

A Phase II Randomized Controlled Trial of Palifosfamide Plus Doxorubicin vs. Doxorubicin in Patients with Soft Tissue Sarcoma (PICASSO)

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Abstract

Objectives: Palifosfamide (ZIO-201, Zymafos™) is a novel DNA alkylator that is the stabilized active metabolite of ifosfamide (IFOS). It lacks the hemorrhagic cystitis and CNS toxicity of IFOS. Palifosfamide has demonstrated broad activity in human sarcoma xenograft models and is active in IFOS-resistant xenografts. In patients with recurrent sarcoma, early activity has been demonstrated, both as a single agent and in combination with doxorubicin. In a Phase I trial of palifosfamide/doxorubicin combination, doses were escalated to 150/75 mg/m² (palifosfamide/doxorubicin), the drug-related side effects were minimal and 3/12 patients had PRs. The current study is a randomized Phase II trial evaluating safety and efficacy of the combination of palifosfamide plus doxorubicin vs. doxorubicin alone in patients with metastatic/unresectable soft tissue sarcoma (STS).

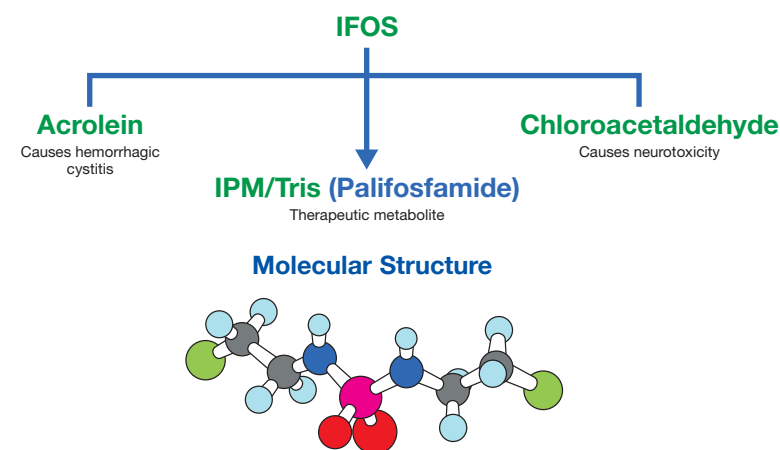
Methods: Multicenter, multinational, stratified for age and histopathologic subtype. Patients may receive up to 6 cycles until disease progression or unacceptable toxicity occurs. Patients who progress on doxorubicin alone by cycle 6 may receive palifosfamide. The primary end-point is PFS; the secondary end-points are safety and survival. This is an interim analysis.

Results: Thus far 67 patients with STS have been randomized with 65 treated and 61 eligible. Randomization was well-balanced for age and histological subtypes. Enrollment was stopped early. A total of 61 patients have been evaluated for PFS (progression-free survival) with 20 documented PFS events (doxorubicin alone = 14 events; palifosfamide + doxorubicin = 6 events). With this analysis based on all randomized and eligible patients, the hazard ratio is 0.63 favoring palifosfamide + doxorubicin (two-sided Wilcoxon-Gehan p-value = 0.026). No significant difference in toxicities between the two arms has been noted, and the combination of palifosfamide/ doxorubicin has been well tolerated.

Conclusions: The combination of palifosfamide + doxorubicin is well tolerated and shows a > 50 percent increase in the time to progression over doxorubicin alone. The data are compelling enough to proceed to a pivotal study in support of product registration.

Rationale

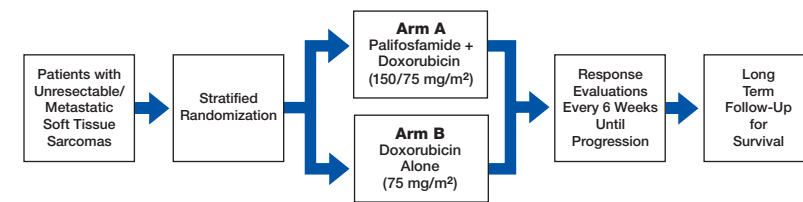
Palifosfamide, a novel, bi-functional DNA cross-linker, is the stabilized active metabolite of ifosfamide (IFOS) that lacks the toxicity associated with other IFOS metabolites. Palifosfamide has broad activity against human sarcoma cell lines *in vitro* and in human xenografts, including in IFOS- and CPA-resistant human osteosarcoma tumors. Mesna administration is not required with palifosfamide.



