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Original Research

A phase II of gemcitabine combined with pazopanib followed by pazopanib maintenance, as second-line treatment in patients with advanced leiomyosarcomas: A unicancer French Sarcoma Group study (LMS03 study)

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Abstract ***Background:*** Options in second-line therapy after doxorubicin-based chemotherapy for metastatic/advanced leiomyosarcoma include gemcitabine (G), trabectedin and pazopanib (P) monotherapy. Currently, no combination therapy is better than monotherapy. LMS03 is an open-label multicentre single-group phase II study designed to assess the efficacy and tolerance of G + P in the second-line setting.

Patients and methods: Patients (pts), ECOG ≤2, with metastatic leiomyosarcomas (LMS) after first-line doxorubicin chemotherapy failure were eligible. Pts were treated with G 1000 mg/m^2 on days 1 and 8 of each 21 days (maximum eight cycles), in combination with oral daily P (800 mg), until disease progression/toxicity. 9-month progression-free survival (PFS) rate was the primary endpoint. Inacceptable and promising 9-month PFS rates were defined, in the intent-to-treat population, as 32% and 44%.

Results: 106 pts were included with a mean age of 59.8 years and an ECOG 0 in 63.5%; the primary tumour site was uterus in 61%. Pts were treated with P + G for a median of 3.8 mo, and P for a median of 4.2 mo. The 9-month PFS rate was 32.1% (95% CI 23.1–41.1). After a median follow-up of 14.2 months, the PFS was 6.5 months (95% CI 5.6–8.2), and the overall survival was 22.4 months (95% CI 16.9–26.5). The best response was 23.8%. The most frequent reported grade 3–4 adverse events were haematological.

Conclusions: LMS03 failed to show that second-line therapy, with gemcitabine combined with pazopanib, followed by pazopanib alone, was beneficial for advanced LMS patients.

Eudract N°2011-001308-36 and NCT01442662.

1. Introduction

The prognosis of patients with advanced or metastatic soft-tissue sarcoma (STS) is poor, with an estimated median of overall survival (OS) of 12–15 months and only a small subgroup of patients achieving long-term survival [1].

Leiomyosarcomas (LMS) are among the most chemosensitive sarcomas and represent about 10%–20% of STS [2]. Currently, doxorubicin-based and gemcitabine-based regimens are the mainstay for early lines of treatment for metastatic LMS. In addition, a number of new treatments including trabectedin and pazopanib have proven activity after the failure of first-line therapy for metastatic disease.

Only a few studies have assessed second-line therapy for relapsed and/or metastatic LMS. The randomised TAXOGEM study compared gemcitabine *versus* gemcitabine plus docetaxel after the failure of doxorubicin-based therapy in metastatic or unresectable LMS (with uterine and soft-tissue subgroups) [3]. In the uterine subgroups, the objective response rates were 19% with gemcitabine alone and 24% with gemcitabine plus docetaxel. In the non-uterine groups, the response rates were 14% with gemcitabine alone and 5% with gemcitabine plus docetaxel. Gemcitabine with or without docetaxel had similar median progression-free survival (PFS). The median PFS was 5.5 months in the uterine and 6.3 months in the non-uterine subgroups with gemcitabine alone, but shorter than 5 months in both groups with the gemcitabine–docetaxel combination. The toxicity was lower with gemcitabine alone.

Angiogenesis is critical for the growth and dissemination of malignancies. Several STS express VEGF [4], and this increased expression is associated with a higher malignancy grade and lower metastasis-free and OS rates in localised disease [5]. A phase II study assessed the efficacy and tolerance of pazopanib after doxorubicin failure. The study enrolled patients in four metastatic/relapsed STS cohorts. In the LMS cohort, the progression-free rate (PFR) at 12 weeks was 44% (18/41 patients), with a median PFS of 91 days (95% CI 84–168) and OS of 354 days (95% CI 318–544). The toxicity was as expected with a tyrosine kinase inhibitor targeting angiogenesis [6]. Pazopanib demonstrates a superior OS over placebo in the phase III PALETTE study (EORTC study 62072) in STS patients, including 165 LMS patients, who had received at least two lines of prior chemotherapy [7]. The LMS cohort specifically had a PFS of 4.6 months *versus* 1.9 months (HR 0.37). Regorafenib, another tyrosine kinase inhibitor, showed efficacy in a randomised placebo-controlled phase II study in four cohorts of STS. In the LMS cohort, 28 pts were treated with either regorafenib or placebo. The median PFS was 3.7 months with regorafenib *versus* 1.8 months with placebo, and the OS was 21.0 months and 9.7 months, respectively [8] but regorafenib is not a standard of care in STS.

