Submitted by:

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NCCN Guidelines Panel: Small Bowel Adenocarcinoma Panel

On behalf of GSK, we respectfully submit to the NCCN Small Bowel Adenocarcinoma Panel the enclosed clinical data for *Jemperli* (dostarlimab-gxly), a programmed death receptor-1 (PD-1)-blocking antibody, for the Panel's consideration.

Specific Change(s) Requested:

We respectfully recommend the following change:

- ***Page SBA-D 1, Principles of Systemic Therapy for Advanced or Metastatic Disease, Subsequent Therapy:*** consider adding dostarlimab-gxly as an option for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options
- ***Page SBA-D 5, Advanced or Metastatic Therapy Regimens***: consider adding dosing regimen for dostarlimab-gxly 500 mg intravenously every 3 weeks for 4 doses followed by 1,000 mg intravenously every 6 weeks until disease progression or unacceptable toxicity

Rationale:

On August 17, 2021, the United States Food and Drug Administration (FDA) approved *Jemperli* (dostarlimab-gxly) for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options. *Jemperli* was previously approved by the FDA on April 22, 2021 for the treatment of adult patients with dMMR recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen. These indications are approved under accelerated approval based on tumor response rate and durability of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).[1]

Clinical data provided reflect results of an interim analysis of patients enrolled in the GARNET trial with dMMR recurrent or advanced solid tumors that had progressed on or following prior treatment and who had no satisfactory alternative treatment options. Results of this analysis were presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in June 2021 and are included in the US Prescribing Information for dostarlimab-gxly.[1,2] To summarize:

Study Design:

GARNET (NCT02715284) is a non-randomized, multicenter, open-label, multi-cohort trial that enrolled patients with dMMR recurrent or advanced solid tumors into two cohorts:[3]

- **Cohort A1** - patients with dMMR endometrial cancer that had progressed on or after treatment with a platinum-containing regimen were included.
- **Cohort F** - a dMMR basket cohort that included patients with non-endometrial dMMR solid tumors that had progressed following systemic therapy and had no satisfactory alternative treatment options. Patients with dMMR colorectal cancer (CRC) must have had progressive disease after or been intolerant to a fluoropyrimidine, oxaliplatin, and irinotecan.

Patients with prior treatment with programmed death-1 (PD-1)/PD-1-ligand-1 (PD-L1)–blocking antibodies or other immune checkpoint inhibitor therapy were excluded from the GARNET trial. Dostarlimab-gxly was administered as 500 mg intravenously every 3 weeks for 4 doses followed by 1,000 mg intravenously every 6 weeks until disease progression or unacceptable toxicity.[1-3]

Efficacy and safety results for patients with dMMR recurrent or advanced solid tumors reflect combined data from Cohorts A1 and F. [1,2] The major efficacy outcomes were overall response rate (ORR) and duration of response (DOR), as assessed using Response Evaluation Criteria in Solid Tumors Version (RECIST v1.1) by blinded independent central review (BICR).[1]

Study Population: [2]

- Data cut-off date was March 1, 2020 with additional follow-up on DOR and safety taken on November 1, 2020.
- Safety population included a total of 316 patients that were enrolled and treated as of the data cut-off date (143 patients in Cohort A1, 173 patients in Cohort F).
- Efficacy population included a total of 209 patients in the safety population with ≥ 6 months of follow-up time as of data cut-off date and with ≥ 1 measurable lesion at baseline (103 patients in cohort A1, 106 patients in cohort F).
- Median age was 63 years, and 57% of patients had received 2 or more lines of prior therapy.

Efficacy:

- The objective response rate (ORR) was 41.6% (95% CI, 34.9% - 48.6%); 19 patients (9.1%) had a confirmed complete response (CR) and 68 patients (32.5%) had a confirmed partial response (PR).[1,2] Disease control rate (DCR) was 60.3% (95% CI, 53.3% - 67.0%).[2] Median duration of response (DOR) was 34.7 months (range, 2.63 to 35.78+ mos), at a median follow-up time of 17.5 months. Responses were durable, with 95.4% of responders having a response that lasted ≥ 6 months.[2]
- Antitumor activity by tumor type is presented in Table 1.[1,2] For the 12 patients with small-intestinal cancer, the ORR was 33.3% an (95% CI, 9.9% - 65.1%) and the DOR range was 11.1+ – 28.0+ months.

