A systematic review of recent phase-II trials in refractory or recurrent osteosarcoma: Can we inform future trial design?

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Systematic or Meta-analysis Studies

A systematic review of recent phase-II trials in refractory or recurrent osteosarcoma: Can we inform future trial design?

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ABSTRACT

Background/Objective: To analyze changes in recurrent/refractory osteosarcoma phase II trials over time to inform future trials in this population with poor prognosis.
Methods: A systematic review of trials registered on trial registries between 01/01/2017–14/02/2022. Comparison of 98 trials identified between 2003 and 2016. Publication search/analysis for both periods, last update on 01/12/2022.
Results: Between 2017 and 2022, 71 phase-II trials met our selection criteria (19 osteosarcoma-specific trials, 14 solid tumor trials with and 38 trials without an osteosarcoma-specific stratum). The trial number increased over time: 13.9 versus 7 trials/year ($p = 0.06$). Monotherapy remained the predominant treatment (62% vs. 62%, $p = 1$). Targeted therapies were increasingly evaluated (66% vs. 41%, $P = 0.001$). Heterogeneity persisted in the trial characteristics. The inclusion criteria were measurable disease (75%), evaluable disease (14%), and surgical remission (11%). 82% of the trials included pediatric or adolescent patients. Biomarker-driven trials accounted for 25% of the total trials. The survival endpoint use (rather than response) slightly increased (40% versus 31%), but the study H_1/H_0 hypotheses remained heterogeneous. Single-arm designs predominated over multiarm trials

Abbreviations: ASCO, American Society of Clinical Oncology; COG, Children's Oncology Group; CTOS, Connective Tissue Oncology Society; DCR, Disease control rates; EFS, Event-free survival; ESMO, European Society for Medical Oncology; FOSTER, Fight OSteosarcoma Through European Research consortium; MTKI, Multi-targeted kinase inhibitors; ORR, Objective response rate; OS, Overall Survival; PFR, Progression free survival rate; PFS, Progression free survival; RECIST, Response evaluation criteria in solid tumors; SIOP, International Society of Paediatric Oncology (SIOP.

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(n = 7). Available efficacy data on 1361 osteosarcoma patients in 58 trials remained disappointing, even though 21% of these trials were considered positive, predominantly those evaluating multi-targeted kinase inhibitors. *Conclusion:* Despite observed changes in trial design and an increased number of trials investigating new therapies, high heterogeneity remained with respect to patient selection, study design, primary endpoints, and statistical hypotheses in recently registered phase II trials for osteosarcoma. Continued optimization of trial design informed by a deeper biological understanding should strengthen the development of new therapies.

Introduction

High-grade osteosarcoma is an aggressive bone sarcoma with a peak incidence in adolescence [1], with one-third of the patients experiencing disease progression/recurrence during or after first-line treatment consisting of multidrug chemotherapy and surgery of the primary tumor and metastatic lesions [2–5]. At progression or recurrence, the 5-year overall survival (OS) is dismal, below 30%, with an extremely poor prognosis, unless a second complete surgical remission is achieved [2,3]. Despite many trials being performed, there is no established standard therapy besides surgery for recurrent/refractory osteosarcoma, nor is it known in which clinical scenarios systemic therapy might be of benefit [6–9].

In 2016, a systematic review evaluating phase-II therapeutic trials [10] and a retrospective evaluation of seven phase-II trials of the Children's Oncology Group (COG) [7] in recurrent/refractory osteosarcoma described the disappointing results of the evaluated therapies and the lack of homogenous design and methodology. The lack of optimal historical cohorts and the strong heterogeneity in trial design were thought to limit the implementation of results into clinical practice and, thereby, the progression towards new therapies in this population. In line with previous studies, both groups underlined that radiological response rates (and equivalent endpoints) were considered suboptimal to identify effective drugs in osteosarcoma, as changes in tumor dimensions might only poorly correlate with reduced viability due to its bony matrix. Instead, the use of survival endpoints was proposed, which also provided the opportunity to include patients with evaluable (non-measurable according to RECIST criteria) disease [7,10].

The aims of our study were to evaluate the impact of these publications [7,10] on the trial design of newly registered phase-II trials for patients with recurrent/refractory osteosarcoma by comparing trends in trial design between recent (2017–2022) and previous (2003–2016) periods [10], and to provide efficacy data for osteosarcoma patients accrued in the identified phase-II trials between 2003 and 2022.

Methods

Search strategy, selection criteria

We conducted a systematic search for 'Phase-II clinical efficacy trials in recurrent osteosarcoma' open or planning to start recruitment between 1 and 1-2017 and 14–2-2022, as previously described for the 2003–2016 period [10], with the terms: osteosarcoma, bone sarcoma, phase-2, phase-II, and phase-I/II; on clinical trial registries (ClinicalTrials.gov; WHO database; European Clinical Trials Register; UMIN registry). We updated the study status of all 99 phase-II trials identified in our previous 2003–2016 review [10]. We then searched for peer-reviewed publications and abstracts with the last update for publication status on 01/12/2022, for trials identified for both periods on the following websites: PubMed, the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), Connective Tissue Oncology Society (CTOS), and International Society of Pediatric Oncology (SIOP). Two authors independently reviewed the trials and publications for inclusion in the study. Disagreements were resolved by consensus with a third reviewer.

Data extraction

We recorded the evaluated interventions as mono- or combination therapies and classified them according to their mechanism of action: chemotherapy, targeted therapy (small molecules, excluding monoclonal antibodies), immunotherapy (antibodies, lymphocytes, cytokines, and viruses), radiotherapy, and others. For each trial, we collected data on current trial status, date of start and estimated completion, eligibility criteria (histopathological diagnosis, need for biomarker, disease stage, age range), location of investigational sites, study design (primary response endpoint, endpoint definition, single or multi-arm, blinding/randomization, statistical design, estimated number of patients to be accrued), and reported results (number of accrued (osteosarcoma) patients, response/survival rates). For all trials, including the previous review [10], we added the following: the minimum/maximum lines of prior therapy, disease eligibility criteria (measurable disease only, evaluable disease eligible, or not required, i.e., surgical remission), and trial sponsor.

Statistics analysis

We calculated the descriptive statistics of the identified trials and compared both period reviews (2017–2022, 2003–2016). After an analysis of all trials, we evaluated trials specifically designed for osteosarcoma (accruing osteosarcoma only or solid tumor trials with an osteosarcoma stratum). Differences in trial characteristics at baseline were analyzed using the Pearson Chi-Square test, Fisher's exact test, Independent Student's *t*-test, and Mann-Whitney *U* test, where applicable. All statistical analyses were performed using R software version 4.1.1. Statistical tests were two-tailed, with an α level of 0.05. We analyzed the outcome data of trials designed for osteosarcoma and solid tumor trials without a stratum, including 10 or more patients. The number of patients achieving complete response (CR), partial response (PR), or disease stabilization (SD) at the trial-specified time was extracted from the publications/abstracts to calculate objective response rates (ORR = CR + PR) and disease control rates (DCR = CR + PR + SD). Survival endpoint definitions were extracted from the identified trials (progression-free survival [PFS], progression-free survival rate [PFR], event-free survival [EFS], and overall survival [OS]).

