

Epacadostat Plus Pembrolizumab in Patients With SCCHN: Preliminary Phase 1/2 Results From ECHO-202/KEYNOTE-037

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PD-1 Inhibitors in Metastatic/Recurrent SCCHN

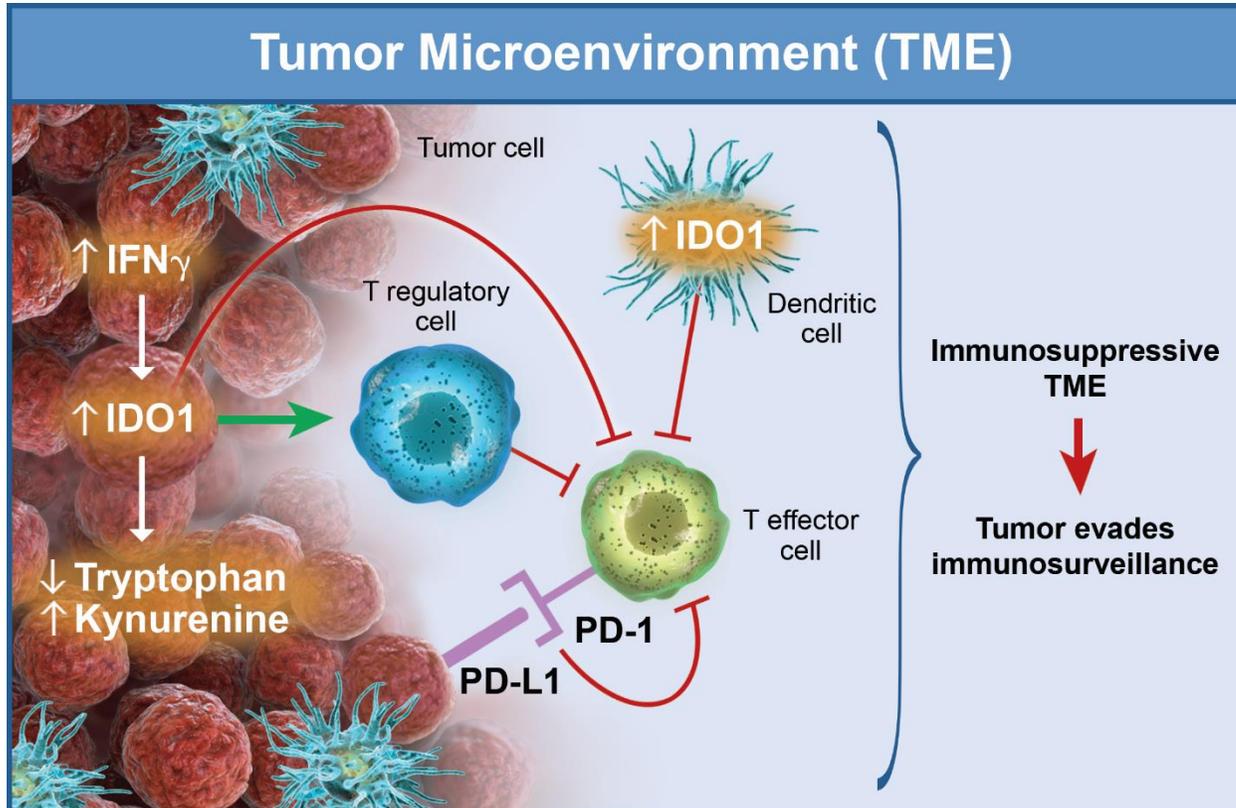
- Patients with metastatic or recurrent squamous cell carcinoma of the head and neck (SCCHN) have a poor prognosis and limited treatment options¹
 - Conventional second-line chemotherapy treatments are associated with a 3–6% ORR and a median OS of approximately 5–6 months²
- The introduction of immune checkpoint inhibitors has provided new treatment options for SCCHN patients
- Pembrolizumab and nivolumab are currently approved by the FDA for patients with metastatic or recurrent SCCHN with disease progression on or after platinum chemotherapy^{3,4}
 - Pembrolizumab treatment resulted in an ORR of 16% to 18%^{5,6} and a median duration of response of 8 months⁵; treatment with nivolumab was associated with a 13% ORR⁷
 - Both had favorable safety and tolerability profiles⁵⁻⁷
- 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, programmed death 1.

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Head and Neck Cancers. Version 1.2017. (https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf). 2. Argiris A, et al. *Front Oncol.* 2017;7(72). 3. KEYTRUDA® (pembrolizumab). Full Prescribing Information, Merck Sharp & Dohme Corporation, Whitehouse Station, NJ, 2017.

4. Opdivo® (nivolumab). Full Prescribing Information, Bristol-Myers Squibb Company, Princeton, NJ, 2017. 5. Bauml J, et al. *J Clin Oncol.* 2017;35(14):1542-1549. 6. Chow LQM, et al. *J Clin Oncol.* 2016;34(32):3838-3845. 7. Ferris RL, et al. *N Engl J Med.* 2016;375(19):1856-1867.

