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Review

Efficacy thresholds for clinical trials with advanced or metastatic leiomyosarcoma patients: A European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group meta-analysis based on a literature review for soft-tissue sarcomas

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Abstract ***Background:*** In 2002, the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group reported well-established values for conducting phase II trials for soft-tissue sarcomas. An update is provided for leiomyosarcoma (LMS). ***Materials and methods:*** Clinical trials with advanced or metastatic LMS were identified via literature review in PubMed (published 2003–2018, ≥10 adult LMS patients). End-points

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Study design

were 3- and 6-month progression-free survival rates (PFSR-3m and PFSR-6m). When estimates could not be derived from publications, data requests were sent out. Treatments were classified as recommended (R-T) or non-recommended (NR-T) according to the ESMO 2018 guidelines. A random effects meta-analysis was used to pool trial-specific estimates for first-line (1L) or pre-treated (2L+) patients separately. The ESMO Magnitude of Clinical Benefit Scale was used to guide the treatment effect to target in future trials.

Results: From 47 studies identified, we obtained information on 7 1L and 16 2L+ trials for 1500 LMS patients. Overall, in 1L, PFSR-3m and PFSR-6m were 74% (95% confidence interval [CI] 64–82%) and 58% (95% CI 50–66%), respectively. For 2L+, PFSR-3m was 48% (95% CI 41–54%), and PFSR-6m was 28% (95% CI 22–34%). No difference was observed between R-T and NR-T for first or later lines. Under the alternative that the true benefit amounts to a hazard ratio of 0.65, a PFSR-6m $\geq$70% can be considered to suggest drug activity in 1L. For 2L+, a PFSR-3m $\geq$62% or PFSR-6m $\geq$44% would suggest drug activity. Specific results are also provided for uterine LMS.

Conclusions: This work provides a new benchmark for designing phase II studies for advanced or metastatic LMS.

1. Introduction

Non-gastrointestinal stromal tumour soft-tissue sarcomas (STS) constitute a very heterogeneous group of mesenchymal rare malignancies, accounting for 1% of all adult malignancies, with widely varying genetics, prognostic factors, and sensitivity to treatments [1]. The tumours metastasise predominantly to the lungs [1,2]. Gastrointestinal stromal tumour (GIST) is generally considered separately because it is responsive to receptor tyrosine kinase inhibitors, most notably imatinib. The prognosis of patients with advanced or metastatic STS is poor, with a median overall survival (OS) of 12–17 months after first-line treatment and an estimated 2-year OS of 20–30% after treatment with standard cytotoxic chemotherapy drugs [3,4]. In these patients, treatment is often palliative to delay progression and severe morbidity. Doxorubicin and ifosfamide are considered the most active drugs used either singly or in combination for first line with a response rate (RR) of 10–25% [5]. Dacarbazine and the combination of docetaxel and gemcitabine are also treatments with some recognised activity [6,7]. Frequently used drugs, particularly for the second and further lines of treatment of LMS, are trabectedin, dacarbazine, pazopanib, and gemcitabine [8].

In total, more than 100 histologic subtypes have been recognised occurring in the trunk, extremity, and retroperitoneum [1]. The commonest histotypes are leiomyosarcoma (LMS; ~20%), liposarcoma (~20%), undifferentiated pleiomorphic sarcoma (~15%), and synovial sarcoma (~6%), with the remaining histotypes being individually rarer [9].

LMS—one of the most common STS—has a wide anatomical distribution exhibiting complex genetic alterations. LMS occurs most frequently in the uterus and is the most prevalent form of gynaecologic sarcoma. It comprises ~20% of STS being rare but aggressive [10,11]. First-line patients with locally advanced or metastatic LMS have poor prognosis (median OS ~17 months) and are usually treated with doxorubicin alone, or in combination with ifosfamide, or dacarbazine [7,12]. Non-uterine and uterine LMS (uLMS) should be considered separately since different gene patterns are expressed and different clinical behaviour has been reported that might make uLMS more chemosensitive [13,14]. Systemic treatment for advanced uterine LMS with doxorubicin or gemcitabine-based regimens results in median progression-free survival (PFS) of 6–8 months and median OS of <2 years [15].

As historical benchmarking, Van Glabbeke *et al.* published in 2002 a pooled analysis on behalf of the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) estimating progression-free rate for various groups of STS patients who participated in EORTC phase II trials [16]. In this work, thresholds for activity were provided separately for first-line and pre-treated patients dividing drugs into active and inactive: a rate at 6 months of 30–56% was suggested as a reference for first line (depending on histology), and for second line, a 3-month rate was $\geq$40% for drug activity and $\leq$20% for inactivity (for any STS subgroup).

The aforementioned thresholds have been widely used (more than 400 citations) to design new studies for all STS or for specific histology subgroups. As they were calculated almost two decades ago, it is of great importance to provide updates to reflect current treatment practices. Moreover, in the previous decade, STS studies were designed based on the one-size-fits-all principle mixing several histologic subtypes. However, more recently, there is a clear trend towards histology-specific tailored research [1,13]. To elaborate on this, the

2002 thresholds should not only be updated but also be evaluated separately for the most prevalent STS subtypes to aid the design of histology-specific trials. This is more relevant with the increased survival trend from the standard of care (i.e. doxorubicin) and multiple other agents such as eribulin, pazopanib, and trabectedin; all associated with improvements in supportive and multidisciplinary care [17,18].

An extensive literature search was performed to identify all phase II or subsequent clinical trials of advanced or metastatic STS from 2003 to 2018, thus documenting the current landscape. Because of the heterogeneity among clinical trials (e.g. different treatments, subtypes, and phases), it was decided to focus first on LMS – the most commonly occurring STS subtype. Moreover, given the fact that PFS rates (PFSRs; counting death as an event) are nowadays a preferred and more frequently reported end-point than progression-free rates (censoring non-disease–related death), the primary end-point of interest in this work is PFSR at 3 and 6 months. The aim is to provide a new benchmark for designing phase II studies for advanced or metastatic LMS patients using PFS rates as the primary end-point.

2. Methods

2.1. Search strategy and selection criteria

This literature review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [19]. The details are provided in the Appendix pp 3–5. In summary, MEDLINE was searched through PubMed for phases II, III, or IV clinical trials for advanced or metastatic STS published from 1 January 2003 to 31 December 2018. Three investigators (G.K., A.N., and M.V.) independently examined the database. Two search algorithms were combined using the terms 'sarcoma', 'clinical trial', 'advanced', 'metastatic', and 'human'.

Only articles published in English were included. Eligible study designs included randomised controlled or non-randomised clinical trials as well as prospective real-life studies. The study domain included any systemic therapy in non-resectable advanced or metastatic STS for first or later lines of treatment. Case–control studies, case series, review papers, early phase trials (phase I, I-II), reports, pooled analyses, and substudies were excluded. Articles with paediatric population or with retrospective clinical data were considered ineligible, as well as those dedicated exclusively to GIST or bone sarcomas.

A two-step procedure was performed by the three investigators. The first step included screening of titles and abstracts, the second step of full text. During the first step, the name of study, first author and year of publication were extracted. At the second step, study design, study phase, number of patients registered, line of treatment, subtypes included/excluded, primary end-points, drugs used in the trial, and more summary estimates filling in total 41 variables in our database. In case of discordance, discussion followed to find a compromise. It was decided to first focus on LMS, the most frequent STS subtype in the screened trials.