Reporting

The systematic review was reported according to the PRISMA guidelines [11,12].

Results

Eligible trials

Our systematic search led to the identification of 296 trials potentially recruiting patients with osteosarcoma between 01/01/2017 and 14/02/2021. After the eligibility criteria assessment, 225 trials were excluded (188 not including recurrent/refractory osteosarcoma and 37 phase-I trials without phase II). Finally, 71 trials were further analyzed and identified through Clinicaltrials.gov (n = 56), WHO (n = 6), European registries (n = 3), UMIN-CTR (n = 1), PubMed (n = 4), and ASCO (n = 1 (Fig. 1). This yielded a mean number of 11.8 eligible trials/year as

compared to 7 trials/year in 2003–2016 (p = 0.06).

Published results were searched for all trials identified within the whole 2003–2022 period: 71 between 2017 and 2022, 99 between 2003 and 2016. One trial between 2003 and 2016 was excluded as it did not meet the inclusion criteria (not designed for osteosarcoma and no osteosarcoma patients accrued). For the 71 trials between 2017 and 2022, eight trials (11%) had results available in peer-reviewed publications [13–20] and nine (13%) in abstract form [21–30]. For the 98 trials between 2003 and 2016, 33 previously had an abstract or publication available [10] and we identified results for 40 additional trials (34 new publications [31–64], 6 new abstracts [65–70]). Of all 169 trials between 2003 and 2022, 71 had fully published results and 20 had preliminary data in an abstract. Among the 78 trials without any identified results, 3 were not yet recruiting; 33 were recruiting; 12 were active, not recruiting (estimated completion date between 2016 and 2026); 10 were terminated due to poor accrual, business priorities, or loss of funding; 4 were withdrawn due to unavailable investigational new drug application, inability to enroll patients, and unknown reason; 2 were suspended after phase I completion or completion of accrual; and 5 had an unknown study status (Supplement Table-1). Of all 169 trials, 9 were completed between 2017 and 2022 and are still without any published results.

Trial characteristics

Between 2017 and 2022 compared to 2003–2016 period, the primary geographic trial distribution significantly changed over time (p = 0.05), with an increase in Asia (n = 18, 25% vs. n = 10, 10%) and a decrease in Europe (n = 8, 11% vs. n = 19, 19%), while trials from North America/USA remained predominant (n = 36, 51% vs. n = 57, 58%, respectively). The contribution of industry-sponsored trials between 2017 and 2022 was stable (n = 17, 24% vs. n = 23, 23%).

Trials between 2017 and 2022 investigated more monotherapies (n = 44, 62%) than combination therapies, similar to the previous period. The proportion of trials evaluating chemotherapy decreased over time (n = 56, 79% vs. n = 62, 63%, p = 0.03), whereas the proportion of trials

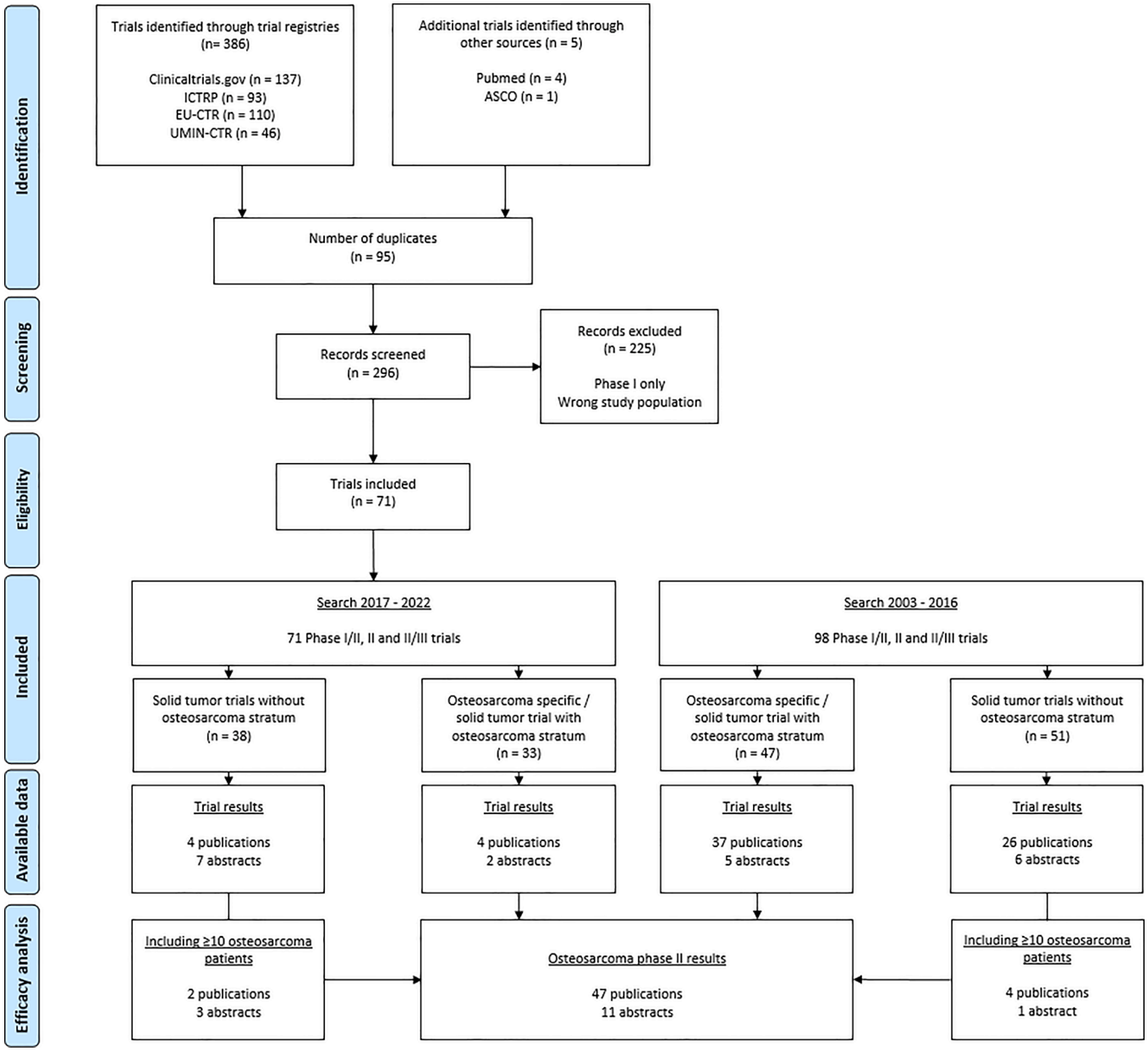

Fig. 1. Flow diagram trial search 2017–2022 and publication search 2017–2022 and 2003–2016.

evaluating targeted therapy significantly increased (n = 47, 66% vs. n = 40, 41%, p = 0.001). The proportion of trials evaluating immunotherapy also increased over time, but the difference was not significant between the two periods (p = 0.15) (Fig. 2A).

