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SAKK57/16 Nab-paclitaxel and Gemcitabine in Soft Tissue Sarcoma (NAPAGE): a phase I/II trial☆

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ABSTRACT

Background: To determine whether the combination of nab-paclitaxel with gemcitabine has activity in patients with pretreated soft tissue sarcoma (STS).

Patients and Methods: NAPAGE is a phase Ib/II clinical trial investigating the combination of nab-paclitaxel (nab-pc) with gemcitabine employing two cohorts. One of a dose-de-escalation phase and one of expansion. In phase I, nab-pc was given at 150 mg/m^2 in combination with gemcitabine 1000 mg/m^2 every two weeks, until disease progression or unacceptable toxicity. This dose was recommended for phase II (RP2D), as there was no dose limiting toxicity (DLT) or discontinuations due to adverse events (AEs). The primary endpoint of the phase II was progression-free rate (PFR) at 3 months (H0: 20%, H1:40%). The secondary endpoints included progression free survival (PFS), overall survival (OS), AEs, objective response and patient-reported outcomes (PRO). Efficacy analysis was by intention to treat.

Results: The 3-month PFR was 56.4% (95% confidence interval CI: 39.6–72.2%). The 3-month and 6-month PFS 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 12.8 months (95% CI: 10.5–39.2). The most common treatment-related grade $\geq$ 3 AE were neutropenia (18%), followed by anemia (2.6%), hypertension (2.6%) and alanine aminotransferase increase (2.6%). Grade 1 and grade 2 peripheral sensory neuropathy (PNP) occurred in 15.4% and 20.5%, respectively. No grade 3–4 PNP was reported.

Conclusions: Combining nab-pc and gemcitabine is safe. Promising activity is observed in pretreated STS patients with manageable toxicity. This regimen should be considered for further exploration.

1. Introduction

The last decade has been characterized by drug development including tyrosine kinase inhibitors and immunotherapy (i.e., checkpoint inhibitors) for several cancer subtypes, leading to unprecedented clinical benefit. Unfortunately, efficacy of these agents in an unselected soft tissue sarcoma (STS) population is limited because STS are heterogeneous, with more than 150 different histological subtypes that vary in their clinical behavior and response to systemic therapies [1]. In this context, STS remain a therapeutic challenge. Until today palliative chemotherapy is the mainstay of treatment in advanced setting and first-line treatment with doxorubicin, alone or in combination with ifosfamide, is the standard of care with a median overall survival (OS) ranging from 15 to 20 months [2].

☆ This study was registered with ClinicalTrial.gov, number NCT03524898

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Although several agents including gemcitabine/docetaxel, trabectedin, eribulin and pazopanib have shown activity beyond first-line with a different toxicity profile each, no standard regimen has been established as of yet [2,3].

Nab-paclitaxel (nab-pc) is an albumin-bound formulation of paclitaxel particles (Abraxane®, Celgene, Summit, NJ). This drug is approved in Europe and the US for the management of patients with advanced breast cancer and pancreatic cancer in combination with carboplatin and gemcitabine, respectively [4–6].

Nab-pc has been shown to have an improved endothelial cell transport leading to higher intra-tumor paclitaxel concentrations and antitumor activity in preclinical models of solid tumor xenografts including sarcoma at equivalent doses of paclitaxel [4,6,7]. This led us to assess the combination of biweekly nab-pc with gemcitabine as a valuable option for patients with pre-treated advanced STS.

2. Materials and methods

2.1. Study design and procedures

NAPAGE is an open-label, multicenter, single-arm phase Ib/II trial combining a dose des-escalation phase, followed by one expansion phase II in advanced or metastatic pretreated STS.

Main inclusion criteria were patients $\geq$ 18 years with 1) histologically confirmed and centrally reviewed STS, 2) locally advanced or metastatic disease, 3) maximum two lines of standard therapy in the palliative setting 4) measurable and progressive disease (PD) at inclusion according to RECIST v1.1, 6) a performance status of 0–2 and an estimated life expectancy of $\geq$ 3 months, 7) adequate hematological, renal, metabolic and hepatic functions. For complete inclusion/exclusion criteria see protocol in supplementary material.

All patients provided written informed consent. The trial was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. This study is registered on ClinicalTrials.gov (NCT03524898).

