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)

August 2023

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 advice: August 2023

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 12 months 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 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. April 2023. Available at: https://www.medicines.org.uk/emc/product/12669. Accessed June 2023.
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 July 2023
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

One Wales Medicine Assessment Group summary of decision rationale

Medicine: **dostarlimab (Jemperli®)**
Indication: **For the first-line treatment of locally advanced stage II/III deficient mismatch repair (dMMR) / high microsatellite instability (MSI-H) rectal cancer**

Meeting date: **19 June 2023**

Criteria	OWMAG opinion
Clinical effectiveness	OWMAG notes that the main clinical effectiveness evidence for off-label dostarlimab monotherapy for 1st line treatment of locally advanced stage II/III dMMR/MSI-H rectal cancer is from an ongoing single centre, single arm open label trial. Interim results demonstrate 100% clinical complete response (cCR) in the 23 patients who have completed treatment with dostarlimab. Eleven patients had sustained cCR for 12 months post treatment. However, patient numbers were small and there is a lack of longer term follow up. The group also noted the lack of comparator arm for this study. OWMAG notes the current standard of care treatment options available to patients of radiotherapy with/without capecitabine followed by total mesorectal excision possibly followed by chemotherapy. The group acknowledge that availability of dostarlimab may replace current standard of care or could delay the need for radiotherapy/surgery/chemotherapy, although these treatments would remain as an option for patients if they did relapse. OWMAG note that the prospective clinical trial of dostarlimab, Azur-1, will not have centres in Wales and will not be an option for accessing dostarlimab for patients in Wales. OWMAG considers that the evidence, whilst immature, provided sufficient clinical effectiveness for using dostarlimab as an alternative to standard care for this patient subgroup.

Cost-effectiveness	There is no cost effectiveness evidence available for this treatment. The group considered the watch and wait analyses presented as a proxy for treatment with dostarlimab. The group considered the cost effectiveness analyses for total neoadjuvant therapy (TNT) versus standard of care presented as a proxy for dostarlimab. The group noted the dominance of TNT over standard of care. Whilst acknowledging the differences between patient groups and treatments the group felt that the inputs to the models would be suitably similar to broadly apply as a proxy for treatment with dostarlimab. The group noted that one of the studies were based on US costings and therefore would differ from the NHS perspective. The group noted the sensitivity of the models to relapse/recurrence of disease.
Budget impact	OWMAG considers the clinical estimate of patient numbers to be reasonable. The group acknowledge that as routine genomic testing is a relatively recent development there is likely to be some uncertainty around the estimates presented. Patient numbers may rise in accordance with the roll out of routine monitoring in people 50 years and over. The group note the multiple possible treatment combinations which may be used for this patient group and acknowledge the range in costs. OWMAG acknowledge the potentially offset costs associated with stoma reversal and/or long-term stoma care and that these costs are not included in the budget impact. The differences in monitoring requirements following treatment were considered, these had not been included in the budget impact but the expected surveillance recommendations were discussed. Based on the results from the Cercek study and the costs provided OWMAG consider the budget impact to be reasonable value for money for NHS Wales.
Resource use	Whilst taking into account the increase surveillance requirements for patients following treatment with dostarlimab. The group were of the opinion that, if clinical complete response is maintained the resource use would be expected to be lower when compared with standard care.
Other factors	OWMAG acknowledge that dostarlimab may offer an alternative treatment for dMMR/MSI-H rectal cancer, potentially avoiding or delaying the need for radical life-changing surgery. The group note that the rollout of colorectal cancer testing for all patients aged 50 years over

	the next couple of years may lead to earlier detection of rectal cancer in younger patients. This group of patients would consequently be living with the long-term effects of radical surgery – total mesorectal excision for a greater proportion of their lives than other rectal cancer patients. Patients may be diagnosed whilst still employed and dostarlimab may offer a higher possibility of continuing work than radical surgery. Radical surgery and lifelong stoma are expected to have a negative impact on all aspects of a patient's life.
Final recommendation	OWMAG recommends the use of dostarlimab 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 and is subject to the development of appropriate start/stop criteria.
Summary of rationale	Despite the limited clinical evidence to demonstrate the long-term efficacy of dostarlimab in sustaining clinical complete response OWMAG are of the opinion that dostarlimab may avoid or delay the need for radical surgery thus offering improved quality of life for these patients.