

Epacadostat Plus Nivolumab in Patients With Advanced Solid Tumors: Preliminary Phase 1/2 Results of ECHO-204

Raymond P. Perez,¹ Matthew J. Riese,² **Karl D. Lewis**,³ Mansoor N. Saleh,⁴ Adil Daud,⁵ Jordan Berlin,⁶ James J. Lee,⁷ Sutapa Mukhopadhyay,⁸ Li Zhou,⁹ Gul Serbest,⁹ Omid Hamid¹⁰

¹University of Kansas Clinical Research Center, Fairway, KS; ²Medical College of Wisconsin, Milwaukee, WI; ³University of Colorado, Anschutz Medical Campus, Aurora, CO; ⁴UAB Comprehensive Cancer Center, Birmingham, AL; ⁵University of California, San Francisco, San Francisco, CA; ⁶Department of Medicine, Division of Hematology & Oncology, Vanderbilt University Medical Center, Nashville, TN; ⁷University of Pittsburgh School of Medicine, Pittsburgh, PA; ⁸Bristol-Myers Squibb, Princeton, NJ; ⁹Incyte Corporation, Wilmington, DE; ¹⁰The Angeles Clinic and Research Institute, Los Angeles, CA

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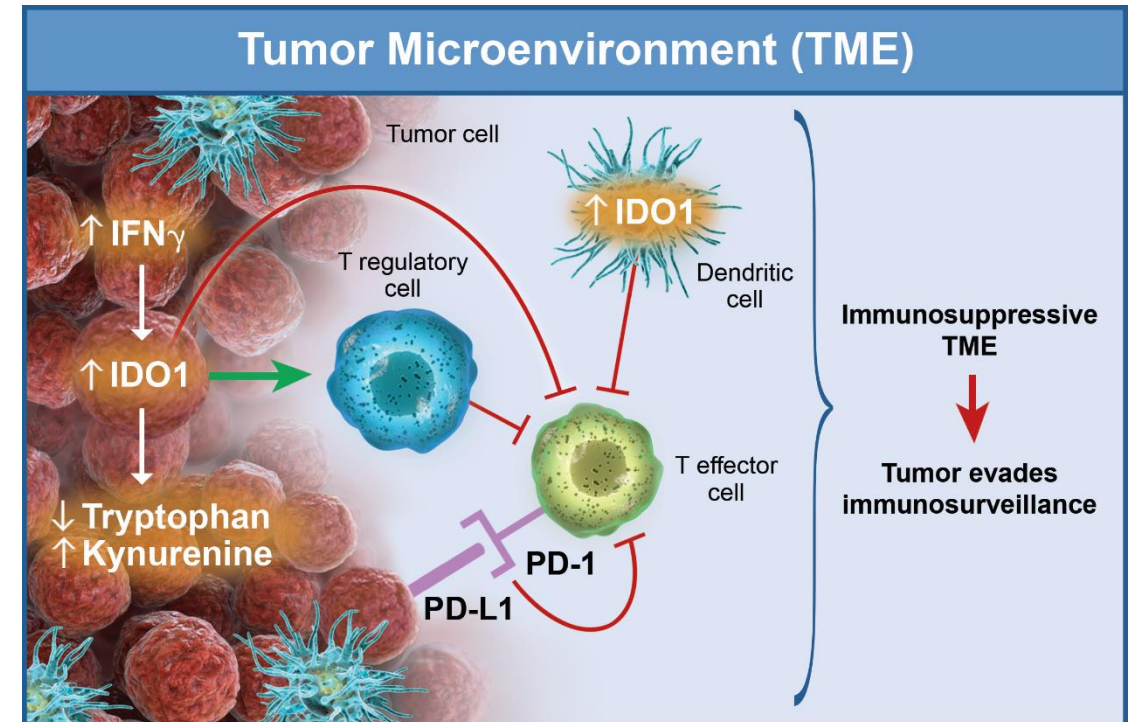
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IDO1 Enzyme and Epacadostat

- 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
- In cancer, depletion of tryptophan and production of kynurenine and other metabolites in the TME 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 TME²
- Combining epacadostat with an immune checkpoint inhibitor may improve patient outcomes



Objective

- To report preliminary safety, tolerability, and efficacy of epacadostat in combination with nivolumab in patients with advanced solid tumors in the phase 1/2 ECHO-204 study:
 - Phase 1/2 safety and tolerability results for the overall study population (all tumor types)
 - Phase 2 efficacy data for the combination of epacadostat and nivolumab in patients with recurrent or metastatic MEL, SCCHN, OC, or CRC
- Data cutoff: February 13, 2017

