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Salvage Therapy in Advanced Adult Soft Tissue Sarcoma: A Systematic Review and Meta-Analysis of Randomized Trials

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Background. Prognosis for patients with metastatic soft tissue sarcomas (STS) is dismal, with median overall survival (OS) of 8–12 months. The role of second-line therapy has been inconsistently investigated over the last 20 years. This systematic review and meta-analysis was performed to assess the efficacy of salvage treatment in pretreated adult type STS, gastrointestinal stromal tumor (GIST) excluded.

Material and Methods. PubMed, Web of Science, SCOPUS, EMBASE, CINAHL, and The Cochrane Library were searched for randomized phase II/phase III trials exploring second- or beyond therapy lines in pretreated metastatic STS. Two independent investigators extracted data; the quality of eligible studies was resolved by consensus. Hazard ratio (HR) of death and progression (OS and progression-free survival [PFS]) and odds ratio (OR) for response rate (RR) were pooled in a fixed- or random-effects model according to heterogeneity. Study quality was assessed with the Cochrane's risk of bias tool, and publication bias with funnel plots.

Results. Overall, 10 randomized trials were selected. The pooled HR for death was 0.81 (95% confidence interval [CI] 0.73–0.9). Second-line therapy reduced the risk of progression by 49% (HR = 0.51, 95% CI 0.34–0.76). This translated into an absolute benefit in OS and PFS by 3.3 and 1.6 months, respectively. Finally, RR with new agents or chemotherapy doublets translated from 4.3% to 7.6% (OR = 1.78, 95% CI 1.22–2.50).

Conclusion. Better survival is achieved in patients treated with salvage therapies (chemotherapy, as single or multiple agents or targeted biological agents). A 3-months gain in OS and an almost double RR is observed. Second lines also attained a reduction by 50% the risk of progression. *The Oncologist* 2017;22:1518–1527

Implications for Practice: There is some evidence that salvage therapies after first-line failure are able to improve outcome in metastatic soft tissue sarcoma (STS). Trabectedin, gemcitabine-based therapy, and pazopanib are currently approved drugs used after conventional upfront treatment. This meta-analysis reviews the benefit of new agents used in randomized trials in comparison with no active treatments or older agents for recurrent/progressed STS. The results show that modern drugs confer a statistically significant 3-month benefit in terms of overall survival, and an increase in response rate. Despite a limited improvement in outcome, currently approved second-line therapy should be offered to patients with good performance status.

Introduction

Soft tissue sarcomas (STS) are rare tumors of mesenchymal origin. They account for 1%–2% of malignant neoplasms, and more than 50 different histotypes are recognized [1]. Local control has improved over the past 30 years with the standard surgical procedure including a wide excision with R0 margins. A wide excision is followed by radiotherapy for high-grade, deep lesions that are larger than 5 cm [2, 3].

Adjuvant chemotherapy is not accepted as standard treatment in adult STS; however, some authors recommend it for some stages of disease (e.g., in stages II and III, National Comprehensive Cancer Network guidelines provide level 2B recommendation for adjuvant chemotherapy) [4–9].

Nonetheless, even with the optimal multidisciplinary approach, 45% of patients die from the disease at 5 years and 50% at 10 years [10]. For metastatic disease, more than 100 phase II studies and more than 20 randomized studies have been published [11–14]. Among the investigated drugs, only doxorubicin, ifosfamide, and dacarbazine have given a response rate >15% [15–17], with a short progression-free survival (PFS) of 2–4 months. The combination of these drugs results in a higher response rate ranging from 25%–40%, but median overall survival (OS) does not exceed 12 months [18, 19]. Thus, the treatment of metastatic STS usually remains palliative even if about 5% of patients with metastatic STS may be cured after multidisciplinary treatment mainly in limited, resectable lung metastasis [20].

In the last 10 years, the term "histology-driven therapy" was coined for a new concept indicating that some agents are more active in particular families of STS. As a consequence, in some subtypes of sarcomas, some agents scarcely active or inactive in other histologies can be applied with satisfactory results [13]. Leiomyosarcoma has a limited sensitivity to ifosfamide, but trabectedin as single agent, gemcitabine plus docetaxel, and doxorubicin plus dacarbazine are valid options [13, 21, 22]. Low-grade liposarcomas (LS) are in general chemoresistant, whereas myxoid LS is sensitive to trabectedin and undifferentiated LS to anthracyclines [23, 24]. Angiosarcoma is sensitive to paclitaxel [25], synovial sarcoma to high-dose ifosfamide [19], and solitary fibrous tumor to temozolomide plus bevacizumab [26]. Pazopanib is the first targeted therapy with some activity in different sarcomas, such as leiomyosarcomas and synovial sarcomas, but not in adipocytic sarcomas [27].

In light of these recent results and evolving strategies, determining appropriate second-line chemotherapy options is a current focus in STS. Second-line therapy of a tumor describes any subsequent intervention with a new regimen after treatment failure because of disease progression or unacceptable toxicity with initial therapy. Herein, we performed a systematic review and a meta-analysis of phase II/III randomized studies published in recent decades, including both newer and older agents. The objective of our study was to compare the main outcome endpoints: PFS, OS, and objective response rate (ORR) between trials investigating second-line therapy in STS to define the importance and the role of subsequent treatment after first-line failure.

