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Study EV-103: New Cohorts Testing Enfortumab Vedotin Alone or in Combination with Pembrolizumab in Muscle Invasive Bladder Cancer

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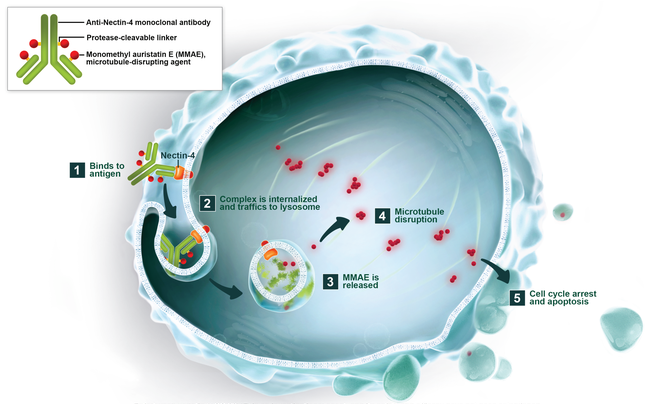
Current Treatments for Muscle Invasive Bladder Cancer

- Up to 25% of patients diagnosed with urothelial cancers present with muscle invasive bladder cancer (MIBC)[1]
- Cisplatin-based chemotherapy is the standard of care for the neoadjuvant cisplatin-eligible MIBC population
- Many patients (>40%)[2] are cisplatin-ineligible for a variety of reasons, such as impaired renal function
- Radical cystectomy (RC) with bilateral lymph node dissection (PLND) is the standard of care for the neoadjuvant *cisplatin-ineligible* MIBC population
- Programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors are not approved for MIBC in the neoadjuvant setting
- There are no other treatments approved for *cisplatin-ineligible* patients

Enfortumab Vedotin is an Investigational Antibody-Drug Conjugate Targeting Nectin-4

- Enfortumab vedotin consists of a fully human monoclonal antibody targeting Nectin-4 and the microtubule-disrupting agent monomethyl auristatin E (MMAE), conjugated by a protease-cleavable linker
- Nectin-4 is a transmembrane cell adhesion molecule[3] that is expressed in multiple tumor types, including urothelial cancer[4]
- Nectin-4 was expressed in all 120 samples tested from patients with locally advanced or metastatic urothelial cancer (la/mUC) in the ongoing phase 2 study (EV-201; NCT3219333)[5] of enfortumab vedotin monotherapy; expression was uniformly high[5]

Figure 1: Enfortumab Vedotin Proposed Mechanism of Action



Enfortumab vedotin (ASG-22ME) is an investigational agent, and its safety and efficacy have not been established.
Enfortumab vedotin is being developed in collaboration with Astellas Pharma Inc. ©2020 Seattle Genetics, Inc. All rights reserved.

Enfortumab Vedotin Monotherapy in Locally Advanced and Metastatic Urothelial Carcinoma

- Study EV-201 (NCT03288545) evaluated enfortumab vedotin monotherapy (1.25 mg/kg) in adults with la/mUC who previously received a PD-1 or PD-L1 inhibitor and a platinum-containing chemotherpay in the neoadjuvant/adjuvant, la/mUC setting
- 44% ORR in these heavily pre-treated patients (n=125)[5]

Enfortumab Vedotin Combined with Pembrolizumab in Locally Advanced and Metastatic Urothelial Carcinoma

- In the ongoing phase 1b/2 study EV-103 (enfortumab vedotin as monotherapy or in combination with other anticancer therapies for the treatment of bladder cancer):
  - Interim results from cisplatin-ineligible patients with la/mUC treated with enfortumab vedotin 1.25 mg/kg + pembrolizumab 200 mgin the 1L setting show an ORR of 73.3%, a manageable safety profile and no new safety signals have been identified
- Enfortumab vedotin + pembrolizumab may also be suitable for research in MIBC

