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Enfortumab Vedotin in Cisplatin-Ineligible Patients with Locally Advanced or Metastatic Urothelial Cancer who Received Prior PD-1/PD-L1 Inhibitors: An Updated Analysis of EV-201 Cohort 2

Bradley McGregor, MD[1]; Arjun V. Balar, MD[2]; Jonathan Rosenberg, MD[3]; Michiel van der Heijden, MD, PhD[4]; Se Hoon Park, MD[5]; Jae-Lyun Lee, MD, PhD[6]; Takahiro Kojima, MD[7]; Michael R. Harrison, MD[8]; Elisabeth I. Heath, MD, FACP[9]; Mark N. Stein, MD[10]; Yohann Loriot, MD, PhD[11]; Andrea Necchi, MD[12]; Joyce Steinberg, MD[13]; Shang-Ying Liang, PhD[14]; Janet Trowbridge, MD[14]; Daniel Petrylak, MD[15]; Evan Y. Yu, MD[16]

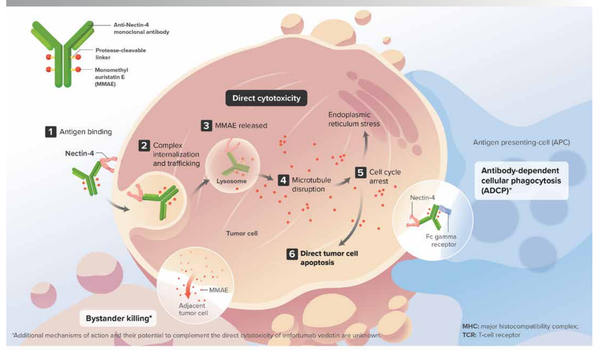
[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Perlmutter Cancer Center at NYU Langone Health, New York, NY, USA; [3]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [4]The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; [5]Samsung Medical Center, Seoul, South Korea; [6]Asan Medical Center and University of Ulsan College of Medicine, Seoul, Korea; [7]University of Tsukuba, Tsukuba, Ibaraki, Japan; [8]Duke Cancer Institute, Center for Prostate and Urologic Cancers, Duke University, Durham, NC, USA; [9]Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA; [10]Columbia University Herbert Irving Comprehensive Cancer Center, New York, NY, USA; [11]Institut de Cancérologie Gustave Roussy, Paris, France; [12]Vita-Salute San Raffaele University; IRCCS San Raffaele Hospital and Scientific Institute, Milan, Italy; [13]Astellas, Northbrook, IL, USA; [14]Seagen Inc., Bothell, WA, USA; [15]Yale Cancer Center, New Haven, CT, USA; [16]Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA, USA

Cisplatin-Ineligible Patients with Advanced Urothelial Carcinoma have Limited Treatment Options

- Cisplatin-based chemotherapy is the first-line standard of care for advanced urothelial carcinoma and is associated with an overall survival benefit[1]
- Approximately half of patients with advanced urothelial carcinoma in the United States are cisplatin-ineligible[2]
- PD-1/PD-L1 inhibitors are approved in the first line for cisplatin-ineligible patients with advanced urothelial carcinoma whose tumors express PD-L1[3,4]
  - Objective responses occur in ~20–30% of patients unselected for PD-L1 expression
- Enfortumab vedotin has demonstrated survival benefit in patients who have received both platinum-containing chemotherapy and a PD-1/PD-L1 inhibitor[5]
- Cisplatin-ineligible patients have a high unmet need for treatment options after first-line PD-1/PD-L1 inhibitors
  - To our knowledge EV-201 is the first trial to report results in this patient population[6]
  - Previously presented Primary Analysis results of EV-201 Cohort 2 included a 52% Overall Response Rate with a 20% Complete Response Rate, and a median Duration of Response of 10.9 months[5]
  - Here we present an updated analysis with an additional 3 months of follow-up

Primary Analysis Data Cutoff: 08 Sep 2020; 3 month updated Data Cutoff: 04 Dec 2020

