EFFICACY AND SAFETY OF BOTENSILIMAB PLUS BALSTILIMAB COMBINATION THERAPY IN REFRACTORY METASTATIC SARCOMA PATIENTS: FINDINGS FROM AN ONGOING EXPANDED PHASE 1B STUDY

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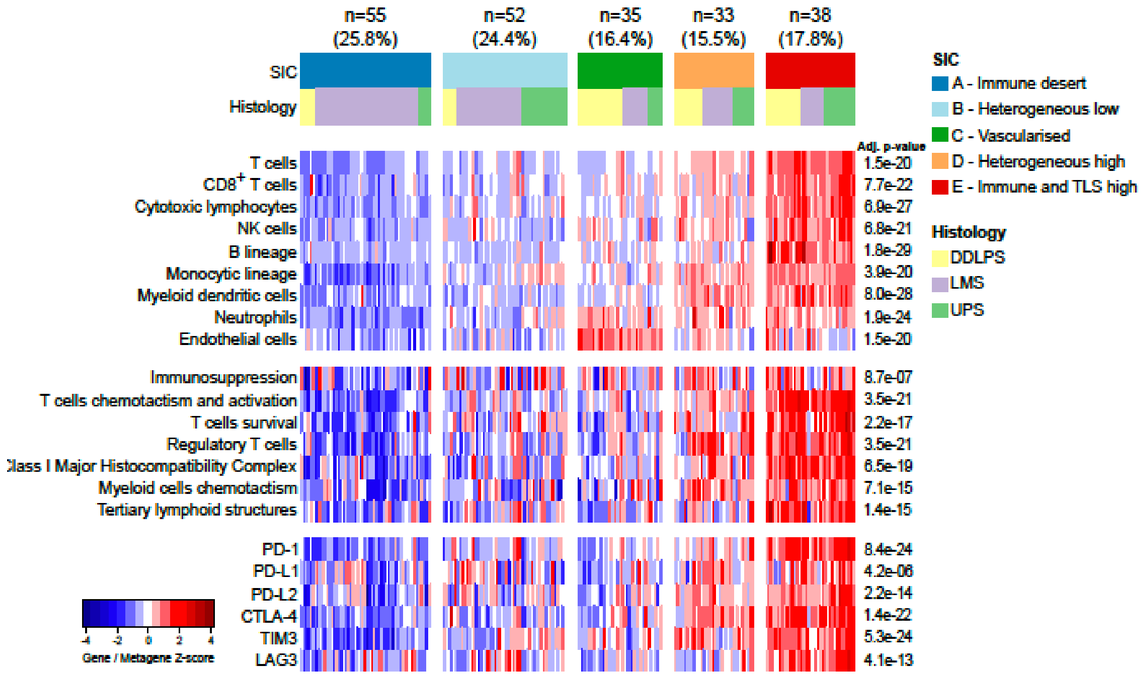
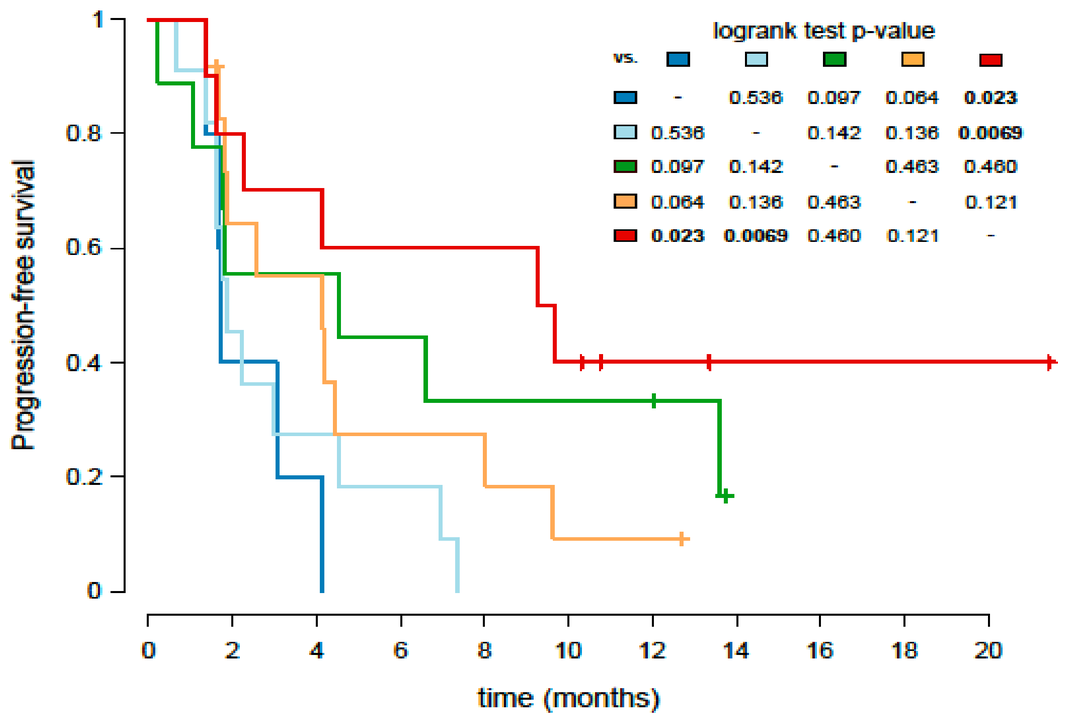
DISCLOSURES