Trial population

Between 2017 and 2022, 19/71 trials were osteosarcoma-specific, 14 solid tumor trials had an osteosarcoma-specific stratum, and 38 accrued wider solid tumors/sarcomas. The distribution of disease requirements differed significantly from that in the previous period (p = 0.023). Although measurable disease remained an eligibility criterion in most trials, this proportion was lower than before (n = 53, 75% vs. 88%). In contrast, evaluable disease was more frequently allowed (n = 10, 14% in 2017–2022 vs 3% in 2003–2016). Patients with surgical remission remained eligible in approximately 10% of the trials (11% vs. 9%) (Table 1). A few trials limited their inclusion to pulmonary recurrent/refractory osteosarcoma only (n = 5). Nearly all trials required a minimum of one previous line of (chemo)therapy (n = 70), with usually no upper limit of defined lines (n = 64). Biomarker assessment was an entry criterion in 25% of the trials (n = 18/71), but only two for the osteosarcoma-specific/strata trial (NCT04616560-HER2 / NCT04040205-CDK pathway abnormality).

The age for inclusion was below 12 years in 36 trials, between 12 and 17 years in 22 trials, and 18 years or higher in 13 trials. The upper age limit was 18 years in one trial (n = 1), while most trials allowed young adults with an upper age limit between 18 and 35 years (n = 23) and older patients (n = 47 trials) either up to 40 years or without an upper limit (Fig. 2B). Over time, these led to more trials being open to pediatric/adolescent patients (51% vs. 46% and 31% vs. 23% for < 12 years and 12–17 years, respectively), and fewer included only adult patients (18% vs. 31%) (p = 0.07).

Trial design

In both study periods, the single-arm design remained the predominant trial design (n = 64/71, 90% vs. 87%). Only 7/71 trials had a multiple-arm design, including three randomized open-label and one randomized double-blind trial; 6/7 had two or more arms investigating combination therapy.

ORR remained the most used primary efficacy endpoint (40% vs. 37%, in 2017–2022 and 2003–2016, respectively), while DCR use decreased (11% vs. 24%) in favor of survival endpoints (40% vs. 31% in PFS, PFR, EFS, and OS combined). RECIST 1.0/1.1 was the main methodology to evaluate response irrespective of the period (77% vs. 69%), with no further use of the WHO response criteria (8% vs. 0%).

Osteosarcoma-specific/solid tumor trials with osteosarcoma strata

In 2017–2022, 33/71 trials were osteosarcoma-specific or had a separate osteosarcoma stratum (Table 1), with an increase in the number of osteosarcoma-specific/strata trials over time (on average 7.4 trials/year vs 3.8 trials/year in 2003–2016), although the proportion was similar (46% vs. 48%, p = 0.85). The 33 osteosarcoma trials explored kinase inhibitors (multi-targeted n = 7 trials; specific n = 8, i.e., VEGFR, ATR, PI3K, CDK), cell cycle/DNA repair inhibitors (n = 4; WEE-1, PARP, histone chaperone FACT complex), nuclear transport inhibitors (XPO1), immunosuppressive agents (IMPDH inhibition), checkpoint inhibitors (PD-1n = 6; PD-L1n = 4), and monoclonal antibodies (anti-HER2, anti-CD73, anti-α4-integrin, anti-semaphorin 4D).

The primary endpoints were survival (58%) and DCR (24%) over response rates (18%). The statistical design and hypotheses were available in 15/33 (2017–2022) and 25/47 (2003–2016) osteosarcoma-specific trials, respectively. In these 40 trials, a wide range of H_0/H_1 hypotheses were observed (Fig. 2C). The ORR H_0 hypotheses ranged from 3% to 40% and H_1 20%-60%. PFS H_0 hypotheses ranged from 5 to 40% and H_1 from 22 to 67% and were assessed at different time points (8 weeks; 4, 6, and 24 months). Eight USA trials and one from Thailand referred to the benchmarks of Lagmay et al. [7] in the methodology [40,41,56,61,70–72] or discussion sections [19,52].

Results of phase-II trials accruing recurrent/refractory osteosarcoma

Between 2003 and 2022, of the 91 trials with available data (71 publications, 20 abstracts), 58 phase-II trials were either osteosarcoma-specific (n = 48) or reported on a minimum of 10 patients with osteosarcoma in a trial with broader inclusion criteria (n = 10).

These 58 trials included 1361 patients with recurrent/refractory osteosarcoma, with a median of 18 patients per trial (range 4–103) (Supplement Table-2). Monotherapy (chemotherapy, n = 8; targeted therapy, n = 14; immunotherapy, n = 12; radiotherapy, n = 2) and combination therapies (combined chemotherapy, n = 6; combined immunotherapy, n = 4; chemotherapy with targeted therapy, n = 4; targeted with immunotherapy, n = 4; other combinations, n = 4) were investigated in 36 (62%) and 22 trials, respectively. The primary efficacy endpoints were PFS/PFR (n = 22), ORR (n = 20), DCR (n = 10), and others (n = 6). In 38/58 trials (65%), efficacy results did not reach the H_1 hypothesis of the specified primary endpoint, eight trials did not report their primary endpoint, and 12 trials (20%) were considered positive (H_1 hypothesis reached) (Table 2).

The reported median ORR was 5.3% (range 0–43.2%) in 48 trials with available ORR. The ORR was 0% in of 19/48 trials (Fig. 3A). The highest ORR was 43.2% in a phase II trial investigating apatinib [47]. Two trials evaluating cabozantinib reached the defined threshold for efficacy based on the composite ORR/DCR primary endpoint, with respectively: ORR = 12% (4–26%) and DCR = 33% (20–50%) at 6 months [52] and ORR = 7% and DCR = 34% at 4 months [24].

The reported median DCR was 33.3% (range 0–81.4%) in 43/58 trials with DCR available. The DCR was 0% in 5/43 trials (Fig. 3A). One trial evaluating Rexin-G was reported positive based on the DCR (DCR = 59% at 4 weeks, range 33–85%) [73]. The highest DCR was reported for apatinib/camrelizumab combination (DCR = 85.4% after one cycle of treatment = 8 weeks), but the 6 month-PFS primary endpoint of 50.9% (range 35–65%) was below the H_1 hypothesis of 60% [15].

