

Epacadostat Plus Durvalumab in Patients With Advanced Solid Tumors: Preliminary Results of the Ongoing, Open-Label, Phase 1/2 ECHO-203 Study

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Abstract #8992

Presented at the AACR Annual Meeting 2018

Chicago, IL

April 14-18, 2018

Disclosure Information

American Association for Cancer Research Annual Meeting, April 14–18, 2018
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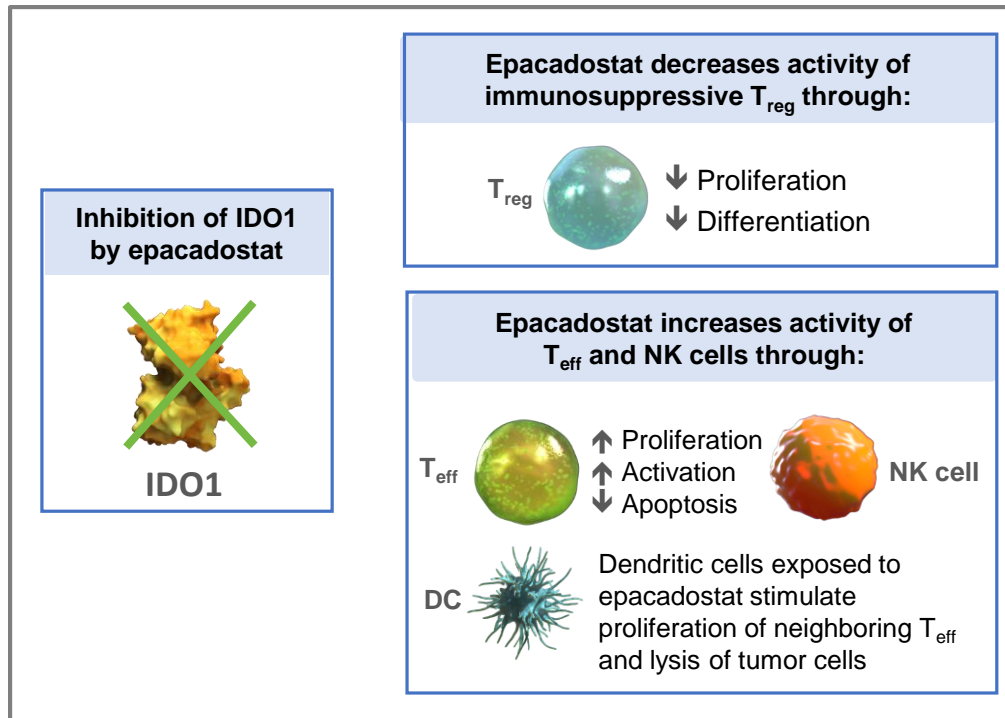
I have the following financial relationships to disclose:

- **Grant/research support from:** National Cancer Institute, EMD Serono, MedImmune, Healios Oncology Nutrition, Atterocor, Amplimmune, ARMO BioSciences, Karyopharm Therapeutics, Incyte, Novartis, Regeneron, Merck, Bristol-Myers Squibb
- **Advisory board member for:** CytomX and Novartis
- **Travel and accommodation expenses from:** ARMO BioSciences

I will discuss investigational use in my presentation

Introduction: Epacadostat and ECHO-203

- IDO1, an intracellular enzyme that catalyzes the first and rate-limiting step of tryptophan degradation in the kynurenine pathway, is a potential therapeutic target¹



- Epacadostat is a potent and highly selective IDO1 enzyme inhibitor²
- Phase 1 and 2 data suggest that epacadostat plus PD-1 inhibitors is generally well tolerated and may be active in multiple solid tumors³⁻⁷
- Combining epacadostat with durvalumab, an anti-PD-L1 antibody,⁸ may improve patient outcomes
- ECHO-203 (NCT02318277) is an ongoing, phase 1/2 study evaluating the safety, tolerability, and efficacy of epacadostat in combination with durvalumab across multiple tumor types

DC, dendritic cell; IDO1, indoleamine 2,3-dioxygenase 1; NK, natural killer; PD-1/PD-L1, programmed death protein 1/programmed death ligand 1; T_{eff}, effector T cell; T_{reg}, regulatory T cell.