- Breelyn A. Wilky, MD
  - **Consultant/Advisory Role:** Adaptimmune, Adcendo,
  - Daiichi Sankyo, Deciphera, Epizyme, Polaris, Springworks
  - **Institutional Research Funding:** Exelixis
  - **Institutional Coordinating PI:** Agenus

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

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

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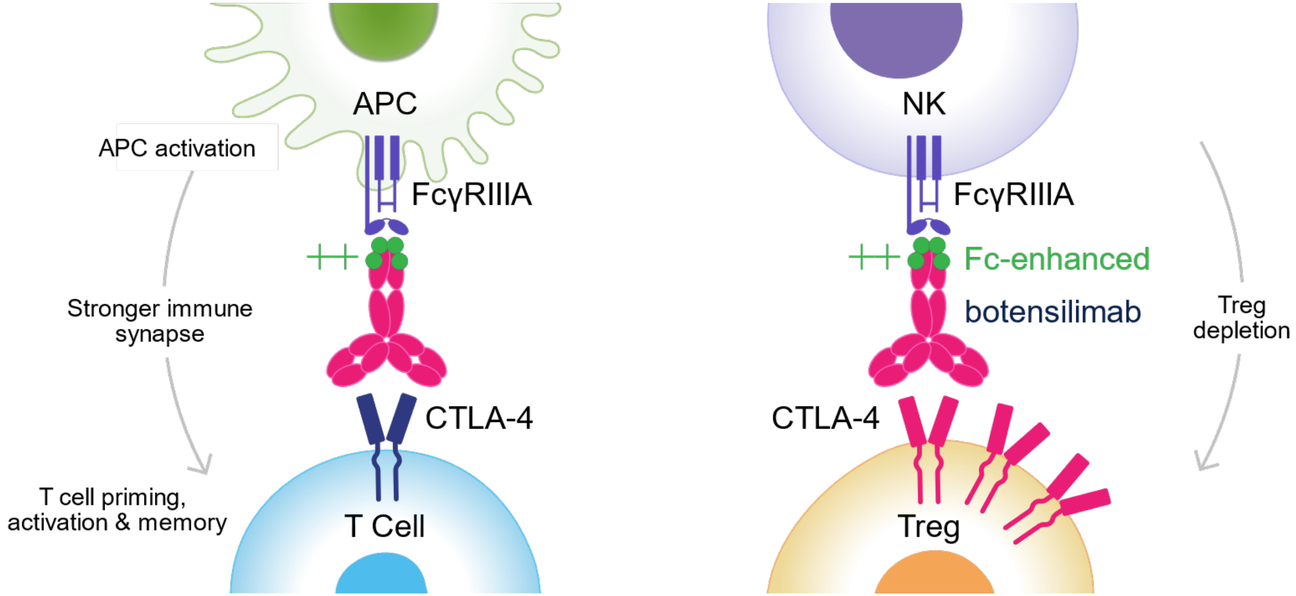
BOTENSILIMAB IS A NOVEL INNATE & ADAPTIVE IMMUNE ACTIVATOR