2.2. Data extraction

To perform the meta-analysis, a line per treatment arm database was designed. For each line, G.K. extracted the year of study activation, LMS subgroup (all or uterine only), number of evaluable LMS patients (those who meet the statistical plan criteria for inclusion in efficacy data sets) for PFSR at 3/6 months with 95% confidence intervals (95% CIs). Placebo arms, treatment arms with less than 10 LMS patients, studies activated before 2000, or those with mixed treatment lines were excluded. When information on the end-points could not be extracted from a publication, first authors and/or study sponsors were contacted.

2.3. Statistical methods

The main analysis focused on the activity of drugs or drug combination, distinguishing between recommended (R-T)/non-recommended treatment (NR-T) regimens for LMS patients, measured in terms of the overall PFSR at 3/6 months. The ESMO 2018 guidelines were used as a criterion to perform drug classification [7]. A random effects model was used for each drug (or drug combination) to estimate an overall PFSR. A necessary component for the calculation of study heterogeneity was the variance of PFS (not available in publications). Therefore, for each treatment arm, the number of cases (patients alive and progression-free) at 3 and 6 months was approximated according to the number of evaluable LMS patients and a given PFS proportion (defined as cases/evaluable patients). Followingly, the estimated number of cases was used under a binomial distribution to calculate the variance and the 95% CIs for each drug/combination (see more details in Appendix pp 11–12) [20].

The inverse variance method, giving more weight to larger trials, was used to pool treatment-specific PFS estimates. These are reported on forest plots alongside the 95% CIs. To estimate the between-study variance, the DerSimonian-Laird's method was employed [21,22]. An overall test on heterogeneity between studies was performed for each meta-analysis (value I^2 in figures) [23]. The association of drug groups (R-T/NR-T) with PFS was tested with a Z-statistic. The risk of publication bias was assessed with funnel plots and formal regression tests [24–26]. The Baujat plot was applied to detect sources of heterogeneity and potentially influential studies [27]. Meta-regressions were performed to test the effect of phase, study design, year of activation, and sample size on efficacy for all LMS,

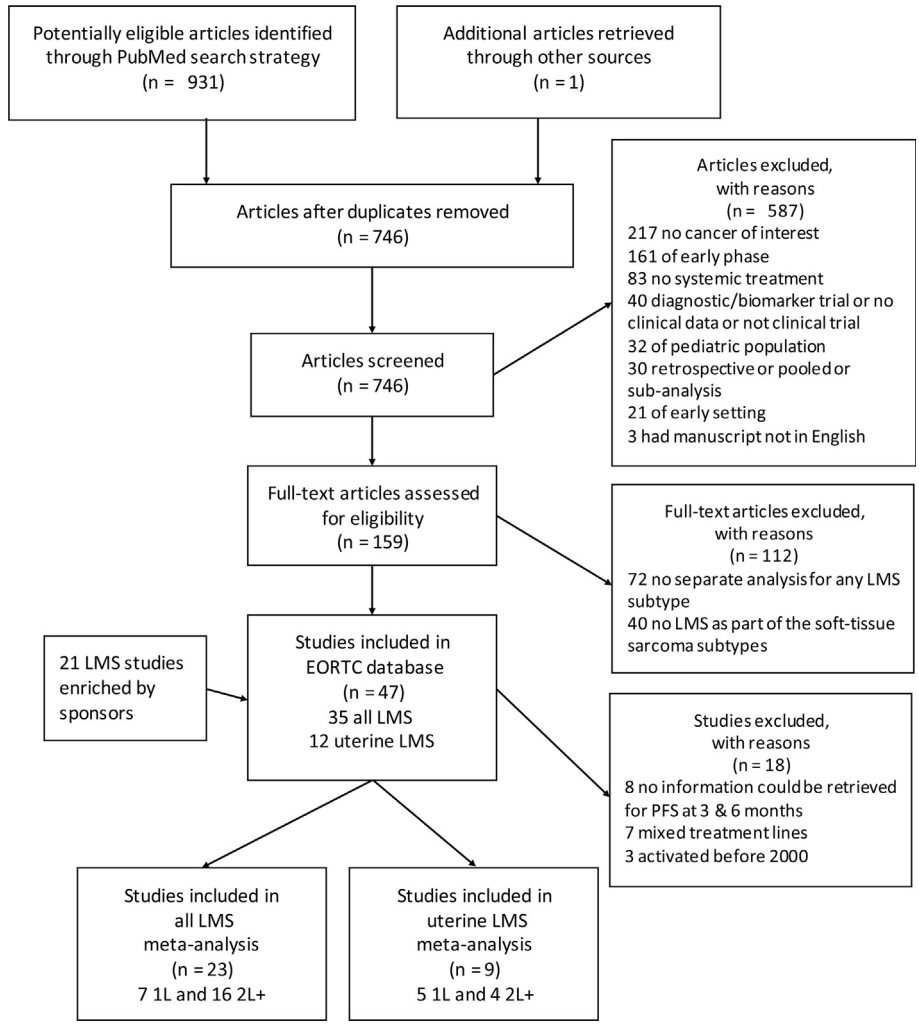


Fig. 1. Study selection. For the uterine LMS meta-analysis, nine studies were included: six studies designed for uterine LMS and three designed for (all) LMS for which estimates for the uterine LMS subgroup were provided.

but not for uLMS (because of the small number of specific studies). First, the predictors were tested separately in univariate models and then any prognostic factors were added in multivariate models, including the drug groups, to investigate whether some part of the residual heterogeneity can be explained.

The ESMO Magnitude of Clinical Benefit Scale (MCBS) was used to guide the choice of treatment effect to target in future trials [28]. All reported P values are two sided. Analyses were performed using the packages *metafor* and *meta* in R (version 4.0.2) [29,30].

3. Results

3.1. Included clinical trials

The search strategy identified 745 publications; 159 potentially relevant articles for STS were selected after abstract and full-text screening. A noticeable amount of variation was observed (e.g. different treatments, subtypes, and end-points). For this work, the focus is on LMS, which appeared more than 100 times (as LMS, uLMS, soft-tissue LMS etc). Forty-seven studies were identified for the meta-analyses. Overall, twenty-three trials were included in the all LMS meta-analysis (excluding trials designed only for uLMS patients) [3,5,9,18,31–49], and nine trials were included in the uLMS-specific meta-analysis [37,45,49–55] (see study selection in Fig. 1).

3.2. Characteristics of included trials

A total of 1500 patients were evaluable for the LMS analysis (range 10–157; Table 1) and 421 for the uLMS analysis (range 18–54; Table 1). The most common drug regimen in first line for LMS was doxorubicin, either monotherapy (five times) or in combination with evofosfamide, ifosfamide, or trabectedin. Eribulin was the most common drug in pre-treated population (three times). For uLMS patients, the most frequent therapeutic option for any line was docetaxel + gemcitabine (five times).

Table 1
Main characteristics and results of studies included in the LMS meta-analyses.

