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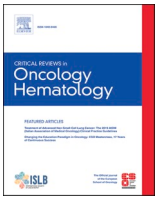

Patient-reported outcomes in randomized clinical trials of systemic therapy for advanced soft tissue sarcomas in adults: A systematic review☆

Evelyne Roets [a], Winette van der Graaf [a,b], Bauke H.G. van Riet [c], Rick L. Haas [c,d], Eugenie Younger [e], Francesco Sparano [f], Roger Wilson [g,j], Stevie van der Mierden [h], Neeltje Steeghs [a], Fabio Efficace [f], Olga Husson [a,i,*]

[a] Department of Medical Oncology, The Netherlands Cancer Institute, Plesmanlaan 121, Amsterdam 1066 CX, the Netherlands
[b] Department of Medical Oncology, ErasmusMC Cancer Institute, Erasmus University Medical Center, Doctor Molewaterplein 40, Rotterdam 3015 GD, the Netherlands
[c] Department of Radiotherapy, The Netherlands Cancer Institute, Plesmanlaan 121, Amsterdam 1066 CX, the Netherlands
[d] Department of Radiotherapy, Leiden University Medical Center, Albinusdreef 2, Leiden 2333 ZA, the Netherlands
[e] Sarcoma Unit, Royal Marsden NHS Foundation Trust, Fulham Road, London SW3 6JJ, United Kingdom
[f] Health Outcomes Research Unit, Italian Group for Adult Hematologic Diseases (GIMEMA) Data Center, Rome, Italy
[g] Sarcoma Patients Advocacy Global Network, Untergasse 36, Wölfersheim D-61200, Germany
[h] Scientific information service, The Netherlands Cancer Institute, Plesmanlaan 121, Amsterdam 1066 CX, the Netherlands
[i] Department of Surgical Oncology, ErasmusMC Cancer Institute, Erasmus University Medical Center, Doctor Molewaterplein 40, Rotterdam 3015 GD, the Netherlands
[j] Sarcoma UK, 17/18 Angel Gate, City Road, London, UK

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ABSTRACT

Background: This systematic review evaluates reporting of patient-reported outcomes (PROs) within randomized clinical trials (RCTs) for advanced soft tissue sarcoma (STS) patients.
Methods: A systematic literature search from January 2000 – August 2022 was conducted for phase II/III RCTs evaluating systemic treatments in adult patients with advanced STS. Quality of PRO reporting was assessed using the CONSORT PRO extension.
Results: Out of 7294 abstracts, 59 articles were included; comprising 43 RCTs. Only 15 RCTs (35%) included PROs, none as primary endpoints. Only 10 of these RCTs reported PROs, either in the primary (6/10) or secondary publication (1/10) or in both (3/10), with a median time interval of 23 months. The median CONSORT PRO adherence score was 5.5/14, with higher scores in publications focusing exclusively on PROs.
Conclusion: These results highlight the need for improved and more consistent PRO reporting to inform patient care in the setting of advanced STS.

1. Introduction

Soft tissue sarcomas (STS) are rare, heterogeneous tumors of mesenchymal origin, which account for approximately 1% of all cancers in adults (Amankwah et al., 2013). Surgery with (neo)adjuvant radiotherapy is the mainstay of treatment for localized disease, however around half of patients with initially localized (intermediate or high grade) tumors will eventually develop advanced, incurable disease (Coindre et al., 2001; Gronchi et al., 2021). Patients with advanced STS often experience a substantial burden of symptoms and generally have a poor prognosis (Gough et al., 2011), with a median overall survival (OS) of around 12–18 months (Italiano et al., 2011; Verschoor et al., 2020). Palliative chemotherapy is the principal treatment modality and anthracyclines have been the standard first-line treatment since the 1970 s (Gronchi et al., 2021; Benjamin et al., 1975). Several recent randomized phase 2–3 clinical trials have failed to demonstrate a survival benefit for doxorubicin combination therapies compared to single-agent doxorubicin treatment (Benjamin et al., 1975; Ryan et al., 2013; Tap et al., 2017, 2020; Judson et al., 2014; Demetri et al., 2012; Maurel et al., 2009).

The evaluation of systemic anti-cancer treatments within clinical trials has traditionally focused on outcomes such as radiological

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* Corresponding author at: Department of Medical Oncology, The Netherlands Cancer Institute, Plesmanlaan 121, Amsterdam 1066 CX, the Netherlands
E-mail address: o.husson@nki.nl (O. Husson).

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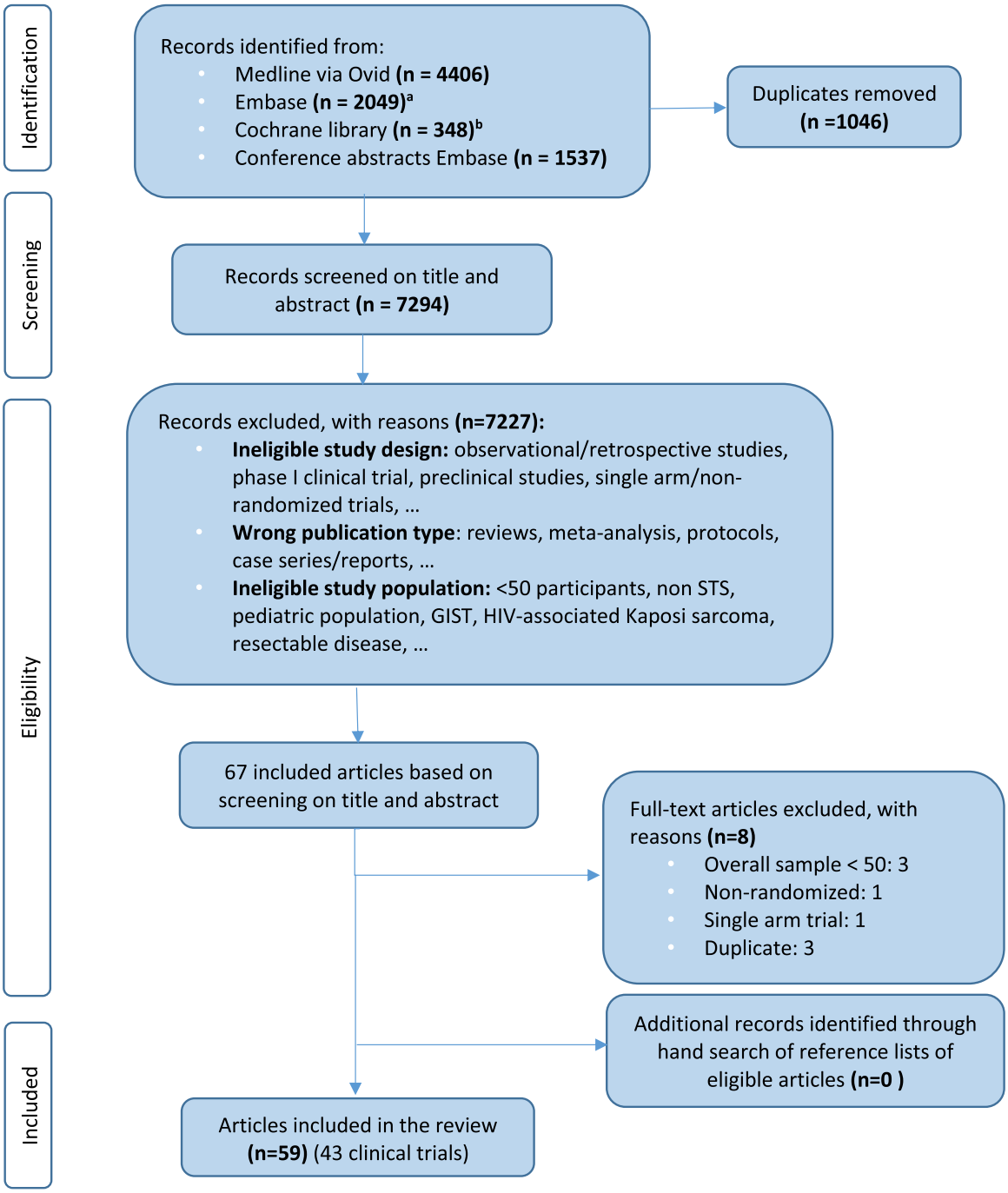

Fig. 1. Schematic breakdown of literature search. STS, soft tissue sarcoma. [a]Without conference abstracts [b]Results limited to sources: international Clinical Trials Registry Platform, ClinicalTrials.gov, CINAHL database.

response, progression free survival (PFS) and OS. Physician-reported symptomatic adverse events are usually presented alongside survival data, however, they can underestimate the frequency and severity of toxicity from the patient's perspective (Di Maio et al., 2016). In recent years, a more patient-centered approach has been adopted, including the incorporation of patient-reported outcomes (PROs) such as health-related quality of life (HRQoL), as clinical trial endpoints. PROs can be defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" (FDA, 2009). Patient reported outcomes can be combined with survival data to determine the net clinical treatment benefit and they may enhance patient-centered decision-making through tailored information provision. In 2006 and 2009 the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA), respectively, issued guidance papers, describing the contribution of PROs in the process of drug approval (FDA, 2009; EMA, 2005). More recently, the EMA and FDA published multiple guidance papers to support patient-centered drug development (FDA, 2020, 2022a, 2022b; EMA, 2016, 2020).

Despite increasing recognition of the importance of PROs, it is widely acknowledged that PRO results are often under-reported and also subject to delay in publication, thereby limiting their potential to impact on real-world clinical practice (Van Hemelrijck et al., 2019; Rees et al., 2015; Kyte et al., 2019; Efficace et al., 2014a; Mercieca-Bebber et al., 2016; Dirven et al., 2014; Marandino et al., 2018). This publication bias has been attributed to heterogeneity pertaining to PRO instruments,

Table 1
Inclusion of PROs according to characteristics of the RCT and publication.

