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NCCN Cervical/Uterine Cancers Guidelines Panel:

On behalf of Seagen Inc., in consideration of TIVDAK™'s (tisotumab vedotin-tftv) recent approval and as follow-up to our previous submission, we respectfully request the NCCN Cervical Cancer Guidelines Panel to review the enclosed data and prescribing information for inclusion of tisotumab vedotin in the guidelines.

Specific Request:
Consistent with the U.S. Food and Drug Administration (FDA)-approved label, we request the NCCN Cervical Cancer Guideline to please consider the inclusion of tisotumab vedotin as a preferred second-line systemic therapy option for patients with recurrent or metastatic cervical cancer (CERV-F, 1 of 3).

FDA Clearance:
TIVDAK™ is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.[1]

This indication is approved under accelerated approval based on tumor response rate and durability of response.[1] Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Rationale:
Recurrent or metastatic cervical cancer is an incurable disease with no standard of care for patients unselected for biomarkers who progress on or after first-line treatment. Current second-line monotherapy options generally demonstrate objective response rates (ORRs) of <15%, with limited data from small studies that do not reflect modern first-line standard of care treatment options.[2–8] Additionally, as the landscape evolves with emerging treatments for locally advanced, recurrent, and metastatic cervical cancer, data for multiple immunotherapy options has showed either limited activity or activity limited to selected patient populations.[8–12]

Tisotumab vedotin, an antibody-drug conjugate directed towards tissue factor, demonstrated an ORR of 24%, and a median duration of response (DOR) of 8.3 months with a tolerable safety profile in the pivotal phase 2 study,[13,14] published in The Lancet Oncology. Tisotumab vedotin represents a differentiated treatment modality in a rapidly evolving treatment landscape.

Clinical Data:
innovaTV 204 (NCT03438396) was a global phase 2, open-label, multicenter, single-arm study evaluating tisotumab vedotin monotherapy in patients with recurrent or metastatic cervical cancer with disease progression on or after doublet chemotherapy with bevacizumab, if eligible.[13] The primary endpoint was confirmed ORR per RECIST v1.1 by independent review committee (IRC). Secondary endpoints included DOR, time to response (TTR), and progression-free survival (PFS) by IRC and ORR, DOR, TTR, PFS, and overall survival (OS) assessed by investigator.

The ORR was 24% (95% CI: 16 to 33), including 7% complete response and 17% partial response, among 101 patients treated with tisotumab vedotin and a median follow-up of 10.0 months (range: 0.7 to 17.9).[13] Median DOR and TTR was 8.3 months (95% CI: 4.2 to not reached) and 1.4 months (range: 1.1 to 5.1), respectively. The observed disease control rate was 72% (95% CI: 63 to 81), including 49% stable disease, which is considered a clinically meaningful outcome for this patient population. Responses were generally consistent regardless of tumor histology (non-squamous vs. squamous cell carcinomas), responses to prior therapy, and tissue factor expression. Median PFS was 4.2 months (95% CI: 3.0 to 4.4) with a 6-month PFS rate of 30% (95% CI: 21 to 40). Median OS was 12.1 months (95% CI: 9.6 to 13.9) with a 6-month OS rate of 79% (95% CI: 69 to 86).

The safety profile of tisotumab vedotin was manageable with most adverse events (AEs) being mild to moderate, including prespecified AEs of interest: peripheral neuropathy, ocular, and bleeding events.[13] An eye care plan to reduce the risk of and manage ocular AEs was implemented and mandated for all patients in the study. The most common treatment-related adverse events (TRAEs) were alopecia (38%), epistaxis (30%), nausea (27%), conjunctivitis (26%), fatigue (24%), and dry eye (23%). Serious TRAEs were reported in 13 (13%) patients. One treatment-related death occurred due to septic shock. TRAEs led to treatment discontinuation in 12 (12%) patients.

Summary:
Thank you for considering the evidence supporting tisotumab vedotin as a preferred second-line systemic therapy option in the recurrent or metastatic section of the NCCN Cervical Cancer Guidelines. Results from the innovaTV 204 global phase 2 study indicate that tisotumab vedotin has a 24% ORR and a manageable safety profile. Tisotumab vedotin is a differentiated treatment option addressing patients' unmet need in the rapidly evolving recurrent or metastatic cervical cancer treatment landscape.

Sincerely,

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