MATERIALS AND METHODS

In conducting the meta-analysis, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement [28].

Search Strategy and Study Selection

For the purpose of this analysis, a systematic search of the PubMed, Web of Science, SCOPUS, EMBASE, and CINAHL databases and The Cochrane Library was performed from inception to February 7, 2016. Search terms were (("sarcoma" [MeSH Terms] OR "sarcoma" [All Fields]) AND ((second [All Fields] AND "line" [All Fields])) OR pretreated [All Fields] OR (previously [All Fields] AND treated [All Fields]) OR progressing [All Fields] OR progressed [All Fields] OR failure [All Fields]) AND (("random allocation" [MeSH Terms] OR ("random" [All Fields] AND "allocation" [All Fields]) OR "random allocation" [All Fields] OR "randomized" [All Fields]) OR randomized [All Fields]).

We included in the systematic review all randomized, controlled phase II/III trials that compared standard (single agent or doublet chemotherapy) therapy with experimental agents or placebo/best supportive care in adult patients with advanced/metastatic, progressing STS after first-line therapy. Trials were only included if they were published in full and in English. We excluded trials that included primarily bone sarcoma, Ewing/rhabdomyosarcoma, Kaposi sarcoma, gastrointestinal stromal tumor (GIST), and childhood/adolescent sarcomas. Two authors (FP and AB) independently evaluated each reference title identified by the search and then applied the inclusion criteria. In cases of disagreement between the two reviewers, the full article was obtained and inspected independently by a third senior reviewer (AC).

Data Extraction

To be included in the analysis, a trial had to compare a modern agent (experimental drug or a modern chemotherapy), either alone or in combination with another (doublet), with a single agent (either a standard cytotoxic drug or other agents), placebo, best supportive care (BSC), or observation alone. Modern agents were those developed starting from trabectidin studies era. For each trial, the data extracted were as follows: (a) year of publication; (b) type of study; (c) number of patients enrolled in experimental and control arms; (d) treatment arms and schedules; (e) first-line therapy; (f) ORR according to World Health Organization or Response Evaluation Criteria In Solid Tumors criteria; (g) median PFS or time to progression (TTP) with the corresponding hazard ratio (HR) and 95% confidence interval (CI) for each treatment comparison; and (h) median OS with the corresponding HR and 95% CI for each treatment comparison. Data extraction was conducted independently by two investigators (FP and AB), and any discrepancies were resolved by consensus in frequent meetings in the presence of the senior investigator (AC).

Statistical Analysis

We considered OS as the primary efficacy endpoint of this meta-analysis, and ORR, PFS, or TTP as secondary endpoints. For the main analysis, in which all experimental arms were compared with all control arms as second-line therapies for STS, we performed a meta-analysis of HRs for PFS/TTP and OS and a meta-analysis of odds ratios (ORs) for ORR using a random- or fixed-effects model. A random-effects model based on an estimate and standard error was used to pool the estimate across studies using the Der Simonian-Laird method [29]. Heterogeneity between studies was quantified by the between-study variance tau^2 and the Cochran's Q test and/or I^2 statistics, which describes the percentage of variation across studies due to heterogeneity rather than chance [30]. Studies were classified as showing low (I$^2 \leq 50\%$), moderate (I$^2 > 50\%$ and $\leq 75\%$), or high (I$^2 \geq 75\%$) heterogeneity. A p value $\leq .05$ was considered statistically significant. All statistical tests were two-sided. The Cochrane risk of bias tool was assessed for included studies.

Subgroup analysis for OS only was performed for doublet versus single-agent studies, for single-agent versus no active therapy studies, and experimental versus control arms with active treatment as control arms.

A quantitative analysis for publication bias for OS meta-analysis included the Begg's and Egger's rank correlation test [31], and the Egger intercept test [32]. A 2-sided alpha error of 0.05 was used to determine statistical significance. Publication bias analyses were performed using the RevMan v5.3 and Comprehensive Meta-analysis version 2 (Biostat Inc., Englewood, NJ, https://www.meta-analysis.com).

