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Sunitinib With Concomitant Radiation Therapy In Inoperable Sarcomas:

Final results from the dose escalation and expansion parts of a Multicenter Phase I Study

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Conflict of interest

The authors declared no potential conflicts of interest.

Author contributions

All authors declare to have participated to the recruitment, results and discussion, have seen and approved the final version.

Data sharing statements

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Abstract

Introduction. Local control in sarcoma is rarely achieved with exclusive radiotherapy (RT). We aim to assess the feasibility and safety of sunitinib continuously administrated with concomitant RT in inoperable non-GIST sarcomas patients.

Methods. This multicentric French 3+3 dose escalation study included patients with inoperable locally advanced or recurrent sarcoma, ECOG-PS <2, ≤2 metastatic sites and no brain metastases, adequate organ functions and absence of uncontrolled hypertension, who had never received sunitinib or radiotherapy. The escalation phase planned to use sunitinib dose levels (DL1: 25; DL2: 37.5; DL3: 50 mg/day) with standard RT (60 Gy, 30 fractions, 5 fractions/week/6 weeks). The primary endpoint was to determine the incidence of dose-limiting toxicities (DLT) in the first 14 weeks and the maximal tolerated dose (MTD). Secondary endpoints included safety (acute and late toxicities), local control at 6 months including local progression free rate (L-PFR) progression free survival (PFS), overall survival (OS), proportion of patients eligible for surgery after treatment.

Results. From May 2011 to April 2016, the dose-escalation phase enrolled 10 patients (DL1 N=4; DL2 N=6). No DLT was observed in at DL1. One DLT (grade 4 thrombopenia) occurred at DL2. The 19 patients treated at DL2 (including the 13 patients from the expansion phase) received sunitinib for a median duration of 42.7 (2.8-79.1) days, and radiotherapy for 6.4 (1-8) weeks; all but 3 patients received 60 Gy (40 Gy, early progression (N=1); 8 Gy, early death (N=1), prescribed dose, 50 Gy (N=1)). With a median follow-up of 19.5 (14-36.5) months, the median PFS was 6.5 (1.9-31.1) months. Median OS was not reached. At 6 months, L-PFR was 73.3% (95%CI 44.9%-92.2%). One patient was amendable to surgery after treatment. Sunitinib-related grade ≥3 adverse events occurred in 58% of the patients treated at DL2 (Escalation N=4; Expansion N=7). Seven (36.8%) deaths related to disease progression were reported.

Conclusion. This is the first trial assessing the combination of continuous administration of sunitinib 37.5 mg with exclusive RT in non-GIST sarcoma. Whereas this combination was found feasible, efficient, further investigations of combinations of more recent multikinase inhibitors with RT need to be explored.

Keywords. Inoperable non-GIST Sarcomas; sunitinib; radiation therapy; escalation phase I study; tyrosine kinase inhibitor; combined treatment.

Introduction

Soft-tissue sarcomas (STS) constitute a rare group of malignant tumors, accounting for 1-2% of all adult cancers. Substantial heterogeneity exists among this group, which gathers nearly one hundred histological subtypes according to the new WHO classification (1). Besides histological features which remain crucial for classification, recent discoveries in molecular genetics led to refinements in diagnosis and prognostication (1;2). Suspected sarcoma should be managed in expert reference centers involving multidisciplinary tumor board, as this has been shown to improve patient outcome (3;4). STS are considered in general poorly responsive to systemic therapy, thus R0 surgery is the mainstay of treatment, as the quality of surgical margins impacts local control and survival (5). Indeed, local control is achieved in approximately 90% of extremities STS with R0 surgery (6). Factors such as tumor size, tumor site, histological grade, and surgical margins have been reported to impact local control, disease free survival, overall survival (OS), and are used to determine radiation indications (7). Age, size, resection margin status, grade of tumor, and histology also predict the 3- and 5-year-risk of local recurrence after limb-sparing surgery in the absence of adjuvant radiotherapy. Despite the high rate of initial tumor control, approximatively 50% of the patients are likely to experience tumor recurrence, often consisting in distant failure. In a cohort of 1452 patients with STS of the extremities who underwent surgery in expert centers (R0 surgical margins, 88%; inframillimetric margins, 12%), the 10-year OS and 10-year crude cumulative incidence of distant metastases were 72·9% and 25·0% respectively, with variable rates according to histologic subtypes (8). The risk of local recurrence, regardless of the use of radiation therapy, is higher (up to 25%) for large, high-grade STS of the extremities with R1/R2 resection, as well as operated STS at specific sites such as head and neck or retroperitoneum (9-15). For patients with inoperable sarcomas, exclusive radiotherapy (RT) has been shown to yield approximatively 30% of tumor control at 5 years despite the use of doses increased from 64 to 70 Gy (16-18). Neutron therapy in inoperable STS and in inoperable osteosarcomas and chondrosarcomas increases the 5-year local control rate to 56-68% (18). Proton and carbon ion-based therapy has also shown encouraging results with a median follow-up of 32 months, and reported 3-year OS, PFS, and local control of 83%, 72%, and 92%; however, access to these medical technologies remains limited (19).

Tumor angiogenesis has a critical role in cancer (20-22). Preliminary studies have shown the feasibility of combining RT with the receptor tyrosine kinase inhibitor (TKI) sunitinib presenting anti-angiogenic activity, and different mechanisms including vascular normalization, modulation of cell growth and apoptosis, as well as alteration of the immune response supported further investigations with sunitinib associated with RT for cancer treatment (23-25). Efficacity and tolerance of sunitinib and other TKIs has been reported in cancers from different localizations (23;26-31), and more specifically in STS (32-39). Sunitinib combined with RT thus seemed promising to increase tumor control. This study aims to assess the feasibility and safety of sunitinib associated with concomitant RT in inoperable STS.

