A PHASE IA/IB STUDY OF BOTENSILIMAB, A NOVEL INNATE/ADAPTIVE IMMUNE ACTIVATOR, PLUS BALSTILIMAB FOR THE TREATMENT OF PATIENTS WITH SARCOMA

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DISCLOSURES

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

Institutional Coordinating PI: Agenus

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RECENT I-O TRIALS IN SARCOMA

Summary of Responses in All-comer Soft-Tissue Sarcoma Patients

Study Agents	Study N Range	Median Prior Treatments Range	ORR Range (All-Comers)	Median OS Range
PD-(L)1 as Monotherapy[1-3]	40-79	2	16-37%	11.3-13.0 months
PD-1 + CTLA-4[4-7]	16-48	2-3	12-16%	13.1-NR months
Chemotherapy Combinations[8-11]	12-88	0	19-37%	14.0-27.6 months
Alkylating Agent Combinations[12]	50	2	2%	5.6-NR months
Receptor Tyrosine Kinase Inhibitor Combinations[13-14]	33-58	0-2	21-25%	24 months

1. Tawbi HA, et al. *Lancet Oncol*. 2017;18(11):1493-1501. 2. Burgess MA, et al. *J Clin Oncol*. 2019;37(15)_suppl:11015-11015. 3. Naqash AR, et al. *J Clin Oncol*. 2021;39(15)_suppl:11519-11519.
4. Somaiah N, et al *Lancet Oncol.* 2022;23(9):1156-1166. 5. D'Angelo SP, et al. *Lancet Oncol.* 2018;19(3):416-426. 6. Chen JL, et al. *J Clin Oncol.* 2020;38(15)_suppl:11511-11511.
7. Wagner MJ, et al. *J Immunother Cancer.* 2021;9:e002990. 8. EM Gordon, et al. *J Clin Oncol*. 2022;40(16)_suppl:11573-11573. 9. Pollack SM, et al. *JAMA Oncol.* 2020;6(11):1778-1782.
10. Livingston MB, et al. *Clin Cancer Res*. 2021;27(23):6424-6431. 11. Rosenbaum E, *J Clin Oncol*. 2022;40(16)_suppl:11516-11516. 12. Toulmonde M, et al. *JAMA Oncol*. 2018;4(1):93-97.
13. Martin-Broto J, et al. *J Immunother Cancer.* 2020;8:e001561. 14. Wilky BA, et al. *Lancet Oncol.* 2019;20(6):837-848.