RESULTS

A total of 2,596 publications were identified through the electronic search. After applying the previously described criteria, we included 10 randomized trials ($n = 4$ phase III and $n = 6$ phase II trials) [21, 22, 27, 33–39]. A flow diagram describing the inclusion of trials is presented in Figure 1. These trials enrolled a total of 2,267 patients. Among these, $n = 3$ compared doublets versus single agents, $n = 4$ single agents versus single agents, and $n = 3$ single agents versus placebo or BSC.
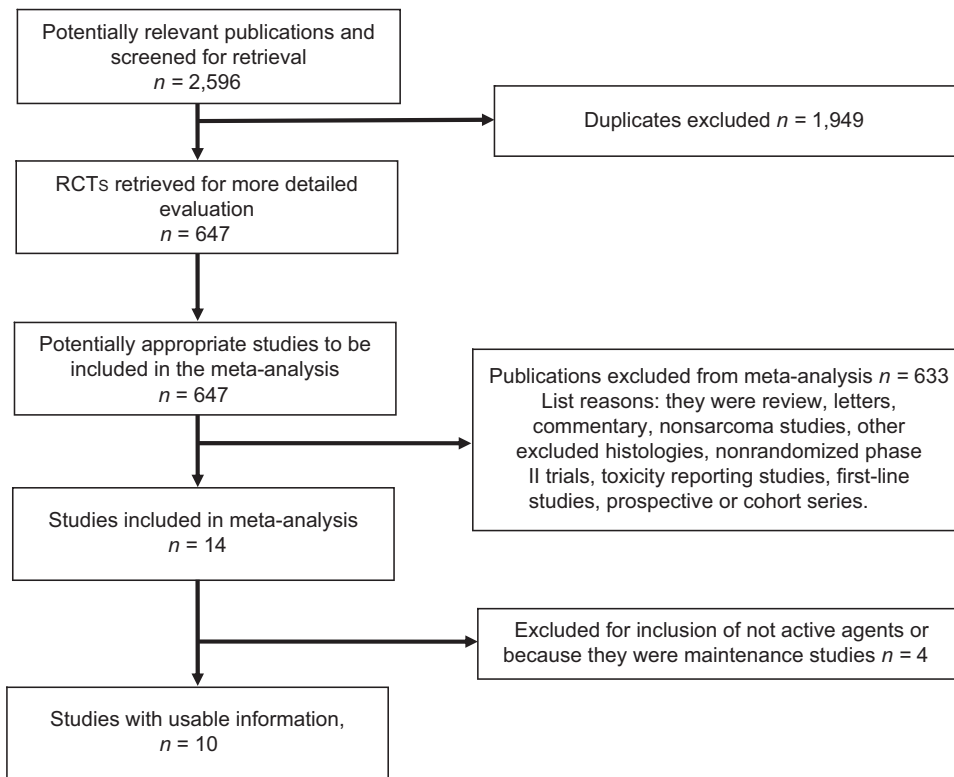
Figure 1. Randomized controlled trials search and selection procedure.
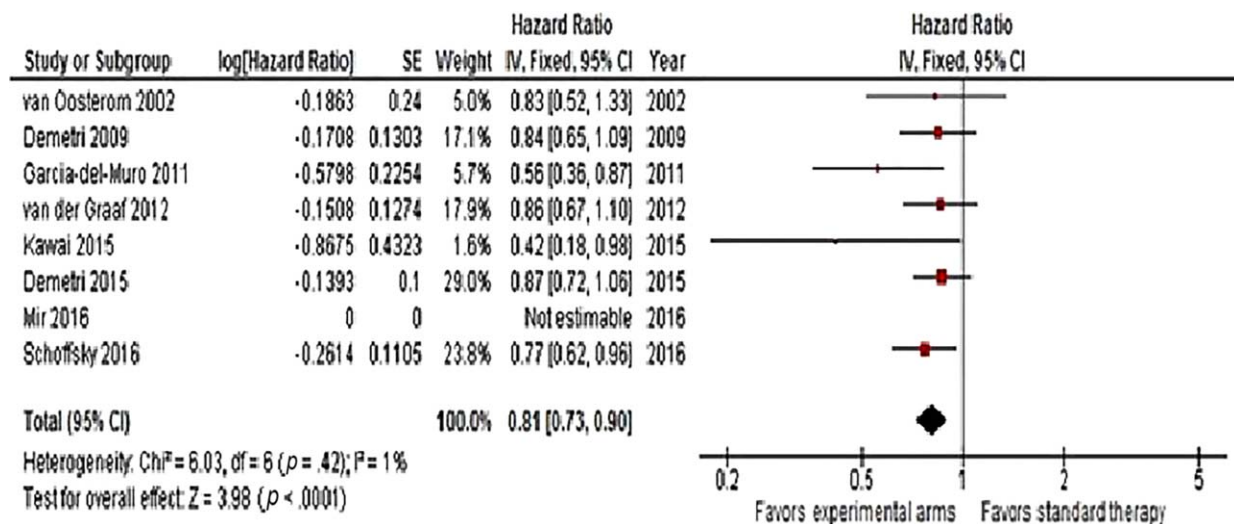Abbreviation: RCT, randomized controlled trial.

Figure 2. Forest plot of hazard ratios comparing overall survival for all patients who received modern versus conventional (or best supportive care/placebo) second-line chemotherapy ($n = 10$ studies).
Abbreviations: CI, confidence interval; IV, intravenous; SE, standard error.

Experimental and control arms included 1,287 and 966 subjects, respectively. Among experimental arms, $n = 2$ were targeted therapies and $n = 8$ cytotoxic drugs (either alone or in combination). Control arms were targeted therapies, cytotoxic, and placebo (or BSC) in 0, $n = 7$, and $n = 3$ cases, respectively.

Pooled ORR, Median PFS, and OS in Control and Experimental arms

Overall, $n = 10$ control arms provided a pooled ORR of 4.3% (95% CI 1.8%–6.8% according to the random-

effects model), and conversely, the corresponding experimental arms were associated with a pooled ORR of 7.6% (95% CI 6.4%–8.8% according to the random-effects model).

