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Original Article

European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Experience with Advanced/Metastatic Epithelioid Sarcoma Patients Treated in Prospective Trials: Clinical Profile and Response to Systemic Therapy

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Abstract

Aims: Epithelioid sarcoma is a soft tissue sarcoma associated with a high rate of local recurrence after wide resection and high incidence of distant metastasis. Little is known about the clinical course and response to systemic treatments in epithelioid sarcoma patients. We carried out a retrospective analysis of clinical data from epithelioid sarcoma patients to provide a reference for the design of future epithelioid sarcoma-specific studies.

Patients and methods: Data from patients with epithelioid sarcoma entered in prospective multi-sarcoma phase II/III trials were pooled: EORTC trial 62012 (doxorubicin versus doxorubicin/ifosfamide), 62043 (pazopanib), 62072 (pazopanib versus placebo) and 62091 (doxorubicin versus trabectedin). Patients had either a local or a centrally confirmed diagnosis of epithelioid sarcoma, had inoperable/metastatic disease at study entry and were eligible for the according trial. Response was assessed according to RECIST 1.1. Progression-free survival (PFS) and overall survival were calculated from date of entry.

Results: Among 976 patients with advanced sarcomas, 27 epithelioid sarcoma patients (2.8%) were eligible for the analysis (17 men, median age at diagnosis 50 years, range 19–72). Eighteen (66.7%) received chemotherapy as first-line treatment (five doxorubicin, eight doxorubicin/ifosfamide, two pazopanib, three trabectedin) and nine (33.3%) received pazopanib as second line or later. The primary tumour was located in the lower extremity ($n = 8$; 29.6%), upper extremity ($n = 5$; 18.5%), retro/intra-abdominal ($n = 4$; 14.8%) and in other locations ($n = 10$; 37.0%). At entry, metastases were mainly found in lung ($n = 17$; 63%), lymph nodes ($n = 9$; 33.3%), bone ($n = 8$; 29.6%) and soft tissue ($n = 7$; 25.9%). The best response for first-line patients was four partial responses (22.2%), 10 stable disease (55.6%) and four progressive disease (22.2%). In subsequent lines, pazopanib achieved one partial response (11.1%), four stable disease (44.4%) and four progressive disease (44.4%). All patients but one progressed on treatment. The median PFS and overall survival were 3.8 (95% confidence interval 2.2–4.8) and 10.8 months (95% confidence interval 8.1–21.3), respectively. Five patients were still alive at the time of the according trial analysis.

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Conclusion: With all limitations of such a rare disease and small data set, objective response and survival outcomes are similar in epithelioid sarcoma to non-selected sarcoma populations. The clinical testing of novel systemic treatments for epithelioid sarcoma remains an unmet medical need and a high priority. © 2018 Published by Elsevier Ltd on behalf of The Royal College of Radiologists.

Key words: Epithelioid sarcoma; metastases; systemic therapy

Introduction

First reported by Laskowski in 1961 [1] and further described by Enzinger [2], epithelioid sarcoma is a very rare disease representing less than 1% of all sarcomas [3]. Due to its particular pathological aspect, this sarcoma was formerly difficult to diagnose because of confusion with a variety of tumours with similar morphology. Epithelioid sarcomas are currently assessed by tissue biopsy and require examination by an experienced pathologist. An important component of the diagnostic process of this disease is the demonstration of the loss of INI1 expression by immunohistochemistry [4,5].

Epithelioid sarcomas are classified by two recognised subtypes, the distal type and the less frequent proximal type. Both entities are predominant in young male adults. Distal-type epithelioid sarcoma has a high tendency to occur in the extremities, especially in the upper limb [6–8]. Conversely, proximal-type epithelioid sarcomas most commonly affect trunk or deep tissue sites and tend to have a more aggressive clinical course. Tumour grading of epithelioid sarcoma is based on the Fédération Nationale des Centres de Lutte Contre le Cancer system and is considered as a relevant prognostic factor [9–11]. Epithelioid sarcoma has a high rate of locoregional recurrence after wide resection as well as metastatic spread, with a specific high incidence of synchronous or metachronous distant metastasis [12,13]. Metastases regularly involve lung and more particularly lymph nodes, representing one of the typical clinical special features of epithelioid sarcoma [3,6]. With 5 year survival rates ranging from 55 to 70%, the prognosis of epithelioid sarcoma patients is generally poor but relatively comparable with other soft tissue sarcomas (STS) [12,14,15]. Surgical resection with or without radiotherapy is the accepted standard treatment for localised disease [13,16]. The role of systemic therapies in patients with advanced stage epithelioid sarcoma is unclear. Only a few retrospective analyses and case reports have assessed the value of systemic treatment [17,18]. In these studies, the observed median progression-free survival (PFS) ranged from 3 to 9 months and the overall response rate (ORR) varied between 0 and 60% across the diverse drugs and lines. Prospective disease-specific trials with a focus on epithelioid sarcoma patients are not available.