	All included RCTs n	RCTs with PRO endpoint[b] n (%)	RCTs without PRO endpoint n (%)
Number of RCTs	43	15 (35%)	28 (65%)
Publication year[a]			
≥2000 < 2005	4	0 (0%)	4 (100%)
≥2005 < 2010	6	0 (0%)	6 (100%)
≥2010 < 2015	5	0 (0%)	5 (100%)
≥2015 < 2022 (August)	28	15 (54%)	13 (46%)
Journal impact factor ≤ 5[a]			
Yes	8	4 (50%)	4 (50%)
No	35	11 (31%)	24 (69%)
Industry supported[c]			
Yes	32	14 (44%)	18 (56%)
No	10	1 (10%)	9 (90%)
Not reported	1	0 (0%)	1 (100%)
Primary endpoint[d]			
Overall survival	6	4 (66%)	2 (33%)
Progression free survival	25	8 (32%)	17 (68%)
Progression free survival rate	3	2 (66%)	1 (33%)
Unclear	4	0 (0%)	4 (100%)
Other[e]	6	2 (33%)	4 (66%)
Study result (primary endpoint)			
Positive[f]	14	7 (50%)	7 (50%)
Negative[g]	19	6 (32%)	13 (68%)
Not applicable[h]	10	2 (80%)	8 (80%)

RCT=randomized clinical trial; PRO=patient reported outcome.

[a] For RCTs that resulted in multiple publications, the journal impact factor, first author, year of publication, were extracted from the primary publication or from the publication reporting the most relevant PRO results (if available).

[b] PRO endpoint (primary, secondary, tertiary, exploratory) defined in the article or in the description of outcomes measures at CT.gov.

[c] Assessed if explicitly stated or if one or more authors were affiliated to a pharmaceutical company. This evaluation is based solely on information extracted from the paper and information reported on CT.gov.

[d] One study had two primary endpoints.

[e] Toxicity (1), objective response rate (1), proportion of patients alive and progression free at 24 weeks post-randomisation (1), time to progression (2), tumor response (complete or partial response or stable disease) (1).

[f] Positive trials were defined as any superiority trial which demonstrates that the experimental treatment was superior to the control, or non-inferiority trials where the experimental treatment was declared non-inferior to the control.

[g] Negative trials were defined as any superiority trial which has demonstrated that the experimental treatment was not superior to the control, or non-inferiority trials where the experimental treatment did not meet a predefined threshold to declare non-inferiority.

[h] Non-comparative studies (6), unclear primary endpoint (4).

methodology and statistical analyses, and a lack of standardized guidelines for interpreting findings (Pe et al., 2018). Between 2013 and 2020 guidelines have been published for PRO reporting in randomized clinical trials (CONSORT PRO), incorporation of PROs in study protocols (SPIRIT-PRO) and the statistical analysis of PROs (SISAQOL) (Coens et al., 2020; Calvert et al., 2018, 2013). These reporting guidelines aim to assist researchers in the interpretation of PRO results, enhance patient-centered decision-making and guide health policies (Calvert et al., 2013; Brundage et al., 2013). In 2015 the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) was introduced, a tool that aims to assess the clinical benefit of new treatments and facilitates the decision-making process, taking into account both the impact on OS or surrogates and the impact on HRQoL (Cherny et al., 2015; Oosting et al., 2023).

Several studies examined the quality of PRO reporting in RCTs for other tumor types (Van Hemelrijck et al., 2019; Rees et al., 2015; Mercieca-Bebber et al., 2016; Marandino et al., 2019). In advanced STS, where cure is rarely achieved, improvement of HRQoL is one of the primary goals of treatment. The primary objective of this systematic review is to assess to which extent PROs are reported within RCTs of systemic treatments for patients with advanced STS. The secondary objectives are to describe the type of PRO instruments used, how often PROs are reported in the primary or secondary publication, the interval between primary and secondary publication, the methods used to collect PRO data (e.g. paper, electronic) and the quality of PRO reporting.

2. Methods

2.1. Search strategy and selection criteria

This systematic review was registered through PROSPERO (CRD42020173903) and followed the methodology outlined in the PRISMA reporting guidelines for systematic reviews (Page et al., 2021). The used search resources were: Medline via Ovid, Embase.com and the Cochrane Library. A full list of the search terms is included in the appendix (supplementary 1). For the Cochrane Library the results were limited to ICTRP, CT.gov and CINAHL sources. References published before 2000 were excluded. The search strategies were checked by two independent other information specialists. The searches were executed on August 11, 2022. For the RCT filter the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision) and Cochrane Highly Sensitive Search Strategy for identifying RCTs in Embase: (2020 revision) were used (Lefebvre, 2022). The remainder of the search was not based on prior work.

The search results yielded by the above search strategy were screened by one single reviewer (ER). In case of the slightest doubt regarding the inclusion or exclusion of an article, one of the senior co-authors (OH) was asked for advice, and a discussion was completed until consensus was reached. Additionally, reference lists of eligible articles were manually screened for other suitable publications that were not identified through the search strategy. No other methods of acquiring references were used. We did not seek unpublished studies. The online systematic review manager 'Rayyan' was used to store references, to mark eligible articles and to mark excluded articles with the reason for exclusion (Ouzzani et al., 2016).

2.2. Criteria for considering studies

Studies were considered for inclusion if they included patients aged ≥18 years with histologically confirmed advanced STS. 'Advanced' was defined as either metastatic or locally-advanced but unresectable disease. Studies addressing both adults and children were only included if data for adults (aged ≥18 years) were reported separately. RCTs for patients with advanced bone sarcoma, gastrointestinal stromal tumor (GIST) or HIV-associated Kaposi sarcoma were excluded. Studies could contain multiple STS subtypes. RCTs evaluating any anti-cancer systemic treatment(s) (including chemotherapy, immunotherapy and targeted therapy) for patients with advanced STS were considered. RCTs evaluating radiotherapy, surgery, supportive medications, alternative or complementary medications were excluded. All RCTs of systemic treatment for patients with advanced STS which have been published in English between January 2000 and August 11 2022 were included if they contained a minimum of 50 patients. Phase 1 studies, case series, observational studies and case reports were excluded.

Eligible RCT publications were scrutinized for study endpoints related to any PRO, either as a primary or secondary outcome measure. Any PRO that reflects the direct impact of the disease and/or its treatment on patient symptoms, functioning, health status, or HRQoL was considered. Only measures that were self-reported by the patient were included.

Table 2
RCTs that included PROs without reporting PRO results.

Author[a]	Year of publication[a]	Title[a]	PRO
C.W. Ryan et al.	2016	PICASSO III: A Phase III, placebo-controlled study of doxorubicin with or without palifosfamide in patients with metastatic soft tissue sarcoma	PROs mentioned as a secondary outcome on CT.gov
P. Schoffski et al.	2021	Randomised phase 2 study comparing the efficacy and safety of the oral tyrosine kinase inhibitor nintedanib with single agent ifosfamide in patients with advanced, inoperable, metastatic soft tissue sarcoma after failure of first-line chemotherapy: EORTC-1506-STBSG "ANITA"	PROs mentioned in 'method' section of publication.[b]
A. Le Cesne et al.	2015	Interruption versus continuation of trabectedin in patients with soft-tissue sarcoma (T-DIS): a randomised phase 2 trial	PROs mentioned as a secondary outcome on CT.gov
J. Hartmann et al.	2019	Randomised phase II trial of trofosfamide vs. doxorubicin in elderly patients with untreated metastatic soft-tissue sarcoma	PROs mentioned as a secondary outcome on CT.gov
G. Demetri et al.	2016	Efficacy and Safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial	PROs mentioned in 'method' section of publication.[c]

[a] For RCTs that resulted in multiple publications the author, year and title that apply to the first publication where filled in.
[b] PROs were not reported because of the early closure of the trial for futility.
[c] PROs were only mentioned as an outcome measure in the 'method' section of the secondary publication of Hensley et al. (2017).

2.3. Methods of study evaluation

The management of the review and storing process was performed via the PROMOTION database (Patient-Reported Outcome Measurements Over Time In Oncology), which uses a consolidated double blind data entry procedure (Efficace et al., 2014b). For the purpose of this study, a predefined electronic-data extraction form (eDEF), including three sections, was developed. Section A addresses general information and descriptive characteristics of the study; section B is the latest version of the CONSORT PRO extension (supplementary 2) (Calvert et al., 2013); section C includes a section about PROs and clinical outcomes, and a section about concordance between PROs and clinical outcomes. For trials with multiple publications, relevant data from all articles were combined in one single eDEF. Two independent reviewers (ER and BvR) completed the eDEF for eligible articles. All data were entered by the reviewers into a password-protected online database (REDCap) (Harris et al., 2009). A third senior reviewer (OH) was consulted in case of any discrepancies. When consensus was reached a final eDEF was imputed and used for the purpose of this paper.

2.4. Type of data extracted

2.4.1. Basic trial characteristics

For each eligible RCT the following basic study characteristics were extracted: trial name, sponsor, study, publication year, first author, journal and impact factor (for the year of publication, according to the journal of citation reports), study sample size, disease stage, broad treatment type, primary and secondary endpoints, PRO endpoint (stated in the article or in the description of outcomes measures at CT.gov or the WHO International Clinical Trials Registry Platform (ICTRP)). For RCTs with multiple publications, the journal impact factor, first author, year of publication, were extracted from the primary publication or from the publication reporting the most relevant PRO results. Positive trials were defined as any superiority trial which demonstrated that the experimental treatment was superior to the control, or non-inferiority trials where the experimental treatment was declared non-inferior to the control. Negative trials were defined as any superiority trial which has demonstrated that the experimental treatment was not superior to the control, or non-inferiority trials where the experimental treatment did not meet a predefined threshold to declare non-inferiority.

2.4.2. PROs as endpoint

All eligible articles were scrutinized for PRO endpoints. Additionally, CT.gov and ICTRP were screened to assess inclusion of PRO endpoints. The following information was gathered: 1) the number of RCTs with or without a PRO endpoint; 2) whether PROs were included in the primary or secondary publication (i.e. published after the original RCT report); 3) the time interval between primary and secondary publication(s) (if applicable). For RCTs including a PRO endpoint and no published PRO results, authors were contacted for additional information regarding PRO results. Where a PRO endpoint was defined in the article, details of the measured PRO domains and the PRO instruments used (e.g. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) were collected. Also, we noted any statistically and/or clinically significant differences between treatment arms in the PRO data, and which domains showed these PRO differences.