The reported median 4-month PFS was 44% (range 0–76%) in 18 trials with 4-month PFS available (Fig. 3B). Nine trials were considered positive based on a PFS primary efficacy endpoint at a specific but variable time point: one randomized trial investigating regorafinib showed an 8-week PFS of 65% [39]; three trials showed a 4-month PFS of 46% (28–63%) for sorafenib [74], 44% (27–61%) for the combination sirolimus/gemcitabine [33], and 57% for apatinib [47]; one trial evaluating sunitinib/nivolumab combination showed a 6-month PFS of 32% [21]. In 27 trials median PFS was available and the median PFS was 3 months (range 1.2–19.4). Four of these 27 trials were considered positive based on median PFS, evaluating apatinib (med-PFS = 7.93 months for 11 osteosarcoma patients among 64 other sarcoma patients) [20], regorafinib in a randomized trial (med-PFS = 3.6 months vs 1.7 for placebo; hazard ratio = 0.42, range 0.21–0.85) [38], apatinib (med-PFS = 9.2 months, range 7.5–11) [14], and anlotinib (med-PFS = 4.8 months, range 3.5–7.1) [19].

The reported median OS was 9.9 months (range 5.5–27.4) in 20 trials with OS as the primary endpoint, and all concluded that the agent was ineffective.

Discussion

We performed a comprehensive analysis of 71 relevant therapeutic phase-II trials for recurrent/refractory osteosarcoma identified between 2017 and 2022 and compared it to a previously published analysis of 98 trials identified between 2003 and 2016 [10]. We observed: (I) an increase in the number of recurrent/refractory osteosarcoma therapeutic phase-II trials, with a quarter of the osteosarcoma-specific/strata trials

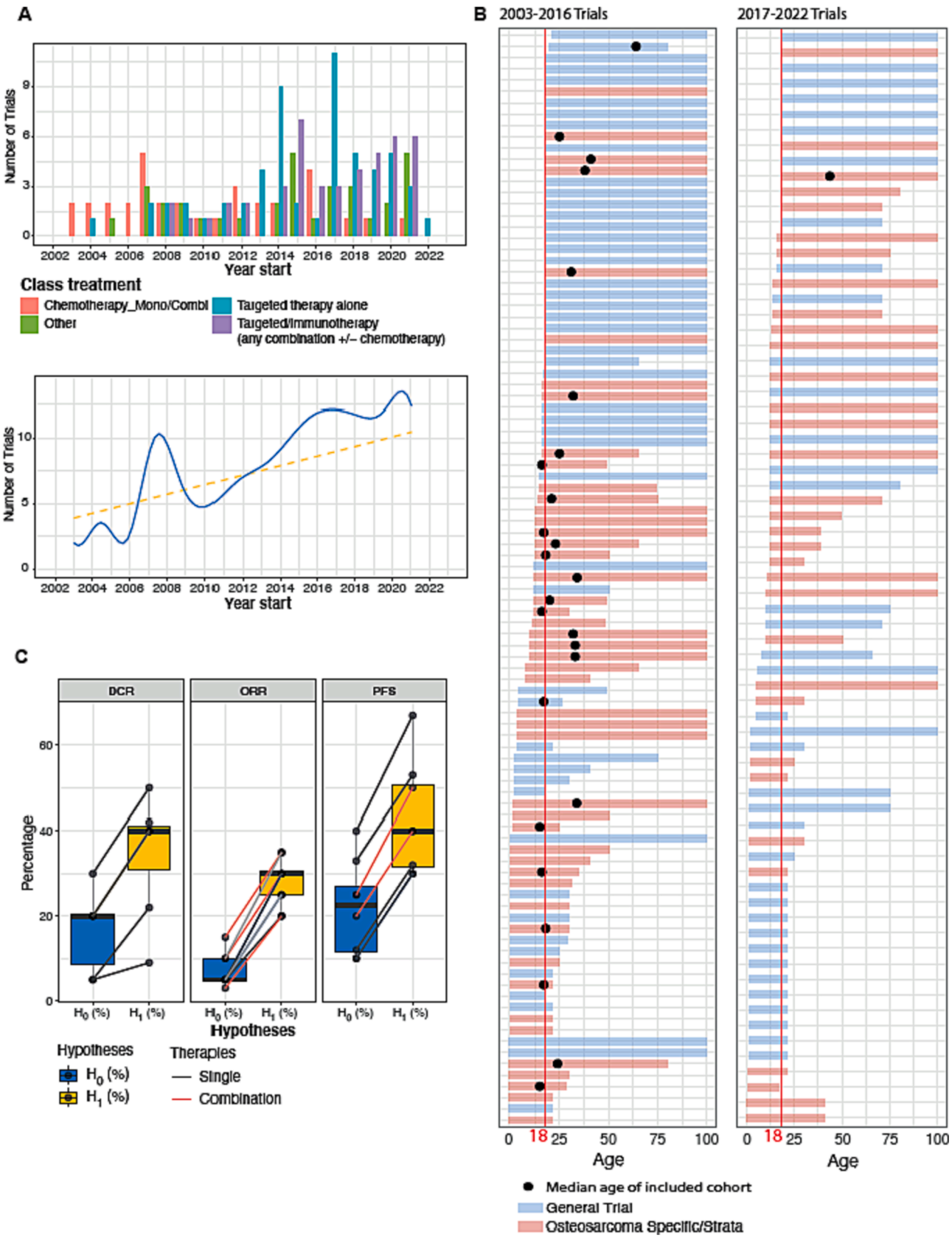

Fig. 2. Trials characteristics: 2A - Number of trials initiated and therapeutic approaches per year eligible for recurrent/refractory osteosarcoma. 2B - Trial age inclusion criteria (minimal to maximum), specified for solid tumor trials and osteosarcoma specific/strata, comparing 2003–2016 and 2017–2022 study period and providing median age of patients included. 2C - Trial statistical hypotheses (H_0/H_1) for osteosarcoma specific/strata trials.

Table 1
General trial characteristics, trial status, study population and design.

