

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

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Abstract # 3003

Session: Developmental Therapeutics—Immunotherapy

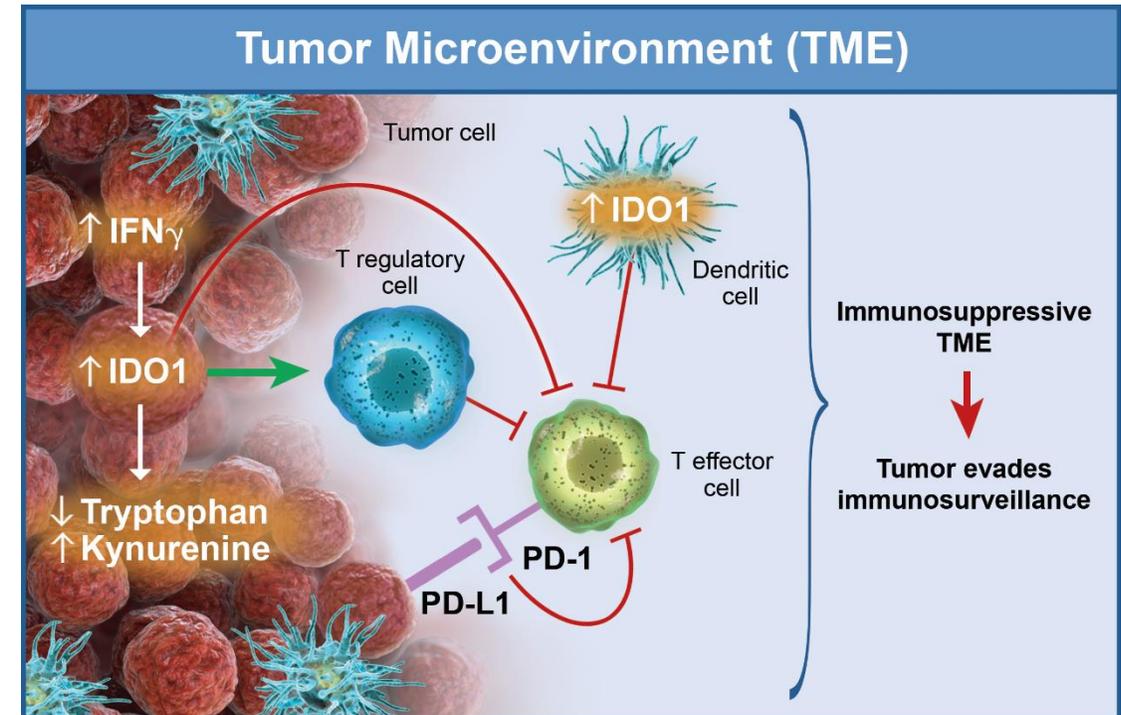
Presented at the ASCO Annual Meeting 2017