IDO1 Enzyme and Epacadostat

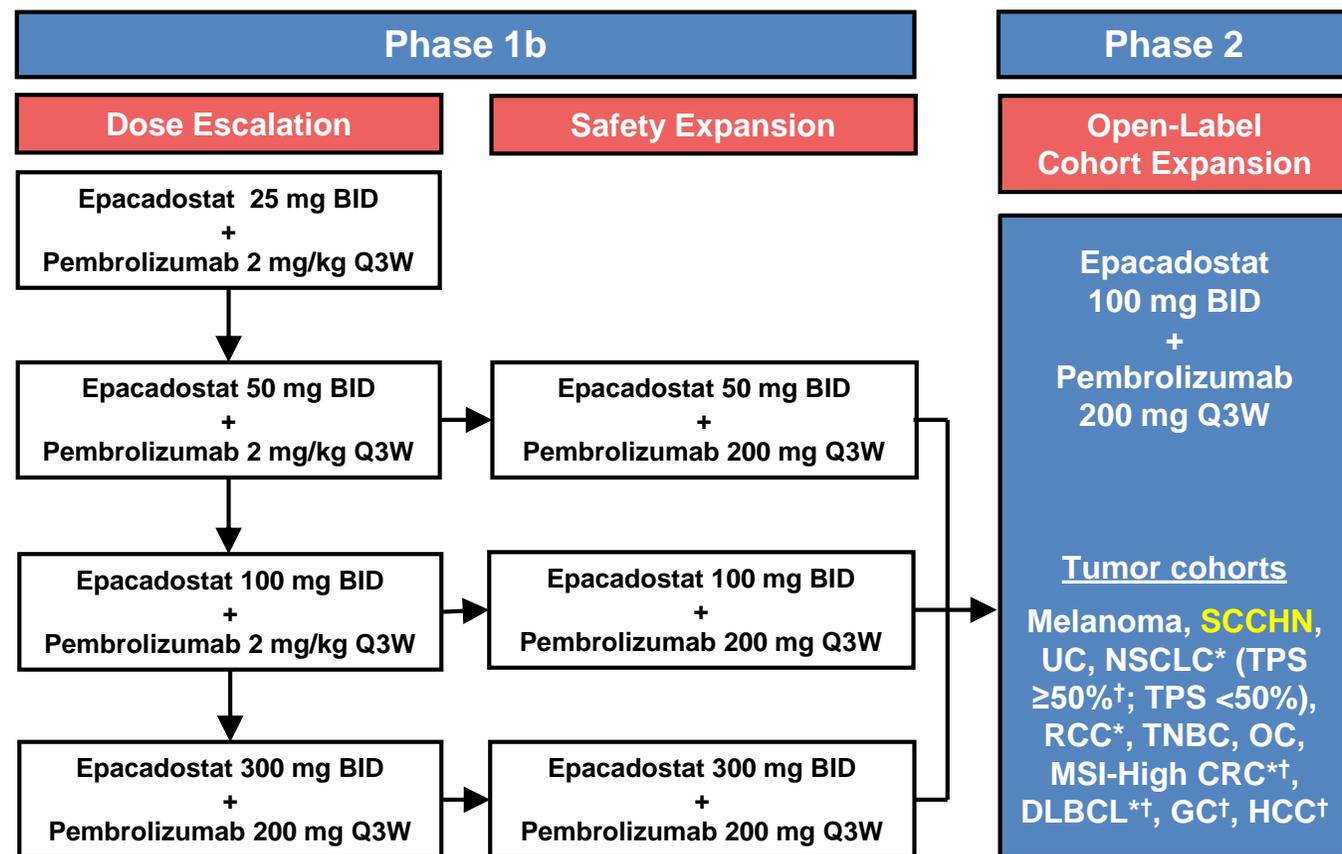


- Tumors can evade immunosurveillance through a number of mechanisms including immune checkpoint inhibition of T-cell activation and upregulation of the IDO1 enzyme
- IDO1 is an IFN γ -induced, intracellular enzyme that catalyzes the first and rate-limiting step of tryptophan degradation in the kynurenine pathway¹
- Depletion of tryptophan and production of kynurenine and other metabolites shifts the local immune microenvironment to an immunosuppressive state¹
- Epacadostat is a potent and specific oral inhibitor of IDO1, inhibiting tryptophan metabolism and augmenting immunosurveillance in the tumor microenvironment²
- Combining epacadostat with a checkpoint inhibitor may improve patient outcomes

IDO1, indoleamine 2,3 dioxygenase 1; IFN γ , interferon gamma.

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

ECHO-202/KEYNOTE-037: Study Design



BID, twice daily; CRC, colorectal cancer; DLBCL, diffuse large B-cell lymphoma; GC, gastric cancer; HCC, hepatocellular carcinoma; 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; UC, urothelial carcinoma.

Note: GC and HCC cohorts were not yet open for patient enrollment at data cutoff (February 27, 2017).

* Ongoing patient enrollment at data cutoff (February 27, 2017). † Ongoing patient enrollment at time of ASCO presentation (June 6, 2017).