First author (year of publication)	Study period	Study type	Phase	Treatment line	Total patients registered	Drug or drug combination	Recommended	Evaluable LMS patients for PFS (%)	PFS 3 months (95% CI)	PFS 6 months (95% CI)	Analysed group
Long *et al.* (2005)	2002−2003	Non-randomised trial	2	1	18	D+M+D+C+S	No	18 (100.00%)	0.78 (0.54 −0.91)	0.50 (0.28−0.72)	Uterine LMS
Hartmann *et al.* (2007)	2002−2006	Non-randomised trial	2	2+	36	Bendamustine	No	15 (41.67%)	0.40 (0.19 −0.65)	0.33 (0.15−0.59)	All LMS
Reichardt *et al.* (2007)	2002−2004	Non-randomised trial	2	2+	39	Exatecan	No	16 (41.03%)	0.56 (0.32 −0.78)	0.12 (0.03−0.39)	All LMS
Hensley *et al.* (2008)	2003−2006	Non-randomised trial	2	1	42	Docetaxel + Gemcitabine	No	42 (100.00%)	0.57 (0.42 −0.71)	0.36 (0.23−0.51)	Uterine LMS
Hensley *et al.* (2008)	2003−2006	Non-randomised trial	2	2+	51	Docetaxel + Gemcitabine	Yes	48 (94.12%)	0.73 (0.59 −0.84)	0.52 (0.38−0.66)	Uterine LMS
Hensley *et al.* (2009)	2006−2007	Non-randomised trial	2	2+	25	Sunitinib	No	23 (92.00%)	0.35 (0.18 −0.56)	0.17 (0.07−0.38)	Uterine LMS
Sleijfer *et al.* (2009)	2005−2007	Non-randomised trial	2	2+	142	Pazopanib	Yes	41 (28.87%)	0.44 (0.30 −0.59)	0.32 (0.19−0.47)	All LMS
Schöffski *et al.* (2011)	2007−2009	Non-randomised trial	2	2+	128	Eribulin	No	38 (29.69%)	0.32 (0.19 −0.48)	0.26 (0.15−0.42)	All LMS
Chawla *et al.* (2011)	2004−2005	Non-randomised trial	2	2+	216	Ridaforolimus	No	57 (26.39%)	NA	0.21 (0.12−0.34)	All LMS
van der Graaf *et al.* (2012)	2008−2010	Randomised trial	3	2+	372	Pazopanib	Yes	92 (24.73%)	0.58 (0.47 −0.67)	0.38 (0.29−0.48)	All LMS
Pautier *et al.* (2012)	2006−2008	Randomised trial	2	2+	90	Docetaxel + gemcitabine	Yes	21 (23.33%)	0.71 (0.49 −0.87)	0.48 (0.28−0.68)	Uterine LMS
						Docetaxel + gemcitabine	Yes	40 (44.44%)	0.62 (0.47 −0.76)	0.48 (0.33−0.63)	All LMS
						Gemcitabine	Yes	21 (23.33%)	0.57 (0.36 −0.76)	0.48 (0.28−0.68)	Uterine LMS
						Gemcitabine	Yes	43 (47.78%)	0.63 (0.48 −0.76)	0.49 (0.34−0.63)	All LMS
Schuetze *et al.* (2012)	2008−2009	Non-randomised trial	2	2+	49	Cyclophosphamide + sirolimus	No	16 (32.66%)	0.75 (0.49 −0.90)	0.31 (0.14−0.57)	All LMS
Cassier *et al.* (2013)	2010	Non-randomised	2	2+	47	Panobinostat	No	10 (21.28%)	NA	0.20 (0.05−0.54)	All LMS

(*continued on next page*)

Table 1 (*continued*)

First author (year of publication)	Study period	Study type	Phase	Treatment line	Total patients registered	Drug or drug combination	Recommended	Evaluable LMS patients for PFS (%)	PFS 3 months (95% CI)	PFS 6 months (95% CI)	Analysed group
		trial									
Santoro *et al.* (2013)	2006–2010	Non-randomised trial	2	2+	100	Sorafenib	No	30 (30.00%)	0.63 (0.45–0.78)	0.40 (0.24–0.58)	All LMS
Schöffski *et al.* (2013)	2008–2012	Non-randomised trial	2	2+	113	Cixutumumab	No	22 (19.47%)	0.27 (0.13–0.49)	NA	All LMS
Chawla *et al.* (2014)	2009–2011	Non-randomised trial	2	1	91	Doxorubicin + evofosfamide	No	28 (30.77%)	NA	0.64 (0.45–0.80)	All LMS
Duska *et al.* (2014)	2010–2014	Non-randomised trial	2	2+	26	Ixabepilone	No	23 (88.46%)	0.09 (0.02–0.29)	0.04 (0.01–0.25)	Uterine LMS
Gelderblom *et al.* (2014)	2006–2008	Randomised trial	2	1	118	Brostallicin	No	29 (24.58%)	0.28 (0.14–0.46)	0.21 (0.10–0.39)	All LMS
						Doxorubicin	Yes	14 (11.86%)	0.79 (0.51–0.93)	0.64 (0.38–0.84)	All LMS
Judson *et al.* (2014)	2003–2010	Randomised trial	3	1	455	Doxorubicin + ifosfamide	Yes	57 (12.53%)	0.77 (0.65–0.86)	0.56 (0.43–0.68)	All LMS
						Doxorubicin	Yes	53 (11.65%)	0.66 (0.52–0.77)	0.51 (0.38–0.64)	All LMS
Bui-Nguyen *et al.* (2015)	2011–2012	Randomised trial	2|3	1	133	Trabectedin 3h	No	18 (13.53%)	0.56 (0.33–0.76)	0.44 (0.24–0.67)	All LMS
						Doxorubicin	Yes	13 (9.77%)	0.92 (0.61–0.99)	0.77 (0.48–0.92)	All LMS
Eroglu *et al.* (2015)	2010–2013	Randomised trial	2	2+	71	Selumetinib	No	10 (14.08%)	0.20 (0.05–0.54)	0.00 (0.00–0.45)	All LMS
						Selumetinib + temsirolimus	No	11 (15.49%)	0.45 (0.20–0.73)	0.36 (0.14–0.66)	All LMS
Hensley *et al.* (2015)	2009–2013	Randomised trial	3	1	107	Bevacizumab + docetaxel + gemcitabine	No	53 (49.53%)	0.64 (0.51–0.76)	0.42 (0.29–0.55)	Uterine LMS
						Docetaxel + gemcitabine	No	54 (50.47%)	0.65 (0.51–0.76)	0.50 (0.37–0.63)	Uterine LMS
Pautier *et al.* (2015)	2010–2013	Non-randomised trial	2	1	109	Doxorubicin + trabectedin	No	47 (43.12%)	0.87 (0.74–0.94)	0.72 (0.58–0.83)	Uterine LMS
						Doxorubicin + trabectedin	No	108 (99.08%)	0.90 (0.83–0.94)	0.81 (0.73–0.88)	All LMS
Mir *et al.* (2016)	2013–2014	Randomised trial	2	2+	182	Regorafenib	No	28 (15.38%)	0.57 (0.39–0.74)	0.21 (0.10–0.40)	All LMS
Schöffski *et al.* (2016)	2011–2013	Randomised trial	3	2+	452	Eribulin	No	157 (34.73%)	0.36 (0.29–0.43)	0.17 (0.12–0.24)	All LMS
						Dacarbazine	Yes	152 (33.63%)	0.39 (0.31–0.47)	0.18 (0.13–0.25)	All LMS
Schuetze *et al.* (2016)	2007–2009	Non-randomised	2	2+	200	Dasatinib	No	47 (23.50%)	0.43 (0.29–0.57)	0.13 (0.06–0.26)	All LMS