As part of the European Organisation for Research and Treatment of Cancer (EORTC) clinical trial activities, several drugs for the treatment of advanced and metastatic sarcoma have been explored over the past decades. The EORTC has created a large database compiling clinically relevant information from all trial participants. The aim of the current study was to investigate the outcome of patients with

epithelioid sarcoma treated with systemic agents in historic prospective EORTC trials. These data provide an important reference for the design of future epithelioid sarcoma-specific clinical trials.

Materials and Methods

Patient Population

This study combined clinical data of patients from the EORTC trials 62012 (NCT00061984), 62043 (NCT00297258), 62072 (NCT00753688) and 62091 (NCT01189253). These trials were performed by the EORTC's Soft Tissue and Bone Sarcoma Group (STBSG). The phase III 62012 trial assessed whether results obtained with doxorubicin in advanced, inoperable STS can be improved by adding ifosfamide [19]. The phase II 62043 and phase III 62072 PALETTE trials investigated the activity of the tyrosine kinase inhibitor pazopanib in advanced/metastatic STS after failure of standard chemotherapy [20,21]. The phase II 62091 TRUSTS trial evaluated whether the cytotoxic compound trabectedin given as first-line chemotherapy for advanced/metastatic STS improves the outcome of patients as compared with doxorubicin [22]. We used these study populations as the basis for the current subgroup analysis focusing on patients with epithelioid sarcoma. Patients received either doxorubicin, doxorubicin/ifosfamide, trabectedin or pazopanib. Trial participants treated with placebo (EORTC 62072) were excluded from this analysis. The diagnosis of epithelioid sarcoma was based on local pathology or centrally reviewed by reference pathologists of STBSG when possible. The database does not differentiate between distal and proximal types of epithelioid sarcoma.

Endpoints

The best response was locally assessed per RECIST 1.1 [23]. The objective response rate was defined as the proportion of patients either achieving a partial or complete response as best response to treatment. The duration of the objective response was determined from the first documentation of complete/partial response to RECIST progression.

PFS was calculated from the date of evaluation start to the first documentation of progression or death, whichever occurred first. The date of evaluation start corresponded to the date of randomisation for the 62012, 62072 and 62091 trials and the date of registration for the 62043 trial. Overall survival was calculated from the date of evaluation start to

the date of death. Patients without an event were censored at the time of last follow-up.

Statistical Analysis

Survival estimates and corresponding 95% confidence intervals for PFS and overall survival were generated using the Kaplan–Meier method. Survival curves were reported overall and according to the line of treatment for advanced disease (first line versus second line or later). All statistical analyses were carried out using SAS software version 9.4 (SAS Institute).

Results

Patient and Tumour Characteristics

In total, 976 patients with advanced STS were entered and treated with systemic therapy in the four prospective clinical trials. This included only 27 patients (2.8%) with epithelioid sarcoma who were found to be eligible for the current analysis (10 patients from 62012, four from 62043, seven from 62072 and six from 62091), illustrating the orphan character of this STS subtype. The diagnosis was based on local pathology in nine cases and on central review in 18 cases. Baseline tumour and patient characteristics are summarised in Table 1.

The median age at diagnosis was 50 years (range 19–72 years) and male gender was predominant (63%). The clinical trials selected patients with good performance status; 11 patients (40.7%) had a performance status of 1 according to the World Health Organization criteria.

The most common sites of primary tumour were the lower extremities ($n = 8$, 29.6%), upper extremities ($n = 5$, 18.5%) and intra-abdominal locations ($n = 4$, 14.8%). Epithelioid sarcoma were incidentally found in the chest ($n = 2$, 7.4%), gynaecological organs ($n = 2$, 7.4%), breast ($n = 1$, 3.7%), trunk ($n = 1$, 3.7%), head and neck ($n = 1$, 3.7%) or other locations ($n = 3$, 11.1%).

