvant long course chemoradiotherapy (LCRT) or short course radiotherapy (SCRT)[23,24]. Adoption of TNT is highly variable across the UK, current guidelines of the National Institute for Health and Care Excellence (NICE) are also yet to feature TNT. Based on clinical expert opinion TNT was not considered as a routine option for the subgroup of patients with dMMR/MSI-H stage II-III rectal cancer due to the poorer response of these tumours to chemotherapy[2,21].

Welsh clinicians confirm the current preferred treatment regimen for the cohort of patients within this indication is LCRT (45Gy x 25 fractions plus capecitabine) followed by TME and then possibly adjuvant chemotherapy.

Summary of evidence on clinical effectiveness

A literature search conducted by AWTTC identified a single-group, prospective phase 2 study[4]. There are currently two clinical trials underway with estimated completion in 2025 and 2028[9,25].

Efficacy

Cercek et al (2022) are conducting a single-group, prospective phase 2 study to assess if dostarlimab is effective in patients with dMMR, locally advanced rectal cancer[4]. The two primary end points are:

1. sustained clinical complete response 12 months after completion of dostarlimab therapy (in patients who do not undergo surgery) or pathological complete response (in patients who undergo surgery after completion) of dostarlimab therapy with or without chemoradiotherapy;
2. overall response to neoadjuvant dostarlimab therapy with or without chemoradiotherapy.

The first peer-reviewed publication included 16 of a planned 30 patients. The median age of the 16 enrolled patients is 54 years (range 26–78). Twelve patients had

received 6 months of dostarlimab (500 mg every three weeks) and undergone at least 6 months follow up from study enrolment and formed the basis of the report. The paper only reported on overall response based on magnetic resonance imaging (MRI) of the rectum, 18F-fluorodeoxyglucose–positron-emission tomography (FDG-PET), endoscopic visualisation, digital rectal examination or biopsy. All 12 patients had a clinical complete response (95% confidence interval [CI], 74 to 100) with no evidence of tumour on MRI, FDG-PET, endoscopic visualisation or digital rectal examination. At the time of publication, no patients had received chemoradiotherapy or undergone surgery, and no cases of progression or recurrence had been reported during follow-up (range, 6 to 25 months)[4]. Because none of the 12 patients who completed 6 months of dostarlimab therapy had undergone surgery, evaluation of pathological complete response was not possible. The primary end point involving the durability of response (sustained clinical complete response at 12 months) was not reported in its finality as only four patients had completed one year of follow up after completion of dostarlimab. All four patients had a sustained clinical complete response [4].

Updated figures for this study, were presented at the Japanese Society of Medical Oncology (JSMO) in March 2023. These latest figures at time of writing reports on 23 patients with median age of 50 years (range 26 to 78). All patients have had a clinical complete response, with a median follow up of 9.3 months (range, 0.0 to 36.3). Eleven patients have now had one year of sustained clinical complete response after completion of dostarlimab alone. No patients have required chemotherapy, radiation or surgery.

There are two trials that are currently recruiting participants:

- A phase 2 single-arm, open-label study with dostarlimab monotherapy in participants with untreated stage II/III dMMR/MSI-H locally advanced rectal cancer (AZUR-1) (NCT05723562). This study is due to complete October 2029 (primary completion date November 2025)[9].
- A phase 2 single-arm, open-label study of neoadjuvant dostarlimab in Stage II and III Deficient Mismatch Repair Colon Cancers (NAIO) (NCT05239546) This study is due to complete December 2030 (primary completion date April 2026)[25].

Safety

The safety of dostarlimab has been evaluated in 515 patients with endometrial cancer or other advanced solid tumours who received dostarlimab monotherapy in the GARNET study[5]. The most common adverse reactions (> 10%) were anaemia (25.6%), nausea (25.0%), diarrhoea (22.5%), vomiting (18.4%), arthralgia (13.8%), pruritus (11.5%), rash (11.1%), pyrexia (10.5%) and hypothyroidism (10.1%). Dostarlimab (Jemperli®) was permanently discontinued due to adverse reactions in 17 (3.3%) patients; most of them were immune-related events. Adverse reactions were serious in 8.7% of patients and were most commonly immune-related[5].

