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

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Locally Advanced or Metastatic Urothelial Carcinoma in First Line Setting

- Carboplatin-based regimens for cisplatin ineligible patients are associated with poor outcomes in the first-line (1L) setting
- The FDA recently granted accelerated approval to enfortumab vedotin-ejfv, a Nectin-4 directed antibody-drug conjugate*
- PD-1/PD-L1 inhibitor responses have promising durability, but 1L indication is restricted to patients with high PD-L1 expression or platinum ineligibility[2,3]
- Initial data from Study EV-103, enfortumab vedotin + pembrolizumab had encouraging activity for this platinum-free approach in cisplatin-ineligible patients[4]
- We present the first durability, PFS and OS data of enfortumab vedotin + pembrolizumab in 1L as well as an update on safety and efficacy

- Adults with locally advanced or metastatic urothelial cancer who have previously received a PD1/L1 inhibitor and a platinum-containing chemotherapy in the nedoadjuvant/adjuvant, locally advanced or metastatic setting. This indication is approved under accelerated approval based on tumor response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

[1]Grande et al. *Ann Oncol.* 2019;30(Suppl 5):Abstract LBA14_PR; [2]Balar et al. *J Clin Oncol.* 2017;35:6(Suppl):284; [3]Balar et al. *Lancet*. 2017;389(10064):67-76; [4]Hoimes et al. *Ann Oncol.* 2019;30(Suppl 5):Abstract 9010.

EV-103 – First-line Cohorts of Enfortumab Vedotin + Pembrolizumab

Enfortumab vedotin 1.25 mg/kg + pembrolizumab (200 mg) in 1L cisplatin-ineligible la/mUC patients (N=45)

Patient Population

Locally Advanced or Metastatic Urothelial Carcinoma

Dose Escalation[1]

enfortumab vedotin + pembrolizumab

cisplatin-ineligible

(n=5)

Dose Expansion Cohort A

enfortumab vedotin + pembrolizumab

cisplatin-ineligible

(n=40)

Dosing: Enfortumab vedotin on days 1 and 8 and pembrolizumab on day 1 of every 3-week cycle

Enfortumab vedotin exposure: Comparable to enfortumab vedotin monotherapy on 4-week schedule (Days 1, 8, and 15)[2]

Primary endpoints: safety and tolerability

Key secondary endpoints: dose-limiting toxicities, ORR, DOR, PFS, OS

[1] Not included in the current analysis: three 1L patients treated with EV 1 mg/kg + pembrolizumab 200 mg and two 2L patients treated with EV 1.25 mg/kg + pembrolizumab 200 mg

[2] Rosenberg et al. *J Clin Oncol.* 2019;37(29):2592-600.

Key Demographics and Disease Characteristics

Enfortumab vedotin 1.25 mg/kg + pembrolizumab in 1L setting 8 Oct 2019 data cut-off	Patients (N=45) n (%)
Male sex, n (%)	36 (80)
Age, yrs, Median (min, max)	69 (51, 90)
ECOG performance status, n (%)	
0	16 (36)
1	23 (51)
2	6 (13)
Primary tumor location, n (%)	
Lower tract	31 (69)
Upper tract	14 (31)
Metastasis sites, n (%)	
Lymph nodes only	4 (9)
Visceral disease	41 (91)
Liver	15 (33)
PD-L1 status by combined positive score,[1] n (%)	
<10	19 (42)
≥10	14 (31)
Not evaluable/Not available	12 (27)