1. Moon YW, et al. *J Immunother Cancer*. 2015;3:51. 2. Liu X, et al. *Blood*. 2010;115(17):3520-3530. 3. Gangadhar TC, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2017; Chicago, IL [abstract 9014]. 4. Lara PN, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2017; Chicago, IL [abstract 4515]. 5. Smith DC, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2017; Chicago, IL [abstract 4503]. 6. Perez RP, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2017; Chicago, IL [abstract 3003]. 7. Hamid O, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2017; Chicago, IL [abstract 6010].

8. Imfinzi® (durvalumab) Full Prescribing Information. AstraZeneca Pharmaceuticals LP. Wilmington, DE. February 2018.

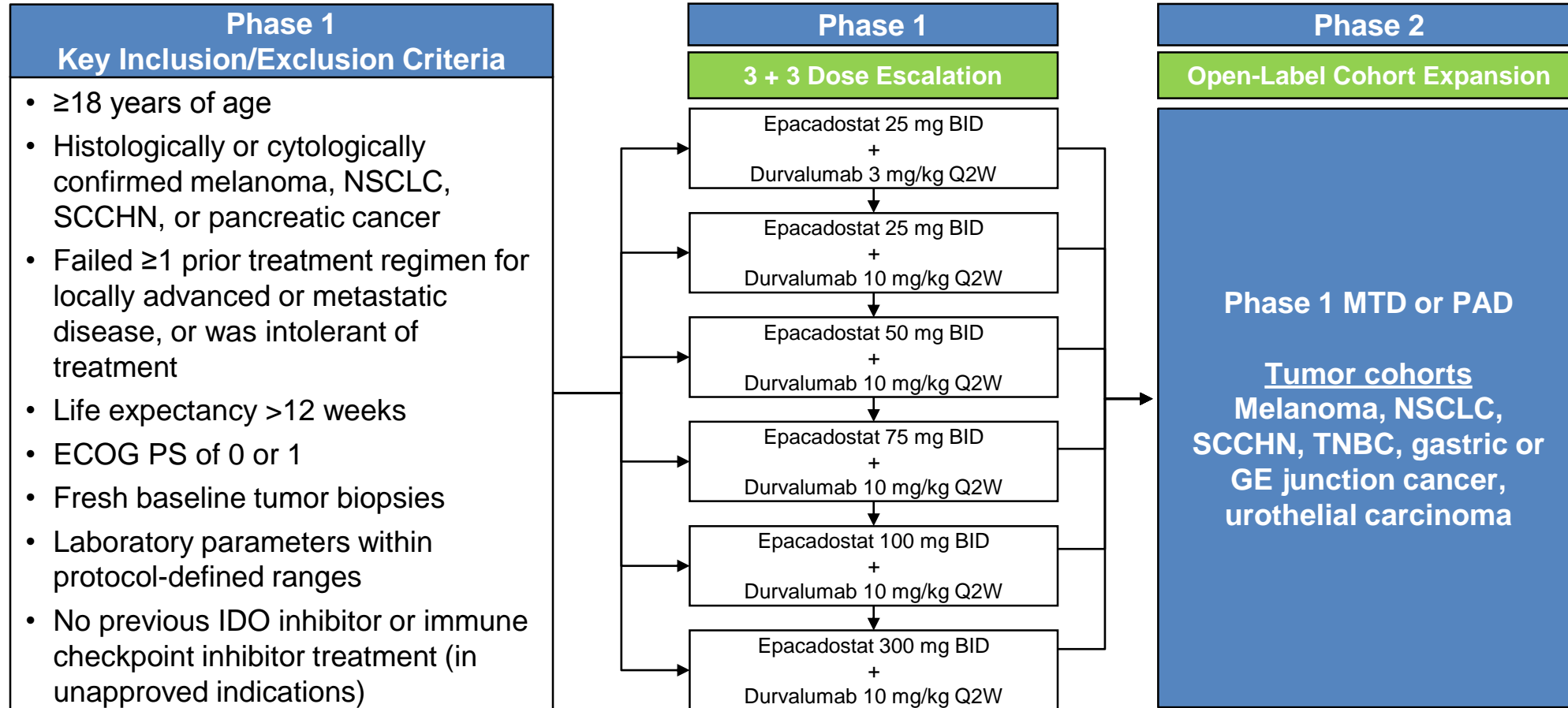
Objectives

To present the:

- Safety and tolerability and MTD or a PAD of epacadostat in combination with durvalumab in patients with selected advanced solid tumors in phase 1 of the study
- Efficacy in patients with pancreatic cancer
- Pharmacokinetics of epacadostat plus durvalumab

Study Design

ECHO-203: Epacadostat Plus Durvalumab



- Combination therapy was planned for 12 months followed by optional epacadostat monotherapy

Study Assessments

Safety and tolerability

- Dose-limiting toxicities were assessed during a 42-day period
- Adverse events were assessed by CTCAE v4.0
- Adverse events of special interest were assessed based on a predefined list associated with durvalumab monotherapy
- Safety evaluable: ≥ 1 dose of study treatment as of data cutoff

Efficacy

- Response was assessed every 8 weeks for the first 12 months and then every 12 weeks thereafter beginning at Week 56 using modified RECIST v1.1
- Efficacy evaluable: ≥ 1 postbaseline scan or discontinuation or death as of data cutoff

Pharmacokinetics

- Pharmacokinetic samples were collected on Cycle 1, Day 8 and/or Cycle 2, Day 1

Data cutoff: October 29, 2017

Baseline Demographics and Disease Characteristics

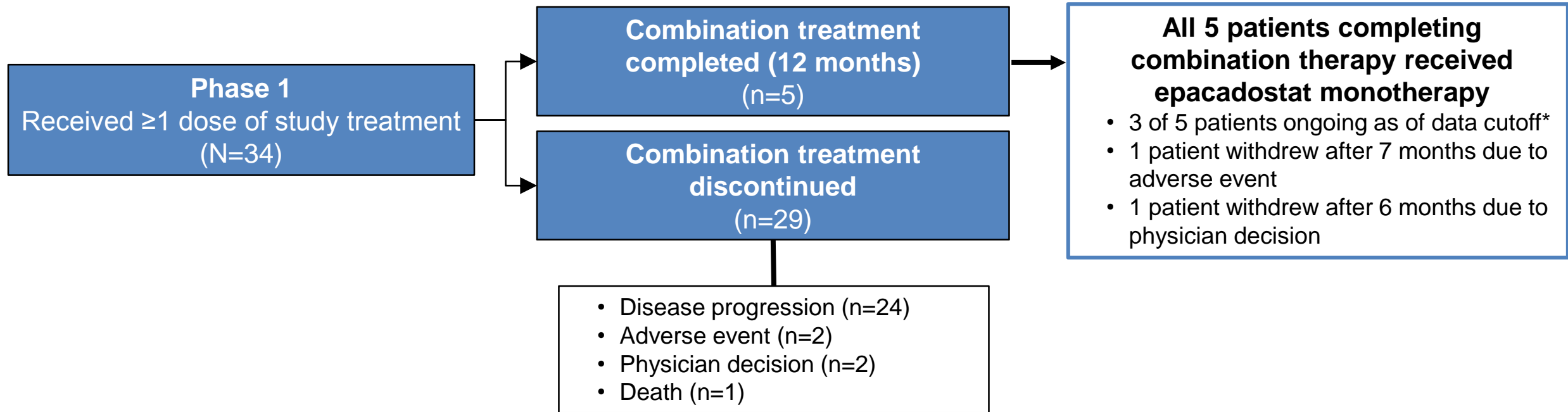
Phase 1

Variable	Total (N=34)
Age Median (range), y ≥65 y, n (%)	68 (46–84) 22 (65)
Male, n (%)	21 (62)
Race, n (%) White Black or African American	33 (97) 1 (3)
Tumor type, n (%) Pancreatic NSCLC SCCHN Melanoma	15 (44) 10 (29) 8 (24) 1 (3)

