Phase 3 Study of Aldoxorubicin vs Investigator's Choice as Treatment for Relapsed/Refractory Soft Tissue Sarcomas

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Conflict of Interests: Consulting to

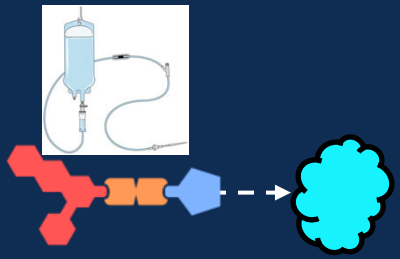
- Amgen
- Berg Pharma
- Bristol Myer Squibb
- Counterpoint Biomedica
- CytRx
- EISAI
- GSK
- Heron Therapeutics
- Immune Design
- Janssen
- J&J
- Morphotek
- Novartis
- Pharmamar
- Prana
- Roche
- Threshold
- Tracon
- Uptick Health

Proposed Mechanism

Targeting Ability
Localization of drug at tumor using albumin

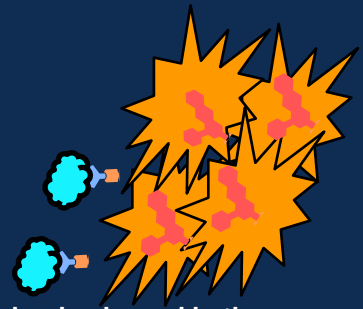
Cleavable Linker
Chemistries for controlled release of drug either extra- or intra-cellularly

Drug Payload
High potency cytotoxic agents: auristatins, maytansanoids, calicheamicin