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

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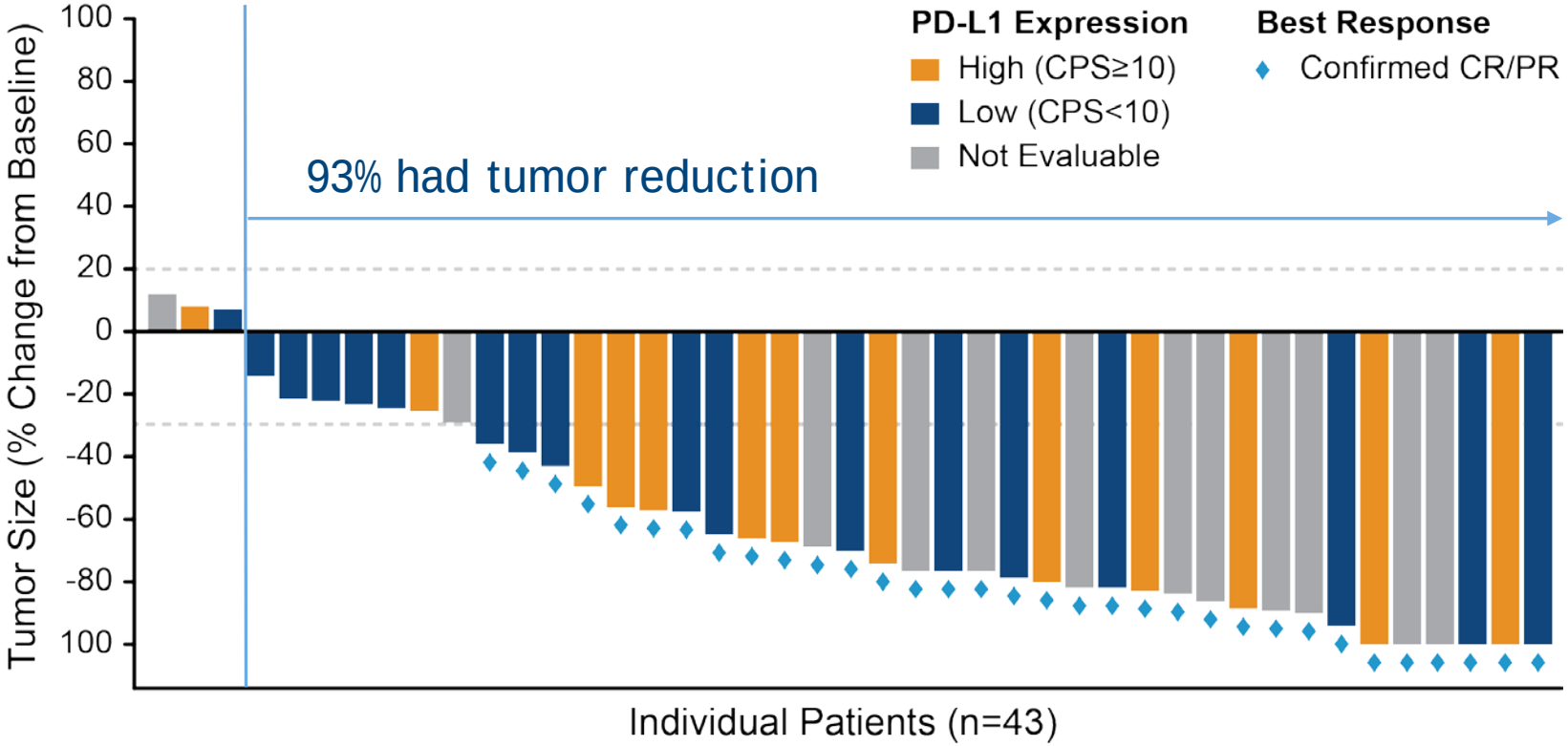
Maximal Target Lesion Reduction by PD-L1 status and Objective Response Rate per Investigator