Materials and Methods

Study design

The main objective of this multicenter open-label single-arm phase I/II study was to determine the maximum-tolerated dose (MTD) of continuous administration of sunitinib in combination with RT. Eligible patients had locally advanced, histologically confirmed, non-operable, non-GIST sarcoma. A 3+3 dose-escalation design was used to escalate the dose of sunitinib. The following dose levels (DL) were planned DL1=25, DL2=37.5 and DL3=50 mg/day combined with constant dose of RT (60 Gy in 30 fractions, 5 fractions per week, during 6 weeks) and 3 to 6 patients should be enrolled at each dose level (Figure 1). Escalation to the next dose level was allowed based on safety assessment during at least 14 weeks from treatment initiation (dose-limiting toxicity observation period) of all patients enrolled at a given DL and validation by an Independent Data Safety Monitoring Board (iDSMB). The MTD was defined as the highest dose level of sunitinib at which less than 2 patients experienced a dose-limiting toxicity (DLT) during the first 14 weeks. An expansion cohort was decided for additional evaluation of efficacy and safety. The main efficacy endpoint was the local control rate at six months (local progression-free rate at 6 months (6M-L-PFR) with tumor assessment of the localization treated with magnetic resonance imaging, performed according to Response Evaluation Criteria In Solid Tumors RECIST v.1.1. (40), i.e. defined with a complete or partial response, or stable tumor; Secondary objectives were safety, including the incidence of late toxicities occurring within the first 12 months after treatment initiation, progression free survival (PFS), overall survival (OS), and proportion of patients amenable to surgery after combined treatment.

The study was performed in three institutions from the NETSARC network, according to the declaration of Helsinki and the International Conference of Good Clinical Practices after local approval of the Ethic Committee of Lyon Sud-Est IV. An IDSMB was in charge of assisting the steering committee in conducting the trial. All patients provided a written informed consent before enrolment. The study was registered on ClinicalTrials.gov, number NCT01308034.

Patients

Adult patients (≥18 years) with histologically confirmed diagnosis of sarcoma including soft tissue sarcoma, osteosarcoma, chondrosarcoma or chordoma, with locally advanced or recurrent tumor with no previous RT, and for whom surgery had been considered inappropriate, were eligible. Patient files were reviewed by a) multidisciplinary expert sarcoma tumor board in one of the national reference centers, including surgeons with sarcoma expertise. Eligible patients had Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 or 1, , and adequate organ functions defined as absolute neutrophil count ≥1,500 cells/µL, platelets ≥100,000 cells/µL, alkaline phosphatase ≤1.5 x upper limit of normal [ULN], hepatic aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤2.5 x ULN, total bilirubin ≤1.5 x ULN, serum creatinine ≤1.5mg/dL or creatinine clearance ≥50mL/min, calcium ≤12mg/dL and serum glycose ≤ 150 mg/dL. Patients with GIST, Ewing sarcoma, rhabdomyosarcoma, or patients with >2 metastatic sites, with brain metastases, patients previously treated with sunitinib, or patients with uncontrolled hypertension were excluded.

Treatment

Patients received continuous oral sunitinib (Sutent®, Pfizer, Paris, France) at a daily dose of 25, 37.5, or 50 mg (DL1, 2, or 3) during RT according to the study dose-level plan. RT delivered 60 Gy in 30 fractions with high-energy

photons (≥6 MV) during 6 weeks. The choice of Intensity Modulation radiotherapy (IMRT) or three-dimensional (3D) radiotherapy was left at the investigator discretion depending on tumor location. Personalised contention was provided for accurate repositioning of the patient, according to the location of the disease. Radiotherapy used 3D-computed tomography (CT) for dose calculation. Radiotherapy was performed by experienced physicians in one of the reference centers.

Toxicity and response assessments

Toxicity was continuously evaluated during radiotherapy by radiation and medical oncologists. Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Moreover, dermatitis was scored using http://ctep.cancer.gov/protocolDevelopment/electronic applications/ctc.htm ; desquamation was scored as none, dry, or moist; pruritus and oedema as absent or present. For all patients, responses assessments were performed at the regularly scheduled dates, at 10 and 14 weeks, and thereafter at 1, 3, 6, and 9 months according to RECIST version 1.1.(40), which corresponds to a global follow-up duration of 12 months or until death, whichever occurs first. Clinical or radiological tumor assessment (including local and distant tumor assessments) was performed at the date of last contact, close to the date of data cutoff in october 18, 2019.

Endpoints

The primary endpoint was the incidence of DLT at each sunitinib dose level during 14 weeks after treatment initiation. Secondary endpoints included the evaluation of safety of sunitinib, including acute toxicities during the first 14 weeks after treatment initiation and late toxicities from 14 weeks to 12 months after treatment initiation, specifying for each adverse event type, frequencies, and severity (grade). A DLT included any adverse event (AE) defined as a musculoskeletal or cutaneous grade ≥3 toxicity occurring in the irradiation area with irradiation <30Gy, or >30Gy with no toxicity decrease to grade ≤2 within 4 weeks, and any grade ≥4 AE. Any temporary discontinuation of sunitinib ≥9 days, consecutive or not, was also considered as DLT.

Secondary endpoints included the local control rate or local progression-free rate at 6 months (6M-L-PFR) defined as the proportion of patients without local progression (i.e. complete or partial response, or stable tumor) at 6 months according to RECIST v.1.1. (40); PFS defined as the time from first study drug administration to the date of event defined as the first documented progression, local or metastatic, as per RECIST v.1.1. or death from any cause*;* OS defined as the time from first study drug administration to the date of death from any cause; the rate of patients amenable to surgery.