The safety profile for patients with dMMR/MSI-H endometrial cancer in the GARNET study (n = 129) was not different from that of the overall monotherapy population[5].

Results from the Cercek et al study showed adverse events of any grade occurred in 12 of the 16 patients (75%; 95% CI, 48 to 92)[4]. No adverse events of grade 3 or

higher were reported. The most common adverse events of grade 1 or 2 included rash or dermatitis (31%), pruritus (25%), fatigue (25%), and nausea (19%). Thyroid-function abnormalities occurred in one patient (6%)[4]. No new safety signals were identified.

Discussion

Currently, treatment options for locally advanced treatment-naïve stage II/III dMMR/MSI-H rectal cancer in routine UK clinical practice is limited and responses to neoadjuvant chemotherapy are lower in patients with dMMR than proficient mismatch repair (pMMR) colon cancers[2,21]. Dostarlimab could offer a neoadjuvant treatment option for this group which potentially may spare or delay patients from chemoradiotherapy and/or surgery.

The main source of evidence comes from a non-comparative single arm, open label, phase 2 study in one cancer centre in the US, which is currently ongoing[4]. The lack of comparator and the immaturity of data for some relevant outcomes, make interpretation of the actual clinical relevance of the results challenging. How this treatment fares in a broader more diverse population is unknown but the multinational AZUR-1 trial will be useful in addressing these issues[9]. Results from the GARNET Study, show mature results for tumour responses, duration of responses and overall survival results are available for an extended number of patients with advanced or recurrent dMMR/MSI-H endometrial cancer[26], however these assumptions will be based on values from another disease area so should be interpreted with caution.

The interim results from Cercek et al are positive, but due to the immaturity of data, cannot be regarded a curative treatment approach. An editorial by Sanoff (2022) commented on the Cercek et al results and noted that the end point presented, clinical complete response, is not considered a gold standard outcome measure for long-term cancer control[27]. Sanoff also stated that although patients who have a clinical complete response after chemotherapy and radiation therapy have a better prognosis than those who do not, cancer regrowth occurs in 20 to 30% of such patients when the cancer is managed nonoperatively[27]. The results of the KEYNOTE-177 trial were highlighted where only 55% of patients treated with pembrolizumab for dMMR metastatic colorectal cancer were reported to be alive without cancer progression at 12 months. Although responses lasted longer among the patients who had an initial strong response only approximately 70% had an ongoing response three years later[3,27]. Sanoff does point out that these recurrence dynamics may (or may not) differ between immunotherapy and chemoradiotherapy and between early- and late-stage disease. It is currently unknown how long patients will need to be remain progression-free to find out whether a clinical complete response to dostarlimab equates to cure[27].

Overall, the available information suggests that dostarlimab 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.

Cost-effectiveness evidence

There are no studies on the cost-effectiveness of dostarlimab for this indication. However, other publications in the broader colorectal cancer indication were identified. Studies investigating the use of a watch-and-wait approach following neoadjuvant therapy which may include chemotherapy and/or radiotherapy have been investigated and are considered below.

In 2020 NICE published an evidence review on the deferral of surgery in people having neoadjuvant therapy for rectal cancer[28]. Although surgery is the gold standard treatment for rectal cancer some people whose rectal cancer shows a complete clinical response to neoadjuvant therapy (chemotherapy and/or radiotherapy) wish to defer surgery and opt for an organ preserving 'watch and wait' strategy instead. While this approach avoids the harms associated with surgery, to avoid disease progression a surveillance protocol with repeated examinations is required, this has associated costs and may be inconvenient for some patients[1]. In the absence of cost effectiveness evidence for dostarlimab for this indication, clinician sought opinion was that a watch and wait approach of neoadjuvant chemotherapy and/or radiotherapy would be a suitable proxy for treatment with dostarlimab. This assumes that patients in both groups would not receive surgery and would be monitored with a watch and wait approach.