Botensilimab

Multifunctional Fc-enhanced Anti-CTLA-4 Antibody



Driving Activity in Cold or I-O Refractory Tumors[1-4]

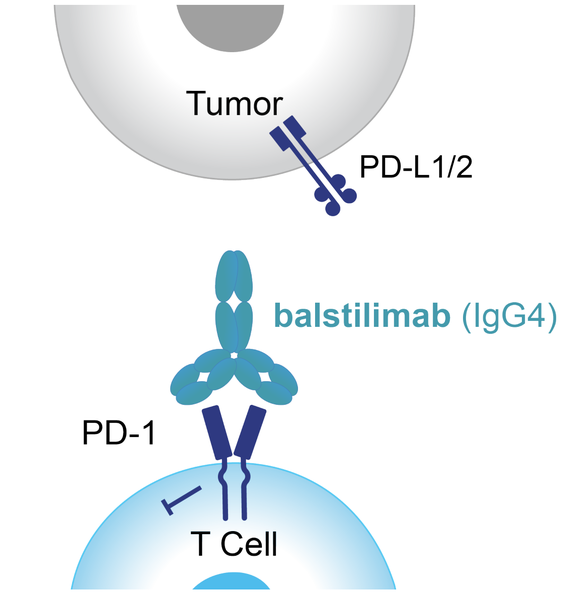
- **Enhanced** T cell priming, expansion, memory[5,6]
- **Enhanced** frequency of APCs
- **Enhanced** Treg depletion
- **Reduced** complement mediated toxicity

1. Wilky B. SITC 2022 Annual Meeting. Oral #778. **2.** Wilky B, et al. Oral Presentation at CTOS 2022. Vancouver, CA. #1294633. **3.** El-Khoueiry A, et al. Oral Presentation at ASCO GI 2023. San Francisco, CA, USA. Rapid Oral #LBA8. **4.** Bockorny B, et al. Scientific Plenary Presentation at SGO 2023. Tampa, Florida. #2. **5.** Waight et al. Cancer Cell. 2018;33(6): 1033-1047. **6.** Delepine C, et al. Poster Presentation at SITC 2022. Boston, MA, USA. #470

BALSTILIMAB IS A CLINICALLY VALIDATED PD-1 INHIBITOR

Balstilimab

Anti PD-1 Antibody



Highly Active Anti-PD-1 mAb[1,2]

- **Complete blocker** of PD-1- PD-L1/2 interactions
- **Enhanced** T cell activation and effector function

1. O'Malley, et al. *Gynecol Oncol*. 2021; 163: 274-280. **2.** 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]

Key Eligibility

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

Endpoints

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

Treatment (*up to 2 years*)

bot*

[Fc-enhanced CTLA-4]

