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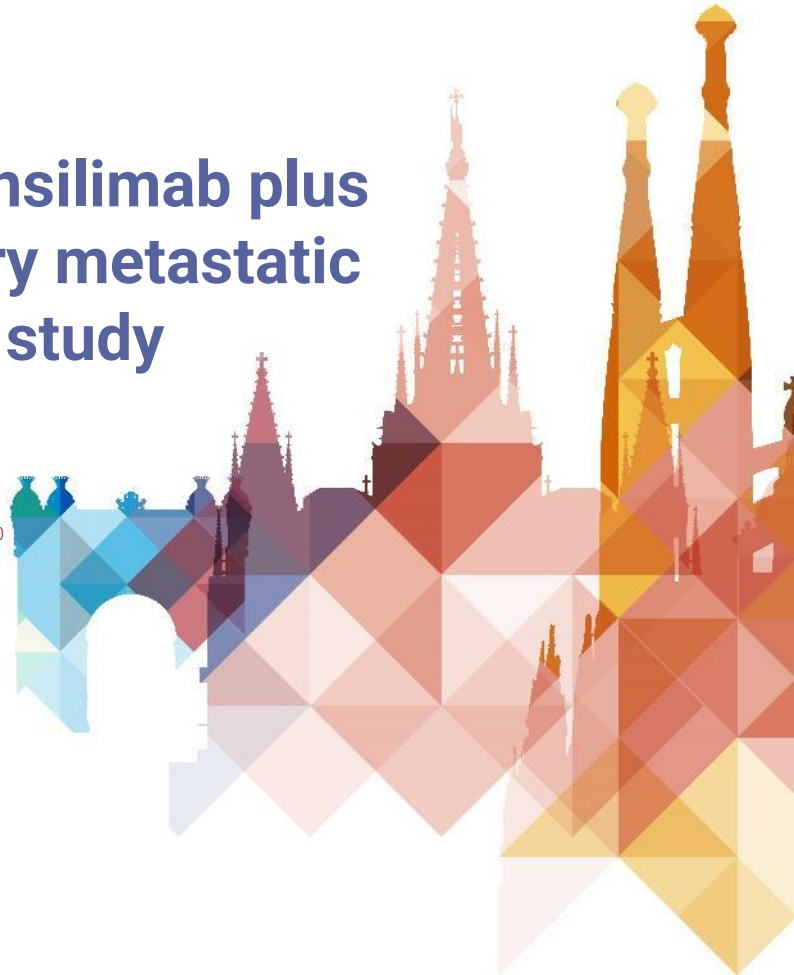
Updated efficacy and safety of botensilimab plus balstilimab in patients with refractory metastatic sarcoma from an expanded phase 1 study



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13 September 2024

Declaration of Interests

Breelyn A. Wilky

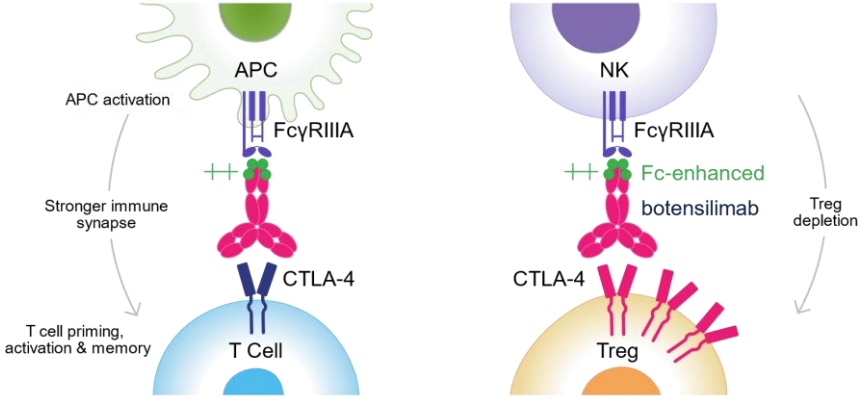
- Consulting or advisory role for Aadi Bioscience, Adcendo, Boehringer Ingelheim, Deciphera, Epizyme, Polaris and SpringWorks
- Research funding from Exelixis
- Travel, accommodations or expenses support from Agenus Inc.

