Abstract 11565: A phase 2 trial with a safety lead-in to evaluate the addition of sotigalimab, a CD40 agonistic monoclonal antibody, to standard-of-care doxorubicin for the treatment of advanced sarcoma

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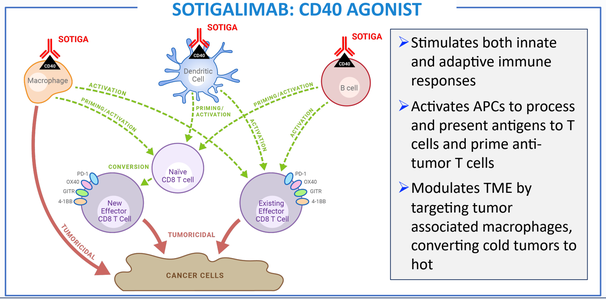
SCAN ME

Background

- Standard first-line doxorubicin provides objective response rate (ORR) <15% and median progression free survival (mPFS) of 4-6 mos in advanced soft tissue sarcoma (STS).
- Immune checkpoint inhibitors have limited efficacy in STS due to insufficient T-cell activation and infiltration by immunosuppressive macrophages.
- Sotigalimab, a high-affinity humanized monoclonal antibody for CD40, promotes antigen presentation, stimulates T-cells, and reprograms immunosuppressive macrophages.

Study Rationale

- In preclinical studies, CD40 agonists can increase the effectiveness of cancer vaccines, chemotherapy, and radiation, as well as increase *in vivo* expansion and efficacy of adoptive T cell therapies and CAR-T approaches.
- In clinical studies, sotigalimab demonstrated single-agent activity and safety in immunotherapy naïve patients with melanoma and has demonstrated that a single dose can induce intense immune infiltration in several cancers – turning a "cold" tumor "hot"[1].



- Stimulates both innate and adaptive immune responses
- Activates APCs to process and present antigens to T cells and prime anti-tumor T cells
- Modulates TME by targeting tumor associated macrophages, converting cold tumors to hot

Figure 1. Sotigalimab mechanism of action harnessing both innate and adaptive immunity.

Study Design and Endpoints

- This is an open-label, single-arm, multicenter, phase 2 study with a safety lead-in to evaluate the combination of the CD40 agonist, sotigalimab (0.3mg/kg), with standard doxorubicin (75mg/m^2) chemotherapy in anthracycline-naïve advanced STS.
  - Primary endpoint: Objective response rate (ORR)
  - Secondary endpoints: Safety, progression free survival (PFS)

Key Eligibility Criteria:

- Age ≥ 18 years
- Histologically confirmed, unresectable or metastatic soft tissue sarcoma (excluding Kaposi sarcoma and gastrointestinal stromal tumor)*
- Measurable disease per RECIST v1.1, amenable to biopsy
- Any number of prior lines of therapy, including none
- Anthracycline-naïve as well as appropriate for anthracycline therapy
- No prior immunotherapy

Study Design (cont.)

- Statistical Plan
  - Initially designed as a 27-patient study open to all STS subtypes except GIST and KS. Study subsequently was amended to include 32 patients and limit enrollment to undifferentiated pleomorphic sarcoma (UPS), leiomyosarcoma (LMS) and dedifferentiated liposarcoma (DDLPS).
  - 85% power with $\alpha = 0.05$ to test ORR 16% versus 32%.
  - Simon Stage 1 criteria was met and the trial proceeded to Stage 2 (32 patients). If ≥ 7/32 respond in Stage 2, the primary endpoint is met.
- A safety lead-in of 6 patients demonstrated that the combination regimen had a favorable safety profile.