Linker covalently binds within minutes to serum albumin

Albumin transports drug to the tumor and is taken up by the tumor



Linker is cleaved in the acidic environment, releasing the drug payload

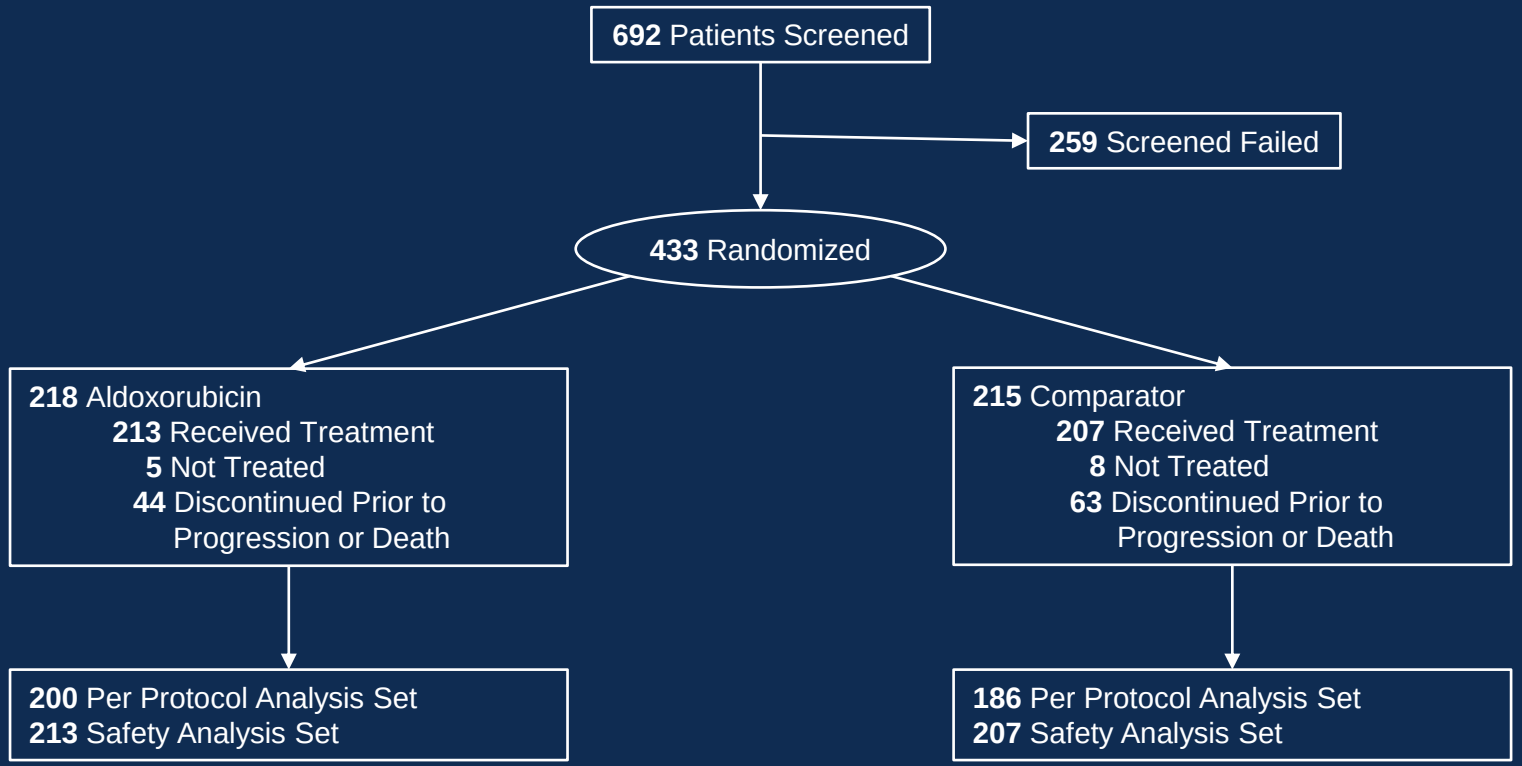
Study Design

- Aldoxorubicin 350 mg/m^2 (260mg/m^2 doxorubicin equivalents) every 3 weeks vs:
- Investigators choice of : pazopanib, gemcitabine/docetaxel, dacarbazine, doxorubicin, ifosfamide; administer each per institution standard tx
- Each site chooses 3 of 5 investigator choice drugs prior to enrollment of patients
  - May use any of the 3 drugs on patients
  - CytRx provides ALL chosen drugs + G-CSF to sites

Endpoints: Response/Progression per Blinded Central Review

- Primary: Progression-free survival (PFS)
- Secondary:
  - Overall Response Rate
  - Disease Control Rate (ORR + SD≥ 4 months)
  - PFS at 4 and 6 months
  - Overall Survival
  - Adverse Events
- Pre-specified analyses: Geography (North America + Australia vs Europe + Israel/Chile), Sarcoma Type (L-sarcomas, Others), Prior Doxorubicin

Flow of Study Patient Disposition



Demographics

Variable	Aldoxorubicin (N = 218)	Investigator's Choice (N = 215)
Age (Years)		
Median (min, max)	58.0 (26, 83)	57.0 (19, 87)
Age Group (%)		
<65 years	77.1	70.7
≥ 65 years	22.9	29.3
Sex (%)		
Female	56.4	59.5
Male	43.6	40.5

Demographics cont'd

Variable	Aldoxorubicin (N = 218)	Investigator's Choice (N = 215)
Prior exposure to Doxorubicin (%)		
Yes	65.6	66.0
No	34.4	34.0
Histopathological diagnosis (Central) (%)		
Leiomyosarcomas	42.2	43.7
Liposarcoma	12.8	14.9
Synovial sarcoma	9.6	8.4
All other sarcomas	34.9	32.1
Missing	0.5	0.9

% of Subjects By Region & Country

NA/AUS		Western EU		Eastern EU	
U.S.	68.4%	Spain	4.8%	Hungary	4.2%
Canada	1.8%	Italy	4.2%	Russia	2.3%
Australia	1.8%	France	3.2%	Bulgaria	0.2%
		Denmark	2.3%	Poland	1.2%
		UK	1.2%		
		Israel	3.9%		
		Chile	0.5%		
Total	72.0%		20.1%		7.9%

Aldoxorubicin Exposure

Variable	Aldoxorubicin (N = 213)	Doxorubicin equivalents of Aldoxorubicin (N = 213)
Cumulative dose administered (mg/m^2)		
n	213	213
Mean (SD)	1830.5 (1380.83)	1359.8 (1025.76)
Median	1400.0	1040.0
Min, Max	350, 14700	260, 10920

PFS Central Radiology Review

Variable	Aldoxorubicin (N = 218)	Investigator's Choice (N = 215)
ITT [Time to Progression or Death (Months)]		
Median (95% Confidence Interval)	4.11 (2.79, 5.06)	2.96 (2.56, 4.17)
p-value	0.0870	
Hazard Ratio (95% Confidence Interval)	0.81 (0.64, 1.03)	
L-Sarcomas [Time to Progression or Death (Months)]		
Median (95% Confidence Interval)	5.32 (3.45, 7.16)	2.96 (2.10, 4.37)
p-value	**0.0070**	
Hazard Ratio (95% Confidence Interval)	0.62 (0.44, 0.88)	