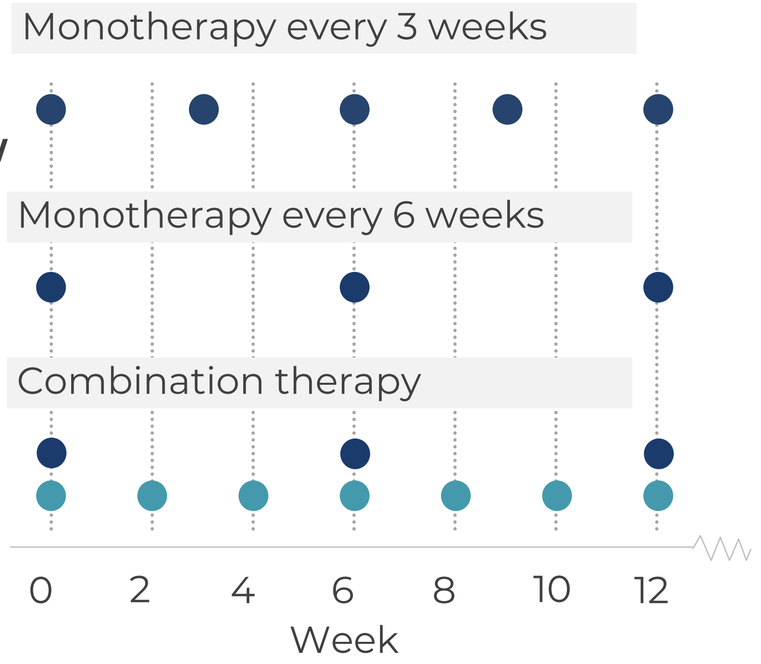
0.1, 0.3, 1, 2, 3 mg/kg Q3W

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.
*Crossover to combination from bot monotherapy was permitted.

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C-800-01 STUDY: SARCOMA COHORT

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

Evaluable Study Population*

- **41** treated with 1 or 2 mg/kg bot + bal as of 06 April 2023 with ≥1 Q6W imaging assessment

Treatment (*up to 2 years*)

[1]https://clinicaltrials.gov/ct2/show/NCT03860272.
*Nine additional patients were treated as of 06 April 2023 but had not received the first 6-week tumor assessment (ITT/Safety population=50).
Data cutoff: 17-Aug-2023.

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PATIENT CHARACTERISTICS

	All Sarcoma N=41
Age, median (range)	61 (31–80)
Sex, n (%)	
Male	13 (32)
Female	28 (68)
ECOG PS at baseline, n (%)	
0	16 (39)
1	25 (61)
Prior lines of therapy, n/N (%)	
Median (range)	3 (1–10)
≥3	20/38 (53)
Botensilimab dose, n (%)	
1 mg/kg	27 (66)
2 mg/kg	14 (34)
Prior PD-(L)1 therapy, n/N (%)	6/38 (16)
TMB >10 mut/Mb, n/N (%)	2/16 (13)
PD-L1 (≥1% positive), n/N (%)	7/27 (26)

	All Sarcoma N=41
Sarcoma subtype, n (%)	
Angiosarcoma (AS)	**12 (29)**
Cutaneous	7 (17)
Visceral	5 (12)
Leiomyosarcoma (LMS)	**16 (39)**
Soft tissue	13 (32)
Uterine	3 (7)
Other	**13 (32)**
Dedifferentiated liposarcoma (ddLipo)	4 (10)
Undifferentiated pleiomorphic (UPS)	4 (10)
Undifferentiated spindle cell	2 (5)
Myxofibrosarcoma	1 (2)
Osteosarcoma/spindle cell	1 (2)
Myxoid liposarcoma	1 (2)