Updated results from 1L patients with locally advanced or metastatic urothelial cancer treated with enfortumab vedotin + pembrolizumab presented on Friday, February 14, Poster Board A4/Abstract 441

Figure 2: Rationale for Combining Enfortumab Vedotin + Pembrolizumab

- Enfortumab vedotin and pembrolizumab each have single agent activity in la/mUC
- Preclinical studies show that antibody-drug conjugates (brentuximab vedotin, ladiratuzumab vedotin, and tisotumab vedotin)[6-8] linked to MMAE induce immunogenic cell death and may enhance anti-tumor immunity
- Clinical data suggests the combination of enfortumab vedotin + pembrolizumab may have the potential to induce greater antitumor activity in la/mUC compared to either agent alone

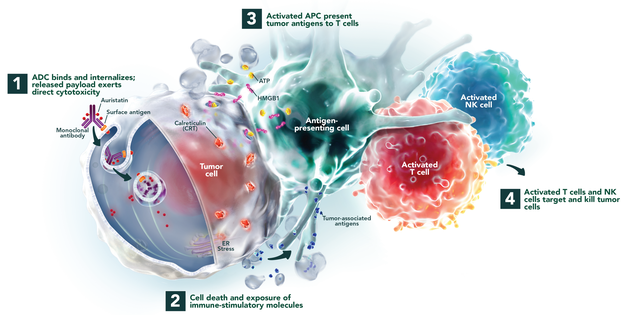


Figure 3: EV-103 Study Design (NCT03288545)

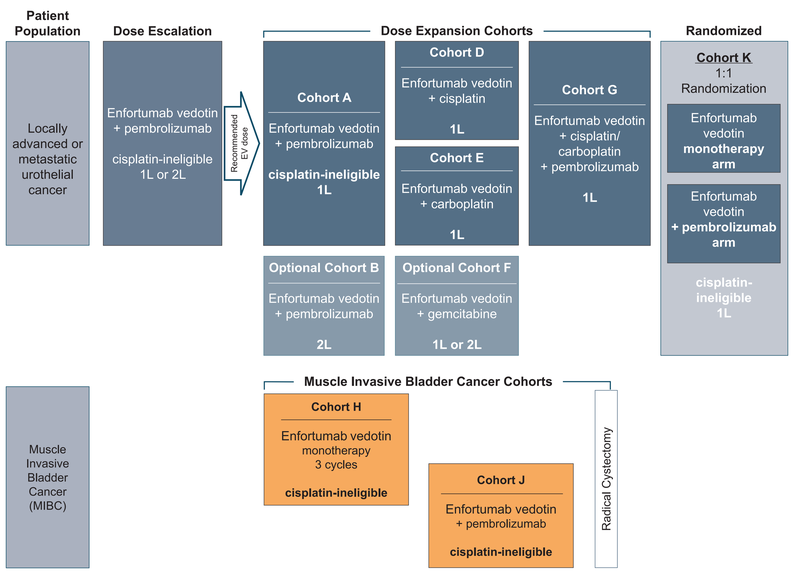
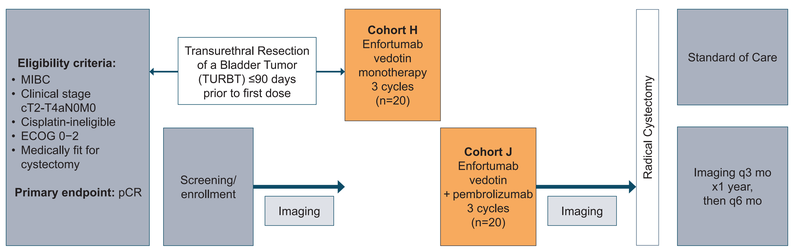


Figure 4: Enfortumab Vedotin + Pembrolizumab in Cisplatin-Ineligible MIBC Patients