2.4.3. Assessment of PRO reporting in RCTs

Publications in which PRO results were reported, were reviewed for completeness in accordance with the CONSORT PRO Extension recommendations. This includes 14 items: five PRO-specific extension items and nine PRO-specific elaborations to CONSORT-2010 items (Calvert et al., 2013). Following the most recently published CONSORT PRO recommendations, multi-component items (i.e. P2b, P6a, 13a, 17a, P20/21) were divided into separate sub-items so that all components could be correctly evaluated (Mercieca-Bebber et al., 2022). For this study, items 4a and 7a were not evaluated because none of the included RCTs used PRO as an eligibility or stratification criteria and none had PROs as primary endpoint. Each RCT was thus rated with a score ranging from 0 to 14 (appendix pp 19–21).

2.4.4. Reporting and analysis

Descriptive data are reported as frequencies and percentages. Where appropriate, data are summarized using median and range. The number of RCTs adhering to each CONSORT PRO item and the total CONSORT PRO adherence score for each RCT are reported. Text and table format are used to provide a qualitative overview of the findings.

3. Results

The literature search resulted in 7294 records that were screened on title and abstract. Fifty-nine articles, comprising 43 RCTs, met the eligibility criteria (Ryan et al., 2013; Tap et al., 2017, 2020; Judson et al., 2014; Demetri et al., 2012; Maurel et al., 2009; Chawla et al., 2015; Ray-Coquard et al., 2015; Gelderblom et al., 2014; Chawla et al., 2022; Seddon et al., 2017; Verweij et al., 2000; Judson et al., 2001; Van Tine et al., 2022; Tap et al., 2016; Younger et al., 2020; Cranmer et al., 2017; Worden et al., 2005; Le Cesne et al., 2000; Lorigan et al., 2007; Pautier et al., 2022; Martin-Broto et al., 2016; Bui-Nguyen et al., 2015; Schoffski et al., 2016; Blay et al., 2019; Demetri et al., 2017; Hudgens et al., 2017; Del Muro et al., 2009; Maki et al., 2007; Jones et al., 2019a; Hensley et al., 2015; Somaiah et al., 2021; Bui-Nguyen et al., 2012; Blay et al., 2015; Fayette et al., 2009; van Oosterom et al., 2002; Schoffski et al., 2021; van der Graaf et al., 2012; Coens et al., 2015; Cesne et al., 2019; Grunwald et al., 2020; Schmoll et al., 2021; Mir et al., 2016;

Table 3
Characteristics of RCTs reporting PROs and type of PRO measures.

	RCTs reporting PROs n (%)
International	
No	3 (30%)
Yes	7 (70%)
Industry supported (fully or in part)[a]	
No	1 (10%)
Yes	9 (90%)
Overall study sample size[b]	
≤200 patients	4 (40%)
>200 patients	6 (60%)
Disease stage	
Only metastatic/advanced	10 (100%)
Only non-metastatic/local	0 (0%)
Both	0 (0%)
Broad treatment type	
Chemotherapy	8 (80%)
Targeted therapy	6 (60%)
Hormonal therapy	0 (0%)
Immunotherapy	0 (0%)
Primary endpoint	
Overall survival	3 (30%)
Progression free survival	5 (50%)
Pain (physician reported)	0 (0%)
Disease free survival	0 (0%)
Toxicity	1 (10%)
Time to treatment failure	0 (0%)
PROs	0 (0%)
Other[c]	2 (20%)
Secondary endpoint	
Overall survival	7 (70%)
Progression free survival	5 (50%)
Disease free survival	0 (0%)
Toxicity	7 (70%)
Time to treatment failure	0 (0%)
PROs	8 (80%)
Other	9 (90%)
Statistically significant difference between treatment arms in the primary endpoint	
No	5 (50%)
Yes	5 (50%)
Overall survival difference favoring experimental treatment	
No	9 (90%)
Yes	1 (10%)
PRO instrument used	
EORTC instruments	9 (90%)
EQ-VAS	1 (10%)
EQ-5D	2 (20%)
FA-13	1 (10%)
mBPI-sf	1 (10%)
Length of PRO assessment during RCT	
Up to 6 months	5 (50%)
Up to 1 year	3 (30%)
Unknown	2 (20%)
Secondary paper on PRO	
No	6 (60%)
Yes[d]	4 (40%)

RCT=randomized clinical trial; PRO=patient reported outcome; EORTC=European Organisation for Research and Treatment of Cancer; EQ-VAS=EQ visual analogue scale; FA-13=Fatigue-specific FA-13 questionnaires; mBPI-sf=modified Brief Pain inventory-short form

[a] Assessed if explicitly stated or if one or more authors were affiliated to a pharmaceutical company. This evaluation is based solely on information extracted from the paper and information reported on ClinicalTrials.gov.

[b] Overall study sample size, regardless of patients included in the PRO analysis.

[c] The proportion of patients alive and progression free at 24 weeks after the date of randomization (n=1); Progression free survival rate at 12 weeks (n=1)

[d] Assessed as 'yes' if PROs were published in addition to the original RCT report.

Brodowicz et al., 2018; Berry et al., 2017; Gounder et al., 2022, 2021; Eroglu et al., 2015; Demetri et al., 2009; Blay et al., 2014; Demetri et al., 2016; Hensley et al., 2017; Jones et al., 2018; Patel et al., 2019; Jones et al., 2019b; Le Cesne et al., 2021; Hartmann et al., 2020). A full list of articles, with and without PRO endpoints, is included in the appendix (supplementary 3). Fig. 1 summarizes the selection process.

3.1. Inclusion of PROs according to characteristics of the RCT and publication

Fifteen out of 43 RCTs (35%) had PROs as an endpoint (Table 1). In the remaining RCTs, PROs were not listed among endpoints. None of the RCTs published before 2015 included PROs as an endpoint. In contrast, 54% of RCTs (1528) published in 2015 or later had PROs as an endpoint. Seven out of 14 RCTs (50%) with a positive primary clinical endpoint also had a PRO endpoint. Trials that included PROs but did not report PROs are listed in Table 2. In one of these RCTs PROs were not reported due to the early closure of the trial (Schoffski et al., 2021).The contacted authors did not provide any additional information regarding PROs.

3.2. Characteristics of RCTs reporting PROs and type of PRO instruments

PRO results were reported in 10/15 (67%) RCTs with a PRO endpoint. Demographic characteristics of the RCTs and PRO-related characteristics are summarized in Table 3. PROs were a secondary or an exploratory endpoint in 8/10 and in 2/10 RCTs, respectively. None of the RCTs had PROs as a primary endpoint. PROs were reported in the primary (6/10) or secondary publication (1/10) or in both the primary and secondary publication (3/10). The median time between primary and secondary publication was 23 months (range 12–39 months). In nearly all RCTs (9/10) PROs were assessed with EORTC questionnaires, including the EORTC QLQ-C30 (9/10) and the EORTC QLQ-ELD14 (1/10). In three RCTs EORTC questionnaires were used in conjunction with another PRO instrument such as the fatigue-specific FA-13 questionnaire (1/10), the EQ-5D questionnaire (1/10) and the modified Brief Pain inventory-short form (mBPI-sf) (1/10). In one RCT PROs were assessed solely with the EQ visual analogue scale (EQ-VAS) and the EQ-5D questionnaire. In one RCT the method section referred both to the EORTC QLQ-C30 and EQ-5D questionnaires, but only results for the EORTC QLQ-C30 were reported (Hudgens et al., 2017; Schöffski et al., 2016).

3.3. Effects of experimental intervention on clinical outcomes and PROs

Table 4 describes clinical outcomes and PRO results. In the ANNOUNCE trial and in the SARC021 trial, PROs were only described for the overall study population (Van Tine et al., 2022) or compared between age groups (Younger et al., 2020), respectively. The RCT of Grunwald et al., comparing pazopanib versus doxorubicin, only reported baseline PRO results (Grunwald et al., 2020). In the RCT of Schmoll et al., comparing pazopanib plus gemcitabine versus pazopanib, only a descriptive analysis was done for comparison of PROs between treatment arms (Schmoll et al., 2021).

In 5/10 RCTs, for the primary clinical outcome, a difference favoring the experimental treatment arm (5/6) (Hudgens et al., 2017; Coens et al., 2015; Cesne et al., 2019; Schmoll et al., 2021; Gounder et al., 2021) was seen. This improvement in clinical outcomes was associated with improved PROs (for at least one domain) in the RCTs comparing selinexor versus placebo and eribuline mesilate versus dacarbazine (Hudgens et al., 2017; Gounder et al., 2021). Conversely, in the PALETTE trial and in Schmoll et al.'s RCT improvement of the primary clinical outcome was associated with a deterioration of PROs (for at least one domain) (Coens et al., 2015; Schmoll et al., 2021). In the T-SAR trial the longer PFS observed in the trabectedin arm was not associated with a difference in PROs (Le Cesne et al., 2021). Somaiah et al.'s RCT showed improved PROs (for at least one domain) in the experimental treatment arm, without a significant difference in the primary outcome (Somaiah et al., 2021).

Table 4
Summary of RCTs reporting PROs published between January 2000 and August 2022.