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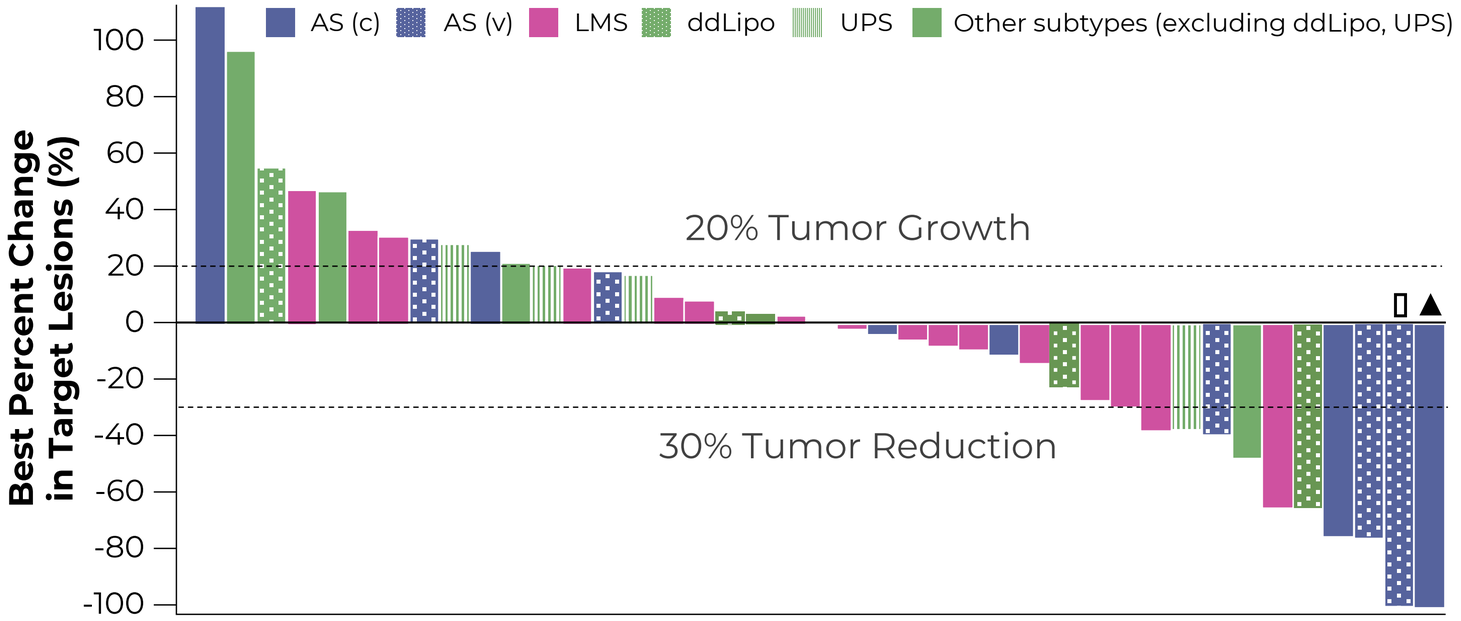
BROAD ACTIVITY IN HETEROGENOUS SARCOMA POPULATION



Two additional patients showed significant clinical response (NOT INCLUDED in RECIST v1.1 response rate):

▯ 1 deep PR in AS (v) by iRECIST; patient had minor early progression at 6 weeks followed by a deep response in target lesion (-98%) that is durable at 102+ weeks.

▲ 1 unconfirmed CR in AS (c); patient had a visible skin lesion that disappeared on exam, images on file.

All Sarcoma (N=41)*	iRECIST	RECIST v1.1
ORR†, % (95% CI)	**20%** (9–35)	**17%** (7–32)
ORR at 1mg/kg (%) n=27	15%	11%
ORR at 2mg/kg (%) n=14	29%	29%
BOR, n (%)		
CR	0	0
PR	8 (20)	7 (17)
SD	18 (44)	18 (44)
PD	15 (37)	16 (39)
Median DOR, months (95% CI)	**19.4** (1.9–NR)	**11.8** (1.9–NR)
DCR (CR + PR + SD), % (95% CI)	**63%** (47–78)	**61%** (45–76)
CBR (CR + PR + SD at 6 months), % (95% CI)	**27%** (14–43)	**24%** (12–40)
6-month PFS, % (95% CI)	**40%** (23–57)	**37%** (20–54)

* Median f/u: 5.7 months (range: 1.4-28.4).
† One response confirmed after data cutoff.

