Epacadostat Plus Pembrolizumab in Patients With Advanced Urothelial Carcinoma: Preliminary Phase 1/2 Results of ECHO-202/KEYNOTE-037

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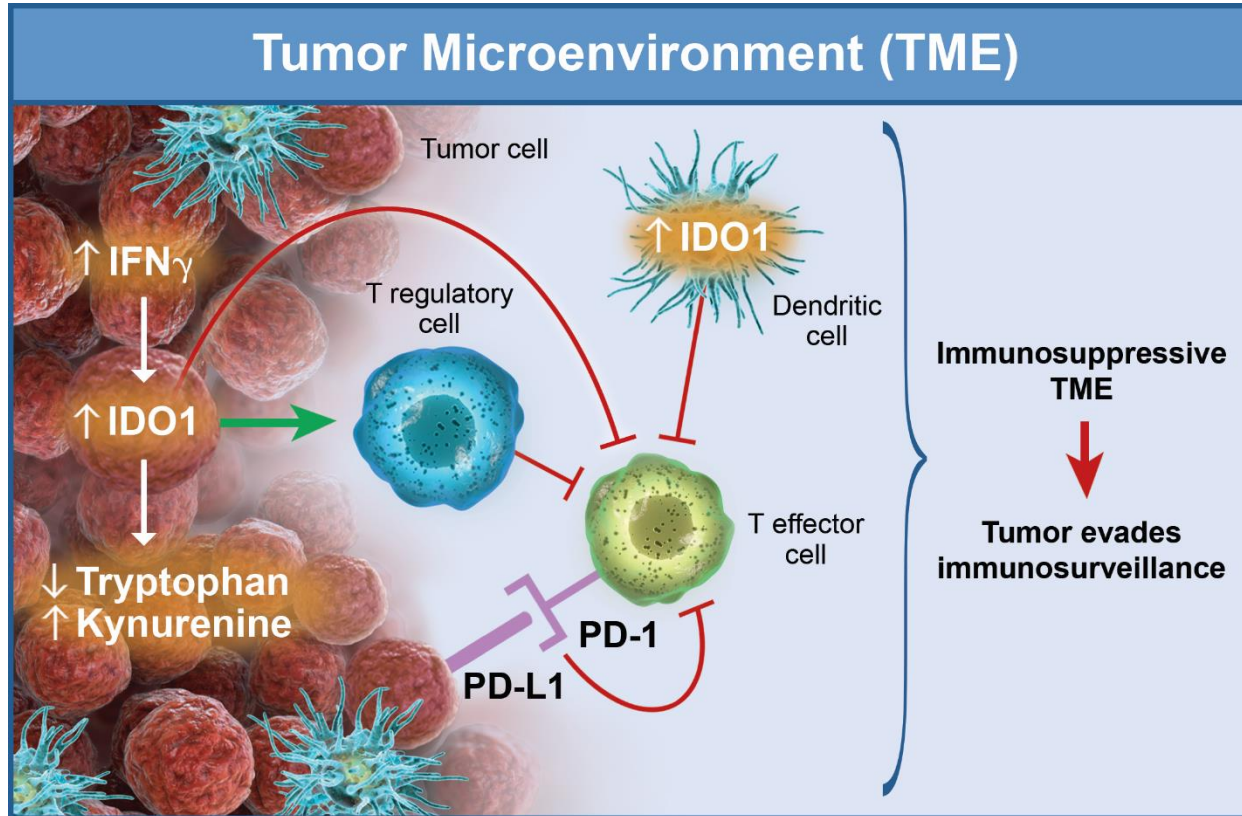
PD-1/PD-L1 Inhibitors in Advanced Urothelial Carcinoma

- Immune checkpoint inhibitors have significant activity in urothelial carcinoma

- Atezolizumab, avelumab, durvalumab, and nivolumab have received accelerated approvals by the FDA for patients with locally advanced or metastatic urothelial carcinoma[1-4]
  - In single-arm phase 2 trials, these agents demonstrated ORR ranging from 13% to 24%[2,3,5,6]

- Pembrolizumab has received regular approval for urothelial carcinoma patients with disease progression following platinum chemotherapy, based on OS benefits and a favorable safety and tolerability profile[7]
  - The median OS was 10.3 months compared with 7.4 months for chemotherapy; the ORR was 21% and the duration of response ranged from 1.6+ to 15.6+ months[7]

- Pembrolizumab has also received an accelerated approval as first-line treatment in patients ineligible for cisplatin; the ORR was 29% and the duration of response ranged from 1.4+ to 17.8+ months[7]

- Although these data are encouraging, novel combination treatment strategies are needed to improve efficacy with limited additive toxicity

FDA, Food and Drug Administration; ORR, objective response rate; OS, overall survival; PD-1/PD-L1, programmed death 1/programmed death ligand 1.
1. Tecentriq® (atezolizumab). Full Prescribing Information, Genetech, Inc, South San Francisco, CA, 2017. **2.** Bavencio® (avelumab). Full Prescribing Information. EMD Serono, Inc. and Pfizer Inc., New York, NY, 2017. **3.** Imfinzi® (durvalumab). Full Prescribing Information, AstraZeneca Pharmaceuticals LP, Wilmington, DE, 2017. **4.** Opdivo® (nivolumab). Full Prescribing Information, Bristol-Myers Squibb Company, Princeton, NJ, 2017. **5.** Sharma P, et al. *Lancet Oncol.* 2017;18(3):312-322. **6.** Rosenberg JE, et al. *Lancet.* 2016;387(10031):1909-1920. **7.** Keytruda® (pembrolizumab). Full Prescribing Information, Merck & Company, Whitehouse Station, NJ, 2017.

