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Study EV-103: Durability Results of Enfortumab Vedotin Plus Pembrolizumab for Locally Advanced or Metastatic Urothelial Carcinoma

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Enfortumab vedotin + pembrolizumab provided encouraging preliminary activity (73% ORR) and durability as well as manageable safety in first line cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer. This platinum-free combination has received **Breakthrough Therapy Designation** based on these data and is undergoing further evaluation in Cohort K of EV-103.

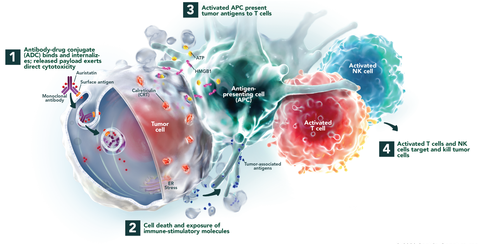
Background

There remains a high unmet need in first line (1L) locally advanced or metastatic urothelial carcinoma (la/mUC), particularly for patients who are ineligible for cisplatin-based therapies

- Platinum-based chemotherapy ± programmed death-ligand 1 (PD-L1) inhibitor has demonstrated modest activity, reinforcing the urgent unmet need in the 1L setting for patients with la/mUC.[1]
- Preliminary data from an ongoing Phase 3 trial of triplet therapy showed a modest, but statistically significant increase in progression-free survival (PFS) (6.3 versus 8.2 months) further suggesting additional 1L options are needed.[1]
- Additionally, the reported objective response rate (ORR) and durability were limited.
- Enfortumab vedotin (EV), an antibody-drug conjugate, delivers the microtubule-disrupting agent monomethyl auristatin E (MMAE) to cells expressing Nectin-4, which is highly expressed in UC.[2]
- Programmed cell death protein 1 (PD-1)/PD-L1 inhibitor responses have promising durability, but 1L indication is restricted to patients with high PD-L1 expression, or who are platinum-ineligible regardless of PD-L1 status.[3,4]
- Initial data from Study EV-103, investigational agents enfortumab vedotin + pembrolizumab, are encouraging. Data are still evolving and represent a potential platinum-free option for cisplatin-ineligible patients in 1L.[5]
- Herein, we present the initial results for durability of response, PFS and overall survival (OS) data of enfortumab vedotin + pembrolizumab in cisplatin-ineligible 1L la/mUC and an update on safety and ORR.
- On 18 Feb 2020, the Food and Drug Administration (FDA) granted Breakthrough Therapy Designation to enfortumab vedotin + pembrolizumab for the treatment of patients with la/mUC who are unable to receive cisplatin-based chemotherapy in the 1L setting.

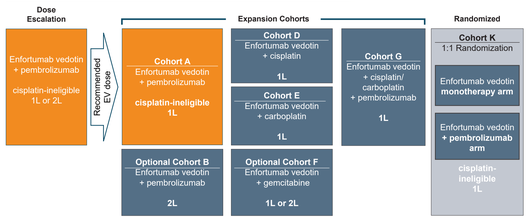
Rationale for Enfortumab Vedotin + Pembrolizumab Combination

- 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.

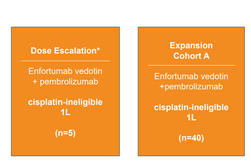


Antibody-drug conjugates are investigational agents, and their safety and efficacy have not been established.

EV-103 Study Design for la/mUC Cohorts



Dose Escalation and Expansion Cohort A Reported



* Not included in the current analysis: three 1L patients treated with enfortumab vedotin 1 mg/kg + pembrolizumab 200 mg and two 2L patients treated with enfortumab vedotin 1.25 mg/kg + pembrolizumab 200 mg

- **Dosing:** Enfortumab vedotin on days 1 and 8 and pembrolizumab on day 1 of every 3-week cycle
- **Primary endpoints:** adverse events (AEs), lab abnormalities
- **Key secondary endpoints:** dose-limiting toxicities, ORR, duration of response (DOR), PFS, OS