		trial								
Kawai *et al.* (2017)	2011–2012	Non-randomised trial	2	2+	52	Eribulin	No	19 (36.54%)	0.47 (0.27 −0.69)	0.32 (0.15–0.55) All LMS
Tap *et al.* (2017)	2011–2014	Randomised trial	3	1	640	Doxorubicin + evofosfamide	No	115 (17.97%)	0.76 (0.67 −0.83)	0.63 (0.53–0.71) All LMS
						Doxorubicin	Yes	103 (16.09%)	0.83 (0.74 −0.89)	0.59 (0.50–0.68) All LMS
Seddon *et al.* (2017)	2010–2014	Randomised trial	3	1	257	Docetaxel + gemcitabine	No	35 (13.62%)	0.71 (0.55 −0.84)	0.57 (0.41–0.72) Uterine LMS
						Docetaxel + gemcitabine	No	58 (22.57%)	0.76 (0.63 −0.85)	0.60 (0.47–0.72) All LMS
						Doxorubicin	Yes	36 (14.01%)	0.75 (0.59 −0.86)	0.39 (0.25–0.55) Uterine LMS
						Doxorubicin	Yes	60 (23.35%)	0.78 (0.66 −0.87)	0.50 (0.38–0.62) All LMS

Treatments were classified as recommended (yes or no) according to ESMO 2018 guidelines [7]. Study period = period of first to last patient accrual. NA = not available. Evaluable are those patients who meet the study's statistical plan criteria for inclusion in efficacy data sets. D + M + D + C + S = dacarbazine, mitomycin, doxorubicin, and cisplatin with sargramostim. Trabectedin 3h = trabectedin 3-h infusion treatment schedule. The 24-h infusion treatment arm was excluded from the meta-analysis because of the limited number of LMS patients (n = 6). PFS proportion at 3 or 6 months is defined as the (approximate) proportion of patients alive and without progression based on tumour response at 3 or 6 months after the start of treatment (cases at 3/6 months divided by the corresponding sample size). A binomial 95% CI is assumed. Equivalently, PFSR is the proportion*100.

3.3. Risk of bias

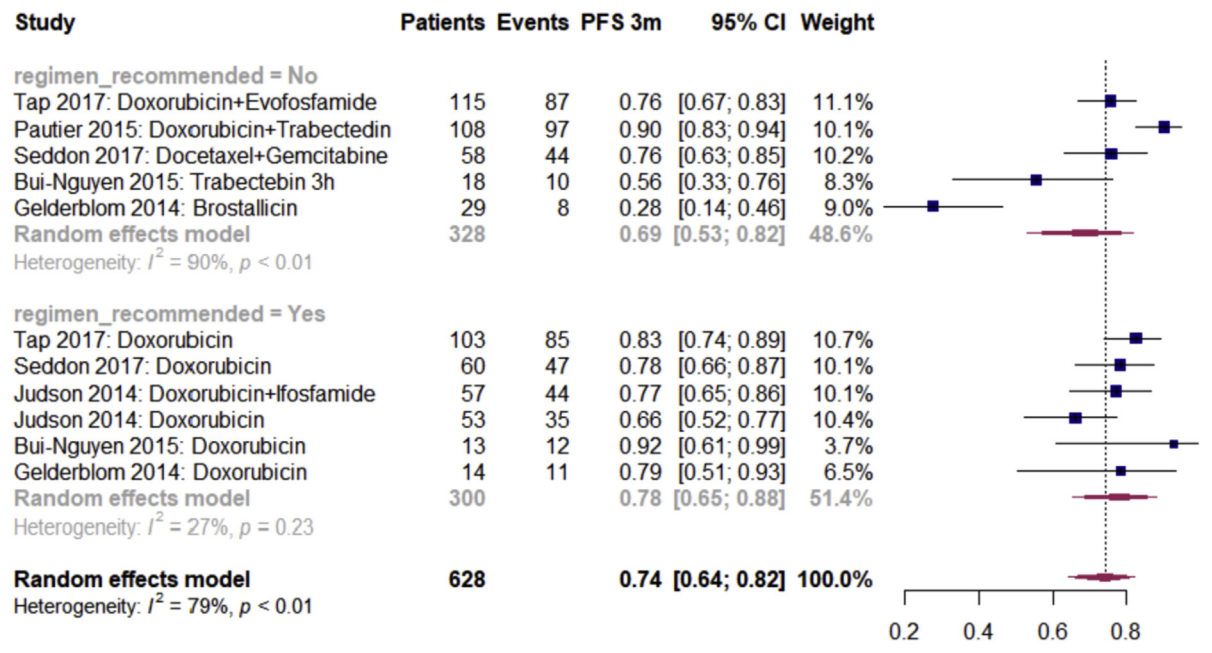
Contour-enhanced funnel plots did not portray any systematic asymmetry between studies for all LMS. Formal tests for publication bias for all LMS patients were non-significant ($P > 0.05$), indicating low risk of bias. On the contrary, a number of formal tests were significant for uLMS subanalysis ($P < 0.05$), indicating high risk of publication bias there (see Appendix section 2.4 for further details).

3.4. All LMS meta-analyses

Starting with the all LMS meta-analyses, the pooled PFSR-3m for the first-line setting (Fig. 2) were 78% (95% CI 65−88%) and 69% (95% CI 53−82%) for drugs classified as recommended/non-recommended, respectively. At 6 months, PFSR were 58% (95% CI 45−69%) and 59% (95% CI 47−70%), respectively. Differences between R-T and NR-T were not significant at 3 or 6 months (P value 0.32 and 0.90). Variability between the effect sizes that could not be explained was very high as indicated by overall heterogeneity ($I^2 > 70\%$, $P < 0.01$). Univariate meta-regressions showed that sample size >38 (median value) is a prognostic factor for PFS at 3 months. Nevertheless, multivariate meta-regression adding this variable did not explain much of the residual 3-month heterogeneity ($I^2 = 73\%$, $P < 0.01$). No significant factor was identified for PFSR-6m (see Appendix). For the pre-treated population (Fig. 3), the pooled PFSR-3m were 52% (95% CI 42−63%) for R-T and 45% (95% CI 37−53%) for NR-T. PFSR-6m for R-T and NR-T were 35% (95% CI 26−46%) and 24% (95% CI 18−31%), respectively. Similarly, differences were not significant between the R-T/NR-T (P values 0.27 and 0.06). Remaining variability was high ($I^2 > 60\%$, $P < 0.01$). None of the tested variables was prognostic at 3 months. Year of activation was a prognostic factor for PFSR-6m. Multivariate adjustment with it explained a part of the residual heterogeneity at 6 months ($I^2 = 39\%$, $P = 0.06$).

