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Study EV-103: Update on Durability Results and Long Term Outcome of Enfortumab Vedotin Plus Pembrolizumab in First Line Locally Advanced or Metastatic Urothelial Carcinoma (la/mUC)

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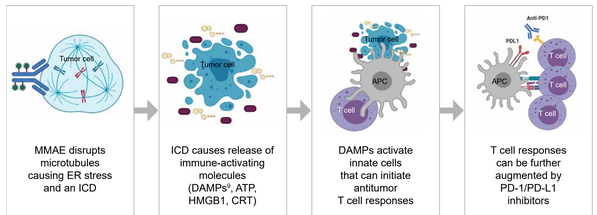
Background

- A high unmet need remains for first line (1L) cisplatin-ineligible patients with locally advanced or metastatic urothelial carcinoma (la/mUC)
- In the 1L setting, carboplatin-based regimens have demonstrated poor tolerability, modest objective response rate (ORR) and limited durability[1]
- Despite promising durability, programmed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors are restricted to 1L cisplatin-ineligible patients with high PD-L1 expression or who are ineligible for platinum[2]
- Only those patients who have disease control (complete response (CR), partial response (PR), or stable disease (SD)) with 4–6 cycles of gem-carbo (~36%)[3] may go on to receive avelumab maintenance therapy.[4] However, this does not obtain the level of benefit observed after cisplatin-based therapy followed by avelumab
- Enfortumab vedotin has shown an overall survival (OS) benefit versus chemotherapy in la/mUC patients who have received PD-1/PD-L1 inhibitors and platinum[5] and promising response rates and durability in the cisplatin-ineligible population post-PD-1/PD-L1 inhibitors[6]
- FDA granted **Breakthrough Therapy Designation** to enfortumab vedotin plus pembrolizumab based on preliminary data from this study population[7]
- With 2 years of follow-up, we present an update on our safety, efficacy, and survival data (Data cutoff: 13OCT2020)

ADCs linked to MMAE induce cell death in a manner consistent with immunogenic cell death (ICD), and may enhance antitumor immunity[9–12]

- Enfortumab vedotin, an antibody-drug conjugate (ADC), delivers the microtubule-disrupting agent monomethyl auristatin E (MMAE) to cells expressing Nectin-4, which is highly expressed in urothelial cancer[8]



APC=antigen-presenting cell; ATP=adenosine triphosphate; CRT=calreticulin; DAMPs=Damage-associated molecular patterns; ER=endoplasmic reticulum; HMGBI=high mobility group protein B1; ICD=immunogenic cell death

Data from Dose Escalation and Expansion Cohort A

Patient Population

Locally Advanced or Metastatic Urothelial Carcinoma

Dose Escalation*

enfortumab vedotin + pembrolizumab

cisplatin-ineligible 1L

(n=5)

Cohort A (Dose Expansion)

enfortumab vedotin + pembrolizumab

cisplatin-ineligible 1L

(n=40)

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

*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

Acknowledgements

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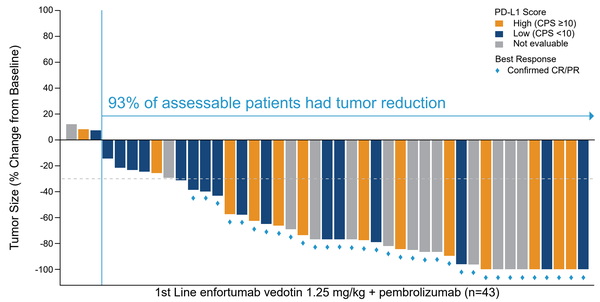
Key Demographics and Disease Characteristics

Characteristic	Patients (N=45)
Male sex, n (%)	36 (80)
Median age (range), years	69.0 (51, 90)
Eastern Cooperative Oncology Group (ECOG) performance status, n (%)	
0	15 (33.3)
1	22 (48.9)
2	8 (17.8)
Primary disease site of origin, n (%)	
Lower tract	30 (66.7)
Upper tract	15 (33.3)
Baseline metastatic disease site[a], n (%)	
Lymph nodes only	7 (15.6)
Visceral disease	38 (84.4)
Liver	14 (31.1)
PD-L1 status by Combined Positive Score (CPS)[b], n (%)	
CPS <10	18 (40.0)
CPS ≥10	14 (31.1)
CPS not available	13 (28.9)

a. A patient may have metastatic disease in more than one location
b. Unselected patient population. PD-L1 tested using a validated IHC assay with monoclonal mouse anti-PD-L1, clone 22C3. CPS<10 is PD-L1 low and CPS≥10 is PD-L1 high
Data Cutoff: 13OCT2020