Variable, n (%)	Total (N=34)
Number of prior treatments for advanced/metastatic disease 0 1 ≥2	1 (3) 11 (32) 22 (65)
ECOG PS 0 1	6 (18) 28 (82)

Patient Disposition

Phase 1: Epacadostat Plus Durvalumab



- Median (range) epacadostat exposure was 12.1 (2–121.9) weeks[†]

* Two ongoing patients with squamous cell carcinoma of the head and neck; 1 with melanoma. † Inclusive of epacadostat monotherapy.

Safety: Treatment-Related Adverse Events and DLT Evaluation Results

Phase 1: Epacadostat Plus Durvalumab

Treatment-Related Adverse Events (Any Grade) Occurring in ≥5% of Phase 1 Patients

Adverse Event, n (%)	Epacadostat Doses*					Total (N=34)
	25 mg BID (n=9)	50 mg BID (n=4)	75 mg BID (n=4)	100 mg BID (n=8)	300 mg BID (n=9)	
Total	7 (78)	3 (75)	3 (75)	5 (63)	9 (100)	27 (79)
Fatigue	4 (44) [§]	2 (50)	1 (25)	2 (25) ^{†,§}	2 (22)	11 (32)
Pruritus	1 (11)	1 (25)	0	1 (13)	2 (22)	5 (15)
Diarrhea	1 (11)	0	1 (25)	1 (13)	1 (11) [†]	4 (12)
Nausea	2 (22)	0	0	1 (13)	1 (11)	4 (12)
Rash [‡]	0	1 (25) [§]	0	0	3 (33) ^{†,§}	4 (12)
Decreased appetite	1 (11)	1 (25)	0	0	1 (11)	3 (9)
Pyrexia	0	2 (50)	0	1 (13)	0	3 (9)
Tumor flare	0	1 (25)	0	1 (13)	1 (11)	3 (9)
Anxiety	1 (11)	0	1 (25) [§]	0	0	2 (6)
Bone pain	0	1 (25)	0	0	1 (11)	2 (6)
Constipation	1 (11)	1 (25)	0	0	0	2 (6)
Cough	1 (11)	0	0	0	1 (11)	2 (6)
Dizziness	1 (11) [§]	1 (25)	0	0	0	2 (6)
Dry mouth	0	0	0	0	2 (22)	2 (6)
Dyspnea	1 (11) [§]	0	1 (25)	0	0	2 (6)
Hyponatremia	0	1 (25)	0	0	1 (11)	2 (6)
Influenza-like illness	2 (22)	0	0	0	0	2 (6)

BID, twice daily; DLT, dose-limiting toxicity; Q2W, every 2 weeks.

* Plus durvalumab 3 mg/kg or 10 mg/kg. † One patient had dose reduction. ‡ Rash includes the following MedDRA preferred terms: rash, rash macular, and rash maculo-papular.

§ One patient had dose interruption.

- There was 1 DLT during the 42-day observation period: grade 3 rash requiring systemic steroids (epacadostat 300 mg BID plus durvalumab 10 mg/kg Q2W)
- Grade ≥3 treatment-related adverse events were observed in 7 patients (21%)
 - Those occurring once included dyspnea, fall, and hyponatremia
 - Those occurring in >1 patient included fatigue and rash (n=3 [9%] each)
- Treatment-related adverse events led to dose interruptions in 7 patients (21%)
 - The only adverse events that occurred in >1 patient were fatigue and rash (n=2 each)
- 3 patients (9%) had dose reductions due to treatment-related adverse events
- 1 patient (3%) experienced serious treatment-related adverse events
- There were no treatment-related adverse events leading to death