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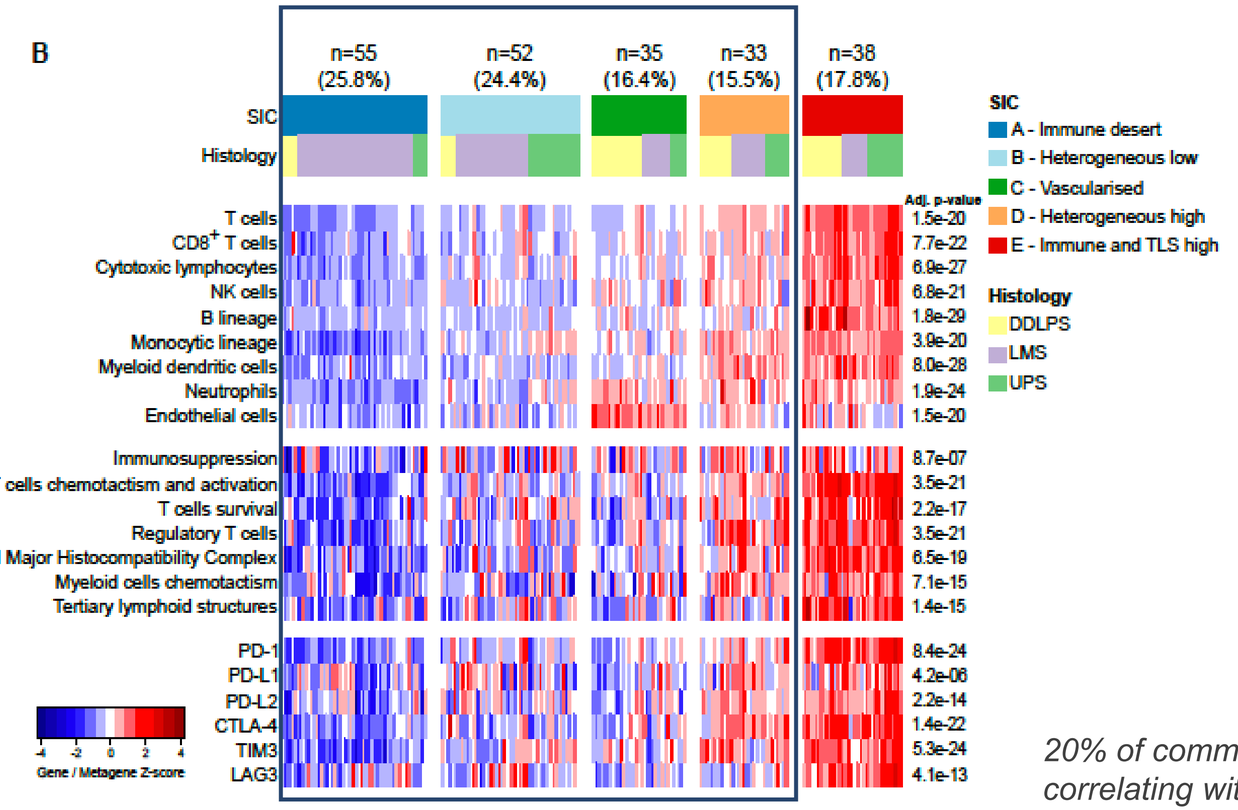
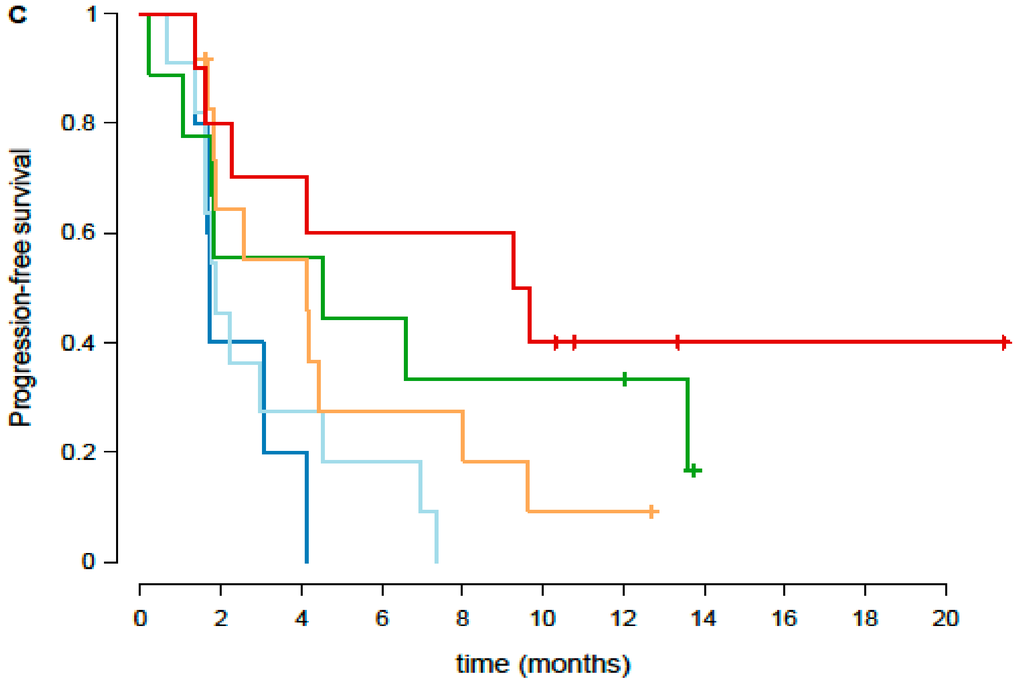
STANDARD ICIs INEFFECTIVE FOR MAJORITY OF SARCOMA PATIENTS





20% of common adult type sarcomas have high expression of immune related genes, correlating with to response to ***checkpoint inhibitor monotherapy***

1. Petitprez F, et al. *Nature*. 2020;577:556-560.
2. Progression-free survival graph based on the multicenter Phase 2 clinical trial of pembrolizumab in soft-tissue sarcoma (SARC028).