IDO1 Enzyme and Epacadostat

Tumor Microenvironment (TME)

↑IFNγ
↑IDO1
↓Tryptophan ↑Kynurenine
Tumor cell
T regulatory cell
↑IDO1
Dendritic cell
T effector cell
PD-1
PD-L1
Immunosuppressive TME
Tumor evades immunosurveillance

- Tumors may evade immunosurveillance through a number of mechanisms including immune checkpoint inhibition of T-cell activation and upregulation of IDO1

- IDO1 is an IFNγ-induced, intracellular enzyme that catalyzes the first and rate-limiting step of tryptophan degradation in the kynurenine pathway[1]

- Tryptophan depletion and production of kynurenine and other metabolites shift the local immune microenvironment to an immunosuppressive state[1]

- Epacadostat is a potent and specific oral inhibitor of IDO1, inhibiting tryptophan metabolism and augmenting immunosurveillance in the tumor microenvironment[2]

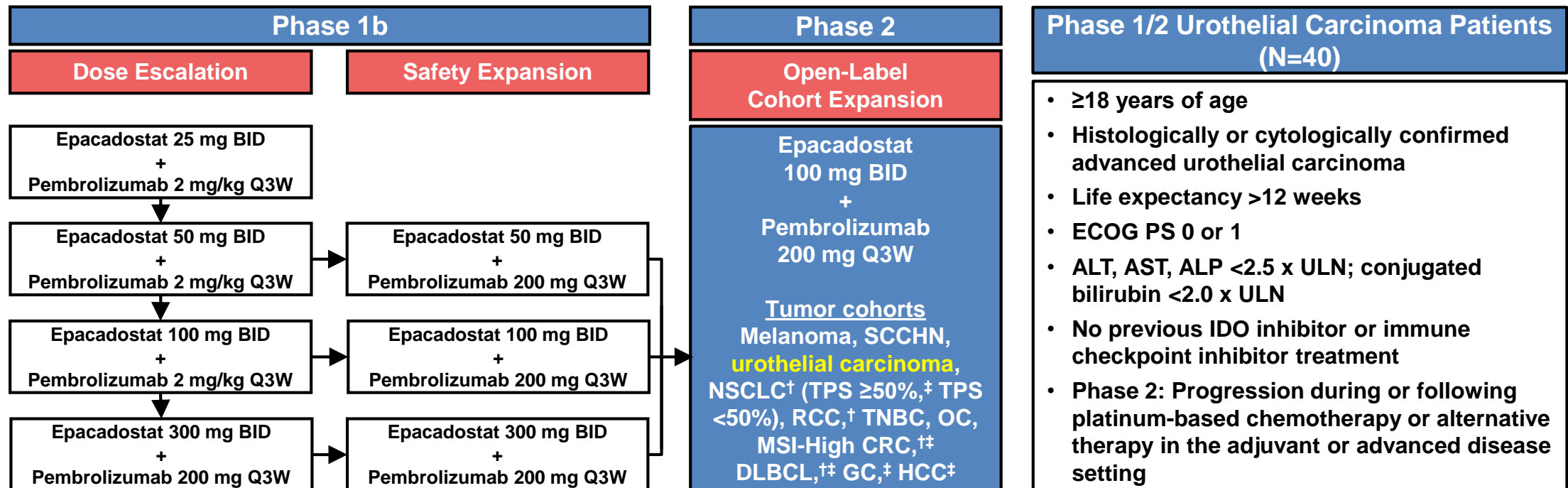- Combining epacadostat with a checkpoint inhibitor may improve patient outcomes

IDO1, indoleamine 2,3 dioxygenase 1; IFNγ, interferon gamma.

1. Moon YW, et al. *J Immunother Cancer*. 2015;3:51. 2. Liu X, et al. *Blood*. 2010;115(17):3520-3530.

Objective and Study Design

Objective: To report efficacy, safety, and tolerability data for epacadostat plus pembrolizumab in patients with advanced urothelial carcinoma

ECHO-202/KEYNOTE-037* study design:

Phase 1b		Phase 2	Phase 1/2 Urothelial Carcinoma Patients (N=40)
Dose Escalation	**Safety Expansion**	**Open-Label Cohort Expansion**	

Phase 1b – Dose Escalation:
- Epacadostat 25 mg BID + Pembrolizumab 2 mg/kg Q3W
- Epacadostat 50 mg BID + Pembrolizumab 2 mg/kg Q3W
- Epacadostat 100 mg BID + Pembrolizumab 2 mg/kg Q3W
- Epacadostat 300 mg BID + Pembrolizumab 200 mg Q3W