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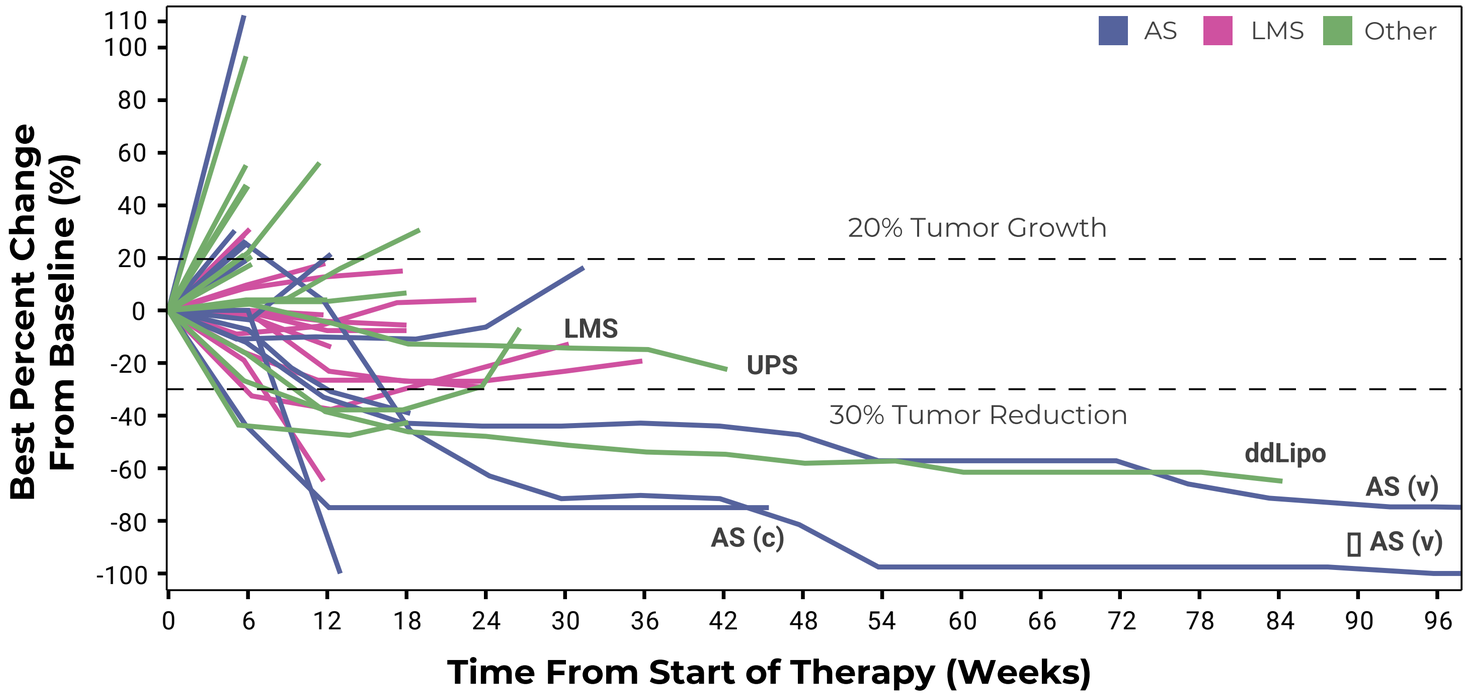
DURABILITY OF BENEFIT IN HETEROGENOUS SARCOMA POPULATION



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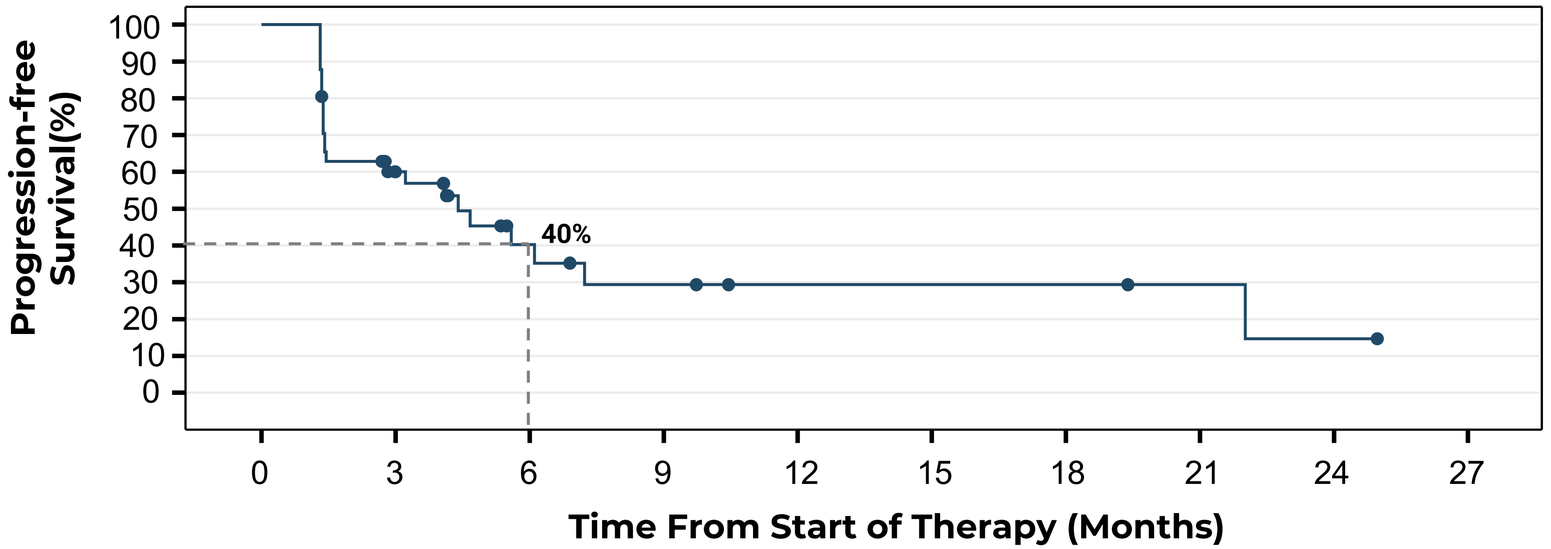
PROGRESSION-FREE SURVIVAL



