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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?

Roelof van Ewijk [a], Morgane Cleirec [b], Nikolas Herold [c], Marie-Cécile le Deley [d,e], Natasha van Eijkelenburg [a], Pascaline Boudou-Rouquette [f], Séverine Risbourg [d], Sandra J. Strauss [g], Emanuela Palmerini [h], Kjetil Boye [i], Leo Kager [j,k], Stefanie Hecker-Nolting [l], Antonin Marchais [m,n], Nathalie Gaspar [m,n,*], On behalf of the FOSTER Consortium (Fight OsteoSarcoma Through European Research), work package 3 on recurrent/refractory osteosarcoma trials

[a] *Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands*
[b] *Department of Pediatric Oncology, CHU Nantes, Nantes, France*
[c] *Paediatric Oncology, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden, and Childhood Cancer Research Unit, Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden*
[d] *Unité de Méthodologie et Biostatistiques, Centre Oscar Lambret, Lille, France*
[e] *Université Paris-Saclay, Université Paris-Sud, UVSQ, CESP, INSERM, U1018 ONCOSTAT, F-94085 Villejuif, France*
[f] *Department of Medical Oncology, Cochin Hospital, Cochin Institute, INSERMU1016, Paris Cancer Institute, CARPEM, AP-HP, Paris, France*
[g] *Department of Oncology, University College London Cancer Institute, London, UK*
[h] *Osteoncology, Bone and Soft Tissue Sarcomas and Innovative Therapies, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy*
[i] *Department of Oncology, Oslo University Hospital, Norway*
[j] *St. Anna Children's Hospital, Department of Pediatrics, Medical University Vienna, Vienna, Austria*
[k] *St. Anna Children's Cancer Research Institute (CCRI), Vienna, Austria*
[l] *Klinikum Stuttgart-Olgahospital, Stuttgart, Germany*
[m] *Department of Oncology for Child and Adolescents, Gustave Roussy Cancer Center, Paris-Saclay University, Villejuif, France*
[n] *National Institute for Health and Medical Research (INSERM) U1015, BiiOSTeam, Gustave Roussy Institute, Villejuif, France*

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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.

* Corresponding author at: Department of Oncology for Child and Adolescent, Gustave Roussy Cancer Campus, 114 Rue Edouard Vaillant, 94805 Villejuif Cedex, France.
*E-mail address:* nathalie.gaspar@gustaveroussy.fr (N. Gaspar).

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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 $\alpha$ 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

