Submitted By:

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NCCN Guidelines Panel: Uterine Neoplasms

On behalf of GSK, this letter is a follow-up to the formal request submitted on 15 May 2020 to the NCCN Uterine Neoplasms Panel for review and consideration of the data for dostarlimab-gxly monotherapy as summarized below. This update is based on the United States (US) Food and Drug Administration (FDA) approval of *Jemperli* (dostarlimab-gxly) for the treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer (EC), as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).[1]

Specific Changes Requested:

As requested in previous submission on 15 May 2020, we respectfully ask the NCCN Panel to consider the following changes:

- **Page ENDO-D1:** Add dostarlimab-gxly as a treatment option for recurrent, metastatic or high-risk disease under the ***biomarker-directed systemic therapy for second-line treatment*** category.
- **Page ENDO-D3**: Add a footnote stating "dostarlimab-gxly is indicated for patients with dMMR recurrent or advanced EC that has progressed on or following prior treatment with a platinum-containing regimen."

Rationale:

The US FDA accelerated approval of dostarlimab-gxly is based on the results of an interim analysis of patients enrolled in the GARNET trial with dMMR recurrent or advanced EC that has progressed on or after treatment with a platinum-containing regimen. GARNET is currently the largest study specifically evaluating the activity of single agent anti-PD-1 therapy in this setting. Results of this interim analysis were presented at the SGO Annual Meeting in April 2020[2] and were previously submitted to the NCCN Uterine Neoplasms Panel on 15 May 2020. These data are included in the US Prescribing Information for dostarlimab-gxly[1] and were published in *JAMA Oncology* in October 2020.[3] To highlight results:

<u>Efficacy</u>

- Seventy-one patients with dMMR EC were included in the interim efficacy analysis.[3]
- The objective response rate (ORR) (primary endpoint) was 42.3% (95% CI, 30.6% - 54.6%); 9 patients (12.7%) had a confirmed complete response (CR) and 21 patients (29.6%) had a confirmed partial response (PR).[1,3] Disease control rate (DCR) (secondary endpoint) was 57.7% (95% CI, 45.4% - 69.4%) at data cutoff date (July 2019).[3]
- Median duration of response (DOR, primary endpoint) was not reached (range, 2.6 to 22.4+ mos), at a median follow-up for DOR of 14.1 months (measured from time of first response). In responding patients, 93.3% had a DOR ≥ 6 months.[1]
- Median progression free survival (PFS) (secondary endpoint) was 8.1 months (95% CI, 3.0 - 18.0 months).[3]
- Median overall survival (OS) (secondary endpoint) was not reached. Kaplan-Meier estimation of survival at 12 months after treatment initiation was 72.7%.[3]

Safety

- One hundred and four patients with dMMR EC were included in the safety population.[1,3]
- Most treatment-related adverse events (TRAEs) were grade 1-2. The most common (≥10%) any-grade TRAEs were asthenia, diarrhea, fatigue and nausea (15.4%, 15.4%, 14.4% and 12.5%, respectively).[3]
- Any-grade immune-related treatment related adverse events (irTRAEs) were reported in 24 (23.1%) patients; diarrhea (5.8%) and hypothyroidism (5.8%) were reported most frequently. Grade ≥ 3 irTRAEs were reported in 8 (7.7%) patients; diarrhea (2.9%) was the most common grade ≥ 3 irTRAE.[3]
- Two (1.9%) patients discontinued treatment due to TRAEs. There were no deaths that were attributed to dostarlimab-gxly by the investigators.[3]

Response rate, duration of response and safety data for patients enrolled in GARNET with dMMR EC from a later data cutoff date (March 1, 2020) were presented at the 2020 European Society of Medical Oncology Annual Conference and at the 2020 European Society of Gynaecological Oncology Conference. In addition, the time course of adverse events during dostarlimab-gxly treatment in patients with dMMR EC was presented at the 2021 Oncology Nursing Society (ONS) Annual Conference. Results were consistent with the data presented above.[4,5,6]

Summary

There are few effective options for the treatment of endometrial cancer patients who progress on or after a platinum-containing regimen.[7] Dostarlimab-gxly monotherapy has demonstrated durable clinical activity and an acceptable safety profile in this setting for patients whose tumors are dMMR.[1,3] The US FDA approval for dostarlimab-gxly is based on data from GARNET, the largest study to date specifically evaluating the activity of single anti-PD-1/PD-L1 therapy in this setting.[3]

We sincerely appreciate the opportunity to provide this information for consideration by the NCCN Uterine Neoplasm Panel. If any questions arise or if you require any additional information, please do not hesitate to contact Alexis Williams, Pharm D, RPh at alexis.8.williams@gsk.com.

Sincerely,

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Please find the attached enclosures, in addition to the data disclosures submitted on 15 May 2020, in support of this proposed change.

Bibliography

1. *Jemperli* [package insert]. Research Triangle Park, NC: GlaxoSmithKline, Inc.
2. Oaknin A, Tinker AV, Gilbert L, et al. Safety and efficacy of the anti-PD-1 monoclonal antibody dostarlimab in patients with recurrent or advanced dMMR endometrial cancer. Presented by R. Sabatier at the Society of Gynecologic Oncology Annual Meeting Webinar Series, April 23rd, 2020. (Abstract LBA-9).
3. 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.
4. 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.
5. Oaknin A, Gilbert L, Tinker AV, et al. Safety and antitumour activity of dostarlimab in patients with advanced or recurrent DNA mismatch mutation repair deficient or proficient endometrial cancer: results from the GARNET study. Poster Presented at European Society of Gynaecological Oncology (ESGO)

(Virtual). December 14-16, 2020. Poster No 385.
6. Oaknin A, Gilbert L, Tinker A, et al. The Time Course of Adverse Events During Dostarlimab Treatment in Mismatch Mutation Repair Deficient and Proficient Endometrial Cancer Patients in the GARNET Trial. Oral Presentation by Dr. Pothuri at The 46th Annual Oncology Nursing Society's (ONS) Congress (Virtual). April 20, 22, 27, and 29, 2021. Abstract #10455.
7. Brooks RA, Fleming GF, Lastra RR, et al. Current recommendations and recent progress in endometrial cancer. *CA Cancer J Clin*. 2019;69(4):258-279. doi:http://dx.doi.org/10.3322/caac.21561.