Enfortumab Vedotin: Nectin-4 Directed Therapy Proposed Mechanism of Action



Enfortumab vedotin is an investigational agent in some settings, and its safety and efficacy have not been established

EV-201: Non-Comparative, Pivotal Phase 2 Trial

Enfortumab vedotin
1.25 mg/kg[a] intravenous (IV) on days 1, 8, and 15 of each 28-day cycle

Enrollment
59 Global Sites

Previously treated locally advanced or metastatic urothelial carcinoma

Target Enrollment:
~100 patients/cohort

Cohort 1
Prior PD-1/PD-L1 inhibitor and platinum-based therapy

Enrollment Completed July 2018
N=125[b]

Cohort 2
Prior PD-1/PD-L1 inhibitor, platinum-naive, cisplatin-ineligible

Enrollment Completed February 2020
N=89[c]

Primary Endpoint:
- Confirmed ORR as determined by BICR

Select Secondary Endpoints
- DOR
- PFS
- OS
- Safety and Tolerability

a. Maximum dose permitted is 125 mg
b. 3 additional patients were enrolled but did not receive enfortumab vedotin due to patient decision, clinical deterioration, and low hemoglobin, respectively
c. 2 additional patients were enrolled but did not receive enfortumab vedotin due to admission to the hospital for disease progression and hospice care, respectively

Acknowledgments

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6. Balar AV, et al. ASCO-GU 2021:Abstract 394.

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Key Eligibility Criteria

Key Inclusion Criteria

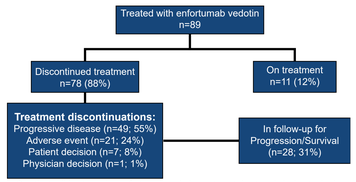
- Locally advanced unresectable or metastatic urothelial carcinoma (including divergent differentiation)
- Previously treated with a PD-1/PD-L1 inhibitor
- No prior exposure to platinum-containing chemotherapy in the locally advanced or metastatic setting and ineligible for cisplatin-containing chemotherapy due to:
  - Impaired renal function (creatinine clearance ≥30 and <60 mL/min)
  - Hearing loss ≥Grade 2
  - ECOG PS score ≥2
- Progression during or following most recent treatment

Key Exclusion Criteria

- Ongoing sensory or motor neuropathy ≥Grade 2
- Active central nervous system metastases
- Uncontrolled diabetes mellitus[a]

a. Hemoglobin A1C (HbA1c) ≥8% or HbA1c of 7% to <8% with associated diabetes symptoms, polyuria or polydipsia, that were not otherwise explained

Patient Disposition



- 91 enrolled[a] between Oct 2017 to Feb 2020
- Data Cutoff dates
  - Primary Analysis: 08 Sep 2020
  - Updated Analysis: 04 Dec 2020
- Median time on treatment: 6 months (range 0.3–24.6 months)

a. 2 patients did not receive enfortumab vedotin treatment due to admission to the hospital for disease progression and pursuing hospice care, respectively

Key Demographics and Disease Characteristics

Characteristic	Patients (N=89)
Median age (range), years	75 (49, 90)
Male sex, n (%)	66 (74%)
ECOG performance status	
0 or 1, n (%)	78 (88%)
2, n (%)	11 (12%)
Body mass index ≥30 kg/m^2, n (%)	13 (15%)
Renal function based on creatinine clearance	
Normal/Mild decrease: ≥60 mL/min, n (%)	27 (30%)
Moderate decrease: ≥30 and <60 mL/min, n (%)	60 (67%)
Severe decrease: ≥15 and <30 mL/min, n (%)	2 (2%)
Primary tumor location	
Upper tract[a], n (%)	38 (43%)
Bladder/other, n (%)	51 (57%)
Metastasis sites	
Lymph nodes only, n (%)	18 (20%)
Visceral disease[b], n (%)	70 (79%)
Liver, n (%)	21 (24%)
Received prior PD-1/PD-L1 therapy in first line, n (%)	87 (98%)
Responder[c] to PD-1/PD-L1-containing therapy, n (%)	22 (25%)