The dose de-escalation phase followed a 3 + 3 classical design. In the dose de-escalation phase, the first dose level of nab-pc was assessed at 150 mg/m2 combined with gemcitabine 1000 mg/m2 every two weeks, and led to no DLTs or discontinuations due to AEs. Thus, in the expansion cohort, all patients were treated with this dose regimen. Treatment continued until disease progression or unacceptable toxicity. Dose reductions were permitted, according to the protocol (supplementary material). Safety was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Efficacy was assessed using computed tomography scans as per RECIST 1.1 criteria every six weeks within the first 24 weeks and every 12 weeks thereafter and upon clinical indication. In the phase I dose escalation trial, investigating nab-paclitaxel and gemcitabine administration on days 1, 8 and 15 of a 28 day cycle for pancreatic cancer patients, the MTD was established at dose level 2 (125 mg/m2 of *nab*-paclitaxel) due one of the three patients at dose level 3 (150 mg/m2 of *nab*-paclitaxel), died as a result of treatment-related systemic infection (neutropenia in the presence of a biliary stent) during cycle 1 [8]. Due to our adapted schema of biweekly administration, we decide to start our dose-de-escalation at 150 mg/m2 of nab-pac.

Study endpoints.

The primary endpoint of the dose escalation phase was to assess safety and determine the dose-limiting toxicity during the first cycle of treatment, as well as to determine the recommended phase II dose of nab-pc combined with gemcitabine. The primary endpoint of the phase II was the proportion of patients with no PD as per RECIST v1.1 at 12 weeks (progression free rate, (PFR)). Secondary endpoints were OS, progression free survival (PFS), objective response and PRO (see protocol in supplementary material for additional details).

2.2. Statistical methods

Dose-limiting toxicity was defined as an adverse event occurring during the first 28 days of treatment, at least possibly related to study treatment, and meeting one of these criteria: any grade 3 toxicity, any treatment-related AE that leads to a delay of treatment > 14 days, grade 4 neutropenia with fever, or grade > 2 thrombocytopenia with bleeding or requiring transfusion. A minimum of three and a maximum of six patients were to be included in each dose level. The maximum tolerated dose of nab-pc was defined as the highest dose at which no more than one in six patients experienced a dose-limiting toxicity during the observation period of the first 28 days. A maximum of 12 patients were planned to be included. The patients treated at the recommended phase II dose will be also evaluated during the phase II part of the study.

The phase II was planned at the recommended dose of nab-pc combined with gemcitabine assuming a promising PFR of 40% (response or stabilization), a limit of 20% for drug inactivity a significance level of 10% and a power of 80%. Using Simon's optimal two-stage phase II design, thirty-seven patients were needed including the six from phase I treated at the recommended dose. The sample size was calculated with PASS 11.0 (NCSS, LLC. Kaysville, Utah, USA). Analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC) and R 3.6.3 (R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2020. https://www.R-project.org/). Time-to-event endpoints were evaluated by the Kaplan-Meier method and summarized by the median and corresponding 95% confidence interval (CI). Binary endpoints were presented by the point estimate along with the two-sided 95% Clopper-Pearson CI (except the primary endpoint with 80% CI to be concordant with the design). Explorative subgroup analyses for PFS were performed. Subgroups were subtypes, grades, age > 65 years, type of metastases and doxorubicin exposure, respectively. All efficacy analyses were based on the full analysis set, including all patients who received at least one dose of trail treatment, yet excluding those with major eligibility violations.

2.3. Patient reported outcomes

Patient-reported symptoms were assessed with the MD Anderson Symptom Inventory (MDASI), which measures the severity of 13 cancer-related symptoms (symptom severity) and their interference with daily life (symptom interference) on a 0–10 scale [9]. To assess patient-reported chemotherapy-induced sensory neuropathy, we used the 4-item subscale of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity (FACT/GOG-Ntx, score range 0–16) [10–12]. Patients completed the two questionnaires at baseline, at week 2, 4, 6, 9 12, 18 and at the end of treatment. Changes in patient-reported symptoms were descriptively summarized for each time point. A mixed model for repeated measurements tested changes over time.

We considered 1.21 as a minimally important difference (MID) based on half a standard deviation of 1.95 for the 13 MDASI core symptoms and 2 points for the FACT/GOG-NTX-4 [9,12]. Exploratory associations between overall response and symptom severity and interference (minimum MDASI difference to baseline before end of treatment) (best change) were analyzed by spearman correlation.