The aim of our single-arm phase II trial was to evaluate the efficacy and tolerance of pazopanib combined with gemcitabine followed by pazopanib maintenance monotherapy as second-line treatment, after first-line doxorubicin-based therapy, in patients with uterine and non-uterine metastatic LMS.

2. Methods

2.1. Study design

The LMS03 study (EudraCT No. 2011-001308-36 and NCT01442662) was designed as multicentre, open-label, non-randomised phase II study. It was conducted in accordance with the declaration of Helsinki, ICH good clinical practice guidelines, and all applicable French and European laws. The study was approved by a French ethics committee: 'Comité de Protection des Personnes, Ile-de-France VII'.

2.2. Participants

Patients older than 18 years with an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 and a histologically confirmed (by an expert pathologist at the local French Sarcoma Group centre) relapsed or metastatic uterine or soft-tissue LMS with only one previous line of doxorubicin-containing chemotherapy were eligible. Patients with disease relapse within 1 year of adjuvant therapy were considered to have received first-line therapy. Patients with central nervous system metastases were not eligible. Eligible patients required adequate blood, renal, liver, and cardiac functions. Exclusion criteria included classical contraindications to oral anti-angiogenics.

2.3. Procedures

Patients could receive a maximum of eight cycles of combined gemcitabine 1000 mg/m^2 at a fixed-dose rate infusion of 10 mg/m^2/min on day 1 and day 8 and daily oral pazopanib at 800 mg/day (taken without food) of each 21-day cycle. This treatment combination and dosage were selected following the reporting of the results of a phase I study. The study reported that at the highest dose level tested, pazopanib 800 mg/day plus gemcitabine 1000 mg/m^2, more than 80% of patients received their planned dose, with the combination considered safe and tolerable [9].

After eight cycles of gemcitabine combined with pazopanib, and if a complete or partial response, or stable disease was observed, pazopanib was to be continued until disease progression or unacceptable toxicity. The study allowed for two doses reduction levels pazopanib, from 800 mg/day to 600 mg/day and 400 mg/day, and for gemcitabine from 1000 mg/m^2 to 800 mg/m^2 and 650 mg/m^2 depending on the toxicity observed.

2.4. Outcomes

Our primary objective was the efficacy of gemcitabine combined with pazopanib as second-line treatment, after first-line doxorubicin-based therapy, for patients with metastatic or relapsed LMS, in terms of the 9-month PFS rate. The 9-month PFS rate was defined as the percentage of patients without disease progression, death from any cause, or the occurrence of second cancer during the 9 months after starting treatment. Computed tomography scan or magnetic resonance imaging was performed at baseline, every 6 weeks for the first 9 months, and then every 2 months until disease progression. Tumour responses were assessed using RECIST v1.1.

Other efficacy outcomes included the 12-week disease control rate, the best response rate during treatment, and OS. Safety data were collected throughout the study and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v3.0.

2.5. Statistical analyses

The study analysis was planned according to a two-step Simon's procedure ('Optimum design') [10]. The sample size required was calculated based on the two-stage Simon method. The statistical assumptions, based on the results of TAXOGEM study, were as follows: a 9-month PFR of 32% (P0) would be considered as insufficient and a rate of 44% (P1) would be considered as promising (a median PFS of 5.5 months was considered equivalent to a 32% PFS rate at 9 months; similarly, a median PFS of 7.5 months was considered equivalent to 44% PFS rate at 9 months).

For an α-risk of 15% and a β-risk of 10%, overall 94 evaluable patients, including 43 evaluable patients at the first step, were required. Initiation of the second step required that <30 progressions in 43 patients be observed at 9 months. At the primary endpoint analysis, the experimental treatment would be considered promising if ≥ 60 patients were without disease progression at 9 months.