Author	Journal impact factor	Study design	Primary endpoint	PRO endpoint	PRO instrument	Treatment	Histological subtype of STS	Overall sample size	Baseline PRO sample size	Summary of main clinical results	Summary of PRO results
Seddon B et al., 2017 (GeDDiS)	36•4	Superiority	The proportion of patients alive and progression free at 24 weeks postrandomisation	Secondary	EORTC QLQ-C30, Fatigue-specific FA-13 questionnaires, ED-5D	Doxorubicin (D) vs gemcitabine plus docetaxel (G+T)	All types	257	132	The proportion of patients alive and progression free at 24 weeks did not differ between treatment arms (D: 46·3% [95% CI 37·5–54·6] vs G+T: 46·4% [37·5–54·8]. Median PFS did not significantly differ (p=0.06).	No statistically significant differences between treatment groups at 12 weeks postrandomisation. Clinically meaningful differences for PRO domains were not defined.
Van Tine BA et al., 2022 (ANNOUNCE)	0•9	Superiority	OS	Secondary	EORTC QLQ-C30, mBPI-sf	Doxorubicin plus olaratumab (D+O) vs doxorubicin plus placebo (D)	All types	509	460	OS did not significantly differ between treatment arms (D+O: median 20•4 mo; D: 19•7 mo; p=0•69)	PROs data were described overall and by cumulative dose of doxorubicin received. PROs were not compared between treatment arms. Overall, there was a rapid (time until first worsening: range 0•9–2•1 months) worsening (change of ≥10 points) for the domains of fatigue, nausea/vomiting, physical function, mean health status. Median time to first worsening of pain was 7•9 months.
Younger E et al., 2020 (SARC021)	2•8	Superiority	OS	Exploratory	EQ-VAS, EQ-5D-5 L	Doxorubicine (D) vs doxorubicine plus evofosfamide (D+E)	All types	640	188	OS did not significantly differ between treatment arms (D: median 19•0 mo [95% CI 16•2–22•4] vs D+E: 18•4 mo [95% CI 15•6–22•1]).	PROs were only compared between older patients and patients <65 years. Patients aged <65 years had a statistically significantly worse anxiety/depression score at baseline compared with older patients (p = 0•004). There were no differences in EQ-VAS scores between both age groups. Clinically meaningful differences for PRO domains were not defined.
Hudgens S et al., 2017	0•9	Superiority	OS	Exploratory	EORTC QLQ-C30, EQ-5D	Eribuline mesilate vs dacarbazine	Liposarcoma, leiomyosarcoma	454	442	OS was significantly higher in the eribulin arm (median 13·5 vs 11·5 mo; p=0·0169).	No statistical significant differences between treatment arms at baseline. Of the 399 patients with disease progression, patients treated with dacarbazine had statistically significantly worse scores for Global Health Status, Physical Functioning, Nausea and Vomiting, Insomnia, and Appetite loss (all differences ≤10 points).
Somaiah N et al., 2021	6•9	Non-comparative	PFS and toxicity	Secondary	EORTC QLQ-C30	Gemcitabine plus docetaxel (G+T) vs gemcitabine plus pazopanib (G+P)	All types	90	Not reported	Median PFS did not significantly differ between treatment arms (4•1 mo for each arm, p=0•3). The rate of related grade ≥3 AEs was 82% for the G+T arm and 78% for the G+P arm. No significant difference in OS (G+T: median 15•9 [95% CI 9•2–24•2] vs G+P: 12•4 mo [95% CI 8•8–21•8]).	In the G+P arm nausea and vomiting scores significantly improved over time (p=0•0001). Scores in the G+T group remained stable over time. For fatigue, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial stress there were no differences between treatment arms. Clinically meaningful differences for PRO domains were not defined.

(*continued on next page*)

Table 4 (*continued*)

Author	Journal impact factor	Study design	Primary endpoint	PRO endpoint	PRO instrument	Treatment	Histological subtype of STS	Overall sample size	Baseline PRO sample size	Summary of main clinical results	Summary of PRO results
Coens C et al., 2015 (PALETTE)	6•2	Superiority	PFS	Secondary	EORTC QLQ-C30	Pazopanib vs placebo	All types	369	347	Median PFS was 4·6 mo for pazopanib compared with 1.6 mo for placebo (p<0·0001). OS 12.5 mo with pazopanib vs 10·7 mo with placebo (p=0•25).	Statistically and clinically significantly worse symptom scores for diarrhea, loss of appetite, nausea/vomiting, and fatigue In the pazopanib arm. No significant differences for global health or function scales between treatment arms. Overall, pazopanib was not associated with an improvement in PROs.
Grunwald V et al., 2020	50•7	Non-inferiority	PFS	Secondary	EORTC QLQ-C30, EORTC QLQ-ELD14	Pazopanib vs doxorubicin	Chemotherapy-sensitive STS subtypes	120	Completion rate for baseline >90%	PFS was noninferior (Pazopanib: median 4·4 mo [95% CI 2·7–6·0]; doxorubicin: median 5·3 [95% CI 1·7–8·2]). OS did not significantly differ between treatment arms (Pazopanib: 12·3 mo vs doxorubicin: 14·3 mo; p=0•7350).	Only baseline PRO results were reported. No significant differences for the domains of the EORTC QLQ-C30 and EORTC QLQ-ELD14 between treatment arms. Clinically meaningful differences for PRO domains were not defined.
Schmoll HJ et al., 2021	31•8	Superiority	PFS rate at 12 weeks	Secondary	EORTC QLQ-C30	Pazopanib plus gemcitabine (P+G) vs pazopanib	All types	90	73	PFS rate at 12 weeks was significantly higher in the P+G arm (74% vs 47%, p = 0•01). No significant difference for OS (13·1 mo vs 11·2 mo, p=0•83).	Only descriptive analysis for PROs. PROs were similar (differences <10 points) for both treatment arms, except for fatigue, with worse scores over time in the combination arm (scores in the pazopanib only arm remained stable). Clinically meaningful differences for PRO domains were not defined.
Gounder M et al., 2021	3•7	Superiority	PFS	Secondary	EORTC QLQ-C30	Selinexor vs placebo	Dedifferentiated liposarcoma	285	255	PFS was significantly longer with selinexor vs placebo (median PFS 2•8 v 2•1 mo p=0•011). No significant difference for OS (median 10·0 vs 12·9 mo, p=0·54).	Over time pain scores worsened for placebo vs selinexor across all visits (differences were not statistically significant for all visits). For other domains scores did not significantly differ between arms, however scores worsened over time. Intermediate value of 10 points was selected as the meaningful change threshold for all EORTC QLQ-C30 scales.
Le Cesne A et al., 2021 (T-SAR)	51•8	Superiority	PFS	Secondary	EORTC QLQ-C30	Trabectedin vs BSC	All types	103	92	Median PFS was significantly higher in the trabectedin arm (3•1 months vs 1•5 months, p < 0•001). There was no significant difference for OS (13·6 vs 10·8, p=0•87).	No statistical differences in PROs between the arms at any time point. Clinically meaningful differences for PRO domains were not defined.

RCT=randomized clinical trial; PRO=patient reported outcome; STS=soft tissue sarcoma; OS=overall survival; PFS=progression free survival; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Questionnaire Core-30; EQ-VAS=EQ visual analogue scale; mBPI-sf=modified Brief Pain inventory-short form; BSC=best supportive care.

3.4. Adherence to CONSORT PRO recommendations

Table 5 summarizes the quality of PRO reporting according to the CONSORT PRO extension. Some items were reported frequently; the statement of the person completing the PRO measure (7/10 RCTs), the number of questionnaires available at baseline and at the time of PRO analysis (8/10 RCTs), estimate of precision (e.g. confidence interval) (9/10 RCTs). Other items were poorly documented; identification of PROs as a primary/secondary endpoint in the abstract (3/10); presence of a PRO hypothesis (2/10 RCTs), specification of PRO domains in the hypothesis (0/10 RCTs); the mode of administration of questionnaires (1/10 RCTs, i.e. paper); reporting of the approach for dealing with missing data (4/10 RCTs); provision of PRO study limitations (4/10 RCTs), discussion of generalizability of PRO results (3/10 RCTs); interpretation of PROs in relation to clinical outcomes (4/10 RCTs). The median adherence score for the CONSORT PRO extension was 5.5/14 (range 2/14–11/14). The adherence score was higher in publications focusing exclusively on PROs (11/14, 10/14, 11/14 and 11/14) (Van Tine et al., 2022; Hudgens et al., 2017; Coens et al., 2015; Gounder et al., 2021).

4. Discussion

This is the first systematic review evaluating the use of PROs and PRO reporting in RCTs in STS patients. Our results show that PROs were infrequently included in phase II-III RCTs in STS patients with advanced disease. Our data show a lower frequency of PRO inclusion in RCTs for advanced STS patients, compared to a previous systematic review of phase III RCTs in all solid tumors, published between 2012 and 2016, which showed that HRQoL was included as a primary or secondary endpoint in 53% of RCTs (236/446) (Marandino et al., 2018). Furthermore, these data were often under-reported, subject to delay in publication, and of poor quality according to CONSORT standards. Although many treatments that were evaluated in these RCTs were considered or approved for use in clinical practice, there was a paucity of data related to the impact of these drugs on HRQoL.

Over recent years a more patient-centered approach is being applied in oncology research and for drug regulation, recognizing the importance of incorporating PROs in cancer research (FDA, 2020, 2022a, 2022b; Bottomley et al., 2009). This evolution is demonstrated in our results, as 57% of RCTs conducted after 2015 including a PRO endpoint, whereas none of the RCTs conducted before 2015 included a PRO endpoint. Nevertheless, only 10/43 RCTs publications (23%) reported PRO results. This may be due to the lack of validated PRO instruments for sarcoma (den Hollander et al., 2020a) and the cost associated with developing, measuring and analyzing PROs. Furthermore, in many RCTs, PFS is used as a surrogate endpoint for OS, and sometimes even as a surrogate endpoint for HRQoL (Del Muro et al., 2009; Maki et al., 2007). However, HRQoL is influenced by other factors (e.g. adverse events) and to date there is insufficient evidence for an association between HRQoL and PFS (Del Muro et al., 2009; Jones et al., 2019a). Moreover, endpoints of interest to researchers, sponsors and physicians might not align with those of the patients (Hensley et al., 2015). For example, a study in STS patients starting with palliative chemotherapy showed that 57% of patients prioritized length of life or valued length of life and QoL equally (Somaiah et al., 2021). However, in our systematic review, PROs were only reported in 50% (7/14) of RCTs with a positive primary endpoint.