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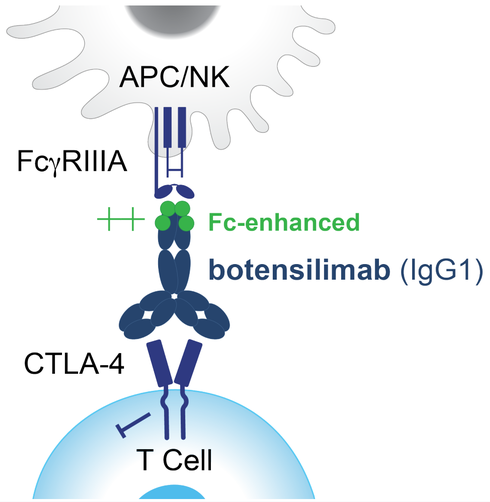
NOVEL IMMUNOTHERAPY AGENTS

botensilimab

Fc-enhanced CTLA-4 Inhibitor

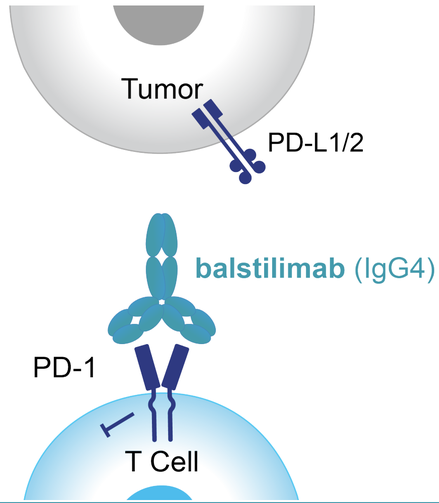


Active in cold and I-O refractory tumors[1]:

- ↑ 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.

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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**

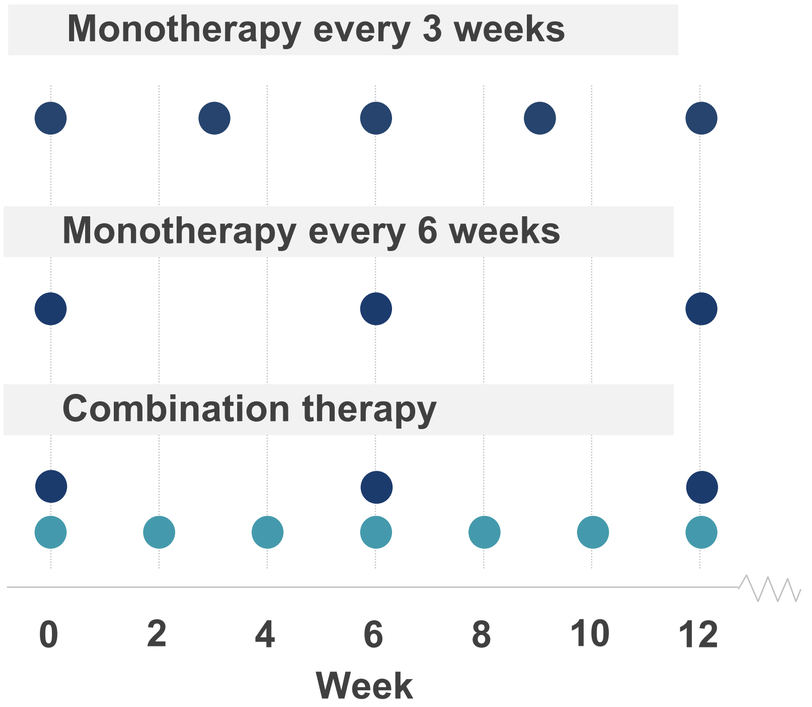
bot† + bal†

[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.

*Crossover to combination from bot monotherapy permitted.

†Fixed-dosing also permitted (bot 150 mg Q6W + bal 450 mg Q3W).