Study Design

Phase 1	Phase 2	Patients (All Tumor Types)
Dose Escalation	Open-Label Cohort Expansion	
<p>Epacadostat PO 25, 50, 100, or 300 mg BID + Nivolumab IV 3 mg/kg Q2W</p>	<p>Epacadostat 100 mg or 300 mg BID + Nivolumab 240 mg IV Q2W</p> <p><u>Tumor cohorts</u></p> <ul style="list-style-type: none"> MEL SCCHN OC CRC NSCLC GBM Lymphoma 	<ul style="list-style-type: none"> ≥18 years of age, with recurrent or metastatic advanced cancer ECOG PS 0 or 1 ALP, ALT, AST ≤2.5 x ULN No previous IDO inhibitor or ICI treatment, except anti-CTLA4 as first-line therapy for metastatic MEL Phase 2 <ul style="list-style-type: none"> MEL: ≤1 prior treatment for metastatic disease SCCHN: ≤2 prior treatments for advanced disease OC: epithelial OC with prior treatment (platinum-taxane based therapy required) CRC: ≥1 prior treatment (including VEGF) NSCLC: ≤1 prior treatment for advanced disease GBM: 1 prior treatment w/ radiotherapy and temozolomide and documented relapse/recurrence of GBM Lymphoma: relapsed or refractory DLBCL
<ul style="list-style-type: none"> Phase 1 MTD not exceeded RP2D: 100 and 300 mg BID Phase 2 cohorts enrolled at 100 mg BID in parallel to further 300 mg BID evaluation in phase 1 Phase 2 cohorts completed enrollment with 300 mg BID once RP2D established 		

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CRC, colorectal carcinoma; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBM, glioblastoma; ICI, immune checkpoint inhibitor; IDO, indoleamine 2,3-dioxygenase; IV, intravenous; MEL, melanoma; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PO, oral; Q2W, every 2 weeks; RP2D, recommended phase 2 dosing; SCCHN, squamous cell carcinoma of the head and neck; ULN, upper limit of normal; VEGF, vascular endothelial growth factor.

Study Assessments

- **Data cutoff:** February 13, 2017
- **Safety and tolerability** (Phase 1/2; overall study population)
 - AEs were assessed by CTCAE v4.0
 - irAE terms derived from the irAE term list used in the nivolumab clinical development program
 - Safety-evaluable: ≥ 1 dose of study treatment as of data cutoff
- **Efficacy** (Phase 2 only; MEL, SCCHN, OC, CRC tumor cohorts)
 - Dual primary endpoints: ORR and landmark PFS (6 months)
 - Response was assessed every 8 weeks per RECIST v1.1 and a modification of RECIST v1.1 (mRECIST) to account for pseudoprogression*
 - Efficacy-evaluable: ≥ 1 postbaseline scan, or discontinuation, or death as of data cutoff
- **Biomarker analysis**
 - PD-L1 expression assessed by Dako 28-8 assay
 - PD-L1 positivity: $\geq 1\%$ (≥ 1 staining tumor cell per 100 tumor cells)

AE, adverse event; CRC, colorectal carcinoma; CTCAE, Common Terminology Criteria for Adverse Events; irAE, immune-related AEs; MEL, melanoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; OC, ovarian cancer; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival; SCCHN, squamous cell carcinoma of the head and neck. * If imaging showed progressive disease, tumor assessment was repeated ≥ 4 weeks later to confirm progressive disease with the option of continuing treatment for clinically stable subjects.

Phase 1 Treatment-Related AEs* (≥15%; All Tumor Cohorts)

Epacadostat in combination with nivolumab

AE, n (%)	E 25 mg BID (n=3)		E 50 mg BID (n=6)		E 100 mg BID (n=14)		E 300 mg BID (n=13)	
	All Grade	Grade 3/4 [†]	All Grade	Grade 3/4 [†]	All Grade	Grade 3/4 [†]	All Grade	Grade 3/4 [†]
Total	3 (100)	0	3 (50)	1 (17)	11 (79)	1 (7)	9 (69)	5 (39)
Rash [‡]	0	0	0	0	3 (21)	0	5 (39)	2 (15)
Fatigue	2 (67)	0	1 (17)	1 (17)	2 (14)	0	2 (15)	1 (8)
Pruritus	2 (67)	0	0	0	1 (7)	0	3 (23)	0

- No DLT during 42-day observation period
- Manageable toxicity up to the 300-mg BID maximum epacadostat dose tested
- E 100 mg BID and 300 mg BID doses + nivolumab 240 mg IV Q2W dosing were selected to test in phase 2

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; DLT, dose limiting toxicity; E, epacadostat; IV, intravenous; Q2W, every 2 weeks; MedDRA, Medical Dictionary for Regulatory Activities.

* Related to epacadostat or nivolumab.