Rao et al (2017) compared the cost-effectiveness of watch and wait and radical surgery for patients with rectal cancer after a clinical complete response following chemoradiotherapy[29]. There were three cohorts included in the study; 60 and 80-year–old male cohorts with no comorbidities and 80-year–old male cohorts with significant comorbidities. The analysis was a cost-utility analysis measuring effectiveness in terms of quality adjusted life years (QALYs) from an NHS perspective. Watch and wait was the dominant intervention in the base case for all subgroups leading to a reduction in both costs (ranging from £6,274 to £8,095) and an increase in QALYs (ranging from 0.56 to 0.72). Probabilistic sensitivity analysis estimated the probability of watch and wait being cost effective when QALYs are valued at £20,000 each, is over 74% for all sub-groups. In deterministic sensitivity analysis, the model used was sensitive to relative recurrence rates after watch and wait and surgery and the degree to which HRQoL was reduced by radical surgery. The model became sensitive to changes in perioperative mortality when the HRQoL benefit of watch and wait was reduced[29].

Cui, et al (2022) conducted a cost-effectiveness analysis comparing watch and wait with abdominoperineal resection (APR) and with low anterior resection (LAR) among patients with stage II/III rectal cancer[30]. All patients received neoadjuvant chemoradiotherapy in these cost-utility analyses from a US payer perspective. The results suggest that watch and wait was dominant (more effective and less costly) than surgery at a willingness to pay threshold of $100,000. Watch and wait increased effectiveness by 0.17 and 0.23 QALYs compared with APR and LAR respectively. The model was most sensitive to rates of distant recurrence and regrowth after watch and wait[30].

The primary reason for undertaking an organ preserving approach is the improved health-related quality of life (HRQoL) associated with the avoidance of stoma and other morbidity associated with major surgery[31]. Outcomes known to be associated with good HRQoL, such as -stoma free survival and good functional outcomes, have been reported in patients managed with a watch and wait approach. Some papers

have reported that there are not significant differences, however these may be explained by differences in patient demographics and pre-existing comorbidities[31]. Poorer functional outcomes and global HRQoL are often associated with more elderly comorbid populations which are likely to differ from the target cohort in this report.

The potential of dostarlimab to prevent or delay the need for stoma care may provide some offset costs in this cohort. Stoma management post colorectal surgery is associated with a substantial long-term cost burden[32]. In the UK, £233.5 million is spent annually on stoma products alone. Permanent stoma costs were higher in patients with higher long-term survival, as could be expected at younger treatment age, which may be of more relevance for the indication under consideration in this report[32].

Health economics issues

The existing literature suggests that watch and wait is more cost-effective than initial TME[31]. However, it is heavily reliant on poor-quality health-related quality of life data. Furthermore, the cost-effectiveness of organ preservation from a broader societal perspective has not been studied. The cost-effectiveness of emerging adjuncts to watch and wait for organ preservation, such as contact X-ray brachytherapy, local excision and TNT needs to be characterised.

There are obvious limitations when considering the cost-effectiveness of watch and wait and other organ-preserving strategies, compared with removal of the rectum with TME[31]. These include the HRQoL and societal factors of avoiding invasive procedures versus the risk of tumour regrowth, local recurrence and distant metastasis. Lack of long-term outcome data for use of dostarlimab makes comparison of strategies difficult. A key aspect of the analysis by Rao et al is the quality of life gain with watch and wait, however it is important to note this is based on values from another disease area (prostate cancer)[29]. Patients included in the Rao et al study were a 60 and 80-year-old male cohorts with no comorbidities and 80-year-old male cohorts with significant comorbidities[29]. Individuals with Lynch syndrome have 40% to 70% risk of CRC with a mean age at first diagnosis of 40 to 45 years, and 40% of the tumours are diagnosed under age 40[33]. This is a different cohort to the patients who typically are diagnosed with CRC (43% are aged 75 and over [15]) and younger than those in the Rao et al study[29]. Patients with dMMR/MSI-H rectal cancer would routinely be offered surgery and therefore the inputs used for the cost effectiveness analyses may not represent these patients accurately. This leads to uncertainty as to how representative this analysis is to the patient group under consideration.

Cui uses American data for treatments and costs. The findings in this paper may not directly correlate to the treatment pathways and costs used by the NHS.