Transparent reporting of PROs is crucial to guide the clinical decision-making process. Despite development of the CONSORT PRO extension in 2013 and all publications reporting PROs being published from 2015 onward, quality of PRO reporting was disappointedly low (Calvert et al., 2013). Multiple factors explain the low quality of PRO reporting. Soft tissue sarcomas are a heterogeneous group of tumors and PROs are influenced by several factors, such as the sarcoma subtype, location and treatment (den Hollander et al., 2020a; Davidson et al., 2016; Eichler et al., 2020). Most RCTs that reported PROs, used generic HRQoL questionnaires (i.e. EORTC QLQ-C30). However, these questionnaires are not disease-specific and might not capture all HRQoL aspects relevant to sarcoma patients. These limitations might be overcome by a flexible strategy that is being developed by the EORTC, where validated EORTC items from existing tumor-, site-, or population-specific modules are combined in the EORTC Item Library, which can be used to create item lists for sarcoma trials (Bootsma, 2022; den Hollander et al., 2020b). This method was used recently by Barrett et al. (2023) to assess patient-reported pain and fatigue in STS patients (Barrett et al., 2023). Additionally, this method allows to compare PROs between a variety of cancer types. Another key factor for the low quality of PRO reporting could be the fact that PROs were only included as secondary endpoints, meaning that PRO results are reported together with the primary outcome results and leaving limited room for PRO reporting. This theory is supported by higher CONSORT PRO adherence scores observed in publications focusing exclusively on PROs. Furthermore, PRO results have to be interpreted with caution as only 2 RCTs included the PRO hypothesis (without specifying the PRO domains) and in most RCTs clinically meaningful changes were not defined.

In this systematic review, 15/43 (35%) RCTs had a PRO endpoint. In four of these RCTs, with primary results published between 2015 and 2021, PRO results have not been published. We were not able to obtain additional information about PRO results after contacting the authors of these RCTs. This raises the question of whether collecting PROs in RCTs is ethical, if the data are never made available then patients may have completed questionnaires in vain. Lidington et al. (2022) indicated that omission of PRO results might be linked to missing data (Lidington et al., 2022). Missing data can introduce bias, as poor health status could be one of the reasons for dropping out of the study. Concerns have been raised about the patient burden when collecting PROs (FDA, 2020, 2022a, 2022b; EMA, 2016), emphasizing the need for a PRO study design that balances the need for sufficient PRO data with patient's capacity to complete HRQoL questionnaires. The use of electronic questionnaires could possibly reduce the burden and minimize missing data (Rebecca et al., 2016).

Aside from the low quality of PRO reporting, interpretation of PRO results is limited by the publication strategy. Secondary publications reporting PROs were typically published in a different journal to the primary publication, with a lower impact factor (range 0.9–6.2). There was also significant delay between the publication with the primary results and the publication reporting PROs. Therefore, PRO results might not reach the target audience and this may restrict the comprehensive evaluation of the net clinical treatment benefit; determined by survival data and HRQoL impact. These findings align with systematic reviews in other tumor types (Mercieca-Bebber et al., 2016; Dirven et al., 2014). We suggest that PROs should be included as an exploratory or co-primary endpoint (along with survival data) and preferably be published in the primary publication or in an extensive data supplement of the primary publication. Alternatively, PRO results could be published in a secondary publication within a reasonable timeframe, preferably in the same journal as the primary publication.

Consistent and clear PRO reporting enables patients and physicians to make more informed treatment decisions and could improve patient care. To achieve this, a shift is needed regarding RCT design, drug approval processes, communication of RCT results and delivery of care. Therefore, in 2023 the Common Sense Oncology (CSO) movement was created, consisting of oncologists, researchers and patient advocates (Booth et al., 2023). The CSO focuses on three principles: evidence generations, evidence interpretation and evidence communication and its primary goal is to ensure patient-centered clinical care.

A key strength of this review is that we included RCTs regardless of PRO endpoints, allowing us to report the prevalence of RCTs including PROs. Also we reported the time interval between primary and secondary publication(s) and we included RCTs published in a broad time interval, between January 2000 – August 2022.

This study has some limitations. Search results were only screened by

Table 5
Quality of PROs according to the CONSORT PRO extension.

		Seddon et al.	Van Tine et al.	Younger et al.	Hudgens et al.	Somaiah et al.	Coens et al.	Grunwald et al.	Schmoll et al.	Gounder et al.	Le Cesne et al.	**Total number of RCTs adhering to each item *n* (%)**
Item of CONSORT PRO extension	score											
PRO noted as primary/secondary endpoint in the abstract												
Yes	1				■				■	■		3 (30%)
PRO mentioned but unclear endpoint status	0.5		■					■			■	3 (30%)
Background and rationale for including PROs	1		■		■		■			■	■	5 (50%)
PRO hypothesis present	0.5				■		■					2 (20%)
PRO domains specified in hypothesis	0.5											0 (0%)
Evidence of PRO instrument validity provided/cited[a]	1		■		■		■	■		■	■	6 (60%)
Statement of the person completing the PRO measure (e.g. 'patients completed', or 'self-report')	0.5		■	■	■	■	■	■		■		7 (70%)
Mode of administration specified (e.g. paper, e-PRO)	0.5							■				1 (10%)
Statistical approach for dealing with missing data specified (e.g. imputation, omission of cases with missing data)	1		■				■	■		■		4 (40%)
Report number of questionnaires submitted/available for analysis at baseline	0.5		■	■	■		■	■	■	■	■	8 (80%)
Report number of questionnaires submitted/available for analysis principle timepoint for PRO analysis	0.5	■	■	■	■		■		■	■	■	8 (80%)
Table including baseline PRO findings	1	■			■		■	■		■		5 (50%)
Number of patients (denominator) included in each PRO analysis and whether this was intention to treat	1	■	■		■		■			■		5 (50%)
PRO results reported for the hypothesized domains and time point specified in the hypothesis –OR- reported for each domain of the PROM if no PRO hypothesis provided	0.5	■	■		■		■	■				5 (50%)
Results include confidence intervals, effect size or some other estimate of precision	0.5	■	■	■	■	■	■	■		■	■	9 (90%)
Results of any subgroup/adjusted/exploratory analyses are reported	1		■		■	■	■			■		5 (50%)
PRO study limitations provided	1		■	■			■			■		4 (40%)
Implications of PRO results for generalizability, use in clinical practice	1		■	■	■							3 (30%)
PROs interpreted in relation to clinical outcomes	1		■				■			■	■	4 (40%)
Total CONSORT PRO score[b]	14	3.5	11	4	10	2	11	6	2	11	5	

PRO=patient reported outcome; CONSORT=Consolidated Standards of Reporting Trials.
Studies using multiple PRO instruments were also rated as "using PRO validated instruments" if at least one of the PRO instruments used was validated.
As none of the RCTs had PROs as a primary outcome and none of the RCTs used PROs for trial stratification the maximum achievable score for the checklist was 14.

one single reviewer. We decided to include only RCTs with more than 50 participants, as this sample size is required for robust multivariate or longitudinal analyses of quality of life data. However, we recognize that this threshold may be perceived as arbitrary and could potentially exclude relevant studies with smaller sample sizes. Despite the extensive search strategy and the use of multiple databases it is possible that some studies have been missed. Due to the heterogeneity of the RCTs, risk of bias was not analyzed. Therefore, we could not assess a possible relation between the risk of bias and the quality of PRO reporting. Additionally, we did not compare the published RCT endpoints and methods with the protocol, but we did screen CT.gov for additional (PRO) endpoints.

5. Conclusion

HRQoL is a critical aspect in patients with advanced STS, however our review showed that the majority of RCTs conducted thus far in these patients did not include HRQoL or other types of PROs as an endpoints. Despite the availability of clear guidelines for reporting PROs the quality of PRO reporting is still poor. Future RCTs should routinely include PRO endpoints and report high-quality PROs to enable physicians, patients and regulators to more comprehensively evaluate the potential benefits of new treatment options for patients with STS.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2024.104345.

References

Amankwah, E.K., Conley, A.P., Reed, D.R., 2013. Epidemiology and therapies for metastatic sarcoma. Clin. Epidemiol. 5, 147–162.

Barrett, L., Elliott, E., Voorhaar, M., Ingelgård, A., Griebsch, I., Wong, B., et al., 2023. A mixed-methods study to better measure patient-reported pain and fatigue in soft tissue sarcoma. Oncol. Ther. 11 (1), 129–143.

Benjamin, R.S., Wiernik, P.H., Bachur, N.R., 1975. Adriamycin: a new effective agent in the therapy of disseminated sarcomas. Med. Pedia Oncol. 1 (1), 63–76.

Berry, V., Basson, L., Bogart, E., Mir, O., Blay, J.Y., Italiano, A., et al., 2017. REGOSARC: regorafenib versus placebo in doxorubicin-refractory soft-tissue sarcoma-a quality-adjusted time without symptoms of progression or toxicity analysis. Cancer 123 (12), 2294–2302.

Blay, J.Y., Casali, P., Nieto, A., Tanovic, A., Le Cesne, A., 2014. Efficacy and safety of trabectedin as an early treatment for advanced or metastatic liposarcoma and leiomyosarcoma. Future Oncol. 10 (1), 59–68.

Blay, J.Y., Papai, Z., Tolcher, A.W., Italiano, A., Cupissol, D., Lopez-Pousa, A., et al., 2015. Ombrabulin plus cisplatin versus placebo plus cisplatin in patients with advanced soft-tissue sarcomas after failure of anthracycline and ifosfamide chemotherapy: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 16 (5), 531–540.

Blay, J.Y., Schoffski, P., Bauer, S., Krarup-Hansen, A., Benson, C., D'Adamo, D.R., et al., 2019. Eribulin versus dacarbazine in patients with leiomyosarcoma: subgroup analysis from a phase 3, open-label, randomised study. Br. J. Cancer 120 (11), 1026–1032.

Booth, C.M., Sengar, M., Goodman, A., Wilson, B., Aggarwal, A., Berry, S., et al., 2023. Common sense oncology: outcomes that matter. Lancet Oncol. 24 (8), 833–835.