In all studies with data necessary for analysis (median PFS or TTP), the pooled median PFS was 2.35 months for control arms and 3.95 months for experimental arms. In $n = 10$ and $n = 9$ control and experimental arms with data for OS available (median OS), the pooled median OS was 10.1 and 13.4 months, respectively.
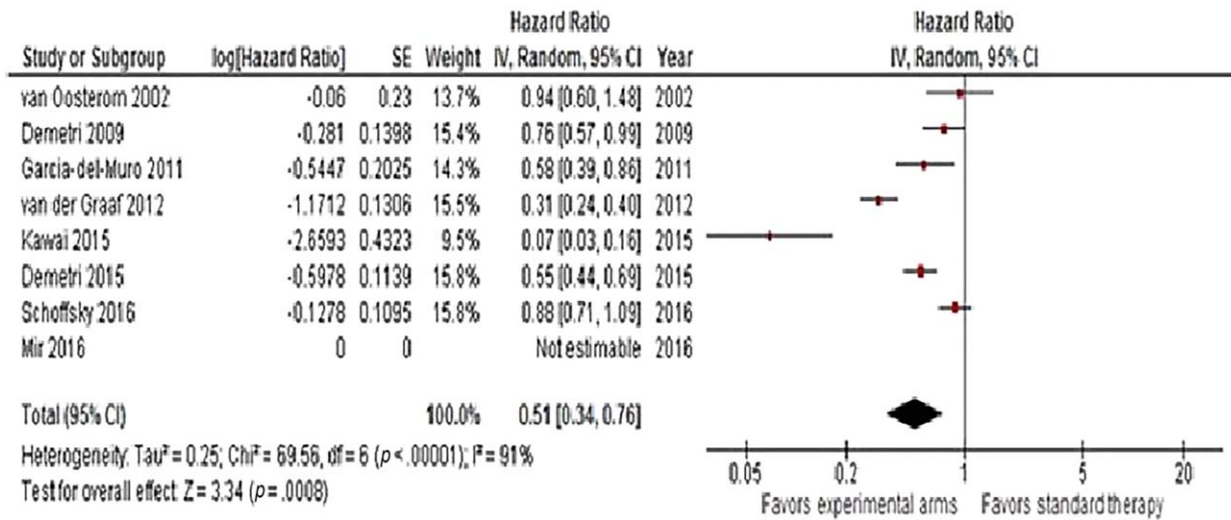
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Figure 3. Forest plot of hazard ratios comparing progression-free survival for patients who received modern versus conventional (or best supportive care/placebo) second-line chemotherapy ($n = 11$ studies).
Abbreviations: CI, confidence interval; IV, intravenous; SE, standard error.
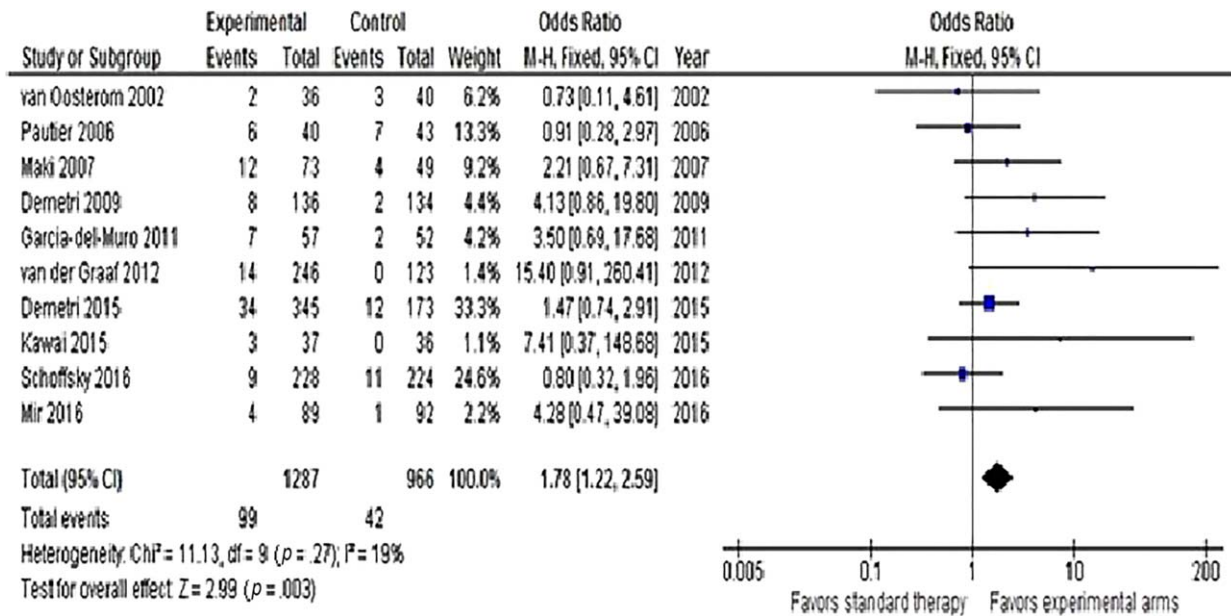

Figure 4. Forest plot of odds ratios comparing overall response rate for patients who received modern versus conventional (or best supportive care/placebo) second-line chemotherapy ($n = 14$ studies).
Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

Meta-Analysis of ORR, PFS, and OS

Hazard ratios for OS were available for $n = 8$ trials. A significant reduction in the risk of death (HR = 0.81, 95% CI 0.73–0.9, $p < .0001$) was observed with second-line therapy, as shown in Figure 2. No heterogeneity was detected. Progression-free survival was available in $n = 8$ studies (including Van Oosterom et al. trial that reported TTP). Overall, second-line therapy reduced the risk of progression or death by 49% (HR = 0.51, 95% CI 0.34–0.76, $p = .0008$). Heterogeneity was high, so a random-effects model was used (Fig. 3). In the trial of Van Osterom et al., only one death due to progressive disease was not accounted in each arm for TTP analysis. Finally, ORR was determined in all articles.