PFS Central Radiology Review cont'd

Variable	Aldoxorubicin (N = 218)	Investigator's Choice (N = 215)
North America + Australia [Time to Progression or Death (Months)]		
Median (95% Confidence Interval)	4.21 (2.92, 6.21)	2.96 (2.76, 4.07)
p-value	**0.0225**	
Hazard Ratio (95% Confidence Interval)	0.71 (0.53, 0.96)	
EU + Latin America [Time to Progression or Death (Months)]		
Median (95% Confidence Interval)	2.96 (1.58, 4.14)	3.02 (1.48, 5.68)
p-value	0.6439	
Hazard Ratio (95% Confidence Interval)	1.11 (0.71, 1.73)	

Overall Survival

Variable	Aldoxorubicin (N = 218)	Investigator's Choice (N = 215)
ITT [Time to Death (Months)]		
Median (95% Confidence Interval)	12.88 (10.05, 15.11)	12.16 (10.38, 13.31)
p-value	0.8555	
Hazard Ratio (95% Confidence Interval)	0.97 (0.74, 1.28)	

Objective Response Rate (ORR)

Variable	Aldoxorubicin (N = 218)	Investigator's Choice (N = 215)
ITT		
ORR [CR + PR (%)]	8.3	4.2
p-value	0.1106	
L-Sarcomas		
ORR [CR + PR (%)]	10.0	4.0
p-value	0.0790	

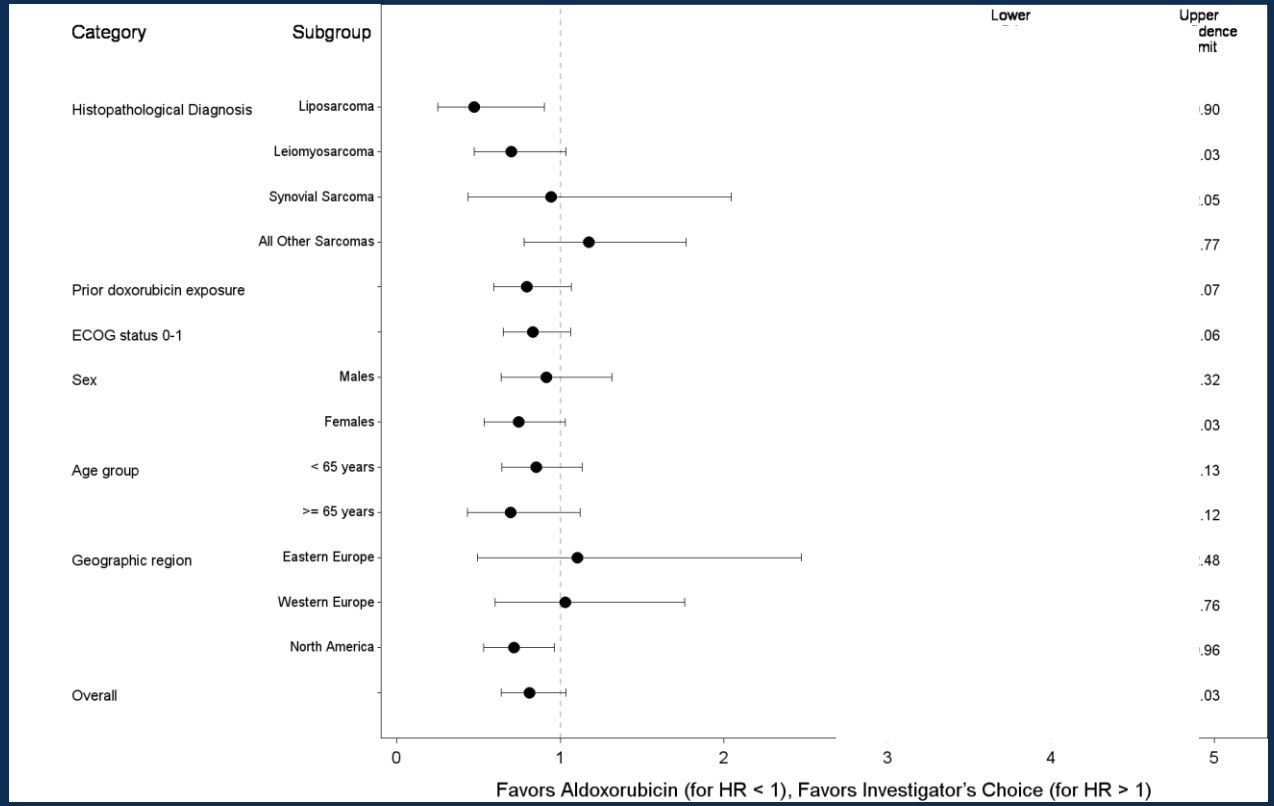
Disease Control Rate (DCR)