Statistics and data analysis

Sample size for the 3+3 dose-escalation part was set to screen patients for major toxicity occurring in a large proportion of the target population. Based on binomial probabilities, there is a 90% probability of observing toxicity event in one or more patients, if that event occurs in at least 54% and 32%, in 3 and 6 patients respectively. Up to 18 patients were planned to be included (3 to 6 patients per dose level). Inclusion of 12 additional patients was scheduled for the expansion part, based on the first stage of a Gehan design allowing to quickly identify treatments with low efficacy: a sample size of 12 patients is needed to eliminate a treatment with response rate

lower than 25%. If no clinical responses are observed among 12 patients, the probability that the response rate is greater than 25% will be less than 5%.

Patients included in the dose escalation part followed for at least 14 weeks after treatment initiation or with a DLT observed during the first 14 weeks were included in the DLT population. All patients who received at least one dose of treatment were included in safety and efficacy analyses.

Dose escalation was determined at each dose level according to the following rules: i) 0/3 patient experienced a DLT: the dose was increased to the next higher dose level (DL). ii) 1/3 patient experienced a DLT: 3 additional patients were to be accrued at the same DL; If 1 additional patient experienced a DLT (i.e. 2/6 patients with a DLT), the dose escalation should be stopped; If no additional patient experienced a DLT (i.e. 1/6 patients with a DLT), the dose escalation to the next DL was investigated. iii) If ≥2/3 patients experienced a DLT, no further dose escalation was allowed.

Based on the local progression assessed as per RECIST v1.1., the 6m-L-PFR was assessed in terms of success and failure, defined as success for no local progression at 6 months, and failure for local disease progression within the 6 months following treatment initiation. 6m-L-PFR was evaluated at DL2. Patients without local progression at 6 months but for whom metastatic progression before 6 months was observed, and patients with no tumor evaluation at 6 months and at last contact (missing data) were considered as non-evaluable. The 6m-L-PFR is presented as a proportion of patients with its 95% confidence interval (CI).

PFS and OS were estimated using the Kaplan-Meier method, and described in terms of median survival, along with the associated 2-sided 95%CIs for the estimates. PFS was censored at the date of last tumor assessment for event-free patients at the time of the analysis. Median follow-up (min-max) was calculated by a reverse Kaplan-Meier estimate.

Descriptive statistics were performed to describe patient demographics and clinical characteristics, occurrence of adverse events (AE). All analyses were performed using SAS (version 9.4). The date of data cutoff for the final analysis was October 18, 2019.

RESULTS

Between May 2011 and April 2016, 25 patients (10 in escalation part, DL1 N=4; DL2 N=6], and 15 in the expansion part at DL2) were included in three investigation sites. Two patients did not receive study treatment at DL2, the global analysis consequently considered 23 patients, among them 19 patients had received sunitinib DL2 (Figure 1).

Among the 23 patients, the median age of 55 (38-82) years, 9 (39%) male, 8 (40%) patients had ECOG-PS 0, 11 (55%) had ECOG-PS 1, 1 (5%) had ECOG-PS 2 (3 patients with no specified ECOG-PS). Most patients (N=16, 70%) had an undifferentiated pleomorphic sarcoma without translocation (escalation phase: N=6, 60%; expansion phase: N=10, 77%). Among the 23 patients, 7 patients had metastases (Table 1). The median time from diagnosis to inclusion was 6.2 (1-136) months. To note, 4 patients with minor deviations at inclusion (contraception criteria

not specified (N=1), reduced neutrophils and platelets (N=1), 3 metastatic sites at inclusion (N=2), previous anticancer treatment discontinuation within the last 6 months (everolimus stopped 18 days before sunitinib initiation) (N=1)) were included in the analysis.

One out of the first 3 patients receiving DL1 sunitinib was withdrawn from the study for refusal of antihypertensive treatment and therefore non-evaluable for dose limiting toxicity (DLT); a 4th patient received sunitinib DL1. In the first 3 patients receiving DL2 37.5 mg/day sunitinib, 1 patient experienced a DLT (grade 4 thrombocytopenia). Three additional patients were consequently treated at DL2 and no other DLT was reported. After review of the safety data, and considering that the study planned for DL3 an administration of sunitinib 50 mg/day during 6 weeks continuously -i.e. higher than the standard schedule of 50 mg/day sunitinib (4 consecutive weeks, and 2-week rest period), the iDSMB decided to stop dose escalation and to further include patients in an expansion cohort at DL2; the protocol was amended accordingly. In the 15 patients enrolled in the expansion, 13 received study treatment at DL2 (e.g. sunitinib 37.5 mg/day)(Figure 1). Indeed, two patients were withdrawn due to early progression and did not initiate sunitinib neither the planned course of RT (hemoptysis (N=1), therapy change due to detection of new metastases (N=1)). In total, 4 patients having received sunitinib at DL1, and 19 patients who had received sunitinib at DL2 (37.5 mg/day) were analysed (Escalation phase, N=6; expansion phase N=13).

The incidence of DLT at each dose level is listed in Figure 1. No DLTs were reported at the first dose-level (DL1). One DLT occurred at DL2 (grade 4 thrombopenia). In the six patients having received sunitinib at DL2 in the escalation phase, all experienced at least one sunitinib-related adverse event. Dose escalation was stopped based on the iDSMB recommendations.

Of 19 patients treated at 37.5 mg/day sunitinib, 16 (84%) reported at least one adverse event (AE), including 15 (79%) who experienced at least one sunitinib-related AE (grade ≥3 sunitinib-related AEs (N=11), among them 7 were enrolled in the expansion phase), at least one RT-related AE (N=10, among them no RT-related grade ≥3 AEs or SAE in the expansion phase). No other patient experienced SAEs related to sunitinib or to RT in the expansion phase. No late toxicities related to RT were declared.

