A PHASE 1B/2 STUDY OF LIPOSOMAL ANNAMYCIN (ANN) IN PATIENTS WITH PREVIOUSLY TREATED SOFT-TISSUE SARCOMAS (STS) WITH PULMONARY METASTASES

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Objectives: The most common site of STS metastases is the lungs. Doxorubicin (DOX) remains a mainstay for standard treatment, but clinical benefit is not prolonged and toxicities, especially cardiotoxicity, limit its use. L-Annamycin ("ANN" or "Annamycin")" is a multilamellar liposomal formulation active against multidrug-resistant tumors and does not elicit cardiotoxicity. As preclinical studies documented ANN localizes in pulmonary tissues at higher concentrations than DOX, it is an ideal candidate to explore in subjects with lung metastases. The primary objective of the Phase 1b portion of the study was to evaluate safety and to identify the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D). The primary objective of Phase 2 was to assess efficacy, including, but not limited to, overall response rate (ORR), ORR targeted to pulmonary metastases, disease control rate (DCR), and progression-free and overall survival (PFS and OS, respectively).

Methods: ANN was administered on Day 1, followed by 20 days off. Safety monitoring included ECHOs, ECGs, cardiac biomarkers, and laboratory evaluations. Treatment continued every 21 days until disease progression, clinical deterioration, or unacceptable toxicity. Efficacy was monitored radiographically every 6 weeks while on therapy, then every 3 months. In Phase 1b, dose escalation proceeded according to a 3 + 3 design. During Phase 2, up to 25 subjects were to be enrolled at the RP2D. Eligible subjects were ≥18 years of age with a confirmed diagnosis of STS, unresectable, measurable disease in the lung, progression on prior therapy, and no significant comorbidities. Subjects evaluable for efficacy were assessed for response to treatment by radiologic imaging.

Results: 19 subjects were enrolled in the Phase 1b portion of the study. The median number of cycles administered was 2. There were no significant safety concerns or unexpected SAEs up to the 390 mg/m^2 dose. The RP2D was defined as 330 mg/m^2. The most frequently reported AEs related to ANN were in the system organ class of Investigations (Table 1). There was no evidence of cardiotoxicity as measured by ejection fraction, strain analyses, ECGs, and cardiac biomarkers including Troponin-I and T. In Phase 2, 14 subjects (median # of prior therapies = 3) received at least 2 cycles of 330 mg/m^2. Of these 14 subjects, 9 (64%) showed stable disease (SD) through 2 cycles (5 [36%] of whom continued to show SD through 4 cycles), and 2 (14%) showed SD through 6 cycles. Of these 2, one subject maintained SD through the end of 6 cycles prior to progressing ~6.2 months after initiating treatment with ANN. The other subject maintained SD through 8 cycles prior to progressing ~6.9 months after initiating treatment with ANN. 3 subjects continue to be followed for PFS, and 12 of 14 subjects in the Phase 2 efficacy population continue to be followed for OS.

Table 1: L-Annamycin-Related Adverse Events by Decreasing Frequency of MedDRA Coded PT- Ph1b

Preferred Term	210 mg/m² (N=4)	270 mg/m² (N=3)	330 mg/m² (N=3)	360 mg/m² (N=3)	390 mg/m² (N=6)	Total (N=19)
Number of Subjects Reporting One or More L-Annamycin-related TEAE	4 (100)	3 (100)	3 (100)	1 (33.3)	6 (100)	17 (89.5)
Neutrophil count decreased	1 (25.0)	3 (100)	3 (100)	1 (33.3)	5 (83.3)	13 (68.4)
Platelet count decreased	2 (50.0)	1 (33.3)	2 (66.7)	1 (33.3)	5 (83.3)	11 (57.9)
Hemoglobin decreased	2 (50.0)	0	3 (100)	1 (33.3)	3 (50.0)	9 (47.4)
Nausea	2 (50.0)	1 (33.3)	0	1 (33.3)	3 (50.0)	7 (36.8)
Vomiting	2 (50.0)	1 (33.3)	0	1 (33.3)	2 (33.3)	6 (31.6)
Fatigue	1 (25.0)	0	0	1 (33.3)	1 (16.7)	3 (15.8)
Febrile neutropenia	0	0	0	0	3 (50.0)	3 (15.8)
White blood cell count decreased	0	0	0	1 (33.3)	1 (16.7)	2 (10.5)
Alopecia	0	1 (33.3)	0	0	0	1 (5.3)
Back pain	0	0	0	0	1 (16.7)	1 (5.3)
Blood potassium decreased	0	0	0	0	1 (16.7)	1 (5.3)
Blood sodium decreased	0	0	0	0	1 (16.7)	1 (5.3)
Carbuncle	1 (25.0)	0	0	0	0	1 (5.3)
Diarrhoea	0	0	0	1 (33.3)	0	1 (5.3)
Dyspepsia	0	0	0	0	1 (16.7)	1 (5.3)
Dyspnoea	0	0	0	0	1 (16.7)	1 (5.3)
Headache	0	0	0	0	1 (16.7)	1 (5.3)
Hypophagia	1 (25.0)	0	0	0	0	1 (5.3)

TEAE = Treatment Emergent Adverse Event; PT = Preferred Term.
Reporting period from Study Start through 9/22/2022
Denominator is the number (N) of subjects in each column.
Preferred terms coded using the Medical Dictionary for Regulatory Activities V24.0.
Note: A subject reporting the same AE multiple times will be counted once within each preferred term.
Note: Treatment-emergent is defined as occurring after first dose of study drug and no more than 30 days after last dose of study drug.

**Preliminary data subject to change following final data cleaning efforts*

Conclusions: This trial has established the RP2D dosing regimen of ANN as 330 mg/m^2. Preliminary efficacy findings at the RP2D are encouraging with a DCR of 64% at the end of cycle 2 in this heavily pretreated population. To date, there has been no evidence of cardiotoxicity. This further supports that ANN may have significant advantages over currently approved anthracyclines for which effectiveness and duration of treatment are hampered due to cardiotoxic properties.