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

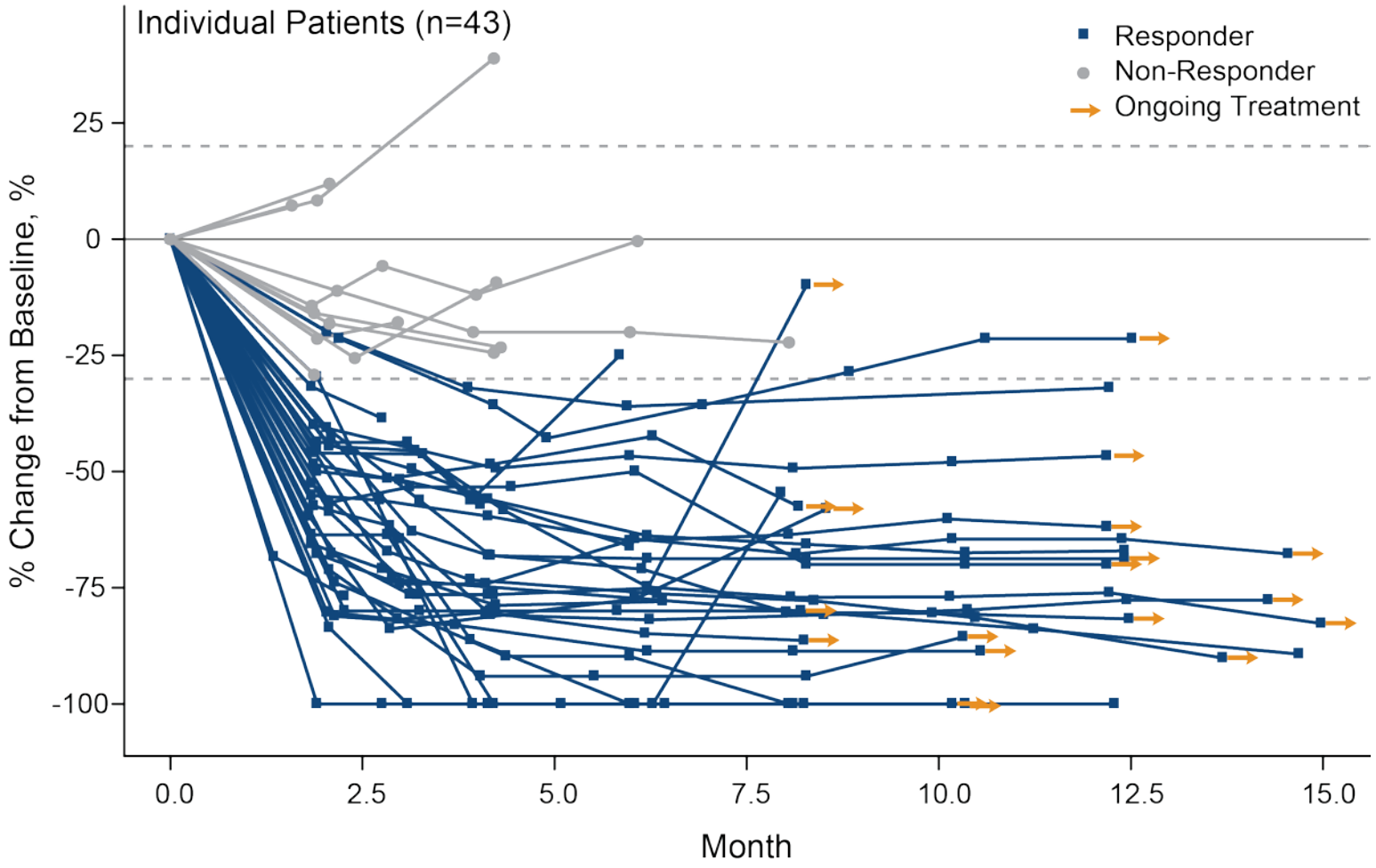
Best Overall Response Per RECIST v 1.1 by investigator (N=45)

- Responses observed regardless of PD-L1 expression level

Two patients did not have post-baseline response assessments before end-of-treatment: 1 withdrew consent and 1 died before any post-baseline response assessment. These patients are included in the full analysis set used to calculate ORR, but are not included in the figure above.

Horizontal lines at positive 20% and negative 30% denote thresholds for target lesions for disease progression and response, respectively.

Percent Change from Baseline in Sum of Diameters of Target Lesions



- 88% of responses observed at first assessment (Week 9 ± 1 week)
- Median time to response = 2 months (range: 1.4 to 4.2 mo)

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Horizontal lines at positive 20% and negative 30% denote thresholds for target lesions for disease progression and response, respectively.