3.5. Uterine LMS meta-analyses

For first-line treatment of uLMS patients (Fig. 4), the pooled PFSR-3m were 75% (95% CI 51−90%) and 70% (95% CI 60−78%) for R-T and NR-T, respectively. The PFSR-6m for R-T and NR-T were 39% (95% CI 18−65%) and 51% (95% CI 40−62%), respectively. Differences were not significant at 3 and 6 months (P values 0.66 and 0.41). Overall heterogeneity was moderate to high at 3 months ($I^2 = 48\%$; $P = 0.07$) and high at 6 months ($I^2 = 62\%$; $P = 0.01$). For pre-treated patients (Fig. 5), the PFSR-3m for R-T and NR-T were 68% (95% CI 52−81%) and 23% (95% CI 10−44%), respectively. The PFSR-6m for R-T and NR-T were



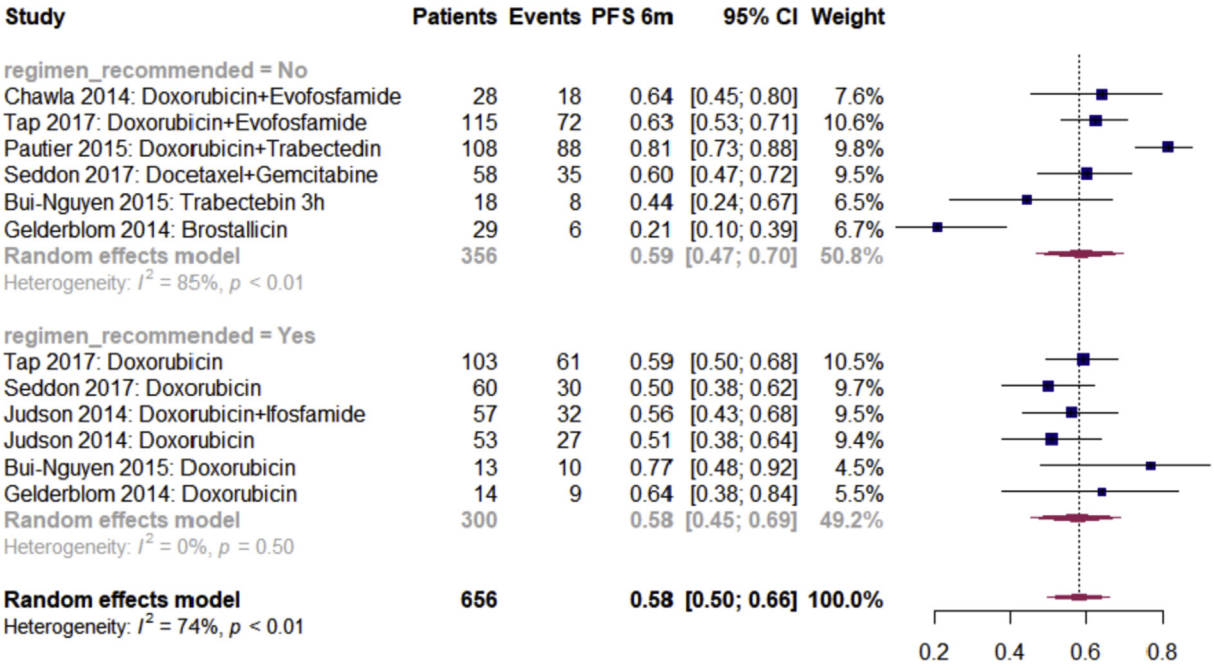
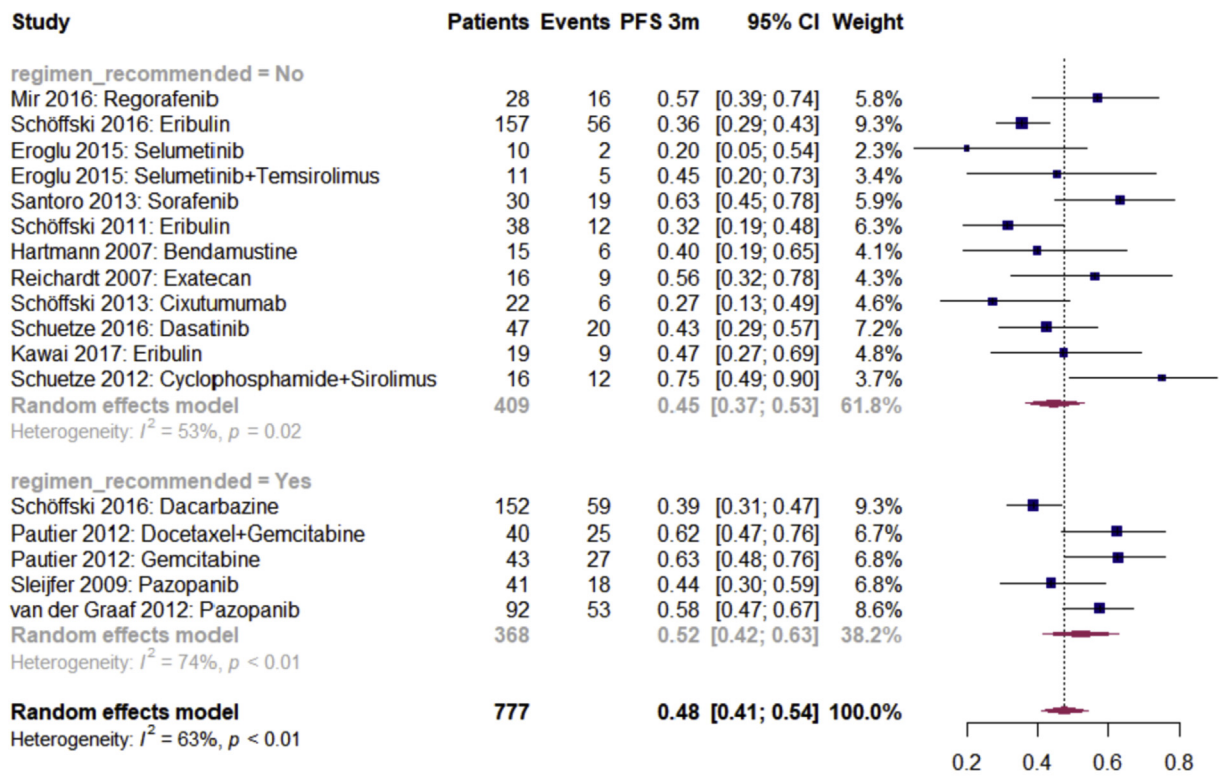


Fig. 2. Forest plots of PFS at 3 (upper panel) and 6 (low panel) months for first line (all) LMS patients. PFS proportion at 3 or 6 months was defined as the (approximate) proportion of patients alive and without progression at 3 or 6 months after the start of treatment. Treatments were classified as recommended or non-recommended according to ESMO 2018 guidelines [7]. Heterogeneity refers to the variability between the study-specific effect sizes that cannot be explained by a random variation.

50% (95% CI 40–60%) and 13% (95% CI 5–28%), respectively. Notably, there was a statistically significant difference between the classified drugs (P values < 0.01 at both 3 and 6 months). Overall variation between studies was high ($I^2 > 70\%$, $P < 0.01$).