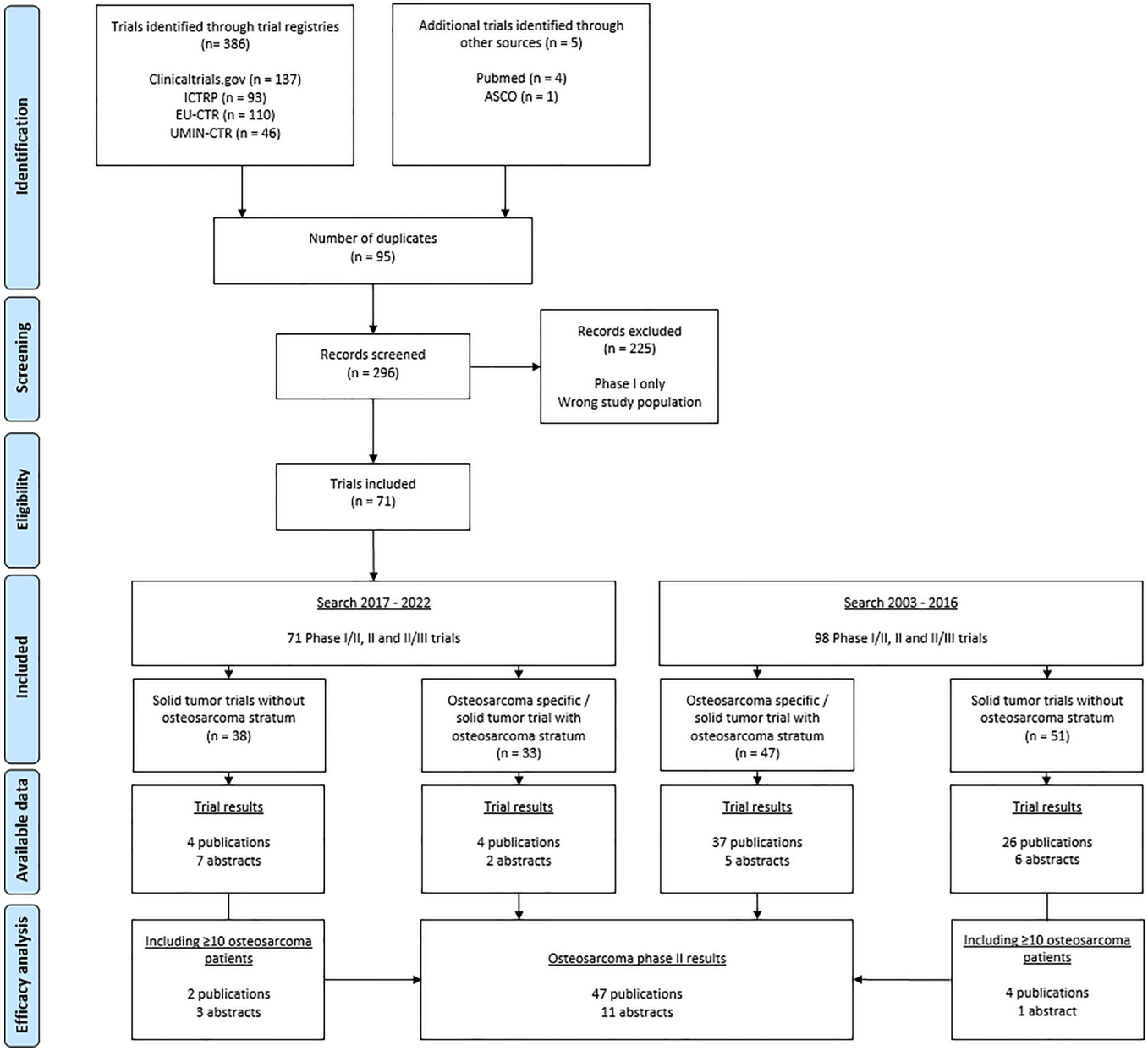


**Fig. 1.** Flow diagram trial search 2017–2022 and publication search 2017–2022 and 2003–2016.

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

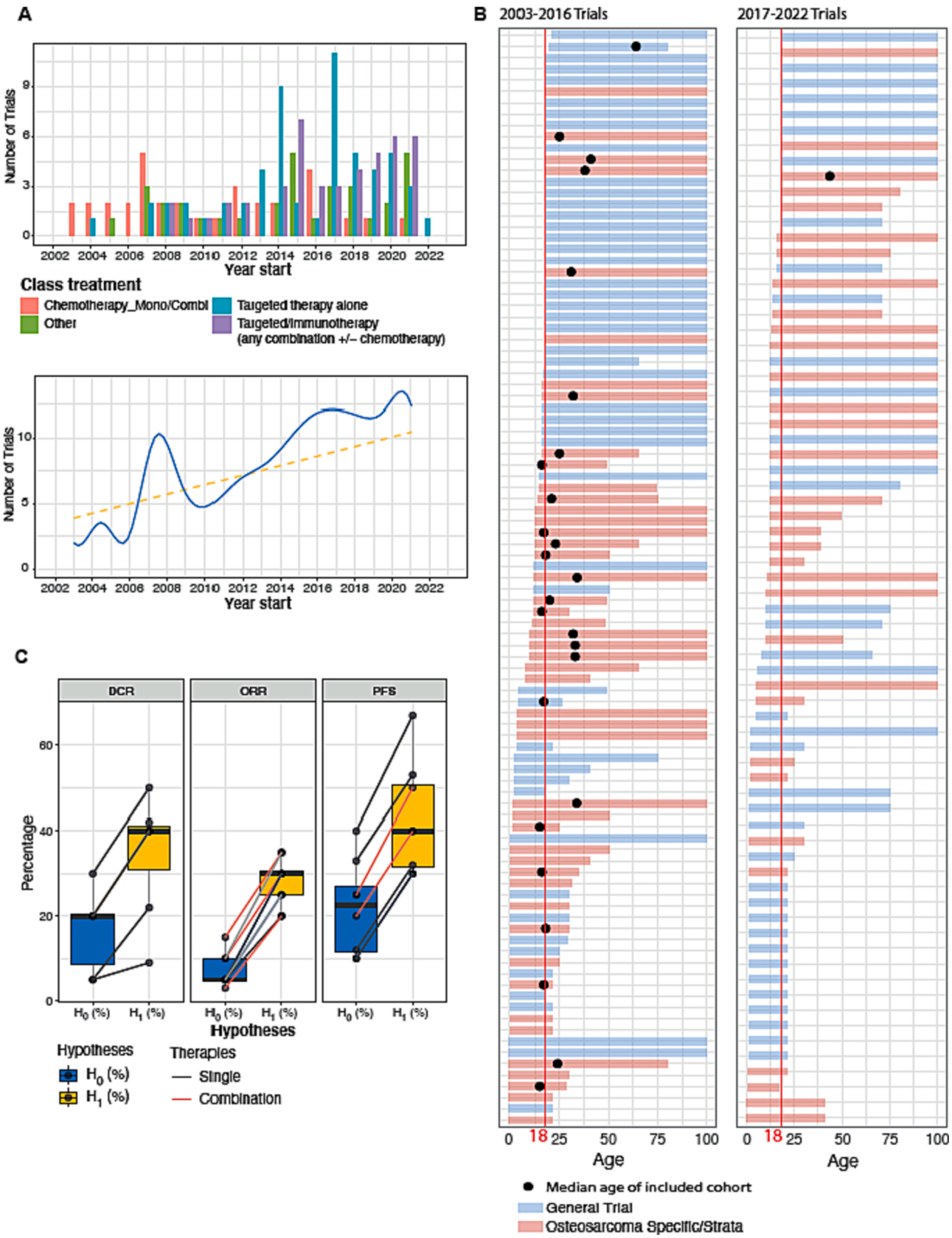


**Fig. 2.** Trials characteristics: 2A - Number of trials initiated and therapeutic approaches per year eligible for recurrent/refractory osteosarcoma. 2B - Trial age inclusion criteria (minimal to maximum), specified for solid tumor trials and osteosarcoma specific/strata, comparing 2003–2016 and 2017–2022 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 %) | |

(*continued on next page*)