	All trials included			Osteosarcoma specific/strata trials		
	2003–2016(N = 98)	2017–2022(N = 71)	P-value	2003–2016(N = 47)	2017–2022(N = 33)	P-value
Publication status			<0.001			<0.001
No data available	23 (23 %)	54 (76 %)		5 (11 %)	26 (79 %)	
Abstract only	12 (12 %)	9 (13 %)		5 (11 %)	3 (9 %)	
Peer-reviewed publication	63 (64 %)	8 (11 %)		37 (79 %)	4 (12 %)	
Study organization			0.97			0.83
Multicenter	65 (66 %)	46 (65 %)		35 (74 %)	23 (70 %)	
One	33 (34 %)	25 (35 %)		12 (26 %)	10 (30 %)	
Study location			0.05			0.12
North America/USA	57 (58 %)	36 (51 %)		24 (51 %)	16 (48 %)	
Asia	10 (10 %)	18 (25 %)		3 (6 %)	8 (24 %)	
Europe	19 (19 %)	8 (11 %)		13 (28 %)	6 (18 %)	
Other/Intercontinental[(1)]	12 (12 %)	9 (13 %)		7 (15 %)	3 (9 %)	
Trial sponsor			1.00			0.47
Academic	75 (77 %)	54 (76 %)		36 (77 %)	22 (67 %)	
Pharma	23 (23 %)	17 (24 %)		11 (23 %)	11 (33 %)	
Mono or combination therapy			1			0.35
Monotherapy	61 (62 %)	44 (62 %)		29 (62 %)	16 (48 %)	
Combination	37 (38 %)	27 (38 %)		18 (38 %)	17 (52 %)	
Chemotherapy			0.03			0.27
No	62 (63 %)	56 (79 %)		27 (57 %)	23 (70 %)	
Yes	36 (37 %)	15 (21 %)		20 (18 %)	10 (30 %)	
Targeted therapy			0.001			0.004
No	58 (59 %)	24 (34 %)		31 (66 %)	11 (33 %)	
Yes	40 (41 %)	47 (66 %)		16 (34 %)	22 (67 %)	
Immunotherapy			0.15			0.24
No	71 (72 %)	44 (62 %)		33 (70 %)	19 (58 %)	
Yes	27 (28 %)	27 (38 %)		14 (30 %)	14 (42 %)	
Patient age			0.07[(2)]			0.76[(2)]
Children < 12 eligible	45 (46%)	36 (51%)		27 (57%)	13 (39%)	
Teenagers eligible	23 (23%)	22 (31%)		14 (30%)	15 (45%)	
Adults only	30 (31%)	13 (18%)		6 (13%)	5 (15%)	
Patient population						
Solid tumors	51 (52 %)	38 (54 %)	0.91			
Osteosarcoma stratum	22 (22 %)	14 (20 %)		22 (47 %)	14 (42 %)	0.87
Osteosarcoma only	25 (26 %)	19 (27 %)		25 (53 %)	19 (58 %)	
Disease requirement						
Measurable disease only	86 (88 %)	53 (75 %)	0.023	39 (83 %)	25 (76 %)	0.11
Evaluable disease allowed	3 (3 %)	10 (14 %)		0 (0 %)	3 (9 %)	
Surgical remission allowed	9 (9 %)	8 (11 %)		8 (17 %)	5 (15 %)	
Biomarker driven trial						
No	83 (85 %)	53 (75 %)	0.15	46 (98 %)	31 (94 %)	0.75
Yes	15 (15 %)	18 (25 %)		1 (2 %)	2 (6 %)	
Pulmonary only disease						
No	92 (94 %)	66 (93 %)	1	43 (91 %)	30 (91 %)	1
Yes	6 (6 %)	5 (7 %)		4 (9 %)	3 (9 %)	
Lines of (chemo)therapy (minimal)						
0	0 (0 %)	1 (1 %)	0.03[(3)]	0 (0 %)	1 (3 %)	0.03[(3)]
1	92 (94 %)	70 (99 %)		41 (87 %)	32 (97 %)	
2	6 (6 %)	0 (0 %)		6 (13 %)	0 (0 %)	
Lines of (chemo)therapy (maximal)			0.05[(4)]			0.05[(4)]
1	8 (8 %)	3 (4 %)		7 (15 %)	2 (6 %)	
2	6 (6 %)	2 (3 %)		3 (6 %)	2 (6 %)	
3	6 (6 %)	2 (3 %)		5 (11 %)	2 (6 %)	
4	3 (3 %)	0 (0 %)		1 (2 %)	0 (0 %)	
5	1 (1 %)	0 (0 %)		0 (0 %)	0 (0 %)	
No upper limit	74 (76 %)	64 (90 %)		31 (66 %)	27 (82 %)	
Trial arms			0.50[(5)]			0.15[(5)]
Single Arm	85 (87 %)	64 (90 %)		37 (79 %)	30 (91 %)	
Other						
Cross-over	1 (1 %)	0 (0 %)		0 (0 %)	0 (0 %)	
Multi-arm	1 (1 %)	1 (1 %)		1 (2 %)	0 (0 %)	
2 parallel groups	11 (11 %)	6 (8 %)		9 (19 %)	3 (9 %)	
Trial allocation in multi-arm trials						
Randomized	9 (9 %)	4 (6 %)	0.57	6 (13 %)	3 (9 %)	0.88
Trial blinding			0.64[(6)]			0.64[(6)]
Open	95 (97 %)	70 (99 %)		44 (94 %)	32 (97 %)	
Double-blind	3 (3 %)	1 (1 %)		3 (6 %)	1 (3 %)	
Statistical design						
One-stage	3 (3 %)	0 (0 %)		3 (6 %)	0 (0 %)	
Simon two-stage	27 (28 %)	11 (15 %)		16 (34 %)	10 (30 %)	
Bayesian	4 (4 %)	0 (0 %)		4 (9 %)	0 (0 %)	
Dual endpoint	1 (1 %)	0 (0 %)		1 (2 %)	0 (0 %)	
Other	4 (4 %)	2 (3 %)		1 (2 %)	0 (0 %)	

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Table 1 (*continued*)

	All trials included			Osteosarcoma specific/strata trials		
	2003–2016(N = 98)	2017–2022(N = 71)	P-value	2003–2016(N = 47)	2017–2022(N = 33)	P-value
Missing	59 (60 %)	58 (82 %)		22 (7%)	23 (70 %)	
Current primary efficacy endpoint			0.09[7]			0.07[7]
DCR	24 (24 %)	8 (11 %)		9 (19 %)	8 (24 %)	
Response	44 (45%)	34 (49%)		20 (43%)	6 (18 %)	
RR	3 (3 %)	4 (6 %)		1 (2 %)	0 (0 %)	
ORR	36 (37 %)	28 (40 %)		17 (36 %)	5 (15 %)	
CRR	0 (0 %)	1 (1 %)		0 (0 %)	1 (3 %)	
Best OR/RR	5 (5 %)	1 (1 %)		2 (4 %)	0 (0 %)	
Survival	30 (31%)	28 (40%)		18 (38%)	19 (58%)	
PFS/PFR	25 (26 %)	22 (31 %)		16 (34 %)	13 (39 %)	
EFS	2 (2 %)	6 (9 %)		1 (2 %)	6 (18 %)	
OS	3 (3 %)	0 (0 %)		1 (2 %)	0 (0 %)	
Missing	0	1		0	0	
Methodology of response evaluation			0.22[8]			0.30[8]
RECIST 1.0 / 1.1	68 (69 %)	55 (77 %)		32 (68 %)	26 (79 %)	
Other						
WHO	8 (8 %)	0 (0 %)		5 (11 %)	0 (0 %)	
PET response	1 (1 %)	1 (1 %)		1 (2 %)	0 (0 %)	
iRECIST	0 (0 %)	1 (1 %)		0 (0 %)	1 (3 %)	
Not reported	21 (21%)	14 (20%)		9 (19.1%)	6 (18.2%)	

Columns: trials included in this review, previous review (Omer et al 2017.) and characteristics of studies specifically designed for patients with osteosarcoma, either with an osteosarcoma stratum or only including osteosarcoma)

1. Intercontinental is defined when multiple countries located at different continents are study locations
2. p-value of the test comparing < 18 years versus ≥ 18 years
3. p-value of the test comparing 0–1 vs 2 lines of (chemo)therapy (minimal)
4. p-value of the test comparing 1 vs 2–5 vs no upper limit for lines of (chemo)therapy (maximal)
5. p-value of the test comparing single-arm vs other
6. Fisher exact test
7. p-value of the test comparing DCR vs response outcome vs survival outcome
8. p-value of the test comparing RECIST vs Other vs Not reported

DCR: disease control rate; RR: response rate; ORR: objective response rate; CRR: complete response rate; BOR: best objective response; PFS: progression free survival; progression free survival rate; EFS: event-free survival; OS: overall survival; WHO: world health organization; RECIST: response evaluation criteria in solid tumors; PET: Positron emission tomography.