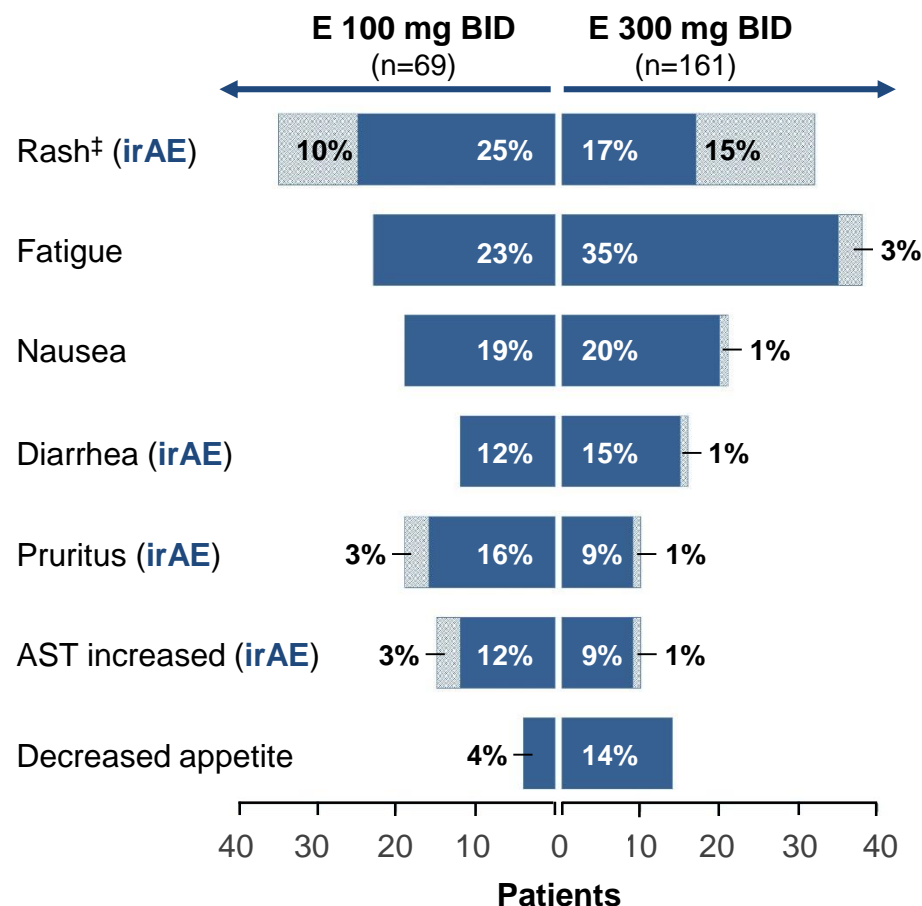
[†] Other grade 3/4 treatment-related AEs in the total patient population (not shown in the table; n=1 each) include ALT increase, amylase increase, AST increase, asthenia, hypopituitarism, hyponatraemia, lipase increase, myoclonus, pancreatic insufficiency, tremor.

[‡] Rash includes the following MedDRA preferred terms: rash, rash generalized, rash maculopapular.

Phase 2 Treatment-Related AEs* ($\geq 10\%$; All Tumor Cohorts)

Epacadostat 100 or 300 mg BID in combination with nivolumab 240 mg IV Q2W

■ Grade 1/2 Treatment-Related AE ■ Grade 3/4 Treatment-Related AE[†]



- Overall frequency of all-grade / grade 3/4 treatment-related AEs*:
 - 83% / 25%, E 100 mg
 - 73% / 27%, E 300 mg
- Frequency of dose interruption due to any-grade treatment-related AEs*:
 - 26% (n=18), E 100 mg
 - 30% (n=48), E 300 mg
- Frequency of dose reduction due to any-grade treatment-related AEs*:
 - 4% (n=3), E 100 mg
 - 5% (n=8), E 300 mg
- Frequency of discontinuation due to any grade treatment-related AEs*:
 - 6% (n=4), E 100 mg
 - 12% (n=20), E 300 mg
- There were no treatment-related deaths

AE, adverse event; AST, aspartate aminotransferase; BID, twice daily; E, epacadostat; irAE, immune-related AE. * Related to epacadostat or nivolumab. [†] Grade 3/4 treatment-related AEs occurring in >1% of all patients (not shown in figure) include decreased lymphocyte count (n=5), hyponatremia (n=4), abnormal liver function test (n=3), ALT increased (n=3), and lipase increased (n=3). [‡] Rash includes the following MedDRA preferred terms: dermatitis, erythema multiforme, rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic.