Variable	Aldoxorubicin (N = 218)	Investigator's Choice (N = 215)
ITT		
DCR [CR + PR + SD* (%)]	33.5	25.1
p-value	0.0583	
L-Sarcomas		
DCR [CR + PR + SD* (%)]	41.7	27.0
p-value	**0.0161**	
*SD ≥ 4 months		

PFS at 4 and 6 Months

Variable	Aldoxorubicin	Investigator's Choice
ITT		
PFS at Four Months (%)	40.8	31.6
PFS at Six Months (%)	24.8	14.9
Prior Doxorubicin		
PFS at Four Months (%)	39.2	29.6
PFS at Six Months (%)	23.1	14.8
L-Sarcomas		
PFS at Four Months (%)	48.3	31.7
PFS at Six Months (%)	30.8	14.3

PFS Forest Plot: ITT



LVEF %: Change from Baseline

	Aldoxorubicin (N = 213) (%)	Investigator's Choice - Doxorubicin (N = 47) (%)
Subjects with ≥ 20% LVEF decreases from baseline at any post-baseline visit	3.8	8.5
Subjects with LVEF below 50% of any post-baseline visit	4.2	19.1

Treatment-Emergent Adverse Events

Adverse Event Category	Aldoxorubicin (N = 213) (%)	Investigator's Choice (N = 207) (%)
All AEs	98.1	98.1
Grade ≥3 AEs	74.2	64.3
Treatment-related AEs	94.4	84.1
Grade ≥3 treatment-related AEs	64.3	46.9
AEs resulting in death	3.3	0.5
Treatment-related AEs resulting in death	1.4	0.0
Serious adverse events	42.7	32.9
Treatment-related serious adverse events	28.6	14.5
AEs leading to study drug discontinuation	10.8	10.1
Treatment-related AEs leading to study drug discontinuation	8.9	6.8

Grade 3/4 Adverse Events (≥ 5%)

Preferred Term	Aldoxorubicin (N = 213) %	Investigator's Choice (N = 207) %
Anemia	22.1	13.5
Neutropenia	23.9	11.6
Febrile neutropenia	15.5	4.3
Thrombocytopenia	9.9	8.2
Leukopenia	6.6	2.4
Stomatitis	15.5	0.5
Hypophosphatemia	5.2	3.4
WBC Decreased	11.3	5.3
Neutrophil Count Decreased	9.9	7.7
Platelet Count Decreased	7.5	4.8
Lymphocyte Count Decreased	5.6	1.4

Aldoxorubicin vs Doxorubicin: Grade 3 or 4 AEs

Preferred Term	Aldoxorubicin (N = 213) %	Doxorubicin (N = 47) %
Neutropenia	23.5	19.1
Anemia	19.7	23.4
Febrile neutropenia	15.5	17.0
Thrombocytopenia	8.9	4.3
Neutrophil Count Decreased	8.5	10.6
Platelet Count Decreased	5.6	6.4
Stomatitis	15.5	2.1
Sepsis	5.2	4.3
Alopecia	0.9	0.0

→ Approximately 66% of aldoxorubicin subjects had received prior doxorubicin.

→ Only 5% of doxorubicin subjects had received prior doxorubicin.

Reduced Alopecia with Aldoxorubicin

No hair loss following 20 cycles of Aldoxorubicin

Conclusions

- Aldoxorubicin significantly prolonged progression-free survival in North American and L-sarcoma subjects compared to standard tx.
- Aldoxorubicin, given at 350 mg/m^2/cycle, has minimal or no cardiotoxicity up to 40 cycles, compared to doxorubicin.
- The non-cardiac grade 3/4 AEs of aldoxorubicin were similar to doxorubicin despite exposure to 3-4 times the doxorubicin dose.
- Taken together, aldoxorubicin may be a superior anthracycline for treating advanced soft tissue sarcoma.
- Finally, aldoxorubicin is a good alternative vs standard therapies for treatment of relapsed or refractory metastatic soft tissue sarcoma.

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