Chicago, IL

June 2–6, 2017

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



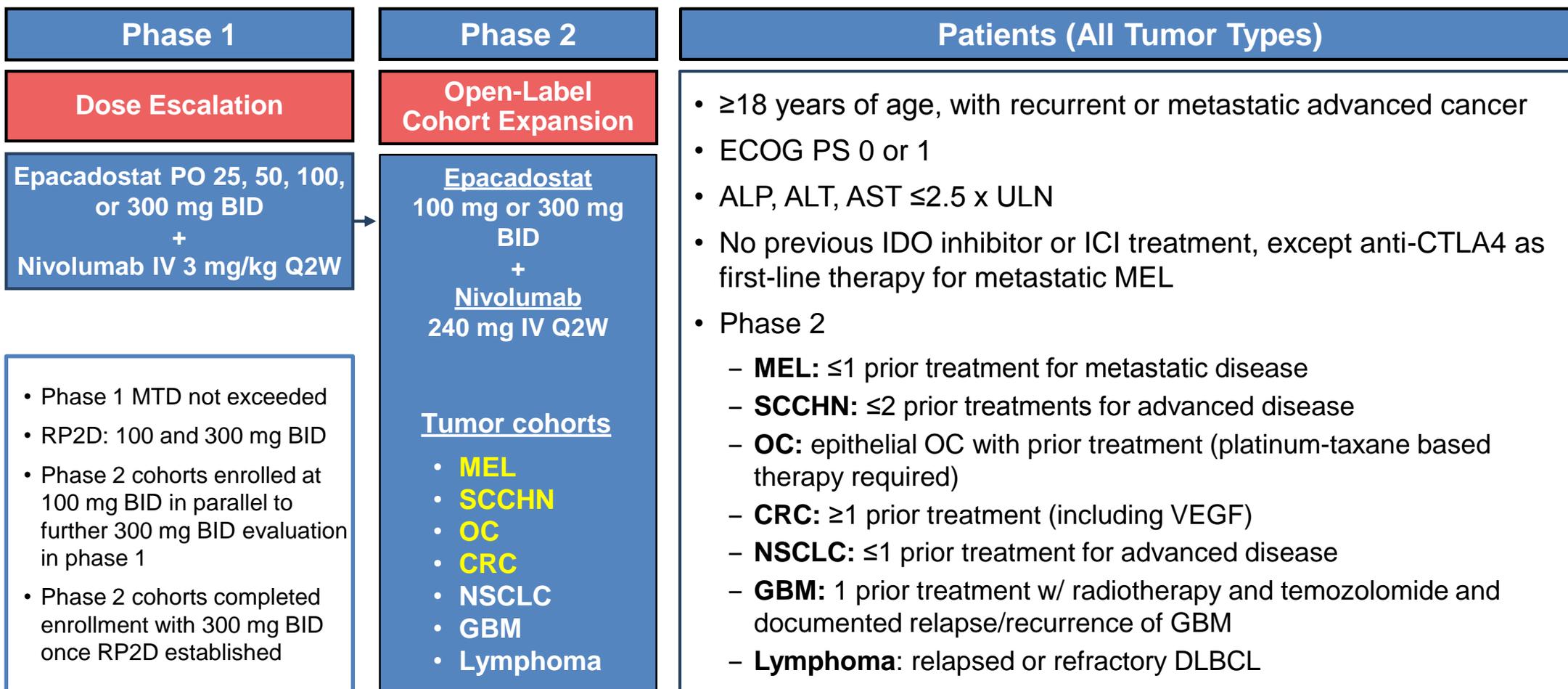
IDO1, indoleamine 2,3 dioxygenase 1; IFN γ , interferon gamma; PD-1, programmed death 1; PD-L1, programmed death ligand-1.

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

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



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)

Phase 1 Treatment-Related AEs* ($\geq 15\%$; 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.

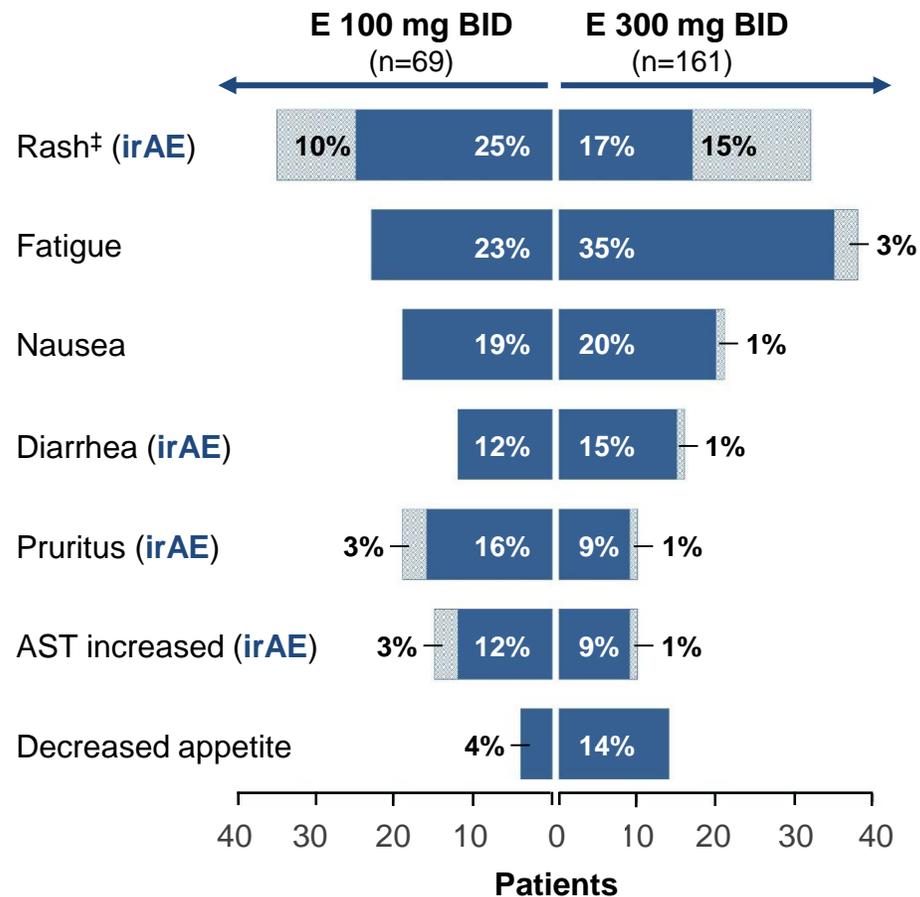
[†] Other grade 3/4 treatment-related AEs in the total patient population (not shown in the table; n=1 each) include ALT increase, amylase increase, AST increase, asthenia, hypopituitarism, hyponatraemia, lipase increase, myoclonus, pancreatic insufficiency, tremor.