Maximum Target Lesion Reduction from Baseline by PD-L1 Status and Confirmed Objective Response Rate per Investigator

Best Overall Response per RECIST v1.1 by Investigator (N=45)

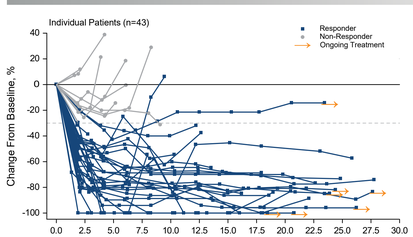


CPS=Combined Positive Score; CR=complete response; PR=partial response; CI=confidence interval
Two patients did not have post-baseline response assessments before end-of-study: 1 withdrew consent and 1 died before any post-baseline response assessment
Dotted horizontal line indicates threshold for partial response (-30%), but is not necessarily indicative of response

- Responses observed regardless of PD-L1 expression level
- 57.1% confirmed ORR in patients with liver metastases

Confirmed ORR 95% CI	73.3% (33/45) (58.1, 85.4)
Complete response	15.6% (7/45)
Partial response	57.8% (26/45)

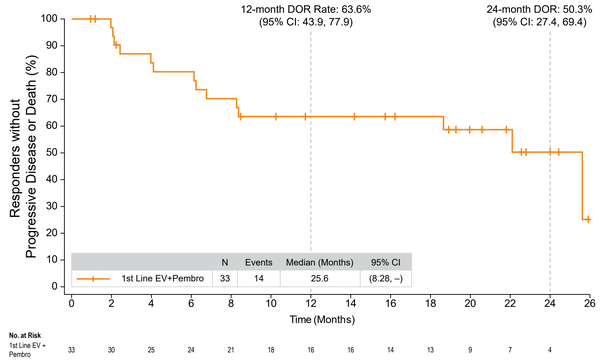
Percent Change from Baseline in Sum of Diameters of Target Lesions



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 line indicates threshold for partial response (-30%), but is not necessarily indicative of response

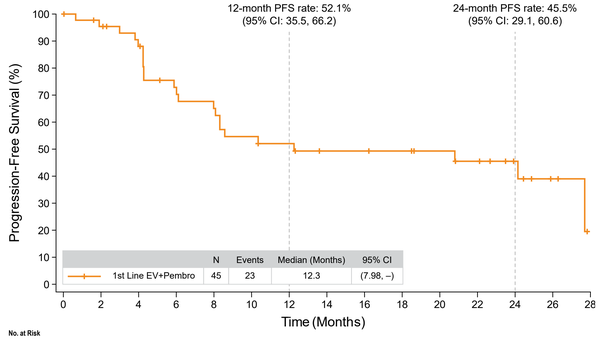
- Median number of treatment cycles is 9 (range: 1, 34)
- 87.9% (29/33) of responses observed at first tumor assessment (week 9 ±1 week)
- Median time to response at 2.1 months (range: 1.4, 4.2)

Median Duration of Response is 25.6 Months with a Median Follow-Up of 20 Months

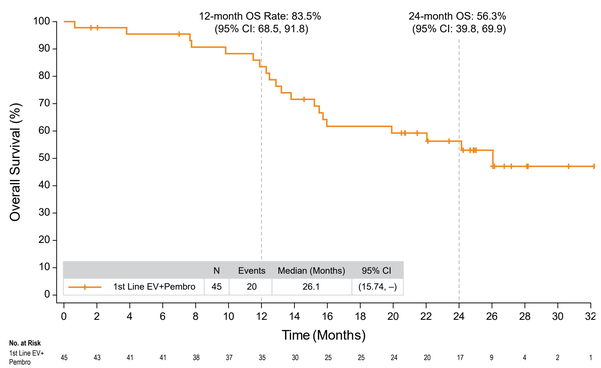


- 33 responders:
  - 12 (36.4%) had an ongoing response
  - 15 patients (45.5%), including 14 patients who progressed or died, and 1 patient who was censored and subsequently died
  - 6 patients (18.2%) were censored due to starting a new antitumor treatment including 2 patients who achieved CR after undergoing surgery with curative intent