Treatment-Naive MEL: Baseline Demographics and Disease Characteristics (Phase 2)

Variable	E 100 mg BID (n=6)	E 300 mg BID (n=34)
Median (range) age, y	66 (62–73)	63 (30–89)
Men, n (%)	4 (67)	26 (76)
Race, n (%)		
White	6 (100)	30 (88)
Black/African American	0	0
Asian	0	0
Other	0	4 (12)
ECOG PS, n (%)		
0	4 (67)	28 (82)
1	2 (33)	6 (18)
LDH level, n (%)		
Normal	3 (50)	25 (74)
Elevated	3 (50)	9 (26)
M1c disease, n (%)	3 (50)	10 (29)

BID, twice daily; E, epacadostat; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; M1c, distant metastases; MEL, melanoma.
Note: Ocular MEL was an exclusion criterion.

Treatment-Naive MEL: Best Objective Response

Epacadostat 100 or 300 mg BID in combination with nivolumab 240 mg IV Q2W (phase 2; mRECIST)

Patients, n (%)	Total (N=40)	Epacadostat Dose		PD-L1 Expression*	
		100 mg BID (n=6)	300 mg BID (n=34)	Positive† (n=7)	Negative (n=7)
ORR (CR+PR)	25 (63)	6 (100)	19 (56)	5 (71)	2 (29)
CR	2 (5)	0	2 (6)	1 (14)	0
PR	23 (58)	6 (100)	17 (50)	4 (57)	2 (29)
SD	10 (25)	0	10 (29)	2 (29)	3 (43)
DCR (CR+PR+SD)	35 (88)	6 (100)	29 (85)	7 (100)	5 (71)
PD	4 (10)	0	4 (12)	0	1 (14)
Not Assessed	1 (3)	0	1 (3)	0	1 (14)

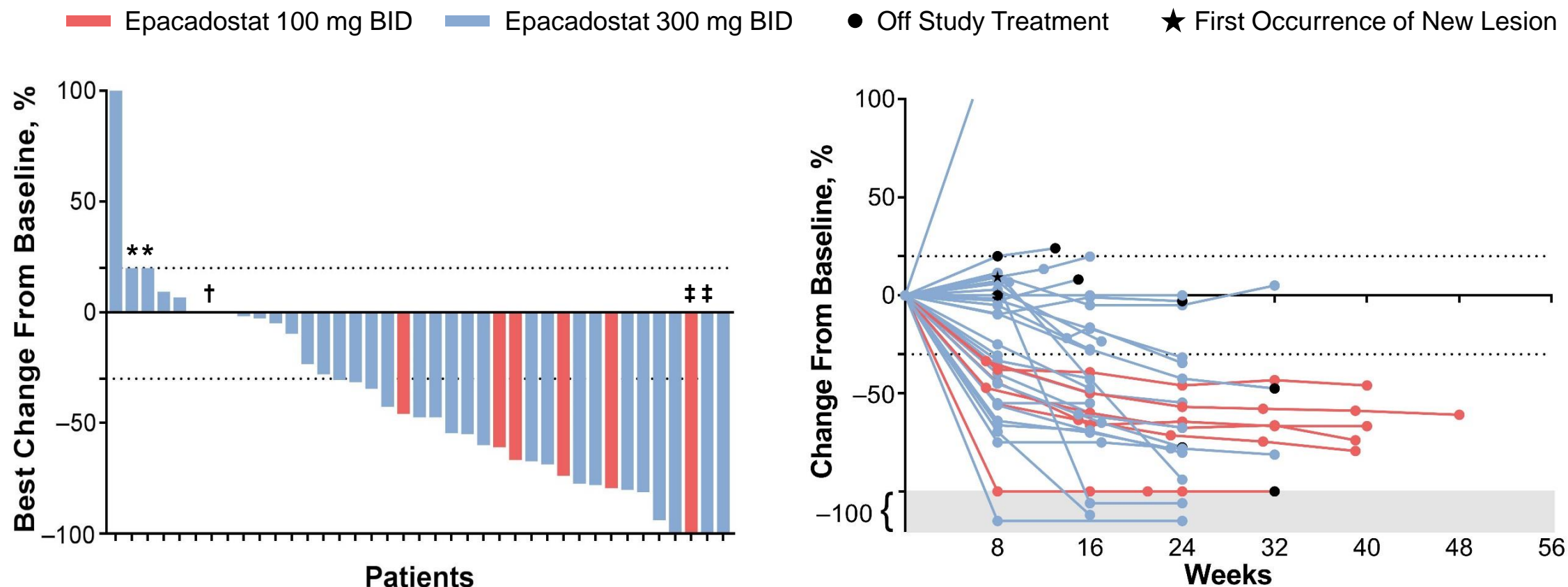
- ORR is the same by mRECIST and RECIST v1.1 criteria
- MEL patients with prior therapy for advanced disease (n=10): 20% ORR (2 PR); 70% DCR (5 SD)

BID, twice daily; CR, complete response; DCR, disease control rate; MEL, melanoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death ligand-1; PR, partial response; SD, stable disease at any time point regardless of confirmation. Not Assessed: patient did not have post-baseline response data and was already off study. * 26 patients with unknown PD-L1 status: 1 CR, 17 PR, 5 SD, 3 PD. † PD-L1 positive = ≥1% (≥1 staining tumor cell per 100 tumor cells; Dako 28-8 assay).

