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

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

October 2024 review

ONE WALES INTERIM DECISION

Dostarlimab (Jemperli®) for the first-line treatment of locally advanced stage II/III deficient mismatch repair (dMMR) / high microsatellite instability (MSI-H) rectal cancer

Date of original advice: August 2023
Date of review: October 2024

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

Using the agreed starting and stopping criteria dostarlimab (Jemperli®) can be made available within NHS Wales for the first-line treatment of locally advanced stage II/III deficient mismatch repair (dMMR) / high microsatellite instability (MSI-H) rectal cancer. This recommendation applies only in circumstances where the approved commercial arrangement price is applied.

The risks and benefits of the off-label use of dostarlimab (Jemperli®) for this indication should be clearly stated and discussed with the patient to allow informed consent. Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 2 years or earlier if new evidence becomes available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Medicines Assessment Group decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Medicines Assessment Group decisions and ensuring that a process is in place for monitoring clinical outcomes.

One Wales advice promotes consistency of access across NHS Wales.

Starting and stopping criteria for dostarlimab for the first-line treatment of locally advanced stage II/III deficient mismatch repair (dMMR) / high

Developed in collaboration with oncologists in Wales.

Starting criteria:

Patients must satisfy all of the following criteria. Treatment may be considered in patients who:

- have histologically confirmed Stage II (T3-T4, N0) or III (any T, N+), locally advanced rectal cancer
- have dMMR/MSI-H tumour status determined using a validated testing method
- have not received prior radiation therapy, systemic therapy, or surgery for management of rectal cancer
- do not have metastatic or recurrent disease
- have not experienced a Grade ≥3 adverse event to a prior immunotherapy
- are not pregnant. Patients of childbearing potential must be willing to use an adequate method of contraception.

A full list of precautions are included in the Summary of Product Characteristics (SmPC)[1].

Dostarlimab should always be initiated by an experienced oncologist following a multidisciplinary team (MDT) discussion.

Patients who satisfy the eligibility criteria will be prescribed dostarlimab following consultation with the patient and/or carer after consideration of potential adverse effects, cautions, contraindications and an explanation of alternative treatment options. This consultation should be recorded in the patient's notes.

The recommended dose for rectal cancer is 500 mg dostarlimab by intravenous infusion every 3 weeks[2]. Treatment should continue up to a maximum of 9 cycles (6 months). Dosing delay or discontinuation may be required based on individual safety and tolerability. Recommended modifications to manage adverse reactions are provided in the SmPC[1].

This treatment is only available when provided in accordance with the approved commercial arrangement price[3].

Monitoring:

- Full blood count
- Urea and electrolytes
- Liver function tests
- Phosphate and calcium
- Blood glucose
- Thyroid function test
- Clinical evaluation of side effects, refer to SmPC

The above tests should be done at baseline and before each cycle of treatment. Refer also to local protocols on scheduling tests.

Whilst on treatment the following investigations are required:

- Magnetic resonance imaging (MRI) of the pelvis and computed tomography of the thorax, abdomen and pelvis (CT TAP) at 3 months
- MRI of the pelvis, CT TAP and flexible sigmoidoscopy at 6 months

Increased surveillance is required for patients receiving dostarlimab to monitor disease status. If there is complete response the following watch and wait surveillance schedule agreed by an international consensus panel[4] is recommended:

- 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;
- 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

Any other monitoring should be in accordance with the SmPC for dostarlimab[1].

Stopping criteria:

- evidence of disease progression or recurrence as agreed in the MDT
- toxicity; dosing delay may be considered, follow the guidance in the SmPC.
- patient request
- after 9 cycles of dostarlimab.

Only one course of treatment may be issued in accordance with this advice. Requests for repeat courses or continuing treatment beyond 9 cycles should be explored through funding mechanisms such as the individual patient funding request process.

Other considerations:

- Patients should be provided with an alert card stating that they have been treated with dostarlimab and advised of the symptoms of immune reactions that should prompt urgent medical care.
- It is important that outcomes are collected for this patient cohort and the outcomes will be reviewed by the One Wales Medicines Assessment Group after 12 months.
- Clinicians may wish to use one of the Cancer Research UK consent forms for SACT (Systemic Anti-Cancer Therapy) to help ensure your patient is fully informed when consenting to SACT.

References

1. GlaxoSmithKline UK. JEMPERLI 500 mg concentrate for solution for infusion. Summary of Product Characteristics. July 2024. Available at: https://www.medicines.org.uk/emc/product/12669. Accessed October 2024.
2. 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
3. All Wales therapeutics and Toxicology Centre. One Wales interim decision. dostarlimab (Jemperli®). Available at: https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/one-wales-dostarlimab-jemperli-for-locally-advanced-rectal-cancer-ow26/. Accessed October 2024
4. 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

This is a summary of new evidence available and patient outcome data collected, to inform the review.

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)

This report was prepared by the All Wales Therapeutics and Toxicology Centre in August 2024. It summarises any new evidence available and patient outcome data collected since the One Wales decision dated August 2023.