**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 $\geq 18$ 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,

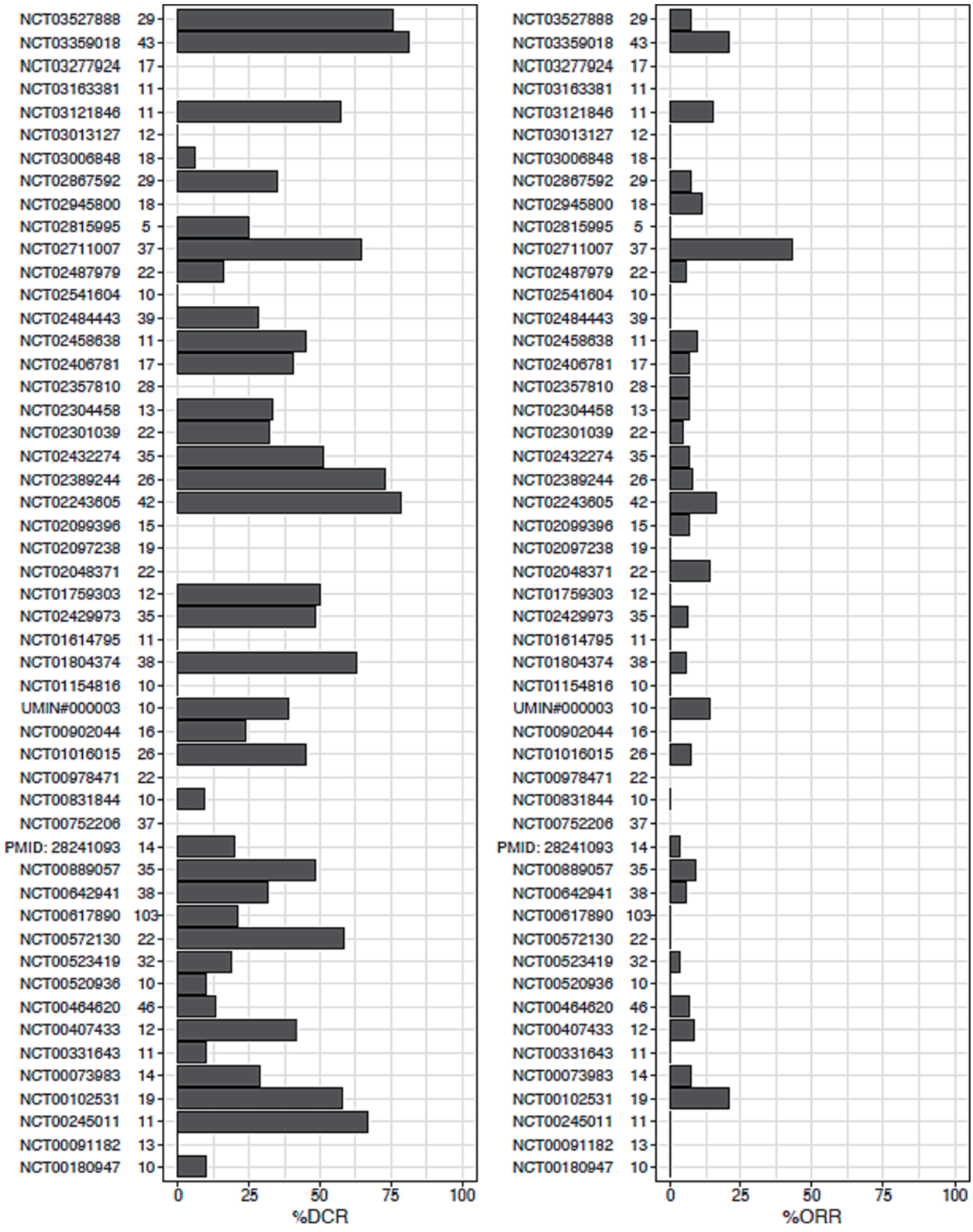


**Fig. 3A.** Reported ORR, DCR in osteosarcoma specific/strata trials or general trials including ≥ 10 patients.

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

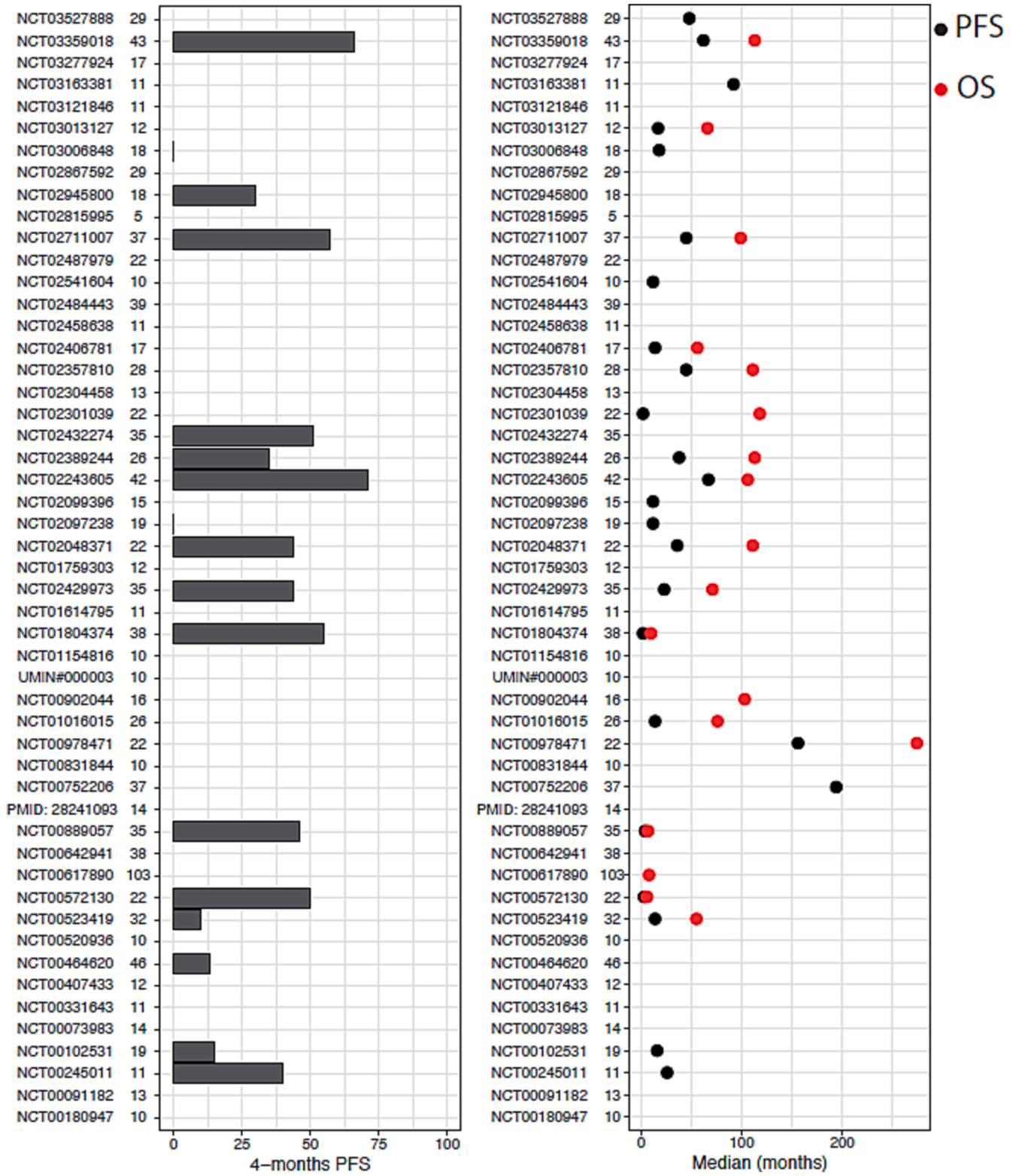


**Fig. 3B.** Reported PFS-4 and median PFS/OS (months) in osteosarcoma specific/strata trials or general trials including ≥ 10 patients.