[‡] 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)

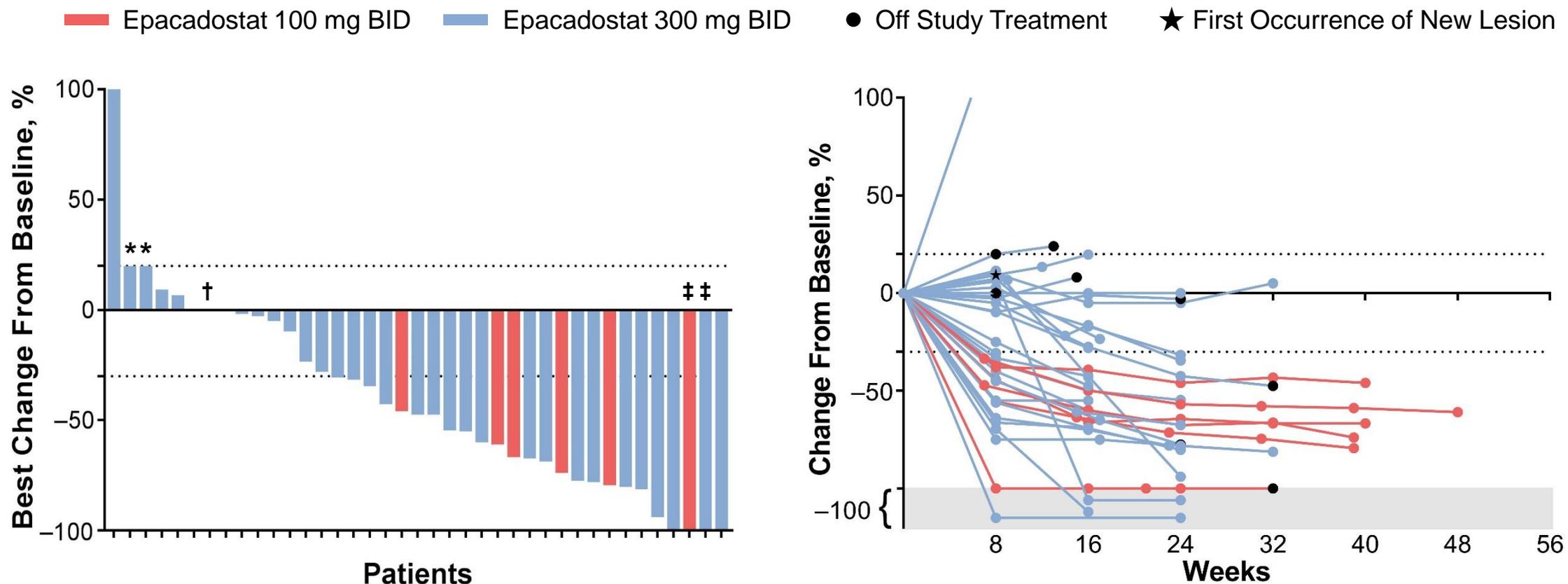
- ORR is the same by mRECIST and RECIST v1.1 criteria
- MEL patients with prior therapy for advanced disease (n=10): 20% ORR (2 PR); 70% DCR (5 SD)