Phase 1b – Safety Expansion:
- Epacadostat 50 mg BID + Pembrolizumab 200 mg Q3W
- Epacadostat 100 mg BID + Pembrolizumab 200 mg Q3W
- Epacadostat 300 mg BID + Pembrolizumab 200 mg Q3W

Phase 2 – Open-Label Cohort Expansion:

Epacadostat 100 mg BID + Pembrolizumab 200 mg Q3W

Tumor cohorts
Melanoma, SCCHN, urothelial carcinoma, NSCLC[†] (TPS ≥50%,[‡] TPS <50%), RCC,[†] TNBC, OC, MSI-High CRC,[†‡] DLBCL,[†‡] GC,[‡] HCC[‡]

Phase 1/2 Urothelial Carcinoma Patients (N=40):
- ≥18 years of age
- Histologically or cytologically confirmed advanced urothelial carcinoma
- Life expectancy >12 weeks
- ECOG PS 0 or 1
- ALT, AST, ALP <2.5 x ULN; conjugated bilirubin <2.0 x ULN
- No previous IDO inhibitor or immune checkpoint inhibitor treatment
- Phase 2: Progression during or following platinum-based chemotherapy or alternative therapy in the adjuvant or advanced disease setting

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CRC, colorectal cancer; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GC, gastric cancer; HCC, hepatocellular carcinoma; IDO, indoleamine 2,3 dioxygenase; MSI, microsatellite instability; NSCLC, non-small cell lung cancer; OC, ovarian cancer; Q3W, every 3 weeks; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; TNBC, triple-negative breast cancer; TPS, tumor proportion score; ULN, upper limit of normal.
Note: GC and HCC cohorts were not yet open for patient enrollment at data cutoff (February 27, 2017).
* NCT02178722. [†] Ongoing patient enrollment at data cutoff (February 27, 2017). [‡] Ongoing patient enrollment at time of ASCO presentation (June 5, 2017).

Study Assessments

- **Efficacy**
  - Response was assessed every 9 weeks per RECIST v1.1 and irRECIST
  - Efficacy-evaluable: ≥1 postbaseline scan, or discontinuation, or death as of data cutoff (N=40)

- **Safety and tolerability**
  - Adverse events were assessed by CTCAE v4.0
  - Adverse events of special interest include adverse events with an immune-related cause, regardless of attribution to study treatment by the investigator
  - Safety-evaluable: ≥1 dose of study treatment as of data cutoff (N=40)

- **Biomarker analysis**
  - Positive PD-L1 staining status was determined based on a provisional 1% cutoff by IHC using an investigational version of the PD-L1 IHC 22C3 pharmDx (Agilent, Carpinteria, CA, USA)
    - The percentage of positive cells is determined using the combined positive score (CPS), which is the number of staining tumor and immune cells relative to total tumor cells; the percentage is defined by the number of staining cells per 100 tumor cells

- **Data cutoff:** February 27, 2017

Baseline Demographics and Disease Characteristics

Phase 1/2 Advanced Urothelial Carcinoma

Variable, n (%)*	Total (N=40)
Median (range) age, y	67 (43–87)
Men	30 (75)
White	35 (88)
ECOG PS	
0	16 (40)
1	24 (60)
Bellmunt risk score[†][1]	
0	5 (13)
1	21 (53)
≥2	14 (35)
Common sites of metastases	
Lymph node	23 (58)
Lung	16 (40)
Bone	9 (23)
Liver	8 (20)
Skin or subcutaneous tissue	1 (3)
Other	14 (35)

Variable, n (%)	Total (N=40)
Prior radiation treatment	10 (25)
Prior surgery	37 (93)
Number of prior treatments for advanced disease	
0[‡] or 1	32 (80)
≥2	8 (20)
Prior platinum-based treatment	
Cisplatin	31 (78)
Carboplatin	12 (30)
PD-L1 expression (CPS)	
Positive (CPS ≥1%)	11 (28)
Negative (CPS <1%)	8 (20)
Unknown[§]	21 (53)

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand 1.