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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## References

[1] Stiller CA, Trama A, Serraino D, Rossi S, Navarro C, Chirlaque MD, et al. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. Eur J Cancer 2013;49(3):684–95.
[2] Kempf-Bielack B, Bielack SS, Jurgens H, Branscheid D, Berdel WE, Exner GU, et al. Osteosarcoma relapse after combined modality therapy: an analysis of unselected patients in the Cooperative Osteosarcoma Study Group (COSS). J Clin Oncol 2005;23(3):559–68.
[3] Thebault E, Piperno-Neumann S, Tran D, Pacquement H, Marec-Berard P, Lervat C, et al. Successive Osteosarcoma Relapses after the First Line O2006/Sarcome-09 Trial: What Can We Learn for Further Phase-II Trials? Cancers (Basel) 2021;13(7).
[4] Bielack SS, Smeland S, Whelan JS, Marina N, Jovic G, Hook JM, et al. Methotrexate, Doxorubicin, and Cisplatin (MAP) Plus Maintenance Pegylated Interferon Alfa-2b Versus MAP Alone in Patients With Resectable High-Grade Osteosarcoma and Good Histologic Response to Preoperative MAP: First Results of the EURAMOS-1 Good Response Randomized Controlled Trial. J Clin Oncol 2015;33(20):2279–87.
[5] Gaspar N, Occean BV, Pacquement H, Bompas E, Bouvier C, Brisse HJ, et al. Results of methotrexate-etoposide-ifosfamide based regimen (M-EI) in osteosarcoma patients included in the French OS2006/sarcome-09 study. Eur J Cancer 2018;88:57–66.
[6] Isakoff MS, Bielack SS, Meltzer P, Gorlick R. Osteosarcoma: Current Treatment and a Collaborative Pathway to Success. J Clin Oncol 2015;33(27):3029–35.
[7] Lagmay JP, Krailo MD, Dang H, Kim A, Hawkins DS, Beaty 3rd O, et al. Outcome of Patients With Recurrent Osteosarcoma Enrolled in Seven Phase II Trials Through Children's Cancer Group, Pediatric Oncology Group, and Children's Oncology Group: Learning From the Past to Move Forward. J Clin Oncol 2016;34(25):3031–8.
[8] Strauss SJ, Frezza AM, Abecassis N, Bajpai J, Bauer S, Biagini R, et al. Bone sarcomas: ESMO-EURACAN-GENTURIS-ERN PaedCan Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2021;32(12):1520–36.
[9] Beird HC, Bielack SS, Flanagan AM, Gill J, Heymann D, Janeway KA, et al. Osteosarcoma Nat Rev Dis Primers 2022;8(1):77.
[10] Omer N, Le Deley MC, Piperno-Neumann S, Marec-Berard P, Italiano A, Corradini N, et al. Phase-II trials in osteosarcoma recurrences: A systematic review of past experience. Eur J Cancer 2017;75:98–108.
[11] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
[12] Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021;372:n160.
[13] Miwa S, Nishida H, Tanzawa Y, Takeuchi A, Hayashi K, Yamamoto N, et al. Phase 1/2 study of immunotherapy with dendritic cells pulsed with autologous tumor lysate in patients with refractory bone and soft tissue sarcoma. Cancer 2017;123(9):1576–84.
[14] Weitao Y, Fangxing W, Qiqing C, Jiaqiang W. Efficacy and safety of apatinib in advanced sarcoma: an open-label, nonrandomized, single-center study of 45 patients. Anticancer Drugs 2019;30(7):e0778.
[15] Xie L, Xu J, Sun X, Guo W, Gu J, Liu K, et al. Apatinib plus camrelizumab (anti-PD1 therapy, SHR-1210) for advanced osteosarcoma (APFAO) progressing after chemotherapy: a single-arm, open-label, phase 2 trial. J Immunother Cancer 2020;8(1).
[16] Boye K, Longhi A, Guren T, Lorenz S, Naess S, Pierini M, et al. Pembrolizumab in advanced osteosarcoma: results of a single-arm, open-label, phase 2 trial. Cancer Immunol Immunother 2021;70(9):2617–24.
[17] Naing A, Thistlethwaite F, De Vries EGE, Eskens F, Uboha N, Ott PA, et al. CX-072 (pacmilimab), a Probody ((R)) PD-L1 inhibitor, in advanced or recurrent solid tumors (PROCLAIM-CX-072): an open-label dose-finding and first-in-human study. J Immunother Cancer 2021;9(7).
[18] Loeb DM, Lee JW, Morgenstern DA, Samson Y, Uyttebroeck A, Lyu CJ, et al. Avelumab in paediatric patients with refractory or relapsed solid tumours: dose-escalation results from an open-label, single-arm, phase 1/2 trial. Cancer Immunol Immunother 2022;71(10):2485–95.
[19] Tang L, Niu X, Wang Z, Cai Q, Tu C, Fan Z, et al. Anlotinib for Recurrent or Metastatic Primary Malignant Bone Tumor: A Multicenter. Single-Arm Trial Front Oncol 2022;12:811687.
[20] Liao Z, Li F, Zhang C, Zhu L, Shi Y, Zhao G, et al. Phase II trial of VEGFR2 inhibitor apatinib for metastatic sarcoma: focus on efficacy and safety. Exp Mol Med 2019;51(3):1–11.