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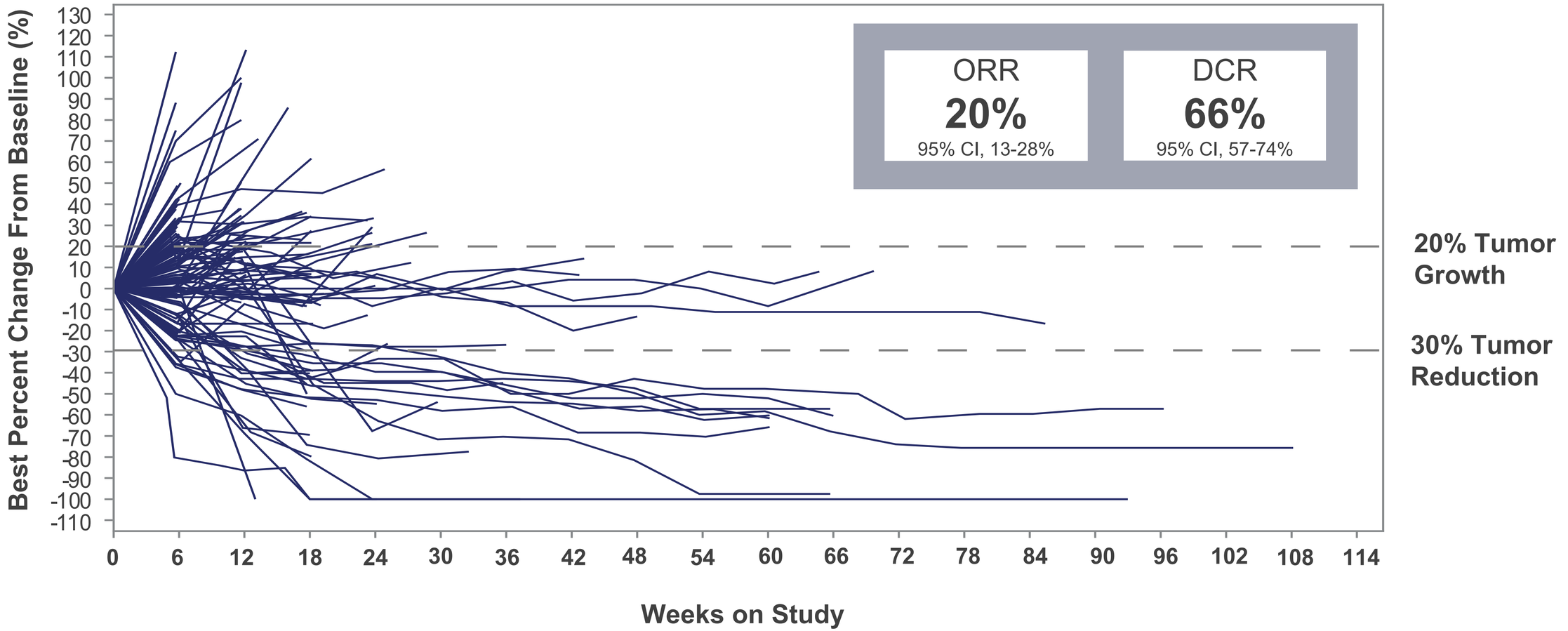
BOTENSILIMAB/BALSTILIMAB EFFICACY IN COLD AND I-O RESISTANT TUMORS (N=125)*



Wilky BA, et al. SITC 2022 Annual Meeting. Oral Presentation #778.

*Evaluable patients were treated with bot + bal as of 19 May,2022, and had ≥1 Q6W imaging assessment. Includes combination patients who received 1 or 2 mg/kg bot Q6W plus 3 mg/kg bal Q2W, fixed dose patients (150 mg bot Q6W plus 450 mg bal Q3W), and rescue patients who crossed over from monotherapy to combination therapy.

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CLINICAL RESPONSES IN SELECT EXPANSION COHORTS

	Select Expansion Cohorts*		
	MSS CRC (n=59)	**Ovarian (n=19)**	**Anti-PD-(L)1 R/R NSCLC (n=5)**
ORR, %	**22%** (95% CI, 12-35%)*	**26%** (95% CI, 9-51%)*	**60%†**
BOR, n (%)			
CR	1 (2)	1 (5)	0 (0)
PR	12 (20)	4 (21)	3 (60)‡
SD	30 (51)	7 (37)	1 (20)
PD	16 (27)	7 (37)	1 (20)
DCR (CR + PR + SD), %	**73%** (95% CI, 60-84%)	**63%** (95% CI, 38-84%)	**80%‡**
Median DOR, months	NR (95% CI, 2.8-NR)	NR (95% CI, 4.2-NR)	NR (95% CI, 4.5-NR)
Median F/U, months	6.2 (Range, 1.6-29.3)	6.5 (Range, 2.0-24.0)	5.3 (Range, 3.3-16.2)

Wilky BA, et al. SITC 2022 Annual Meeting. Oral Presentation #778.
*Includes unconfirmed responses.
†Includes one additional evaluable patient since the data cutoff (ongoing confirmed PR).

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C-800-01 SARCOMA ANALYSIS POPULATION

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

POPULATION

Evaluable Combination Patients*

13 treated with 1 or 2 mg/kg bot + bal as of 16 June 2022 with ≥1 Q6W imaging assessment

- **11** *de novo* combination patients
- **2** *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.
*ITT population (N=20): Seven additional patients were treated as of 16 June 2022 but were not included in the analysis as they did not have at least one 6-week imaging scan either due to progression (n=5), withdrawal of consent (n=1), or due to coming off study due to an unrelated AE (n=1).
†Fixed-dosing also permitted (bot 150 mg Q6W + bal 450 mg Q3W).