Budget impact

The recommended dose as monotherapy is 500 mg dostarlimab by intravenous infusion every 3 weeks for 9 cycles based on the AZUR-1 study protocol[9]. The list price of a 500 mg vial is £5887 and there is a commercial arrangement in place which reduces the cost to [commercial in confidence text removed] for a 500 mg vial

(excluding VAT). The total cost for 9 cycles of dostarlimab is [commercial in confidence text removed] which includes administration and VAT.

According to clinical experts in Wales, a maximum of 20 patients each year would be treated with dostarlimab. Should patients relapse with locally advanced disease then they would be eligible for chemoradiotherapy and surgery.

The addition of dostarlimab as a monotherapy is estimated to increase the spend associated within this patient group in Wales [commercial in confidence text removed] in Year 1. The analysis does not include costs of monitoring or adverse events.

Table 1 shows the costs associated with a range of treatment options for people with stage II/III rectal cancer. Clinical expert sought opinion suggests that in some cases, people will receive neoadjuvant treatment then surgery then adjuvant treatment after surgery. The table estimates the net drug acquisition costs (including VAT), net drug administration costs (taken from 2021/22 National Schedule of NHS Costs[34]) and associated costs including surgery costs. Cost of surgery was taken from 2020-21 National Schedule of NHS Costs for complex large intestine procedures (HRG code FF31A-D) using weightings for comorbidities and complications provided in the economic model for the NICE guideline NG151[1]. NICE had calculated costs for individual procedures (including TME) using breakdown costs from a cost-effectiveness analysis of surgical approaches in prostate cancer published in 2012 inflated to 2016 prices. It was considered to be more robust to use the broader reference cost code and 2020-21 prices rather than further inflating the TME costs to present. Monitoring costs are not included.

Table 1. Total costs of each treatment arm option per patient**

Treatment			Cost
Neo-adjuvant treatment	Surgery	Adjuvant treatment	
Dostarlimab monotherapy (9 cycles)	None	None	¶¶
None	Surgery*	FOLFOX (6 months) †	¶¶
None	Surgery*	CAPOX (3 months) †	¶¶
SCRT (25 Gy in 5 daily fractions)	Surgery*	None	£19,132
SCRT (25 Gy in 5 daily fractions)	Surgery*	FOLFOX (6 months) †	¶¶
SCRT (25 Gy in 5 daily fractions)	Surgery*	CAPOX (3 months) †	¶¶
LCCRT (45 Gy x 25 fractions plus capecitabine)	Surgery*	None	¶¶
LCCRT (45 Gy x 25 fractions plus capecitabine)	Surgery*	FOLFOX (6 months) †	¶¶
LCCRT (45 Gy x 25 fractions plus capecitabine)	Surgery*	CAPOX (3 months) †	¶¶
LCRT (45 Gy x 25 fractions)	Surgery*	None	£34,136
LCRT (45 Gy x 25 fractions)	Surgery*	FOLFOX (6 months) †	¶¶

LCRT (45 Gy x 25 fractions)	Surgery*	CAPOX (3 months) †	¶¶

LCCRT; long-course chemoradiotherapy, LCRT; long-course radiotherapy, SCRT; short-course radiotherapy
*National Schedule of Reference Costs: Complex large intestine procedures, 19 years and over (HRG code FF31A-D)
†Including 2020-2021 National Schedule of Reference Costs: assumes 'Deliver Simple Parenteral Chemotherapy at first attendance' (HRG code SB12Z) for the first dose, followed by 'Deliver Subsequent Elements of a Chemotherapy Cycle' for the other five doses (HRG code SB15Z)
§2020-21 National Schedule of Reference Costs: Preparation for Simple Radiotherapy with Imaging and Dosimetry (SC45Z); Deliver a Fraction of Treatment on a Megavoltage Machine (HGR code SC22Z)
**may not compute due to rounding
¶¶commercial in confidence figure removed

Table 2 shows the net budget impact assuming that all eligible people receive dostarlimab if approved instead of the current treatment options. For simplicity, current treatment options are assumed to have an equal split of people between them. This was deemed appropriate by the clinicians who have reviewed the ESR.