Table 2
Recurrent/relapse osteosarcoma phase-II trials that concluded efficacy (H_1 hypothesis reached) for the 2003–2022 period.

Trial ID	Drug	Population	Continent	Outcome	N	ORR (%)	DCR (%)	4-mPFS (%) [95% - CI]	Med-PFS (m) [95% CI]
NCT00572130	Rexin-G	Specific	USA	DCR	22	0	58.8	50	3
NCT00889057	Sorafenib	Specific	Europe	PFS	35	8.6	48.6	46 [28–63]	4 [3–5]
NCT02429973	Sirolimus + Gemcitabine	Specific	Europe	PFS	35	6.1	48.5	44 [27–61]	2.3 [0–5.2]
NCT02048371	Regorafenib	Stratum	USA	PFS	22	13.6	NA	44	3.6 [2.0–7.6]
NCT02389244	Regorafenib	Stratum	Europe	PFS	26	7.7	73.1	35 [17–52]	3.8 [1.8–6.3]
NCT02243605	Cabozantinib	Stratum	Europe	DCR	42	16.7	78.6	71 [55–83]	6.7 [5.4–7.9]
NCT02711007	Apatinib	Specific	Asia	PFS	37	43.2	64.9	57 [36–71]	4.5 [3.5–6.3]
NCT03277924	Sunitinib + Nivolumab	Solid	Europe	PFS	17	NA	NA	NA	3.7 [3.4–4.0]
NCT03121846	Apatinib	Solid	Asia	PFS	11	15.3	57.6	NA	NA
NCT03163381	Apatinib	Specific	Asia	PFS	11	NA	NA	NA	9.2 [7.5–11]
NCT02867592	Cabozantinib-S-Malate	Solid	USA	ORR	29	6.9	34.5	NA	NA
NCT03527888	Anlotinib	Stratum	Asia	PFS	29	6.9	75.9	NA	4.8 [3.5–7.1]

Population: Specific: osteosarcoma only; stratum: osteosarcoma stratum; Solid: Solid tumor wider inclusion. N: Number of osteosarcoma patients.

industry-sponsored; (II) an increased evaluation of targeted and immune therapy over chemotherapy including in combination, and few biomarker-driven trials; and (III) persistent heterogeneity in trial entry criteria (age, disease localization, tumor burden), primary endpoint (although survival endpoints were more often used since 2017), and statistical hypotheses, but no increase in the number of randomized trials. Exploitable efficacy results of 58 phase-II trials during the 19 years period between 2003 and 2022 with at least partially published data showed limited impact on outcomes in recurrent/refractory osteosarcoma. Twenty percent of recurrent/refractory osteosarcoma-specific/strata trials have reported positive efficacy results, mostly evaluating multi-targeted kinase inhibitors (MTKI). A class effect was observed for MTKI monotherapy, with a 4-month PFS of 38–71%, significantly better than placebo in randomized trials [38,39,52,74,75], but trial heterogeneity complicates the prioritization of one MTKI over another for further development, as highlighted in the dedicated ACCELERATE pediatric prioritization forum on MTKI in bone sarcomas [76].

Joint adolescent/adult trials represented 85% of recurrent/refractory osteosarcoma-specific trials, paralleling recurrent osteosarcoma epidemiology (90% of occurrences after 12 years of age) (3), in line with multi-stakeholder expert opinion [77] and FDA recommendations [78] to include adolescents from 12 years of age in adult trials when medically justified, even if pediatric phase-I data are not yet available [76–80]. In the USA, after 2017, 96% of osteosarcoma-specific trials included patients aged 12 years or younger, compared to 50% between 2003 and 2016 [10]. Evaluable disease at trial entry was increasingly used (9% vs. 0%, respectively), allowing more patients in need of novel therapies/strategies to accrue. However, the heterogeneity of trial inclusion criteria remained in terms of measurable/evaluable,

