

# 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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# Disclosure Information

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Aung Naing, MD, FACP*

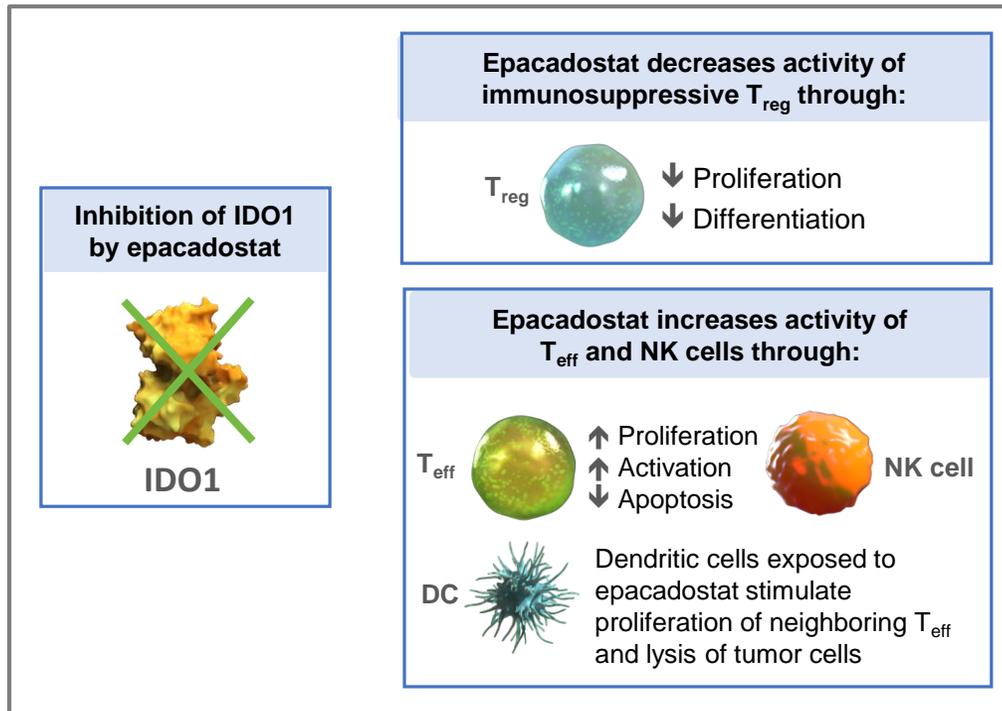
**I have the following financial relationships to disclose:**

- **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
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- **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 target<sup>1</sup>



- Epacadostat is a potent and highly selective IDO1 enzyme inhibitor<sup>2</sup>
- Phase 1 and 2 data suggest that epacadostat plus PD-1 inhibitors is generally well tolerated and may be active in multiple solid tumors<sup>3-7</sup>
- Combining epacadostat with durvalumab, an anti-PD-L1 antibody,<sup>8</sup> 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<sub>eff</sub>, effector T cell; T<sub>reg</sub>, 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

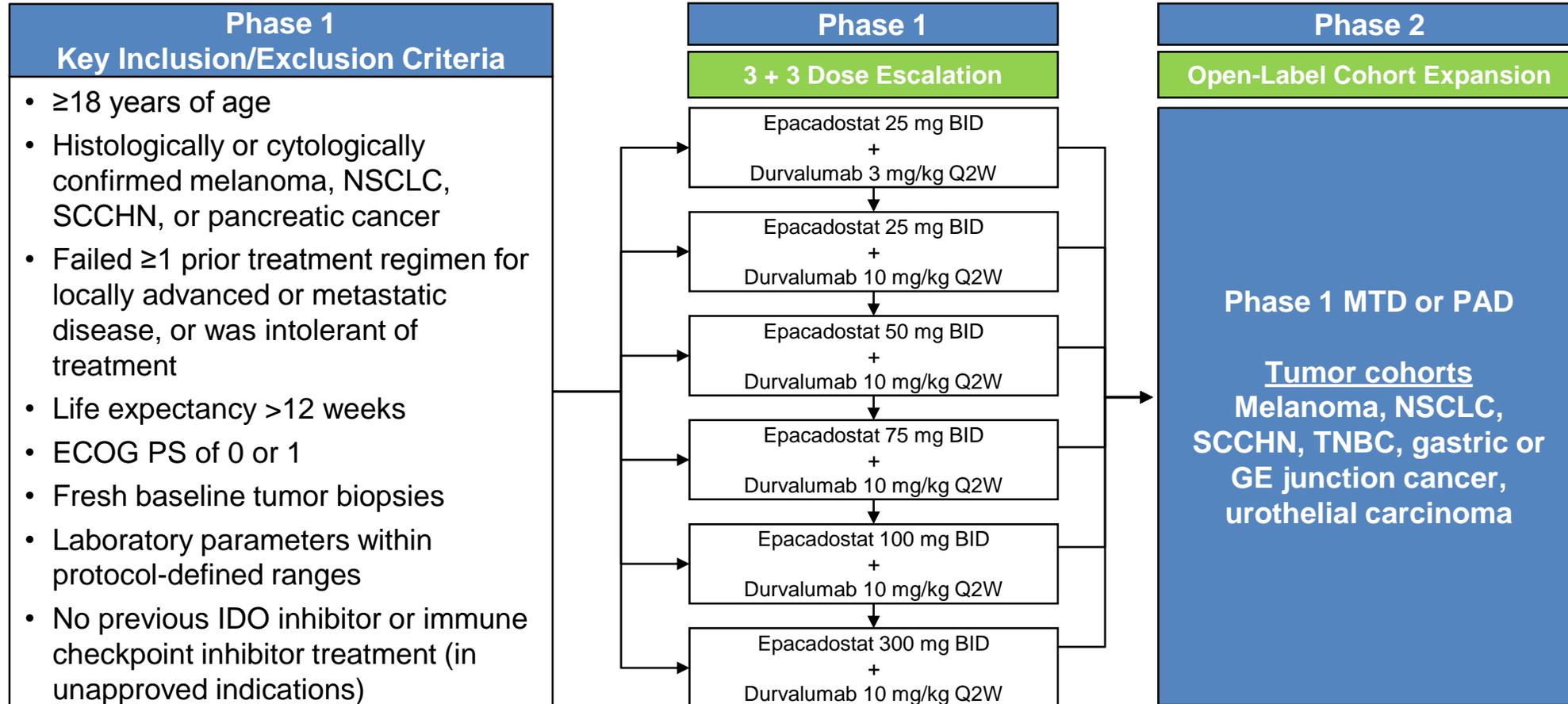
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To present the:

- 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

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## 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:  $\geq 1$  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:  $\geq 1$  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

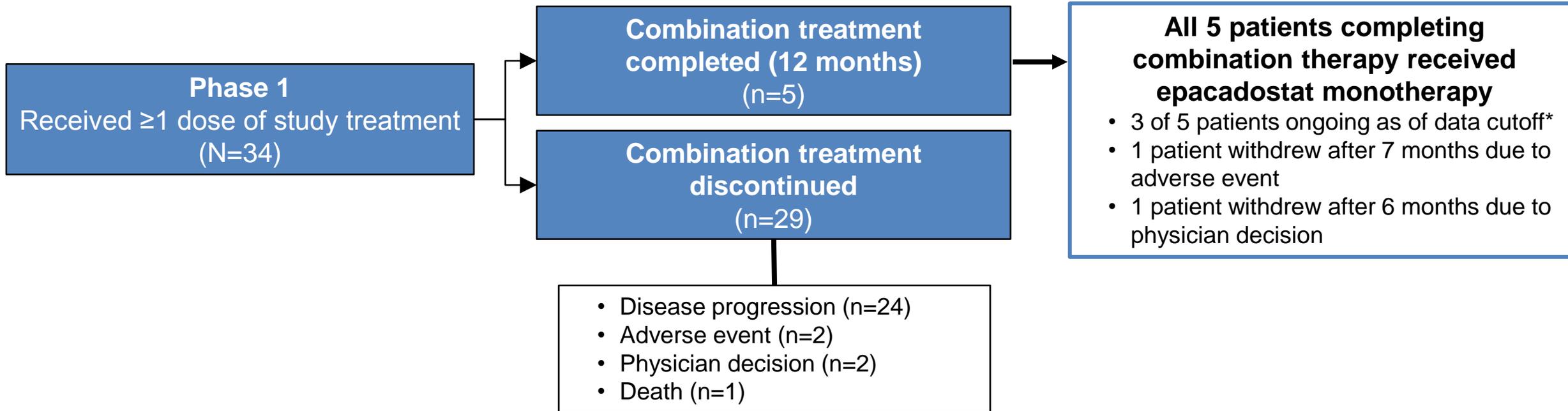
## Phase 1

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

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

# Patient Disposition

## Phase 1: Epacadostat Plus Durvalumab



- Median (range) epacadostat exposure was 12.1 (2–121.9) weeks<sup>†</sup>

\* 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)	
<b>Total</b>	<b>7 (78)</b>	<b>3 (75)</b>	<b>3 (75)</b>	<b>5 (63)</b>	<b>9 (100)</b>	<b>27 (79)</b>
Fatigue	4 (44) <sup>§</sup>	2 (50)	1 (25)	2 (25) <sup>†,§</sup>	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) <sup>†</sup>	4 (12)
Nausea	2 (22)	0	0	1 (13)	1 (11)	4 (12)
Rash <sup>‡</sup>	0	1 (25) <sup>§</sup>	0	0	3 (33) <sup>†,§</sup>	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) <sup>§</sup>	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) <sup>§</sup>	1 (25)	0	0	0	2 (6)
Dry mouth	0	0	0	0	2 (22)	2 (6)
Dyspnea	1 (11) <sup>§</sup>	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 (%) <sup>†</sup>	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)	
<b>Total</b>	<b>3 (33)</b>	<b>2 (50)</b>	<b>1 (25)</b>	<b>4 (50)</b>	<b>8 (89)</b>	<b>18 (53)</b>
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*

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- 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  $\geq 1$  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*

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

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- Epacadostat plus durvalumab was generally well tolerated in patients with advanced cancers
- The safety profile was consistent with previous reports of durvalumab as monotherapy<sup>1</sup>
- 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.

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