SITC 2022

NOVEMBER 8-12 BOSTON MASSACHUSETTS

The Society for Immunotherapy of Cancer 37th Annual Meeting and Pre-Conference Programs

THE LEADING CANCER IMMUNOTHERAPY AND TUMOR IMMUNOLOGY CONFERENCE

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NOVEMBER 8-12 BOSTON MASSACHUSETTS

Botensilimab, a novel innate/adaptive immune activator with balstilimab (anti-PD-1) in “cold” and I-O refractory metastatic solid tumors

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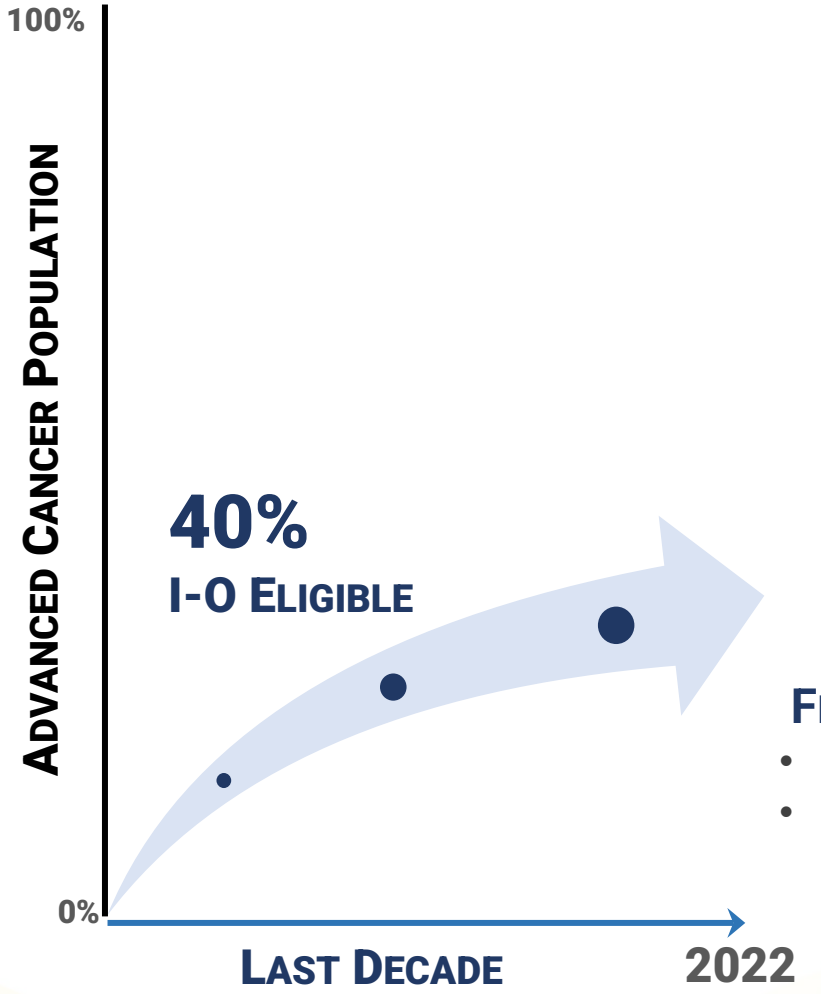
Disclosures

Consultant/Advisory Role: Adaptimmune, Adcendo, Daiichi Sankyo, Deciphera, Epizyme, Polaris, Springworks