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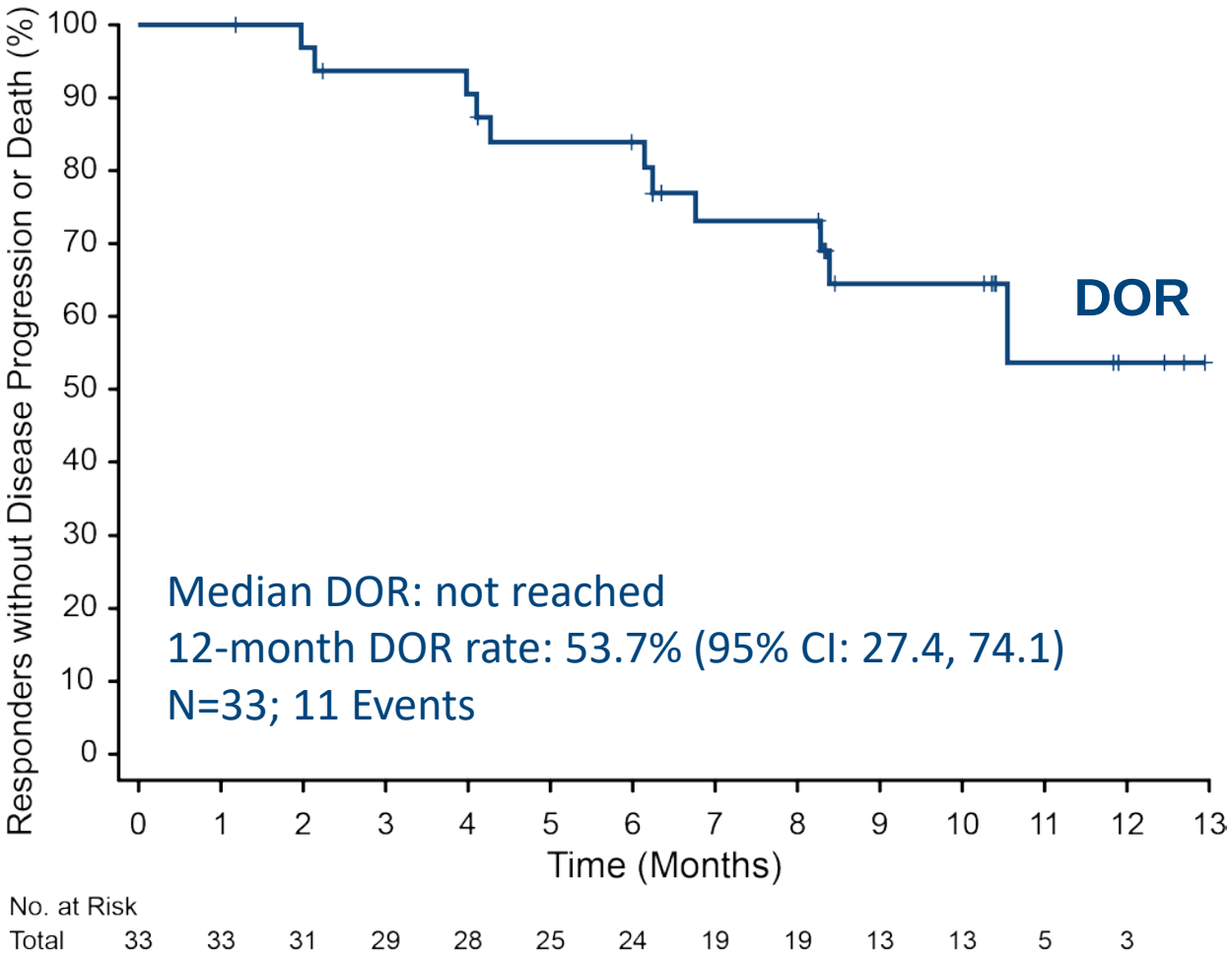
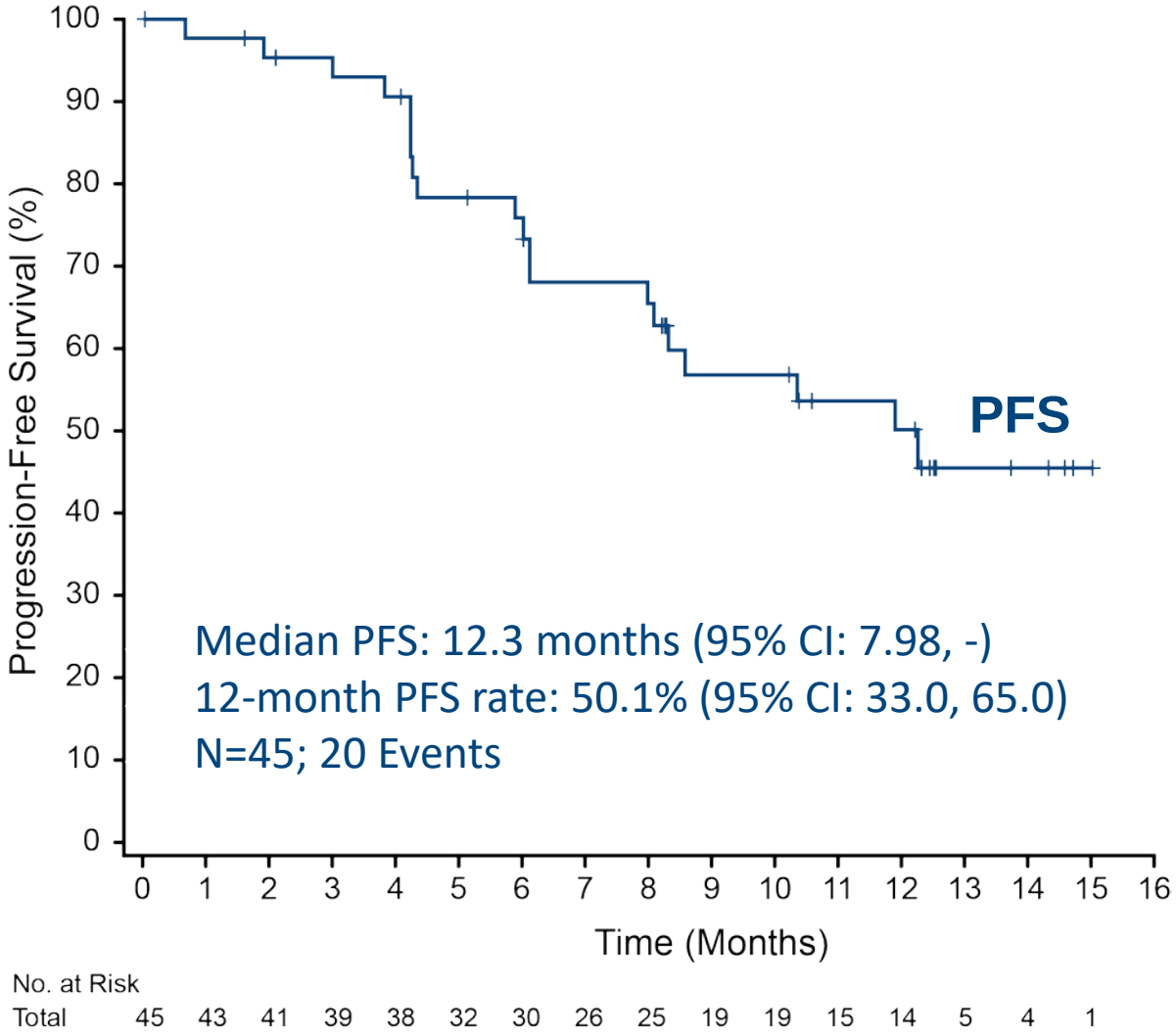
Duration of Response for Enfortumab Vedotin + Pembrolizumab