Treatment-Naive MEL: Percentage Change From Baseline in Target Lesions

Epacadostat 100 or 300 mg BID in combination with nivolumab 240 mg IV Q2W (phase 2; mRECIST)

Responses Were Observed With Epacadostat 100-mg and 300-mg Dosing



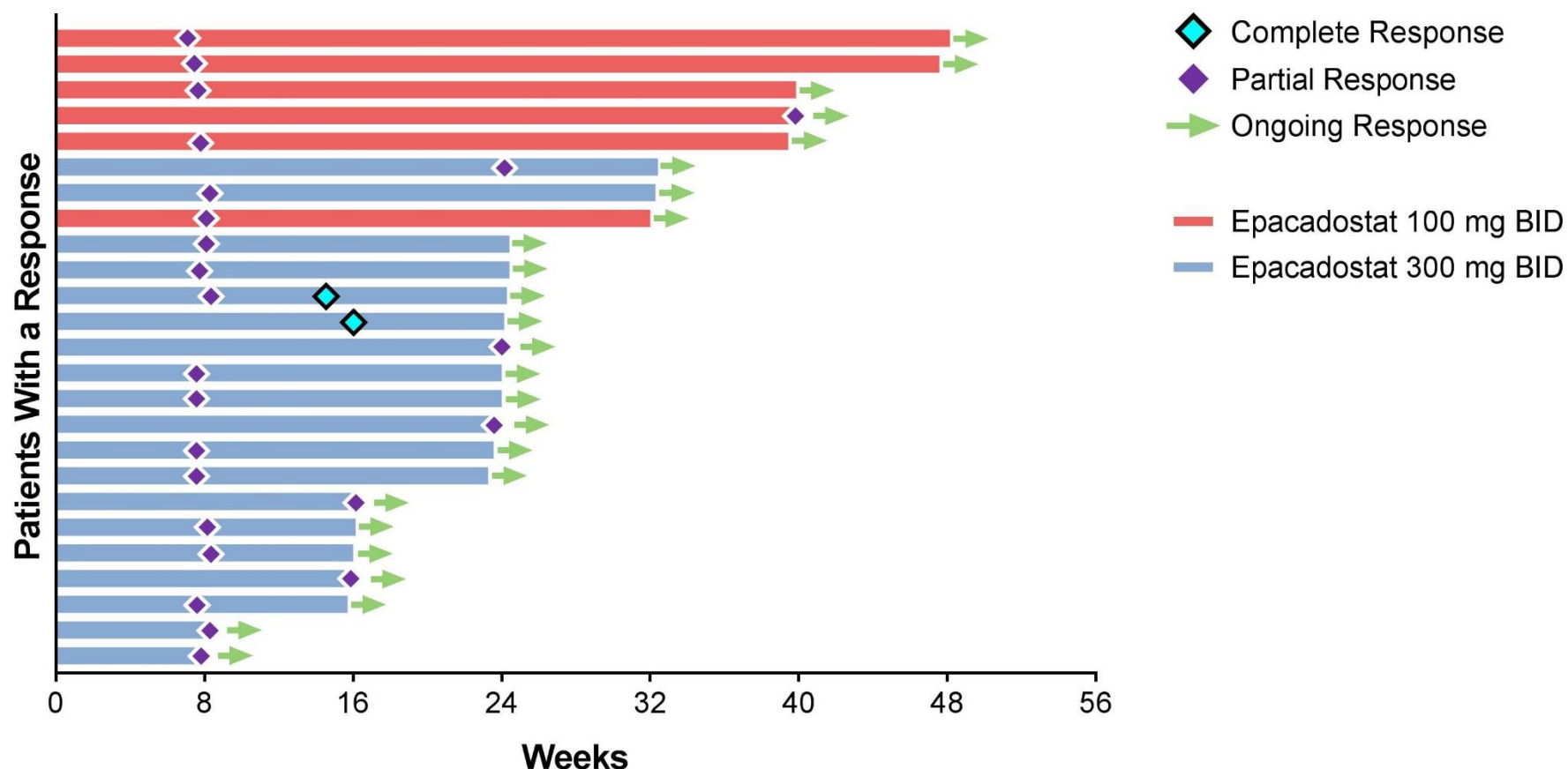
BID, twice daily; MEL, melanoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PD, progressive disease; PR, partial response.