3. Results

3.1. Patient characteristics

Between November 2018 and November 2020, a total of 39 eligible patients were enrolled in eight Swiss centers. The first six patients were treated as part of the phase I dose de-escalation phase. 56.4% of all patients had grade 3 STS, 41.0% grade 2%, and 2.6% no available grade. 77% were treated in the second-line and 23% in the third-line setting, respectively. The median age was 60 years (range 22–85), 53.8% were

Table 1
Patient's characteristics (N = 39).

Characteristic	No. of patients	Summary
Median age (range) – years	39	60 (22 – 85)
Female – no. (%)		21 (53.8)
STS Grade (FNCLCC) – no. (%)	39	
G2		16 (41.0)
G3		22 (56.4)
Gx		1 (2.6)
ECOG/WHO performance status – no. (%)	39	
0		20 (51.3)
1		18 (46.2)
2		1 (2.6)
Subtypes – no. (%)	39	
Angiosarcoma		1 (2.6)
Leiomyosarcoma		14 (35.9)
Liposarcoma		10 (25.6)
Sarcoma NOS		2 (5.1)
Synovial Sarcoma		2 (5.1)
Undifferentiated pleomorphic sarcoma		7 (17.9)
Spindle cell sarcoma		1 (2.6)
Epitheloid sarcoma		1 (2.6)
Pleomorphic rhabdomyosarcoma		1 (2.6)
Sites of metastases – no. (%)	35	
Lung		23 (65.7)
Liver		11 (31.4)
Lymph nodes		11 (31.4)
Bone		7 (20.0)
Brain		0 (0)
Other		15 (42.9)

Table 2
Reasons for treatment discontinuation (N = 39).

Reason	No. (%)
Progressive disease	28 (71.8)
Patient's refusal of trial treatment	5 (12.8)
Physician's decision	2 (5.1)
Patient's withdrawal of consent	1 (2.6)
Trial terminated by sponsor	1 (2.6)
Unacceptable toxicity	1 (2.6)

female. The most frequent primary locations were the retroperitoneum (20.5%), extremities (15.4%) and uterus (15.4%). Most tumors were doxorubicin resistant/refractory although 9 out of 39 patients had not been exposed to doxorubicin. Patients' characteristics with STS subtypes are detailed in Table 1.

3.2. Treatment administration

In the dose de-escalation phase, six patients were treated at dose level 1. No DLT was observed at dose level 1, and only one patient experienced a dose reduction due to skin toxicity. All six patients were included in the phase II part. Five of them continued treatment and stopped later (three stopped due to progressive disease, one refused, and one was still on treatment when the trial was terminated). One patient died at the end of phase I unrelated to the sarcoma. More specifically, the death was due to arterial thrombosis leading to an ischemic stroke and subsequent intracranial hemorrhage, related to the patient's cardiovascular risk factors. The most common treatment-related AEs (TRAEs) were fatigue (3 patients), alopecia (3 patients), and neutropenia (2 patients). There was no DLT or discontinuations due to AEs, as detailed in supplementary material, and we continued with the phase II.

Median follow-up was 26.4 months (range in surviving patients 1.1–39.2 months). A total of 39 patients (100%) received biweekly nab-pac and gemcitabine for a median number of 7 administrations (range, 1–80 administrations). Overall nab-pac and gemcitabine dose reductions occurred in 16 (3.8%) of totally 418 administrations and in 8 of totally 444 administrations, respectively. The main reason for dose

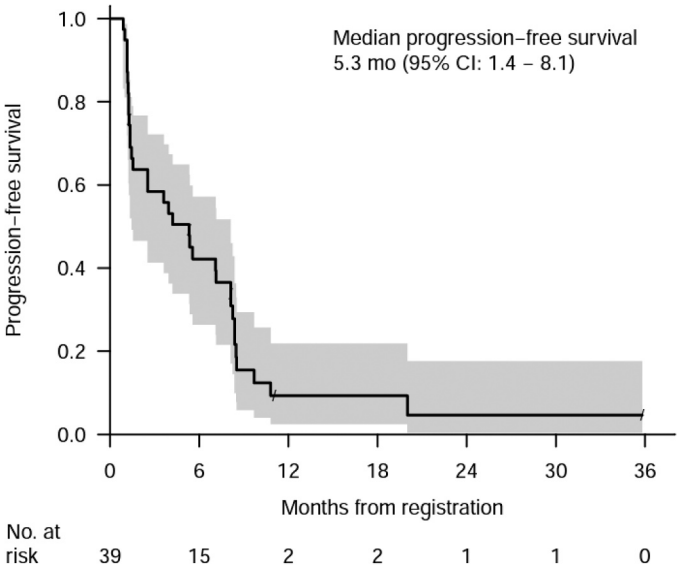

Fig. 1. Progression Free Survival.