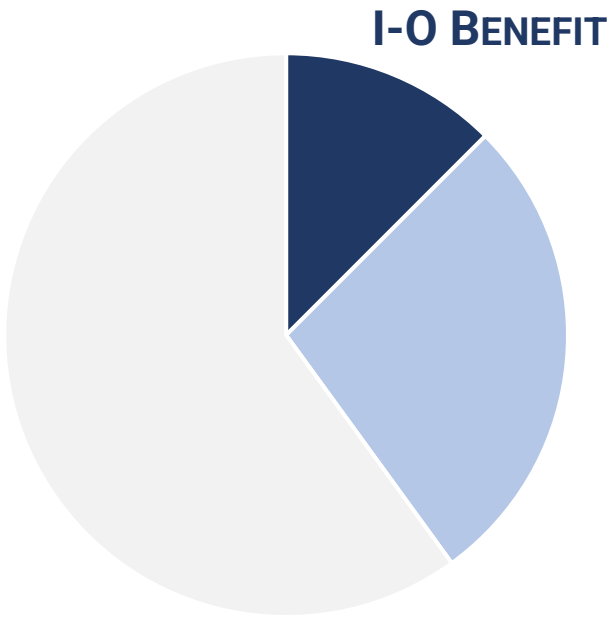
Institutional Coordinating PI: Agenus

Background



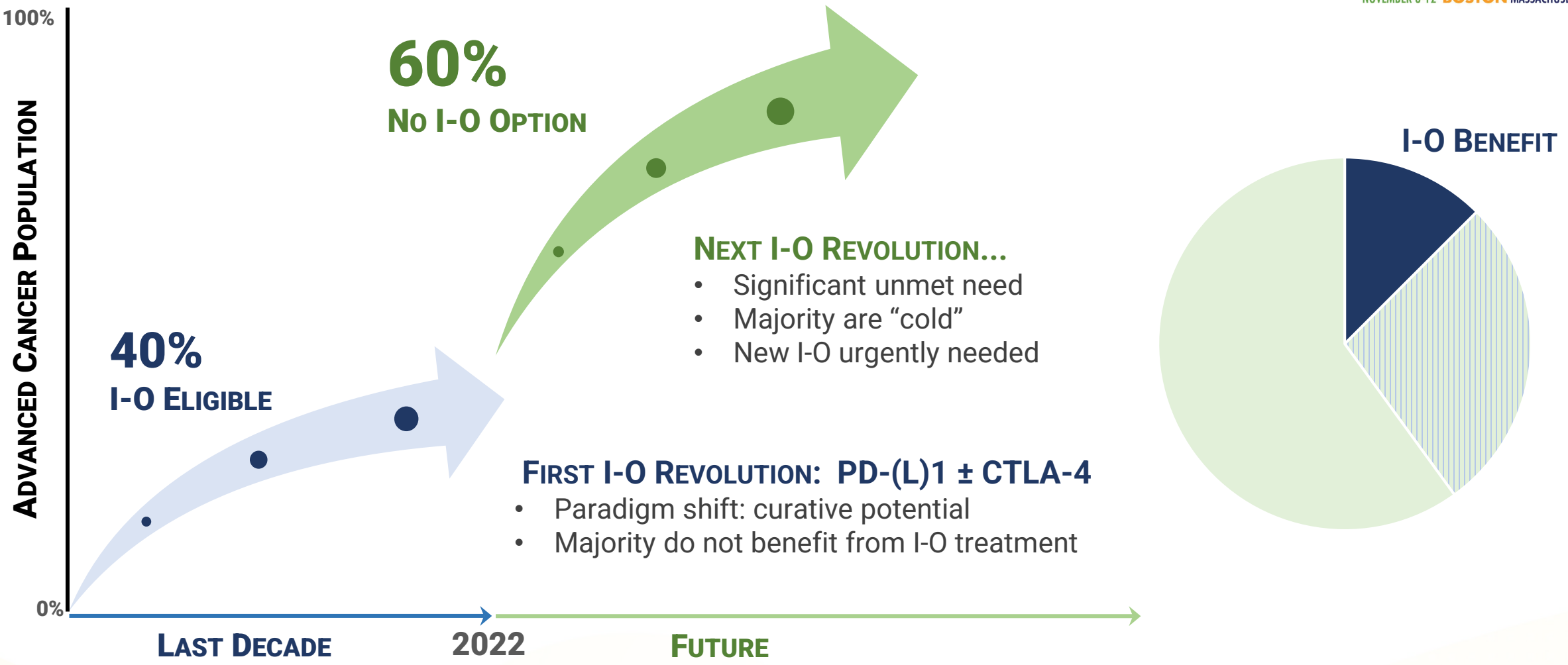
FIRST I-O REVOLUTION: PD-(L)1 ± CTLA-4

- Paradigm shift: curative potential
- Majority do not benefit from I-O treatment



Agenus projections based on Haslam & Prasad, *JAMA* 2019 and Evaluate Pharma 2022 global revenue estimates, I-O treatment benefit defined per Haslam et al as objective response rate.

Background

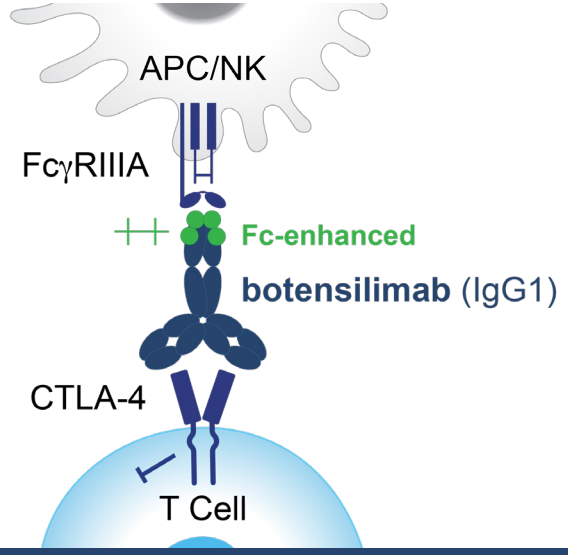


Agenus projections based on Haslam & Prasad, *JAMA* 2019 and Evaluate Pharma 2022 global revenue estimates, I-O treatment benefit defined per Haslam et al as objective response rate.

Novel Immunotherapy Agents

botensilimab

Fc-enhanced CTLA-4 Inhibitor

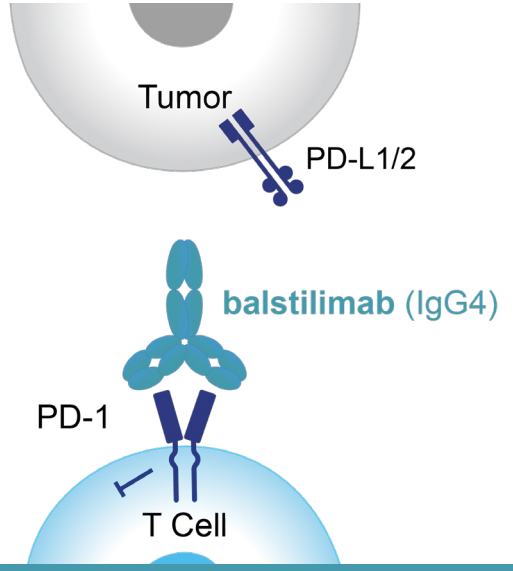


Active in cold and I-O refractory tumors[1]

- ↑ T cell priming, expansion, memory[2,3]
- ↑ Frequency of activated DCs
- ↑ Treg depletion
- ↓ Complement mediated toxicity

balstilimab

PD-1 Inhibitor



Safety and efficacy analogous to approved anti-PD-1 mAbs[4,5]

- >750 patients treated; 10 ongoing trials / 2 completed
- Complete blocker of PD-1-PD-L1/2 interactions
- Enhanced T cell activation and effector function

1. El-Khoueiry AB, et al. SITC 2021 Annual Meeting. Poster #479.
2. Waight et al. *Cancer Cell*. 2018;33(6): 1033-1047. 3. Data on File. Agenus, Inc. November 2022. 4. O'Malley, et al. *Gynecol Oncol.* 2021; 163: 274-280. 5. O'Malley et al, *J Clin Oncol*. 2022; 40(7): 762-771.

