**First line therapy with aldoxorubicin and 14 days continuous infusion of ifosfamide/Mesna in metastatic or locally advanced sarcomas: A phase I-II study**


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**Abstract**

**Background:** Aldoxorubicin (A) is a prodrug of the anticancer agent doxorubicin which is derivatized at its C-13 keto-position with a thiol-binding spacer molecule (6-maleimidocaproic acid hydrazide). In a first-line STS study, aldoxorubicin significantly increased PFS, PFS at 6 months of 24% (95% CI 9-51), and ORR of 33% (95% CI 13-53). Ifosfamide (I) is a nitrosourea derivative that is activated by mitochondrial damage. A 2016 large-scale phase 3 trial showed a non-significant trend in PFS and OS in patients receiving single-agent doxorubicin.

**Objectives**

- To evaluate the overall response rate, PFS, and PFS and OS in months.
- To determine the MTD, moderate and reversible myelosuppression, no liver toxicity and immunotoxicity, and no new toxicity compared to doxorubicin.
- To determine the safety and tolerability of aldoxorubicin and ifosfamide in combination.
- To evaluate the activity of this combination without increasing its toxicity as has been demonstrated for ifosfamide as a single agent.

**Study Design**

- Aldoxorubicin administered at either 170 or 250 mg/m² (I and I+I) of aldoxorubicin as a single agent was given at 0, 2 and 4 days plus day 1 was given at 0, 2, and 4 days for 28 patients (CoH1) with advanced unresectable soft-tissue sarcoma (STS). The combination therapy was continued with aldoxorubicin alone every 21 days at a dose same as used with the combination until disease progression, unacceptable toxicity or withdrawal of consent.
- Tumor response was reassessed every 8 weeks using the RECIST 1.1 criteria.
- Safety assessments including adverse events, physical exam, serum chemistry, CBC and Bone marrow aspiration were performed periodically.
- Toxicity was assessed using modified RECIST 1.1 criteria.

**Results**

- Best Response: Partial Response (RECIST): 36% 13 of 36
- >20% tumor shrinkage: 56% 20 of 36
- >50% tumor shrinkage: 17% 6 of 36
- Progressive Disease: 3% 1 of 36

**Key Eligibility Criteria**

- Advanced histologies included sarcoma, soft tissue sarcoma of intermediate or high grade and gastrointestinal stromal tumors (GIST) (only in subjects that have progressed after receiving treatment with imatinib and sunitinib).
- ECOG performance status 0-2.
- Life expectancy >12 weeks.
- No clinically significant cardiac toxicity.
- No clinically significant cardiotoxicity has been observed. No patients had clinically significant decrease in LVEF or QTc prolongation.
- Adjuvant or neoadjuvant chemotherapy (including doxorubicin) allowed if no tumor residual.

**Background**

- Aldoxorubicin can be administered safely with continuous infusion of ifosfamide/mesna. No DLTs were observed in either cohort.
- Treatment was associated with a high percentage of objective responses and stable disease.
- Common Grade 3 and 4 AE were neutropenia and anemia.
- The median cumulative dose of doxorubicin for the 250 mg/m² cohort is 1836 mg/m² (range: 748-4549) doxorubicin equivalents 1364 mg/m² (range: 546-4813).
- No significant cardiac problems were observed despite administration of medidum cumulative dose of doxorubicin equivalents of 831 mg/m².
- Based on experience gained in this study, the decision was made to stop further aldoxorubicin dose escalation and continue to enroll the 250 mg/m² cohort. mPFS has not been reached at this time.

**References**