* Unless noted otherwise within table. [†] Bellmunt risk score is based on the number of the following risk factors: ECOG PS ≥1, presence of liver metastasis, hemoglobin <10 g/dL, time from last chemotherapy dose (<3 months). [‡] Enrolled patients who had no prior treatment for advanced urothelial carcinoma received platinum-based treatment in adjuvant/neoadjuvant setting.
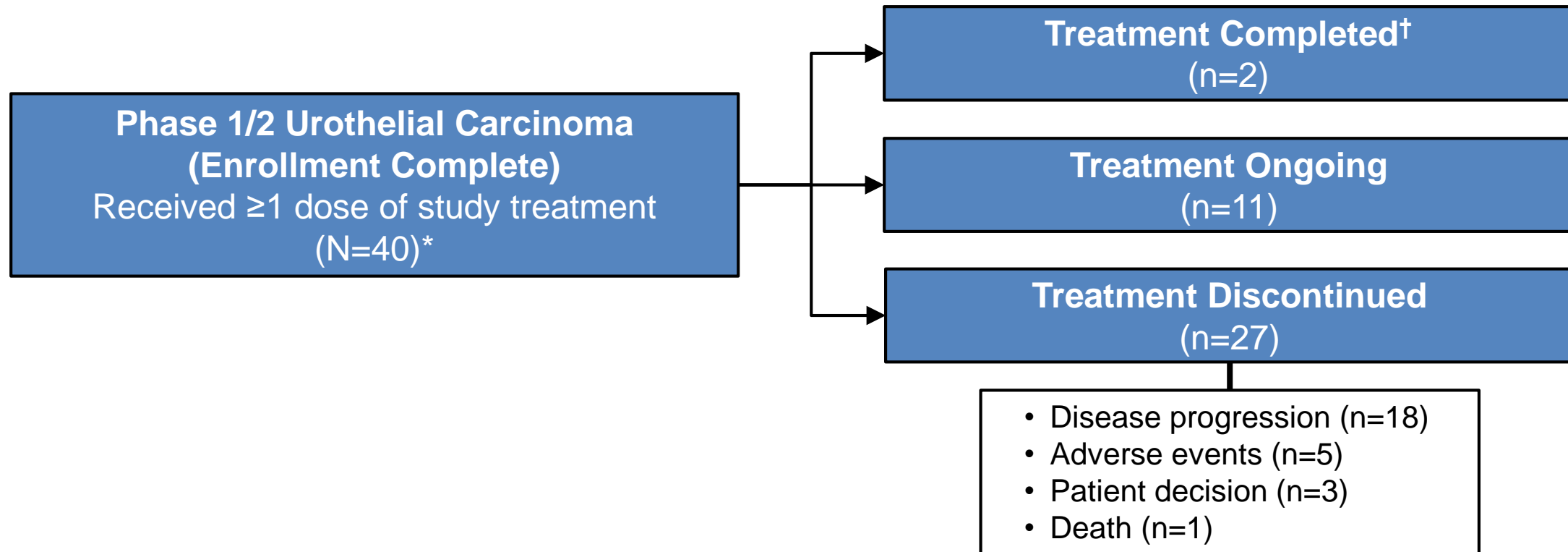[§] Not evaluable, not done, or missing.

1. Bellmunt J, et al. *J Clin Oncol.* 2010;28(11):1850-1855.

Patient Disposition

Epacadostat Plus Pembrolizumab
Phase 1/2 Advanced Urothelial Carcinoma

Phase 1/2 Urothelial Carcinoma (Enrollment Complete)
Received ≥1 dose of study treatment
(N=40)*

Treatment Completed[†]
(n=2)

Treatment Ongoing
(n=11)

Treatment Discontinued
(n=27)

- Disease progression (n=18)
- Adverse events (n=5)
- Patient decision (n=3)
- Death (n=1)

Median (range) follow-up: 33.8+ (3.6 to 131+) weeks

Median (range) epacadostat exposure: 20.1 (1 to 132+) weeks

CR, complete response.
* 1 additional patient was enrolled but data were not yet available at the time of data cutoff. [†] Patients received 24 months of study treatment or achieved CR and elected to discontinue treatment following the protocol-defined minimum amount of treatment (≥24 weeks before discontinuation and ≥2 cycles of combination treatment beyond the date of initial CR).

Best Objective Response by RECIST v1.1

Epacadostat Plus Pembrolizumab
Phase 1/2 Advanced Urothelial Carcinoma

Patients, n (%)	Total (N=40)	Number of Prior Lines of Treatment		PD-L1 Expression (CPS)[†]	
		0*–1 (n=32)	≥2 (n=8)	Positive (CPS ≥1%) (n=11)	Negative (CPS <1%) (n=8)
ORR (CR+PR)	**14 (35)**	**12 (38)**	**2 (25)**	**7 (64)**	**1 (13)**
CR	3 (8)	3 (9)	0	0	0
PR	11 (28)	9 (28)	2 (25)	7 (64)	1 (13)
SD	7 (18)	7 (22)	0	1 (9)	1 (13)
DCR (CR+PR+SD)	**21 (53)**	**19 (59)**	**2 (25)**	**8 (73)**	**2 (25)**
PD	14 (35)	10 (31)	4 (50)	2 (18)	6 (75)
Not evaluable	5 (13)	3 (9)	2 (25)	1 (9)	0

- Based on irRECIST: ORR=38% (4 CR, 11 PR); DCR=60% (9 SD)