C-800-01 Study

NCT03860272: First-in-human trial of **botensilimab (bot)** ± **balstilimab (bal)** in patients with advanced cancer[1,2]

POPULATION

Key Eligibility

- Refractory to standard treatment
- Prior I-O therapy allowed

ENDPOINTS

- Efficacy: ORR, DCR, PFS, DOR, OS
- Safety: AEs

DESIGN

bot
[Fc-enhanced CTLA-4]

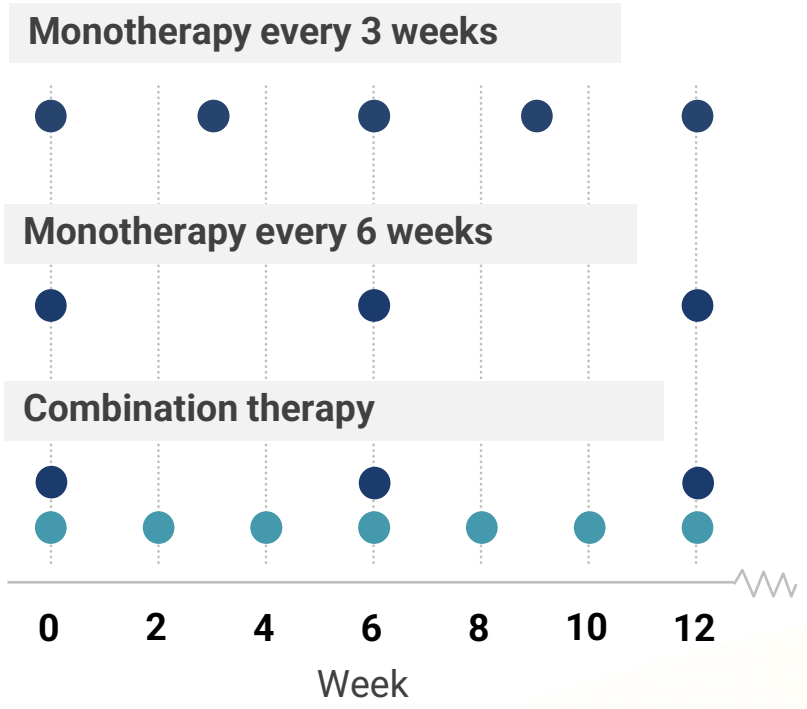
0.1, 0.3, 1, 2, 3 mg/kg **Q3W**

1 or 2 mg/kg **Q6W**

bot* + bal*

[Fc-enhanced CTLA-4] 0.1, 0.3, 1, 2 mg/kg **Q6W**

[PD-1] 3 mg/kg **Q2W**



1. https://clinicaltrials.gov/ct2/show/NCT03860272. 2. El-Khoueiry AB, et al. SITC 2021 Annual Meeting. Poster #479. *Fixed-dosing also permitted (bot 150 mg Q6W + bal 450 mg Q3W).

C-800-01 Analysis Population

NCT03860272: First-in-human trial of **botensilimab (bot)** ± **balstilimab (bal)** in patients with advanced cancer[1,2]

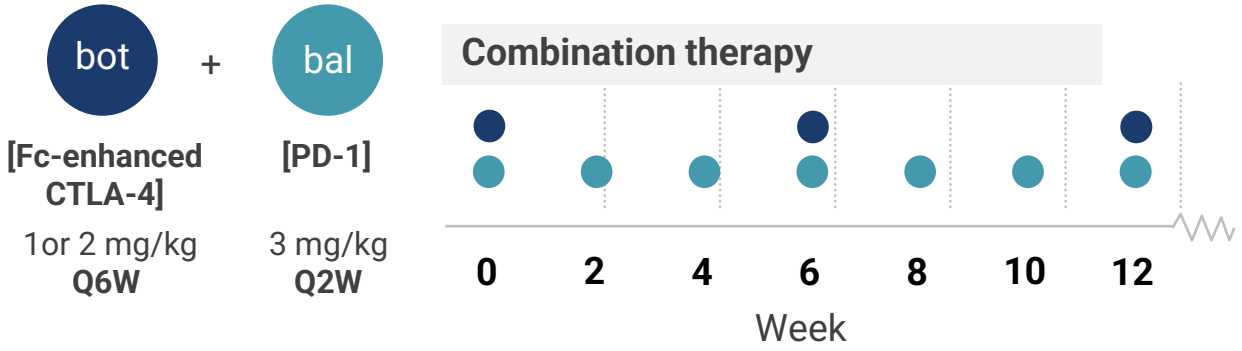
POPULATION

Evaluable Combination Patients

125 treated with 1 or 2 mg/kg bot + bal* as of 19 May 2022 with ≥1 Q6W imaging assessment†

- **115** *de novo* combination patients
- **10** *rescue* patients who received combination therapy after bot monotherapy

DESIGN



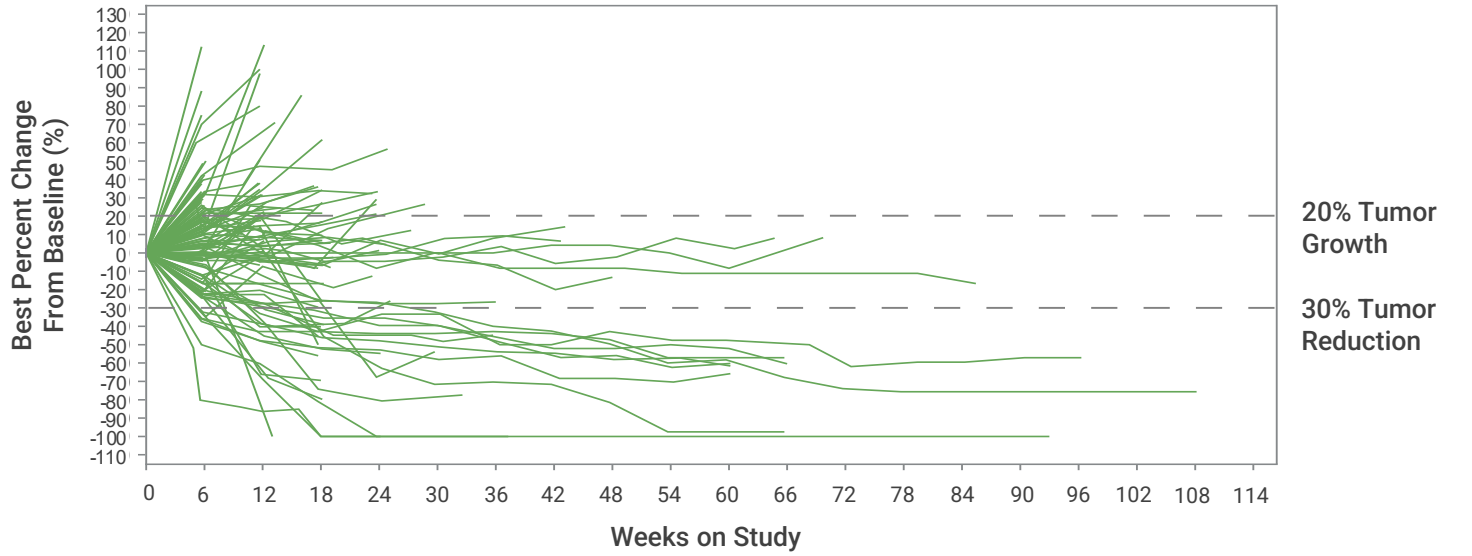
1. https://clinicaltrials.gov/ct2/show/NCT03860272. 2. El-Khoueiry AB, et al. SITC 2021 Annual Meeting. Poster #479. *Fixed-dosing also permitted (bot 150 mg Q6W + bal 450 mg Q3W). †An additional 34 patients who started treatment as of 19 May 2022 were not evaluable due to early or clinical PD (n=22), withdrawal of consent (n=6), patient decision (n=3), need for a prohibited medication (n=1), a dose-limiting toxicity (n=1), or an unrelated AE (n=1).