The tumour grade was assessed for 21 patients and described as high for 10 patients (47.6% of known grade), intermediate for 10 (47.6%) and low for one (4.8%). Most patients had metastatic disease ($n = 24$, 88.9%) and metastases were seen in lung ($n = 17$, 63%), lymph nodes ($n = 9$, 33.3%), bone ($n = 8$, 29.6%) and soft tissue ($n = 7$, 25.9%). The primary tumour was still *in situ* in 15 patients (55.6%), reflecting the early and aggressive metastatic spread of this disease.

Systemic Treatment

As first line of treatment, five patients (18.5%) received doxorubicin alone, eight (29.6%) doxorubicin and ifosfamide, two (7.4%) pazopanib and three (11.1%) trabectedin. Nine (33.3%) were treated with pazopanib as second or later line (second line: four patients; third line: four patients; fourth line: one patient). Five patients (18.5%) had received previous systemic adjuvant therapy and nine (33.3%) had

Table 1
Patient and tumour characteristics

	Total ($n = 27$) n (%)
Diagnosis of epithelioid sarcoma	
Local diagnosis only (no central review)	9 (33.3)
Central diagnosis	18 (66.6)
Study	
62012 (doxorubicin, doxorubicin + ifosfamide)	10 (37.0)
62043 (pazopanib)	4 (14.8)
62072 (pazopanib)	7 (25.9)
62091 (doxorubicin, trabectedin)	6 (22.2)
Gender	
Male	17 (63.0)
Female	10 (37.0)
Age at diagnosis	
≤ 40	10 (37.0)
40–50	4 (14.8)
50–70	12 (44.4)
> 70	1 (3.7)
Performance status (WHO criteria)	
0	16 (59.3)
1	11 (40.7)
Site of primary tumour	
Lower extremity	8 (29.6)
Upper extremity	5 (18.5)
Intra-abdominal	4 (14.8)
Thoracic	2 (7.4)
Gynaecological	2 (7.4)
Head and neck	1 (3.7)
Trunk	1 (3.7)
Breast	1 (3.7)
Other	3 (11.1)
Tumour grade at study entry (FNCLCC criteria)	
Low	1 (3.7)
Intermediate	10 (37.0)
High	10 (37.0)
Missing	6 (22.2)
Extension of disease at entry*	
Primary	15 (55.6)
Metastatic	24 (88.9)
Lung	17 (63.0)
Lymph nodes	9 (33.3)
Bone	8 (29.6)
Soft tissue	7 (25.9)
Skin	4 (14.8)
Pleural effusion	4 (14.8)
Liver	2 (7.4)
Ascites	0 (0.0)
Other site	4 (14.8)
Administered treatment	
Doxorubicin	5 (18.5)
Doxorubicin + ifosfamide	8 (29.6)
Pazopanib	11 (40.7)
Trabectedin	3 (11.1)
Treatment line	
First-line chemotherapy	18 (66.7)
Second and later lines of chemotherapy	9 (33.3)

WHO, World Health Organization; FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer.

* Percentages are not cumulative.

Table 2

Best response and objective response rate according to RECIST 1.1

	Patients (n)	Tumour response			Objective response rate
		Partial response	Stable disease	Progressive disease	
First line of treatment	18	4 (22.2)	10 (55.6)	4 (22.2)	4/18 = 22.2%
Doxorubicin	5	0	3	2	0/5
Doxorubicin + ifosfamide	8	1	6	1	1/8
Pazopanib	2	2	0	0	2/2
Trabectedin	3	1	1	1	1/3
Second or later line of treatment (only pazopanib)	9	1 (11.1)	4 (44.4)	4 (44.4)	1/9 = 11.1%
All patients	27	5 (18.5)	14 (51.9)	8 (29.6)	5/27 = 18.5%

Table 3

Progression-free survival and overall survival according to the line of treatment and overall

	Patients (n)	Observed events	Median (95% confidence interval) (months)	% at 6 months (95% confidence interval)	% at 9 months (95% confidence interval)	% at 12 months (95% confidence interval)
Progression-free survival duration from evaluation start						
First line of treatment	18	17	4.04 (2.73, 7.52)	38.9 (17.5, 60.0)	22.2 (6.9, 42.9)	16.7 (4.1, 36.5)
Second or later line of treatment	9	9	2.73 (0.76, 4.47)	11.1 (0.6, 38.8)	11.1 (0.6, 38.8)	11.1 (0.6, 38.8)
All patients	27	26	3.75 (2.20, 4.80)	29.6 (14.1, 47.0)	18.5 (6.8, 34.8)	14.8 (4.7, 30.5)
Overall survival duration from evaluation start						
First line of treatment	18	16	10.83 (8.44, 21.29)	77.8 (51.1, 91.0)	61.1 (35.3, 79.2)	44.4 (21.6, 65.1)
Second or later line of treatment	9	6	9.79 (4.63, 24.71)	87.5 (38.7, 98.1)	50.0 (15.2, 77.5)	33.3 (5.6, 65.8)
All patients	27	22	10.83 (8.11, 21.29)	80.8 (59.8, 91.5)	57.7 (36.8, 73.9)	42.0 (23.1, 59.8)