CPS, combined positive score; CR, complete response; DCR, disease control rate; irRECIST, immune-related RECIST; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
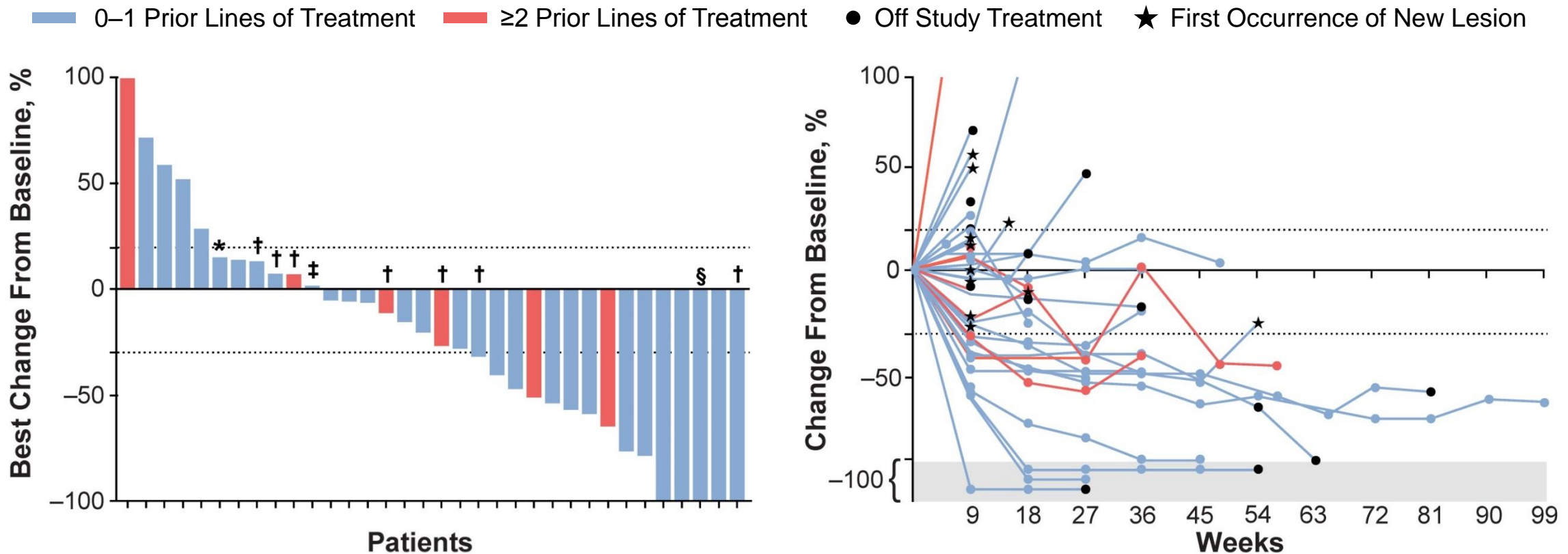* Enrolled patients who had no prior treatment for advanced urothelial carcinoma received platinum-based treatment in adjuvant/neoadjuvant setting. [†] Of 21 patients with unknown PD-L1 expression, there were 3 CR, 3 PR, 5 SD, 6 PD, and 4 not evaluable by RECIST v1.1.

Percentage Change From Baseline in Target Lesions

Epacadostat Plus Pembrolizumab
Phase 1/2 Advanced Urothelial Carcinoma by Number of Prior Lines of Treatment

Patients With 0–1 Prior Lines of Treatment: ORR=38%, DCR=59% by RECIST v1.1

■ 0–1 Prior Lines of Treatment   ■ ≥2 Prior Lines of Treatment   ● Off Study Treatment   ★ First Occurrence of New Lesion

DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Of the 40 evaluable patients, data are shown for the 34 patients with postbaseline scans that included assessment of target lesions. 6 patients were not shown in this figure: 1 patient discontinued treatment for PD per nontarget lesion (target lesions not assessed) and 5 patients died prior to the first postbaseline scan.

* Objective response is PD per investigator assessment at data cutoff; target lesions did not meet criteria for PD but rather SD. † Objective response is PD per new lesions or nontarget lesions.