Botensilimab Mechanism of Action

- SOC chemotherapy in 3L setting is limited with response rates between 6–12% and currently available ICIs are ineffective for the majority of sarcoma patients[1-4]
- Botensilimab is a multifunctional Fc-enhanced CTLA-4 inhibitor with potential to expand current reach of immunotherapy[5]
- Botensilimab has proven activity in multiple cold / I-O refractory solid tumors via enhanced innate and adaptive antitumor functionalities[5-7]
- Balstilimab is a highly active and clinically validated PD-1 inhibitor[8,9]

Botensilimab

Multifunctional Fc-enhanced Anti-CTLA-4 Antibody



- **Enhanced** T cell priming, expansion, memory
- **Enhanced** frequency of activated APCs
- **Enhanced** Treg depletion
- **Reduced** complement binding thereby potentially reducing complement-mediated toxicities

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Breelyn A. Wilky, MD

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2. Van der Graaf W, et al. *Lancet*. 2012;379:1879-1886.
3. Demetri GD, et al. *J Clin Oncol;* 2016; 34:786-793.
4. Petitprez F, et al. *Nature*. 2020;577:556-560.
5. Bullock A, et al. *Nature Medicine*. 2024; doi:10.1038/s41591-024-03083-7.
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7. Chand D, et al. *Cancer Discov*. 2024;doi: 10.1158/2159-8290.CD-24-0190.
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Baseline Characteristics

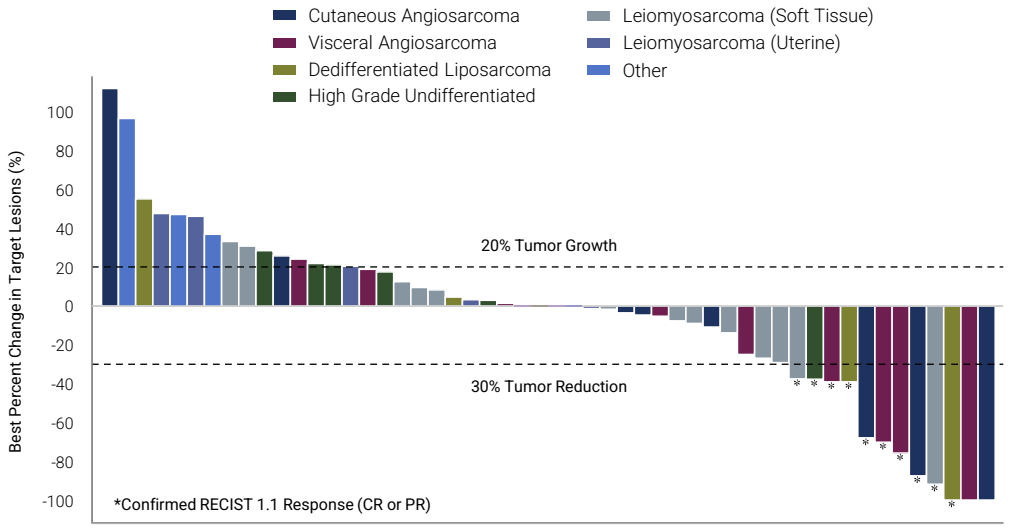
	N=64
Age, median (range)	61 (30–81)
Sex, n (%)	
Male	22 (34%)
Female	42 (66%)
ECOG PS at baseline, n (%)	
0	26 (41%)
1	38 (59%)
Prior lines of therapy, n(%)	
Median (range)	3 (0–10)
≥3	34 (53%)
Prior PD-(L)1 or CTLA-4 therapy, n/N (%)	10/60 (17%)
Botensilimab dose, n (%)	
1 mg/kg	47 (73%)
2 mg/kg	15 (23%)
Crossover[b]	2 (3%)

Sarcoma subtype, n (%)	
Angiosarcoma	25 (39%)
Cutaneous	14 (22%)
Visceral	11 (17%)
Leiomyosarcoma	22 (34%)
Soft tissue	16 (25%)
Uterine	6 (9%)
High grade undifferentiated	8 (13%)
Dedifferentiated liposarcoma	6 (9%)
Other[a]	3 (5%)

[a]'Other' subgroup consists of one patient with myxoid liposarcoma, one patient with osteosarcoma/spindle cell sarcoma, and another patient with synovial sarcoma.
[b]Two rescue patients received 2 mg/kg bot alone and then transitioned to the combination of 2 mg/kg bot + bal.