[21] Palmerini E, Lopez-Pousa A, Grignani G, Redondo A, Hindi N, Stacchiotti S, et al. IMMUNOSARC: a collaborative Spanish (GEIS) and Italian (ISG) sarcoma groups phase I/II trial of sunitinib and nivolumab in advanced soft tissue and bone sarcoma: Results from the phase II part, bone sarcoma cohort. J Clin Oncol 2020;38(15_suppl):11522-.
[22] Chua VS, Chawla SP, Zheng K, Kim T, Priore GD, Kim S. Phase II study of SM-88 in Ewing's and other sarcomas. J Clin Oncol 2021;39(15_suppl):e23505-e.
[23] Greengard EG, Williams RL, Liu X, Militano O, Fisher TL, Evans EE, et al. A phase I/II trial of VX15/2503 in children, adolescents, and young adults with relapsed or refractory solid tumors (ADVL1614). J Clin Oncol 2019;37(15_suppl):e21519-e.
[24] Akshintala S, Widemann BC, Barkauskas DA, Hall D, Reid JM, Voss SD, et al. Phase 2 trial of cabozantinib in children and young adults with refractory sarcomas, Wilms tumor, and rare tumors: Children's Oncology Group Study (ADVL1622). Journal of Clinical Oncology. 2021;39(15_suppl):10010-.
[25] Tang L, Niu X, Wang Z, Cai Q, Tu C, Fan Z, et al. A phase II study of anlotinib in treating patients with relapsed or metastatic primary malignant bone tumor. J Clin Oncol. 2020;38(15_suppl):11525-.
[26] Bishop MW, Kaste SC, Sykes A, Pan H, Cruz FSD, Whittle S, et al. OSTPDL1: A phase II study of avelumab, a monoclonal antibody targeting programmed death-ligand 1 (PD-L1) in adolescent and young adult patients with recurrent or progressive osteosarcoma. Journal of Clinical Oncology. 2020;38(15_suppl):10521-.
[27] Ye LL, Li R, Dou S, Shao Z, Ji T, Zhu G. A Phase II Trial of Radiotherapy Concurrent with Apatinib in Locally Advanced Bone and Soft Tissue Sarcoma of the Head and Neck: Preliminary Results. Red Journal 2020;108(3):S131–2.
[28] Chi SN, Yi JS, Williams PM, Roy-Chowdhuri S, Patton DR, Coffey B, et al. Tazemetostat in patients with tumors with alterations in EZH2 or the SWI/SNF complex: Results from NCI-COG Pediatric MATCH trial Arm C (APEC1621C). Journal of Clinical Oncology. 2022;40(16_suppl):10009-.
[29] Vo KT, Sabnis AJ, Williams PM, Roy-Chowdhuri S, Patton DR, Coffey B, et al. Ulixertinib in patients with tumors with MAPK pathway alterations: Results from NCI-COG Pediatric MATCH trial Arm J (APEC1621J). Journal of Clinical Oncology. 2022;40(16_suppl):3009-.
[30] Gaspar N, Hung G-Y, Strauss S, Campbell-Hewson Q, Cruz FD, Bender JG, et al., editors. A Multicenter, Open-label, Randomized, Phase 2 Study to Compare the Efficacy and Safety of Lenvatinib in Combination With Ifosfamide and Etoposide Versus Ifosfamide and Etoposide in Children, Adolescents, and Young Adults With Relapsed or Refractory Osteosarcoma (OLIE; ITCC-082). Connective Tissue Oncology Society Annual Meeting; 2022 November 16-19, 2022.
[31] Yoon JH, Kwon MM, Park HJ, Park SY, Lim KY, Joo J, et al. A study of docetaxel and irinotecan in children and young adults with recurrent or refractory Ewing sarcoma family of tumors. BMC Cancer 2014;14:622.
[32] Savage PD, Lovato J, Brosnihan KB, Miller AA, Petty WJ. Phase II Trial of Angiotensin-(1–7) for the Treatment of Patients with Metastatic Sarcoma. Sarcoma 2016;2016:4592768.
[33] Martin-Broto J, Redondo A, Valverde C, Vaz MA, Mora J, Garcia Del Muro X, et al. Gemcitabine plus sirolimus for relapsed and progressing osteosarcoma patients after standard chemotherapy: a multicenter, single-arm phase II trial of Spanish Group for Research on Sarcoma (GEIS). Ann Oncol 2017;28(12):2994–9.
[34] Tawbi HA, Burgess M, Bolejack V, Van Tine BA, Schuetze SM, Hu J, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. Lancet Oncol 2017;18(11):1493–501.
[35] D'Angelo SP, Mahoney MR, Van Tine BA, Atkins J, Milhem MM, Jahagirdar BN, et al. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. Lancet Oncol 2018;19(3):416–26.
[36] Hirbe AC, Jennings J, Saad N, Giardina JD, Tao Y, Luo J, et al. A Phase II Study of Tumor Ablation in Patients with Metastatic Sarcoma Stable on Chemotherapy. Oncologist 2018;23(7):760–e76.
[37] Moreno L, Casanova M, Chisholm JC, Berlanga P, Chastagner PB, Baruchel S, et al. Phase I results of a phase I/II study of weekly nab-paclitaxel in paediatric patients with recurrent/refractory solid tumours: A collaboration with innovative therapies for children with cancer. Eur J Cancer 2018;100:27–34.
[38] Davis LE, Bolejack V, Ryan CW, Ganjoo KN, Loggers ET, Chawla S, et al. Randomized Double-Blind Phase II Study of Regorafenib in Patients With Metastatic Osteosarcoma. J Clin Oncol 2019;37(16):1424–31.