Results - 8 Oct 2019 Data Cutoff

Key Demographics and Disease Characteristics

Enfortumab vedotin 1.25 mg/kg + pembrolizumab 200 mg in 1L	Patients (N=45) n (%)
Male sex	36 (80)
Age, yrs, Median (min, max)	69 (51, 90)
ECOG performance status	
0	16 (36)
1	23 (51)
2	6 (13)
Primary disease site of origin	
Lower tract	31 (69)
Upper tract	14 (31)
Metastasis sites	
Lymph nodes only	4 (9)
Visceral disease	41 (91)
Liver	15 (33)
PD-L1 status by combined positive score*	
<10	19 (42)
≥10	14 (31)
Not evaluable/Not available	12 (27)

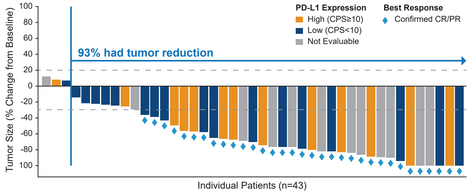
* Unselected patient population; PD-L1 tested using the 22C3 PharmDx assay from Agilent/Dako

Efficacy

Best Overall Response Per Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 by Investigator (N=45)	% (n)
Confirmed ORR	**73.3 (33)**
95% CI	(58.1, 85.4)
Complete response	15.6 (7)
Partial response	57.8 (26)
Stable disease	20.0 (9)
Progressive disease	2.2 (1)
Not evaluable	4.4 (2)
ORR in patients with liver metastasis	53.3 (8/15)
ORR by PD-L1 Expression	
High expression:	78.6 (11/14)
Low expression:	63.2 (12/19)

- Enfortumab vedotin + pembrolizumab demonstrated an ORR of 73.3% in 1L cisplatin-ineligible la/mUC patients.
- Responses observed regardless of PD-L1 expression level.

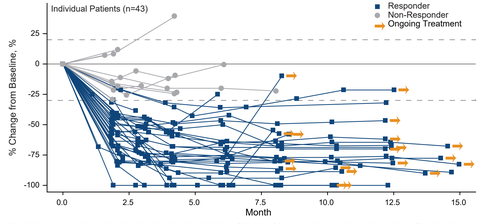
Maximum Percent Reduction from Baseline in Sum of Diameters of Target Lesions Per Investigator by PD-L1 Status



CPS = combined positive score, CR=complete response, PR=partial response
Two patients did not have post-baseline response assessments before end-of-study: 1 withdrew consent and 1 died before any post-baseline response assessment
Dotted horizontal lines at positive 20% and negative 30% denote the target lesion thresholds for disease progression and response, respectively.

Durability

Percent Change from Baseline in Sum of Diameters of Target Lesions

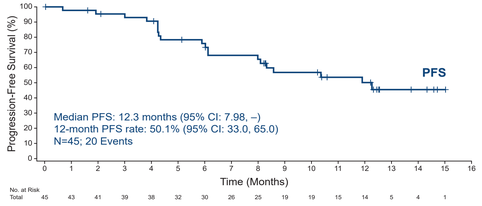


Two patients did not have post-baseline response assessments before end-of-study: 1 withdrew consent and 1 died before any post-baseline response assessment.

Dotted horizontal lines at positive 20% and negative 30% denote the target lesion thresholds for disease progression and response, respectively

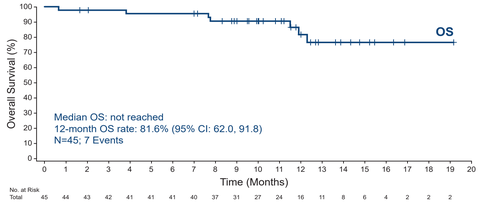
- Rapid responses that appear durable,
  - 88% of responses observed at first assessment (Week 9 ± 1 week)
  - Median time to response = 2 months (range: 1.4 to 4.2 months)
- Median PFS 12.3 months (95% CI: 7.98, –) and median OS not reached, 81.6% OS rate at 12 months. These results suggest a favorable trend in these key endpoints.