The analyses, efficacy and tolerance, were planned in the intent-to-treat (ITT) population: consisting of all enrolled patients who received at least one dose of study treatment. A sensitivity per-protocol (PP) efficacy analysis was planned. The PP population consisted of all patients that received at least one dose of study treatment without any major protocol deviation. The 12-week disease control rate and the best response rate during treatment were analysed in the efficacy population defined as patients in the ITT population with baseline tumour evaluations.

The Kaplan–Meier method was used for the analysis of time-to-event outcomes. The associated plots were produced together with estimates of the medians and the corresponding confidence intervals (CIs).

In June 2013, after the inclusion of 43 patients, the planned interim analysis was performed. At analysis, 28 of the 43 patients (65.12%) had disease progression within 9 months of starting treatment. Thus, since fewer

Table 1
Patient baseline characteristics in the study population (n = 106).

		Study population (n = 106)
Demographic characteristics		
Age, years		
	Mean (SD)	59.8 (8.7)
	Median [range]	59.0 [38–81]
Sex, n (%)		
	Male	15 (14.2)
	Female	91 (85.8)
ECOG PS, n (%)		
	0	66 (63.5)
	1	31 (29.8)
	2	7 (6.7)
	Missing data	2
Disease characteristics		
Primary tumour localisation, n (%)		
	Uterine	64 (61.0)
	Non-uterine	41 (39.0)
	Missing data	1
Location of metastatic lesions (multiple responses possible), n (%)		
	Pulmonary	87 (82.9)
	Hepatic	43 (41.0)
	Bone	22 (21.0)
	Peritoneal	19 (18.1)
	Lymph nodes	12 (11.4)
	Pleural	11 (10.5)
	Mediastinal	10 (9.5)
	Cutaneous	8 (7.6)
	Renal	7 (6.7)
	Adrenal gland	3 (2.9)
	Other locations	33 (31.4)
	Missing data	1
Prior therapy		
Surgery of primary tumour, n (%)		99 (94.3)
Radiotherapy of primary tumour, n (%)		55 (52.4)
Adjuvant chemotherapy, n (%)		25 (24%)
Chemotherapy for relapsed or metastatic disease, n (%)		105 (100.0)

SD: standard deviation, ECOG PS: Eastern Cooperative Oncology Group performance status.

patients than the futility limit (30 patients) had progressed or died, the study proceeded to the second stage. In August 2013, the study was temporarily interrupted due to a fatal liver toxicity reported in a similar study. Following this event, the independent data monitoring committee recommended that the protocol be amended. Additional hepatic evaluations on day 2 and 8 of the first cycle of gemcitabine and a dosage of cytidine deaminase (cytidine deaminase polymorphism predicts toxicity of gemcitabine) at baseline were added [11]. In November 2014, patient enrolment was resumed.

3. Results

From October 2011 to June 2016, 106 patients were enrolled in 18 French centres. Of the 106 patients enrolled, 105 patients were treated and 10 patients did not meet the eligibility criteria (2 patients with >2 lines of prior chemotherapy and 1 who did not receive doxorubicin previously, 3 with non-eligible tumour histology, 1 without target lesion, 2 patients due to the interruption of the study, and one with known cerebral metastasis at inclusion). The ITT population comprised 105 patients, and the PP population comprised 95 patients. The efficacy population comprised 101 patients since four patients did not have baseline tumour evaluations.

Patient demographic and disease characteristics, and prior treatments at baseline are presented in Table 1.

Overall, 69 patients (65.7%) received ≥4 cycles of gemcitabine and 40 (38.1%) received 8 cycles. Similarly, 64 patients (60.1%) received ≥4 cycles of pazopanib and 36 (34.3%) received ≥8 cycles. The median number of gemcitabine cycles administered was 6 (range 2–8). At analysis, no patient was still on treatment. Treatment discontinuations were mainly due to disease progression, completion of the eight cycles of planned treatment, and toxicity. Among 41 patients who started maintenance pazopanib, 34 stopped for progression, 3 for toxicity, and 4 for other reason.