Table 1. Antitumor Activity by Tumor Type

		Confirmed ORR (RECIST v1.1)		DOR
Tumor type	**Patients, N**	**n (%)**	**95% CI, %**	**Range, months**
Overall	**209**	**87 (41.6)**	**(34.9–48.6)**	**2.6, 35.8+**
Endometrial Cancer (EC)	**103**	**46 (44.7)**	**(34.9–54.8)**	**2.6, 35.8+**
Colorectal Cancer (CRC)	**69**	**25 (36.2)**	**(25.0–48.7)**	**5.6, 30.1+**
Non-CRC	**37**	**16 (43.2)**	**(27.1–60.5)**	**N/A**
Small-intestinal cancer	12	4 (33.3)	(9.9–65.1)	11.1+, 28.0+
Gastric and gastroesophageal junction cancer	8	3 (37.5)	(8.5–75.5)	8.4+, 17.5
Pancreatic carcinoma	4	SD, 3 PD	(0.0–60.2)	NA
Ovarian cancer	2	PR, SD	NA	25.1+
Hepatocellular carcinoma	2	PR, PD	NA	13.8+
Biliary neoplasm	2	2 CR	NA	8.4+, 13.5+
Breast cancer	1	CR	NA	16.8+
Adrenal cortical carcinoma	1	PR	NA	19.5+
Malignant neoplasm of the female genitals	1	PR	NA	22.2+
Pleural cancer	1	PR	NA	15.2+
Unknown origin	1	PR	NA	20.4+
Renal cell carcinoma	1	SD	NA	NA
Esophageal cancer	1	PD	NA	NA

CR, complete response; CRC, colorectal cancer; EC, endometrial cancer; NA, not applicable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Safety:

- Most treatment-related adverse events (TRAEs) were grade 1-2 (any grade TRAEs, 69.3%; grade ≥ 3 TRAEs, 13.6%). The most common any grade treatment-emergent adverse events (TEAEs) reported in ≥ 20% of patients were anemia, diarrhea, asthenia, nausea, and fatigue (31.6%, 26.3%, 24.4%, 22.5%, and 20.3%, respectively).[2]
- The most common grade ≥ 3 immune-related (ir)-TEAEs reported in ≥ 1% of patients were ALT increased, lipase increased, AST increased, diarrhea, and hyperglycemia (2.5%, 2.2%, 1.6%, 1.6%, and 1.3%, respectively.) Grade ≥ 3 irTRAEs had an incidence of ≤ 1.6% each (including 2 reports [0.6%] of grade ≥ 3 treatment-related colitis).[2]
- Sixteen patients (5.1%) discontinued treatment due to TRAEs. Two treatment-related deaths associated with dostarlimab-gxly, as deemed by the investigator, were reported (1 hepatic ischemia and 1 suicide).[2]

Summary

Jemperli (dostarlimab-gxly) is approved under accelerated approval for the treatment of adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.[1] Antitumor activity of dostarlimab-gxly was observed across multiple dMMR tumor types, with an ORR of 41.6% (34.9%-48.6%).[1,2] Responses were durable, with a median duration of response of 34.7 months (range, 2.63 to 35.78+) after a median follow-up time of 17.5 months.[2] Dostarlimab-gxly demonstrated a manageable safety profile across different tumor types.[2,4-6]

We sincerely appreciate the opportunity to provide this information for consideration by the NCCN Small Bowel Adenocarcinoma Panel. If any questions arise or if you require any additional information, please do not hesitate to contact Ji Chung, PharmD, RPh at ji.8.chung@gsk.com.

Sincerely,

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Please find the attached enclosures in support of this submission.

Bibliography

1. *Jemperli* [package insert]. Research Triangle Park, NC: GlaxoSmithKline, Inc.
2. Berton D, Banerjee S, Curigliano G, et al. Antitumor Activity of Dostarlimab in Patients with Mismatch Repair–Deficient (dMMR) Tumors: a Combined Analysis of 2 Cohorts in the GARNET Study. Poster presented at American Society for Clinical Oncology (ASCO), Virtual Meeting, June 4–8, 2021. [Abstract ID: 2564].
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4. Oaknin A, Tinker AV, Gilbert L, et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. *JAMA Oncol.* 2020. doi:http://dx.doi.org/10.1001/jamaoncol.2020.4515.
5. Oaknin A, Gilbert L, Tinker AV, et al. Safety and antitumor activity of dostarlimab in patients with recurrent or advanced mismatch repair deficient (dMMR) or proficient (MMRp) endometrial cancer: Results from GARNET. Oral Presentation at the European Society of Medical Oncology (ESMO) Annual Congress (Virtual). September 18th, 2020. Presentation ID LBA36. doi: https://doi.org/10.1016/j.annonc.2020.08.2266.
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