Study Design

Randomized, controlled trial to evaluate palifosfamide administered with doxorubicin, compared to single-agent doxorubicin in patients diagnosed with unresectable or metastatic soft-tissue sarcoma (STS).

Randomization is stratified by age (≥ 65 or < 65) and defined histologic subtype (leiomyosarcoma, synovial sarcoma or other).



Major Inclusion Criteria

- Histological or cytological documentation of sarcoma (excluding alveolar soft-part sarcoma, chondrosarcoma, dermatofibrosarcoma, Ewing sarcoma, GIST, Kaposi sarcoma, mixed mesodermal tumor, osteosarcoma, radiation induced sarcomas, and unresectable low grade liposarcoma)
 - ▲ First or second line
 - ▲ Treatment with doxorubicin is considered medically acceptable
 - ▲ Prior treatment with IFOS is acceptable
- Have measurable disease as per RECIST
- Doxorubicin naïve
- Adequate bone marrow, liver, and renal function (serum creatinine ≤ ULN)

Major Exclusion Criteria

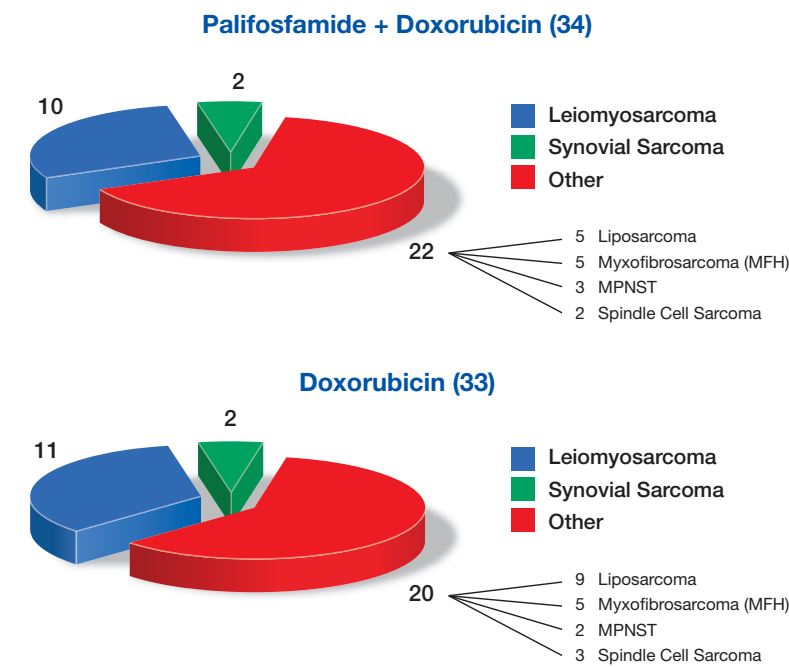
- Clinically evident congestive heart failure > Class II of the New York Heart Association (NYHA) guidelines
- Serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia, or ventricular arrhythmias classified as Lown III, IV, or V
- History and/or signs of active coronary artery disease/ischemia with or without angina pectoris
- Serious myocardial dysfunction defined as scintigraphically (MUGA [multiple gated acquisition scan], myocardial scintigram) or ultrasound-determined absolute left ventricular ejection fraction (LVEF) < 45%
- Prior nephrectomy or history of urinary tract obstruction

Endpoints

- Primary Endpoint: progression free survival (PFS)
 - ▲ Time from randomization to the date of documented, objective PD, radiological or clinical, whichever is earlier, or death (if prior to progression)
- Secondary Endpoints:
 - ▲ Safety and tolerability
 - ▲ Overall response rate (ORR)

Results: Randomization

Baseline Characteristics: Defined Histologic Sub-Types



Baseline Characteristics: Age and Line of Therapy

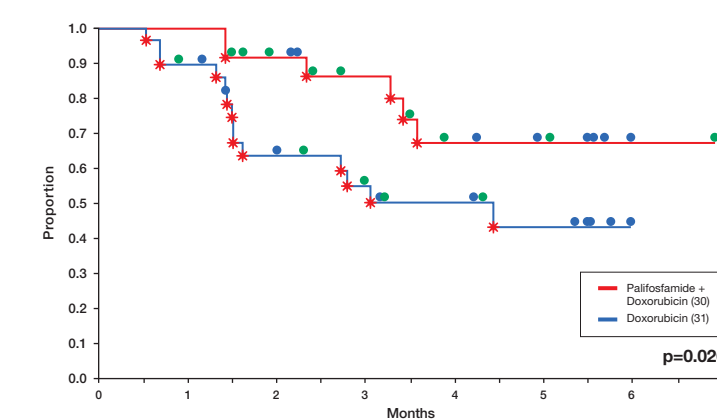
Age	All	Palifosfamide + Doxorubicin	Doxorubicin
≥ 65	23	12	11
< 65	44	22	22