Objective and Patients

- **Objective**

- To report efficacy, safety, and tolerability data for epacadostat plus pembrolizumab in patients with metastatic or recurrent SCCHN in the phase 1/2 ECHO-202/KEYNOTE-037 study (NCT02178722)

- **Patients**

- Aged ≥ 18 years
- Histologically or cytologically confirmed metastatic or recurrent SCCHN (excluding nasopharynx/salivary gland)
- Life expectancy > 12 weeks
- ECOG PS 0 or 1
- ALT, AST, ALP $< 2.5 \times$ ULN; conjugated bilirubin $< 2.0 \times$ ULN
- No previous IDO inhibitor or immune checkpoint inhibitor treatment
- Phase 2: ≥ 1 prior systemic chemotherapy regimen, including a platinum-based therapy

Study Assessments

- **Data cutoff:** February 27, 2017
- **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=38)
- **Safety and tolerability**
 - AEs were assessed by CTCAE v4.0
 - AEs of special interest include AEs 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=38)
- **Biomarker analysis**
 - Positive PD-L1 staining status was determined based on a 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

Baseline Demographics and Disease Characteristics

Phase 1/2 Metastatic or Recurrent SCCHN

Variable, n (%) [*]	Total (N=38)
Median (range) age, y	63 (33–87)
Men	33 (87)
White	36 (95)
ECOG PS	
0	17 (45)
1	21 (55)
Location of primary tumor	
Oropharynx	17 (45)
Oral cavity	12 (32)
Larynx	4 (11)
Other	5 (13)
HPV status [†]	
HPV associated	13 (34)
Non-HPV associated	24 (63)
Unknown	1 (3)

Variable, n (%)	Total (N=38)
Prior smoking history	27 (71)
Prior radiation treatment	38 (100)
Prior surgery	31 (82)
Prior cetuximab treatment	25 (66)
Prior chemotherapy	37 (97)
Number of prior treatments for advanced disease	
1	12 (32)
2	19 (50)
≥3	7 (18)
PD-L1 expression (CPS)	
Positive (CPS ≥1%)	22 (58)
Negative (CPS <1%)	7 (18)
Unknown [‡]	9 (24)

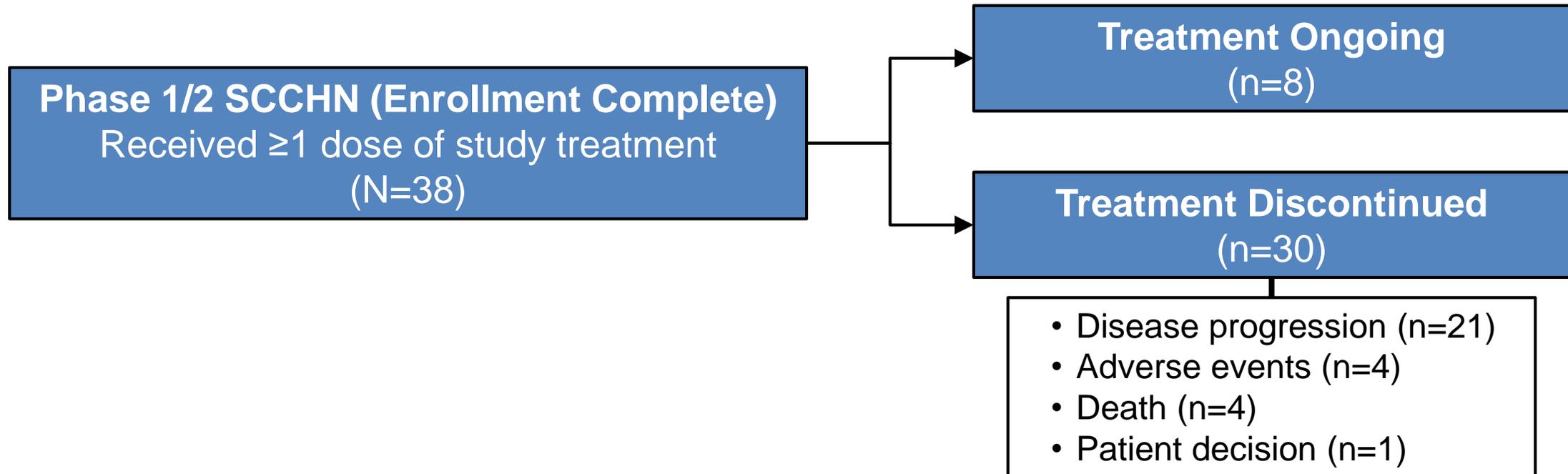
CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papillomavirus; PD-L1, programmed death ligand 1; SCCHN, squamous cell carcinoma of the head and neck.

^{*} Unless noted otherwise within table. [†] Determined by p16 or HPV status in patients with oropharynx as primary tumor location; patients with primary tumor location outside the oropharynx were considered non-HPV associated. [‡] Not evaluable, not done, or missing.

