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NCCN Bladder Cancer Guidelines Panel:

On behalf of Seattle Genetics, Inc. and Astellas Pharma Global Development, Inc., we respectfully request the NCCN Bladder Cancer Guidelines Panel to review the enclosed data for inclusion of enfortumab vedotin in the Guidelines for the treatment of patients with locally advanced or metastatic urothelial carcinoma (la/mUC).

Specific Request: Please consider the inclusion of enfortumab vedotin in the NCCN Bladder Cancer Guidelines as a preferred therapy for la/mUC in the post-PD-1/L1 inhibitor and post-platinum-containing chemotherapy setting. Additional data has been shared for completeness and to allow for comprehensive review.

FDA Clearance: Enfortumab vedotin is an investigational antibody-drug conjugate (ADC). On September 13, 2019, the FDA accepted the Biologics License Application and granted Priority Review for enfortumab vedotin for the following proposed indication:

The treatment of patients with locally advanced or metastatic urothelial cancer who have received a programmed death receptor-1 or programmed death-ligand 1 inhibitor and who have received platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.

Rationale: mUC is an incurable disease with high unmet need and an estimated 5-year survival rate of <5%.¹ The standard of care in first-line cisplatin-ineligible patients (gemcitabine/carboplatin) has a 36% confirmed overall response rate (ORR), limited survival and poor tolerability (21% discontinuation due to AEs).² In the post-platinum setting, PD-1/L1 therapies have demonstrated response rates of 13% to 23%.³⁻⁷ For those who do not respond or progress, options are limited, underscoring the need for safe and effective treatment options. Enfortumab vedotin is a novel ADC that targets Nectin-4 as a new approach to treating la/mUC.

Clinical Data:

EV-201, Cohort 1

EV-201 is an ongoing two-cohort single-arm, phase 2 pivotal trial of enfortumab vedotin in la/mUC patients previously treated with a PD-1/L1 inhibitor that includes patients who received prior platinum-containing chemotherapy (cohort 1). Cohort 1 included 125 patients who received enfortumab vedotin, 1.25 mg/kg on Days 1, 8, and 15 every 28 days until disease progression or unacceptable toxicity. The primary endpoint was confirmed ORR as determined by blinded independent central review (BICR). Key secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), safety, and tolerability. Median follow-up was 10.2 months and the confirmed ORR, by BICR, was 44% (95% CI: 35.1, 53.2) with a 12% complete response (CR) rate and a 32% partial response (PR) rate. The DOR was 7.6 months (95% CI: 4.93, 7.46).⁸ Similar activity was seen in hard-to-treat subpopulations including those with liver metastases and upper tract disease. Target lesion reduction occurred in 84% of evaluable patients and PFS and OS were 5.8 (95% CI: 4.9, 7.5) and 11.7 months (95% CI: 9.1, not reached), respectively. Additionally, patient-reported outcomes data from EV-201 demonstrated that health-related quality of life was maintained throughout treatment with enfortumab vedotin.⁹

The most frequently reported treatment-related adverse events (AEs) were mostly Grade 1 or 2, and included fatigue (50% any grade, 6% Grade ≥3), alopecia (49% any grade, none Grade ≥3), decreased appetite (44% any

grade, 1% Grade ≥ 3), dysgeusia (40% any grade, none Grade ≥ 3), and peripheral sensory neuropathy (40% any grade, 2% Grade ≥ 3).⁸ Pre-specified AEs of interest (evaluated as composite terms) included peripheral neuropathy (50%), rash (48%), and hyperglycemia (11%), the majority of which were Grade 1 or 2; most events improved or resolved.

Publicly disclosed Supplemental Data: EV-101 and EV-103

EV-101, a phase 1 dose-escalation and expansion study including 112 patients with mUC who were previously treated with ≥ 1 prior line of chemotherapy and received ≥ 1 enfortumab vedotin dose produced results consistent with EV-201.¹⁰ EV-101 showed a confirmed ORR of 43% (95% CI: 33.6, 52.6) and a 44% ORR was observed in patients naïve to anti-PD-1/L1 therapy (n=10/23) who received prior treatment with chemotherapy. The median DOR was 7.4 months (95% CI: 5.6, 9.6) with an estimated median PFS and OS of 5.4 months (95% CI: 5.1, 6.3) and 12.3 months (95% CI: 9.3, 15.3), respectively. The OS at 1 year was 51.8%. The most common adverse events seen in this population were: peripheral neuropathy (any type) was reported in 49% of patients and maculo-papular rash was reported in 21% of patients. There were four deaths considered possibly related to treatment (respiratory failure, urinary tract obstruction, diabetic ketoacidosis, and multi-organ failure) across the study. Enfortumab vedotin is being further evaluated in a confirmatory, randomized phase 3 trial (EV-301, NCT03474107) in previously treated la/mUC patients as well as following anti-PD-1/L1 treatment in platinum naïve patients (EV-201 cohort 2, NCT03219333) and EV-101 in la/mUC with severe renal dysfunction.

EV-103 is a phase 1 dose-escalation and dose-expansion study that included 45 cisplatin-ineligible patients with la/mUC who received enfortumab vedotin, 1.25 mg/kg on Days 1 and 8 in combination with pembrolizumab 200 mg on Day 1 of each 3-week cycle in the first-line setting.¹¹ After a median follow-up of 7.7 months, the confirmed ORR as assessed by investigator was 71% (95% CI: 55.7, 83.6) with a 13% CR rate and reduction in target lesions in 93% of evaluable patients; furthermore, responses were observed regardless of PD-L1 status. At last follow-up, DOR ranged from 1 to 10.5 months (ongoing) and median duration of response had not been reached. The safety profile, including AEs of interest (peripheral neuropathy, rash, and hyperglycemia), was similar to that of enfortumab vedotin monotherapy in EV-201 cohort 1. Any grade and Grade ≥ 3 immune-mediated AEs of interest requiring systemic steroids occurred in 20% and 11% of patients, respectively, and were similar to those reported for pembrolizumab monotherapy.

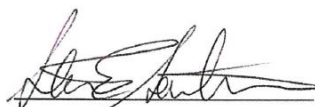
EV-103 continues to evaluate enfortumab vedotin in combination with other therapies in 1L la/mUC as well as alone or in combination with PD-1 inhibitor in muscle invasive urothelial carcinoma (NCT03288545).

Summary: Thank you for considering the enclosed data. These data provide evidence to support the inclusion of enfortumab vedotin, once approved, as a preferred therapy for la/mUC in the post-PD-1/L1 inhibitor, post-platinum setting.

Sincerely,



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