‡ Objective response is PR per investigator assessment at data cutoff; target lesions did not meet criteria for PR but rather SD. § Objective response is PR (nontarget lesions still present).
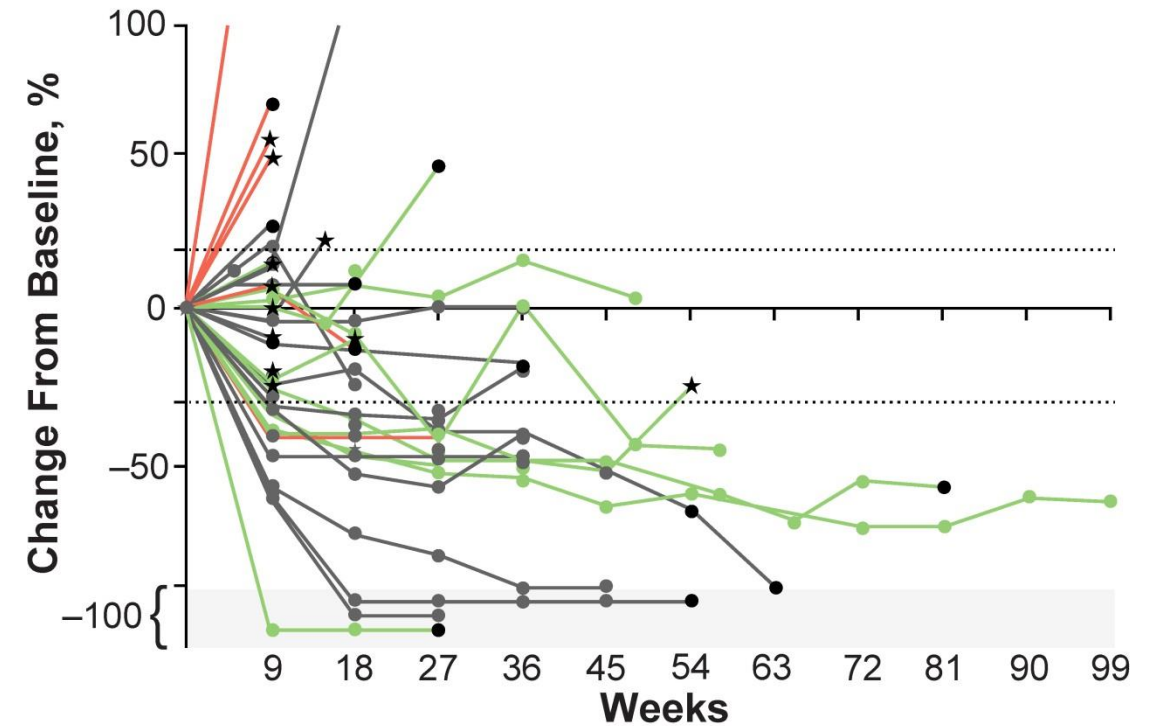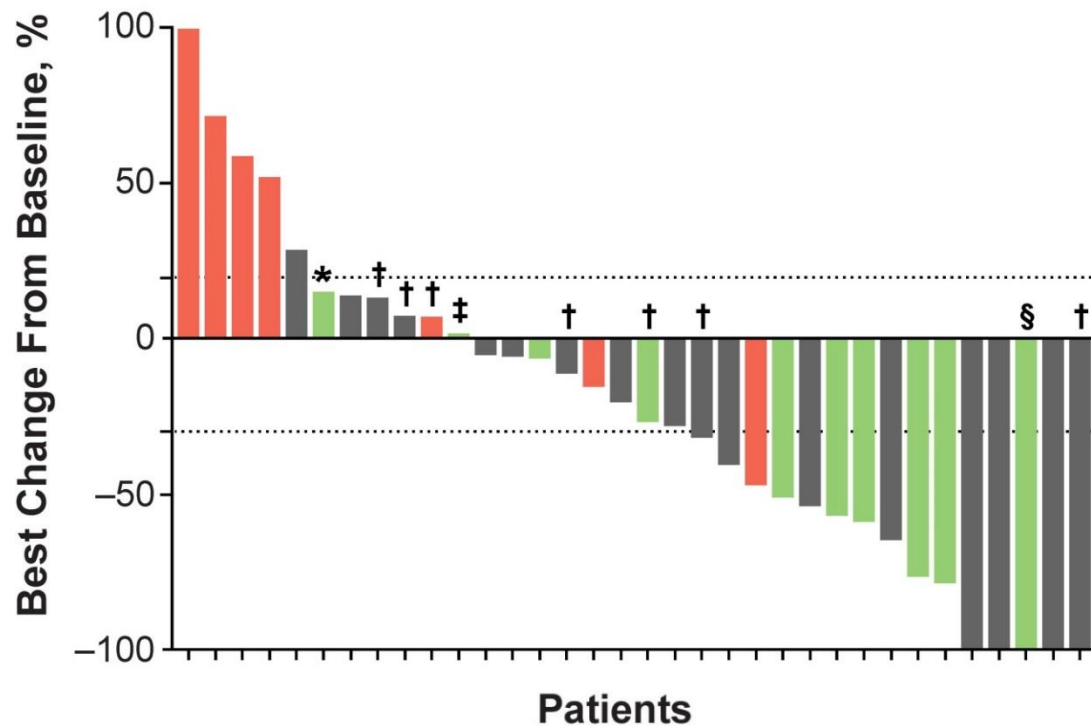
Percentage Change From Baseline in Target Lesions

Epacadostat Plus Pembrolizumab
Phase 1/2 Advanced Urothelial Carcinoma by PD-L1 Expression

The Majority of Responses Were Observed in PD-L1 Positive Patients

CPS, combined positive score; PD, progressive disease; PD-L1, programmed death ligand 1; PR, partial response; SD, stable disease.

Of the 40 evaluable patients, data are shown for the 34 patients with postbaseline scans that included assessment of target lesions. 6 patients were not shown in this figure: 1 patient discontinued treatment for PD per nontarget lesion (target lesions not assessed) and 5 patients died prior to the first postbaseline scan.