Bootsma T. Assessing Health-related Quality of Life in Sarcoma Patients: clinicaltrials. gov; 2019 [updated January 6th 2022. Available from: ⟨https://classic.clinicaltrials.gov/ct2/show/NCT04071704⟩.

Bottomley, A., Jones, D., Claassens, L., 2009. Patient-reported outcomes: assessment and current perspectives of the guidelines of the food and drug administration and the reflection paper of the European medicines agency. Eur. J. Cancer 45 (3), 347–353.

Brodowicz, T., Mir, O., Wallet, J., Italiano, A., Blay, J.Y., Bertucci, F., et al., 2018. Efficacy and safety of regorafenib compared to placebo and to post-cross-over regorafenib in advanced non-adipocytic soft tissue sarcoma. Eur. J. Cancer 99, 28–36.

Brundage, M., Blazeby, J., Revicki, D., Bass, B., de Vet, H., Duffy, H., et al., 2013. Patient-reported outcomes in randomized clinical trials: development of ISOQOL reporting standards. Qual. Life Res. 22 (6), 1161–1175.

Bui-Nguyen, B., Butrynski, J.E., Penel, N., Blay, J.Y., Isambert, N., Milhem, M., et al., 2015. 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 51 (10), 1312–1320.

Bui-Nguyen, B., Ray-Coquard, I., Chevreau, C., Penel, N., Bay, J.O., Coindre, J.M., et al., 2012. High-dose chemotherapy consolidation for chemosensitive advanced soft tissue sarcoma patients: an open-label, randomized controlled trial. Ann. Oncol. 23 (3), 777–784.

Calvert, M., Blazeby, J., Altman, D.G., Revicki, D.A., Moher, D., Brundage, M.D., 2013. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. Jama 309 (8), 814–822.

Calvert, M., Kyte, D., Mercieca-Bebber, R., Slade, A., Chan, A.W., King, M.T., et al., 2018. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: the SPIRIT-pro extension. Jama 319 (5), 483–494.

Cesne, A.L., Bauer, S., Demetri, G.D., Han, G., Dezzani, L., Ahmad, Q., et al., 2019. Safety and efficacy of pazopanib in advanced soft tissue sarcoma: PALETTE (EORTC 62072) subgroup analyses. BMC Cancer 19 (1), 794.

Le Cesne, A., Blay, J.Y., Cupissol, D., Italiano, A., Delcambre, C., Penel, N., et al., 2021. A randomized phase III trial comparing trabectedin to best supportive care in patients with pre-treated soft tissue sarcoma: T-SAR, a french sarcoma group trial. Ann. Oncol. 32 (8), 1034–1044.

Le Cesne, A., Judson, I., Crowther, D., Rodenhuis, S., Keizer, H.J., Van Hoesel, Q., et al., 2000. Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: a trial of the European organization for research and treatment of cancer/Soft tissue and bone sarcoma group. J. Clin. Oncol. 18 (14), 2676–2684.

Chawla, S.P., Papai, Z., Mukhametshina, G., Sankhala, K., Vasylyev, L., Fedenko, A., et al., 2015. First-line Aldoxorubicin vs doxorubicin in metastatic or locally advanced unresectable soft-tissue sarcoma: a phase 2b randomized clinical trial. JAMA Oncol. 1 (9), 1272–1280.

Chawla, S.P., Van Tine, B.A., Pollack, S.M., Ganjoo, K.N., Elias, A.D., Riedel, R.F., et al., 2022. Phase II randomized study of CMB305 and Atezolizumab compared with Atezolizumab alone in soft-tissue sarcomas expressing NY-ESO-1. J. Clin. Oncol. 40 (12), 1291–1300.

Cherny, N.I., Sullivan, R., Dafni, U., Kerst, J.M., Sobrero, A., Zielinski, C., et al., 2015. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European society for medical oncology magnitude of clinical benefit scale (ESMO-MCBS). Ann. Oncol. 26 (8), 1547–1573.

Coens, C., Pe, M., Dueck, A.C., Sloan, J., Basch, E., Calvert, M., et al., 2020. International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. Lancet Oncol. 21 (2), e83–e96.

Coens, C., van der Graaf, W.T., Blay, J.Y., Chawla, S.P., Judson, I., Sanfilippo, R., et al., 2015. Health-related quality-of-life results from PALETTE: a randomized, double-blind, phase 3 trial of pazopanib versus placebo in patients with soft tissue sarcoma whose disease has progressed during or after prior chemotherapy-a European Organization for research and treatment of cancer soft tissue and bone sarcoma group global network study (EORTC 62072). Cancer 121 (17), 2933–2941.

Coindre, J.M., Terrier, P., Guillou, L., Le Doussal, V., Collin, F., Ranchère, D., et al., 2001. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of cancer centers sarcoma group. Cancer 91 (10), 1914–1926.

Cranmer, L.D., Lu, Y., Ballman, K.V., Loggers, E.T., Pollack, S., 2017. Toxicity and efficacy of bolus (BOL) versus continuous intravenous (CIV) dosing of doxorubicin (DOX) in soft tissue sarcoma (STS): post hoc analysis of a prospective randomized trial. J. Clin. Oncol. 35 (15).

Davidson, D., Barr, R.D., Riad, S., Griffin, A.M., Chung, P.W., Catton, C.N., et al., 2016. Health-related quality of life following treatment for extremity soft tissue sarcoma. J. Surg. Oncol. 114 (7), 821–827.

Demetri, G.D., Chawla, S.P., von Mehren, M., Ritch, P., Baker, L.H., Blay, J.Y., et al., 2009. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. J. Clin. Oncol. 27 (25), 4188–4196.

Demetri, G.D., Le Cesne, A., Chawla, S.P., Brodowicz, T., Maki, R.G., Bach, B.A., et al., 2012. First-line treatment of metastatic or locally advanced unresectable soft tissue sarcomas with conatumumab in combination with doxorubicin or doxorubicin alone: a phase I/II open-label and double-blind study. Eur. J. Cancer 48 (4), 547–563.

Demetri, G.D., Schoffski, P., Grignani, G., Blay, J.Y., Maki, R.G., Van Tine, B.A., et al., 2017. Activity of eribulin in patients with advanced liposarcoma demonstrated in a subgroup analysis from a randomized phase III study of eribulin versus dacarbazine. J. Clin. Oncol. 35 (30), 3433–3439.

Demetri, G.D., von Mehren, M., Jones, R.L., Hensley, M.L., Schuetze, S.M., Staddon, A., et al., 2016. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. J. Clin. Oncol. 34 (8), 786–793.

Dirven, L., Taphoorn, M.J., Reijneveld, J.C., Blazeby, J., Jacobs, M., Pusic, A., et al., 2014. The level of patient-reported outcome reporting in randomised controlled trials of brain tumour patients: a systematic review. Eur. J. Cancer 50 (14), 2432–2448.

Efficace, F., Feuerstein, M., Fayers, P., Cafaro, V., Eastham, J., Pusic, A., et al., 2014a. Patient-reported outcomes in randomised controlled trials of prostate cancer: methodological quality and impact on clinical decision making. Eur. Urol. 66 (3), 416–427.

Efficace, F., Rees, J., Fayers, P., Pusic, A., Taphoorn, M., Greimel, E., et al., 2014b. Overcoming barriers to the implementation of patient-reported outcomes in cancer clinical trials: the PROMOTION registry. Health Qual. Life Outcomes 12, 86.

Eichler, M., Hentschel, L., Richter, S., Hohenberger, P., Kasper, B., Andreou, D., et al., 2020. The health-related quality of life of sarcoma patients and survivors in Germany-Cross-Sectional results of a nationwide observational study (PROSa). Cancers 12 (12).

EMA. Regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products - Scientific guideline 2005 [Available from: ⟨https://www.ema.europa.eu/en/regulatory-guidance-use-health-related-quality-life-hrql-measures-evaluation-medicinal-products⟩.

EMA. Appendix 2 to the Guideline on the Evaluation of Anticancer Medicinal Products in Man—the Use of Patient-reported Outcome (PRO) Measures in Oncology Studies (European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP)). 2016.

EMA. Reflection paper on the pharmaceutical development of medicines for use in the older population 2020 [Available From: ⟨https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-pharmaceutical-development-medicines-use-older-population-first-version_en.pdf⟩.

Eroglu, Z., Tawbi, H.A., Hu, J., Guan, M., Frankel, P.H., Ruel, N.H., et al., 2015. A randomised phase II trial of selumetinib vs selumetinib plus temsirolimus for soft-tissue sarcomas. Br. J. Cancer 112 (10), 1644–1651.

Fayette, J., Penel, N., Chevreau, C., Blay, J.Y., Cupissol, D., Thyss, A., et al., 2009. Phase III trial of standard versus dose-intensified doxorubicin, ifosfamide and dacarbazine (MAID) in the first-line treatment of metastatic and locally advanced soft tissue sarcoma. Invest N. Drugs 27 (5), 482–489.

FDA. Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims 2009 [Available from: ⟨https://www.fda.gov/media/77832/download⟩.

FDA. Patient-focused drug development: collecting comprehensive and representative input.2020. Available from: ⟨https://www.fda.gov/media/139088/downloadg⟩.

FDA. Patient-focused drug development: methods to identify what is important to patients. 2022a.

FDA. Patient-focused drug development: selecting, developing, or modifying Fit-for Purpose clinical outcome assessments. 2022b. 2022.

Gelderblom, H., Blay, J.Y., Seddon, B.M., Leahy, M., Ray-Coquard, I., Sleijfer, S., et al., 2014. Brostallicin versus doxorubicin as first-line chemotherapy in patients with advanced or metastatic soft tissue sarcoma: an European organisation for research and treatment of cancer soft tissue and bone sarcoma group randomised phase II and pharmacogenetic study. Eur. J. Cancer 50 (2), 388–396.

Gough, N.J., Smith, C., Ross, J.R., Riley, J., Judson, I., 2011. Symptom burden, survival and palliative care in advanced soft tissue sarcoma. Sarcoma 2011, 325189.