Progression-Free Survival



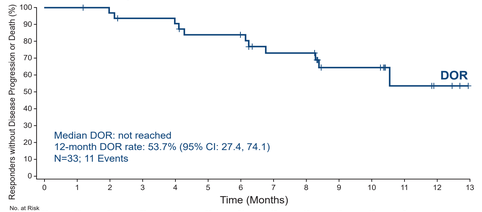
Median PFS: 12.3 months (95% CI: 7.98, –)
12-month PFS rate: 50.1% (95% CI: 33.0, 65.0)
N=45; 20 Events

Overall Survival



Median OS: not reached
12-month OS rate: 81.6% (95% CI: 62.0, 91.8)
N=45; 7 Events

Duration of Response



Median DOR: not reached
12-month DOR rate: 53.7% (95% CI: 27.4, 74.1)
N=33; 11 Events

- Median DOR has not been reached with a median follow-up of 10.4 months,
  - DOR (range: 1.2, 12.9+ months)
  - 12-month DOR rate: 53.7% (95% CI: 27.4, 74.1)
- Out of the 33 responders,
  - 18 (55%) had an ongoing response
  - 11 (33%) had progressed or died
  - 4 (12%) had started a new antitumor treatment before progressive disease

Safety

- 7 patients had treatment-related serious AEs (TRSAEs) (16%)
  - The only TRSAE occurring in more than 1 patient was colitis (2 patients)
- 6 discontinuations of enfortumab vedotin + pembrolizumab due to treatment-related AEs (13%)
  - Peripheral sensory neuropathy was most common (3 patients)
- 1 treatment-related death as reported by investigator (2%)
  - Multiple organ dysfunction syndrome

Treatment-Related Adverse Events (TRAEs)

TRAEs by preferred term	Patients (N=45) n (%) Any Grade ≥20% of patients	≥Grade 3 ≥10% of patients
Overall	43 (96)	26 (58)
Fatigue	22 (49)	4 (9)
Alopecia	22 (49)	–
Peripheral sensory neuropathy	22 (49)	2 (4)
Diarrhea	20 (44)	3 (7)
Decreased appetite	17 (38)	0
Dysgeusia	15 (33)	–
Rash maculo-papular	14 (31)	4 (9)
Nausea	13 (29)	0
Pruritus	13 (29)	1 (2)
Anemia	9 (20)	3 (7)
Weight decreased	9 (20)	0
Lipase increased	8 (18)	8 (18)

Treatment-Related Adverse Events of Clinical Interest (AECI)

AECI: categorized by related MedDRA terms	Patients (N=45) n (%) Any Grade	≥Grade 3*	Time to first onset (months) median (min, max) Any Grade
Peripheral neuropathy	25 (56)	2 (4)	2.3 (1, 9)
Rash	28 (62)	6 (13)	0.8 (0, 12)
Hyperglycemia†	5 (11)	3 (7)	0.5 (0, 4)
AECI: determined by investigator			
Immune-mediated AE requiring systemic steroids	13 (29)	8 (18)‡	

* No Grade 5 TRAE of Clinical Interest
† Blood glucose assessments were non-fasting
‡ Grade 3 events: arthralgia, dermatitis bullous, pneumonitis, lipase increased, rash erythematous, rash maculo-papular, tubulointerstitial nephritis; Grade 4 events: dermatitis bullous, myasthenia gravis

Summary and Conclusions

- **Patients with la/mUC in 1L who are ineligible for cisplatin-based therapies have a high unmet need.**
- **Enfortumab vedotin + pembrolizumab demonstrated activity in 1L cisplatin-ineligible la/mUC patients.**
  - 73.3% ORR, with activity regardless of PD-L1 expression level.
  - Rapid responses (88% at first assessment [9 weeks ± 1 week]); median DOR not reached (range: 1.2, 12.9+ months).
  - Median PFS 12.3 months (95% CI: 7.98, –).
  - Median OS not reached; 81.6% OS rate at 12 months.
- **The safety profile of enfortumab vedotin in combination with pembrolizumab appears to be tolerable and manageable. No new safety signals have been identified with the combination therapy.**
  - Most common treatment-related adverse events: fatigue, alopecia, and peripheral sensory neuropathy.
  - One treatment-related death of multiple organ dysfunction syndrome related to treatment per investigator.
- **Based on these results, further investigation of the platinum-free regimen of enfortumab vedotin + pembrolizumab is warranted in patients with untreated la/mUC.**
- **Enfortumab vedotin + pembrolizumab has received Breakthrough Therapy Designation based on these data and further investigation of this combination is underway in Cohort K of this trial.**
- **Additionally, a Phase 3 trial, EV-302 has been initiated and will evaluate enfortumab vedotin in combination with pembrolizumab ± chemotherapy versus standard of care in patients with la/mUC in 1L setting.**

Acknowledgements

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