previous systemic therapy for palliation of advanced disease.

The median duration of the administered treatment in the EORTC trials was 13.3 weeks and more specifically 14.3 weeks for doxorubicin alone, 12.4 weeks for doxorubicin and ifosfamide, 17.3 weeks for pazopanib and 10.7 weeks for trabectedin. The median follow-up was 45.3 months, regardless of the study and one patient was still on trabectedin at the time of the corresponding trial's final analysis.

Response to Treatment and Survival

As shown in [Table 2](#), the best response for first-line treatment patients was four partial responses (22.2%), 10 stable diseases (55.6%) and four progressive diseases (22.2%). There was one partial response (11.1%), four stable diseases (44.4%) and four progressive diseases (44.4%) among patients treated in second line or later. Overall, five patients (18.5%) experienced an objective response. For responders, the median duration of response and the time to onset of response from treatment/evaluation start were 56 and 86 days, respectively. The partial responder on second-line treatment had the shortest response duration, which lasted 28 days.

All patients but one progressed. No patient died without having experienced progressive disease. The overall median

PFS was 3.8 months (95% confidence interval 2.2–4.8). The median PFS was 4 months (95% confidence interval 2.7–7.5) and 2.7 months (95% confidence interval 0.8–4.5) for first-line treatment and second line or later, respectively ([Table 3](#)).

The median overall survival for the whole cohort was 10.8 months (95% confidence interval 8.1–2.3). Five patients were still alive or without reported death at the time of the analyses cut-offs. A total of 13 patients died because of progressive disease. The Kaplan–Meier curves overall and stratified by the line of treatment are shown in [Figures 1 and 2](#).

Discussion

Aiming to document the outcome and response of advanced/metastatic epithelioid sarcoma patients to systemic therapy, this retrospective study has the advantage of combining high-quality data from various prospective clinical trials, providing a detailed and continued follow-up of the patients. Epithelioid sarcoma is a very rare disease that represents only 2.8% of the 976 eligible patients entered and treated with systemic therapy into prospective multi-sarcoma trials carried out by the EORTC between 2003 and 2012. Although restricted by the small sample size, our results can provide guidance for the development of future epithelioid sarcoma-specific trials.

Fig 1. Progression-free survival (left) and overall survival (right).

Fig 2. Progression-free survival (left) and overall survival (right) by line of treatment: first line of treatment in red and second line or later in blue.

The response rate to chemotherapy in epithelioid sarcoma seems to be similar to pooled populations of multiple STS subtypes, ranging from 5 to 25% in the different trials. However, the median PFS and overall survival for epithelioid sarcoma patients were lower than for STS patients in all trials, which would indicate that even with an equivalent response to treatment, epithelioid sarcoma patients have a worse prognosis than other STS. It can also be noted that a relatively low response rate (1/13, ORR = 8%) was observed in patients with doxorubicin-based regimen compared with those with other first-line regimens (3/5, ORR = 60%).

Although not considered in this analysis, five epithelioid sarcoma patients were randomised to the placebo arm of the 62072 trial (pazopanib versus placebo) and the median PFS was 0.9 months (95% confidence interval 0.62–1.84), whereas the median overall survival was 11.5 months (95% confidence interval 0.69–N).