Safety is detailed in Table 2. In the 19 patients treated at DL2, 15 (79%) patients had at least one sunitinib-related AE including 11 (58%) grade ≥3 sunitinib-related AEs. Among these AEs: sunitinib-related anemia, trombopenia, lymphopenia occurring in 9 (47%) patients, and neutropenia in 7 (37%) and 10 (52.6%) patients had at least one RT-related AE (including 1 (5%) grade ≥3 RT-related AEs). Three patients had treatment-related SAEs: sunitinib-related SAE (lymphopenia, trombopenia (N=1); anemia (N=1)), and RT-related SAEs (dyspnea, N=1). Dose-escalation was interrupted based on recommendation from the IDSMB before MTD was reached, thus no formal MTD could not be determined (Table 2).

In the 4 patients enrolled at DL1, median duration for sunitinib was 44.1 (27.3-55.3) days, and 6.4 (6-8) weeks for radiotherapy. To note, one patient had sunitinib premature discontinuation and 6 weeks of radiation therapy (60 Gy).

In the 19 patients treated at DL2, the median duration for sunitinib was 42.7 (2.8-79.1) days and the median duration for radiotherapy was 6.4 (1-8) weeks. A total of 16 patients treated at DL2 received more than 4 weeks

of combined study treatments (2 patients prematurely stopped sunitinib and radiotherapy (early progression (N=1); early death (N=1)) and 1 prematurely stopped sunitinib at 4 weeks. The characteristics of radiotherapy in terms of volume reported 272.5 (6-2975) cm^3 for median GTV and 799.5 (34-4660) cm^3 for median PTV; detailed information is available in supplementary Table S1.

At DL2, 7 patients permanently discontinued sunitinib: discontinuation for toxicity and progression (grade 4 thrombopenia (DLT) and lung infection after 28 days, tumor progression prevented this patient from resuming treatment after management of these toxicities (N=1); asthenia and thrombopenia (N=1); thrombopenia and neutropenia (N=1); arterial hypertension (N=1); skin allergy (diffuse erythema outside the radiation field), this latter patient received a total of 5 weeks of sunitinib, he was nevertheless considered as evaluable for DLTs (N=1). and two patients progressed.

To note, one patient receiving DL2 and 40 Gy radiotherapy discontinued RT for disease progression, and discontinued sunitinib after experiencing a DLT (grade 4 thrombopenia). One patient in the expansion phase died after 4 days of treatment; death occurred for progression and was not related to treatment, in the absence of hemorrhagic or thromboembolic event. One patient received treatment during 8 weeks for technical reasons. One patient with critical tumor location received RT deliberately limited to 50Gy in order to prevent unavoidable irradiation of surrounding healthy tissue and preserve organs.

The efficacy was evaluated in the 19 patients treated with DL2 (sunitinib 37.5 mg/day; escalation phase (N=6); expansion phase N=13). With a median follow-up of 19.5 (14-36.5) months, the median PFS was 6.5 (1.9-31.1) months, a total of 14 patients presented local or metastatic progressions according to RECIST v.1.1., or deaths. At six months, four patients had no tumor evaluation (early metastatic progression (N=3); premature death (N=1) and among the 15 patients evaluable for the 6M-LPFR, 11 patients were free of local disease progression at 6 months, the 6m-L-PFR was therefore 73.3% (95%CI 44.9%-92.2%). One patient was amenable to surgery after treatment; the operative report indicates that tumor necrosis post-treatment account for less than 50% of the tumor volume. Seven (36.8%) deaths were reported, the median OS was not reached. All deaths were due to disease progression (Figure 2).

Figure 3 shows local and distant progressions, and deaths. In the two patients with no disease recurrence during the follow-up, relapses occurred in the long term (time to local recurrence: 28 months (N=1), time to metastatic recurrence: 32 months (N=1). Best response at DL2 included complete response (N=1, 5.3%), partial response (N=9, 47.4%), and stable disease (N=5, 26.3%). The last 4 (21.1%) patients had progressive disease. The median duration of response in the patients treated at DL2 was 6.4 (3-39) months.

Discussion

This study was the first prospective trial evaluating the combination of sunitinib with exclusive RT in non-GIST sarcoma. Previous studies reported the use of sunitinib combined with radiotherapy as preoperative treatment (35;41). Our trial showed that combining RT with 37.5 mg/day sunitinib was feasible, and showed some promising

response with local progression-free rate at 6 months of 73.3% (95%CI 44.9%-92.2%) in this population of locally advanced inoperable patients with sarcomas. The safety profile was manageable with adverse events (AEs) mainly related to sunitinib and rarely related to RT or to the combined treatment (58% of the patients had at least one grade ≥3 sunitinib-related AEs; 5% had at least one grade ≥3 RT-related AE)(31;42-44). Treatment-related SAEs were reported in two patients: one patient with sunitinib-related anemia, and one patient with thrombopenia and lymphopenia and possibly RT-related dyspnea. The safety profile of the combined treatment was overall consistent with that of sunitinib as single agent (26-28).

Results in this underserved population with a dismal prognosis showed very encouraging local, and distant control rate, and survival as compared to results of trials in such inoperable patients. To note, the current population of interest differed greatly from previous studies involving patients in neoadjuvant setting.

Yoon *et al*. reported more than 80% necrosis in 9 (45%) patients treated with neoadjuvant bevacizumab and RT (39). In a phase I study investigating sorafenib combined with preoperative radiotherapy, 3 (38%) patients had a near complete histological response (≥95% tumor necrosis) (33). Sunitinib combined with preoperative radiotherapy in 16 patients with STS (34) led to a near complete response (necrosis ≥90%) in 5(36%) out of the 14 patients who underwent surgery. In contrast, Lewin *et al.* reported no improvement in median tumor necrosis rate in patients with STS treated with irradiation and sunitinib (35). However, these limited series of patients with unbalanced histological subtypes required interpretation to be cautious.