Number at Risk										
All Sarcoma	41	19	8	5	3	3	3	2	1	0

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SAFETY

TRAEs in ≥10% of All Sarcoma Patients in the ITT/Safety Population (N=50)

	All Grades	Grade 3	Grade 4
Any*	39 (78)	6 (12)	0
Gastrointestinal			
Immune-mediated diarrhea/colitis†	17 (34)	4 (8)	0
Nausea	7 (14)	1 (2)	0
Vomiting	6 (12)	1 (2)	0
Constitutional			
Fatigue	12 (24)	1 (2)	0
Pyrexia	9 (18)	0	0
Chills	7 (14)	0	0
Endocrine			
Hypothyroidism	5 (10)	0	0
Musculoskeletal			
Myalgia	6 (12)	1 (2)	0
Skin			
Rash	7 (14)	1 (2)	0
Rash maculo-papular	6 (12)	0	0

- No new safety signals
- Safety consistent across tumor types
- No cases of related hypophysitis, pneumonitis, hepatitis or myocarditis
- 8% discontinued due to a TRAE
- No grade 4 or 5 TRAEs

* Note: A higher frequency of any TRAEs was observed in patients receiving 2 mg/kg of botensilimab (93%) relative to the 1 mg/kg dose (70%).
† Patient received immunosuppressants (eg, steroids and/or a TNF-α inhibitor).

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CONCLUSIONS & FUTURE DIRECTIONS

- Botensilimab and balstilimab demonstrates objective responses, durability, and disease stabilization in poorly immunogenic or “cold” sarcoma subtypes
- Durable and broad clinical benefit observed in visceral and cutaneous angiosarcoma, leiomyosarcoma, dedifferentiated liposarcoma, and undifferentiated pleomorphic sarcoma
- Relapsed/refractory sarcoma represents an unmet medical need where previous immunotherapies have shown limited activity
- Safety profile is manageable, and reversible with diarrhea/colitis the most clinically significant immune-mediated adverse event
- The current phase 1 study (C-800-01) is actively enrolling patients in an expansion sarcoma cohort (NCT03860272)

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ACKNOWLEDGEMENTS

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- 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.

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ABBREVIATIONS

AE, adverse event
APC, antigen presenting cell
bal, balstilimab
BOR, best overall response
bot, botensilimab
CI, confidence interval
CBR, clinical benefit rate
CR, complete response
CTLA-4, cytotoxic T-lymphocyte antigen-4
DCR, disease control rate
DOR, duration of response
ECOG, Eastern Cooperative Oncology Group
Fc, fragment crystallizable
F/U, follow-up
ICI, immune checkpoint inhibitors
I-O, immunotherapy
ITT, intent-to-treat
NSCLC, non-small cell lung cancer
NR, not reached
ORR, objective response rate
PD, progressive disease
PD-1, programmed death receptor-1
PD-L1, programmed death-ligand 1
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
TRAE, treatment-related adverse event

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