Median Progression-Free Survival is 12.3 Months



Median Overall Survival is 26.1 Months with a Median Follow-Up of 24.9 Months



Treatment-Related Adverse Events (TRAEs)

TRAEs[a] in ≥20% of patients (any Grade) or ≥10% (≥Grade 3)	Patients (N=45) n (%)	
	Any Grade	≥Grade 3
Overall	43 (95.6)	29 (64.4)
Peripheral sensory neuropathy	25 (55.6)	2 (4.4)
Fatigue	23 (51.1)	5 (11.1)
Alopecia	22 (48.9)	–
Diarrhoea	21 (46.7)	2 (4.4)
Decreased appetite	18 (40.0)	1 (2.2)
Rash maculopapular	16 (35.6)	5 (11.1)
Dysgeusia	15 (33.3)	–
Pruritus	15 (33.3)	1 (2.2)
Nausea	13 (28.9)	–
Weight decreased	11 (24.4)	1 (2.2)
Dry skin	10 (22.2)	–
Alanine aminotransferase (ALT) increased	9 (20.0)	–
Anaemia	9 (20.0)	4 (8.9)
Aspartate aminotransferase (AST) increased	9 (20.0)	–
Lipase increased	8 (17.8)	8 (17.8)[b]

- 7 patients had treatment-related serious AEs (15.6%)
- 11 discontinuations of enfortumab vedotin + pembrolizumab due to TRAEs (24.4%)
  - Peripheral sensory neuropathy was most common reason (8.9%)
- 1 treatment-related death as reported by investigator (2.2%) due to multiple organ dysfunction syndrome

a. Treatment-Related Adverse Events, by preferred term
b. No ≥Grade 3 treatment-related lipase increased events were clinically significant

Treatment-Related Adverse Events of Special Interest (AESI)

AESI[a]	Patients (N=45) n (%)		Median Onset, months (min,max)	Resolution/ Improvement[b] n (%)
	Any Grade	≥Grade 3[c]	Any Grade	Any Grade
Any peripheral neuropathy	28 (62.2)	2 (4.4)	2.4 (0.7,12.5)	19/28 (67.9)
Any skin reactions	30 (66.7)	9 (20.0)	0.7 (0.1,15.7)	27/30 (90.0)
Any hyperglycemia[d]	5 (11.1)	4 (8.9)	0.5 (0.3,3.5)	5/5 (100.0)

AESI: imAEs[a,e]	Patients (N=45) n (%)	
	Any Grade	≥Grade 3
Immune-mediated AE	20 (44.4)	12 (26.7)[f]

a. Categorized by related Medical Dictionary for Regulatory Activities (MedDRA) terms, MedDRA v. 23.0
b. Resolution/Improvement as of last follow-up. For events that are not resolved, improvement is defined as at least one grade improvement from the worst grade at the last assessment
c. No Grade 5 TRAE of Clinical Interest; two Grade 4 skin reaction events (dermatitis bullous, toxic epidermal necrolysis)
d. Blood glucose assessments were non-fasting
e. imAEs=immune-mediated adverse events. In July 2020, Merck & Co., Inc., Kenilworth, NJ, USA approach/search strategy adopted to identify imAEs
f. Grade 3 events: dermatitis bullous, pneumonitis, rash erythematous, rash maculo-papular, tubulointerstitial nephritis, colitis, lichen planus, pruritus, myositis; Grade 4 events: dermatitis bullous, myasthenia gravis, toxic epidermal necrolysis

Summary and Conclusions

- Enfortumab vedotin + pembrolizumab demonstrates promising activity with durable responses in 1L cisplatin-ineligible la/mUC patients
  - ORR (73.3%), with activity regardless of PD-L1 expression level. Majority of responses at first assessment (87.9%) with a median DOR of 25.6 months
  - Median PFS 12.3 months
  - Median OS 26.1 months
- The safety profile of enfortumab vedotin in combination with pembrolizumab appears to be tolerable
  - Most common treatment-related adverse events: peripheral neuropathy, fatigue, alopecia, diarrhoea, and decreased appetite
- Randomized Cohort K of Study EV-103 is actively enrolling cisplatin-ineligible patients with la/mUC to enfortumab vedotin monotherapy or enfortumab vedotin + pembrolizumab
- The Phase 3 trial EV-302 (NCT04223856) is currently enrolling enfortumab vedotin in combination with pembrolizumab versus chemotherapy in patients with la/mUC in the 1L setting