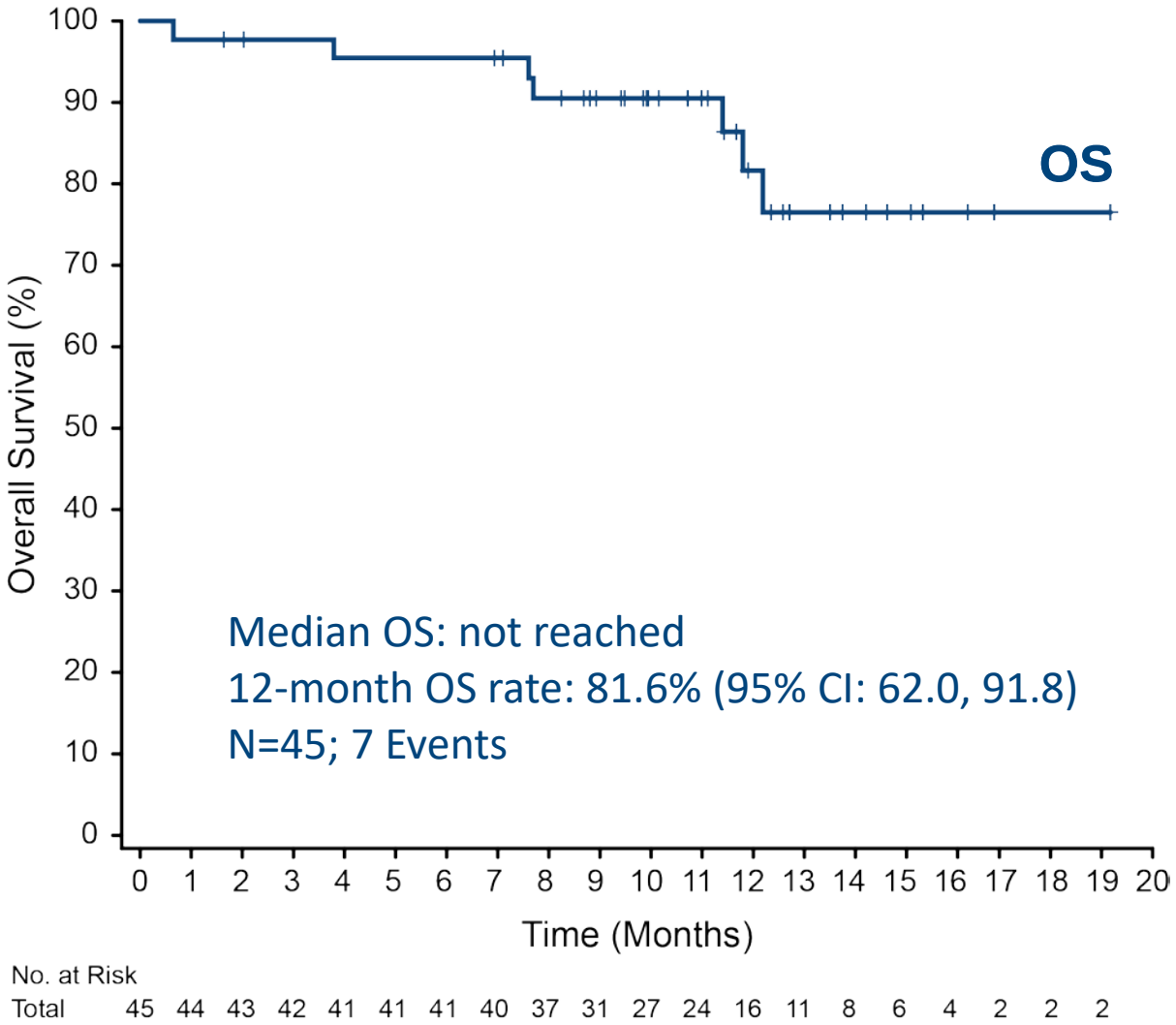
- With a median follow-up of 10.4 months, median DOR has not been reached
  - DOR (range: 1.2, 12.9+ months)