In the ITT population (n = 105) after a median follow-up of 14.2 months (95% CI 11.5–22.2), the study failed to meet its primary objective with a 9-month PFS rate (primary endpoint) of 32.1% (95% CI 23.1–41.1) (Fig. 1). In addition, the median PFS was 6.5 months (95% CI 5.6–8.2) and the OS was 22.4 months (95% CI 16.9–26.5) (Fig. 2). But the study was nearly positive in the PP population (n = 95) after a median follow-up of 14.1 months (95% CI 10.5–15.7), with a 9-month PFS rate of 34.6% (95% CI 24.9–44.4), a median PFS of 7.1 months (95% CI 5.7–8.3), and a median OS of 24.3 months (95% CI 17.3–29.7). In the efficacy population (n = 101), at the time of analysis the tumour response was complete response in one patient (1%), partial response in 23 (22.8%), stable disease in 63 (62.4%), and progressive disease in 14 (13.9%). The 12-week disease

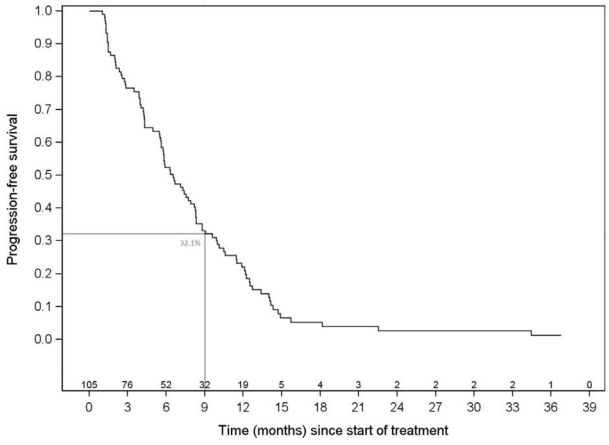

Fig. 1. Progression-free survival curve (ITT population): 32.1% at 9 months.

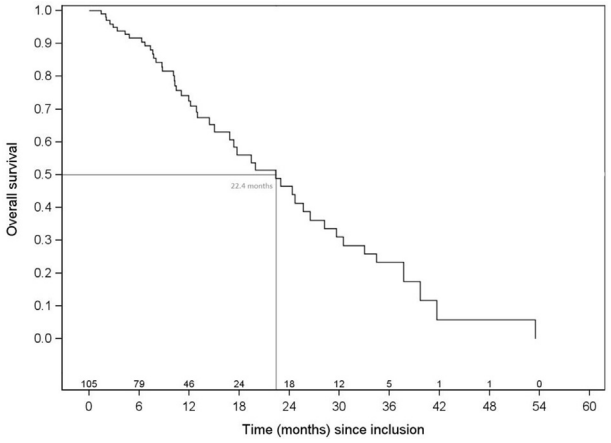

Fig. 2. Overall survival curve.

control rate was 83.6% and the best response during treatment was 23.8%.

The adverse events (AEs) reported in ≥20% of patients during treatment, either gemcitabine combined with pazopanib ($n = 105$) or during pazopanib monotherapy ($n = 41$) are shown in Table 2. During gemcitabine–pazopanib combined treatment, 91 patients (86.7%) reported grade 3–4 haematological AEs. However, there were few non-haematological grade 3–4 AEs; the most frequents were hypertension in 9 patients (8.6%), fatigue in 15 patients (14.3%), and elevated transaminase in 24 patients (22.9%). During pazopanib monotherapy, six patients (14.6%) reported grade 3–4 haematological AEs. During the study, no deaths considered related to the study treatment was reported. Overall, 56 patients (53.3%) needed one or more dose reductions, and 28 (26.9%) discontinued treatment for toxicity.

4. Discussion

The objective of the LMS03 study was to assess the efficacy of gemcitabine combined with pazopanib as second-line therapy for patients with relapsed/metastatic LMS. A 9-month PFS ≥44% was required for the study to be considered positive. Thus, with a 9-month PFS rate of only 32.1%, the study failed to meet its primary objective. This result was confirmed in the PP population with a 9-month PFS rate of 34.6%.

Table 2
The adverse events reported in ≥20% of patients during gemcitabine–pazopanib combined treatment ($n = 105$) and pazopanib monotherapy ($n = 41$).