The present study initially planned a three-dose-level-design; Even though the grade ≥3 toxicities observed at DL2 were not identified as dose limiting toxicities, continuous administration at the highest level (50 mg/day for 6 weeks) exceeding the registered dosing regimen (50 mg/day on 4 weeks on/2 weeks off schedule) was anticipated as too toxic in this population and administration at DL3 was cancelled. The protocol was subsequently amended and showed the expansion phase at DL2. The high rate of AEs (84% including 63% of grade ≥3 AEs) at DL2 was consistent with the toxicity profile of sunitinib used as single agent (26-28;), notably grade 3/4 AE rates as high as 50% in GIST and 86% in renal carcinoma have been reported (27). Such toxicity profiles were considered as manageable. The daily dose of 37.5 mg administered during the 6 weeks of radiotherapy in our study does not lead to increased radiation-related morbidity in the context of STS mainly localised in the limbs. Our results are consistent other series using sunitinib combined to RT in sarcoma (41). Pre-operative combination of sunitinib and fractionated irradiation in STS patients reported usual and manageable toxicities and postoperative complications requiring reintervention occurred in 4 out of the 16 patients, which was considered as acceptable in this series involving 4 sarcomas of the retroperitoneum and one thoracic sarcoma (26;34). In contrast, Lewin *et al*. prematurely stopped for toxicity a phase II study investigating sunitinib and radiotherapy after the inclusion of 9 patients. Indeed, 78% of the patients presented a grade 3/4 toxicity, all were exclusively sunitinib-related toxicities except in 2 patients for whom symptoms (rash, pain) were potentially imputable to the combination of RT and sunitinib (35).

Sunitinib is currently used to treat patient with GIST, pancreatic neuroendocrine tumors, and renal-cell carcinoma, potentially combined with RT. Indeed, our results are consistent with those reported by Jacob *et al.* and show that

combining treatments was feasible, with no gastrointestinal toxicities evidenced; Nevertheless, interpreting results from small series required to be cautious and increased vigilance is required with hypofractionated RT to allow early detection of gastrointestinal toxicities. Some fatal hemorrhage and digestion perforations have been reported following combined treatment with stereotactic body radiotherapy (SBRT) and TKI in various cancer localisations (31;43,44). These AEs were more likely to be related to TKI than to radiotherapy.

Pazopanib showed efficacy in patients with STS (36) and has been approved in patients with metastatic STS after failure of one line of systemic therapy. If further phase 3 studies investigating sunitinib are unlikely, the use of TKIs combined to radiotherapy remains a relevant option to prevent rapid progression of the disease while potentializing local treatment. Such combined approach deserves to be further explored in patients with inoperable sarcoma or oligometastatic requiring radiotherapy. The trial prematurely stopped at the interim analysis notwithstanding the histological response improved in the group receiving pazopanib. Currently, 81 patients were allocated to preoperative radiotherapy *versus* radiotherapy group. Indeed, a pathological response rate of at least 90% was obtained in 14 (58%) out of the 24 patients in the pazopanib group *versus* 4 (22%) out of the 18 patients in the control group (14). To note, the role of neoadjuvant chemotherapy is still debated in adult patients, and such treatment is currently reserved for specific subgroups (45). It should be noted that this population mixed pediatric and adult patients, while our series is more representative of locally advanced sarcoma in adults.

The present results are encouraging regarding LPFR, DPFR, and survival as compared to the outcomes of patients with locally advanced non metastatic sarcoma, while avoiding the use of combined chemotherapy. Toxicity of the combined treatment may be critical in the case of digestive location, and further studies should help to better define subgroups of patients likely to benefit from combined treatment.

Conclusion

Sunitinib combined with radiotherapy was found feasible and do not show increased irradiation toxicity. Promising results in terms of local control were observed in this population of inoperable sarcomas managed in reference centers.