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



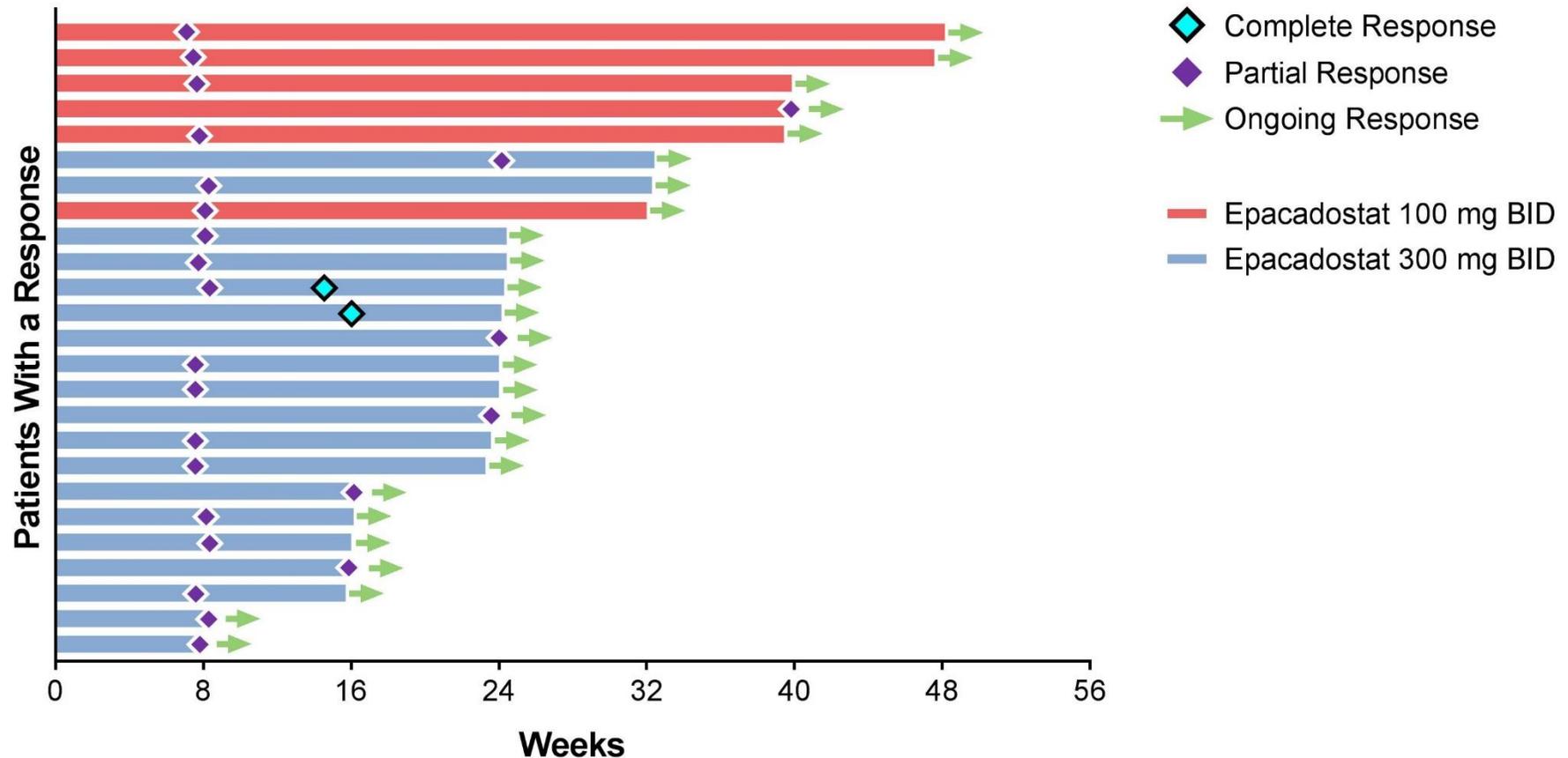
BID, twice daily; MEL, melanoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PD, progressive disease; PR, partial response.