Gounder, M., Abdul Razak, A.R., Gilligan, A.M., Leong, H., Ma, X., Somaiah, N., et al., 2021. Health-related quality of life and pain with selinexor in patients with advanced dedifferentiated liposarcoma. Future Oncol. 17 (22), 2923–2939.

Gounder, M.M., Razak, A.A., Somaiah, N., Chawla, S., Martin-Broto, J., Grignani, G., et al., 2022. Selinexor in advanced, metastatic dedifferentiated liposarcoma: a multinational, randomized, double-blind, placebo-controlled trial. J. Clin. Oncol. 40 (22), 2479–2490.

van der Graaf, W.T., Blay, J.Y., Chawla, S.P., Kim, D.W., Bui-Nguyen, B., Casali, P.G., et al., 2012. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 379 (9829), 1879–1886.

Gronchi, A., Miah, A.B., Dei Tos, A.P., Abecassis, N., Bajpai, J., Bauer, S., et al., 2021. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS clinical practice guidelines for diagnosis, treatment and follow-up(☆). Ann. Oncol. 32 (11), 1348–1365.

Grunwald, V., Karch, A., Schuler, M., Schoffski, P., Kopp, H.G., Bauer, S., et al., 2020. Randomized comparison of pazopanib and doxorubicin as first-line treatment in patients with metastatic soft tissue sarcoma age 60 years or older: results of a German intergroup study. J. Clin. Oncol. 38 (30), 3555–3564.

Harris, P.A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., Conde, J.G., 2009. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J. Biomed. Inf. 42 (2), 377–381.

Hartmann, J.T., Kopp, H.G., Gruenwald, V., Piperno-Neumann, S., Kunitz, A., Hofheinz, R., et al., 2020. Randomised phase II trial of trofosfamide vs. doxorubicin in elderly patients with untreated metastatic soft-tissue sarcoma. Eur. J. Cancer 124, 152–160.

Van Hemelrijck, M., Sparano, F., Josephs, D., Sprangers, M., Cottone, F., Efficace, F., 2019. Patient-reported outcomes in randomised clinical trials of bladder cancer: an updated systematic review. BMC Urol. 19 (1), 86.

Hensley, M.L., Miller, A., O'Malley, D.M., Mannel, R.S., Behbakht, K., Bakkum-Gamez, J. N., et al., 2015. Randomized phase III trial of gemcitabine plus docetaxel plus bevacizumab or placebo as first-line treatment for metastatic uterine leiomyosarcoma: an NRG Oncology/Gynecologic oncology group study. J. Clin. Oncol. 33 (10), 1180–1185.

Hensley, M.L., Patel, S.R., von Mehren, M., Ganjoo, K., Jones, R.L., Staddon, A., et al., 2017. Efficacy and safety of trabectedin or dacarbazine in patients with advanced uterine leiomyosarcoma after failure of anthracycline-based chemotherapy: subgroup analysis of a phase 3, randomized clinical trial. Gynecol. Oncol. 146 (3), 531–537.

den Hollander, D., Fiore, M., Martin-Broto, J., Kasper, B., Casado Herraez, A., Kulis, D., et al., 2020b. Incorporating the patient voice in sarcoma research: how can we assess health-related quality of life in this heterogeneous group of patients? A study protocol. Cancers 13 (1).

den Hollander, D., Van der Graaf, W.T.A., Fiore, M., Kasper, B., Singer, S., Desar, I.M.E., et al., 2020a. Unravelling the heterogeneity of soft tissue and bone sarcoma patients' health-related quality of life: a systematic literature review with focus on tumour location. ESMO Open 5 (5), e000914.

Hudgens, S., Forsythe, A., Kontoudis, I., D'Adamo, D., Bird, A., Gelderblom, H., 2017. Evaluation of quality of life at progression in patients with soft tissue sarcoma. Sarcoma 2017, 2372135.

Italiano, A., Mathoulin-Pelissier, S., Cesne, A.L., Terrier, P., Bonvalot, S., Collin, F., et al., 2011. Trends in survival for patients with metastatic soft-tissue sarcoma. Cancer 117 (5), 1049–1054.

Jones, R.L., Chawla, S.P., Attia, S., Schoffski, P., Gelderblom, H., Chmielowski, B., et al., 2019a. A phase 1 and randomized controlled phase 2 trial of the safety and efficacy of the combination of gemcitabine and docetaxel with ontuxizumab (MORAb-004) in metastatic soft-tissue sarcomas. Cancer 125 (14), 2445–2454.

Jones, R.L., Demetri, G.D., Schuetze, S.M., Milhem, M., Elias, A., Van Tine, B.A., et al., 2018. Efficacy and tolerability of trabectedin in elderly patients with sarcoma: subgroup analysis from a phase III, randomized controlled study of trabectedin or dacarbazine in patients with advanced liposarcoma or leiomyosarcoma. Ann. Oncol. 29 (9), 1995–2002.

Jones, R.L., Maki, R.G., Patel, S.R., Wang, G., McGowan, T.A., Shalaby, W.S., et al., 2019b. Safety and efficacy of trabectedin when administered in the inpatient versus outpatient setting: clinical considerations for outpatient administration of trabectedin. Cancer 125 (24), 4435–4441.

Judson, I., Radford, J.A., Harris, M., Blay, J.Y., van Hoesel, Q., le Cesne, A., et al., 2001. Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC soft tissue and bone sarcoma group. Eur. J. Cancer 37 (7), 870–877.

Judson, I., Verweij, J., Gelderblom, H., Hartmann, J.T., Schoffski, P., Blay, J.Y., et al., 2014. 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. 15 (4), 415–423.

Kyte, D., Retzer, A., Ahmed, K., Keeley, T., Armes, J., Brown, J.M., et al., 2019. Systematic evaluation of patient-reported outcome protocol content and reporting in cancer trials. J. Natl. Cancer Inst. 111 (11), 1170–1178.

Lefebvre C. Cochrane Handbook for Systematic Reviews of Interventions version 6.3. 2022. Available from: ⟨www.training.cochrane.org/handbook⟩.

Lidington, E., Hogan, H., Gandolfi, A., Lawrence, J., Younger, E., Cho, H., et al., 2022. Assessing the collection and reporting of patient-reported outcome data in interventional cancer trials: a single institution, retrospective systematic evaluation. J. Patient-Rep. Outcomes 6 (1), 128.

Lorigan, P., Verweij, J., Papai, Z., Rodenhuis, S., Le Cesne, A., Leahy, M.G., et al., 2007. Phase III trial of two investigational schedules of ifosfamide compared with standard-dose doxorubicin in advanced or metastatic soft tissue sarcoma: a European organisation for research and treatment of cancer soft tissue and bone sarcoma group study. J. Clin. Oncol. 25 (21), 3144–3150.

Di Maio, M., Basch, E., Bryce, J., Perrone, F., 2016. Patient-reported outcomes in the evaluation of toxicity of anticancer treatments. Nat. Rev. Clin. Oncol. 13 (5), 319–325.

Maki, R.G., Wathen, J.K., Patel, S.R., Priebat, D.A., Okuno, S.H., Samuels, B., et al., 2007. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 corrected. J. Clin. Oncol. 25 (19), 2755–2763.

Marandino, L., De Luca, E., Zichi, C., Lombardi, P., Reale, M.L., Pignataro, D., et al., 2019. Quality-of-life assessment and reporting in prostate cancer: systematic review of phase 3 trials testing anticancer drugs published between 2012 and 2018. Clin. Genitourin. Cancer 17 (5), 332–347 e2.

Marandino, L., La Salvia, A., Sonetto, C., De Luca, E., Pignataro, D., Zichi, C., et al., 2018. Deficiencies in health-related quality-of-life assessment and reporting: a systematic review of oncology randomized phase III trials published between 2012 and 2016. Ann. Oncol. 29 (12), 2288–2295.

Martin-Broto, J., Pousa, A.L., de Las Penas, R., Garcia Del Muro, X., Gutierrez, A., Martinez-Trufero, J., et al., 2016. Randomized phase II study of trabectedin and doxorubicin compared with doxorubicin alone as first-line treatment in patients with advanced soft tissue sarcomas: a spanish group for research on sarcoma study. J. Clin. Oncol. 34 (19), 2294–2302.

Maurel, J., Lopez-Pousa, A., de Las Penas, R., Fra, J., Martin, J., Cruz, J., et al., 2009. Efficacy of sequential high-dose doxorubicin and ifosfamide compared with standard-dose doxorubicin in patients with advanced soft tissue sarcoma: an open-label randomized phase II study of the Spanish group for research on sarcomas. J. Clin. Oncol. 27 (11), 1893–1898.

Mercieca-Bebber, R., Aiyegbusi, O.L., King, M.T., Brundage, M., Snyder, C., Calvert, M., 2022. Knowledge translation concerns for the CONSORT-PRO extension reporting guidance: a review of reviews. Qual. Life Res. 31 (10), 2939–2957.

Mercieca-Bebber, R.L., Perreca, A., King, M., Macann, A., Whale, K., Soldati, S., et al., 2016. Patient-reported outcomes in head and neck and thyroid cancer randomised controlled trials: a systematic review of completeness of reporting and impact on interpretation. Eur. J. Cancer 56, 144–161.

Mir, O., Brodowicz, T., Italiano, A., Wallet, J., Blay, J.Y., Bertucci, F., et al., 2016. Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma (REGOSARC): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol. 17 (12), 1732–1742.

Del Muro, X.G., Fra, J., Lopez Pousa, A., Maurel, J., Martín, J., Martínez Trufero, J., et al., 2009. Randomized phase II study of dacarbazine plus gemcitabine versus DTIC alone in patients with advanced soft tissue sarcoma: a Spanish group for research on sarcomas (GEIS) study. J. Clin. Oncol. 27 (15), 10529.

van Oosterom, A.T., Mouridsen, H.T., Nielsen, O.S., Dombernowsky, P., Krzemieniecki, K., Judson, I., et al., 2002. Results of randomised studies of the EORTC Soft tissue and bone sarcoma group (STBSG) with two different ifosfamide regimens in first- and second-line chemotherapy in advanced soft tissue sarcoma patients. Eur. J. Cancer 38 (18), 2397–2406.