Patient Disposition

Epacadostat Plus Pembrolizumab

Phase 1/2 Metastatic or Recurrent SCCHN



Median (range) follow-up: 25.9+ (3.9 to 108.3+) weeks

Median (range) epacadostat exposure: 18.6 (1 to 111+) weeks

Best Objective Response by RECIST v1.1

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Phase 1/2 Metastatic or Recurrent SCCHN

Patients, n (%)	Total (N=38)	Number of Prior Lines of Treatment		PD-L1 Expression (CPS)*		HPV Status†	
		1–2 (n=31)	≥3 (n=7)	Positive (CPS ≥1%) (n=22)	Negative (CPS <1%) (n=7)	HPV Associated (n=13)	Non-HPV Associated (n=24)
ORR (CR+PR)	13 (34)	12 (39)	1 (14)	6 (27)	3 (43)	6 (46)	7 (29)
CR	3 (8)	3 (10)	0	2 (9)	0	1 (8)	2 (8)
PR	10 (26)	9 (29)	1 (14)	4 (18)	3 (43)	5 (38)	5 (21)
SD	10 (26)	8 (26)	2 (29)	7 (32)	1 (14)	1 (8)	9 (38)
DCR (CR+PR+SD)	23 (61)	20 (65)	3 (43)	13 (59)	4 (57)	7 (54)	16 (67)
PD	11 (29)	8 (26)	3 (43)	7 (32)	1 (14)	6 (46)	5 (21)
Not evaluable	4 (11)	3 (10)	1 (14)	2 (9)	2 (29)	0	3 (13)

- Same response results by irRECIST criteria

CPS, combined positive score; CR, complete response; DCR, disease control rate; HPV, human papillomavirus; 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; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease.

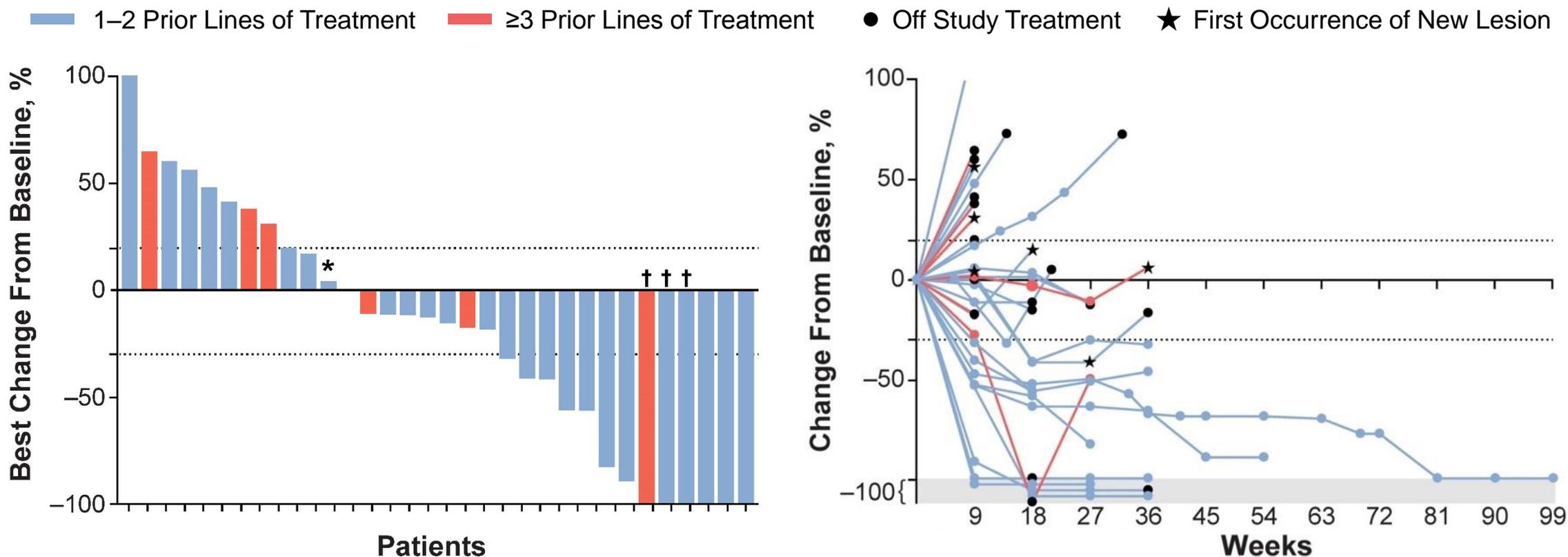
* Of 9 patients with unknown PD-L1 expression, there were 1 CR, 3 PR, 2 SD, and 3 PD by RECIST v1.1. † 1 patient had unknown HPV status and was not evaluable for response by RECIST v1.1.

Percentage Change From Baseline in Target Lesions

Epacadostat Plus Pembrolizumab

Phase 1/2 Metastatic or Recurrent SCCHN by Prior Lines of Treatment

Patients With 1–2 Prior Lines of Treatment: ORR=39%, DCR=65% by RECIST v1.1



CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease.

Of 38 efficacy-evaluable patients, data are shown for the 32 with ≥1 postbaseline scan that included assessment of target lesions. Six patients are not included in this figure: 2 patients were PD per new lesions (target lesions were not assessed); 2 patients had clinical progression and discontinued treatment prior to the first postbaseline scan; and 2 patients died before the first postbaseline scan.