No data from prospective trials have been specifically published yet on the role of systemic therapy in epithelioid sarcoma patients, but a phase II trial investigating tazemetostat, an EZH2 inhibitor, is currently ongoing [24]. This is a single-arm trial where enrolled subjects were allocated according to their tumour type to one of five different cohorts, including a specific epithelioid sarcoma subset. Only a few retrospective case series on epithelioid sarcoma are available. Jones *et al.* [17] documented 21 epithelioid sarcoma patients treated with anthracycline (second line or later) alone, in combination with ifosfamide (first line) as well as trabectedin alone as palliative chemotherapy and observed three partial responses, 12 stable diseases, 5 progressive diseases for first-line treatment (ORR = 15%) and four stable diseases, five progressive diseases for second/third line (ORR = 0%). No clear distinction of the observed response according to first and other lines of treatment was

provided by Pink *et al.* [18], but patients who received anthracycline alone or in combination with ifosfamide experienced six stable diseases, seven progressive diseases (ORR = 0%) and those who had gemcitabine/docetaxel had one complete response, six partial responses, three stable diseases and two progressive diseases (ORR = 58%). The surprisingly high response rate to the latter combination deserves to be confirmed by prospective trials. Tumour responses among epithelioid sarcoma patients from EORTC trials were similar to those on anthracycline and anthracycline/ifosfamide in both first (ORR = 22%) and second or later line of treatment (ORR = 11%), but survival endpoints were shorter. Indeed, median PFS and overall survival were 7.3 (95% confidence interval 5.3–8.1) and 11.8 months (95% confidence interval 6.7–16.8) in Jones *et al.* [17] and eight and 21 months in Pink *et al.* [18], irrespective of the treatment line. Only specific subgroups treated with anthracycline alone or diverse other regimens – such as high-dose ifosfamide, trofosfamide, gemcitabine/cisplatin, cisplatin/dacarbazine or doxorubicin/dacarbazine – had a median PFS of 3 months [18].

As a limitation of our study we could not sub-classify the epithelioid sarcoma cases in this project but we believe that our series included a high proportion of proximal type epithelioid sarcoma (older patients, few primary tumours in the upper limb and relatively poor prognosis). We performed additional exploratory survival analyses by differentiating tumours initially situated in extremities ($n = 13$) versus other locations ($n = 14$), expecting a better prognosis for extremity locations as potentially associated with the distal type. However, PFS and overall survival were nearly equivalent in these epithelioid sarcoma populations.

Another caveat due to the combination of several studies with specific designs is the consistency in the disease assessment schedules. The timing of these evaluations naturally influences the detection of progressive disease and grouping various schedules together may affect the time to progression, particularly for short PFS durations. Actually ranging from 4 to 12 weeks regarding the different stages of each trial, this diversity of time intervals between two concomitant assessments implies caution when interpreting the results based on PFS. In a similar way, the duration used for the definition of stable disease varied across the different protocols, generally related to each trial's disease assessment frequency.

The current standard of care for advanced, inoperable epithelioid sarcoma remains to be defined. There is a strong need for specific, prospective clinical trials in epithelioid sarcoma, ideally involving drugs with a good biological rationale in this disease, and ideally such trials should be randomised. Stratification between first and later lines of treatment, and possibly for proximal-versus distal-type epithelioid sarcoma may be required.

To conclude, this analysis reinforces the existing knowledge on systemic therapy in this rare type of sarcoma, notably with previously unstudied drugs such as pazopanib. The low number of patients in this study and its retrospective nature remain limits to formulating definitive clinical conclusions. This is why systemic treatment of

epithelioid sarcoma remains an unmet medical need and basic, translational research as well as clinical testing of agents for this disease in epithelioid sarcoma-specific trials stands as a high priority for the sarcoma research community.

Conflicts of interest

Patrick Schöffski: institutional support from Epizyme for advisory functions in the context of epithelioid sarcoma; Ian Judson: honoraria from PharmaMar and GSK for speaking engagements; Thomas Brodowicz: personal fees from Roche (lecture fee), Amgen (lecture fee, advisory board), Bayer (lecture fee, advisory board), Novartis (lecture fee, advisory board), PharmaMar (lecture fee), Eisai (lecture fee, advisory board) and Eli Lilly (lecture fee, advisory board) outside the submitted work.