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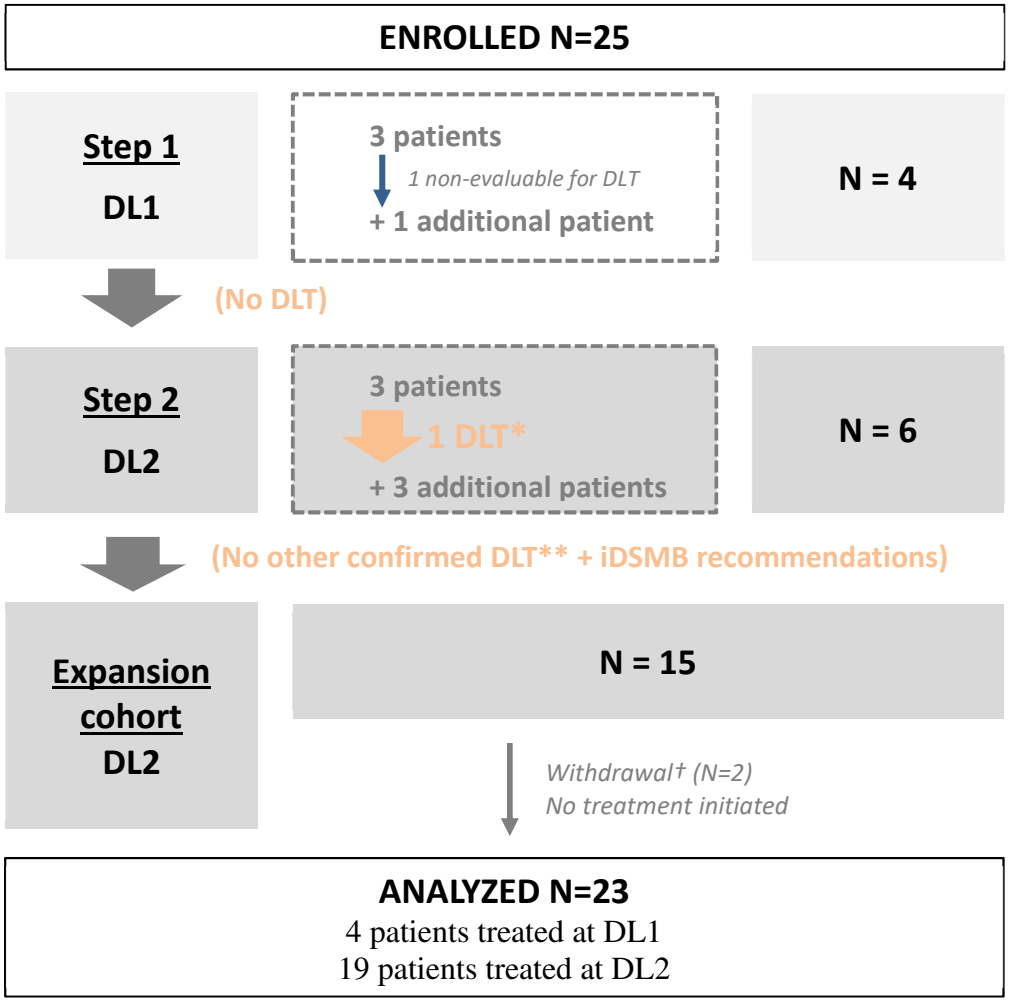
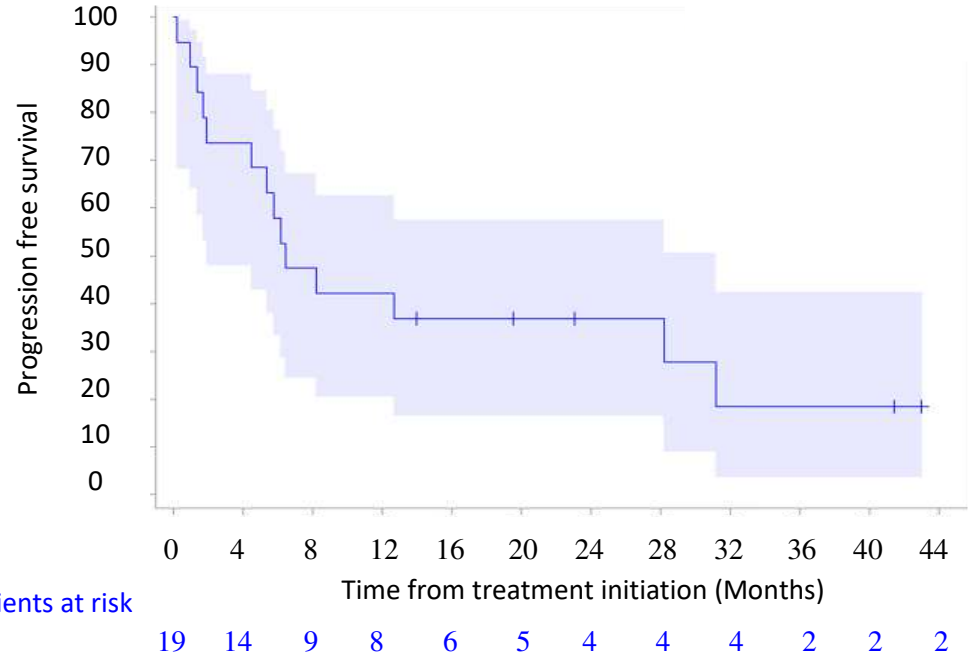
Figure 1. Study design. Study design initially included three dose levels (: DL1=25, DL2=37.5, and DL3=50 mg/day) combined with constant dose of RT (60 Gy in 30 fractions, 5 fractions per week), and DL1 and DL2 were exclusively used after decision of the IDSMB not to pursue administration at DL3 for safety reasons, but to further allow patient inclusions in an expansion cohort at DL2; DL: dose levels; DLT: Dose-limiting toxicities; iDSMB: Independent Data Safety Monitoring Board.*****DLT= grade 4 thrombocytopenia.*****DLT*** initially reported *(grade 4 lymphopenia, associated with grade 3 anemia*) but not confirmed as clinically significant; [±]hemoptysis (N=1), therapy change due to detection of new metastases (N=1).

Figure 2. Progression-free survival and overall survival. PFS considered as event the first documented progression (local or metastatic) as per RECIST v.1.1. or death from any cause.