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PATIENT CHARACTERISTICS (N=13)

Characteristic	Overall (N=13)
Age, median (range)	54 (41-80)
Sex, n (%)	
Male	7 (54)
Female	6 (46)
ECOG PS at baseline, n (%)	
0	9 (69)
1	4 (31)
Prior lines of therapy, n (%)	
Median (range)	3 (0-4)
2	1 (8)
3	4 (31)
4	4 (31)
Prior I-O, n (%)*	4 (31)
Microsatellite stable status, n (%)†	11/11 (100)
TMB >10 mutations/Mb, n/N (%)†	2/11 (18)
PD-L1 (≥1%), n/N (%)†	5/11 (45)
Sarcoma subtype, n (%)	
Cutaneous angiosarcoma	5 (38)
Visceral angiosarcoma	4 (31)
Liposarcoma (leiomyosarcomatous differentiation)	1 (8)
Leiomyosarcoma	2 (15)
Pleiomorphic sarcoma	1 (8)

*Including prior PD-(L)1 and/or CTLA-4 inhibitors, and PD-1/IL-2.
†MSS, TMB, and PD-L1 status was unknown in two patients (TPS or CPS ≥1%).

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EFFICACY (N=13)

Characteristic	Overall (N=13)
ORR, %	**46%** (95% CI, 19-75%)
BOR, n (%)	
CR*	1 (8)
PR	5 (38)
SD	3 (23)
PD	4 (31)
DCR (CR + PR + SD), %	**69%** (95% CI, 39-91%)
Median DOR, months	NR (95% CI, 1.9-NR)
Median OS, months	NR (95% CI, 3.2-NR)
12-months OS, months	77% (95% CI, 35-94%)
Median F/U, months	4.2 (Range, 1.1-18.9)

*One patient with an unconfirmed CR. All other responses confirmed.

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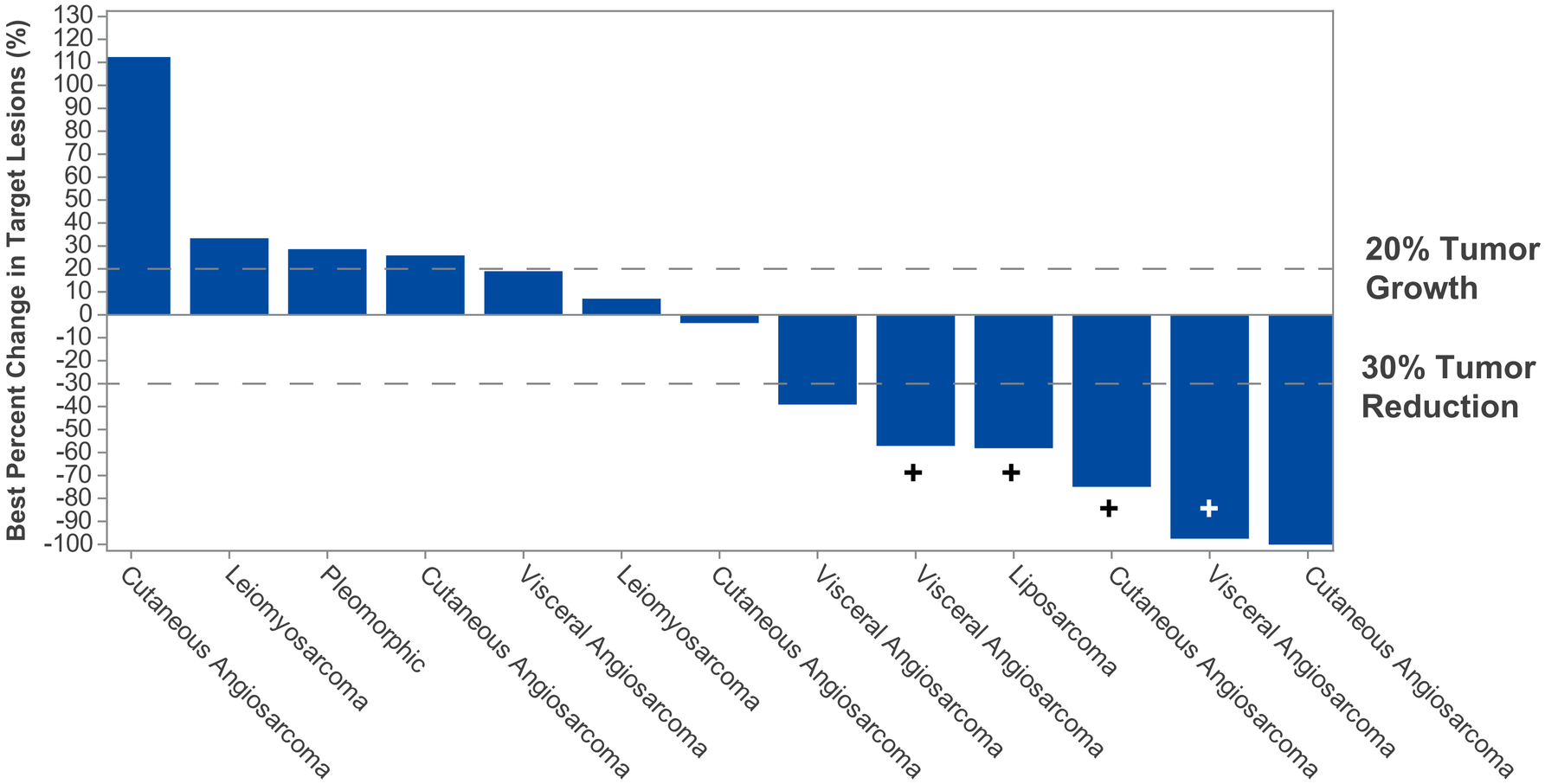
BOTENSILIMAB PROMOTES RESPONSES IN SUBTYPES UNRESPONSIVE TO I-O (N=13)



