Dostarlimab (Jemperli®) for the treatment of patients with mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC)

General information

Drug description [1]	Indication [2]
Dostarlimab (Jemperli®, TSR-042) is an investigational humanized anti–PD-1 immunoglobulin G4 monoclonal antibody that binds with high affinity to the PD-1 receptor and effectively blocks the interaction with PD-L1 and PD-L2.	Dostarlimab (Jemperli®) is indicated as monotherapy for the treatment of adult patients with dMMR/MSI-H recurrent or advanced EC that has progressed on or following prior treatment with a platinum-containing regimen.

Current treatment [3]

- Approximately 30% of primary ECs are MSI-H, and 13% to 30% of recurrent ECs are MSI-H or dMMR.
- Initial EC management consists of surgery followed by radiation and/or cytotoxic therapy for patients with adverse risk factors.
- Advanced or recurrent disease is treated with cytotoxic, targeted, or hormonal therapy and/or palliative radiation depending on the histology, disease location, and extent or bulk of disease.

Regulatory status

EMA [2]

Approval status for this indication: On 25 February 2021, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Jemperli®, intended for the treatment of certain types of recurrent or advanced EC.

UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 21/04/2021

The full indication is:

- Jemperli® is indicated as monotherapy for the treatment of adult patients with dMMR/MSI-H recurrent or advanced EC that has progressed on or following prior treatment with a platinum-containing regimen.

Other indications: none

- ✓ **Medicine received a conditional marketing authorisation[1]**
- ✓ **Medicine under additional monitoring**

FDA

Approval status for this indication:

On 22 April 2021, the FDA granted accelerated approval to Jemperli® (dostarlimab) for treating patients with recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing chemotherapy and whose cancers have a specific genetic feature known as dMMR (which contain abnormalities that affect the proper repair of DNA inside the cell), as determined by an FDA-approved test.

- ✓ Accelerated approval (based on tumour response rate and durability of response
- ✓ Priority review
- ✓ Breakthrough therapy designation

Other indications: Jemperli® is indicated

- for the treatment of adult patients with dMMR recurrent or advanced solid tumours, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options (accelerated approval based on tumour response rate and durability of response).

Costs [6]

Jemperli® concentrate for solution for infusion 500 mg/10 ml = € 6,950.00 (ex-factory price)

Posology

- Dostarlimab must be initiated and supervised by specialist physicians experienced in the treatment of cancer [2].

[1] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

❖ The identification of dMMR/MSI-H tumour status should be determined using a validated testing method such as immunohistochemistry, polymerase chain reaction or next-generation sequencing .

Special warnings and precautions for use

❖ **Immune-mediated adverse reactions** can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and solid organ transplant rejection.
- Monitor for signs and symptoms of immune-mediated adverse reactions. Evaluate clinical chemistries including liver and thyroid function, at baseline and periodically during treatment.
- Withhold or permanently discontinue Jemperli® and administer corticosteroids based on the severity of reaction.

❖ **Infusion-related reactions**: Interrupt, slow the rate of infusion, or permanently discontinue Jemperli® based on severity of reaction.

❖ **Complications of allogeneic HSCT**: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1–blocking antibody.

❖ **Embryo-foetal toxicity**: Can cause foetal harm. Advise females of reproductive potential of the potential risk to a foetus and to use effective contraception.

Study characteristics [1, 7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
GARNET NCT02715284	104	500 mg of dostarlimab IV every 3 weeks for 4 doses, then 1000 mg every 6 weeks until disease progression, treatment discontinuation, or withdrawal	-	ORR & DOR by BICR using RECIST, version 1.1.	**Ongoing**[2], multicentre, open-label, single-group, multicohort, phase I trial	dMMR/MSI-H	GlaxoSmithKline	[1]

Efficacy (interim efficacy population, n=71)

ORR: 42.3%; 95% CI, 30.6-54.6
Confirmed complete response: 12.7%
Confirmed partial response: 29.6%
Median DOR: not reached
Estimated likelihood of maintaining a response: 96.4% at 6 months and 76.8% at 12 months (based on the Kaplan-Meier method)
Disease control rate: 57.7% (95% CI, 45.4-69.4)
Median PFS: 8.1 months (95% CI, 3.0-18.0 months)
Median OS: not reached (with a Kaplan-Meier estimation of 72.7% survival at 12 months after treatment initiation)
QoL: PRO data were available for 43 patients. Compliance rates were high at 98%. Relative to baseline, patients reported meaningful improvements in pain, insomnia, and social and emotional functioning over the trial duration. Appetite, nausea, vomiting, constipation, diarrhoea, and physical and role functioning were stable over the trial duration. QoL and global health status were also maintained => PRO show that disease- and treatment-related symptoms and QoL are improved or maintained while receiving treatment.

UPDATE: Efficacy results at time of data cut-off (March 2020, n=108) [10]:
ORR: 43.5%; 95% CI, 34.0-53.5
Complete response rate: 10.2 %
Partial response rate: 33.3 %
Disease control rate: 55.6% (95% CI, 45.7-65.1)
Stable disease: 12% (95% CI, 6.6-19.7)
Median duration of response: not reached (range, 2.6-28.1)
Probability of maintaining response at 6 months by Kaplan-Meier curve estimate: 97.9% (95% CI,85.8-99.7)
Probability of maintaining response at 12 months by Kaplan-Meier curve estimate: 90.9% (95% CI, 73.7-97.1)

Safety (n=104)

Grade ≥3 TRAEs: n=12 (11.5%)
Any SAE: n=35 (33.7%)
Any related SAE: n=10 (9.6%)
TEAEs leading to death: n=5 (4.8%)
TRAEs leading to death: n=0
Discontinuation due to TRAE: n=2 (1.9%)
Any irTEAE: n=35 (33.7%)
Any irTRAE: n=24 (23.1%)

ESMO-MCBS version 1.1 [11]

[2] The GARNET trial is currently ongoing; estimated study completion date is 07/2024.

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	-	ORR: 42.3%	30.6%-54.6%	ORR (PR+CR) ≥40-<60%	2	-	-	-	2
Adapted	NC	-	-	-	-	-	-	-	-	-	-

Risk of bias - study level (case series) [12]								
1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	yes	yes	unclear	yes	yes
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	unclear	yes	yes	unclear	yes
Overall risk of bias: low								

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Abbreviations: AE=adverse event, AJ=adjustment, BICR=blinded independent central review C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, dMMR= mismatch repair deficient, DNA=deoxyribonucleic acid, DOR=duration of response, EC=endometrial cancer, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HR=hazard ratio, HSCT=hematopoietic stem cell transplantation, I=intervention, Int.=intention, irTEAE=immune-related treatment-emergent adverse event, irTRAE=immune-related treatment-related adverse event, IV=intravenous, MG=median gain, MSI-H=microsatellite instability-high, n=number of patients, ORR=objective response rate, OS=overall survival, PD-1/L1=programmed death receptor-1/ligand 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PRO=patient-reported outcome, QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumors, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse event, TRAE=treatment-related adverse event

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