Table 2. Estimated patient numbers and cost†

	Year 1	Year 2	Year 3
Scenario with dostarlimab			
Dostarlimab	20 patients ¶¶	20 patients ¶¶	20 patients ¶¶
Scenario without dostarlimab			
SCRT + surgery	4 patients £76,529	4 patients £76,529	4 patients £76,529
SCRT + surgery + adjuvant chemo (¶¶-¶¶*)	4 patients ¶¶-¶¶	4 patients ¶¶-¶¶	4 patients ¶¶-¶¶
LCCRT + surgery	4 patients ¶¶	4 patients ¶¶	4 patients ¶¶
LCCRT + surgery + adjuvant chemo (¶¶-¶¶*)	4 patients ¶¶-¶¶	4 patients ¶¶-¶¶	4 patients ¶¶-¶¶
Surgery + adjuvant chemo (¶¶-¶¶*)	4 patients ¶¶-¶¶	4 patients ¶¶-¶¶	4 patients ¶¶-¶¶
Total cost of scenario without dostarlimab	¶¶-¶¶	¶¶-¶¶	¶¶-¶¶
Budget impact	¶¶-¶¶	¶¶-¶¶	¶¶-¶¶

LCCRT; long-course chemoradiotherapy, SCRT; short-course radiotherapy
*Range based on cheapest option (3-month cycle CAPOX) and most expensive option (6-month cycle FOLFOX) with associated administration costs per patient.
†may not compute due to rounding
¶¶commercial in confidence figure removed

All patients undergoing TME require temporary colostomy, with 20% to 30% of patients requiring abdominoperineal resection that ultimately results in permanent colostomy. The National Bowel Cancer Audit 2022 reported that in the UK, a permanent stoma was required in 37% of all patients with rectal cancer[35]. The base case results of a retrospective cohort study by Pietzsch and Geisler (2019) reports the lifetime cost of stoma management post colorectal surgery was £8,167. For patients in whom stoma was reversed, costs were £8,726, while costs for a permanent stoma patient who would not undergo take-down surgery were £5,930[32]. Appliances and accessory costs in primary care can range from £780-£2,300 per patient per annum[36].

Clinical experts state that an increased surveillance schedule would be required in patients receiving dostarlimab to monitor disease status. The watch and wait surveillance schedule agreed by an international consensus panel includes: serum carcinoembryonic antigen (CEA) levels every 3 months during the first 3 years after completion of treatment, and then every 6 months during years 4–5 after treatment; endoscopy, digital rectal examination and MRI should be conducted every 3–4 months during the first 2 years after completion of treatment, and then every 6 months during years 3–5 after treatment; computed tomography (CT) of the chest and/or abdomen is every 6–12 months during the first year after completion of treatment, and annually during years 2–5 after treatment[37]. ESMO guidelines for follow up of average risk patients after surgery includes: clinical assessment every six months for two years; complete colonoscopy within the first year (if not done at diagnostic work up); history and colonoscopy with resection of colonic polyps every 5 years up to the age of 75 years; a minimum of two CTs of the chest, abdomen and pelvis in the first 3 years and regular CEA tests (at least every 6 months in the first 3 years). The guidelines suggest that high risk patients may merit more proactive surveillance for local recurrence[18].

Budget impact issues

The budget impact model does not consider yearly incidence or mortality and assumes that 100% of patients would receive treatment and that they would have a complete clinical response for a minimum of three years. Due to the nature of the indication, patients are assumed to receive 6 months of therapy and no further cycles of treatment with dostarlimab. Additional adverse event costs are also excluded from the budget impact.

The published sources used for estimating number of patients with rectal cancer seem reasonable, although the estimates of patients receiving therapy in this budget impact are based on clinical expert opinion, which is slightly higher and hence are uncertain.

The costs used in the economic model assumed that FOLFOX was given in a 3-month cycle. This report has assumed that all patients receive a full 6-month (12 cycle) treatment, however this is possibly an over-estimate due to individual tolerance levels of chemotherapy.

It is anticipated that the number of patients diagnosed with rectal cancer may increase in the future based on enhanced screening as a result of the work undertaken by Bowel Screening Wales. Currently a test kit is offered every two years to men and women from the age of 55 who are resident in Wales. This will be further lowered to the age of 50 by October 2024.