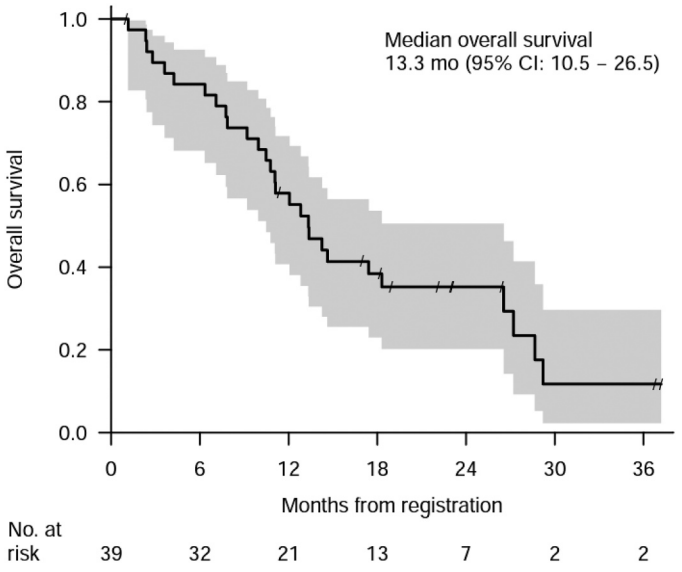

Fig. 2. Overall Survival.

modification was toxicity (50% of cases for both drugs). Discontinuation of the treatment occurred in all 39 patients. Reasons for discontinuation were PD (71.8%), patient's refusal of trial treatment (12.8%), physician's decision due to clinical PD (5.1%), patient's withdrawal of consent (2.6%), unacceptable toxicity (2.6%), trial termination by sponsor, and death (2.6%). Reasons for discontinuation are listed at Table 2.

3.3. Primary endpoint and key secondary endpoints

The PFR, defined as complete response, partial response (PR) or stable disease (SD) at 3 months was 56.4%, the 80% Clopper-Pearson confidence interval (CI) to be compared to the design parameters was 44.9–67.4%, the 95% CI was 39.6–72.2%. As the lower boundary of the 80% CI is above 20% the null hypothesis can be rejected and the treatment can be regarded as promising. One patient started a next treatment line before 3 months without progression and counted as failure for the primary endpoint. This patient leads to a small difference in the 3-months PFS based on the Kaplan-Meier estimator. The 3- and 6-months PFS, based on the Kaplan-Meier estimator, were 58.4% (95% CI:

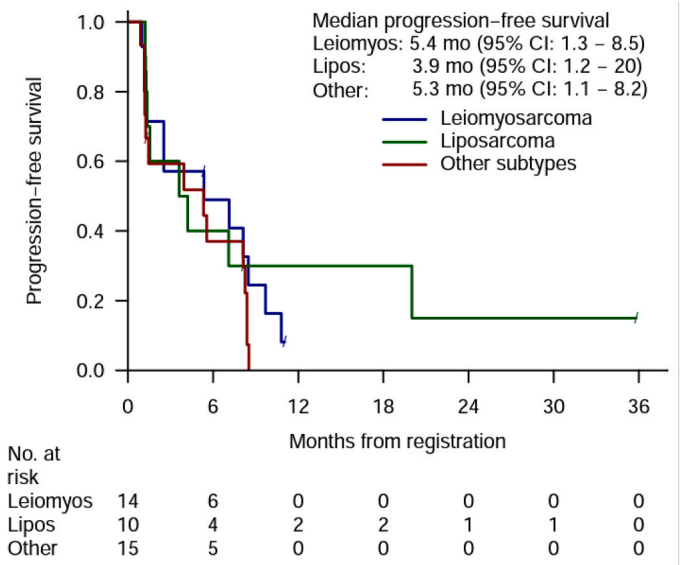

Fig. 3. Progression free survival based on subtypes.