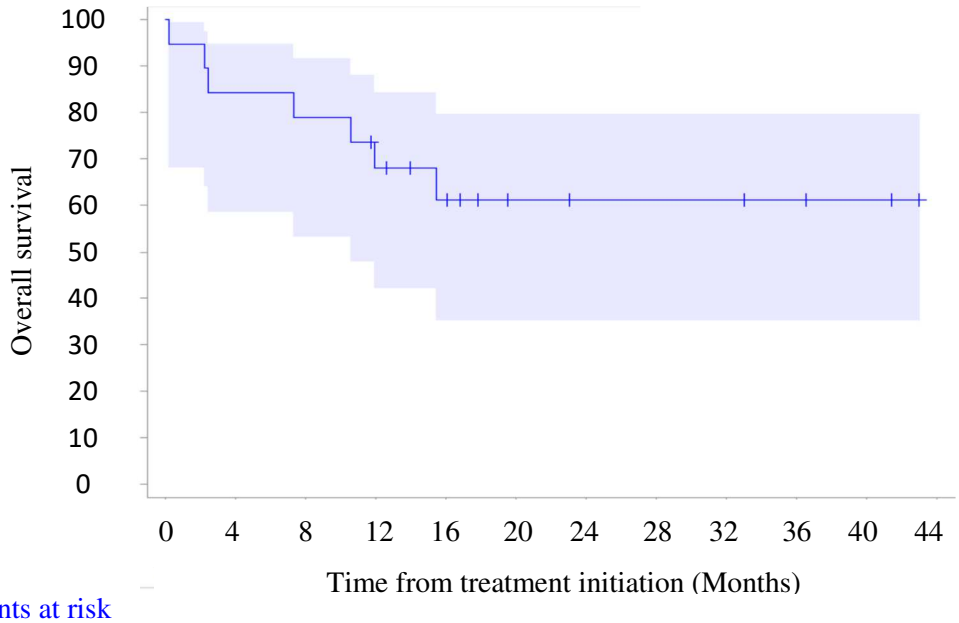
Figure 3. Treatment exposure, local and distant progression, and deaths in patients treated at dose level 2 (DL2) (N=19). Esc: Escalation Phase (N=6); Exp: Expansion phase (N=13). The date of data cutoff for the final analysis was October 18, 2019. The median follow-up was 19.5 (14-36.5) months.


ENROLLED N=25
Step 1
DL1
3 patients
1 non-evaluable for DLT
+ 1 additional patient
N = 4
(No DLT)
Step 2
DL2
3 patients
1 DLT*
+ 3 additional patients
N = 6
(No other confirmed DLT** + iDSMB recommendations)
Expansion cohort
DL2
N = 15
Withdrawal† (N=2)
No treatment initiated
ANALYZED N=23
4 patients treated at DL1
19 patients treated at DL2



Patients at risk

19	14	9	8	6	5	4	4	4	2	2	2



Patients at risk												
	19	16	15	12	9	5	4	4	4	3	2	0

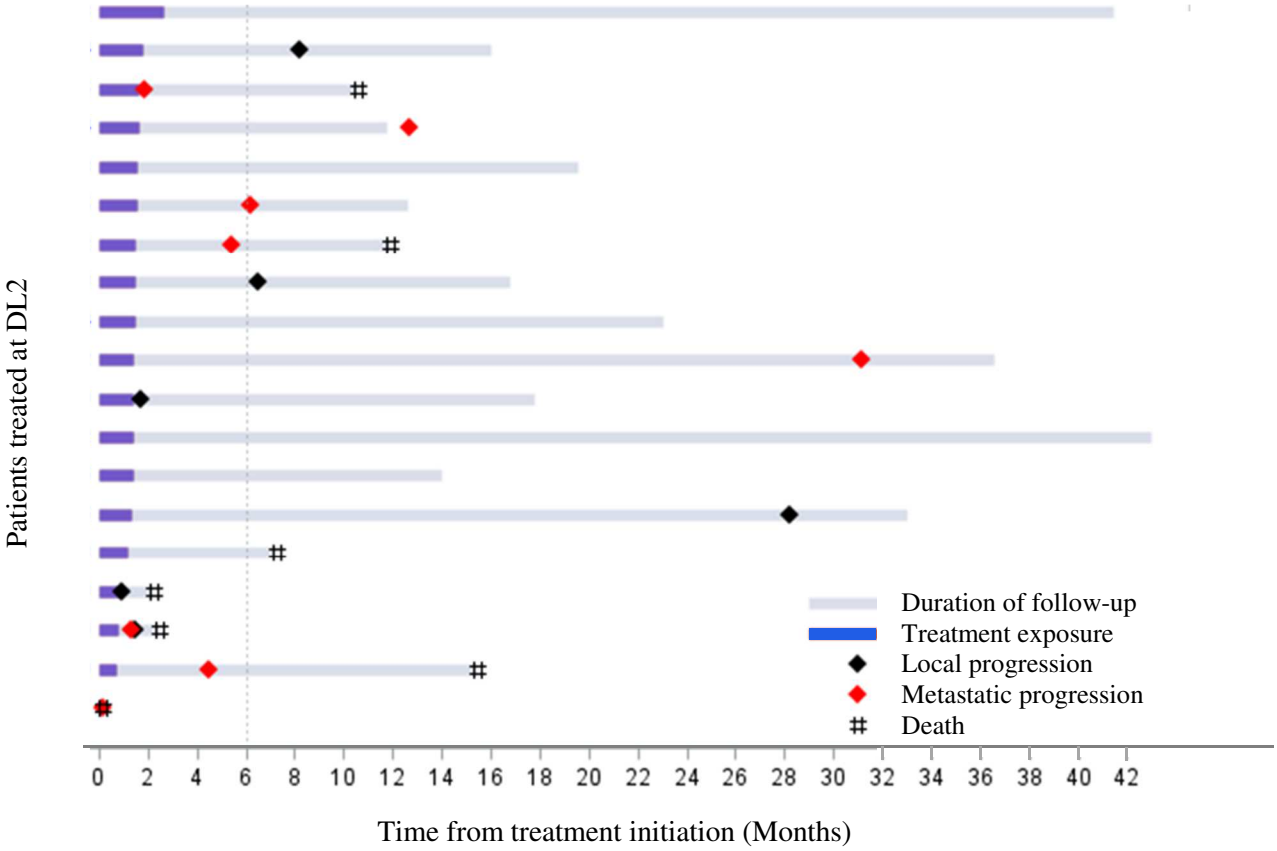

Patients treated at DL2
Duration of follow-up
Treatment exposure
Local progression
Metastatic progression
Death
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42
Time from treatment initiation (Months)

Table 1. Patient characteristics. Data are median (range) or n (%) unless otherwise indicated. *liposarcoma, leiomyosarcoma, fibrosarcoma, myxofibrosarcoma, pleomorphic undifferentiated sarcoma, spindle cell sarcoma; **synovial sarcoma, epithelioid sarcoma. ECOG: Eastern Cooperative Oncology Group.