Data cutoff: 25-Jul-2024.

Broad Activity in Heterogenous Sarcoma Population



	Efficacy Evaluable n=52
ORR[a], % (95% CI)	**23%** (13–37)
BOR, n (%)	
CR	1 (2%)
PR	11 (21%)
SD	23 (44%)
PD	17 (33%)
Median DOR, months (95% CI)	**21.7** (3.4–NR)
CBR (CR + PR + SD at 24 weeks), % (95% CI)	**35%** (22–49)

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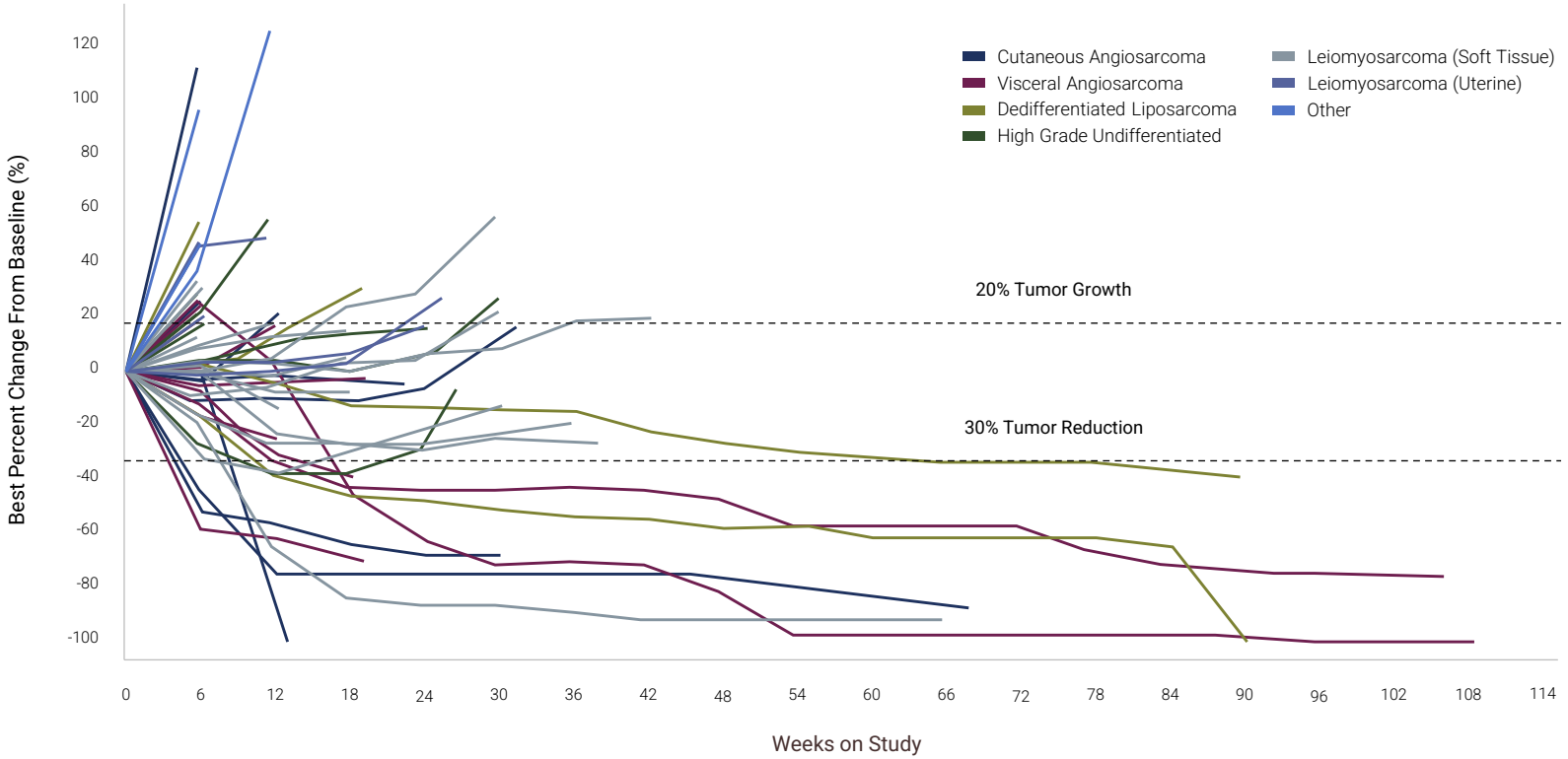
[a]Data include an uCR in a cutaneous angiosarcoma patient who had a visible skin lesion that disappeared on exam (images on file) with subsequent clinical progression and a PR in a visceral angiosarcoma patient with minor early progression at 6 weeks followed by a deep response in a target lesion that is durable beyond 3 years.