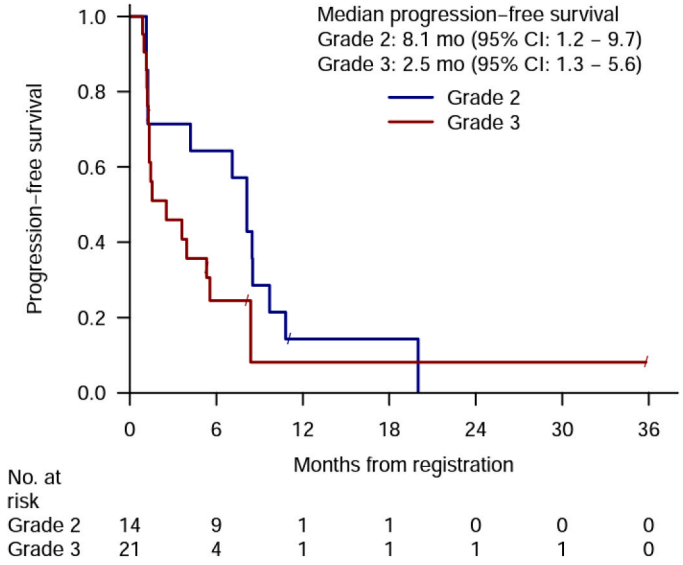

Fig. 4. Progression Free Survival based on grade.

41.3–72.1%) and 42.2% (95% CI: 26.4–57.2%), respectively. Median PFS was 5.3 months (95% CI: 1.4–8.1) and median OS was 13.3 months (95% CI: 10.5–26.5) for the overall study population (Figures 1 and 2). The 1-year PFS rate was 9.3% (95% CI 2.4–21.9%) and the 1-year OS rate was 57.9% (95% CI 40.8–71.7%). Three-months and 6-months PFR for leiomyosarcoma (LMS) patients were 57% (95% CI 28–78%) and 49% (95% CI 22–72%), whereas for liposarcoma were 60% (95% CI 25–83%) and 40% (95% CI 12–67%), respectively (Figure 3).

The objective response rate (ORR) was 10.3% (4/39 patients, 95% CI: 2.9–24.2%) (one patient with angiosarcoma, one with undifferentiated pleomorphic sarcoma (UPS), one with LMS, and one with liposarcoma (LPS)). An additional 21 patients (53.8%) had SD as their objective response. Of note, disease control $\geq$ 9 months was seen in 10 patients (four with LMS, two with LPS, one with epithelioid sarcoma, two UPS and one with angiosarcoma) (supplementary table). Patients who had grade 2 STS seemed to have higher PFR at 3 and 6 months, respectively. However, this was not statistically significant possibly due to the small sample size (Figure 4). In an exploratory analysis, age (less or more than 65 years old), presence of bone or liver metastasis did not significantly impact PFS, whereas doxorubicin exposure were associated with better PFS (supplementary materiel Figures 1–2–3–4).

3.4. Safety and tolerability

AEs for all reasons are listed in Table 3. The most common treatment-related AE was grade 3 or 4 neutropenia (18%). Other treatment-related AEs (of grade $\geq$3) were rare including anemia (2.6%), hypertension (2.6%), grade 3 alanine aminotransferase increase (2.6%) (Supplementary table 1). Grade 1 and grade 2 peripheral sensory neuropathy (PNP) occurred in 15.4% and 20.5% respectively. No grade 3–4 PNP was reported. Grade 1 and grade 2 alopecia occurred in 10.3% and 43.6% of patients, respectively. At trial termination, one patient was still on treatment. The patient continued treatment with nab-pac and gemcitabine outside the protocol.

3.5. Patient-reported outcomes

Completion rates for patient reported outcome (PRO) questionnaires exceeded 90% up to 12 weeks, 89% at week 18% and 54% at the end of treatment. Median scores for the MDASI symptom severity and symptom interference remained stable during treatment (supplementary materiel Figure 5). Most of the patients (74.4%) reported no changes, 10.3% reported an increase and 15.4% a decrease in symptom severity based on the MID at any time during treatment. Patient-reported chemotherapy-induced neuropathy worsened over time ($p = 0.003$) with worsening being statistically significant and clinically relevant (mean change from baseline >3) from week 18 on. Exploratory analysis of the association