[39] Duffaud F, Mir O, Boudou-Rouquette P, Piperno-Neumann S, Penel N, Bompas E, et al. Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study. Lancet Oncol 2019;20(1):120–33.

[40] Isakoff MS, Goldsby R, Villaluna D, Krailo MD, Hingorani P, Collier A, et al. A phase II study of eribulin in recurrent or refractory osteosarcoma: A report from the Children's Oncology Group. Pediatr Blood Cancer 2019;66(2):e27524.

[41] Kopp LM, Malempati S, Krailo M, Gao Y, Buxton A, Weigel BJ, et al. Phase II trial of the glycoprotein non-metastatic B-targeted antibody-drug conjugate, glembatumumab vedotin (CDX-011), in recurrent osteosarcoma AOST1521: A report from the Children's Oncology Group. Eur J Cancer 2019;121:177–83.

[42] Le Cesne A, Marec-Berard P, Blay JY, Gaspar N, Bertucci F, Penel N, et al. Programmed cell death 1 (PD-1) targeting in patients with advanced osteosarcomas: results from the PEMBROSARC study. Eur J Cancer 2019;119:151–7.

[43] Mosse YP, Fox E, Teachey DT, Reid JM, Safgren SL, Carol H, et al. A Phase II Study of Alisertib in Children with Recurrent/Refractory Solid Tumors or Leukemia: Children's Oncology Group Phase I and Pilot Consortium (ADVL0921). Clin Cancer Res 2019;25(11):3229–38.

[44] Peguero J, Sohal DPS, O'Neil BH, Safran H, Kelly K, Grilley-Olson JE, et al. Tissue/Site-Agnostic Study of Ribociclib for Tumors With Cyclin D-CDK4/6 Pathway Genomic Alterations: A Phase II, Open-Label. Single-Arm Basket Study JCO Precis Oncol 2019;3:1–10.

[45] Piha-Paul SA, Taylor MH, Spitz D, Schwartzberg L, Beck JT, Bauer TM, et al. Efficacy and safety of buparlisib, a PI3K inhibitor, in patients with malignancies harboring a PI3K pathway activation: a phase 2, open-label, single-arm study. Oncotarget 2019;10(60):6526–35.

[46] van Tilburg CM, Milde T, Witt R, Ecker J, Hielscher T, Seitz A, et al. Phase I/II intra-patient dose escalation study of vorinostat in children with relapsed solid tumor, lymphoma, or leukemia. Clin Epigenetics 2019;11(1):188.

[47] Xie L, Xu J, Sun X, Tang X, Yan T, Yang R, et al. Apatinib for Advanced Osteosarcoma after Failure of Standard Multimodal Therapy: An Open Label Phase II Clinical Trial. Oncologist 2019;24(7):e542–50.

[48] Baird K, Glod J, Steinberg SM, Reinke D, Pressey JG, Mascarenhas L, et al. Results of a Randomized, Double-Blinded, Placebo-Controlled, Phase 2.5 Study of Saracatinib (AZD0530), in Patients with Recurrent Osteosarcoma Localized to the Lung. Sarcoma. 2020;2020:7935475.

[49] Davis KL, Fox E, Merchant MS, Reid JM, Kudgus RA, Liu X, et al. Nivolumab in children and young adults with relapsed or refractory solid tumours or lymphoma (ADVL1412): a multicentre, open-label, single-arm, phase 1–2 trial. Lancet Oncol 2020;21(4):541–50.

[50] Doebele RC, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AF, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1–2 trials. Lancet Oncol 2020;21(2):271–82.

[51] Geoerger B, Zwaan CM, Marshall LV, Michon J, Bourdeaut F, Casanova M, et al. Atezolizumab for children and young adults with previously treated solid tumours, non-Hodgkin lymphoma, and Hodgkin lymphoma (iMATRIX): a multicentre phase 1–2 study. Lancet Oncol 2020;21(1):134–44.

[52] Italiano A, Mir O, Mathoulin-Pelissier S, Penel N, Piperno-Neumann S, Bompas E, et al. Cabozantinib in patients with advanced Ewing sarcoma or osteosarcoma (CABONE): a multicentre, single-arm, phase 2 trial. Lancet Oncol 2020;21(3):446–55.

[53] Marec-Berard P, Dalban C, Gaspar N, Brugieres L, Gentet JC, Lervat C, et al. A multicentric randomized phase II clinical trial evaluating high-dose thiotepa as adjuvant treatment to standard chemotherapy in patients with resectable relapsed osteosarcoma. Eur J Cancer 2020;125:58–68.

[54] Marrari A, Bertuzzi A, Bozzarelli S, Gennaro N, Giordano L, Quagliuolo V, et al. Activity of regorafenib in advanced pretreated soft tissue sarcoma: Results of a single-center phase II study. Medicine (Baltimore) 2020;99(26):e20719.

[55] Taylor MH, Alva AS, Larson T, Szpakowski S, Purkaystha D, Amin A, et al. A mutation-specific, single-arm, phase 2 study of dovitinib in patients with advanced malignancies. Oncotarget 2020;11(14):1235–43.

[56] Schulte B, Mohindra N, Milhem M, Attia S, Robinson S, Monga V, et al. Phase II study of pazopanib with oral topotecan in patients with metastatic and non-resectable soft tissue and bone sarcomas. Br J Cancer 2021;125(4):528–33.

[57] Barnes DJ, Dutton P, Bruland O, Gelderblom H, Faleti A, Buhnemann C, et al. Outcomes from a mechanistic biomarker multi-arm and randomised study of liposomal MTP-PE (Mifamurtide) in metastatic and/or recurrent osteosarcoma (EuroSarc-Memos trial). BMC Cancer 2022;22(1):629.

[58] Drilon A, Tan DSW, Lassen UN, Leyvraz S, Liu Y, Patel JD, et al. Efficacy and Safety of Larotrectinib in Patients With Tropomyosin Receptor Kinase Fusion-Positive Lung Cancers. JCO Precis Oncol 2022;6:e2100418.

[59] Frankel P, Ruel C, Uche A, Choy E, Okuno S, Somiah N, et al. Pazopanib in Patients with Osteosarcoma Metastatic to the Lung: Phase 2 Study Results and the Lessons for Tumor Measurement. J Oncol 2022;2022:3691025.

[60] Gounder MM, Rosenbaum E, Wu N, Dickson MA, Sheikh TN, D'Angelo SP, et al. A Phase Ib/II Randomized Study of RO4929097, a Gamma-Secretase or Notch Inhibitor with or without Vismodegib, a Hedgehog Inhibitor. Adv Sarcoma Clin Cancer Res 2022;28(8):1586–94.

[61] Hingorani P, Krailo M, Buxton A, Hutson P, Sondel PM, Diccianni M, et al. Phase 2 study of anti-disialoganglioside antibody, dinutuximab, in combination with GM-CSF in patients with recurrent osteosarcoma: A report from the Children's Oncology Group. Eur J Cancer 2022;172:264–75.