Additional factors

Dostarlimab (Jemperli®) is not licensed to treat this indication and is therefore 'off-label'. Providers should consult the relevant guidance on prescribing unlicensed medicines before any off-label medicines are prescribed.

References

1. National Institute for Health and Care Excellence. NICE Guideline, NG151. Colorectal cancer. December 2021. Available at: https://www.nice.org.uk/guidance/ng151. Accessed March 2023.
2. Cercek A, Dos Santos Fernandes G, Roxburgh CS et al. Mismatch Repair-Deficient Rectal Cancer and Resistance to Neoadjuvant Chemotherapy. *Clinical Cancer Research,.* 2020;26(13):3271-3279.
3. Andre T, Amonkar M, Norquist JM et al. Health-related quality of life in patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer treated with first-line pembrolizumab versus chemotherapy (KEYNOTE-177): an open-label, randomised, phase 3 trial. *Lancet Oncology.* 2021;22(5):665-677.
4. Cercek A, Lumish M, Sinopoli J et al. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. *The New England Journal of Medicine.* 2022;386(25):2363-2376.
5. GlaxoSmithKline UK. JEMPERLI 500 mg concentrate for solution for infusion. Summary of Product Characteristics. April 2023. Available at: https://www.medicines.org.uk/emc/product/12669. Accessed May 2023.
6. Zamarin D, and Jazaeri AA. Leveraging immunotherapy for the treatment of gynecologic cancers in the era of precision medicine. *Gynecologic oncology,.* 2016;141(1):86-94.
7. National Institute for Health and Care Excellence. Technology Appraisal 779. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency. March 2022. Available at: https://www.nice.org.uk/guidance/ta779. Accessed March 2023.
8. National Institute for Health and Care Excellence. Technology Appraisal 709. Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency. June 2021. Available at: https://www.nice.org.uk/guidance/ta709. Accessed March 2023.
9. GlaxoSmithKline UK. NCT05723562: A Phase 2 Study With Dostarlimab Monotherapy in Participants With Untreated Stage II/III dMMR/MSI-H Locally Advanced Rectal Cancer (AZUR-1). Available at: https://clinicaltrials.gov/ct2/show/NCT05723562. Accessed March 2023.
10. Feeney G, Sehgal R, Sheehan M et al. Neoadjuvant radiotherapy for rectal cancer management. *World Journal of Gastroenterology.* 2019;25(33):4850-4869.
11. Paschke S, Jafarov S, Staib L et al. Are Colon and Rectal Cancer Two Different Tumor Entities? A Proposal to Abandon the Term Colorectal Cancer. *International Journal of Molecular Sciences.* 2018;19(9).
12. Sung H, Ferlay J, Siegel RL et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians.* 2021;71(3):209-249.
13. Boland CR, and Goel A. Microsatellite instability in colorectal cancer. *Gastroenterology.* 2010;138(6):2073-2087.e2073.
14. The National Data Resource (NDR). Single Cancer Pathway. Available at: https://ndr.cymru/single-cancer-pathway.html. Accessed June 2023.
15. UK. CR. Bowel Cancer (C18-C20): 2016-2018. Distribution of Cases Diagnosed By Anatomical Site, UK. 2022. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence. Accessed March 2023.