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)

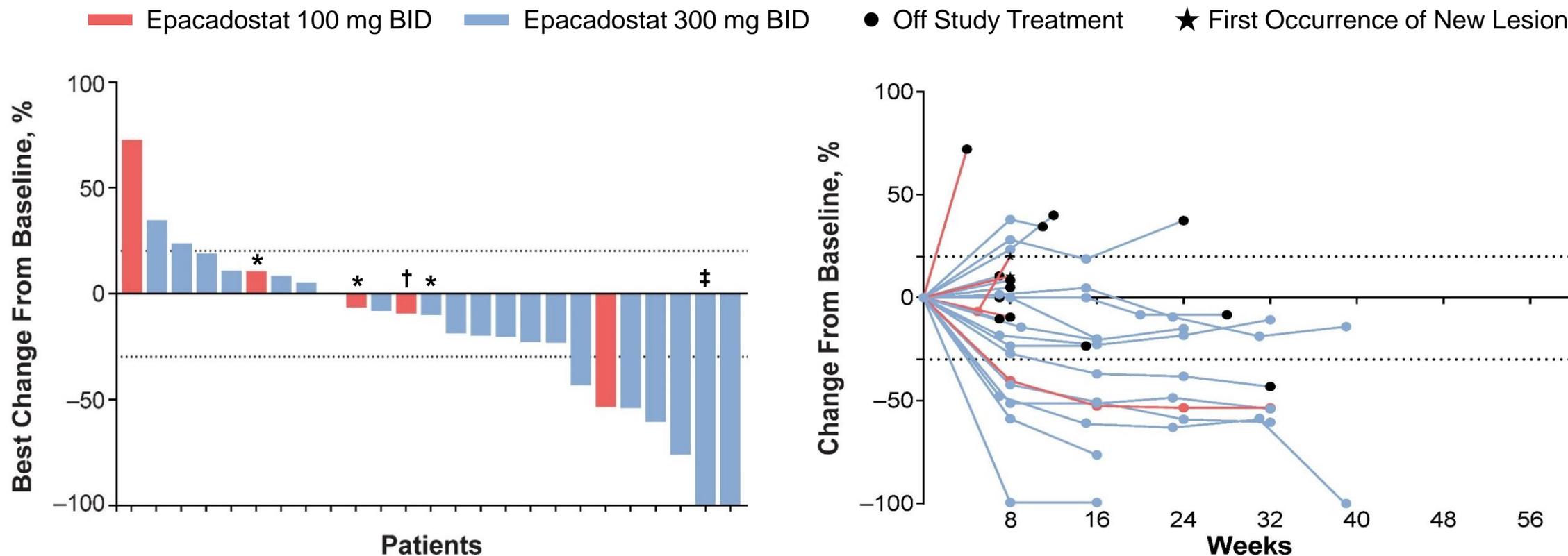
- ORR is the same by mRECIST and RECIST v1.1 criteria

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 = ≥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