* Objective response is PD per investigator assessment at data cutoff; target lesions did not meet criteria for PD but rather SD. † Objective response is PD per new lesions or nontarget lesions.
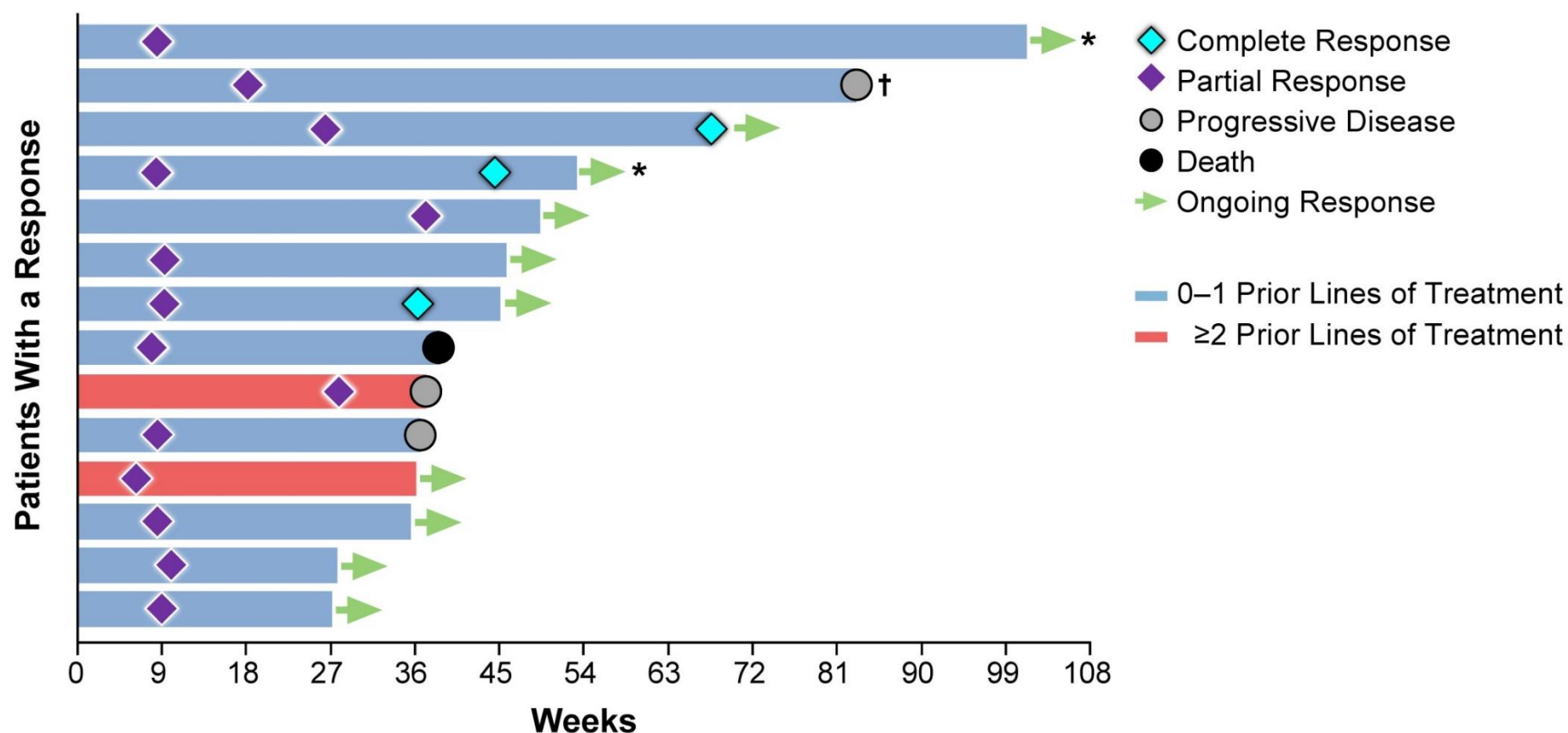
‡ Objective response is PR per investigator assessment at data cutoff; target lesions did not meet criteria for PR but rather SD. § Objective response is PR (nontarget lesions still present).

Time to and Duration of Response (RECIST v1.1)

Epacadostat Plus Pembrolizumab
Phase 1/2 Advanced Urothelial Carcinoma

- 10/14 responses ongoing; median (range) duration of response 30.6+ (9.7 to 93.1+) weeks
  - 2 patients completed study treatment and have maintained ongoing response at last follow-up

RECIST, Response Evaluation Criteria in Solid Tumors.
* Patients completed study treatment; responses were ongoing at last follow-up. † Patient had clinical progression; progressive disease per RECIST v1.1 was not confirmed.