* Overall response is PD (SD per target lesions, PD per new lesions). † Overall response is PR (CR per target lesions, non-CR/non-PD per nontarget lesions).

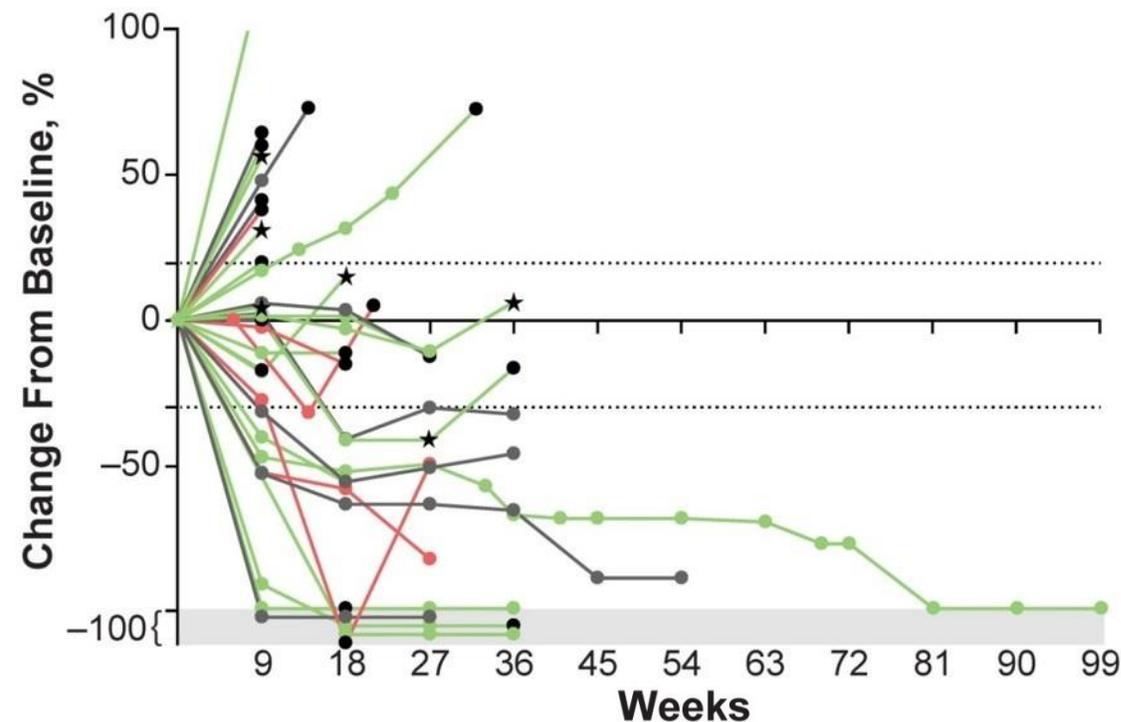
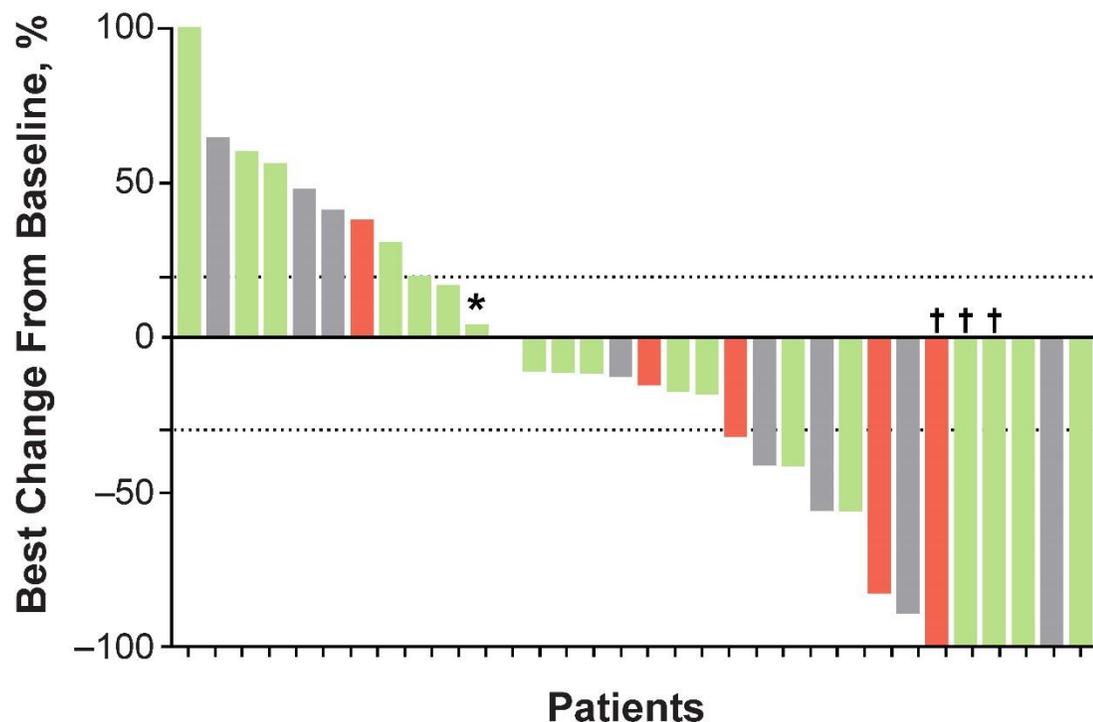
Percentage Change From Baseline in Target Lesions