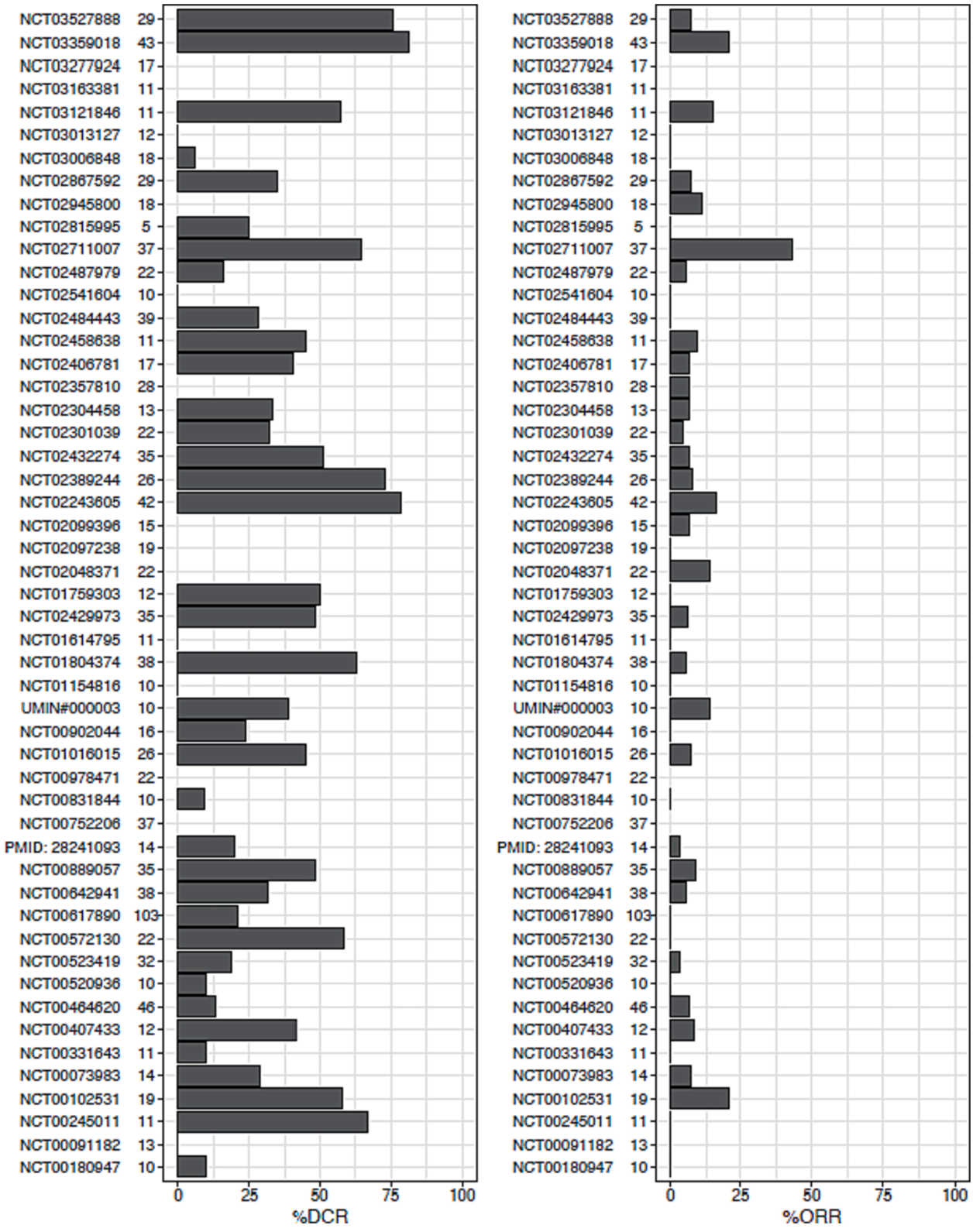

Fig. 3A. Reported ORR, DCR in osteosarcoma specific/strata trials or general trials including ≥ 10 patients.

unresectable/resectable disease, metastatic localizations, and number of previous systemic treatments, which might influence the statistical hypotheses. Recent trials have also included patients with primary disease in the same cohort as recurrent/refractory osteosarcoma to evaluate maintenance treatment after standard therapy (e.g., regomain, NCT04698785). Heterogeneity in terms of surgical resection during trials might also influence the results, as complete surgical resection remains the main prognostic factor in recurrent osteosarcoma [2,81,82].

In 2016, two articles highlighted the lack of historical data and proposed strategies to support statistical hypotheses [7,10], following previous recommendations for the design of phase II clinical trials in oncology [83]. Both studies also recommended the use of survival

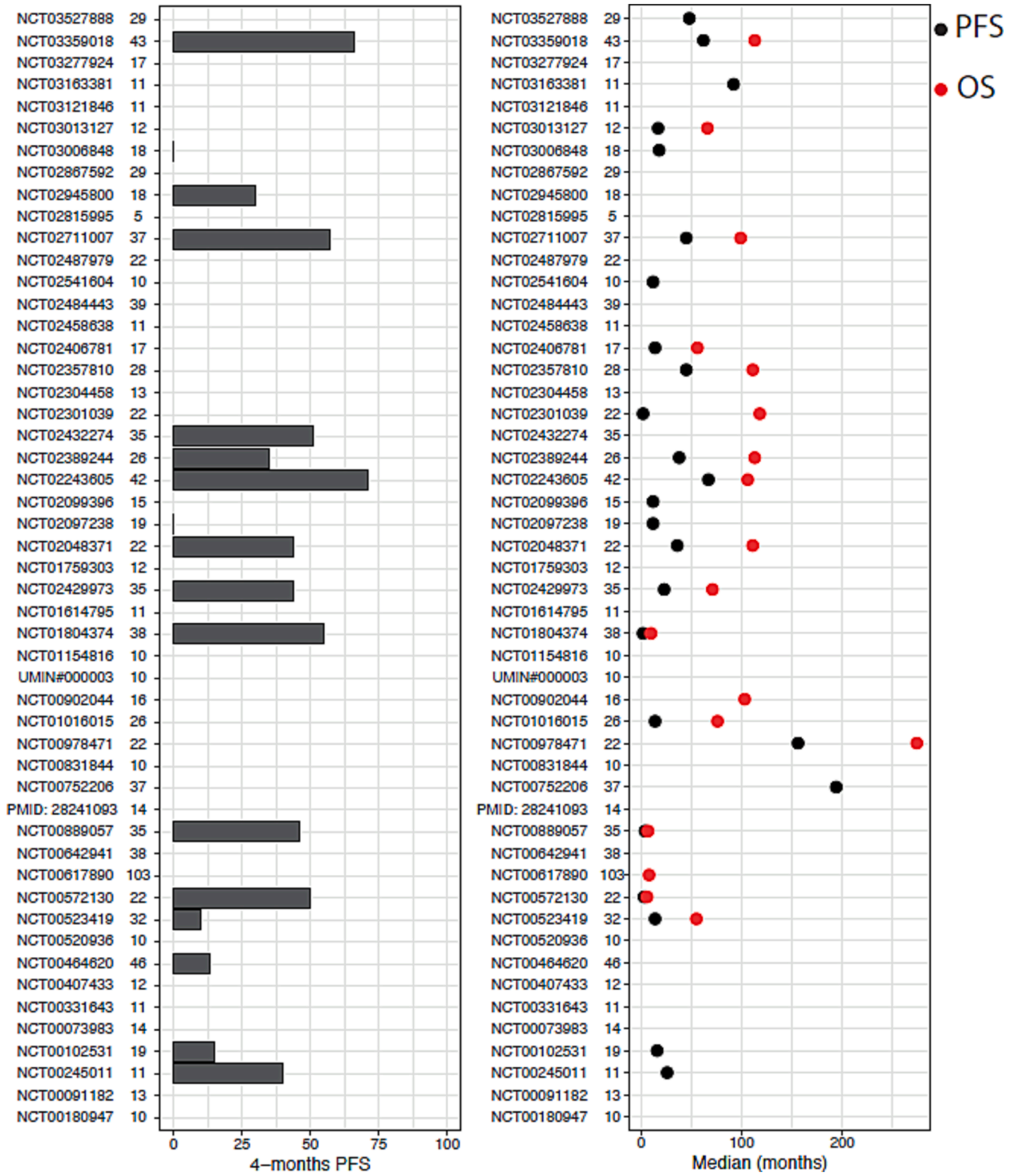

Fig. 3B. Reported PFS-4 and median PFS/OS (months) in osteosarcoma specific/strata trials or general trials including ≥ 10 patients.

primary endpoints, based on osteosarcoma bone-matrix producing capacity limiting tumor shrinkage according to RECIST and no clear association between tumor volumetric response and survival [84]. Between 2017 and 2023, survival primary endpoint use increased up to 58% of recurrent/refractory osteosarcoma-specific/strata phase-II trials, but remained heterogeneous (type, definition, time point), reflecting the debate on the appropriate survival primary endpoint to be used as a surrogate marker of OS to get drugs approved, with PFS being increasingly used [85–87]. Based on seven previous negative COG studies, Lagmay et al. proposed a single-arm phase II trial approach to evaluate single drugs in measurable recurrent/refractory osteosarcomas, with a 4-month EFS of 12% and 40% (H_0/H_1) to conclude a positive trial [7] Omer et al., based on literature analysis, proposed a randomized approach to minimize population bias and lack of historical data for the

evaluation of both mono- and combination therapies [10]. Increased use of the Lagmay approach was seen mainly in the USA (8/9 trials) [40,41,56,61,70–72], while randomized trials were rare, and the number did not increase over time, likely at least in part due to the higher number of patients required and costs. This study had some limitations. For example, the REGOBONE randomized trial evaluating regorafenib against placebo, which concluded positively according to the statistical plan analysis [39], did not reach the Lagmay approach criteria of success.