Treatment-Related Adverse Events (≥5%)

Epacadostat Plus Pembrolizumab
Phase 1/2 Advanced Urothelial Carcinoma

Adverse Event, n (%)	All Grade (N=40)	Grade 3/4* (N=40)
Total	28 (70)	9 (23)
Fatigue	13 (33)	1 (3)
Rash[†]	8 (20)	3 (8)
Amylase increased	5 (13)	0
Pruritus[‡]	4 (10)	0
ALT increased	3 (8)	1 (3)
Chills	3 (8)	0
Lipase increased	3 (8)	1 (3)
Nausea	3 (8)	0
Arthralgia	2 (5)	0
AST increased	2 (5)	0
Dysgeusia	2 (5)	0
Flushing	2 (5)	0
Hyperglycemia	2 (5)	2 (5)

- Treatment-related adverse events led to dose interruptions in 11 patients (28%)
  - None of these adverse events occurred in >1 patient

- 2 patients (5%) had dose reductions due to treatment-related adverse events (rash)

- 3 patients discontinued due to treatment-related adverse events
  - COPD exacerbation, colitis, and rash (n=1 patient each)
  - The adverse events were manageable with supportive care

- There were no treatment-related deaths

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COPD, chronic obstructive pulmonary disorder; MedDRA, Medical Dictionary for Regulatory Activities.
* Other grade 3/4 treatment-related adverse events not included in the table: COPD and diarrhea (n=1 each). † Rash includes the following MedDRA preferred terms: rash, rash macular, rash papular, and rash pruritic. ‡ Pruritus includes the following MedDRA preferred terms: pruritus and pruritus generalized.

Adverse Events of Special Interest*

Epacadostat Plus Pembrolizumab
Phase 1/2 Advanced Urothelial Carcinoma

Adverse event, n (%)	All Grade (N=40)	Grade 3/4 (N=40)
Total	**6 (15)**	**3 (8)**
Severe skin reaction[†]	3 (8)	3 (8)
Colitis	1 (3)	0
Hypothyroidism	1 (3)	0
Pneumonitis	1 (3)	0
Type 1 diabetes mellitus	1 (3)	0

* Adverse events of special interest include adverse events with an immune-related cause, regardless of attribution to study treatment by the investigator. [†] The severe skin reactions in patients with urothelial carcinoma in this study include grade ≥3 rash and rash macular.

Conclusions

Epacadostat Plus Pembrolizumab

- These results suggest that epacadostat plus pembrolizumab is active in patients with advanced urothelial carcinoma

  - Across all patients, the ORR was 35% (CR, 8%) and the DCR was 53% by RECIST v1.1

  - In patients with 0–1 prior lines of treatment, the ORR was 38% (CR, 9%) and the DCR was 59%
  - A higher response rate was observed in PD-L1 positive patients, although responses were also observed in PD-L1 negative patients
  - 10/14 responses were ongoing; median (range) duration of response was 30.6+ (9.7 to 93.1+) weeks

- Epacadostat plus pembrolizumab was generally well tolerated in patients with advanced urothelial carcinoma

  - The safety profile was consistent with the previously reported phase 1 findings,[1] as well as the phase 1/2 safety data in other tumor types and pooled phase 2 safety data from this study (presented at ASCO 2017)
  - In general, the frequency of grade 3/4 treatment-related adverse events, treatment discontinuation due to treatment-related adverse events, and adverse events of special interest observed with this combination were similar to pembrolizumab monotherapy; the frequency of grade 3/4 rash was higher with this combination[2,3]

- The efficacy of epacadostat plus pembrolizumab in urothelial carcinoma patients with 0–1 prior lines of treatment supports phase 3 investigation of this combination in urothelial carcinoma

CR, complete response; DCR, disease control rate; ORR, objective response rate; PD-L1, programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors.
1. Gangadhar TC, et al. Epacadostat plus pembrolizumab in patients with advanced melanoma and select solid tumors: updated phase 1 results from ECHO-202/KEYNOTE-037. Presented at: European Society for Medical Oncology Congress 2016; October 7–11, 2016; Copenhagen, Denmark. **2.** Balar A, et al. *Ann Oncol.* 2016;27(suppl 6):LBA32_PR. **3.** Bellmunt J, et al. *N Engl J Med.* 2017;376(11):1015-1026.

Related Presentations

Presentation/Poster Title	Presentation Date
Abstract #9014: Efficacy and safety of epacadostat plus pembrolizumab treatment of NSCLC: Preliminary phase 1/2 results of ECHO-202/KEYNOTE-037	Poster Discussion Session: *Lung Cancer—Non-Small Cell Metastatic* **6/3/2017**
Abstract #4515: Epacadostat plus pembrolizumab in patients with advanced RCC: Preliminary phase 1/2 results from ECHO-202/KEYNOTE-037	Poster Discussion Session: *Genitourinary (Nonprostate) Cancer* **6/4/2017**
Abstract #1103: Efficacy/safety of epacadostat plus pembrolizumab in triple-negative breast cancer and ovarian cancer: Phase 1/2 ECHO-202 study	Poster Session: *Breast Cancer—Metastatic* **6/4/2017**
Abstract #3012: Safety of epacadostat 100 mg BID plus pembrolizumab 200 mg Q3W in advanced solid tumors: Phase 2 data from ECHO-202/ KEYNOTE-037	Poster Discussion Session: *Developmental Therapeutics—Immunotherapy* **6/5/2017**
Abstract #6010: Epacadostat plus pembrolizumab in patients with SCCHN: Preliminary phase 1/2 results from ECHO-202/KEYNOTE-037	Clinical Science Symposium: *What's Next in Immunotherapy for Head and Neck Cancer?* **6/6/2017**

BID, twice daily; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck.

Acknowledgments

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