Safety: Adverse Events of Special Interest

Phase 1: Epacadostat Plus Durvalumab

Adverse Event, n (%) [†]	Epacadostat Doses*					Total (N=34)
	25 mg BID (n=9)	50 mg BID (n=4)	75 mg BID (n=4)	100 mg BID (n=8)	300 mg BID (n=9)	
Total	3 (33)	2 (50)	1 (25)	4 (50)	8 (89)	18 (53)
Diarrhea	1 (11)	0	1 (25)	2 (25)	2 (22)	6 (18)
Pruritus	1 (11)	1 (25)	0	2 (25)	2 (22)	6 (18)
Rash	0	1 (25)	0	1 (13)	3 (33)	5 (15)
ALT increased	0	0	0	0	3 (33)	3 (9)
AST increased	0	0	0	0	3 (33)	3 (9)
Creatinine increased	0	0	0	0	2 (22)	2 (6)
Erythema	0	1 (25)	0	0	1 (11)	2 (6)
Amylase increased	1 (11)	0	0	0	0	1 (3)
Bilirubin increased	0	0	0	1 (13)	0	1 (3)
Hyperthyroidism	0	0	0	0	1 (11)	1 (3)
Hypothyroidism	0	1 (25)	0	0	0	1 (3)
Intestinal perforation	0	0	0	1 (13)	0	1 (3)
Lipase increased	1 (11)	0	0	0	0	1 (3)
Pneumonitis	1 (11)	0	0	0	0	1 (3)
Transaminase increased	0	0	0	0	1 (11)	1 (3)

BID, twice daily; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

* Plus durvalumab 3 mg/kg or 10 mg/kg. † Based on sponsor-predefined adverse events of special interest associated with durvalumab monotherapy.

MTD and RP2D

Phase 1: Epacadostat Plus Durvalumab

- The MTD of epacadostat was not reached
- Epacadostat 100 mg BID and 300 mg BID are being evaluated in phase 2 in patients with NSCLC, SCCHN, urothelial carcinoma, melanoma, gastric or gastroesophageal junction cancer, or TNBC

Patient Disposition

Phase 1—Pancreatic Cancer: Epacadostat Plus Durvalumab

- 15 patients with pancreatic cancer were enrolled and received ≥ 1 dose of study treatment
 - All had discontinued treatment as of the data cutoff due to disease progression (n=13), physician decision (n=1), or death (n=1)

Epacadostat + Durvalumab Doses	Patients, n (N=15)
Epacadostat 25 mg BID + Durvalumab 3 mg/kg Q2W	2
Epacadostat 25 mg BID + Durvalumab 10 mg/kg Q2W	1
Epacadostat 50 mg BID + Durvalumab 10 mg/kg Q2W	2
Epacadostat 75 mg BID + Durvalumab 10 mg/kg Q2W	1
Epacadostat 100 mg BID + Durvalumab 10 mg/kg Q2W	4
Epacadostat 300 mg BID + Durvalumab 10 mg/kg Q2W	5

- 9 of 15 patients had received epacadostat 100 or 300 mg BID in combination with durvalumab
- Median (range) epacadostat exposure was 8 (2–33) weeks

Baseline Demographics and Disease Characteristics

Phase 1—Pancreatic Cancer

Variable	Total (N=15)
Age Median (range), y ≥65 y, n (%)	66 (46–72) 8 (53)
Male, n (%)	9 (60)
Race, n (%) White Black or African American	14 (93) 1 (7)
ECOG PS, n (%) 0 1	2 (13) 13 (87)

Variable, n (%)	Total (N=15)
Liver metastases Yes No	10 (67) 5 (33)
PD-L1 expression Positive Negative Unknown	2 (13) 5 (33) 8 (53)
Prior surgery Whipple (pancreatoduodenectomy) Distal pancreatectomy	9 (60) 6 (40) 4 (27)
Number of prior treatments for advanced/metastatic disease 0 1 ≥2	1 (7) 6 (40) 8 (53)

Best Objective Response

Phase 1—Pancreatic Cancer: Epacadostat Plus Durvalumab

- No responses were observed among patients with pancreatic cancer
- DCR was 33% (5 patients with stable disease)* per RECIST v1.1 and mRECIST v1.1