Adverse event (graded by the NCI CTCAE v3.0)	Gemcitabine–pazopanib combined treatment ($n = 105$), n (%)		Pazopanib monotherapy ($n = 41$), n (%)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Haematological toxicity				
Neutropenia	20 (19.0)	76 (72.4)	7 (17.1)	3 (7.3)
Anaemia	79 (75.2)	3 (2.9)	17 (41.5)	0 (0)
Leucopoenia	38 (36.2)	59 (56.2)	15 (36.6)	0 (0)
Thrombocytopenia	56 (53.3)	40 (38.1)	9 (22.0)	0 (0)
Digestive toxicity				
Constipation	24 (22.9)	0 (0)	2 (4.9)	0 (0)
Diarrhoea	55 (52.4)	3 (2.9)	22 (53.7)	1 (2.4)
Abdominal pain	21 (20.0)	2 (1.9)	4 (9.8)	1 (2.4)
Mucositis/stomatitis	32 (30.5)	2 (1.9)	4 (9.8)	0 (0)
Nausea	55 (52.4)	0 (0)	9 (22.0)	0 (0)
Vomiting	28 (26.7)	5 (4.8)	2 (4.9)	0 (0)
Skin and hair toxicity				
Alopecia	29 (27.6)	0 (0)	7 (17.1)	0 (0)
Hair/skin depigmentation	17 (16.2)	0 (0)	11 (26.8)	0 (0)
Rash	26 (24.8)	1 (1.0)	5 (12.2)	0 (0)
Cardiac toxicity				
Arterial hypertension	21 (20.0)	9 (8.6)	5 (12.2)	4 (9.8)
Hepatobiliary toxicity				
Elevated transaminases	62 (59.0)	24 (22.9)	13 (31.7)	2 (4.9)
Elevated bilirubin	22 (21.0)	4 (3.8)	3 (7.3)	0 (0)
General toxicity				
Anorexia	18 (17.1)	3 (2.9)	6 (14.6)	0 (0)
Fatigue	73 (69.5)	15 (14.3)	25 (61.0)	1 (2.4)
Fever	23 (21.9)	0 (0)	3 (7.3)	0 (0)
Vascular toxicity				
Haemorrhage	26 (24.8)	0 (0)	2 (4.9)	0 (0)
Ischemic transitory stock	0	0	0	1 (2.4)
Venous profound thrombosis	1 (1)	0	1 (2.4)	0
Pulmonary embolism	1 (1)	2 (1.9)	0	0
Ischemic stroke	0	0	0	1 (2.4)

NCI CTCAE v3.0: National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

In LMS, few studies have evaluated the efficacy of new second-line therapies after doxorubicin failure. In our study, all patients had failed first-line doxorubicin therapy or had disease progression during or within 1 year of adjuvant chemotherapy. Thus, we assessed true second-line therapy, as did the TAXOGEM study [3]. In the LMS cohort ($n = 42$) of the phase II study evaluating pazopanib monotherapy, the vast majority, 29 patients, had chemotherapy for advanced disease; however, 1 patient had not received chemotherapy, 9 had adjuvant chemotherapy, and 3 had adjuvant and advanced disease chemotherapy [6].

With respect to PFS, our results are similar to those reported in the TAXOGEM study. With a median PFS of 5.5 months with gemcitabine alone in patients with uterine LMS and of 6.3 months for pts with non-uterine LMS. Similarly, after treatment with gemcitabine + docetaxel, the median PFS was 4.7 months in patients with uterine leiomyosarcoma and 3.8 months for those with non-uterine leiomyosarcoma. In this study, we reported a median PFS of 6.5 months (ITT population) with gemcitabine combined with pazopanib (maximum of eight cycles), followed by pazopanib monotherapy until disease progression. In the phase II LMS cohort, assessing pazopanib monotherapy, the median PFS was 91 days [6]. The survival benefit, in terms of PFS, seems lower with pazopanib monotherapy. Moreover, the second-line treatment with gemcitabine plus pazopanib followed by pazopanib maintenance therapy, in our study, reports similar median PFS rates that PFS rates reported with gemcitabine alone and gemcitabine plus docetaxel as the second-line therapy in relapsed/metastatic LMS patients (TAXOGEM study).