[62] Somaiah N, Conley AP, Parra ER, Lin H, Amini B, Solis Soto L, et al. Durvalumab plus tremelimumab in advanced or metastatic soft tissue and bone sarcomas: a single-centre phase 2 trial. Lancet Oncol 2022;23(9):1156–66.

[63] Tabernero J, Andre F, Blay JY, Bustillos A, Fear S, Ganta S, et al. Phase II multicohort study of atezolizumab monotherapy in multiple advanced solid cancers. ESMO Open 2022;7(2):100419.

[64] Gaspar N, Campbell-Hewson Q, Gallego Melcon S, Locatelli F, Venkatramani R, Hecker-Nolting S, et al. Phase I/II study of single-agent lenvatinib in children and adolescents with refractory or relapsed solid malignancies and young adults with osteosarcoma (ITCC-050). ESMO Open 2021;6(5):100250.

[65] Quek R, Lim SL, Chay WY, Soh LT, Tan SH, Goh WL, et al. Phase 2 clinical study of metronomic oral cyclophosphamide (MOC) in advanced sarcomas. Ann Oncol 2017;28:x149–50.

[66] Vassal G, Cozic N, Ferretti G, Taieb S, Houot R, Brugieres L, et al. Biomarker-driven access to crizotinib in ALK, MET, or ROS1 positive (+) malignancies in adults and children: The French National AcSé Program. J Clin Oncol. 2018;36(15_suppl):2504-.

[67] Sun Y, Yao Y, Cai Z, Yu X, Wu S, Ye Z, et al. The open, multicenters, double-arms, randomized, parallel controlled clinical trial of lobaplatin or gemcitabine combined with docetaxel as second-line therapy for advanced osteosarcoma-the effectiveness and safety analysis. J Clin Oncol 2017;35(15_suppl):e22506-e.

[68] Yankelevich M, Modak S, Chu R, Lee DW, Thakur A, Cheung N-K-V, et al. Phase I study of OKT3 x hu3F8 bispecific antibody (GD2Bi) armed T cells (GD2BATs) in GD2-positive tumors. J Clin Oncol 2019;37(15_suppl):2533-.

[69] Tine BAv, Mohindra N, Milhem M, Attia S, Robinson SI, Rademaker A, et al. A phase II study of pazopanib with oral topotecan in patients with metastatic osteosarcoma. Ann Oncol (2018); 29: VIII579.

[70] Dela Cruz F, Chou A, Roberts S, Mauguen A, Bonura J, Hilliard J, et al. Preliminary Tolerability Assessment of Naxitamab (Humanized anti-GD2 Monoclonal Antibody). Therapy in a Phase 2 Osteosarcoma Trial. SIOP conference poster session. 2019.

[71] Koonrungsesomboon N, Ngamphaiboon N, Townamchai N, Teeyakasem P, Charoentum C, Charoenkwan P, et al. Phase II, multi-center, open-label, single-arm clinical trial evaluating the efficacy and safety of Mycophenolate Mofetil in patients with high-grade locally advanced or metastatic osteosarcoma (ESMMO): rationale and design of the ESMMO trial. BMC Cancer 2020;20(1):268.

[72] Rao S, Han R, Krailo MD, Buxton A, Hingorani P, Chou AJ, et al. Outcome of patients with recurrent/refractory osteosarcoma enrolled in three recent phase II trials: A report from the Children's Oncology Group. J Clini Oncol 2021;39(15_suppl):11530-.

[73] Chawla SP, Chua VS, Fernandez L, Quon D, Saralou A, Blackwelder WC, et al. Phase I/II and phase II studies of targeted gene delivery in vivo: intravenous Rexin-G for chemotherapy-resistant sarcoma and osteosarcoma. Mol Ther 2009;17(9):1651–7.

[74] Grignani G, Palmerini E, Dileo P, Asaftei SD, D'Ambrosio L, Pignochino Y, et al. A phase II trial of sorafenib in relapsed and unresectable high-grade osteosarcoma after failure of standard multimodal therapy: an Italian Sarcoma Group study. Ann Oncol 2012;23(2):508–16.

[75] Gaspar N, Campbell-Hewson Q, Huang J, Okpara CE, Bautista F. OLIE, ITCC-082: a Phase II trial of lenvatinib plus ifosfamide and etoposide in relapsed/refractory osteosarcoma. Future Oncol 2021;17(32):4249–61.

[76] Pearson AD, Gaspar N, Janeway K, Campbell-Hewson Q, Lawlor ER, Copland C, et al. Paediatric Strategy Forum for medicinal product development of multi-targeted kinase inhibitors in bone sarcomas: ACCELERATE in collaboration with the European Medicines Agency with participation of the Food and Drug Administration. Eur J Cancer 2022;173:71–90.

[77] Pearson ADJ, Weiner SL, Adamson PC, Karres D, Reaman G, Rousseau R, et al. ACCELERATE - Five years accelerating cancer drug development for children and adolescents. Eur J Cancer 2022;166:145–64.

[78] Services. USDoHaH, Administration. USFaD, Excellence USFaDAOoMPaTOCo, (U.S.) CfBEaR, (U.S.) CfDEaR. Considerations for the inclusion of adolescent patients in adult oncology clinical trials. Silver Spring, MD: Center for Drug Evaluation and Research,; 2019. Available from: https://www.fda.gov/media/113499/download http://resource.nlm.nih.gov/101760009.

[79] Vassal G, Rousseau R, Blanc P, Moreno L, Bode G, Schwoch S, et al. Creating a unique, multi-stakeholder Paediatric Oncology Platform to improve drug development for children and adolescents with cancer. Eur J Cancer 2015;51(2):218–24.

[80] Gaspar N, Fern L. Increasing Access to Clinical Trials and Innovative Therapy for Teenagers and Young Adults with Cancer - A Multiple Stakeholders and Multiple Steps Process. Prog Tumor Res 2016;43:38–49.