Data cutoff: 25-Jul-2024.
Median f/u was 9.1 months.

Broad Activity in Heterogenous Sarcoma Population



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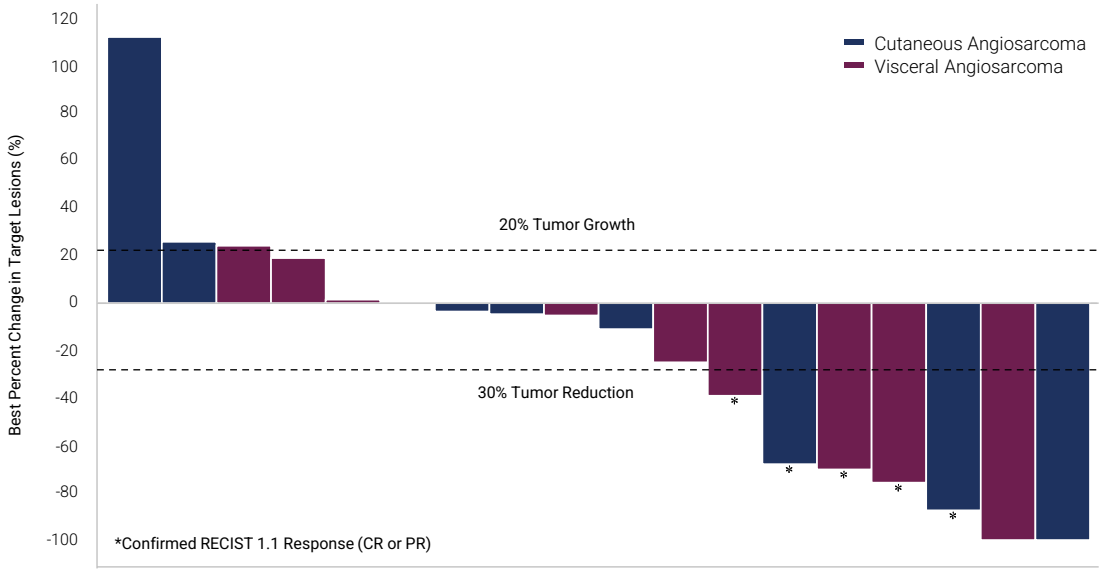
Significant Activity in Cutaneous and Visceral Angiosarcoma



	Angiosarcoma n=18
ORR[a], % (95% CI)	**39%** (17—64)
Cutaneous (n=9)	33%
Visceral (n=9)	44%
BOR, n (%)	
CR	1 (6%)
PR	6 (33%)
SD	8 (44%)
PD	3 (17%)
Median DOR, months (95% CI)	**21.7** (1.9—NR)
CBR (CR + PR + SD at 24 weeks), % (95% CI)	**44%** (22—69)