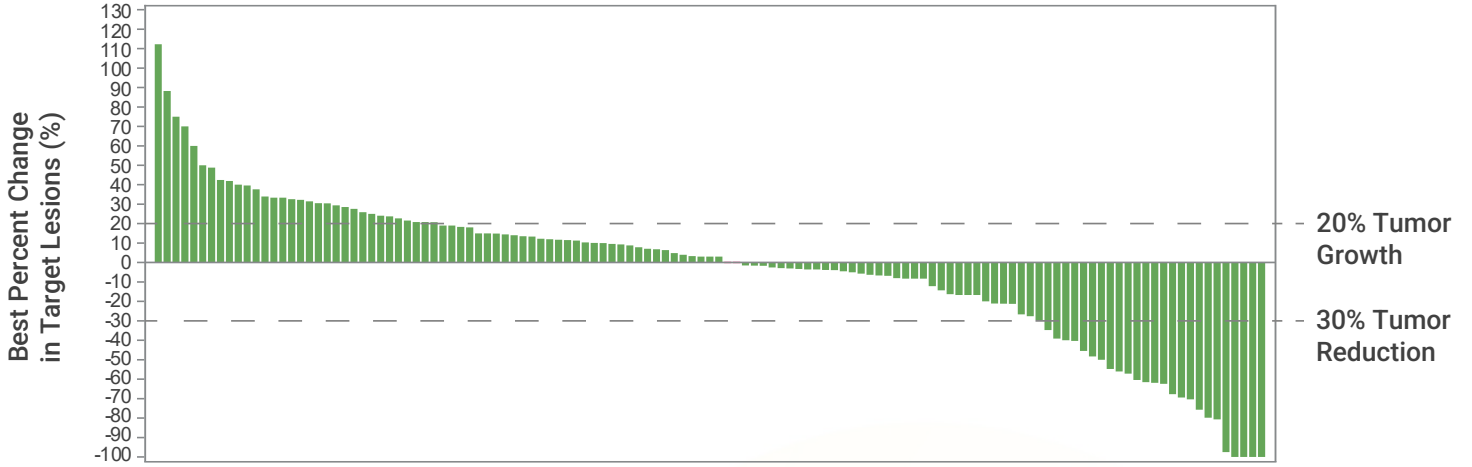
Patient Characteristics (N=125)

	ALL PATIENTS
Age, median (range)	59 (25-83)
Sex, n (%)	
Male	48 (38)
Female	77 (62)
ECOG PS at baseline, n (%)	
0	56 (45)
1	69 (55)
Prior lines of therapy, n (%)	
1L	13 (10)
2L	20 (16)
3L+	61 (49)
Not available	31 (25)
Prior I-O, n (%)	36 (29)

	ALL PATIENTS
Select expansion cohorts, n (%)	
MSS CRC	59 (47)
Recurrent Platinum Resistant/Refractory Ovarian	19 (15)
Sarcoma	12 (10)
Anti-PD-(L)1 R/R NSCLC	4 (3)
15 other tumor types, n (%)	31 (25)
Bot dose, n (%)	
1 mg/kg bot Q6W + bal 3 mg/kg Q2W	19 (15)
2 mg/kg bot Q6W + bal 3 mg/kg Q2W	101 (81)
Fixed-dose (150 mg bot Q6W + bal 450 mg Q3W)	5 (4)

Efficacy in Combination Patients (N=125)





ALL PATIENTS	
ORR, %*	**20%** (95% CI, 13-28%)
BOR, n (%)	
CR	3 (2)
PR	22 (18)
SD	58 (46)
PD	42 (34)
DCR (CR + PR + SD), %	**66%** (95% CI, 57-74%)
Median DOR, months	NR (95% CI, 4.5-NR)
Median PFS, months	2.8 (95% CI, 2.7-4.2)
Median OS, months	NR (95% CI, 12.9-NR)
12-month OS, months	66% (95% CI, 54-76%)
Median F/U, months	6.2 (Range, 1.1-29.3)

*Includes unconfirmed responses.