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References

- [1] Laskowski J. Sarcoma aponeuroticum. *Nowotwory* 1961; 61–67.
- [2] Enzinger F. Epithelioid sarcoma. A sarcoma simulating a granuloma or a carcinoma. *Cancer* 1970;26:1029–1041.
- [3] Ross H, Lewis J, Woodruff J, Brennan M. Epithelioid sarcoma: clinical behavior and prognostic factors of survival. *Ann Surg Oncol* 1997;4:491–495.
- [4] Chbani L, Guillou L, Terrier P, Decouvelaere A, Grégoire F, Terrier-Lacombe M, *et al.* Epithelioid sarcoma: a clinicopathologic and immunohistochemical analysis of 106 cases from the French sarcoma group. *Am J Clin Pathol* 2009;131: 222–227.
- [5] Hornick J, Dal Cin P, Fletcher C. Loss of INI1 expression is characteristic of both conventional and proximal-type epithelioid sarcoma. *Am J Surg Pathol* 2009;33:542–550.
- [6] Chase D, Enzinger F. Epithelioid sarcoma. Diagnosis, prognostic indicators, and treatment. *Am J Surg Pathol* 1985;9: 241–263.
- [7] Spillane A, Thomas J, Fisher C. Epithelioid sarcoma: the clinicopathological complexities of this rare soft tissue sarcoma. *Ann Surg Oncol* 2000;7:218–225.
- [8] Jawad M, Extejn J, Min E, Scully S. Prognostic factors for survival in patients with epithelioid sarcoma: 441 cases from the SEER database. *Clin Orthop Relat Res* 2009;467:2939–2948.
- [9] Casanova M, Ferrari A, Collini P, Bisogno G, Alaggio R, Cecchetto G, *et al.* Italian Soft Tissue Sarcoma Committee. Epithelioid sarcoma in children and adolescents: a report from the Italian Soft Tissue Sarcoma Committee. *Cancer* 2006; 106:708–717.
- [10] Gasparini P, Facchinetti F, Boeri M, Lorenzetto E, Livio A, Gronchi A, *et al.* Prognostic determinants in epithelioid sarcoma. *Eur J Cancer* 2011;47:287–295.
- [11] Fletcher C. World Health Organization and International Agency for Research on Cancer. *Pathology and genetics of tumours of soft tissue and bone* 2013.

- [12] Callister M, Ballo M, Pisters P, Patel S, Feig B, Pollock R, et al. Epithelioid sarcoma: results of conservative surgery and radiotherapy. *Int J Radiat Oncol Biol Phys* 2001;51:384–391.
- [13] Wolf P, Flum D, Tanas M, Rubin B, Mann G. Epithelioid sarcoma: the University of Washington experience. *Am J Surg* 2008;196:407–412.
- [14] Bos G, Pritchard D, Reiman H, Dobyns J, Ilstrup D, Landon G. Epithelioid sarcoma. An analysis of fifty-one cases. *J Bone Jt Surg Am* 1988;70:862–870.
- [15] Livi L, Shah N, Paiar F, Fisher C, Judson I, Moskovic E, et al. Treatment of epithelioid sarcoma at the Royal Marsden Hospital. *Sarcoma* 2003;7:149–152.
- [16] Shimm D, Suit H. Radiation therapy of epithelioid sarcoma. *Cancer* 1983;52:1022–1025.
- [17] Jones R, Constantinidou A, Olmos D, Thway K, Fisher C, Al-Muderis O, et al. Role of palliative chemotherapy in advanced epithelioid sarcoma. *Am J Clin Oncol* 2012;35:351–357.
- [18] Pink D, Richter S, Gerdes S, Andreou D, Tunn P, Busemann C, et al. Gemcitabine and docetaxel for epithelioid sarcoma: results from a retrospective, multi-institutional analysis. *Oncology* 2014;87:95–103.
- [19] Judson I, Verweij J, Gelderblom H, Hartmann J, Schöffski P, Blay J, et al. European Organisation and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. *Lancet Oncol* 2014;15:415–423.
- [20] 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 620). *J Clin Oncol* 2009;27:3126–3132.
- [21] van der Graaf W, Blay J, Chawla S, Kim D, Bui-Nguyen B, Casali P, et al. EORTC Soft Tissue and Bone Sarcoma Group and PALETTE study group. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2012;379(9829):1879–1886.
- [22] Bui-Nguyen B, Butrynski J, Penel N, Blay J, Isambert N, Milhem M, et al. EORTC/STBSG and Sarcoma Alliance for Research through Collaboration. A phase IIb multicentre study comparing the efficacy of trabectedin to doxorubicin in patients with advanced or metastatic untreated soft tissue sarcoma: the TRUSTS trial. *Eur J Cancer* 2015;51.
- [23] Eisenhauer E, Therasse P, Bogaerts J, Schwartz L, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–247.
- [24] Schöffski P, Agulnik M, Stacchiotti S, Davis L, Villalobos V, Italiano A, et al. Phase 2 multicenter study of the EZH2 inhibitor tazemetostat in adults with synovial sarcoma (NCT02601950). *J Clin Oncol* 2017;35(Suppl. 15):11057.