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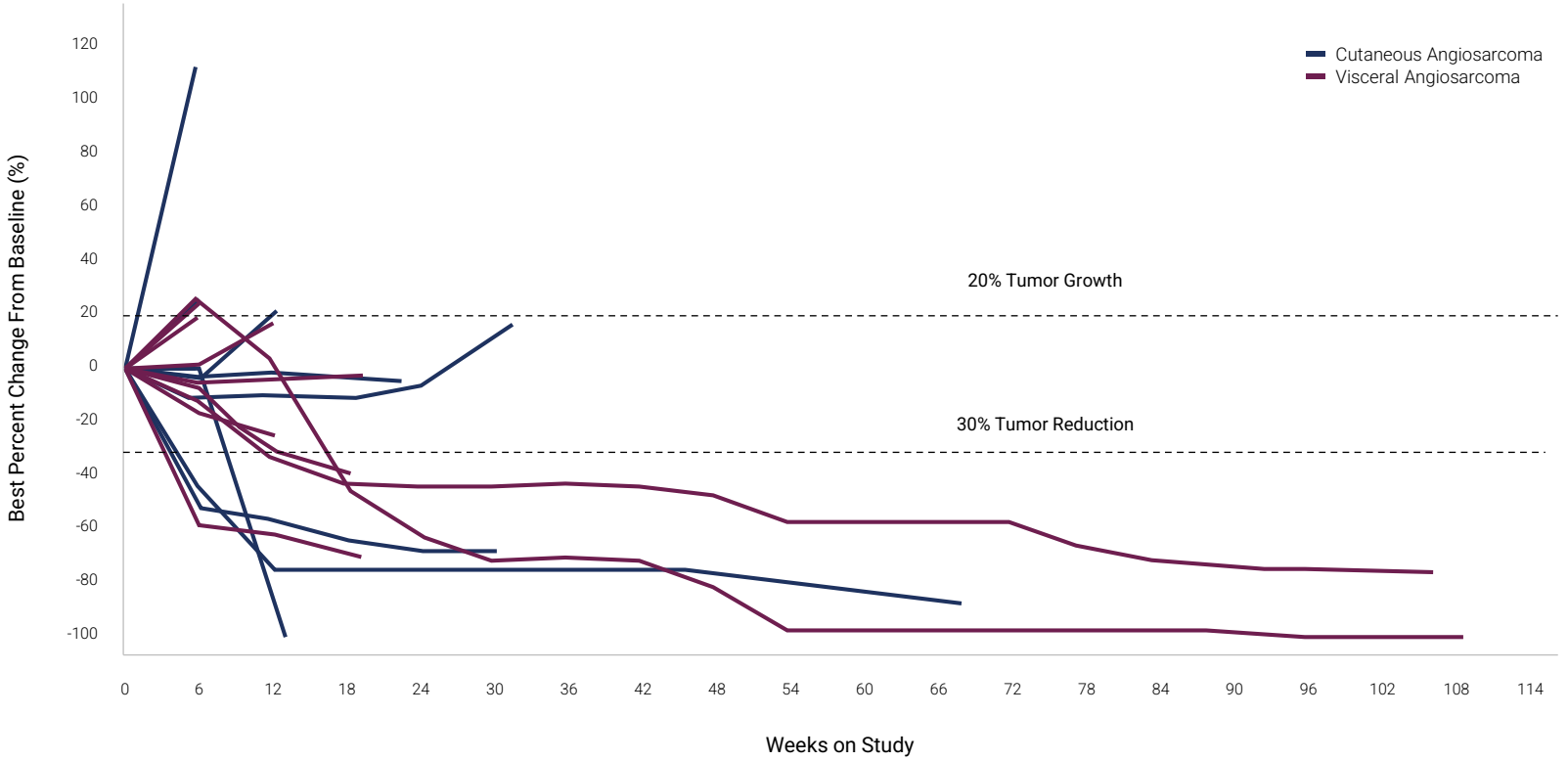
Data cutoff: 25-Jul-2024.
Median f/u was 6.9 months.