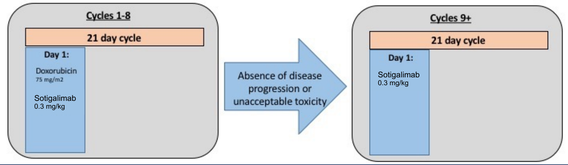


Figure 2. Treatment regimen of doxorubicin (75mg/m2) D1 + sotigalimab (0.3mg/kg) D1 in 21-day cycles

Demographics

	No. (%), n=32
Age (median)	61.5
Sex	
Female	17 (53.1)
Male	15 (46.9)
ECOG PS	
0	21 (65.6)
1	11 (34.4)
Race	
Asian	4 (12.5)
Black	8 (25)
White	20 (62.5)
Ethnicity	
Hispanic	3 (9.4)
Not Hispanic	29 (90.6)

	No. (%), , n=32
Histology	
DDLPS	9 (28)
UPS/MFH	10 (31.2)
LMS	10 (31.2)
Other	3 (9)
LPS, not otherwise specified (NOS)	1 (3)
Malignant hemangioendothelioma	1 (3)
Solitary fibrous tumor	1 (3)
Prior systemic lines	
0	19 (59)
≥ 1	13 (41)
Surgery	9 (28)
Radiation	13 (41)

Table 1. Demographics and clinical characteristics.

Efficacy

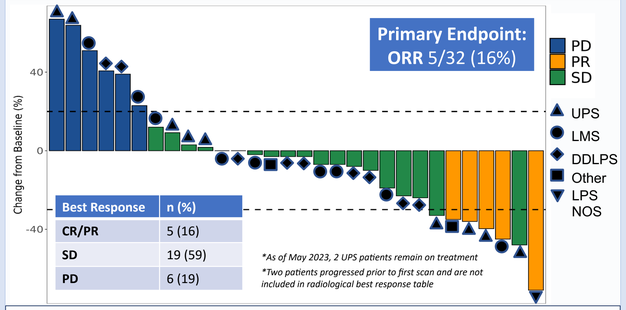


Figure 3. Waterfall plot of best overall response.

Efficacy (cont.)

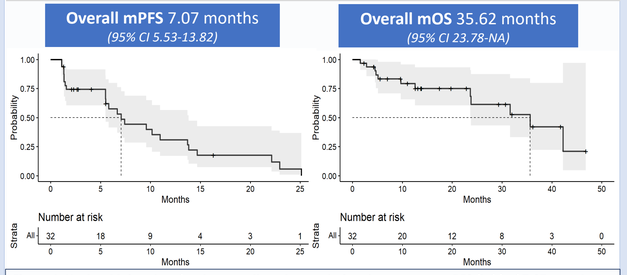


Figure 4. Kaplan-Meier plots for the overall study population demonstrate mPFS (left) of 7.07 months which is longer than historical mPFS for doxorubicin monotherapy of 4-6 months and mOS (right) of 35.62 months which is longer than historical mOS of 12-20 months for doxorubicin monotherapy control arms in recent trials[2,3].

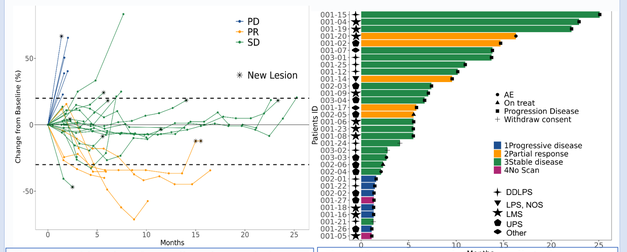


Figure 5. Spider plot of overall study population demonstrates long duration of response with PR lasting > 15 months and SD > 25 months

Figure 6. Swimmer's plot of overall study population. Two UPS patients remain on treatment.

Subtype-specific analysis of mPFS

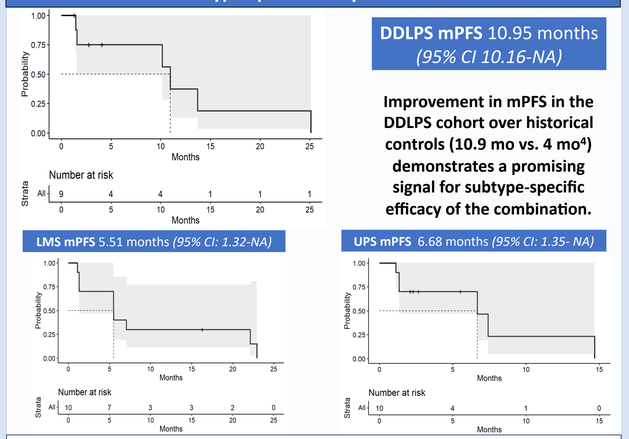


Figure 7. Subtype-specific Kaplan-Meier plots demonstrating PFS.