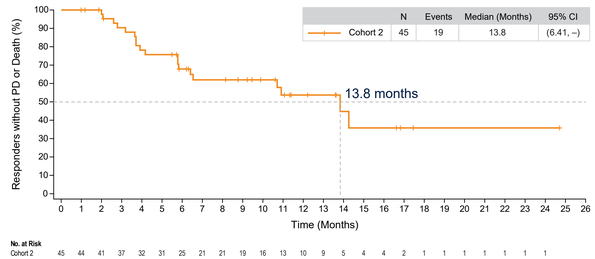
a. Includes renal pelvis and ureter
b. Sites of visceral disease include liver, lung, intra-thoracic or intra-abdominal soft tissue, kidney, spleen, ovary, adrenal glands, and bone
c. Responses were investigator reported

Updated Best Overall Response by BICR

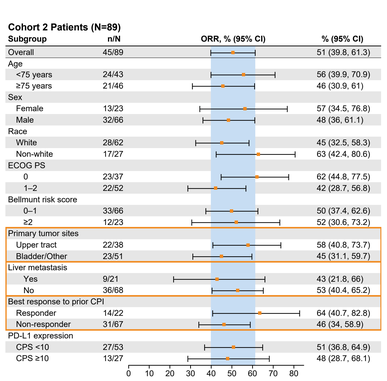
ORR per RECIST v 1.1 assessed by BICR	Patients (N=89), %
Confirmed ORR (95% CI[a])	51 (39.8, 61.3)
Best overall response[b]	
Confirmed complete response	22
Confirmed partial response	28
Stable disease	30
Progressive disease	10
Not evaluable[c]	9

a. CI = Confidence Interval, computed using the Clopper-Pearson method
b. Best overall response according to RECIST v1.1. Complete response and partial response were confirmed with repeat scans ≥28 days after initial response.
c. Includes 5 patients who did not have response assessment post-baseline, 2 patients whose post-baseline assessment did not meet the minimum interval requirement for stable disease, and 1 patient whose response cannot be assessed due to incomplete anatomy.

Updated Duration of Response per BICR

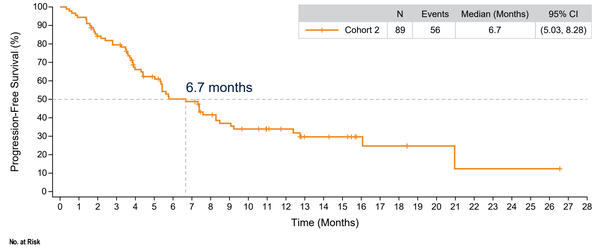


Updated Objective Response Rate per BICR by Subgroup

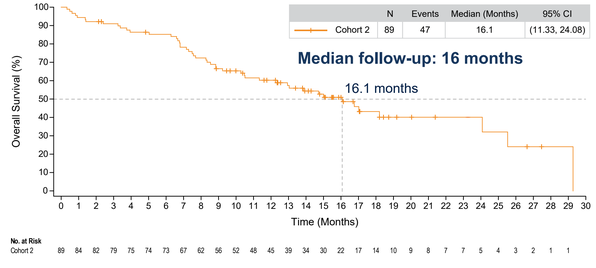


- Responses were observed across all subgroups, including patients:
  - with primary tumor sites in the upper tract (ORR=58%)
  - with liver metastasis (ORR=43%)
  - who did not respond to prior PD-1/PD-L1 inhibitors (ORR=46%)

Updated Progression-Free Survival per BICR



Updated Overall Survival



Treatment-Related Adverse Events (TRAEs)