- 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

Survival for Enfortumab Vedotin + Pembrolizumab



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



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

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Treatment-Related Adverse Events (TRAE)

TRAEs by preferred term 8 Oct 2019 data cut-off	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)

- 7 patients had treatment-related serious AEs (16%)[1]
  - 6 patients had resolution
  - 1 treatment-related death as reported by investigator (2%)
    - Multiple organ dysfunction syndrome
- 6 discontinuations of enfortumab vedotin + pembrolizumab due to treatment-related AEs (13%)
  - Peripheral sensory neuropathy most common: 3 patients

[1] The only treatment-related serious event occurring in more than 1 patient was colitis (2 patients).

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Treatment-Related Adverse Events of Clinical Interest (AECI)

- Rates of peripheral neuropathy, rash, and hyperglycemia similar to enfortumab vedotin monotherapy
- No new safety signal with the combination

AECI: categorized by related MedDRA terms	Patients (N=45) n (%)		Time to first onset (months) median (min, max)
	Any Grade	≥Grade 3[1]	Any Grade
Peripheral neuropathy	25 (56)	2 (4)	2.3 (1, 12)
Rash	28 (62)	6 (13)	0.7 (0, 12)
Hyperglycemia[2]	5 (11)	3 (7)	0.5 (0, 3)

AECI: determined by investigator	Patients (N=45) n (%)	
	Any Grade	≥Grade 3[1]
Immune-mediated AE requiring systemic steroids	13 (29)	8 (18)[3]

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

Summary and Conclusions – EV-103 Enfortumab Vedotin + Pembrolizumab

- **Patients with la/mUC in 1L who are ineligible for cisplatin-based therapies still represent a high unmet need**
- **Enfortumab vedotin + pembrolizumab demonstrates encouraging activity in 1L cisplatin-ineligible la/mUC patients**
  - High ORR (73.3%), with activity regardless of PD-L1 expression level
  - Favorable PFS trend; median PFS 12.3 months (95% CI: 7.98, -)
  - Median OS not reached; 81.6% OS rate at 12 months
  - Rapid responses (88% at first assessment); median DOR not reached (range 1.2, 12.9+ months)
- **Stable safety profile over time, immune-mediated AEs similar to pembrolizumab monotherapy**
  - No new safety signals with combination
  - Most common treatment-related adverse events: fatigue, alopecia, and peripheral sensory neuropathy
  - One treatment-related death of multiple organ dysfunction syndrome
- **Based on these results, further investigation of enfortumab vedotin + pembrolizumab as a platinum-free option is warranted in patients with untreated la/mUC**
- **The pivotal Phase 3 study EV-302 (NCT04223856) will evaluate enfortumab vedotin in combination with pembrolizumab +/- chemotherapy vs gemcitabine/platinum in patients with la/mUC in 1L setting**

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