DISCLOSURE: CJH received honoraria from Seattle Genetics, Inc. DPP and TWF received research funding from Seattle Genetics, Inc./ Astellas Pharma, Inc. JER held an consulting or advisory role with Seattle Genetics, Inc. ASC is an employee of and has an ownership interest in Seattle Genetics, Inc. CS is an employee of Astellas Pharma, Inc. MC is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Objectives

Primary Objective

- To assess antitumor activity of neoadjuvant enfortumab vedotin monotherapy or enfortumab vedotin + pembrolizumab as measured by the pathological complete response (pCR) rate by local pathology review in patients with T2-T4aN0M0 MIBC

Secondary Objectives

- To assess pCR rate by central pathology review
- To assess overall survival
- To assess pathological response rate per downstaging to ≤pT1pN0 by local and central pathology review
- To assess disease-free survival and progression-free survival per RECIST Version 1.1 by investigator assessment
- To assess safety and tolerability of enfortumab vedotin monotherapy or enfortumab vedotin in combination with pembrolizumab
- To assess the percentage of delay in planned surgeries due to treatment-related adverse events

Response Assessments

- pCR will be assessed after RC + PLND with curative intent by pathologic analysis (local and central review)
- Radiologic assessment by CT/urogram or MRI/urogram
  - Within 4 weeks of enrollment
  - 4 to 12 weeks after the last dose of study treatment and prior to RC + PLND
  - Every 3 months after the previous response assessment in the first year, and subsequently every 6 months until radiologically confirmed progressive disease

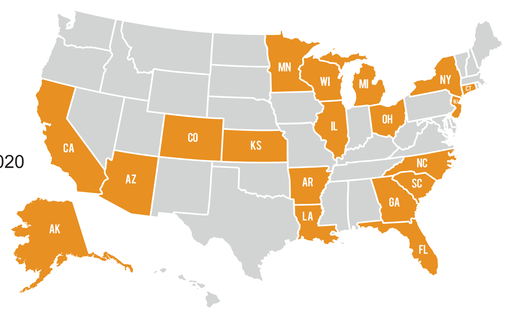
Eligibility

Key Criteria

- Histologically confirmed MIBC (mixed cell types eligible if UC predominant; neuroendocrine tumors are ineligible) at stage cT2-T4a per TURBT within 90 days prior to the first dose of treatment and N0M0 by CT/MRI
- Ineligible for cisplatin-based chemotherapy at time of enrollment due to at least 1 of the following: ECOG performance status of 2, CrCl (calculated or measured) ≥30 and <60 mL/min, hearing loss/dysfunction, age, and/or allergy to cisplatin
- No prior systemic treatment, chemoradiation, or radiation therapy for MIBC
- May have received prior intravesical Bacillus Calmette–Guérin or intravesical chemotherapy for non-muscle invasive bladder cancer
- ≥18 years of age
- Medically fit (i.e., eligible for surgery) and scheduled for RC + PLND
- Tumor samples with associated pathology reports available prior to enrollment and sufficient for pathology review and biomarker analysis
- Adequate hematologic and organ function tests
- ECOG performance status of 0, 1, or 2

Study Sites and Completion Date

- 27 active sites in the US
- Study start: Oct 2017
- MIBC Cohort H open: Jan 2020



References

1 Nielsen ME et al. Cancer. 2014;120:86–95
2 Dash A et al. Cancer. 2006;107:506–13
3 Challita-Eid PM et al. Cancer Res. 2016;76:3003–13
4 Petrylak DP et al. J Clin Oncol. 2017;35:106
5 Rosenberg JE et al. J Clin Oncol. 2019;37:(29):2592–600
6 Cao et al. AACR 2016. Cao et al. Cancer Res 2017;77(13 suppl): Abstract 5588.
7 Cao et al. Cancer Res 2018;78(13 Suppl): Abstract 2742.
8 Alley et al. Cancer Res 2019;79(13 Suppl): Abstract 221.