TRAEs in ≥20% of patients (any Grade) or ≥5% (≥Grade 3)	Patients (N=89), n (%)	
	Any Grade	≥Grade 3
Overall TRAEs	86 (97)	49 (55)
Alopecia	45 (51)	–
Peripheral sensory neuropathy	44 (49)	3 (3)
Fatigue	30 (34)	6 (7)
Decreased appetite	29 (33)	5 (6)
Pruritus	27 (30)	3 (3)
Rash maculo-papular	27 (30)	7 (8)
Dysgeusia	25 (28)	–
Weight decreased	23 (26)	1 (1)
Anemia	22 (25)	5 (6)
Diarrhea	20 (22)	5 (6)
Nausea	20 (22)	1 (1)
Neutropenia	11 (12)	8 (9)
Hyperglycemia	8 (9)	5 (6)
Lipase increased	7 (8)	5 (6)

These safety data are consistent with the primary analysis and the previously reported safety profile of EV

- TRAEs led to discontinuations in 16% of patients
  - Peripheral sensory neuropathy was the most common reason (4%)
- 4 deaths considered to be treatment-related by the investigator were previously reported and included:
  - acute kidney injury, metabolic acidosis and multiple organ dysfunction syndrome, occurred within 30 days of first dose in patients with BMI ≥30 kg/m^2
  - pneumonitis, occurred >30 days of last dose
  - all 4 deaths were confounded by age (≥75 years) and other comorbidities

Treatment-Related Adverse Events of Special Interest[a]

	Skin Reactions	Peripheral Neuropathy	Hyperglycemia
Any grade, %	61	56	10
≥Grade 3, %	17	8	6
Median onset, months	0.5[b]	2.7	0.5[b]
Resolution/improvement[c], %	80	54	89

These events represent composites of related adverse events.

Skin Reactions

- No Grade 5 events, 1 Grade 4 event
- 13 patients with severe cutaneous adverse reactions[d]
  - Most ≤Grade 2, no Grade 4 or 5 events
  - 4 patients with Grade 3 events: stomatitis, skin exfoliation, dermatitis bullous, dermatitis exfoliative generalised
  - 1 treatment discontinuation due to Grade 3 dermatitis bullous

Peripheral Neuropathy (PN)

- PN rate was similar in patients with and without pre-existing PN (60% vs. 55%)

Hyperglycemia (HG)

- Higher rate of HG in patients with pre-existing HG than those without pre-existing HG (20% vs. 7%)
- Higher rate of HG in patients with BMI ≥30 kg/m^2 than those with BMI <30 kg/m^2 (23% vs. 8%)

a. Events categorized based on queries for related MedDRA (Medical Dictionary for Regulatory Activities) terms v. 23.0
b. Most occurred in Cycle 1
c. Resolution/Improvement as of last follow-up
d. A range of skin reaction preferred terms, irrespective of grade

AEs are generally treatable with proper dose modifications and supportive care measures

Summary/Conclusions

- Cisplatin-ineligible patients need effective treatment options following immunotherapy
- The efficacy and safety data in this updated analysis, with an additional 3 months of follow-up for EV-201 Cohort 2, are consistent with those of the Primary Analysis:
  - 51% ORR, with a 22% complete response rate and consistent response rates across subgroups
  - 13.8 months median duration of response
  - Manageable safety profile in an elderly cisplatin-ineligible patient population
- Activity demonstrated in EV-201 Cohort 2 builds upon the results shown in PD-1/PD-L1 inhibitor and platinum-treated patients in EV-301
- These data support inclusion of enfortumab vedotin in the treatment of cisplatin-ineligible patients following immunotherapy and continued investigation of enfortumab vedotin in earlier disease settings

Abbreviations: AE=adverse event(s); BICR=Blinded Independent Central Review; BMI=body mass index; CI=Confidence Interval; CPI=checkpoint inhibitor; CPS=combined positive score; DOR=duration of response; IV=intravenous; ECOG PS=Eastern Cooperative Oncology Group performance status; HG=hyperglycemia; ORR=objective response rate; OS=overall survival; PD=progressive disease; PD-1/PD-L1=programmed cell death protein 1/programmed death-ligand 1; PFS=progression-free survival; PN=peripheral neuropathy; RECIST=Response Evaluation Criteria in Solid Tumors; TRAE=Treatment-Related Adverse Event