Note: Of the 40 evaluable patients, data are shown for the 39 patients with postbaseline scans that included assessment of target lesions; the remaining 1 patient had no postbaseline scan. * Objective response is PD per target lesion increase. † Objective response is PD per new lesion. ‡ Objective response is PR (non-target lesions still present).

Treatment-Naive MEL*: Duration of Response

Epacadostat 100 or 300 mg BID in combination with nivolumab 240 mg IV Q2W (phase 2; mRECIST)

- All responses ongoing; median (range) duration of response 16+ (<1+ to 41+) weeks



BID, twice daily; MEL, melanoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

*Phase 2 MEL cohort began at 100 mg BID and completed at 300 mg BID, as these doses were determined to be safe in phase 1.

SCCHN: Baseline Demographics and Disease Characteristics (Phase 2)

Variable	E 100 mg BID (n=7)	E 300 mg BID (n=24)
Median (range) age, y	58 (43–63)	66 (34–84)
Men, n (%)	6 (86)	18 (75)
Race, n (%)		
White	5 (71)	22 (92)
Black/African American	1 (14)	1 (4)
Asian	0	0
Other	1 (14)	1 (4)
Location of primary tumor		
Oropharynx	3 (43)	8 (33)
Larynx	1 (14)	6 (25)
Oral cavity	0	4 (17)
Supraglottic	0	3 (13)
Hypopharynx	2 (29)	0
Other	1 (14)	3 (13)
HPV status*		
HPV associated	3 (43)	7 (29)
Non-HPV associated	4 (57)	17 (71)

Variable	E 100 mg BID (n=7)	E 300 mg BID (n=24)
Prior smoking history, n (%)	7 (100)	20 (83)
Prior radiation therapy, n (%)	6 (86)	21 (88)
Prior therapy, n (%)		
Cisplatin	4 (57)	14 (58)
Carboplatin	5 (71)	13 (54)
Cetuximab	4 (57)	13 (54)
Number of prior lines of treatment for advanced disease, n (%)		
0–1	5 (71)	21 (88)
≥2	2 (29)	3 (13)
PD-L1 expression, n (%)		
Positive (≥1%)	2 (29)	8 (33)
Negative (<1%)	1 (14)	7 (29)
Unknown [†]	4 (57)	9 (38)

BID, twice daily; E, epacadostat; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papilloma virus; PD-L1, programmed death ligand-1; SCCHN, squamous cell carcinoma of the head and neck. * 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.

SCCHN: Best Objective Response

Epacadostat 100 or 300 mg BID in combination with nivolumab 240 mg IV Q2W (phase 2; mRECIST)

Patients, n (%)	Total (N=31)	Epacadostat Dose		PD-L1 Expression*		HPV Status†	
		100 mg BID (n=7)	300 mg BID (n=24)	PD-L1 Positive† (n=10)	PD-L1 Negative (n=8)	HPV Associated (n=10)	Non-HPV Associated (n=21)
ORR (CR+PR)	7 (23)	1 (14)	6 (25)	3 (30)	1 (13)	3 (30)	4 (19)
CR	1 (3)	0	1 (4)	0	1 (13)	0	1 (5)
PR	6 (19)	1 (14)	5 (21)	3 (30)	0	3 (30)	3 (14)
SD	12 (39)	1 (14)	11 (46)	4 (40)	5 (63)	3 (30)	9 (43)
DCR (CR+PR+SD)	19 (61)	2 (29)	17 (71)	7 (70)	6 (75)	6 (60)	13 (62)
PD	8 (26)	4 (57)	4 (17)	1 (10)	1 (13)	4 (40)	4 (19)
Not Assessed	4 (13)	1 (14)	3 (13)	2 (20)	1 (13)	0	4 (19)