Epacadostat Plus Pembrolizumab

Phase 1/2 Metastatic or Recurrent SCCHN by PD-L1 Expression

Responses Were Observed Regardless of PD-L1 Expression

■ PD-L1 Positive (CPS $\geq 1\%$) ■ PD-L1 Negative (CPS $< 1\%$) ■ PD-L1 Unknown ● Off Study Treatment ★ First Occurrence of New Lesion



CPS, combined positive score; CR, complete response; PD, progressive disease; PD-L1, programmed death ligand 1; PR, partial response; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease.

Of 38 efficacy-evaluable patients, data are shown for the 32 with ≥ 1 postbaseline scan that included assessment of target lesions. Six patients are not included in this figure: 2 patients were PD per new lesions (target lesions were not assessed); 2 patients had clinical progression and discontinued treatment prior to the first postbaseline scan; and 2 patients died before the first postbaseline scan.

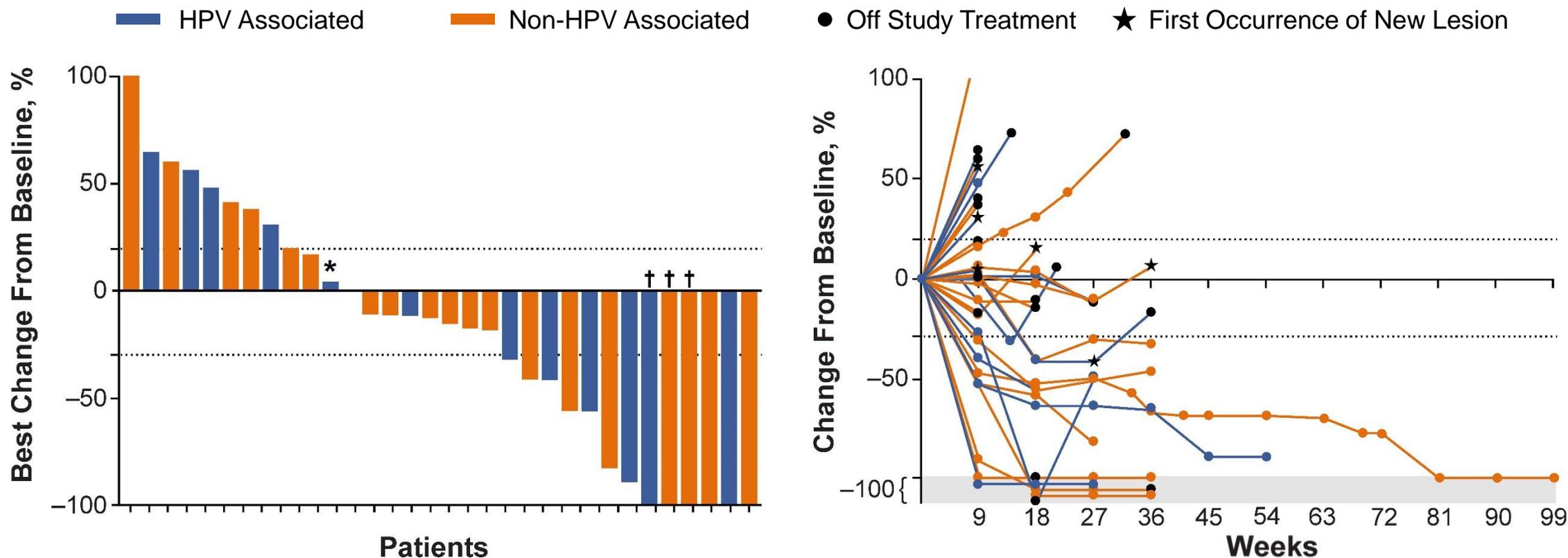
* Overall response is PD (SD per target lesions, PD per new lesions). † Overall response is PR (CR per target lesions, non-CR/non-PD per nontarget lesions).