Line of Therapy	All	Palifosfamide + Doxorubicin	Doxorubicin
1 st Line	46	23	23
2 nd Line	21	11	10

Results: Efficacy

- A total of 61 patients have been evaluated for PFS (progression-free survival) with 20 documented PFS events (doxorubicin alone = 14 events; palifosfamide + doxorubicin = 6 events). With this analysis, based on all randomized and eligible patients, the hazard ratio is 0.63 favoring palifosfamide + doxorubicin (two-sided Wilcoxon-Gehan p-value = 0.026)
- Median PFS for doxorubicin is 4.4 months
- Median PFS for palifosfamide + doxorubicin has not yet been reached
- The corresponding 1st quartile was 1.5 months (doxorubicin alone) vs. 3.5 months (palifosfamide + doxorubicin)

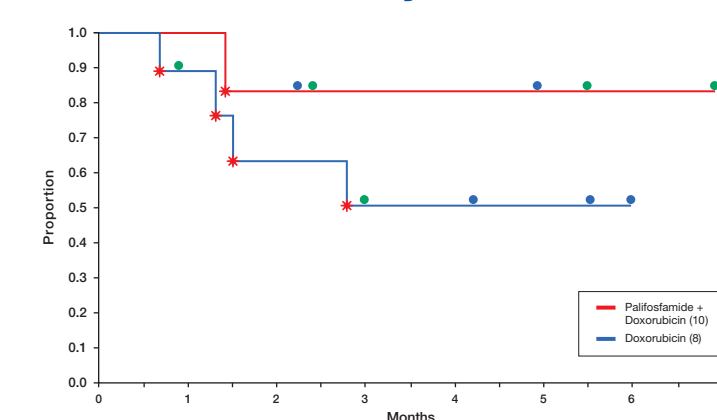
PFS: Eligible, Treated Patients



	Total	Palifosfamide + Doxorubicin	Doxorubicin	P-Value
Failed	20	6	14	0.026
		Palifosfamide + Doxorubicin	Doxorubicin	
1 st Line	20	22		
2 nd Line	10	9		

*Patients are censored at 30 days after coming off treatment, at the time of starting new therapy, or at the date of last follow up if still ongoing

PFS: Leiomyosarcoma



	Total	Palifosfamide + Doxorubicin	Doxorubicin
Failed	5	1	4
Leiomyosarcoma		Palifosfamide + Doxorubicin	Doxorubicin
1 st Line	5	4	
2 nd Line	5	4	

Safety: All Related Events in ≥ 10% of Eligible Treated Patients

	Palifosfamide + Doxorubicin (N=30)		Doxorubicin (N=31)	
	N	%	N	%
Alopecia	8	27	8	26
Anemia	4	13	4	13
Diarrhea	4	13	2	6
Dyspepsia	2	7	4	13
Fatigue	11	37	13	42
Hypokalemia	4	13	1	3
Leukopenia	7	23	6	19
Nausea	14	47	12	39
Neutropenia	6	20	12	39
Stomatitis	7	23	3	10
Vomiting	8	27	6	19

Safety: Related Grade ≥ 3 Events in ≥ 5% of Eligible Treated Patients

	Palifosfamide + Doxorubicin (N=30)		Doxorubicin (N=31)	
	N	%	N	%
Febrile Neutropenia	1	3	2	6
Leukopenia	5	17	5	16
Neutropenia	6	20	9	29
Fatigue	1	3	2	6
Hypokalemia	3	10	0	0

Safety: Related Serious Adverse Events in > 5% of Eligible Treated Patients

	Palifosfamide + Doxorubicin (N=30)		Doxorubicin (N=31)	
	N	%	N	%
Dehydration	2	7	0	0
Neutropenia	0	0	2	6

Conclusions

- The combination of palifosfamide + doxorubicin is well tolerated and shows a statistically significant increase in the PFS over doxorubicin alone
- Median PFS for doxorubicin is 4.43 months; median PFS for palifosfamide + doxorubicin has not yet been reached; The corresponding 1st quartile was 1.5 months vs. 3.5 months
- The data are compelling enough to proceed to a pivotal study in support of product registration