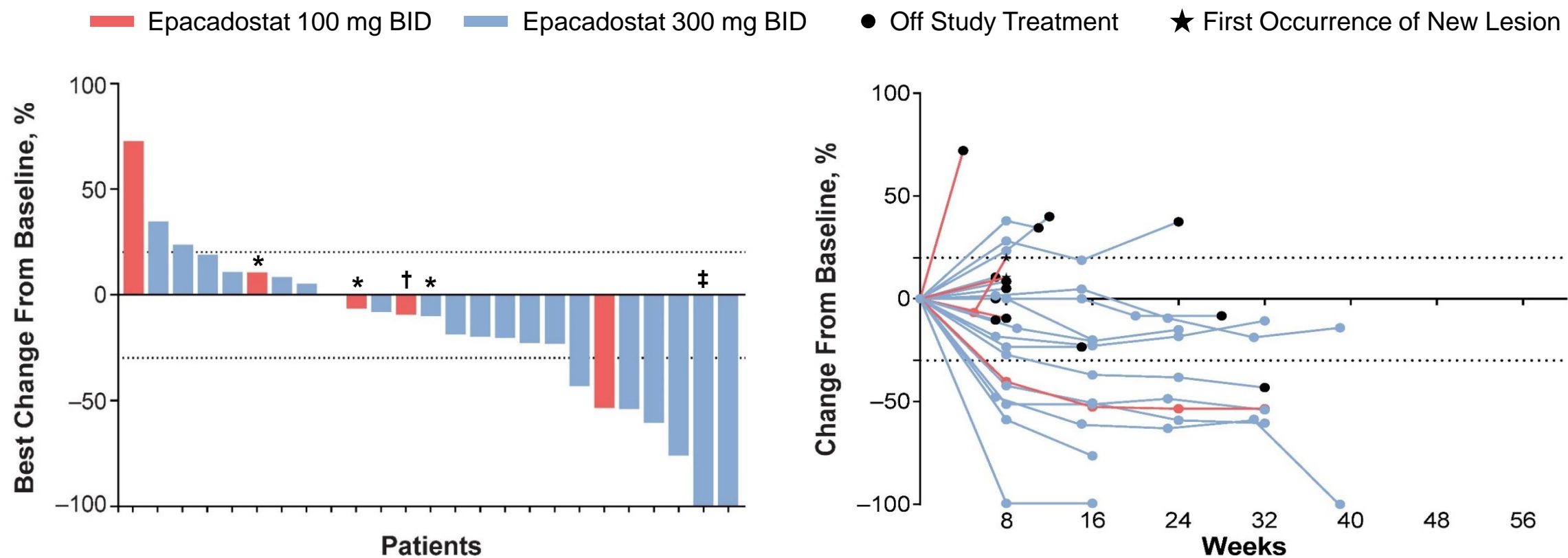
- ORR is the same by mRECIST and RECIST v1.1 criteria

BID, twice daily; CR, complete response; DCR, disease control rate; HPV, human papilloma virus; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death ligand-1; PR, partial response; mRECIST, modified Response Evaluation Criteria in Solid Tumors; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease at any time point regardless of confirmation. Note: Not Assessed: patients did not have any post-baseline response data and are already off study. Phase 1: no patient received epacadostat 100 mg BID; 4 patients received epacadostat 300 mg BID (1 CR, 2 SD, 1 not assessed [off study]). * Of 13 patients with unknown PD-L1 status: 3 PR, 3 SD, 6 PD, and 1 not assessed by mRECIST. † PD-L1 positive = $\geq 1\%$ (≥ 1 staining tumor cell per 100 tumor cells; Dako 28-8 assay). ‡ 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.

SCCHN: Percentage Change From Baseline in Target Lesions

Epacadostat 100 or 300 mg BID in combination with nivolumab 240 mg IV Q2W (phase 2; mRECIST)