The chance of having a response with recent second-line doublets or single agents was almost doubled (OR = 1.78, 95% CI 1.22–2.59, $p = .003$; Fig. 4). Low heterogeneity was observed.

When the analysis was restricted to studies comparing experimental drugs with any active therapies as control (single agents) arms, the result remained significant (HR = 0.77, 95% CI 0.67–0.89, $p = .0005$; Fig. 5). When splitting studies comparing doublets with single agents and newer single agents with older single agents, the results were slightly different (doublets vs. single agents: HR = 0.56; 95% CI 0.36–0.87, $p = .01$; newer single agents vs. older single agents: HR = 0.80; 95% CI 0.69–0.94, $p = .006$; Fig. 5).
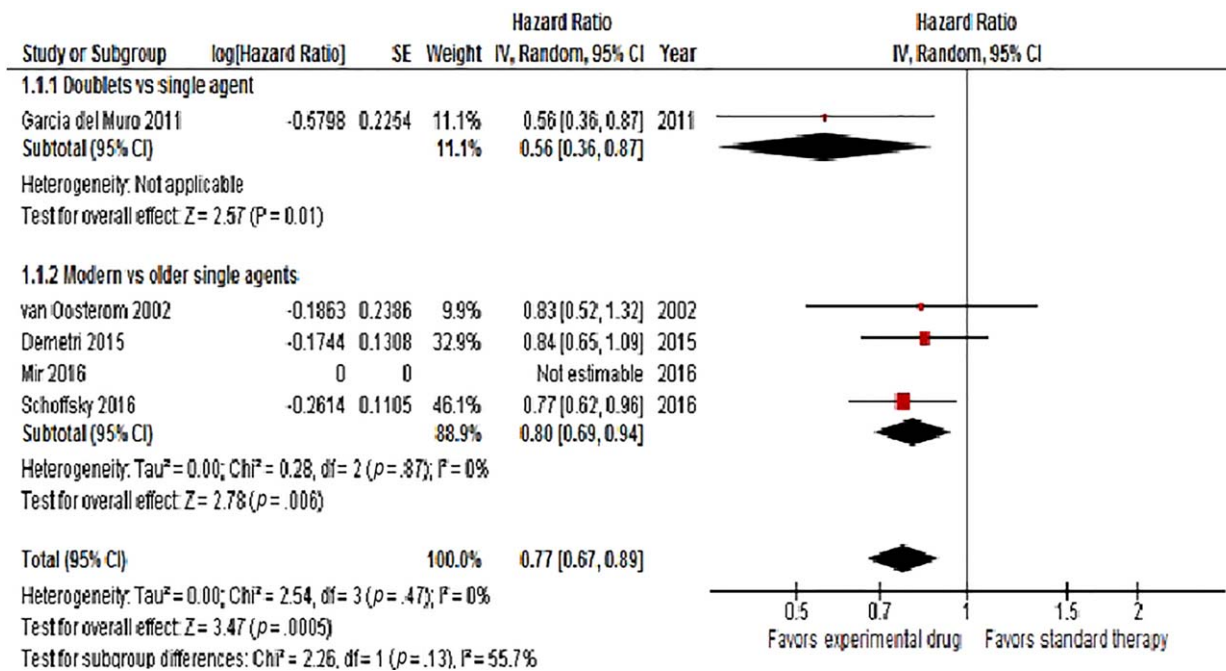
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Figure 5. Forest plot of hazard ratios in subgroup analysis comparing overall survival for patients who received modern versus conventional second-line chemotherapy in doublets versus single agents trials (with control arms including only active therapy).
Abbreviations: CI, confidence interval; IV, intravenous; SE, standard error.

Risk of bias for included trials is reported in Table 2. All randomized patients were included in the analyses, confirming that the issue of incomplete outcome data was addressed. With regard to selective data reporting, outcomes of interest were reported in all studies. Low risk of bias was reported for $n = 2$ studies only. Finally, no obvious publication bias was observed through inspection of the funnel plot (Fig. 6). The Egger test found significant evidence of bias for OS analysis; the Begg and Mazumdar rank correlation test found evidence of publication bias ($p = .066$); and the Duval and Tweedie and trim and fill tests extrapolated the probable absence of $n = 1$ and $n = 29$ studies for OS analysis, respectively. This meant that in the first case, there were only $n = 1$ asymmetric (negative) studies that when put to the right of the mean value of HR would change the final result, and that second, we would need to locate and include $n = 29$ "negative or neutral" studies for the combined two-tailed p value to exceed .050.