Background: Rectal cancer is a tumour arising within 15 cm of the anal verge and accounts for 27.3% of all cases of colorectal cancer. The mismatch repair (MMR) system recognises and corrects DNA replication errors, primarily incorporation of the wrong nucleotide and nucleotide insertions/deletions. Dysfunction of one or more of the MMR proteins (dMMR) causes accumulation of mutations and can lead to cancer cells with a high microsatellite instability (MSI-H) phenotype.

The current treatment pathway for stage II/III rectal cancer is chemoradiotherapy/ radiotherapy and/or surgery with/without adjuvant chemotherapy. Rectal cancer that has tested positive for dMMR / MSI-H is relatively resistant to chemotherapy. Clinicians in Wales 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.

Current One Wales Decision: Dostarlimab is supported for use in this indication

Licence status: Dostarlimab is not currently licensed to treat locally advanced treatment-naïve stage II/III dMMR) / MSI-H rectal cancer; its use in this indication is off-label. [Commercial in confidence information removed]

Guidelines: There have been no relevant updates to existing guidelines identified.

Licensed alternative medicines or Health Technology Assessment advice for alternative medicines: No new medicines or Health Technology Assessment advice reported.

Effectiveness: A repeat literature search conducted by AWTTC identified no new relevant papers pertinent to the dostarlimab recommendation. Since the original report, there has been an update to the ongoing clinical trial (NCT04165772) by Cercek et al which was presented at the 2024 meeting of the American Society of Clinical Oncology. Forty-eight patients with dMMR rectal cancers were enrolled in the Phase II trial. All of the 42 patients who completed treatment achieved a clinical complete response. A clinical complete response was defined as absence of residual disease on digital and endoscopic rectal examination, as well as the absence of residual disease on rectal MRI, with no restricted diffusion on T2-weighted imaging. No patients required any additional therapy, and no patients experienced local or

distant disease recurrence. Twenty-four patients achieved a sustained clinical complete response (clinical complete response for ≥ 12 months after completion of therapy) with a median follow-up of 26.3 months (95% CI 12.4 – 50.5) from first treatment. The median time to complete clinical response was 6.22 months (95% CI 6.18 – 6.45).

There are currently three active trials for use of dostarlimab in rectal and colon cancers:

- 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 2026).
- A phase 3 open-label, randomised study with perioperative dostarlimab in participants with untreated T4N0 or stage III dMMR/MSI-H resectable colon cancer (AZUR-2) (NCT05855200). This study is due to complete December 2030 (primary completion date December 2028).
- A phase 2 single-arm, open-label study of neoadjuvant dostarlimab in Stage II and III dMMR Colon Cancers (NAIO) (NCT05239546) This study is due to complete December 2030 (primary completion date April 2026).

Safety: No relevant safety analyses identified in the repeat literature search. The most commonly reported adverse events (all grades) in the study update by Cercek et al included rash or dermatitis (21%), pruritus (13%), fatigue (11%), and hypothyroidism (11%). No new safety signals were identified. No adverse events of grade 3 or higher were reported.

Cost-effectiveness: No relevant cost-effectiveness analyses were identified in the repeat literature search.

Budget impact: In the original evidence summary it was estimated that 20 patients in Wales start treatment each year with all assumed to have had the full 6-month course of treatment. There has been a total of seven patients who have received dostarlimab treatment for this indication, four since the publication of the original One Wales decision in August 2023. The number of patients who received treatment over the past 12 months is lower than estimated for the original assessment. This may be due to variation in MMR or genetic testing availability, it also may be that clinicians are cautious in adopting such a radical change in treatment pathway from the current standard of care.

Impact on health and social care services: Minimal.

Patient outcome data: Outcome data have been provided for seven patients, five of which have completed dostarlimab treatment. All patients had stage III cancer with T2 (tumour has grown into the muscle layer of the bowel wall) to T4b (tumour has grown through the bowel wall into nearby organs) and node involvement between N1a (1 node) and N2b (> 7 nodes), tumour size ranged from 3 cm to 9 cm. Five of the patients have reported clinical response, with tumour size decreasing to 0 cm

within 6 months (see Appendix 1). All have reported an improvement in their quality of life with lower EQ-5D questionnaire scores from baseline. [Confidential data removed]

Next review date: October 2026

References: a full reference list is available on request.

Appendix 1: [Confidential data removed]

Disclaimer: This document includes evidence published since the last review or full assessment of this medicine for the indication under consideration. It does not replace the original full evidence status report. Any previous reviews and the original full evidence status report are available on request by email to AWTTC@wales.nhs.uk.

Care has been taken to ensure the information is accurate and complete at the time of publication. However, the All Wales Therapeutics and Toxicology Centre (AWTTC) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC accept no liability in association with the use of its content. An Equality and Health Impact Assessment (EHIA) has been completed in relation to the One Wales policy and this found there to be a positive impact. Key actions have been identified and these can be found in the One Wales Policy EHIA document.

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