Safety (N=125)

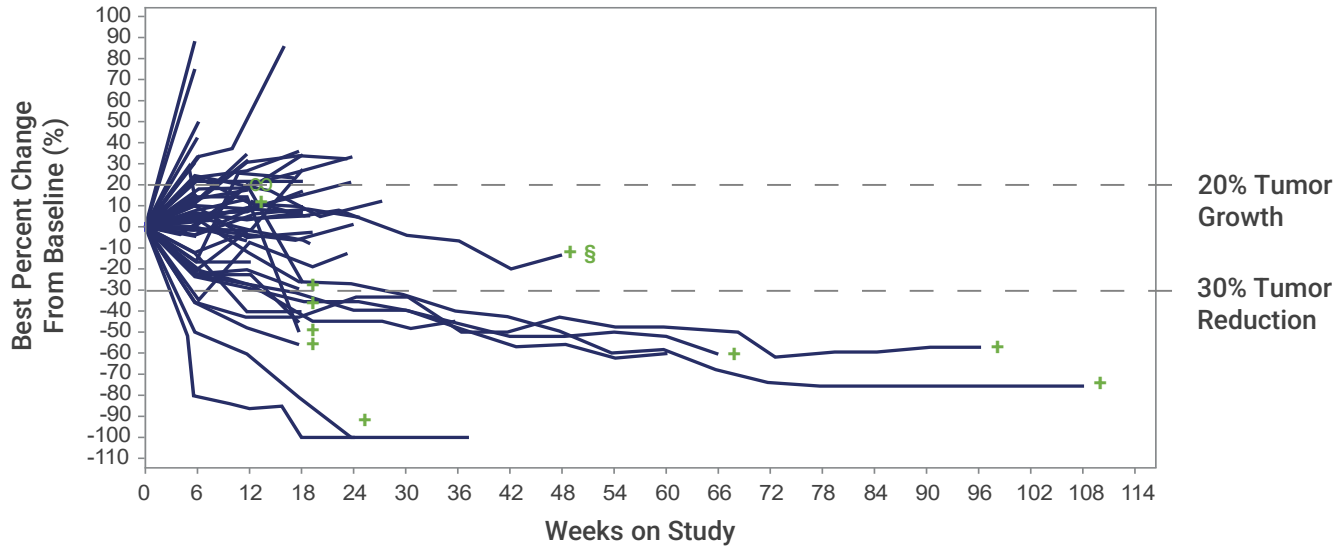
All TRAEs of Any Grade in ≥10% of All Patients

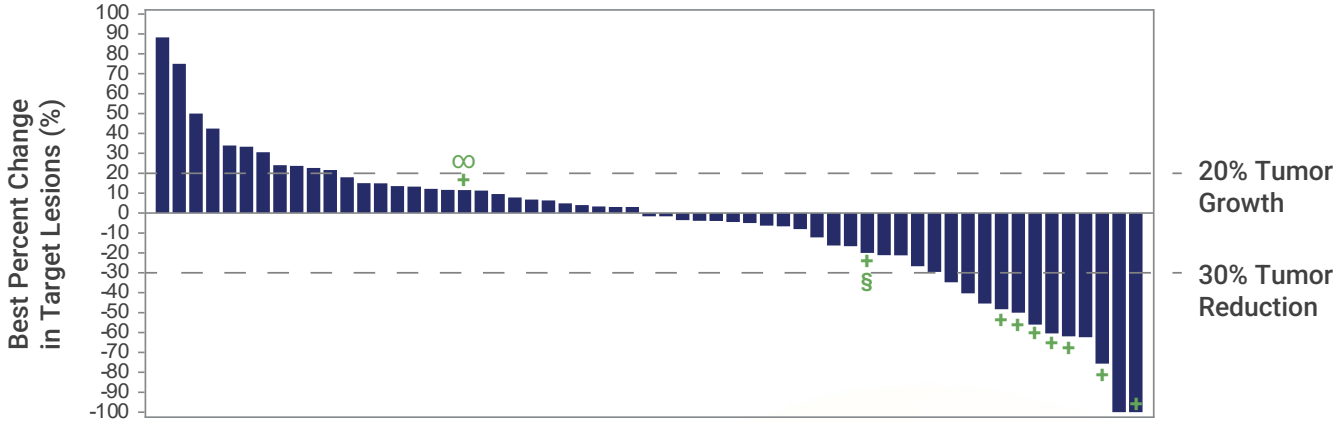
n (%)	ALL GRADE	GRADE 3	GRADE 4
ANY TRAE	111 (89)	40 (32)	3 (2)
GASTROINTESTINAL			
Immune-mediated diarrhea/colitis*	48 (38)	23 (18)	1 (1)
Other diarrhea	16 (13)	0	0
Nausea	32 (26)	1 (1)	0
Vomiting	17 (14)	0	0
CONSTITUTIONAL			
Fatigue	37 (30)	5 (4)	0
Decreased appetite	28 (22)	0	0
Chills	24 (19)	0	0
Pyrexia	20 (16)	4 (3)	0
SKIN			
Rash	27 (22)	2 (2)	0
Pruritus	17 (14)	0	0
HEPATIC			
↑ ALT	13 (10)	3 (2)	0
↑ AST	13 (10)	3 (2)	0
ENDOCRINE			
Hypo/hyperthyroidism	17 (14)	0	0
MUSCULOSKELETAL			
Myalgia	12 (10)	1 (1)	0
Arthralgia	12 (10)	0	0

- **No grade 5 TRAEs**
- **Discontinuation due to a TRAE:**
  - 9% bot only
  - 15% bot and bal

*Immune-mediated diarrhea/colitis includes patients who received steroids or infliximab for diarrhea/colitis.

MSS CRC Efficacy (n=59)





EFFICACY	
ORR, %*	**22%** (95% CI, 12-35%)
BOR, n (%)	
CR	1 (2)
PR	12 (20)
SD	30 (51)
PD	16 (27)
DCR (CR + PR + SD), %	**73%** (95% CI, 60-84%)
Median DOR, months	NR (95% CI, 2.8-NR)
Median PFS, months	4.1 (95% CI, 2.7-4.4)
Median OS, months	NR (95% CI, 9.4-NR)
12-month OS, months	60% (95% CI, 42-75%)
Median F/U, months	6.2 (Range, 1.6-29.3)