[81] Hawkins DS, Arndt CA. Pattern of disease recurrence and prognostic factors in patients with osteosarcoma treated with contemporary chemotherapy. Cancer 2003;98(11):2447–56.

[82] Ferrari S, Briccoli A, Mercuri M, Bertoni F, Picci P, Tienghi A, et al. Postrelapse survival in osteosarcoma of the extremities: prognostic factors for long-term survival. J Clin Oncol 2003;21(4):710–5.

[83] Seymour L, Ivy SP, Sargent D, Spriggs D, Baker L, Rubinstein L, et al. The design of phase II clinical trials testing cancer therapeutics: consensus recommendations from the clinical trial design task force of the national cancer institute investigational drug steering committee. Clin Cancer Res 2010;16(6):1764–9.

[84] Guenther LM, Rowe RG, Acharya PT, Swenson DW, Meyer SC, Clinton CM, et al. Response Evaluation Criteria in Solid Tumors (RECIST) following neoadjuvant chemotherapy in osteosarcoma. Pediatr Blood Cancer 2018;65(4).

[85] Haslam A, Hey SP, Gill J, Prasad V. A systematic review of trial-level meta-analyses measuring the strength of association between surrogate end-points and overall survival in oncology. Eur J Cancer 2019;106:196–211.

[86] Prasad V, Kim C, Burotto M, Vandross A. The Strength of Association Between Surrogate End Points and Survival in Oncology: A Systematic Review of Trial-Level Meta-analyses. JAMA Intern Med 2015;175(8):1389–98.
[87] Mailankody S, Prasad V. Five Years of Cancer Drug Approvals: Innovation, Efficacy, and Costs. JAMA Oncol 2015;1(4):539–40.
[88] Fox E, Patel S, Wathen JK, Schuetze S, Chawla S, Harmon D, et al. Phase II study of sequential gemcitabine followed by docetaxel for recurrent Ewing sarcoma, osteosarcoma, or unresectable or locally recurrent chondrosarcoma: results of Sarcoma Alliance for Research Through Collaboration Study 003. Oncologist 2012;17(3):321.
[89] Lee EM, Rha SY, Lee J, Park KH, Ahn JH. Phase II study of weekly docetaxel and fixed dose rate gemcitabine in patients with previously treated advanced soft tissue and bone sarcoma. Cancer Chemother Pharmacol 2012;69(3):635–42.
[90] Palmerini E, Jones RL, Marchesi E, Paioli A, Cesari M, Longhi A, et al. Gemcitabine and docetaxel in relapsed and unresectable high-grade osteosarcoma and spindle cell sarcoma of bone. BMC Cancer 2016;16:280.
[91] Verschoor AJ, Speetjens FM, Dijkstra PDS, Fiocco M, van de Sande MAJ, Bovee J, et al. Single-Center Experience with Ifosfamide Monotherapy as Second-Line Treatment of Recurrent/Metastatic Osteosarcoma. Oncologist 2020;25(4):e716–21.
[92] Palmerini E, Setola E, Grignani G, D'Ambrosio L, Comandone A, Righi A, et al. High Dose Ifosfamide in Relapsed and Unresectable High-Grade Osteosarcoma Patients: A Retrospective Series. Cells 2020;9(11).
[93] Gentet JC, Brunat-Mentigny M, Demaille MC, Pein F, Avet-Loiseau H, Berger C, et al. Ifosfamide and etoposide in childhood osteosarcoma. A phase II study of the French Society of Paediatric Oncology. Eur J Cancer 1997;33(2):232–7.
[94] Gaspar N-C-H-Q, Bielack SS, Campbell M, Bautista F, Meazza C, Janeway K, et al. A multicenter, open-label, randomized phase II study to compare the efficacy and safety of lenvatinib in combination with ifosfamide and etoposide versus ifosfamide and etoposide in children, adolescents and young adults with relapsed or refractory osteosarcoma (OLIE; ITCC-082). Ann Oncol 2020;31:S914–33.
[95] Gaspar N, Sirvent FJB, Venkatramani R, Longhi A, Lervat C, Casanova M, et al. Phase 1 combination dose-finding/phase 2 expansion cohorts of lenvatinib + etoposide + ifosfamide in patients (pts) aged 2 to_25 years with relapsed/refractory (r/r) osteosarcoma. Ann Oncol 2019;30:v683–709.
[96] McCabe M, Kirton L, Khan M, Fenwick N, Strauss SJ, Valverde C, et al. Phase III assessment of topotecan and cyclophosphamide and high-dose ifosfamide in rEECur: An international randomized controlled trial of chemotherapy for the treatment of recurrent and primary refractory Ewing sarcoma (RR-ES). Journal of Clinical Oncology. 2022;40(17_suppl):LBA2-LBA.
[97] Sayles LC, Breese MR, Koehne AL, Leung SG, Lee AG, Liu HY, et al. Genome-Informed Targeted Therapy for Osteosarcoma. Cancer Discov 2019;9(1):46–63.
[98] da Costa MEM, Droit R, Khneisser P, Gomez-Brouchet A, Adam-de-Beaumais T, Nolla M, et al. Longitudinal characterization of primary osteosarcoma and derived subcutaneous and orthotopic relapsed patient-derived xenograft models. Front Oncol 2023;13:1166063.
[99] Belayneh R, Fourman MS, Bhogal S, Weiss KR. Update on Osteosarcoma. Curr Oncol Rep 2021;23(6):71.
[100] Meazza C, Bastoni S, Scanagatta P. What is the best clinical approach to recurrent/refractory osteosarcoma? Expert Rev Anticancer Ther 2020;20(5):415–28.
[101] Lilienthal I, Herold N. Targeting Molecular Mechanisms Underlying Treatment Efficacy and Resistance in Osteosarcoma: A Review of Current and Future Strategies. Int J Mol Sci 2020;21(18).
[102] Gazouli I, Kyriazoglou A, Kotsantis I, Anastasiou M, Pantazopoulos A, Prevezanou M, et al. Systematic Review of Recurrent Osteosarcoma Systemic Therapy. Cancers (Basel) 2021;13(8).