For trials evaluating combinations of new therapies with chemotherapy, the limitation of a single-arm approach is underlined by the lack of strong historical data on recurrent/refractory osteosarcoma treated with chemotherapy alone. Although potentially useful, no consensus exists on the use of chemotherapy and the optimal regimen for patients with recurrent/refractory osteosarcoma [6,8]. Between 2003 and 2022, trials combining new drugs with chemotherapy (ifosfamide+/-etoposide, n = 6; gemcitabine+/-docetaxel, n = 6) used variably higher H_0/H_1 hypotheses than monotherapy, with no clear rationale. The gemcitabine/docetaxel combination was considered ineffective in two phase-II trials (ORR of 7–17%) [88,89], but effective in retrospective cohorts [90], and remains in use in recent combination trials with other therapeutic classes (NCT04595994, NCT03742192, NCT04833582, and NCT05093322). Few previous studies exist on ifosfamide efficacy in recurrent/refractory osteosarcomas as monotherapy (two retrospective monocentric cohorts: 8 week PFS of 54% [91], 6 month PFS of 51% [92]) and combined with etoposide (pediatric phase-II trial, ORR = 48% [93]) to inform the H_0 hypothesis in phase-II trials. In addition, ifosfamide/etoposide administration schedules and doses vary greatly among trials (NCT04154189 [94]; NCT04824352). The promising results of the phase-Ib single-arm trial investigating lenvatinib + ifosfamide/etoposide combination (PFS-4 estimate 79.9%, 95% CI:60.5–90.5%) [75,95] were not confirmed in the 1:1 randomized phase-II trial comparing lenvatinib + ifosfamide/etoposide to ifosfamide/etoposide alone [30,75]. The ifosfamide/etoposide standard arm had a higher 4-month PFS of 66% (48–79%) than anticipated [30]. It is debatable whether randomized phase II trials with limited patient numbers are sufficient to detect efficacy in combination with chemotherapy. Hence, randomized phase II-III trial designs, such as the rECCur trial for Ewing sarcoma, may also be useful for osteosarcoma [96].

Besides MTKI/chemotherapy combinations, other combinations are being increasingly explored, such as targeted/targeted and targeted/immune therapy. The biological rationale is not always specific for osteosarcoma, and trials include drugs even though they are inefficient as monotherapy (e.g., anti-PD1) and without a clear predictive biomarker of efficacy even when efficacy is described in monotherapy (e.g., MTKI). Biomarker-driven trials could be an option for selecting a subset of patients who are more likely to respond to a given therapy. Proof-of-concept exists in preclinical models that target osteosarcoma cell-specific abnormalities [97]. Biomarker-driven trials exploring monotherapies in single-arm designs for different sarcomas are increasing. Osteosarcoma-specific/strata trials primarily focus on tumor expression profiles (HER2 and GD2) or genetic alterations. Their use, with increased knowledge of osteosarcoma biology, might also facilitate a more rational choice for combination therapy to be evaluated in future trials [98].

The strength of our systematic review lies in the broad inclusion criteria identifying trials regardless of their publication status over a long, 19 years period of time (2003–2022), allowing analysis of evolutionary trends of both specific osteosarcoma trials and those with a larger disease spectrum accruing osteosarcoma. This systematic analysis of trial methodology is not present in expert guidelines or other reviews [99–102]. The long period also allows sufficient follow-up, with 54% of the trials being completed and with published (preliminary) results, to analyze the efficacy of the evaluated drug and/or combination therapy. However, we acknowledge the limitations of this study. We attempted to minimize exhaustiveness bias in trial identification and missing data by a systematic comprehensive search of multiple trial registries and publication sources. However, we did not retrieve individual patient data, but extracted published results. Furthermore, we lack detailed information on statistical hypotheses (approximately 85% of the trials registered in 2017–2022) as such data are commonly not available from registries. In addition, 9 trials completed between 2017 and 2022 had no published results, suggesting a lack of efficacy of the evaluated therapy that could not be verified. This underlines the importance of not only publishing positive results to further inform drug development.

In conclusion, further discussion of more homogenous trial designs and definition of endpoints is essential in recurrent/refractory osteosarcoma to improve the current outcome. Randomized trials are preferred, especially for combination therapies and for the first recurrence. Single-arm trials could be considered more suitable for monotherapy in subsequent recurrences to obtain a signal of efficacy, with the need to accrue a limited number of patients, although no robust historical data could be extracted from identified phase-II trials. As such, trials can address patient needs (define standard treatment strategy according to disease presentation and access to new efficient drugs) and drug development needs (rapidly answered efficacy question with minimum number of patients). In addition, biology/biomarker-driven trials should be further developed to better select patients who might benefit from a specific therapy or combination strategy.

The Fight Osteosarcoma Through European Research (FOSTER) consortium has recently been established to bring together oncologists, researchers, pathologists, radiologists, patients, parents, and other stakeholders involved in the management of patients with osteosarcoma to work together to improve outcomes. A work package is dedicated to trials for recurrent/refractory osteosarcoma with the objective of improving trial design and enhancing the development of new international trials, with more biology-driven approaches, informed by work packages dedicated to biology.

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CRediT authorship contribution statement

Roelof van Ewijk: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization. **Morgane Cleirec:** Investigation, Writing – review & editing. **Nikolas Herold:** Investigation, Writing – review & editing. **Marie-Cécile le Deley:** Methodology, Formal analysis, Writing – review & editing. **Natasha van Eijkelenburg:** Writing – review & editing. **Pascaline Boudou-Rouquette:** Writing – review & editing. **Séverine Risbourg:** Formal analysis, Writing – review & editing. **Sandra J. Strauss:** Writing – review & editing. **Emanuela Palmerini:** Writing – review & editing. **Kjetil Boye:** Writing – review & editing. **Leo Kager:** Writing – review & editing. **Stefanie Hecker-Nolting:** Writing – review & editing. **Antonin Marchais:** Formal analysis, Writing – review & editing, Visualization. **Nathalie Gaspar:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [RE declares funding by the Princess Maxima foundation. KB declares

honoraria for educational events for Novartis and has received honoraria for participation on advisory boards for glaxosmithkline, Bayer, NEC Oncoimmunity and Incyte. NE declares honoraria for educational events by Merck/MSD. NH declares a grant by the Swedish Childhood Cancer Fund. EP declares honoraria for participation on advisory boards for Deciphera Pharmaceutical, Eusa Pharma, SynOx Therapeutics and Daiichy Sankyo. SS declares consulting fees by Ceridwen Oncology, support for travel by Adaptimmune and has received honoraria for participation of an advisory board for glaxosmithkline. All remaining authors have declared no conflicts of interest.].

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Appendix A. Supplementary material

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