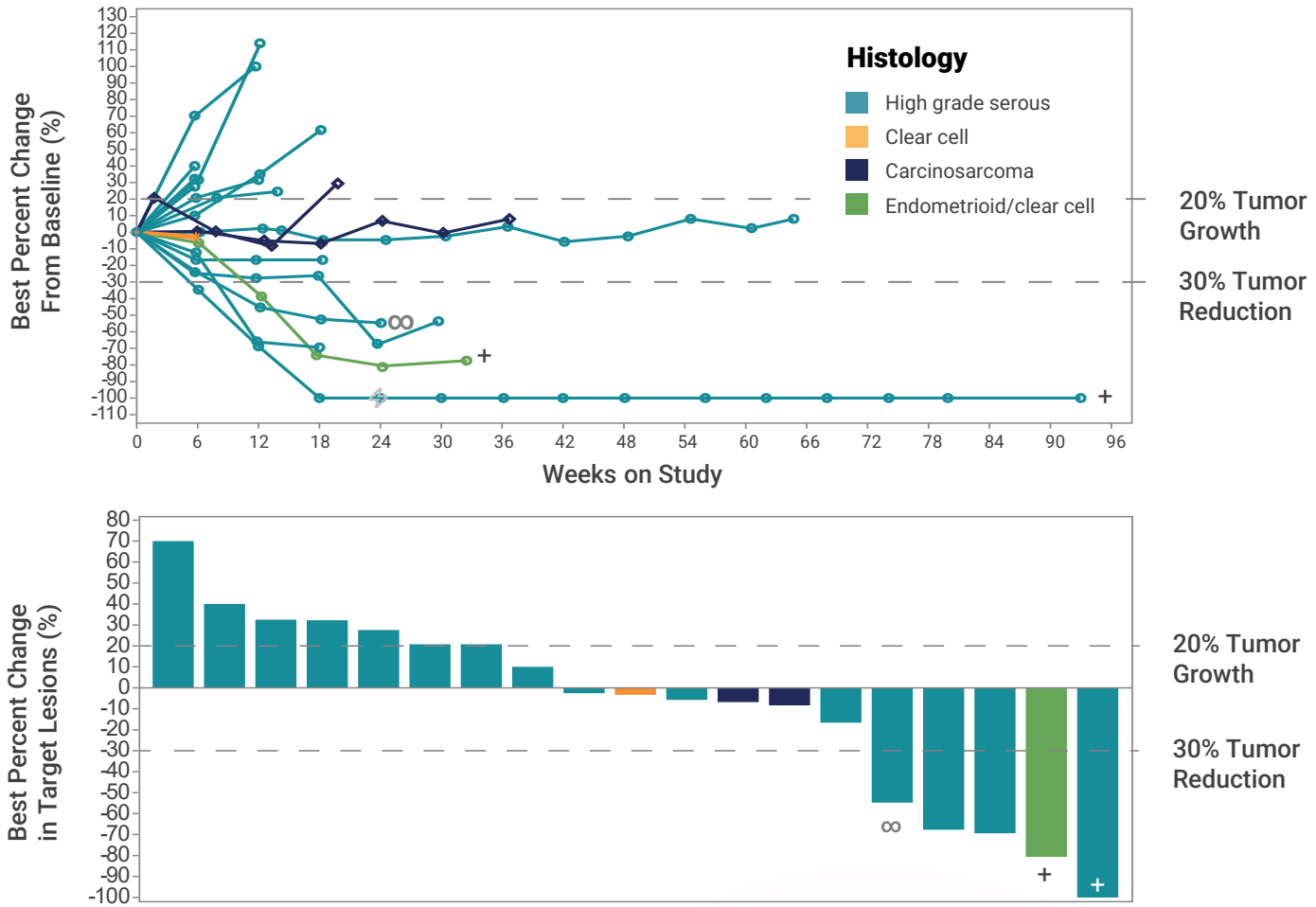
Responder Characteristics (n=13)

- 11/13 (85%) with 3L+ prior LOT
- 2/13 (15%) with prior I-O
- 13/13 (100%) MSS
- 0/10 (0%) TMB >10 mut/Mb
- 1/7 (14%) PD-L1 positive (≥1%)
- 9/13 (69%) RAS mutant
- 0/13 (0%) BRAF mutant
- 9/13 (69%) with ongoing responses

*Includes unconfirmed responses.
§SD by RECIST; metabolic CR by PET.

∞Resected target lesion showed complete pathologic response.
+Ongoing response.

Recurrent Platinum Refractory/Resistant Ovarian Efficacy (n=19)



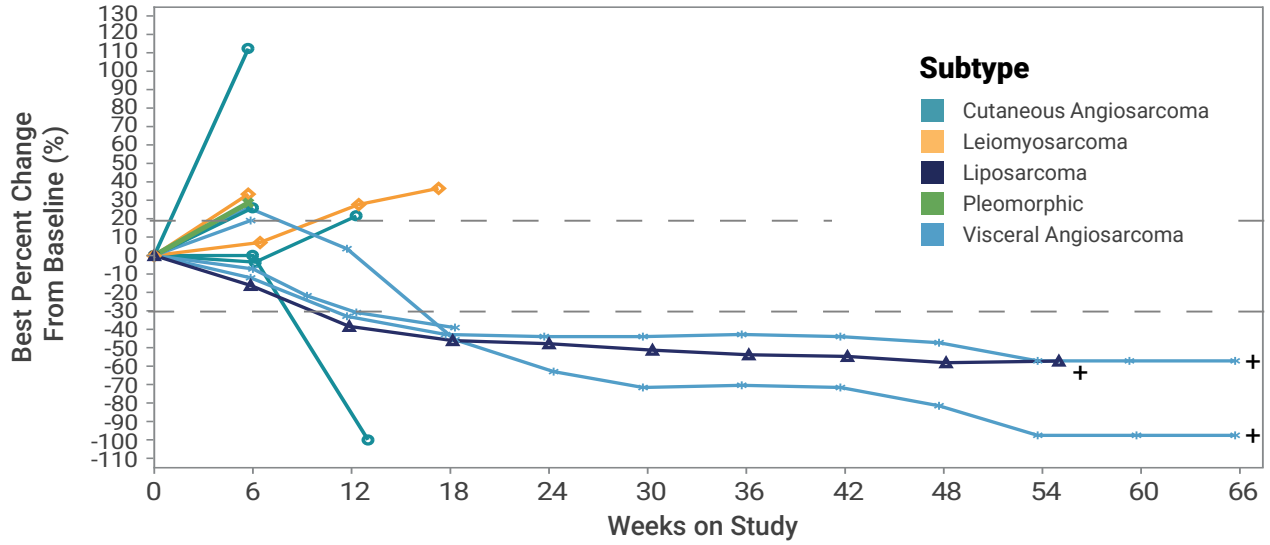
EFFICACY	
ORR, %*	**26%** (95% CI, 9-51%)
BOR, n (%)	
CR	1 (5)
PR	4 (21)
SD	7 (37)
PD	7 (37)
DCR (CR + PR + SD), %	**63%** (95% CI, 38-84%)
Median DOR, months	NR (95% CI, 4.2-NR)
Median F/U, months	6.5 (Range, 2.0-24.0)