Percentage Change From Baseline in Target Lesions

Epacadostat Plus Pembrolizumab

Phase 1/2 Metastatic or Recurrent SCCHN by HPV Association

Responses Were Observed in Both HPV and Non-HPV Associated Disease



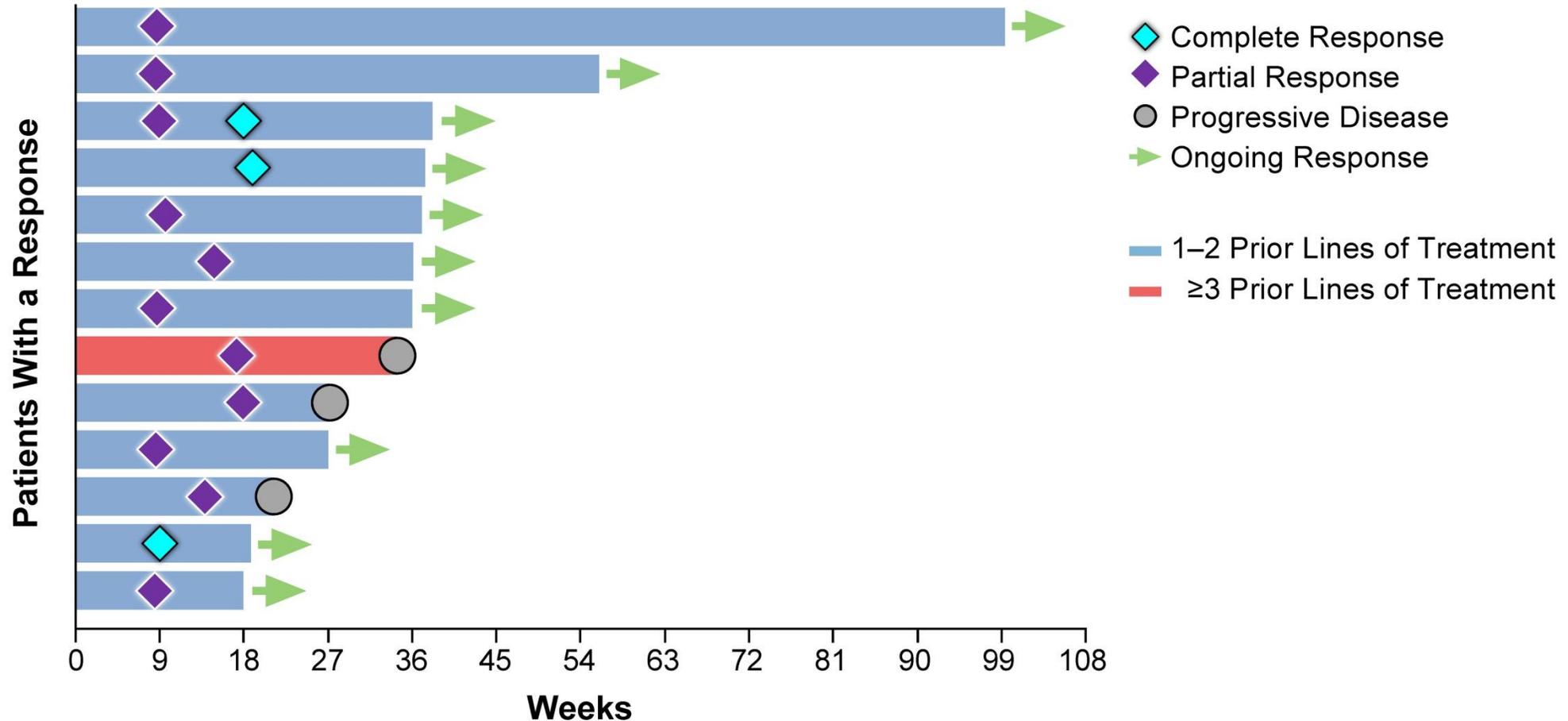
CR, complete response; HPV, human papillomavirus; PD, progressive disease; PR, partial response; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease. Of 38 efficacy-evaluable patients, data are shown for the 32 with ≥ 1 postbaseline scan that included assessment of target lesions. Six patients are not included in this figure: 2 patients were PD per new lesions (target lesions were not assessed); 2 patients had clinical progression and discontinued treatment prior to the first postbaseline scan; and 2 patients died before the first postbaseline scan. * Overall response is PD (SD per target lesions, PD per new lesions). † Overall response is PR (CR per target lesions, non-CR/non-PD per nontarget lesions).

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

Epacadostat Plus Pembrolizumab

Phase 1/2 Metastatic or Recurrent SCCHN

- 10/13 responses were ongoing; median (range) duration of response 18.4+ (7.1 to 90.3+) weeks



Treatment-Related AEs (≥5%)

Epacadostat Plus Pembrolizumab

Phase 1/2 Metastatic or Recurrent SCCHN

AE, n (%)	All Grade (N=38)	Grade 3/4* (N=38)
Total	24 (63)	7 (18)
Fatigue	12 (32)	1 (3)
Rash†	5 (13)	0
Diarrhea	4 (11)	2 (5)
Nausea	4 (11)	0
Blood iron decreased	3 (8)	0
Dizziness	3 (8)	0
Pruritus‡	3 (8)	0
Vomiting	3 (8)	0
Weight decreased	3 (8)	1 (3)
Amylase increased	2 (5)	2 (5)
Asthenia	2 (5)	0
Decreased appetite	2 (5)	1 (3)
Dehydration	2 (5)	1 (3)
Erythema	2 (5)	0
Hypothyroidism	2 (5)	0
Lipase increased	2 (5)	2 (5)
Pyrexia	2 (5)	0

- Treatment-related AEs led to dose interruptions in 7 patients (18%)
 - The most common were fatigue and dizziness (n=2 [5%] each)
- One patient had a dose reduction due to a treatment-related AE (pneumonitis)
- One patient discontinued treatment due to treatment-related AEs (asymptomatic grade 3 amylase increased and grade 3 lipase increased); these were manageable with supportive care
- There was 1 treatment-related death due to respiratory failure (secondary to aspiration pneumonia; pneumonitis could not be ruled out)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SCCHN, squamous cell carcinoma of the head and neck.