DISCUSSION

This systematic review aimed to assess the role of salvage therapy in metastatic pretreated STS. The meta-analysis was based on data extracted from literature reviews of all published trials that had randomized patients in phase II–III studies receiving second-line chemotherapy or biological agent versus conventional therapy. Second and further line of chemotherapy in metastatic STS was prescribed in good performance status patients even before the pubblication of conclusive studies. The oldest studies, performed from 1980 to 1990, compared historical agents in second-line therapy without a histological subanalysis of the STS treated. Notwithstanding, Bramwell et al. [39] demonstrated a higher

activity of ifosfamide (24% ORR) versus cyclophosphamide (5%), and Verveij demonstrated that doxorubicin was better than docetaxel [15]. The conclusions were that docetaxel was inactive in STS, and that its use was not recommended. As a consequence, in daily practice after first line containing antracyclines, salvage monotherapy with high dose ifosfamide, or dacarbazine, or vinorelbine were usually proposed [17, 40, 41].

A phase III trial by Maki et al. comparing gemcitabine + docetaxel versus gemcitabine alone in different subtypes of STS reported a higher activity of the combination on ORR, PFS, and OS in undifferentiated pleomorphic sarcomas and in uterine and nonuterine leiomyosarcomas [22] . Following that study, gemcitabine + docetaxel became the standard mainly in the reported subtypes. A few years later, Pautier and colleagues did not confirm the superiority of the combination over gemcitabine alone, and nowadays this drug as single agent is a common second-line therapy mainly in leiomyosarcomas, undifferentiated pleomorphic sarcomas, and angiosarcomas [37, 42]. Garcia del Muro et al., in a cooperative Spanish study, demonstrated better activity of the combination gemcitabine + dacarbazine than dacarbazine alone in different STS and specifically in leiomyosarcoma [34]. At present, gemcitabine monochemotherapy or in combination is an accepted treatment after first-line progression.

In 2009, Verveij confirmed in an article in the *Journal of Clinical Oncology* [43] and Scurr [13] demonstrated in 2011 that a specific drug can be more active in particular subtypes of STS. The histology-driven theory was very well investigated over the last 10 years in studies on second-line therapy in STS. The revisited old drug ifosfamide showed a specific activity with doxorubicin in synovial sarcoma as ORR

Table 1. Characteristics of the included studies

Study [reference]	Type of study	pts, n	Second-line therapy % (exp/ctr)	Histology % (LPS/LMS/other)	Uterine sarcoma	Treatment (exp vs. arm)	Median cycles n (exp vs. ctr)	ORR (%) (exp vs. ctr)	Median PFS exp arm (mo)	Median PFS ctr arm (mo)	Median OS exp arm (mo)	Median OS ctr arm (mo)
Kawai et al. 2015 [31]	Phase II	76	49/28 (30/56 2–3 previous lines)	33/0/67 (out of n = 73)	NR	Trabectedin 1.2 mg/m²/2h d1 q 3w vs. BSC	3 vs. NR	11 vs. 0	5.6	0.9	Not reached	8
Pautier et al. 2012 [32]	Phase II	83	100/100	0/100/0	50	GEM 900 mg/m² d1,8 + DOC 100 mg/m² d8 q 21d vs. GEM 1,000 mg/m² FDR d1,8,15 q 28d ×8	4 & 5 (nonuterine and uterine)	7.2 vs. 8.4	4.7–3.4[b]	5.5–6.3	23–13	20–15
van der Graaf et al. 2012 [19]	Phase III	372	93% at least 1 previous line	NR	NR	Pazopanib 800 mg/d vs. placebo	16.4 vs. 8.1 w	14 vs. 0	4.6	1.6	12.5	10.7
García-del-Muro et al. 2011 [27]	Phase II	113	100/100 (previous anthra & IFO)	16.8/28.3/54.9	13.2	GEM FDR d1 + DTIC 500 mg/m² d1 q 2w ×12 vs. DTIC 1,200 mg/m² d1 q 3w ×8	6 vs. 2	12 vs. 4	4.2	2	16.8	8.2
Demetri et al. 2009 [13]	Phase II	270	100/100 (1–2 previous lines)	27.8/51.1/21.1	22.2	Trabectedin 1.5 mg/m²/24h d1 vs. trabectedin 0.58 mg/m² d1,8,15 q 28d	5 vs. 2	5.6 vs. 1.6	3.3	2.3	13.9	11.8
Maki et al. 2007 [14]	Phase II	122	Median 1 previous line	16.3/31/52.7	NR	GEM 900 mg/m² d1,8 + DOC 100 mg/m² d8 vs. GEM 1,200 mg/m² d1,8 q 3w ×8[a]	4 vs. 4	16 vs. 8	6.2	3	17.9	11.5
van Oosterom et al. 2002 [26]	Phase II	79	83/77 (anthra)	13/44/43	NR	IFO 5g/m²/24h d1 vs. IFO 3g/m²/4h d1-3 q 3w × 4 (if CR) or until PD or unacceptable toxicity if PR/SD	3 vs. 4	6 vs. 8	6 w	14 w	45 w	36 w
Demetri et al. 2016 [28]	Phase III	518	11/13% (anthra-based CT) (88% ≥2 lines)	27/73/0	40%	Trabectedin 1.5 mg/m² vs. DTIC 1g/m² q 3w	4 vs. 2	9.9 vs. 6.9	4.2 (4.9[c])	1.5 (2.7[c])	12.4	12.9
Schöffski et al. 2016 [37]	Phase III	452	50/50%	31.6/68.4/0	29%	Eribulin 1.4 mg/m² d 1,8 q 21 vs. DTIC 800–1,200 mg/m² d1 q 21	NR	4 vs. 5	2.6	2.6	13.5	11.5
Mir et al. 2016 [38]	Phase II	182	30/70	23/30/47	12%	Regorafenib 160 mg d 1–21 q 28 vs. placebo	NR	5 vs. 1	1.1/3.7/5.6/2.9[d]	1.7/1.8/1/1[d]	4.7/21/13.4/12.1[d]	8.8/9.1/6.7/9.5[d]

[a]Treatment could continue at investigator discretion beyond eight cycles.