20% Tumor Growth

30% Tumor Reduction

+ = Ongoing response.

- **All Sarcoma** (n=13)
- **ORR:** 46%; **DCR:** 69%
- (1 CR, 5 PRs, 3 SDs)
- **Ongoing Responses:** 4/6 (67%)

- **Angiosarcoma** (n=9)
- **ORR:** 56%; **DCR:** 78%
- (1 CR, 4 PRs, 2 SDs)
- **Ongoing Responses:** 3/5 (60%)

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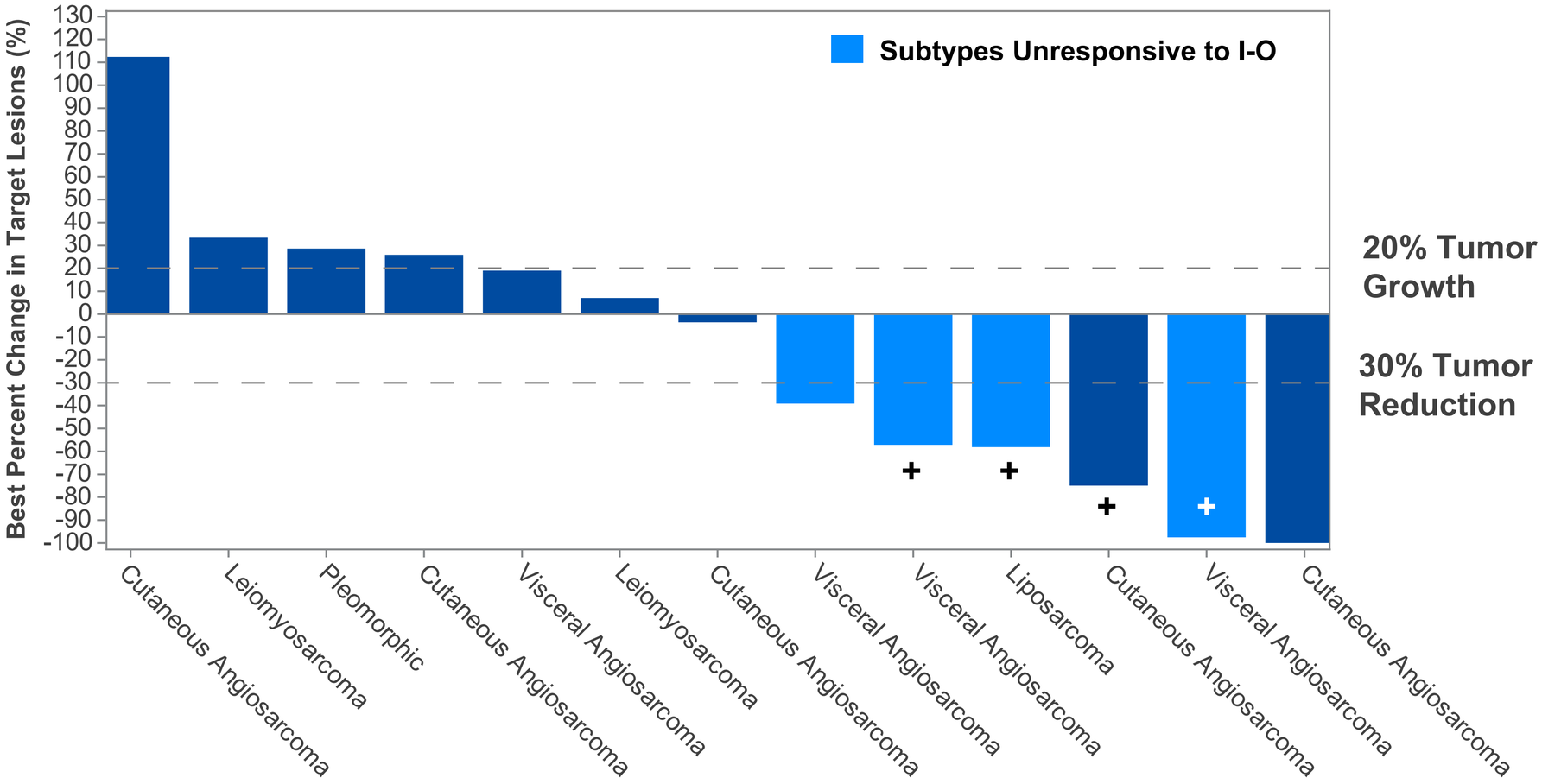
BOTENSILIMAB PROMOTES RESPONSES IN SUBTYPES UNRESPONSIVE TO I-O (N=13)