3.6. Sensitivity analyses

Baujat plots for all LMS identified 'Gelderblom 2014: Brostallicin' as potentially influential for first-line analyses (pooled PFSR at 3 and 6 months increased 4% and



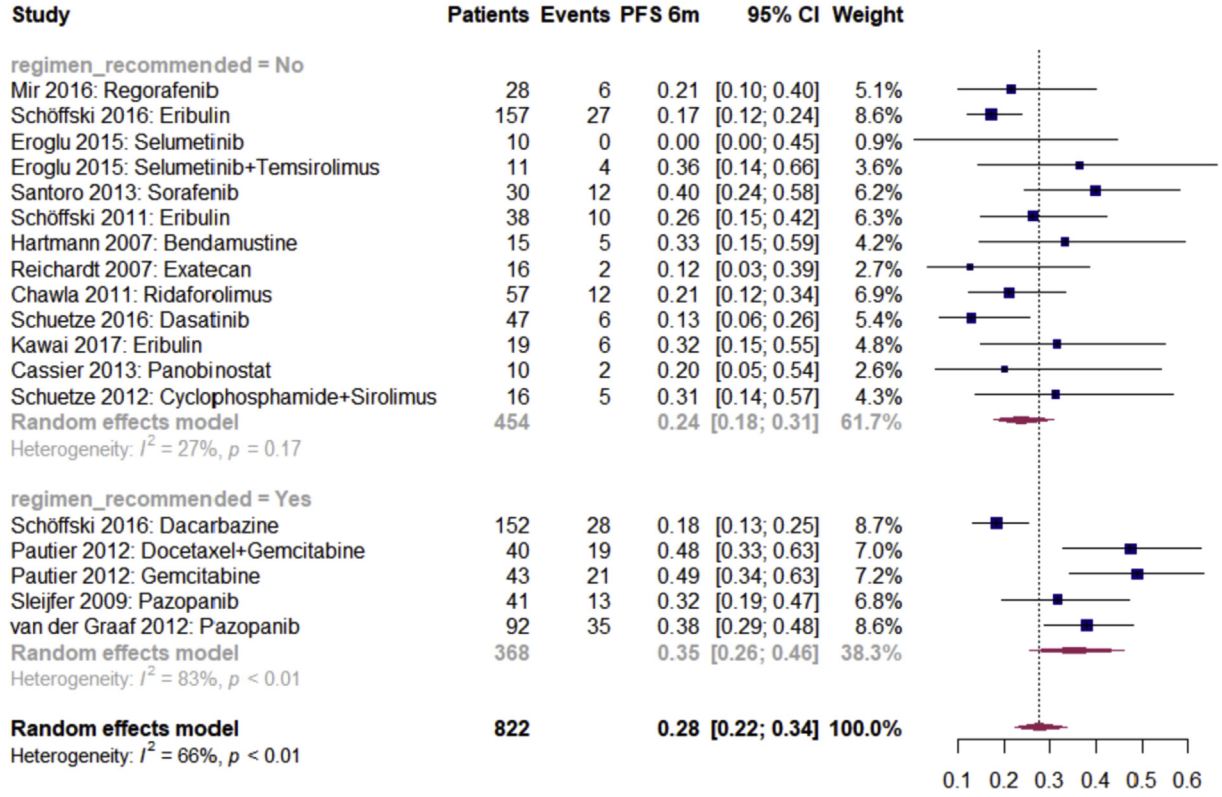


Fig. 3. Forest plots of PFS at 3 (upper panel) and 6 (low panel) months for pre-treated (all) LMS patients.

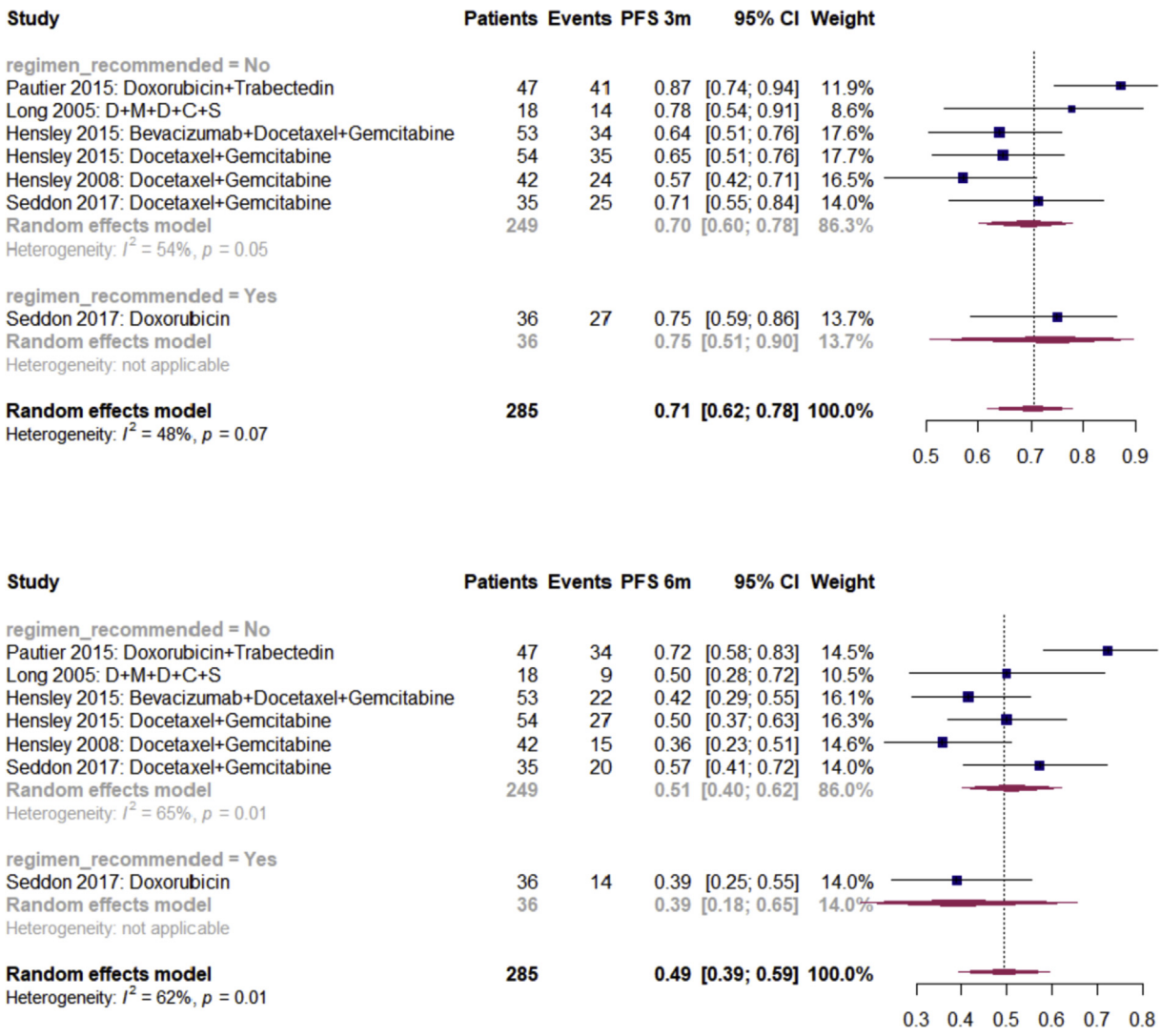


Fig. 4. Forest plots of PFS at 3 (upper panel) and 6 (low panel) months for first-line uterine LMS patients.

3% if this treatment arm is excluded), and in the pre-treated population 'Schuetze 2012: Cyclophosphamide+Sirolimus' (rate decreases 1% if excluded) and 'Schöffski 2016: Dacarbazine' (rate increases 1% if excluded) at 3 and 6 months, respectively [38,42,46]. Removing these treatment arms reduced overall heterogeneity insignificantly. The results in the first-line setting were less robust to the potential outlier than those in the pre-treated setting. Sensitivity analyses specific to uLMS showed low robustness because of the small sample size (seven treatment arms in first line and five in pre-treated). Baujat plots and forest plots removing potential outliers are provided in the Appendix sections 2.3 for all LMS and 2.4 for uLMS.