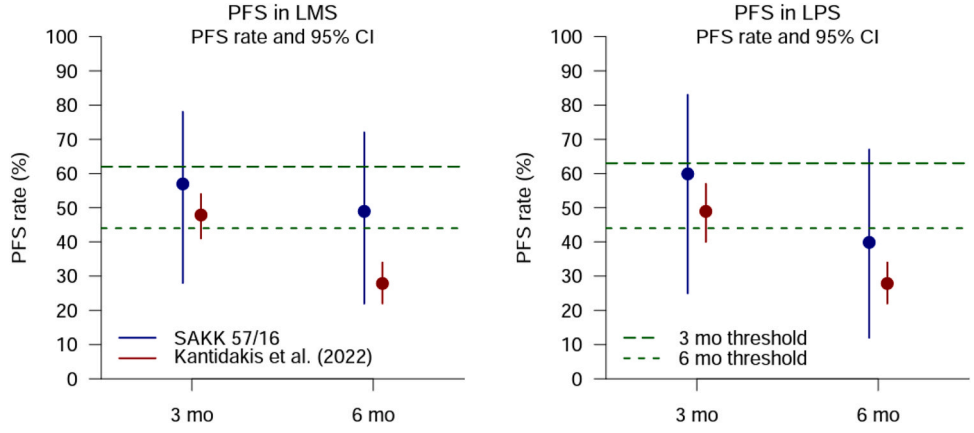

Fig. 5. Activity of nab-pac and gemcitabine combination in L-sarcomas comparing to Kantidakis et al data.

Table 3
Adverse Events grades per patient by event type (N = 39).

Adverse event	No. (%)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders					
Anemia	3 (7.7)	6 (15.4)	1 (2.6)	-	-
Cardiac disorders					
Pericardial tamponade	-	-	-	1 (2.6)	-
Ear and labyrinth disorders					
Vertigo	2 (5.1)	-	-	-	-
Eye disorders					
Visual field limited	1 (2.6)	-	-	-	-
Gastrointestinal disorders					
Abdominal cramps	1 (2.6)	-	-	-	-
Abdominal pain	1 (2.6)	3 (7.7)	-	-	-
Colonic perforation	-	1 (2.6)	-	-	-
Constipation	7 (17.9)	-	1 (2.6)	-	-
Diarrhea	1 (2.6)	1 (2.6)	-	-	-
Dry mouth	2 (5.1)	-	-	-	-
Duodenal ulcer	1 (2.6)	-	-	-	-
Gastritis	-	1 (2.6)	-	-	-
Hemorrhoids	-	1 (2.6)	-	-	-
Ileus	-	-	-	1 (2.6)	-
Mucositis oral	2 (5.1)	-	-	-	-
Nausea	8 (20.5)	1 (2.6)	-	-	-
Pain on lower abdomen during stools	1 (2.6)	-	-	-	-
Stomach pain	1 (2.6)	-	-	-	-
Toothache	1 (2.6)	-	-	-	-
Vomiting	5 (12.8)	-	-	-	-
General disorders and administration site conditions					
Chills	2 (5.1)	-	-	-	-
Edema limbs	5 (12.8)	-	1 (2.6)	-	-
Fatigue	5 (12.8)	8 (20.5)	1 (2.6)	-	-
Fever	7 (17.9)	1 (2.6)	-	-	-
Flu like symptoms	3 (7.7)	1 (2.6)	1 (2.6)	-	-
Night sweat	1 (2.6)	-	-	-	-
Night sweats	1 (2.6)	-	-	-	-
Non-cardiac chest pain	1 (2.6)	1 (2.6)	-	-	-
Pain	2 (5.1)	-	1 (2.6)	-	-
Immune system disorders					
Allergic reaction	1 (2.6)	1 (2.6)	-	-	-
Infections and infestations					
Catheter related infection	-	-	1 (2.6)	-	-
Folliculitis	-	1 (2.6)	-	-	-
Pleural infection	-	-	1 (2.6)	-	-
Rhinitis infective	1 (2.6)	-	-	-	-
Skin infection	-	1 (2.6)	-	-	-
Upper respiratory infection	-	1 (2.6)	-	-	-
Urinary tract infection	-	-	2 (5.1)	-	-
Injury, poisoning and procedural complications					
Hip fracture	-	1 (2.6)	-	-	-
Investigations					
Alanine aminotransferase increased	2 (5.1)	2 (5.1)	1 (2.6)	-	-
Alkaline phosphatase increased	1 (2.6)	-	-	-	-
Aspartate aminotransferase increased	2 (5.1)	1 (2.6)	-	-	-
CRP increased	-	-	1 (2.6)	-	-
Creatinine increased	1 (2.6)	1 (2.6)	-	-	-
Folate deficiency	1 (2.6)	-	-	-	-
GGT increased	-	1 (2.6)	1 (2.6)	-	-
Lymphocyte count decreased	1 (2.6)	3 (7.7)	1 (2.6)	-	-
Neutrophil count decreased	-	4 (10.3)	6 (15.4)	1 (2.6)	-
Platelet count decreased	4 (10.3)	-	-	-	-
Weight loss	3 (7.7)	-	-	-	-
White blood cell decreased	1 (2.6)	1 (2.6)	1 (2.6)	-	-
Metabolism and nutrition disorders					
Anorexia	3 (7.7)	-	-	-	-
Ferritin deficiency	-	1 (2.6)	-	-	-
Folic acid deficiency	-	1 (2.6)	-	-	-
Hyperkalemia	-	-	1 (2.6)	-	-
Hyperuricemia	1 (2.6)	-	-	-	-
Musculoskeletal and connective tissue disorders					
Arthralgia	3 (7.7)	2 (5.1)	-	-	-
Back pain	2 (5.1)	1 (2.6)	1 (2.6)	-	-
Bone pain	2 (5.1)	-	-	-	-
Flank pain	1 (2.6)	-	-	-	-
Intermitent joint pain	1 (2.6)	-	-	-	-
Muscle weakness lower limb	-	1 (2.6)	-	-	-
Myalgia	6 (15.4)	2 (5.1)	-	-	-
Neck pain	1 (2.6)	-	-	-	-
Pain in extremity	2 (5.1)	-	-	-	-
Nervous system disorders					
Dizziness	2 (5.1)	-	-	-	-
Dysesthesia	1 (2.6)	-	-	-	-
Dysgeusia	3 (7.7)	1 (2.6)	-	-	-
Extrapyramidal disorder	-	1 (2.6)	-	-	-
Intracranial hemorrhage	-	-	-	-	1 (2.6)
Neuralgia	1 (2.6)	-	-	-	-
Numbness finger	1 (2.6)	-	-	-	-
Paresthesia	1 (2.6)	-	-	-	-
Peripheral sensory neuropathy	5 (12.8)	9 (23.1)	-	-	-
Stroke	-	-	-	1 (2.6)	-
Psychiatric disorders					
Anxiety	1 (2.6)	-	-	-	-
Insomnia	2 (5.1)	1 (2.6)	-	-	-
Renal and urinary disorders					
Hematuria	1 (2.6)	-	-	-	-
Urinary tract obstruction	1 (2.6)	-	-	-	-
Reproductive system and breast disorders					
Genital edema	1 (2.6)	-	-	-	-
Respiratory, thoracic and mediastinal disorders					
Allergic rhinitis	1 (2.6)	-	-	-	-
Cough	6 (15.4)	1 (2.6)	-	-	-
Dyspnea	4 (10.3)	-	2 (5.1)	-	-
Epistaxis	3 (7.7)	-	-	-	-
Pleural effusion	-	2 (5.1)	1 (2.6)	-	-
Pneumonitis	-	-	1 (2.6)	-	-
Skin and subcutaneous tissue disorders					
Alopecia	4 (10.3)	17 (43.6)	-	-	-
Dry skin	1 (2.6)	-	-	-	-
Exanthema	1 (2.6)	-	-	-	-
Pruritus	1 (2.6)	-	-	-	-
Rash acneiform	1 (2.6)	-	-	-	-
Rash maculo-papular	4 (10.3)	2 (5.1)	-	-	-
Skin rash	-	1 (2.6)	-	-	-
Skin rash (arms)	1 (2.6)	-	-	-	-
Urticaria	1 (2.6)	-	-	-	-
Vascular disorders					
Hypertension	-	1 (2.6)	1 (2.6)	-	-
Hypotension	-	1 (2.6)	-	-	-
Thromboembolic event	-	1 (2.6)	1 (2.6)	-	-
Varicose veins	1 (2.6)	-	-	-	-