Significant Activity in Cutaneous and Visceral Angiosarcoma



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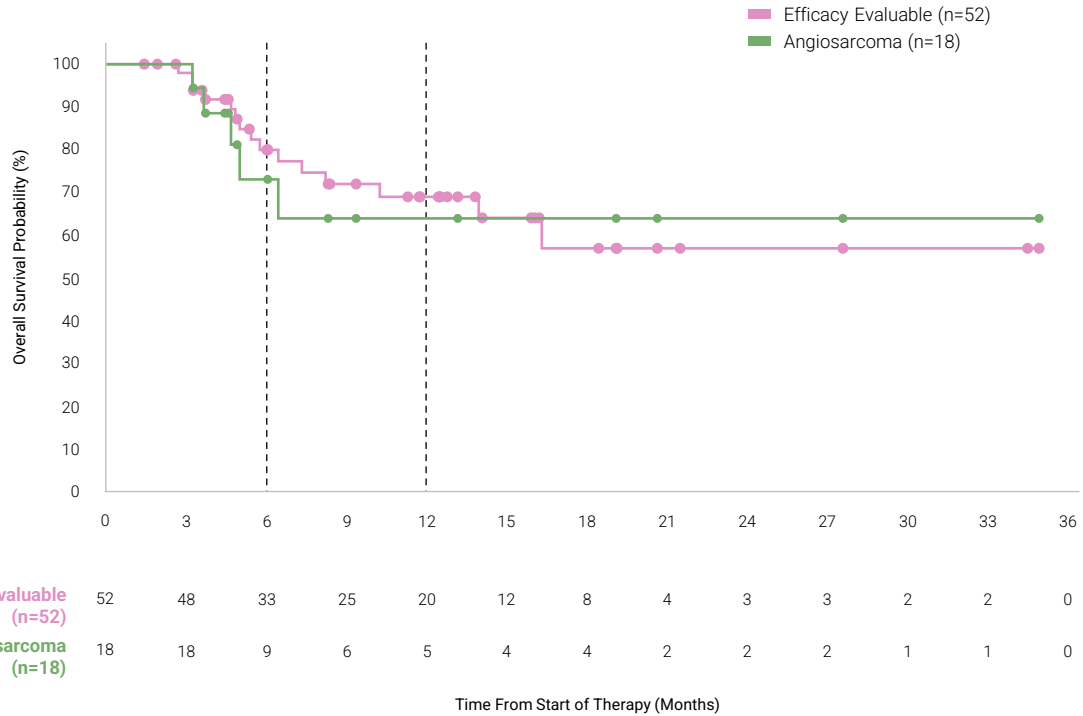
Overall Survival

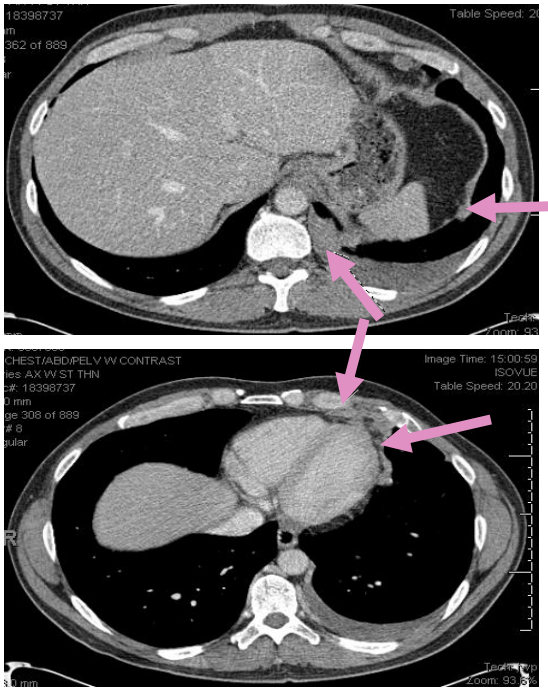


	Efficacy Evaluable n=52	Angiosarcoma n=18
Median OS, months (95% CI)	**NR** (14.0—NR)	**NR** (5.0—NR)
12-month OS, % (95% CI)	**69%** (52—81)	**64%** (33—84)
Median f/u, months (range)	**9.1** (1.4—39.7)	**6.9** (1.4—39.7)

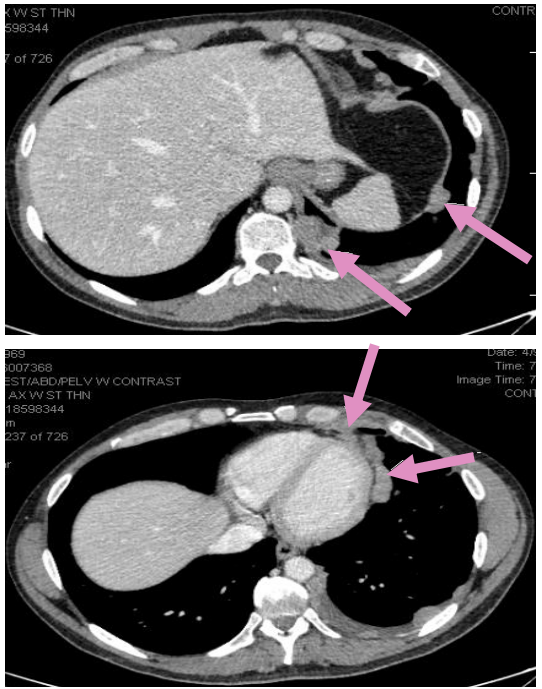
Data cutoff: 25-July-2024.