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- **Angiosarcoma** (n=9)
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- **Ongoing Responses:** 3/5 (60%)

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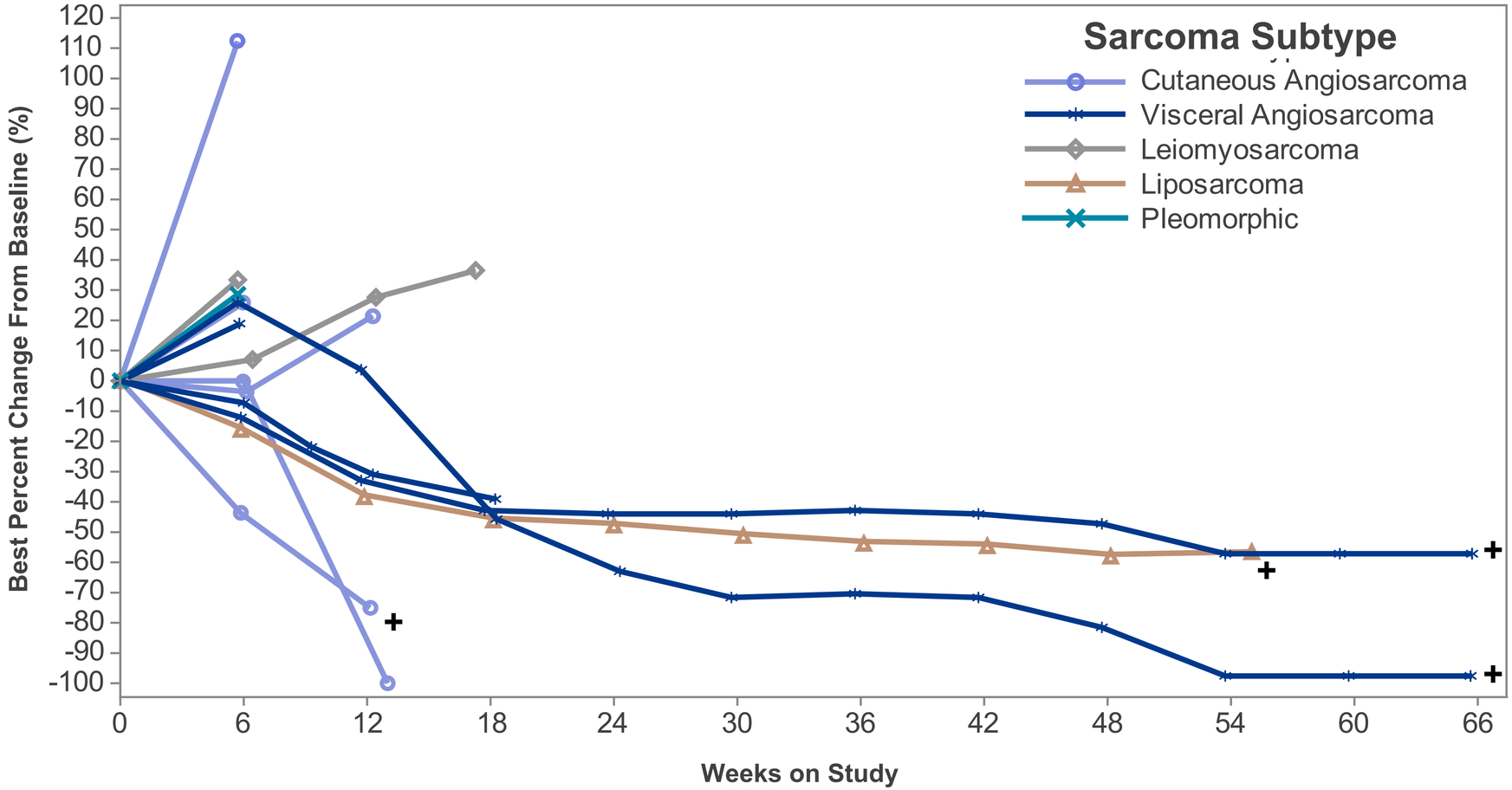
BOTENSILIMAB PROMOTES DURABLE RESPONSES IN MULTIPLE SUBTYPES (N=13)