[b]Uterine and nonuterine cohorts.

[c]Second line only patients.

[d]For liposarcoma, leiomyosarcoma, synovial sarcoma, and other histotypes, respectively.

Abbreviations: %, rate; anthra, anthracycline; BSC, best supportive care; CBR, clinical benefit rate; CDDP, cisplatin; CR, complete response; CT, chemotherapy; ctr, control; d, days; DOC, docetaxel; DTIC, dacarbazine; exp, experimental; FDR, fixed dose rate of infusion; GEM, gemcitabine; IFO, ifosfamide; LMS, leiomiosarcoma; LPS, lyposarcoma; mo, months; NR, not reported; ORR, overall response rate; OS, overall survival; Os bid, orally twice daily; PFS, progression-free survival; PLAC, placebo; PR, partial response; pts, patients; q, every; q 3w, every 3 weeks; SD, stable disease; TEM, temsirolimus; w, weeks.

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Table 2. Assessment of risk of bias

Study [reference]	Adequate sequence generation	Allocation concealment	Masking
Kawai et al. 2015 [31]	Yes	Yes	NA
Pautier et al. 2012 [32]	Yes	Did not describe the allocation concealment method in the available publication (unclear risk)	NA
van der Graaf et al. 2012 [19]	Yes	Yes	Yes (placebo-controlled study)
García-del-Muro et al. 2011 [27]	Yes	Yes	NA
Demetri et al. 2009 [13]	Yes	Yes	NA
Maki et al. 2007 [14]	Yes	Did not describe the allocation concealment method in the available publication (unclear risk)	NA
van Oosterom et al. 2002 [26]	Yes	Yes	NA
Demetri et al. 2016 [28]	Yes	Yes	NA
Schöffski et al. 2016 [37]	Yes	Yes	NA
Mir et al 2016 [38]	Yes	Yes	Yes (placebo-controlled study)

For all studies, all randomized patients were included in the analyses. In all studies, outcomes of interest were reported, with the exception of Eroglu et al. 2015, in which overall survival was not reported (neither hazard ratio nor survival curve were provided).
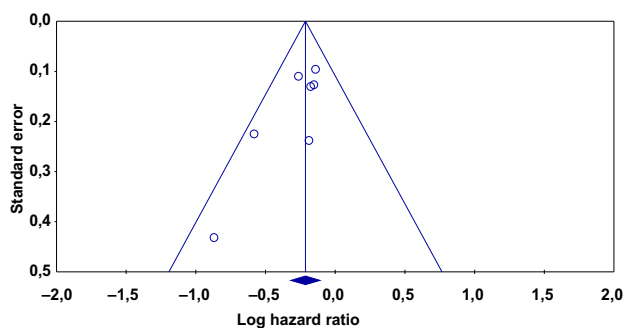Abbreviation: NA, not applicable.

Figure 6. Funnel plot of standard error by hazard ratio (HR) for overall survival (OS). The funnel plot of $n = 8$ studies included in the meta-analysis of OS illustrates the standard error of log HR in Y axis and HRs for OS in X axis.

in the Edmonson's study [19]. Demetri showed a high level of activity of the newer drug trabectedin in patients with advanced myxoid or round cell liposarcoma and leiomyosarcoma after failure of the first-line chemotherapy including anthracyclines, ifosfamide, and other traditional agents [21, 35].

Trabectedin is a marine-derived antineoplastic compound isolated from the Caribbean tunicate Ecteinascidia turbinate that is approved for the treatment of patients with advanced STS. The drug binds the minor groove of DNA and interferes with DNA transcription to RNA by inhibiting the binding of transcription factors [44]. This drug demonstrated specific activity against L-type sarcomas and showed a higher ORR and PFS as compared with the active control with dacarbazine. A recent French study with trabectedin as second-line therapy suggests that the treatment should not be discontinued because its maintenance use significantly reduces the risk of progression in patients with stable disease or in response [45].

Activity has also been reported with pazopanib, a synthetic imidazole pyrimidine, which is a multitarget tyrosine kinase inhibitor with activity against vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3, and platelet derived growth factor receptor (PDGFR). In the PAzopanib ExpLorEd in SofT-Tissue Sarcoma - A phasE III study (PALETTE) study, pazopanib was compared with placebo in many different pretreated STS. The drug showed a better PFS but not OS in leiomyosarcoma and synovial sarcoma [27]. A previous phase II study [46] had shown an inferior PFS in adipocytic STS.

> A recent French study with trabectedin as second-line therapy suggests that the treatment should not be discontinued because its maintenance use significantly reduces the risk of progression in patients with stable disease or in response.

