SAKK 57/16 Nab-Paclitaxel And Gemcitabine in soft tissue sarcoma (NAPAGE): Final results from the phase Ib/II trial with >2y median follow up

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Abstract: #4465

Background

The outcome for patients with locally advanced or metastatic soft tissue sarcoma (STS) is poor. Following failure from first-line doxorubicin based chemotherapy no standard therapy has been established [1]. Combination treatment with docetaxel/gemcitabine (gem) has emerged as an effective regimen but administration is limited to fit patients only due to the toxicity profile [2,3,4]. However, nanoparticle albumin bound paclitaxel (nab-PC) was designed to avoid the toxicities related to polyethylated castor oil [5,6,7]. In this context, we want to evaluated toxicity and antitumor effect of biweekly nab-PC/gem administration in STS patients.

Methods

We conducted a phase Ib/II trial to assess the safety and efficacy of biweekly nab-PC 150mg/m^2 and gem 1000mg/m^2 administration in the 2nd and 3rd line setting of STS.

Patients with STS who progressed after a maximum of two lines of standard treatment with ECOG 0-2 and a life expectancy of >3 months and adequate organ function have been included.

The primary endpoint in phase II was progression-free rate (PFR) at 3 months (H0: 20%, H1: 40%). A Simon's optimal two-stage phase II design with a significance level of 0.1 and a power of 0.9 required a total sample size of 37 patients.

Secondary endpoints included progression-free survival (PFS), adverse events (AEs), overall survival (OS) and patient-reported outcomes. Efficacy analysis was by intention to treat.

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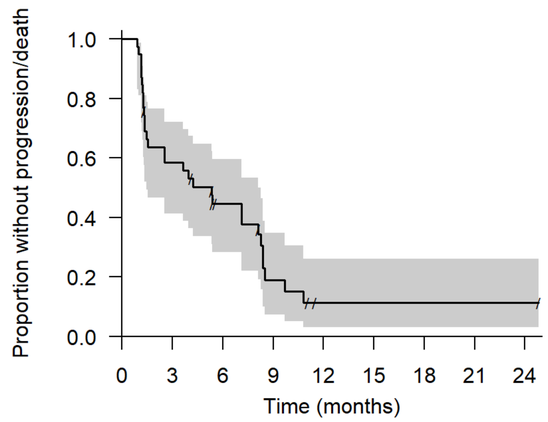
Results

Thirty-nine patients in eight Swiss institutions were registered; the first six were treated as part of the dose-de-escalation part of the trial confirming the safety and tolerability of biweeky regimen. In total, 56.4% patients had grade 3 STS, 77% were treated in the 2nd line and 23% in the 3rd line setting, respectively. The median age was 60 years (range 22 - 85), 53.8% were female. The most frequent primary locations were the retroperitoneum (20.5%), extremity (15.4%) and uterus (15.4%). STS subtypes are listed in table 1. The 3 months PFR (CR/PR/SD rate) was 56.4% (95% confidence interval (CI) 39.6 - 72.2%). The 3 months and 6 months PFS based on the Kaplan-Meier estimator were 58.4% (95% CI: 41.3 - 72.1%) and 44.6% (95% CI: 28.4 - 59.5%), respectively. Median PFS was 5.3 months (95% CI: 1.4 - 8.2) and median OS was 13.3 months (95% CI: 10.5 - 26.5). (Figure 1)

Table 1. Patient characteristics (N = 39)

Characteristic	Summary*
Age	60 (22 – 85)
Female sex	21 (53.8%)
ECOG performance status	
0	20 (51.3%)
1	18 (46.2%)
2	1 (2.6%)
Sarcoma subtype	
Leiomyosarcoma (LMS)	14 (35.9%)
Liposarcoma	10 (25.6%)
Undifferentiated pleomorphic sarcoma (UPS)	7 (17.9%)
Angiosarcoma	1 (2.6%)
* median (range) for continuous variables, frequency (percent) for categorical	

Figure 1: Kaplan Meier curve for PFS with pointwise 95% CI



The ORR according to RECIST was 10.5% (1 patient with angiosarcoma, 1 with UPS and 1 with LMS). An additional 19 patients (48.7%) had SD> 3 months. Median follow-up time was 26.4 months. The most common treatment-related AE of grade ≥ 3 was neutropenia (grade 3 occurred in 15.4%, grade 4 in 2.6%). Other treatment-related AEs (of grade ≥ 3) were rare. Treatment-related grade 1 and grade 2 peripheral sensory neuropathy (PNP) occurred in 12.8 and 23.1%, respectively. No grade 3 - 4 PNP was reported. Patient-reported symptoms and their interferences with daily living remained stable over the first 3 months except for a significant increase in peripheral neuropathy.

Discussion

We were able to confirm the safety and efficacy of the regimen with a meaningful 3 months PFR of 56.4%.

Conclusion

Biweekly nab-paclitaxel and gemcitabine is an active combination in pretreated STS patients with manageable toxicity. This regimen should be considered for further exploration for pre-treated advanced STS patients.

References

1 Skafida, E., et al., Metastatic soft tissue sarcoma: current treatment landscape and future perspectives. Expert Rev Anticancer Ther, 2017. 17(6): p. 537-543. 2 in font type Arial and in the color black
2 Hensley, M.L., et al., Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. J Clin Oncol, 2002. 20(12): p. 2824-31.
3 Bay, J.O., et al., Docetaxel and gemcitabine combination in 133 advanced soft-tissue sarcomas: a retrospective analysis. Int J Cancer, 2006. 119(3): p. 706-11. 14.
4 Maki, R.G., et al., Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. J Clin Oncol, 2007. 25(19): p. 2755-63
5 Desai, N., et al., Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. Clin Cancer Res, 2006. 12(4): p. 1317-24. 21.
6 John, T.A., et al., Quantitative analysis of albumin uptake and transport in the rat microvessel endothelial monolayer. Am J Physiol Lung Cell Mol Physiol, 2003. 284(1): p. L187-96. 22. Ibrahim, N.K., et al.,
7 Phase I and pharmacokinetic study of ABI-007, a Cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. Clin Cancer Res, 2002. 8(5): p. 1038-44

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