Safety

- There were no DLTs during the safety lead in.
- Grade 3/4 TRAEs occurred in 56% (18/32)
  - Most common grade 3/4 TRAEs were hematologic – neutropenia (31%), febrile neutropenia (19%), and anemia (19%) and were consistent with doxorubicin use.
  - 19% of patients had cytokine release syndrome (all grade 1/2).
  - No additive/synergistic and no new unexpected toxicities were observed with the combination.
  - 6/32 (19%) and 11/32 (34%) pts had a dose interruption of doxorubicin and sotigalimab, respectively. 3/32 (9.4%) withdrew study treatment for AEs.

Adverse Event	Overall	Grade 1	Grade 2	Grade 3	Grade 4
Any Type	32 (100%)	5 (15.62%)	9 (28.12%)	6 (18.75%)	12 (37.5%)
Nausea	16 (50%)	10 (31.25%)	5 (15.62%)	1 (3.12%)	0 (0%)
Fatigue	15 (46.88%)	11 (34.38%)	3 (9.38%)	1 (3.12%)	0 (0%)
Alopecia	12 (37.5%)	4 (12.5%)	8 (25%)	0 (0%)	0 (0%)
Neutrophil count decreased	11 (34.38%)	1 (3.12%)	0 (0%)	0 (0%)	10 (31.25%)
Mucositis oral	10 (31.25%)	0 (0%)	8 (25%)	2 (6.25%)	0 (0%)
Fever	9 (28.12%)	7 (21.88%)	2 (6.25%)	0 (0%)	0 (0%)
Infusion related reaction	8 (25%)	2 (6.25%)	5 (15.62%)	0 (0%)	1 (3.12%)
Anemia	7 (21.88%)	0 (0%)	1 (3.12%)	6 (18.75%)	0 (0%)
Constipation	6 (18.75%)	6 (18.75%)	0 (0%)	0 (0%)	0 (0%)
Cytokine release syndrome	6 (18.75%)	3 (9.38%)	3 (9.38%)	0 (0%)	0 (0%)
Febrile neutropenia	6 (18.75%)	0 (0%)	0 (0%)	6 (18.75%)	0 (0%)
Pruritus	6 (18.75%)	3 (9.38%)	3 (9.38%)	0 (0%)	0 (0%)
Vomiting	6 (18.75%)	5 (15.62%)	1 (3.12%)	0 (0%)	0 (0%)
Dysgeusia	5 (15.62%)	5 (15.62%)	0 (0%)	0 (0%)	0 (0%)
Platelet count decreased	5 (15.62%)	1 (3.12%)	1 (3.12%)	1 (3.12%)	2 (6.25%)
Rash maculo-papular	5 (15.62%)	5 (15.62%)	0 (0%)	0 (0%)	0 (0%)
Anorexia	4 (12.5%)	1 (3.12%)	3 (9.38%)	0 (0%)	0 (0%)
Headache	4 (12.5%)	2 (6.25%)	2 (6.25%)	0 (0%)	0 (0%)

Table 2. TRAEs in ≥ 10% of patients treated

Summary and Future Directions

- Although primary endpoint of ORR was not met, encouraging signs of clinical benefit were observed in certain subtypes.
- Sotigalimab (0.3 mg/kg) + doxorubicin (75 mg/m^2) every 21 days is **safe and well tolerated** in STS.
- This data indicates that the combination **improved mPFS for the DDLPS subtype and improved mPFS and mOS for the overall STS study population over historical data.**
- Based on this, a **10 pt expansion cohort** is currently enrolling to investigate the promising signal in DDLPS.

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