+ = Ongoing response.

- **All Sarcoma** (n=13)
- **ORR:** 46%; **DCR:** 69%
- (1 CR, 5 PRs, 3 SDs)
- **Ongoing Responses:** 4/6 (67%)

- **Angiosarcoma** (n=9)
- **ORR:** 56%; **DCR:** 78%
- (1 CR, 4 PRs, 2 SDs)
- **Ongoing Responses:** 3/5 (60%)

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SAFETY

TRAEs OF ANY GRADE IN ≥2 PATIENTS (N=13)

Characteristic	All Grade	Grade 3
Any TRAE	12 (92)	3 (23)
GASTROINTESTINAL		
Diarrhea/colitis	6 (46)	2 (15)
Nausea	3 (23)	0 (0)
CONSTITUTIONAL		
Fatigue	5 (38)	1 (8)
Chills	4 (31)	0 (0)
Decreased appetite	3 (23)	0 (0)
Pyrexia	2 (15)	0 (0)
MUSCULOSKELETAL		
Myalgia	5 (38)	1 (8)
↑ CPK	2 (15)	0 (0)
SKIN		
Rash	5 (38)	1 (8)
ENDOCRINE		
Hypothyroidism/hyperthyroidism	2 (15)	0 (0)
BLOOD		
Lymphopenia	2 (15)	1 (8)
EYE		
Eye pain	2 (15)	1 (8)
RESPIRATORY		
Cough	2 (15)	0 (0)

Similar safety profile to the larger trial overall

No hypophysitis, pneumonitis or myocarditis

No grade 4 or 5 TRAEs

Discontinuation due to a TRAE:

- 8% bot only
- 8% bot and bal

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SUMMARY

- Botensilimab plus balstilimab demonstrates a high ORR with durability and clinical benefit in patients with advanced sarcoma, including subtypes that have been unresponsive to I-O
- The combination 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]
- The current Phase 1 C-800-01 study is actively enrolling an expansion sarcoma cohort
- A Phase 2 trial in sarcoma is planned for 2023

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

ACKNOWLEDGEMENTS

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ABBREVIATIONS

AE, adverse event
APC, antigen presenting cell
bal, balstilimab
BOR, best overall response
bot, botensilimab
CPS, combined positive score
CR, complete response
CRC, colorectal cancer
CPK, creatine phosphokinase
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, Fragment crystallizable gamma receptor IIIA
F/U, follow-up
ICI, immune checkpoint inhibitor
IgG, immunoglobulin G
I-O, immunotherapy
irAE, immune-related adverse event
ITT, intention-to-treat
mAb, monoclonal antibody
MSS, microsatellite stable
NK, natural killer
NR, not reached
ORR, objective response rate
OS, overall survival
PD-1, programmed death receptor-1
PD-L1/2, programmed death-ligand 1/2
PFS, progression-free survival
PR, partial response
PS, performance status
QXW, every X weeks
R/R, relapsed/refractory
SD, stable disease
TMB, tumor mutational burden
TPS, tumor proportion score
TRAE, treatment-related adverse event
Treg, regulatory T cell

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