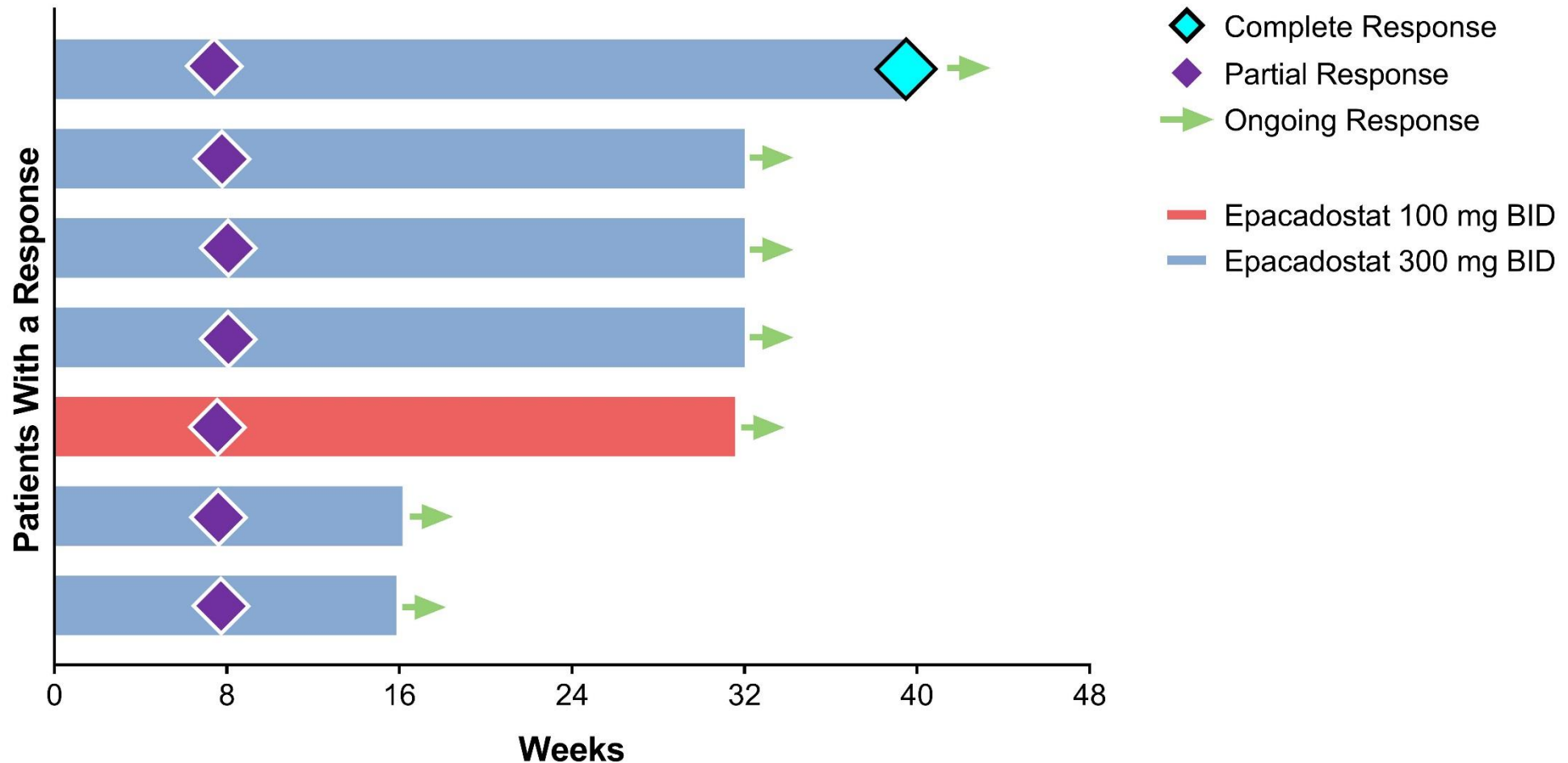
Responses Were Observed With Epacadostat 100-mg and 300-mg Dosing



SCCHN: Duration of Response

Epacadostat 100 or 300 mg BID in combination with nivolumab 240 mg IV Q2W (phase 2; mRECIST)

- All responses ongoing; median (range) duration of response 24+ (8+ to 32+) weeks



OC and CRC Efficacy

Epacadostat 100 or 300 mg BID in combination with nivolumab 240 mg IV Q2W (phase 2; mRECIST)

OC

- 29 efficacy-evaluable patients
 - E 100 mg BID, n=18, E 300 mg BID, n=11
 - Prior treatment: 59% with ≥ 2 prior lines of treatment for advanced disease
- All patients (n=29): 14% ORR (1 CR, 3 PR); 31% DCR (5 SD)
- *BRCA1* or *BRCA2* mutation (n=7): 14% ORR (1 PR); 29% DCR (1 SD)
- 1 CR (treatment-naive for advanced disease, *BRCA*-, PD-L1+)

CRC

- 26 efficacy-evaluable patients
 - E 100 mg BID only
 - Prior treatment: 77% with ≥ 2 prior lines of treatment for advanced disease
- MSI CRC (n=4): 25% ORR and DCR (1 PR)
- MSS CRC (n=18): 0% ORR and 33% DCR (6 SD)

Conclusions

- ECHO-204 study results show that epacadostat (100 or 300 mg BID) plus nivolumab (240 mg Q2W) was generally well tolerated among patients with select advanced solid tumors
 - Treatment-related, grade 3 rash rate was higher with epacadostat 300 mg (15%) vs 100 mg (10%) BID, as was the rate of treatment-related AEs leading to discontinuation (12% vs 6%)
- Epacadostat plus nivolumab was active in phase 2 MEL and SCCHN cohorts
 - In treatment-naïve MEL, ORR was 63% (CR, 5%) and DCR was 88% by mRECIST
 - In SCCHN, ORR was 23% (CR, 3%) and DCR was 61% by mRECIST
 - Response was observed regardless of PD-L1 expression and HPV status
 - All responses were ongoing at data cutoff
- Epacadostat plus nivolumab did not demonstrate an efficacy signal in the unselected populations of refractory OC and CRC patients
- These preliminary safety and efficacy results support further investigation of nivolumab and epacadostat in treatment-naïve patients with MEL and in patients with SCCHN

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