3.7. Benchmarking

To derive the new benchmark for the LMS cohorts, our proposal is to use the overall pooled PFSR estimated from our analysis as reference value for the null hypothesis (H_0) parameter P_0. This choice is guided by the fact that there was no significant difference between R-T and NR-T for all LMS patients but can also be justified that future agents should do better than those currently available. As the ESMO-MCBS recommends a hazard ratio (HR) of at least 0.65 for PFS in advanced or metastatic setting (scale evaluation form 2b) [28], the reference value for the alternative hypothesis (H_1) parameter P_1 is estimated to detect an effect size of HR = 0.65. Table 2 summarises the P_0 and P_1 parameters. A PFSR-3m $\geq$82% or a PFSR-6m $\geq$70% (80% and 63% for uLMS) can be considered to suggest drug activity in first-line studies. For two or further lines, the recommended thresholds are 62% and 44% (66% and 57% for uLMS) at 3 and 6 months, respectively.

It should be underlined that if the minimum required level of efficacy is P_1, the design of the phase II trial focuses on demonstrating that this level is plausible, given the trial results and the efficacy is greater than P_0. In other words, the new agent deserves further testing at

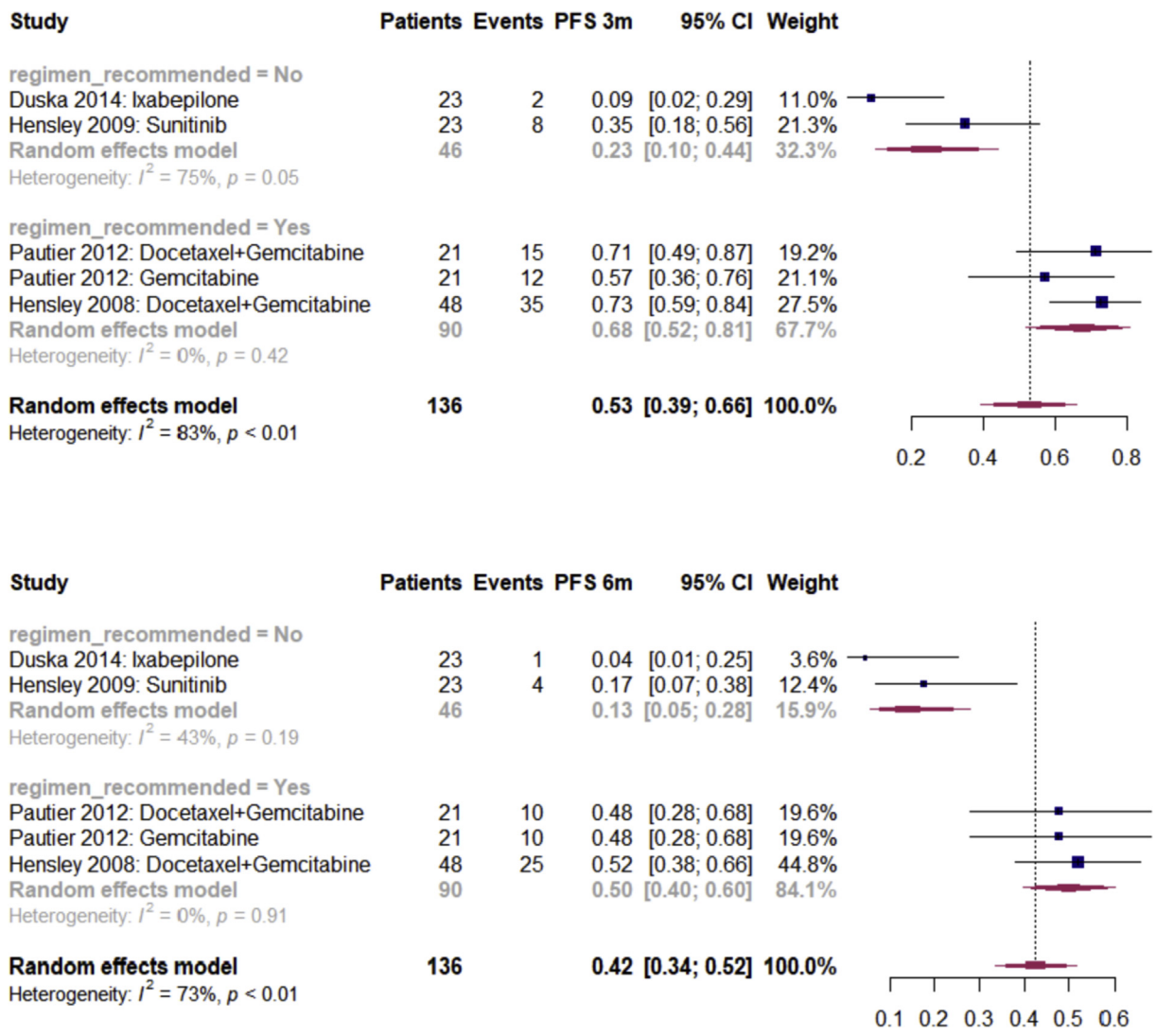


Fig. 5. Forest plots of PFS at 3 (upper panel) and 6 (low panel) months for pre-treated uterine LMS patients.

the end of the phase II trial if the estimated CI does not contain P_0. Following the ESMO-MCBS guidelines, the estimated CI should also encompass P_1. An example is provided in Fig. 6.

4. Discussion

In the present study, we provided updated thresholds for PFS rates to be used for the design of clinical trials in advanced/metastatic and inoperable LMS by a meta-analysis of available data from clinical trials published between 2003 and 2018. Reference values for H_0 and H_1 have been estimated using the ESMO-MCBS recommendations [28].

The historical benchmarking analysis by Van Glabbeke *et al.* (2002) provided pooled progression-free rates for various STS patients who participated in phase II trials [16]. Notably, these have been used to design a large number of new studies. The results and thresholds cannot be directly compared for several reasons: Our meta-analysis focused on defining thresholds for LMS patients using phase II and phase III trials. In addition, most of the phase II trials included in the 2002 publication were conducted before the classification of GIST as a separate entity, and GIST patients were consequently classified as LMS patients. The primary endpoint shifted from progression-free rates to PFSR, counting any death as an event. Van Glabbeke *et al.* exploited independent patient data (IPD, $N = 1534$ overall) from the STBSG database, whereas we used summary estimates, which are less reliable than IPD. On the other hand, we were able to conduct a meta-analysis including over 1500 LMS patients.

We chose not to meta-analyse other common endpoints in clinical trials, such as RR and OS. Here, rather low objective RRs were obtained for the majority of the drugs/drug combinations in our LMS database (several times 0%, frequently less than 15%), which is expected in this population as a decrease of tumour volume greater

Table 2
Treatment effect (PFSR) for the null hypothesis (H_0) parameter P_0 and the alternative hypothesis (H_1) parameter P_1 of a study for LMS.

Treatment line and analysed group	3 months		6 months	
	Ref (P_0)	Min target (P_1)	Ref (P_0)	Min target (P_1)
First-line uterine LMS	71%	80%	49%	63%
First line all LMS	74%	82%	58%	70%
Pre-treated uterine LMS	53%	66%	42%	57%
Pre-treated all LMS	48%	62%	28%	44%

LMS, leiomyosarcoma.
Reference values for P_0 are the overall pooled PFSR at 3 and 6 months. Minimum values to target for P_1 are calculated using the recommended treatment effect for PFS by the ESMO Magnitude of Clinical Benefit Scale (MCBS) [28].

than 30% (needed to qualify a partial response according to RECIST 1.1 [56]) is unlikely with the studied agents. Hence, RR is not the best end-point for simple screening phase II studies in LMS as a basis for further drug development. Furthermore, OS is usually not the primary end-point in phase II studies. On the contrary, PFS (and/or time to progression) is a valuable alternative end-point for the estimation of the biological antitumor activity of a new treatment and thus to justify further investigation in phase III trials. An extensive discussion is provided in the Van Glabbeke paper [16].