Epacadostat + Durvalumab Doses	Patients With Stable Disease, n
Epacadostat 25 mg BID + Durvalumab 3 mg/kg Q2W	1
Epacadostat 100 mg BID + Durvalumab 10 mg/kg Q2W	2
Epacadostat 300 mg BID + Durvalumab 10 mg/kg Q2W	2

- 3 of these 5 patients discontinued treatment because of clinical progression
- 1 patient had a reduction in CA19-9 (baseline, 5276 U/mL; on-study nadir, 4676 U/mL)
- The median duration of disease control was 22 weeks (95% CI, 13–31 weeks)
 - These 5 patients maintained SD for 8, 13, 13, 14, and 31 weeks, respectively

BID, twice daily; CA19-9, carbohydrate antigen 19-9; CI, confidence interval; DCR, disease control rate; Q2W, every 2 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; mRECIST v1.1, modified RECIST v1.1; SD, stable disease.

* Discrepancy between abstract-reported stable disease (27%) and updated stable disease is due to a recent resolution of a site query identifying an additional patient with stable disease.

Pharmacokinetics

Phase 1: Epacadostat Plus Durvalumab

- Epacadostat exposure was generally consistent with previous reports
 - C_{\max} , or peak exposures, of 100 mg BID and 300 mg BID doses were 596 ± 297 nM and 2210 ± 1310 nM, respectively
 - AUC for 100 mg BID and 300 mg BID doses were 3650 ± 2900 h*nM and $12,200 \pm 7870$ h*nM, respectively
- Both 100 mg BID and 300 mg BID doses exhibited similar half-lives ($4.35 \text{ h} \pm 3.54 \text{ h}$ and $5.25 \text{ h} \pm 3.63 \text{ h}$, respectively) which were also consistent with historical data

Pharmacokinetics

Phase 1—Pancreatic Cancer: Epacadostat Plus Durvalumab

- Patients with pancreatic cancer had lower peak exposures (C_{\max})
- When dose-normalized to 100 mg BID, patients who had a Whipple (pancreatoduodenectomy) procedure demonstrated a lower AUC and C_{\max} , suggesting a slight difficulty in absorbing epacadostat
 - These exposures are similar to exposures reported for epacadostat 50 mg BID
 - This could be the result of the intestinal resection with reduced enterohepatic circulation, and/or a change in gut pH

	Whipple (n=6)	No Whipple (n=9)
AUC, h*nM	3060 ± 2160	4690 ± 2210
C_{\max} , nM	653 ± 627	775 ± 321
$T_{1/2}$, h	4.4 ± 2.67	7.23 ± 3.65

Conclusions

ECHO-203 Phase 1: Epacadostat Plus Durvalumab

- Epacadostat plus durvalumab was generally well tolerated in patients with advanced cancers
- The safety profile was consistent with previous reports of durvalumab as monotherapy¹
- In patients with pancreatic cancer, no objective responses were observed; a phase 2 expansion for pancreatic cancer was not conducted
- Epacadostat exposure was generally consistent with previous reports, except in patients with pancreatic cancer, in whom lower peak exposures were observed (potentially due to Whipple procedures)
- Epacadostat 100 and 300 mg BID are being evaluated in phase 2 expansions in patients with non-small cell lung cancer, squamous cell carcinoma of the head and neck, urothelial carcinoma, melanoma, gastric or gastroesophageal junction cancer, or triple-negative breast cancer

BID, twice daily.

1. Imfinzi® (durvalumab) Full Prescribing Information. AstraZeneca Pharmaceuticals LP. Wilmington, DE. February 2018.

Acknowledgments

The authors wish to thank the patients and their families, the investigators, and the site personnel who participated in this study

Other acknowledgments

- This study was sponsored by Incyte Corporation (Wilmington, DE) in collaboration with AstraZeneca Inc. (Wilmington, DE)
- Medical writing assistance was provided by Ann T. Yeung, PhD, CMPP, of ScientificPathways, Inc (a Nucleus Group company) and funded by Incyte