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NCCN Bladder Cancer Guidelines Panel:

On behalf of Seagen Inc. and Astellas Pharma Global Development, Inc., we respectfully request the NCCN Bladder Cancer Guidelines Panel evaluate the enclosed data for an update of enfortumab vedotin on pages 43 and 44 (BL-G, 3 and 4 of 7) of the Guidelines for the treatment of patients with locally advanced or metastatic urothelial carcinoma (la/mUC).

Specific Changes: We request the NCCN Bladder Cancer Guidelines Panel consider:

- Including enfortumab vedotin as a **preferred regimen** for patients with la/mUC who have previously received a programmed death receptor-1 or programmed death-ligand 1 (PD-1/L1) inhibitor on page 43 (BL-G, 3 of 7).
- Updating the current recommendation on page 44 (BL-G, 4 of 7) for enfortumab vedotin to a preferred regimen with **category 1** level of evidence for la/mUC patients previously exposed to a platinum-containing chemotherapy regimen and a PD-1/L1 inhibitor, including in patients treated with platinum followed by PD-1/L1 inhibitor maintenance.

FDA Approval: PADCEV® (enfortumab vedotin-ejfv) is indicated for the treatment of adult patients with la/mUC who have previously received a PD-1/L1 inhibitor and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.[1]

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

Rationale: Metastatic urothelial carcinoma is an incurable disease with high unmet need and an estimated 5-year survival rate of <6%.[2] While cisplatin-based chemotherapy remains the standard of care for the first-line treatment of la/mUC, approximately half of the patients are cisplatin-ineligible and many are treated with PD-1/L1 inhibitors.[3–7] Of those who receive first-line PD-1/L1 inhibitors, only ~20-30% of patients unselected for PD-L1 expression achieve objective responses and the majority experience disease progress within 6 months.[8,9] There is a paucity of data for the treatment of these patients following first-line PD-1/L1 inhibitors and only about one-third (34%) of cisplatin-ineligible patients go on to receive additional therapy, underscoring the need for safe and effective treatment options in this population.[10] Results from Cohort 2 of enfortumab vedotin trial EV-201 demonstrated an objective response rate (ORR) of 52% showing efficacy and tolerability in this cisplatin-ineligible la/mUC population who were previously treated with a PD-1/L1 inhibitor.[11]

Additionally, in the confirmatory trial EV-301, enfortumab vedotin was the first therapy to demonstrate superior overall survival (OS) and progression-free survival (PFS) following platinum-containing chemotherapy and PD-1/L1 inhibitor therapies when compared to standard chemotherapy.[12] Patients with prior exposure to platinum-based chemotherapy and a PD-1/L1 inhibitor, regardless of line of therapy in mUC setting, were eligible for EV-301.[13]

Clinical Data:

EV-201 Cohort 2

EV-201 is a two-cohort, single-arm, Phase 2 trial of enfortumab vedotin in patients with la/mUC who were previously treated with a PD-1/L1 inhibitor.[11] Cohort 2 included 89 patients who were cisplatin-ineligible, platinum-naïve and received enfortumab vedotin until disease progression or unacceptable toxicity.

The primary endpoint was confirmed ORR as determined by blinded independent central review (BICR).[11] Key secondary endpoints included duration of response (DOR), PFS per BICR and investigator, OS, safety, and tolerability. After a median follow-up of 13.4 months, the confirmed ORR per BICR was 52% (95% CI: 40.8 to 62.4) with a 20% complete response rate and a 31% partial response rate. The median DOR was 10.9 months (95% CI: 5.78 to not reached). Consistent ORR was seen in difficult-to-treat subpopulations, including those with liver metastases and upper tract disease. Target lesion reduction occurred in 88% of evaluable patients and median PFS and OS were 5.8 months (95% CI: 5.03 to 8.28) and 14.7 months (95% CI: 10.51 to 18.2), respectively. The most common treatment-related adverse events (TRAEs) were any skin reactions (61%), any peripheral neuropathy (54%), alopecia (51%), fatigue (34%), decreased appetite (33%), and pruritus (30%). Grade ≥3 TRAEs occurred in 55% of patients. The most common Grade ≥3 TRAEs were neutropenia, rash, fatigue, increased lipase, diarrhea, decreased appetite, anemia, and hyperglycemia. Individual TRAEs Grade ≥3 occurred in ≤10% of patients. There were 3 TRAEs leading to death within 30 days of the first dose of enfortumab vedotin in this cohort of older, cisplatin-ineligible patients.

EV-301

EV-301 is a comparative, Phase 3 confirmatory trial of enfortumab vedotin in patients with la/mUC who were previously treated with platinum-based chemotherapy and a PD-1/L1 inhibitor.[13] Overall, 608 patients were randomized 1:1 to receive enfortumab vedotin or investigator's choice chemotherapy of docetaxel, paclitaxel, or vinflunine.

OS was the primary endpoint.[13] Key secondary endpoints were PFS, clinical response, and safety/tolerability. Median follow-up at the prespecified interim analysis was 11.1 months. Enfortumab vedotin reduced the risk of death by 30% (HR 0.70 [95% CI: 0.56 to 0.89]; P=0.00142) compared to chemotherapy, with a median OS of 12.88 months (95% CI: 10.58 to 15.21) vs. 8.97 months (95% CI: 8.05 to 10.74) in the chemotherapy group. Enfortumab vedotin also improved PFS by 38% (HR 0.62 [95% CI: 0.51 to 0.75]; P<0.00001), with a median PFS of 5.55 months (95% CI: 5.32 to 5.82) vs. 3.71 months (95% CI: 3.52 to 3.94) in the chemotherapy group. Rates of all-grade (93.9% vs. 91.8%) and Grade ≥3 TRAEs (51.4% vs. 49.8%) were reported for the enfortumab vedotin and chemotherapy arms, respectively, with no new safety signals for enfortumab vedotin. The study results were reviewed by an independent Data Monitoring Committee following a planned interim analysis, and the study was concluded prior to final analysis due to meeting its primary endpoint of OS compared to chemotherapy.

Summary: Thank you for considering the enclosed enfortumab vedotin data in two mUC patient populations with unmet need. Enfortumab vedotin demonstrated a high and clinically meaningful ORR in patients with la/mUC who have previously received a PD-1/L1 inhibitor as well as an OS advantage for those who have received a platinum-containing chemotherapy regimen and a PD-1/L1 inhibitor. Enfortumab vedotin was effective and tolerable in the post platinum and PD-1/L1 inhibitor treated population of EV-301 as well as the frail, elderly cisplatin-ineligible population of Cohort 2 in EV-201. TRAE rates were comparable to control in EV-301 with no new safety signals. These data support an update to the guideline as highlighted in the specific request section.

Sincerely,

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