**Submitted By:**

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**NCCN Guidelines Panel:** Uterine Neoplasms

On behalf of GSK, this letter is a formal request to the NCCN Uterine Neoplasms Panel to review and consider the enclosed data for dostarlimab as a preferred treatment option for adult patients with recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen whose tumors are mismatch repair deficient (dMMR). This request is based on the GARNET trial data, which has been presented at the Society of Gynecologic Oncology Annual Meeting Webinar Series on April 23, 2020.

**Specific Changes Requested:**

We respectfully request the following changes:

- **Page ENDO-D1:**
    - Consider adding dostarlimab as a ***preferred regimen*** for the treatment of adult patients with recurrent or advanced EC that has progressed on or following prior platinum-containing treatment whose tumors are dMMR.
    - Consider adding a new category, such as ***Biomarker Directed Therapy***, in addition to *Chemotherapy Regimens* category. Consider placing dostarlimab under this new category.
- **Page ENDO-D2**: Consider amending footnote l to include dostarlimab.
- **Page ENDO-A2**: Consider adding recommendation to test, if not previously done, for dMMR in the metastatic or recurrent setting as a biomarker for eligibility for checkpoint blockade therapy.

**FDA Clearance:** GlaxoSmithKline has submitted a Biologics License Application (BLA) to the U.S. Food and Drug Administration (FDA) for the approval of dostarlimab for second line treatment of patients with dMMR recurrent or advanced EC based on the results of the GARNET study.

**Rationale:**

EC has been identified as one of the cancers with the highest rate of dMMR (approximately 30%) varying by EC histology and tumor grade.[1,2] Because of their inability to repair DNA replication errors, dMMR tumors are associated with an increase in mutation rates and express high levels of neoantigens, making the tumor immunogenic[3]; thus patients with dMMR tumors may represent a population likely to respond to anti-programmed death-1(PD-1)/ anti-PD-ligand-1 (PD-L1) agents, such as dostarlimab.[3,4]

Dostarlimab is a humanized monoclonal antibody of the immunoglobulin G4 (IgG4) isotype that binds to PD-1, resulting in inhibition of binding to PD-L1 and PD-L2, releasing inhibition of PD-1 pathway-mediated immune response, including the anti-tumor immune response.

GARNET is a multicenter, open-label, first-in-human phase 1 dose escalation study with expansion cohorts designed to assess the clinical activity and safety of dostarlimab in patients with advanced solid tumors.

An interim analysis of patients enrolled in GARNET with recurrent or advanced dMMR EC that had progressed on or after treatment with a platinum-containing regimen was conducted. Immunohistochemistry was used to determine MMR status. Dostarlimab was administered at the recommended phase 2 dose of 500 mg Q3 weeks for the first 4 doses and 1000 mg Q6 weeks thereafter. The primary endpoints were objective response rate (ORR) and duration of response (DOR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.[5]

Efficacy Results

Seventy-one patients with dMMR EC treated with dostarlimab who had measurable disease at baseline and ≥ 6 months of follow-up by the data cutoff date (July 8, 2019) were included in the interim efficacy analysis. Median age was 64 years. Overall, 49% of patients had stage III/IV EC at diagnosis, and endometrioid carcinoma (grade 1 and 2) was the most common histology (70%).[5]

The ORR (primary endpoint) was 42%. Nine patients (13%) had a confirmed complete response (CR) and 21 patients (30%) had a confirmed partial response (PR). Disease control rate (DCR) was 58% at data cutoff. Of the patients responding, 83% remained in response at data cutoff. The Kaplan–Meier estimated likelihood of maintaining response was 96% at 6 months and 77% at 12 months.[6] Median DOR (primary endpoint) had not been reached (1.87+ to 19.61+ mos), with median follow up of 11.2 months.[5]

Efficacy results are summarized below.[5]

| **Variable** | **dMMR EC n = 71, n (%)** |
|---|---|
| **Objective Response Rate, n (%)** | **30 (42) [95% CI, 31–55]*** |
| Complete Response | 9 (13) |
| Partial Response | 21 (30) |
| Stable Disease | 11 (16) |
| Progressive Disease | 27 (38) |
| Not Evaluable[a] | 3 (4) |
| **Response Ongoing** | **25 of 30 (83)** |
| **Disease Control Rate** | **41 (58) [95% CI, 45–69]*** |

dMMR=mismatch repair deficient; EC=endometrial cancer; RECIST= Response Evaluation Criteria in Solid Tumors
*Exact 2-sided 95% CI for the binomial proportion.
[a]Not evaluable based on RECIST v1.1

Safety Results

The safety population comprised all patients with dMMR EC that received at least one dose of dostarlimab (N = 104). Most treatment emergent adverse events (TEAEs) were grade 1-2. Grade ≥3 immune-related treatment related adverse events (TRAEs) were reported in twelve (11.5%) patients. Two (2%) patients discontinued treatment due to TRAEs. There were no TRAEs deaths that were attributed to dostarlimab by the investigators.[5]

Safety results are summarized below.[5]

| Any-grade TRAEs in ≥5% of patients | dMMR EC N = 104, n (%) |
|---|---|
| Asthenia | 16 (15) |
| Diarrhea | 16 (15) |
| Fatigue | 15 (14) |
| Nausea | 13 (13) |
| Pruritus | 10 (10) |
| Hypothyroidism | 9 (9) |
| Arthralgia | 8 (8) |
| Anemia | 7 (7) |

| Grade ≥3 immune-related TRAEs in any patient | dMMR EC N = 104, n (%) |
|---|---|
| Diarrhea | 3 (3) |
| Colitis | 2 (2) |
| Lipase increased | 2 (2) |
| Transaminases increased* | 2 (2) |
| Amylase increased | 1 (1) |
| Alanine aminotransferase increased | 1 (1) |
| Pancreatitis, acute | 1 (1) |

*One patient had AST/ALT increased, and one patient had solely ALT increased

**Summary**

GARNET is currently the largest study specifically evaluating the activity of single agent anti-PD-1 therapy in recurrent or advanced EC that has progressed on or after platinum therapy.[5] The findings from this interim analysis show clinical activity and an acceptable safety profile for dostarlimab in this setting.

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 Natàlia Creus, PharmD, BCOP, PhD at natalia.x.creusbaro@gsk.com.

Sincerely,

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The following data disclosures are submitted in support of this proposed change.


1. Le DT,et al. *Science*. 2017;357(6349):409-413.
2. Kloor M, von Knebel Doeberitz M. *Trends Cancer*. 2016 Mar;2(3):121-133.
3. Le DT et al. NEJM. 2015;372(26):2509-2520.
4. Marabelle A et al. *J Clin Oncol*. 2020:38(1):1-10.
5. Oaknin A et al. Presented by R. Sabatier at the Society of Gynecologic Oncology Annual Meeting Webinar Series, April 23rd, 2020. (Abstract LBA-9).
6. Oaknin A et al. Society of Gynecologic Oncology Annual Meeting. Abstract LBA-9. Available at: https://www.sgo.org/wp-content/uploads/2020/03/SGO-2020-Annual-Meeting-Oral-Abstracts.pdf