A second targeted agent, regorafenib, has recently demonstrated some activities in second or later lines of therapy in STS [47]. Regorafenib is an oral agent, multikinase inhibitor active against VEGFR 1, VEGFR 2, VEGFR 3, Kit, PDGFR, and Ras. Compared with placebo, it showed an interesting activity on PFS in all groups of sarcomas except adipocitic subtypes.

In 2016, inhibition of PDGFR-α by the monoclonal antibody Olaratumab showed promising clinical activity if associated to doxorubicin both in OS and in PFS, as first-line therapy only [48]. This is going to become another active targeted agent in STS treatment, but no data are currently available in second-line treatment.

Eribulin mesylate, a compound isolated from the marine sponge Halichondria that acts as an inhibitor of microtubule dynamics, was shown to have a particular activity against liposarcomas and general activity against fibroblastic sarcoma,

epithelioid sarcoma, and malignant solitary fibrous tumor, even in a small number of patients included in the study [49]. The benefit was demonstrated in ORR and PFS at 12 weeks. More recently, eribulin demonstrated such activity but only in OS and not in PFS [38].

Besides these four drugs discussed above, no other new agent has shown significant activity either in STS overall or in a specific subtype. Neither selumetinib [50] nor thrombospondin [51] and ombrabulin [52] showed a sufficient activity in metastatic STS to support their use in clinical practice or justify further studies. Limited experiences are reported on the activity of palbociclib in well-differentiated/dedifferentiated liposarcoma [53] and sunitinib in solitary fibrous tumor [54]. Both agents are not approved in many countries for this specific use.

There was a different situation concerning ridaforolimus, an mammalian target of rapamycin (mTOR) inhibitor used as second-line/maintenance treatment in metastatic STS, which achieved an objective response or stable disease compared with first-line therapy. However, the drug failed to demonstrate a clinical impact to maintain the response, although a small statistical benefit was recorded compared with placebo [55]. Some studies included in our meta-analysis investigated the role of the dose or schedule of a specific drug in second-line therapy. Van Oosterom showed better activity in a nonhistology-driven study of a fractionated schedule of ifosfamide versus an only 1-day schedule [33]. Similarly, Demetri et al. showed a better activity of trabectedin administered every 3 weeks instead of weekly administration [21].

The limitations of these studies should be noted. The meta-analysis was based on data extracted from the literature and could suffer from some possible bias. Only eight trials investigated the OS benefit of second-line therapy; PFS was available only in eight, whereas ORR evaluation was present in all studies. The main weakness is the lack of a formal analysis according to histology; in fact, most studies reported efficacy in mixed populations. Some of the studies compared the investigational agent or combination with placebo, failing to give an active drug in these patients. Most of the studies did not include a formal quality of life measurement in spite of the fact that the drugs were not curative and had limited benefit in terms of response or survival. Otherwise, this is the first meta-analysis exploring the efficacy of salvage treatments with novel agents compared with no therapy or use of older ineffective drugs in STS. Finally, the benefit of palliative surgery and of symptomatic radiotherapy cannot be accounted, but it is likely that multidisciplinary treatment would be only exceptionally permitted in this population and investigated in large randomized trials. The benefit was significant for both OS and PFS, and for ORR despite the fact that <10% was almost double compared with historical agents. The heterogeneity for the primary analysis was virtually absent, and no obvious bias was found in funnel plots.

> The reduction by about 40% of the risk of progression highlights the strong activity of new agents even in these previously treated and refractory patients. The importance of the results was confirmed by a significant OS benefit, despite that postprogression therapies or crossover to active agents could have diluted the absolute gain.

The reduction by about 40% of the risk of progression highlights the strong activity of new agents even in these previously treated and refractory patients. The importance of the results was confirmed by a significant OS benefit, despite that postprogression therapies or crossover to active agents could have diluted the absolute gain. In experimental arms, postprogression survival accounted for more than 70% of the entire OS. Because the number of new drugs against metastatic STS is increasing, it will be important to define which is the best endpoint to be considered (e.g., OS, PFS, percentage of PFS at 3 or 6 months, ORR, or TTP) [56].

Conclusion

Although the results of this meta-analysis on ORR, OS, and PFS of salvage therapy in metastatic STS were positive, the prognosis of these patients remains unsatisfactory, with a medium survival of 8–12 months. More research is needed to find a particular biomarker or targets to treat patients not only on the basis of histology-driven activity but also by targeting potentially "druggable" molecular defects.

Author Contributions

Conception/design: Alessandro Comandone, Fausto Petrelli, Antonella Boglione, Sandro Barni
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For Further Reading:
Silvia Stacchiotti, Olivier Mir, Axel Le Cesne et al. Activity of Pazopanib and Trabectedin in Advanced Alveolar Soft Part Sarcoma. *The Oncologist* first published on July 28, 2017.

Implications for Practice:
This retrospective study, conducted among the world reference centers for treatment of sarcoma, confirms the value of pazopanib in patients with advanced alveolar soft part sarcoma (ASPS), with dimensional and durable responses, whereas trabectedin shows a limited activity. Alveolar soft part sarcoma is resistant to conventional cytotoxic chemotherapy. Pazopanib and trabectedin are licensed for treatment of sarcoma from second line; in the lack of prospective clinical trials, these results are relevant to defining ASPS best management and strongly support initiatives aimed at obtaining the approval of pazopanib in the front line of the disease.

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