between overall response and symptom severity and interference indicated that patients with objective response reported less symptom severity and interference (supplementary materiel Figure 6).

4. Discussion

This is the first full report of a study investigating the combination of nab-pc with gemcitabine in STS. The safety and toxicity profiles of nab-pc/gem were acceptable and manageable. Toxicities were mainly related to nab-pc and there was no signs for an increase in toxicity related to the combination with gemcitabine.

Twenty-two of 39 patients (56.4%) achieved disease control at 3 months. Three patients (7.7%) were partial responders and 19 (48.7%) had SD at 3 months. Overall, four patients had an objective response (10.3%) and an additional 21 patients (53.8%) had SD with 15 of them having SD for longer than 3 months. For 14 patients a prolonged PFS (>6 months) was observed. Due to the small number of cases in the respective histotype subgroups, it is difficult to identify those who benefited most from this combination. PFR at 3 and 6 months were equivalent in the LMS and LPS population compared to the UPS population. Good clinical activity has been previously reported for paclitaxel in angiosarcoma and there is also evidence for the use of gemcitabine [13,14]. Hence, it would be interesting to explore the nab-pc combination with gemcitabine, specifically in the STS angiosarcoma subgroup. We only treated one angiosarcoma patient in this study: the patient had a PR and a prolonged disease control.