Oosting, S.F., Barriuso, J., Bottomley, A., Galotti, M., Gyawali, B., Kiesewetter, B., et al., 2023. Methodological and reporting standards for quality-of-life data eligible for European society for medical oncology-magnitude of clinical benefit scale (ESMO-MCBS) credit. Ann. Oncol. 34 (4), 431–439.

Ouzzani, M., Hammady, H., Fedorowicz, Z., Elmagarmid, A., 2016. Rayyan—a web and mobile app for systematic reviews. Syst. Rev. 5 (1), 210.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., et al., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 372, n71.

Patel, S., von Mehren, M., Reed, D.R., Kaiser, P., Charlson, J., Ryan, C.W., et al., 2019. Overall survival and histology-specific subgroup analyses from a phase 3, randomized controlled study of trabectedin or dacarbazine in patients with advanced liposarcoma or leiomyosarcoma. Cancer 125 (15), 2610–2620.

Pautier, P., Italiano, A., Piperno-Neumann, S., Chevreau, C., Penel, N., Firmin, N., et al., 2022. Doxorubicin alone versus doxorubicin with trabectedin followed by trabectedin alone as first-line therapy for metastatic or unresectable leiomyosarcoma (LMS-04): a randomised, multicentre, open-label phase 3 trial. Lancet Oncol. 23 (8), 1044–1054.

Pe, M., Dorme, L., Coens, C., Basch, E., Calvert, M., Campbell, A., et al., 2018. Statistical analysis of patient-reported outcome data in randomised controlled trials of locally advanced and metastatic breast cancer: a systematic review. Lancet Oncol. 19 (9), e459–e469.

Ray-Coquard, I.L., Domont, J., Tresch-Bruneel, E., Bompas, E., Cassier, P.A., Mir, O., et al., 2015. Paclitaxel given once per week with or without bevacizumab in patients with advanced angiosarcoma: a randomized phase II trial. J. Clin. Oncol. 33 (25), 2797–2802.

Rebecca, M.-B., Michael, J.P., Michael, B., Melanie, C., Martin, R.S., Madeleine, T.K., 2016. Design, implementation and reporting strategies to reduce the instance and impact of missing patient-reported outcome (PRO) data: a systematic review. BMJ Open 6 (6), e010938.

Rees, J.R., Whale, K., Fish, D., Fayers, P., Cafaro, V., Pusic, A., et al., 2015. Patient-reported outcomes in randomised controlled trials of colorectal cancer: an analysis determining the availability of robust data to inform clinical decision-making. J. Cancer Res. Clin. Oncol. 141 (12), 2181–2192.

Ryan, C.W., Schoffski, P., Merimsky, O., Agulnik, M., Blay, J.Y., Schuetze, S.M., et al., 2013. PICASSO 3: a phase 3 international, randomized, double-blind, placebo-controlled study of doxorubicin (dox) plus palifosfamide (pali) vs. dox plus placebo for patients (pts) in first-line for metastatic soft tissue sarcoma (mSTS). Eur. J. Cancer 49, S876.

Schmoll, H.J., Lindner, L.H., Reichardt, P., Heissner, K., Kopp, H.G., Kessler, T., et al., 2021. Efficacy of pazopanib with or without gemcitabine in patients with anthracycline- and/or Ifosfamide-refractory soft tissue sarcoma: final results of the PAPAGEMO phase 2 randomized clinical trial. JAMA Oncol. 7 (2), 255–262.
Schoffski, P., Chawla, S., Maki, R.G., Italiano, A., Gelderblom, H., Choy, E., et al., 2016. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet 387 (10028), 1629–1637.
Schöffski, P., Choy, E., Le Cesne, A., Camargo, V., Bauer, S., Young Rha, S., et al., 2016. Phase (ph) 3 study of eribulin (ERI) vs dacarbazine (DTIC) in leiomyosarcoma (LMS) and liposarcoma (LPS) patients (pts). Ann. Oncol. 27, vii74.
Schoffski, P., Toulmonde, M., Estival, A., Marquina, G., Dudzisz-Sledz, M., Brahmi, M., et al., 2021. Randomised phase 2 study comparing the efficacy and safety of the oral tyrosine kinase inhibitor nintedanib with single agent ifosfamide in patients with advanced, inoperable, metastatic soft tissue sarcoma after failure of first-line chemotherapy: EORTC-1506-STBSG "ANITA. Eur. J. Cancer 152, 26–40.
Seddon, B., Strauss, S.J., Whelan, J., Leahy, M., Woll, P.J., Cowie, F., et al., 2017. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. Lancet Oncol. 18 (10), 1397–1410.
Somaiah, N., Van Tine, B.A., Wahlquist, A.E., Milhem, M.M., Hill, E.G., Garrett-Mayer, E., et al., 2021. A randomized, open-label, phase 2, multicenter trial of gemcitabine with pazopanib or gemcitabine with docetaxel in patients with advanced soft-tissue sarcoma. Cancer 127 (6), 894–904.
Tap, W.D., Jones, R.L., Van Tine, B.A., Chmielowski, B., Elias, A.D., Adkins, D., et al., 2016. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet 388 (10043), 488–497.
Tap, W.D., Papai, Z., Van Tine, B.A., Attia, S., Ganjoo, K.N., Jones, R.L., et al., 2017. Doxorubicin plus evofosfamide versus doxorubicin alone in locally advanced, unresectable or metastatic soft-tissue sarcoma (TH CR-406/SARC021): an international, multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 18 (8), 1089–1103.
Tap, W.D., Wagner, A.J., Schoffski, P., Martin-Broto, J., Krarup-Hansen, A., Ganjoo, K.N., et al., 2020. Effect of doxorubicin plus olaratumab vs doxorubicin plus placebo on survival in patients with advanced soft tissue sarcomas: the ANNOUNCE randomized clinical trial. JAMA 323 (13), 1266–1276.
Van Tine, B.A., Krarup-Hansen, A., Hess, L.M., Abdul Razak, A.R., Soldatenkova, V., Wright, J., et al., 2022. Quality of life of patients with soft tissue sarcoma treated with doxorubicin in the ANNOUNCE phase III clinical trial. Rare Tumors 14, 20363613221100033.
Verschoor, A.J., Litière, S., Marréaud, S., Judson, I., Toulmonde, M., Wardelmann, E., et al., 2020. Survival of soft tissue sarcoma patients after completing six cycles of first-line anthracycline containing treatment: an EORTC-STBSG database study. Clin. Sarcoma Res. 10 (1), 18.
Verweij, J., Lee, S.M., Ruka, W., Buesa, J., Coleman, R., van Hoessel, R., et al., 2000. Randomized phase II study of docetaxel versus doxorubicin in first- and second-line chemotherapy for locally advanced or metastatic soft tissue sarcomas in adults: a study of the european organization for research and treatment of cancer soft tissue and bone sarcoma group. J. Clin. Oncol. 18 (10), 2081–2086.
Worden, F.P., Taylor, J.M., Biermann, J.S., Sondak, V.K., Leu, K.M., Chugh, R., et al., 2005. Randomized phase II evaluation of 6 g/m2 of ifosfamide plus doxorubicin and granulocyte colony-stimulating factor (G-CSF) compared with 12 g/m2 of ifosfamide plus doxorubicin and G-CSF in the treatment of poor-prognosis soft tissue sarcoma. J. Clin. Oncol. 23 (1), 105–112.
Younger, E., Ballman, K., Lu, Y., Papai, Z., Van Tine, B.A., Attia, S., et al., 2020. Subgroup analysis of older patients treated within the randomized phase 3 doxorubicin versus doxorubicin plus evofosfamide (SARC021) trial. J. Geriatr. Oncol. 11 (3), 463–469.

Evelyne Roets, MD, PhD candidate, oncology resident. Focusing on clinical projects that involve soft tissue sarcoma patients.

Winette van der Graaf, MD PhD, Internist oncologist and professor in medical oncology, specializing in sarcomas and Adolescents and Young adults ("AYA"). Also serves as a board member of the European Cancer Organisation with experience in clinical and scientific international leadership in oncology and cancer clinical research.

Bauke H.G. van Riet, MD, PhD candidate. The main research projects focus on radiotherapy.

Rick L. Haas, MD PhD, professor in radiation oncology, radiation-oncologist. Focusing on soft tissue sarcomas. Experienced in designing and running clinical trials.

Eugenie Younger, MD PhD, Internist oncologist with research experience focusing on sarcoma.

Francesco Sparano, MSc, Master's degree holder in Health and Communitarian Welfare, serving as a data and project manager for the GIMEMA-ALLIANCE platform a digital health tool for electronic patient-reported outcome (PRO) monitoring in the real-life practice.

Roger Wilson, Patient advocate and co-founder of Sarcoma Patients Advocacy Global Network (SPAGN), working closely with the EORTC QoL Group and involved in various clinical studies, academic research groups, and advisory boards.

Stevie van der Mierden, PhD, Information specialist. Supporting researchers with searches and systematic reviews.

Neeltje Steeghs, MD PhD, internist oncologist. Director of National Platform Early Phase Clinical Trials in the Netherlands. Director Early Drug Development Center at The Netherlands Cancer Institute. Chair of Dutch GIST Consortium. Main scientific interests are new drug development, and the inclusion of pharmacokinetics and pharmacodynamics in these studies.

Fabio Efficace, PhD. More than 15 years of experience in Health Outcomes Research with a main focus on Patient-Centered Outcomes (PCO) and Clinical Outcome Assessment (COA) in oncology (both solid tumors and hematologic malignancies). Principal Investigator of several large-scale international studies whose Patient-Reported Outcome (PRO) results have also contributed to support regulatory approval of novel anticancer targeted therapies.

Olga Husson, PhD. Epidemiologist and associate Group Leader in The Netherlands Cancer Institute focusing on Adolescent and young adult (AYA) oncology, cancer epidemiology, cancer survivorship, late and long-term effects of cancer, patient reported outcomes, health-related quality of life, sarcomas, rare cancers.