16. Papke DJ, Jr., Yurgelun MB, Noffsinger AE et al. Prevalence of Mismatch-Repair Deficiency in Rectal Adenocarcinomas. *The New England Journal of Medicine.* 2022;387(18):1714-1716.
17. Public Health Wales NHS Trust. Cancer Incidence in Wales, 2002-2019. June 2022. Available at: https://phw.nhs.wales/services-and-teams/welsh-cancer-intelligence-and-surveillance-unit-wcisu/cancer-incidence-in-wales-2002-2019/. Accessed May 2023.
18. Glynne-Jones R, Wyrwicz L, Tiret E et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology.* 2017;28(suppl_4):iv22-iv40.
19. Benson AB, Venook AP, Al-Hawary MM et al. Rectal Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network.* 2022;20(10):1139-1167.
20. Onkopedia Guidelines. Rectal Cancer: Recommendations from the society for diagnosis and therapy of haematological and oncological diseases. *DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie.* 2022. Available at: www.onkopedia-guidelines.info. Accessed March 2023.
21. Seligmann J. FOxTROT: neoadjuvant FOLFOX chemotherapy with or without panitumumab (Pan) for patients (pts) with locally advanced colon cancer (CC). *Journal of Clinical Oncology.* 2020;38:4013-4013.
22. Biagi JJ, Raphael MJ, Mackillop WJ et al. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. *Jama.* 2011;305(22):2335-2342.
23. Giunta EF, Bregni G, Pretta A et al. Total neoadjuvant therapy for rectal cancer: Making sense of the results from the RAPIDO and PRODIGE 23 trials. *Cancer Treatment Reviews.* 2021;96:102177.
24. Conroy T, Bosset JF, Etienne PL et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncology.* 2021;22(5):702-715.
25. University of Iowa. NCT05239546: Single Arm Study of Neoadjuvant Dostarlimab in Stage II and III Deficient Mismatch Repair Colon Cancers (NAIO). Available at: https://clinicaltrials.gov/ct2/show/NCT05239546. Accessed March 2023.
26. Oaknin A, Gilbert L, Tinker AV et al. Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer: interim results from GARNET-a phase I, single-arm study. *The Journal for ImmunoTherapy of Cancer.* 2022;10(1).
27. Sanoff HK. Improving Treatment Approaches for Rectal Cancer. *New England Journal of Medicine.* 2022;386(25):2425-2426.
28. National Institute for Health and Care Excellence. Colorectal cancer (update) [C4] Deferral of surgery in people having neoadjuvant therapy for rectal cancer,. January 2020. Available at: www.nice.org.uk/guidance/ng151/evidence/c4-deferral-of-surgery-in-people-having-neoadjuvant-therapy-for-rectal-cancer-pdf-7029391219. Accessed May 2023.
29. Rao C, Sun Myint A, Athanasiou T et al. Avoiding Radical Surgery in Elderly Patients With Rectal Cancer Is Cost-Effective. *Diseases of the Colon & Rectum.* 2017;60(1):30-42.
30. Cui CL, Luo WY, Cosman BC et al. Cost Effectiveness of Watch and Wait Versus Resection in Rectal Cancer Patients with Complete Clinical Response to Neoadjuvant Chemoradiation. *Ann Surg Oncol.* 2022;29(3):1894-1907.

31. Bibi S, Edilbe MW, and Rao C. The Cost-effectiveness of Watch and Wait for Rectal Cancer. *Clinical Oncology journal.* 2023;35(2):132-137.
32. Pietzsch JB, and Geisler BP. PSU9 COSTS OF STOMA MANAGEMENT POST COLORECTAL SURGERY IN THE UK HEALTHCARE SYSTEM AND IMPLICATIONS OF POTENTIAL REDUCTION IN NEED FOR OSTOMY PLACEMENT. *Value in Health.* 2019;22:S893. Available at: https://doi.org/10.1016/j.jval.2019.09.2596. Accessed 2023/05/09.
33. Durhuus JA, Therkildsen C, Kallemose T et al. Colorectal cancer in adolescents and young adults with Lynch syndrome: a Danish register-based study. *BMJ Open.* 2021;11(12):e053538.
34. NHS Improvement. National schedule of reference costs. 2020/21 National Cost Collection data. Available at: https://www.england.nhs.uk/national-cost-collection/#nccdata2. Accessed May 2023.
35. Healthcare Quality Improvement Partnership (HQIP): National Bowel Cancer Audit, Annual Report 2021. An audit of the care received by people with bowel cancer in England and Wales. Available at: https://www.hqip.org.uk/resource/nboca-annual-report-2022/#.ZFrcR3bMKUk. Accessed May 2023.
36. NHS Scotland. National Stoma Quality Improvement SLWG (NSQIG) Final Report. 2019. Available at: https://cdn.ps.emap.com/wp-content/uploads/sites/3/2020/08/STOMA-report-2020-Final.pdf. Accessed May 2023.
37. Fokas E, Appelt A, Glynne-Jones R et al. International consensus recommendations on key outcome measures for organ preservation after (chemo)radiotherapy in patients with rectal cancer. *Nature Reviews Clinical Oncology,.* 2021;18(12):805-816.