Most patients treated in our study had progressive metastatic pretreated STS, a setting with very poor prognosis, low response rates to salvage chemotherapy regimen, and poor outcome. Yet, the mostly moderate efficacy of any second-line treatment in most relapsed bone sarcomas and STSs highlights the need for intensified research to identify novel targets and develop preclinical models to predict drug response in molecularly defined cohorts of patients suffering from refractory and/or recurrent disease [15]. The observed benefit in our study was more favorable compared to that reported in second- and third-line trabectedin and eribulin single agent studies in selected populations [16].

Recently, Kantidakis et al., in their meta-analysis proposed new thresholds for phase II trials using PFSR at 3 or 6 months as endpoints, suggesting drug activity in LMS, LPS and synovial sarcoma (SS) [17]. Interestingly, the PFS rate (PFSR) values for second or later lines of treatment, for L-sarcomas are 63% and 44% at 3 and 6 months, respectively. On the other hand, the data used for the meta-analyses came from trials that took place between 2003 and 2018 that included several STS subtypes and therefore were underpowered for specific subgroup analyses. In our trial, exploratory analysis confirmed the activity of nab-pac and gemcitabine combination in L-sarcomas and performed better than other drugs approved for STS (Figure 5). Designing clinical trials based on specific subtypes and using thresholds may help to identify more efficient drugs. In the recent Consensus on State of Science in Sarcoma, 72% of panelists considered STS subtype agnostic clinical trials no longer appropriate for phase I/II and 76% think the same for phase III trials [18]. However, phase II studies with stratification by subgroups can be informative and may lead into a phase III as demonstrated in the context of pazopanib [19,20]. Obviously, the ultimate goal is to perform subtype specific phase III trials with OS as endpoint.

Our biweekly gem/nab-pc treatment was well tolerated, and grade 3–4 neutropenia and thrombocytopenia occurred in only 15% and 0% of cases. In previous trials, the rate of grade 3–4 neutropenia and thrombocytopenia with gemcitabine/docetaxel were 20–40%, though those who were treated with this regimen as a 1st line therapy were included [21,22]. Compared to this regimen, our study demonstrated a lower toxicity profile. Also, no major alopecia that could be attributed to biweekly administration was reported (43.6% grade 2, no grade 3–4). This suggests that our biweekly treatment may be more tolerable and efficient that gemcitabine/docetaxel. In addition, the administration of this regimen has been considered relatively difficult due to the more frequent and longer hospital visits required, arguing in favor of our regimen.

In our trial, the rates of serious life-threatening AEs were low and acceptable. Overall symptom severity and symptom interference with daily life remained stable for most patients. Patient-reported chemotherapy-induced sensory neuropathy worsened over time. Still, no cases of grade 3–4 AE were reported. This may be of particular importance for patients who are treated for longer periods [23]. A limitation of our study was the lack of dose escalation. We decided not to do that to maintain the quality of life of our patients. Higher does might have led to more severe sensory neuropathy.

The data we have obtained with nab-pc in combination with gemcitabine suggest the combination deserves further exploration in pretreated advanced STS patients, specifically in L sarcomas.

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Declaration of Competing Interest

AD reports honoraria and/or consulting fees from and has served on advisory boards for F. Hoffmann-La Roche Ltd, Pharmamar, Incyte, and AstraZeneca (via institution). MJ. reports honoraria and/or consulting fees for Bristol Myers Squibb, Pfizer, Merck Sharp & Dohme, Bayer, Debiopharm, Novartis, Basilea Pharmaceutica, Sanofi (via institution). CR reports honoraria and/or consulting fees for Bristol Myers Squibb, Pfizer, Merck Sharp & Dohme (via institution). AK, DD, MNK, CB, TR, FK, YM, IC,KR have declared no conflicts of interest.

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Authors contribution

Antonia Digklia and Christian Rothermundt.

All authors contributed to the writing of the manuscript and approved the final version.

Data sharing

Complete study protocol is available online in the supplementary material. Proposals for data access should be submitted to the corresponding author for consideration. Access to de-identified participant data can be granted if the proposal is approved by SAKK; use of the data is intended only for the approved proposal.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113470.

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