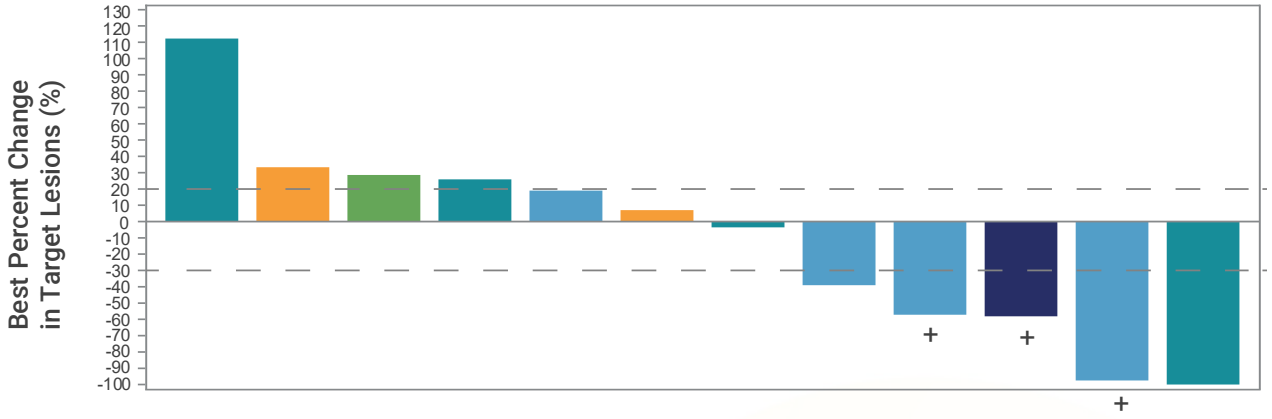
Responder Characteristics (n=5)
- 4 high grade serous (80%), 1 endometrioid/clear cell (20%)
- 3/5 (60%) with 3L+ prior LOT
- 1/5 (20%) with prior I-O (pembrolizumab/PI3Ki PD, nivolumab PD)
- 5/5 (100%) MSS
- 0/3 (0%) TMB >10 mut/Mb
- 3/3 (100%) PD-L1 positive (≥1%)
- 2/5 (40%) responses ongoing

*Includes unconfirmed responses.
∞ SD for 72 weeks on monotherapy prior to switching to combination.

+Ongoing response.
ϟ Received radiation, no evidence of disease.

Sarcoma Efficacy (n=12)





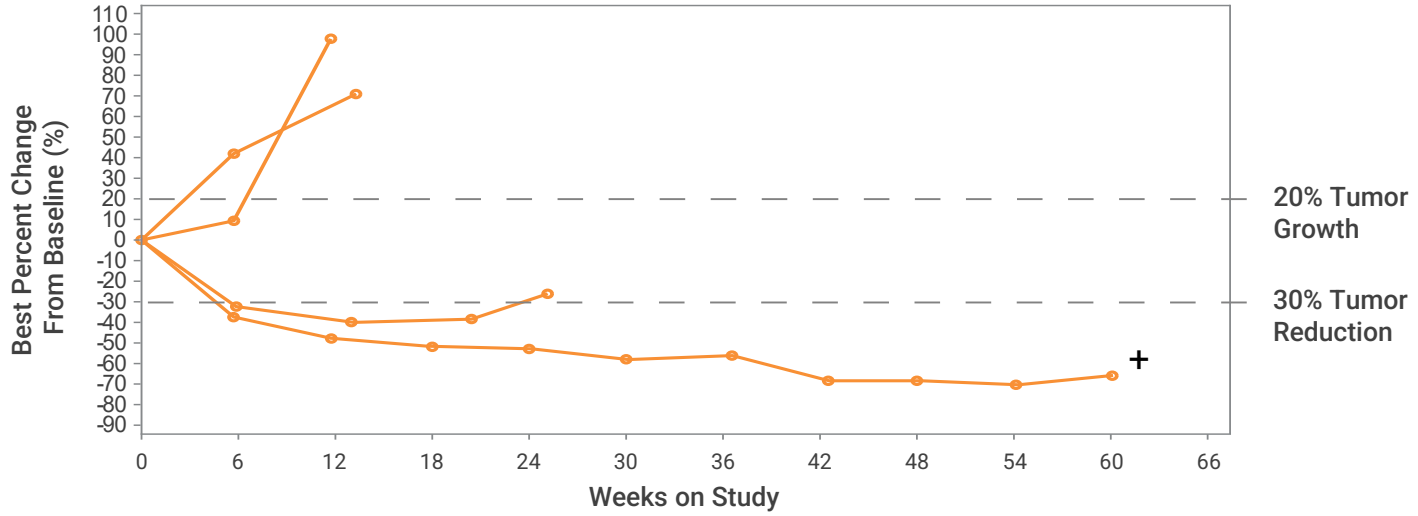
EFFICACY	
ORR, %*	**42%** (95% CI, 15-72%)
BOR, n (%)	
CR	1 (8)
PR	4 (33)
SD	3 (25)
PD	4 (33)
DCR (CR + PR + SD), %	**67%** (95% CI, 35-90%)
Median DOR, months	NR (95% CI, 1.9-NR)
Median F/U, months	4.4 (Range, 1.1-19.6)