Considering the number of treatment options available for treating relapsed/metastatic LMS patients after the failure of the first-line therapy, it is important to consider treatment toxicity [1]. In our study, we observed significant toxicity, especially haematological adverse events during the combined treatment with gemcitabine and pazopanib. Liver toxicity (transaminase increase) was reversible. This toxicity diminished during the pazopanib monotherapy. Overall, the toxicity was considered manageable. Furthermore, the majority of the patients received ≥4 cycles of the gemcitabine plus pazopanib. Treatment tolerance and compliance are critical issues regarding chemotherapy in sarcoma patients often heavily pretreated.

There is some debate concerning the use of maintenance therapy for selected metastatic STS patients who benefit from the first- or second-line treatment. The aim of maintenance therapy is to maintain disease control (or response) while preserving patient quality of life. The European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma group (STBSG) study (NCT02929394 and EudraCT No. 2016-003535-38) assessing trabectedin maintenance therapy after six or eight cycles of doxorubicin has suspended enrolment due to poor accrual; only 13 of the planned 90 patients were enrolled. The T-Dis phase II randomised trial showed that maintenance therapy with trabectedin in patients with disease control after six cycles is superior to stopping and restarting therapy at disease progression [11]. The French EREMISS NCT 03793361 placebo-controlled study will access the benefit of regorafenib after disease stabilisation or response with 6–8 cycles of doxorubicin first-line therapy for metastatic/relapsed STS. In our study, maintenance therapy with pazopanib was well tolerated.

Overall, the LMS03 study assessed gemcitabine combined with pazopanib followed by pazopanib monotherapy, as the second-line therapy for patients with relapsed/metastatic LMS failed to meet its primary objective.

Declaration of competing interest

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Blay JY, van Glabbeke M, Verweij J, Van Oosterom AT, Le Cesne A, Oosterhuis JW, et al. Advanced soft-tissue sarcoma: a disease that is potentially curable for a subset of patients treated with chemotherapy. Eur J Cancer 2003;39:64–9.

[2] George S, Serrano C, Hensley ML, Ray-Coquard I. Soft tissue and uterine leiomyosarcoma. J Clin Oncol 2018;36:144–50.

[3] Pautier P, Floquet A, Penel N, Piperno-Neumann S, Isambert N, Rey A, et al. Randomized multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and docetaxel in patients with metastatic or relapsed leiomyosarcomas: a Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). The Oncologist 2012;17:1213–20.

[4] Potti A, Ganti AK, Tendulkar K, Sholes K, Chitajallu S, Koch M, et al. Determination of vascular endothelial growth factor (VEGF) overexpression in soft tissue sarcomas and the role of overexpression in leiomyosarcoma. J Cancer Res Clin Oncol 2004;130:52–6.

[5] Chao C, Al-Saleem T, Brooks JJ, Rogatkko A, Kraybill WG, Eisenberg B, et al. Vascular endothelial growth factor and soft tissue sarcomas: tumor expression correlates with grade. Ann Surg Oncol 2001;8:260–7.

[6] Sleijfer S, Ray-Coquard I, Papai Z, Le Cesne A, Scurr M, Schöffski P, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). J Clin Oncol 2009;27:3126–32.

[7] van der Graaf WT, Blay JY, Chawla SP, Kim DW, Bui-Nguyen B, Casali PG, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012;379(9829):1879–86.
[8] Mir O, Brodowitz T, Italiano A, Wallet J, Blay JY, Bertucci F, et al. Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma (REGOSARC): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 2016;17:1732–42.
[9] Plummer R, Madi A, Jeffels M, Richly H, Nokay B, Rubin S, et al. A Phase I study of pazopanib in combination with gemcitabine in patients with advanced solid tumors. Cancer Chemother Pharmacol 2013;71:93–101.
[10] Simon R. Optimal two-stage designs for phase II clinical trials. Contr Clin Trials 1989;10:1–10.
[11] Le Cesne A, Blay JY, Domont J, Tresch-Bruneel E, Chevreau C, Bertucci F, et al. Interruption versus continuation of trabectedin in patients with soft-tissue sarcoma (T-DIS): a randomised phase 2 trial. Lancet Oncol 2015;16:312–9.