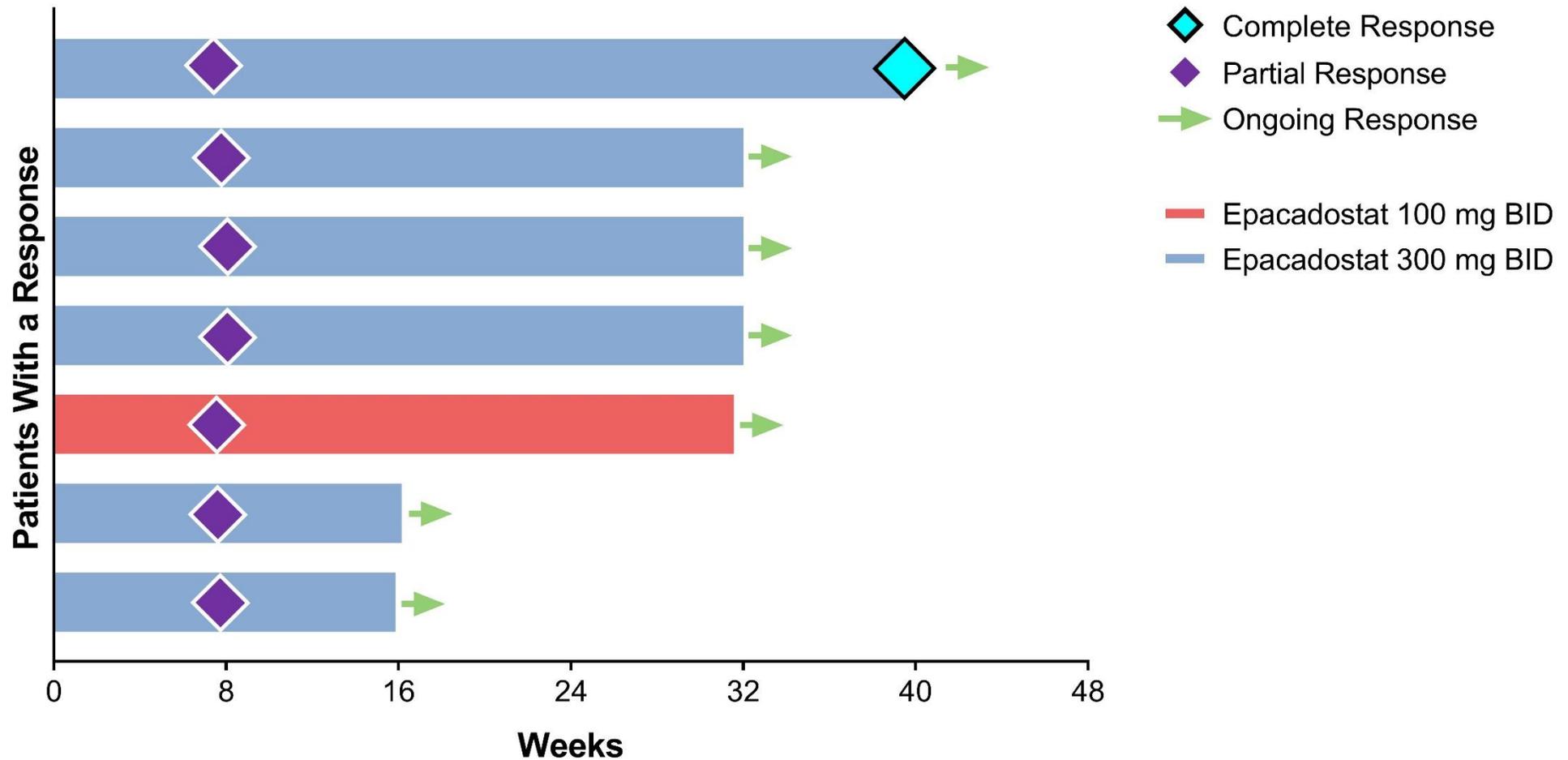


BID, twice daily; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PD, progressive disease; PR, partial response; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease at any time point regardless of confirmation. Of the 31 evaluable patients, data are shown for the 25 patients with postbaseline scans that included assessment of target lesions; the 6 patients not shown had no postbaseline scan assessment. * Objective response is PD per new lesion or non-target lesions. † Objective response is PD per investigator assessment at data cutoff; target lesions did not meet criteria for PD but rather SD. ‡ Objective response is PR (non-target lesions still present).

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-naive 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-naive patients with MEL and in patients with SCCHN

Acknowledgments

Thank you to the patients and their families, the investigators, and the site personnel who participated in this study

Other acknowledgements

- Study sponsored by Incyte Corporation (Wilmington, DE) in collaboration with Bristol-Myers Squibb (Princeton, NJ)
- Medical writing assistance provided by Regina Burris of Complete Healthcare Communications, LLC (funded by Incyte)