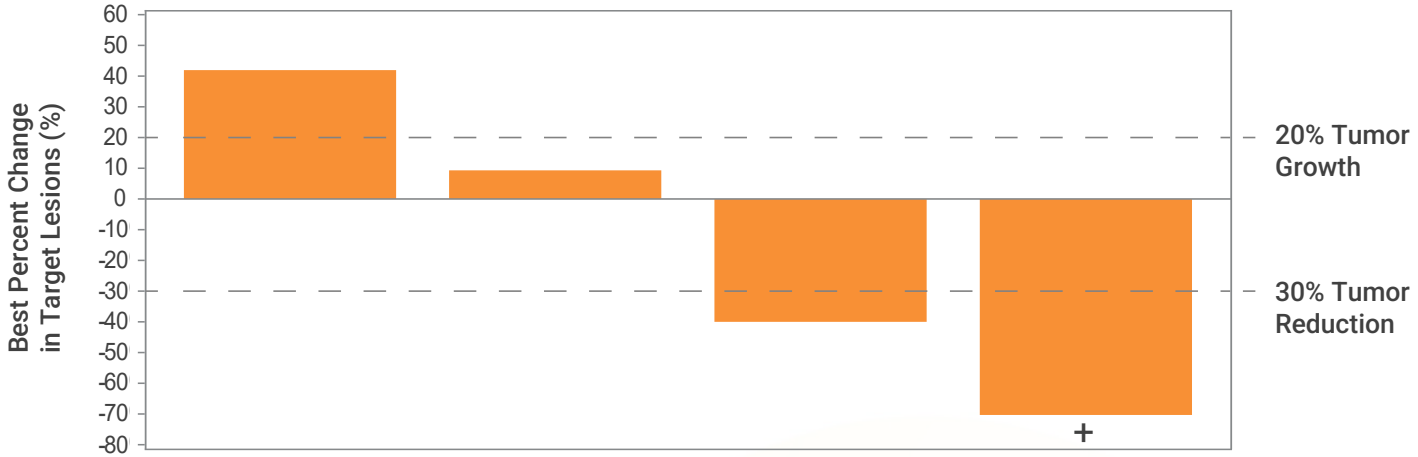
Responder Characteristics (n=5)

- 1 cutaneous angiosarcoma (20%), 3 visceral angiosarcoma (60%), 1 liposarcoma (20%)
- 3/5 (60%) with 3L+ prior LOT
- 4/4 (100%) MSS
- 1/4 (25%) TMB >10 mut/Mb (TMB=15, visceral angiosarcoma)
- 3/4 (75%) PD-L1 positive (≥1%)
- 3/5 (60%) responses ongoing

*Includes unconfirmed responses.
+Ongoing response.

Anti-PD-(L)1 R/R NSCLC Efficacy (n=4)





One additional confirmed PR since the data cutoff, ORR 60% (3/5)

EFFICACY	
ORR, %	**50%** (95% CI, 7-93%)
BOR, n (%)	
CR	0 (0)
PR	2 (50)
SD	1 (25)
PD	1 (25)
DCR (CR + PR + SD), %	**75%** (95% CI, 19-99%)
Median DOR, months	NR (95 % CI, 4.5-NR)
Median F/U, months	5.3 (Range, 3.3-16.2)

Responder Characteristics (n=2)

- *Patient 1*:
  - PD-L1 negative (0%)
  - Prior I-O: Carboplatin/paclitaxel/ **pembrolizumab**, **pembrolizumab** (PD)
  - Response ongoing
- *Patient 2*:
  - PD-L1 negative (0%)
  - Prior I-O: Carboplatin/pemetrexed/ **pembrolizumab**, pemetrexed/ **pembrolizumab** (PD)

+Ongoing response.

Summary & Future Directions

- Botensilimab plus balstilimab demonstrates durable responses across a broad range of heavily pretreated unselected patients with cold and/or I-O relapsed/refractory tumors
- Results presented today in MSS CRC, ovarian, sarcoma (including angiosarcoma and liposarcoma), and anti-PD-(L)1 R/R NSCLC tumors are representative of broad activity in additional diseases including:
  - MSS endometrial, anti-PD-1 R/R HCC, anti-PD-1 R/R cervical, and anti-PD-1/CTLA-4 R/R melanoma
- Botensilimab plus balstilimab is well tolerated and appears differentiated from first-gen CTLA-4-based regimens, with less high-grade visceral toxicity outside of the GI tract, consistent with its molecular design[1,2]
- Three botensilimab Phase 2 ACTIVATE trials are underway

activate AGAINST COLORECTAL CANCER

activate AGAINST MELANOMA

activate AGAINST PANCREATIC CANCER

1. Levey D, et al. SITC Annual Meeting 2022. Poster #470.
2. Krishnan S, et al. SITC Annual Meeting 2022. Poster #941.

Acknowledgements

Agenus Inc. funded and is the sponsor of this study.

- The authors would like to thank the patients and their families for participating in the C-800-01 study, as well as the trial coordinators and investigators for their contributions.

Abbreviations

AE, adverse event
ALT, alanine aminotransferase
APC, antigen presenting cell
AST, aspartate aminotransferase
bal, balstilimab
BOR, best overall response
bot, botensilimab
BRAF, v-raf murine sarcoma viral oncogene homolog B1
CR, complete response
CPK, creatine phosphokinase
CRC, colorectal cancer
CTLA-4, cytotoxic T-lymphocyte antigen-4
DC, dendritic cell
DCR, disease control rate
DOR, duration of response
ECOG, Eastern Cooperative Oncology Group
Fc, fragment crystallizable
FcγRIIIA, Fc gamma receptor IIIA
F/U, follow-up
HCC, hepatocellular carcinoma
ICI, immune checkpoint inhibitor
IgG, immunoglobulin G
I-O, immunotherapy
L, line
LOT, lines of therapy
mAb, monoclonal antibody
Mets, metastases
MSI, microsatellite instability
MSS, microsatellite stable
NK, natural killer
NSCLC, non-small cell lung cancer
ORR, objective response rate
OS, overall survival
PD, progressive disease
PD-1, programmed death receptor-1
PD-L1/2, programmed death-ligand ½
PFS, progression-free survival
PR, partial response
PS, performance status
QXW, every X weeks
RAS, rat sarcoma virus
R/R, relapsed/refractory
SD, stable disease
SOC, standard of care
TMB, tumor mutation burden
TNBC, triple negative breast cancer
TRAE, treatment-related adverse event
Treg, regulatory T cell