Patient characteristics	Escalation phase			Expansion phase	Patients treated at DL2	Total
	DL1 (N=4)	DL2 (N=6)	SubTotal (N=10)	DL2 (N=13)	DL2 (N=19)	(N=23)
Median age at inclusion (years)	70.0 (53-78)	51.5 (39-82)	59.0 (39-82)	50.0 (38-82)	50.0 (38-82)	55.0 (38-82)
ECOG performance status						
Missing data	1	1	2	1	2	3
0	1 (33.3%)	3 (60.0%)	4 (50.0%)	4 (33.3%)	7 (41.2%)	8 (40.0%)
1	2 (66.7%)	2 (40.0%)	4 (50.0%)	7 (58.3%)	9 (52.9%)	11 (55.0%)
2				1 (8.3%)	1 (5.9%)	1 (5.0%)
Gender						
Male	1 (25.0%)	1 (16.7%)	2 (20.0%)	7 (53.8%)	8 (42.1%)	9 (39.1%)
Female	3 (75.0%)	5 (83.3%)	8 (80.0%)	6 (46.2%)	11 (57.9%)	14 (60.9%)
Histologic type						
Undifferentiated pleomorphic sarcoma without translocation*	2 (50.0%)	4 (66.7%)	6 -=(60.0%)	10 (76.9%)	14 (73.7%)	16 (69.6%)
Translocation-related sarcoma**	0 (0.0%)	1 (16.7%)	1 (10.0%)	3 (23.1%)	4 (21.1%)	4 (17.4%)
Osteosarcoma	2 (50.0%)	0 (0.0%)	2 (20.0%)	0 (0.0%)	0	2 (8.7%)
Chordoma	0 (0.0%)	1 (16.7%)	1 (10.0%)	0 (0.0%)	1 (5.3%)	1 (4.3%)
Median time from initial diagnosis (months)	5.2 (1-22)	14.0 (2-68)	6.2 (1-68)	6.2 (2-136)	6.2 (2-136)	6.2 (1-136)

Table 2. Grade ≥3 and all grades (sunitinib or RT)-treatment-related adverse events (AEs). Only AEs>10% are presented. #DLT (N=1); *RT-related grade≥3 AEs; †Sunitinib-related SAEs (N=2), ‡RT-related SAE (N=1).

	Escalated-dose cohort DL2 N=6				Expansion cohort DL2 N=13				Patients treated at DL2 N=19			
	Grade ≥3		Any grade		Grade ≥3		Any grade		Grade ≥3		Any grade	
Anemia	1†	(16.7%)	5†	(83.3%)	0	(0.0%)	4	(30.8%)	1‡	(5.3%)	9†	(47.4%)
Lymphopenia#	3#†	(50.0%)	5#†	(83.3%)	2	(15.4%)	4	(30.8%)	5#†	(26.3%)	9#†	(47.4%)
Trombopenia#	1#†	(16.7%)	4#†	(66.7%)	1	(7.7%)	5	(38.5%)	2#†	(10.5%)	9#†	(47.4%)
Neutropenia	1	(16.7%)	1	(16.7%)	3	(23.1%)	6	(46.2%)	4	(21.1%)	7	(36.8%)
Leucopenia	1	(16.7%)	2	(33.3%)	3	(23.1%)	4	(30.8%)	4	(21.1%)	6	(31.6%)
Asthenia	0	(0.0%)	3	(50.0%)	0	(0.0%)	2	(15.4%)	0	(0.0%)	5	(26.3%)
Diarrhea	0	(0.0%)	3	(50.0%)	0	(0.0%)	2	(15.4%)	0	(0.0%)	5	(26.3%)
Asthenia	0	(0.0%)	3	(50.0%)	0	(0.0%)	2	(15.4%)	0	(0.0%)	5	(26.3%)
Dysgeusia	0	(0.0%)	3	(50.0%)	0	(0.0%)	1	(7.7%)	0	(0.0%)	4	(21.1%)
Hand and foot syndrome	0	(0.0%)	3	(50.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(15.8%)
Anorexia	0	(0.0%)	3	(50.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(15.8%)
Nausea	0	(0.0%)	3	(50.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	3	(15.8%)
Skin lesion and radiodermatitis	0	(0.0%)	2	(33.3%)	0	(0.0%)	1	(7.7%)	0	(0.0%)	3	(15.8%)
Arterial hypertension	0	(0.0%)	0	(0.0%)	2	(15.4%)	2	(15.4%)	2	(10.5%)	2	(10;5%)
Stomatitis	0	(0.0%)	2	(33.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(10.5%)
Erythema	0	(0.0%)	1	(16.7%)	0	(0.0%)	1	(7.7%)	0	(0.0%)	2	(10.5%)
Arm pain	0	(0.0%)	2	(33.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(10.5%)
Epistaxis	0	(0.0%)	1	(16.7%)	0	(0.0%)	1	(7.7%)	0	(0.0%)	2	(10.5%)
Fatigue	0	(0.0%)	2	(33.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(10.5%)
Mucositis	0	(0.0%)	1	(16.7%)	0	(0.0%)	1	(7.7%)	0	(0.0%)	2	(10.5%)
Dyspnea*‡	1*‡	(16.7%)	1*‡	(16.7%)	0	(0.0%)	0	(0.0%)	1*‡	(5.3%)	1*‡	(5.3%)
Skin rashes	1	(16.7%)	1	(16.7%)	0	(0.0%)	0	(0.0%)	1	(5.3%)	1	(5.3%)