* Other grade 3/4 treatment-related AEs not included in the table: liver function test abnormal, facial pain, and respiratory failure (n=1 each). † Rash includes the following MedDRA preferred terms: rash, rash macular, and rash maculopapular. ‡ Pruritus includes the following MedDRA preferred term: pruritus generalized.

AEs of Special Interest

Epacadostat Plus Pembrolizumab

Phase 1/2 Metastatic or Recurrent SCCHN

AE, n (%)	All Grade (N=38)	Grade 3/4 (N=38)
Total	5 (13)	0
Hypothyroidism	3 (8)	0
Adrenal insufficiency	1 (3)	0
Pneumonitis	1 (3)	0

- AEs of special interest include AEs with an immune-related cause, regardless of attribution to study treatment by the investigator

Conclusions

Epacadostat Plus Pembrolizumab

- These phase 1/2 study results show that epacadostat plus pembrolizumab is active in patients with metastatic or recurrent SCCHN
 - In patients with 1–2 prior lines of treatment, the ORR was 39% (CR, 10%) and the DCR was 65% by RECIST v1.1
 - Responses were observed regardless of PD-L1 expression and HPV association
 - 10/13 responses were ongoing; median (range) duration of response was 18.4+ (7.1 to 90.3+) weeks
- Epacadostat plus pembrolizumab was generally well tolerated in patients with metastatic or recurrent SCCHN
 - 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 AEs, treatment discontinuation due to treatment-related AEs, and AEs 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 SCCHN patients was consistent with findings in patients with other tumor types (melanoma, NSCLC, RCC, and UC), supporting phase 3 investigation of this combination in SCCHN

CR, complete response; DCR, disease control rate; HPV, human papillomavirus; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-L1, programmed death ligand 1; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; SCCHN, squamous cell carcinoma of the head and neck; UC, urothelial carcinoma.

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. Bauml J, et al. *J Clin Oncol*. 2017;35(14):1542-1549. 3. Chow LQM, et al. *J Clin Oncol*. 2016;34(32):3838-3845.

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: <i>Lung Cancer—Non-Small Cell Metastatic</i> 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: <i>Genitourinary (Nonprostate) Cancer</i> 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: <i>Breast Cancer—Metastatic</i> 6/4/2017
Abstract #4503: Epacadostat plus pembrolizumab in patients with advanced urothelial carcinoma: Preliminary phase 1/2 results of ECHO-202/KEYNOTE-037	Oral Presentation: <i>Genitourinary (Nonprostate) Cancer</i> 6/5/2017
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: <i>Developmental Therapeutics—Immunotherapy</i> 6/5/2017

Epacadostat Clinical Development Program

STUDY		COMBINATION THERAPY	PHASE 1	PHASE 2	PHASE 3
Ongoing Studies					
Phase 3 Study in Unresectable or Metastatic Melanoma (ECHO 301)	NCT02752074	Pembrolizumab (anti-PD-1)			
Phase 1/2 Study in Selected Cancers (ECHO 202)	NCT02178722	Pembrolizumab (anti-PD-1)			
Phase 1/2 Study in Selected Advanced Solid Tumors (ECHO 203)	NCT02318277	Durvalumab (anti-PD-L1)			
Phase 1/2 Study in Selected Cancers (ECHO 204)	NCT02327078	Nivolumab (anti-PD-1)			
Phase 1/2 Study in Advanced or Metastatic Solid Tumors (ECHO 206)	NCT02959437	Pembrolizumab (anti-PD-1)			
Phase 1/2 Study in Advanced or Metastatic Solid Tumors (ECHO 207)	NCT03085914	Pembrolizumab and Nivolumab			
Phase 1 Study in Advanced Non-Small Cell Lung Cancer and Urothelial Carcinoma (ECHO 110)	NCT02298153	Atezolizumab (anti-PD-L1)			
Phase 1 Study in Advanced Solid Tumors	NCT02559492	Itacitinib (INCB039110, JAK1 inhibitor)*			
Planned Pivotal Programs (expected to begin in 2017)					
Non-Small Cell Lung Cancer (First-Line)		Pembrolizumab (anti-PD-1)			
Bladder Cancer (First- and Second- Line)		Pembrolizumab (anti-PD-1)			
Renal Cell Carcinoma (First-Line)		Pembrolizumab (anti-PD-1)			
Head and Neck Cancer (First-Line)		Pembrolizumab (anti-PD-1)			
Non-Small Cell Lung Cancer (First-Line)		Nivolumab (anti-PD-1)			
Head and Neck Cancer (First-Line)		Nivolumab (anti-PD-1)			

Anti-PD-1, anti-programmed death 1; anti-PD-L1, anti-programmed death ligand 1; JAK1, Janus associated kinase 1.

* Itacitinib (INCB039110; JAK1 inhibitor) is under development by Incyte.

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