Thresholds were defined for all LMS and were shown to be robust by sensitivity analysis. A uLMS-specific subgroup meta-analysis was performed. The results should be interpreted with caution because of the potential publication bias indicated in this subanalysis and the small sample size (seven rows from five trials for first line and five rows from four trials for pre-treated population).

This analysis showed that R-T based on standard clinical practice guidelines do not necessarily exhibit a significant difference in PFSR at 3/6 months versus NR-T for advanced or metastatic LMS, apart from the pre-treated setting for uLMS [7]. This could be explained by the fact that the majority of the trials used as a basis for the clinical practice guidelines were designed for multiple STS subtypes and as a result are underpowered for specific subgroup analyses. They did therefore not lead to specific recommendations.

To the best of our knowledge, this is the first attempt at a meta-analysis of the outcome of patients with advanced or metastatic LMS for both first and further lines. Overall, 1500 patients were included in the analysis for all LMS and 421 patients for uLMS, which is a key strength of this work. A meta-regression was performed to investigate whether the phase of the trial, study design, year of activation, and sample size are prognostic for PFSR separately and if they can mitigate heterogeneity. Sample size was prognostic and could explain a small part of residual heterogeneity (variability between study outcomes not accounted for by the variables) for first line at 3 months and year of activation a larger part for pre-treated population at 6 months. For uLMS patients, meta-regression was not performed because of the limited number of therapeutic combinations. Future research should shed light to whether other factors could explain heterogeneity across studies.

A condition of any meta-analysis is the implied independence of effect sizes between drugs of the same trial [23,57]. In our meta-analysis, a random effects model was used for each treatment regimen in the database and not for each trial. However, for randomised studies (10/23 trials for all LMS), there might be some dependence, as treatment arms were designed for the same patient population/centres. And finally, a source of bias is the use of progression-free rate instead of PFSR for 4/31 treatment regimens, as the required data could not be retrieved. This could lead to a small overestimation of the overall PFSR, as deaths are not taken into account at 3 and 6 months in these four regimens.

Last but not least, the ultimate aim of a clinical trial is to provide evidence of improved OS or improved quality of life. Nonetheless, two recent meta-analyses do not support strong surrogacy properties between PFS and OS in advanced STS randomised clinical trials [58,59]. Consequently, PFS carries the risk of misleading conclusions because of erroneous extrapolation of the results. On the other hand, PFS remains an attractive end-point to identify benefit earlier than OS, and phase II trials are not intended to provide definite proof of the new treatment but rather a justification to further investigation. PFS (or PFSR-3m, PFSR-6m) can thus be used as primary end-points in phase II trials or as futility end-

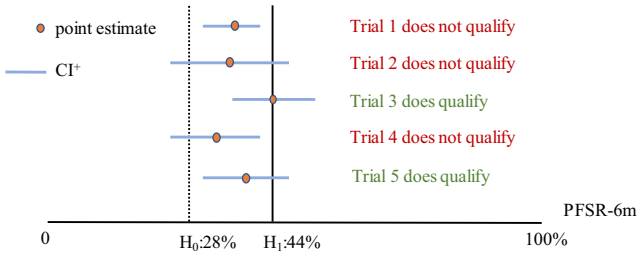


Fig. 6. Example regarding the thresholds estimated for the PFS rate at 6 months of pre-treated all LMS patients. The parameter of null hypothesis (P0) was calculated at 28% and the parameter of the alternative hypothesis at 44%. Trial 1 does not qualify because the point estimate or the upper limit of the CI do not reach 44% (P1). Trial 2 does not qualify because the lower limit of the CI does not surpass 28% (P0). Trial 3 does qualify because the point estimate reaches P1 and the lower limit of the CI surpasses P0. Trial 4 does not qualify because the lower limit of the CI does not surpass P0 and the point estimate or the upper limit of the CI do not reach P1. Trial 5 does qualify because the lower limit of the CI surpasses P0 and the upper limit of the CI surpasses P1.
+The confidence level of the confidence interval (CI) is to be defined based on the statistical parameters of the study design.

points in phase III trials, but OS should remain the primary end-point in phase III trials (whenever possible).

In conclusion, last decade research in STS shifted to a histology-specific approach. Because of the unmet medical need in standard of care alternatives, new studies tailoring therapy to specific histological subtypes should be based on modern thresholds for drug activity. Hereto, we suggest a new benchmark for designing phase II studies for all LMS or uLMS using the overall PFSR-3m and PFSR-6m as primary end-point. Future research is warranted using similar methodology to update thresholds of other common STS subgroups (e.g. liposarcomas).

Authors' contributions

G.K., S.L., A.N., M.V., M.F., and H.G. conceived and designed the study. G.K., A.N., and M.V. searched and selected the trials and collected and validated the data. G.K., S.L., M.F., and H.G. managed and coordinated responsibility for the research activity planning and execution. G.K. carried out the statistical analysis and interpreted the data supervised by S.L., A.N., M.F., and H.G. M.V., I.J., P.S., E.W., S.S., L.D'.A., S.M., W.G., B.K., and H.G. provided clinical input. G.K. wrote the original draft and the other authors critically revised it. All authors read and approved the final version.

Role of the funding source

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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

P.S. has reported honoraria from Deciphera, Blueprint Medicines, Boehringer Ingelheim; consultancy or advisory role for Deciphera, Ellipses Pharma, Blueprint Medicines, Transgene, Exelixis, Boehringer Ingelheim, Medscape, Guided Clarity, Ysios Capital; consultancy or advisory role to the Institution for Blueprint Medicines, Ellipses Pharma, Adaptimmune, Intellisphere, Transgene, Advanced Medical; has received support for travel, accommodation, expenses from Boehringer Ingelheim, MSD, Ipsen; research funding to the Institution from CoBioRes NV, Eisai, G1 Therapeutics, Novartis, PharmaMar; all outside the scope of the submitted work. S.S. has reported honoraria, consultancy or advisory role for Adaptimmune, Bayer, Daiichi-Sankyo, Deciphera, Epizyme, Eli Lilly, Glaxo, Immunedesign, Karyopharm, Maxivax, Novartis, PharmaMar; institutional financial interests with Advenchen, Amgen-Dompè, Bayer, Epizyme, Eli Lilly, Daiichi-Sankyo, Glaxo, Hutchinson MediPharma, Karyopharm, Novartis, Pfizer, PharmaMar, and Springworks; all outside the scope of this article. L.D'.A. has reported advisory boards for PSI, GSK, and Eisai; performed editorial activity for Novartis; received travel support from PharmaMar, Eli Lilly, and Celgene; all outside the submitted article. W.G. has reported advisory role for Bayer, GSK, and Springworks; received research grant support to the Institute from Eli Lilly and Novartis; all outside the submitted work. All remaining authors have declared no conflicts of interest.

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or views of the clinical trial investigators, the NCTN, or the NCI.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.06.025.

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