Deep Response in a Visceral Angiosarcoma Patient

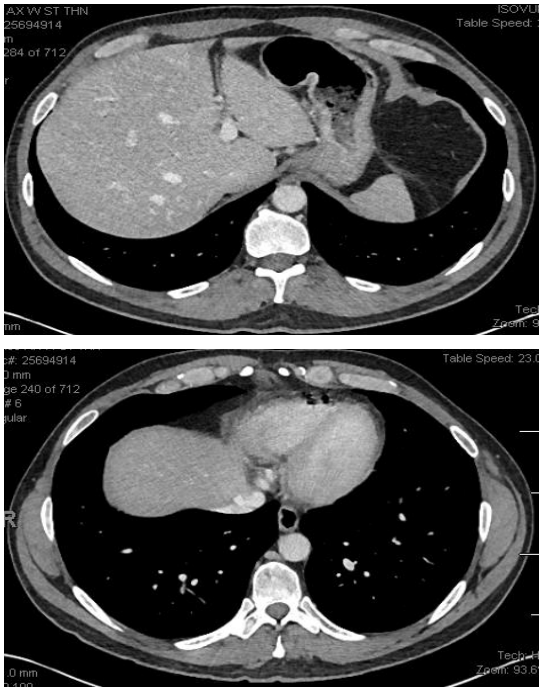
I. Baseline Scan



II. Pseudoprogression at 6 Weeks



III. Best Response



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This patient is included in efficacy and safety analyses.

Safety

TRAEs in ≥10% of All Treated Sarcoma Patients (N=64)

	All Grades	Grade 3	Grade 4
Any, n (%)	53 (83)	11 (17)	0
Gastrointestinal			
Diarrhea/colitis	23 (36)	4 (6)	0
Nausea	8 (13)	1 (2)	0
Vomiting	7 (11)	1 (2)	0
Skin			
Rash	19 (30)	1 (2)	0
Constitutional			
Fatigue	17 (27)	1 (2)	0
Pyrexia	14 (22)	0	0
Chills	11 (17)	0	0
Endocrine			
Hypothyroidism	7 (11)	0	0
Musculoskeletal			
Myalgia	7 (11)	1 (2)	0

- Sarcoma safety similar to other tumor types in the trial with no new safety signals
- No cases of related hypophysitis, pneumonitis, or myocarditis
- 13% discontinued bot due to a bot-related TRAE
- No grade 4 or 5 TRAEs

Conclusions & Future Directions

- Deep, durable responses resulting in extended survival were observed in a broad range of sarcoma subtypes
- The angiosarcoma cohort is particularly promising given the high percentage of colder visceral angiosarcomas
    - ORR in visceral angiosarcoma was 44%
- The adverse event profile is manageable and reversible with no new safety signals identified
    - Diarrhea/colitis — most frequent TRAE (36% of patients; 6% grade 3)
- The phase 1 study (C-800-01) continues to enroll patients in the angiosarcoma cohort (NCT03860272) at the University of Colorado (USA) and the Royal Marsden (UK)
- A phase 2 study is currently under consideration

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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 at 24 weeks
CR, complete response
CTLA-4, cytotoxic T-lymphocyte antigen-4
DCR, disease control rate at 6 weeks
DOR, duration of response
EE, efficacy evaluable
ECOG, Eastern Cooperative Oncology Group
Fc, fragment crystallizable
F/U, follow-up
ICI, immune checkpoint inhibitors
I-O, immunotherapy
ITT, intention-to-treat
NR, not reached
ORR, objective response rate
OS, overall survival
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
RECIST, Response Evaluation Criteria In Solid Tumors
R/R, relapsed/refractory
SD, stable disease
TRAE, treatment-related adverse event
Treg, regulatory T cell
uCR, unconfirmed complete response

Acknowledgements

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