Management of recurrent or refractory Ewing sarcoma: A systematic review of phase II clinical trials in the last 15 years

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Abstract. The aim of the present study was to evaluate the antitumor activity of drugs in phase II clinical trials for recurrent or refractory EWS. A systematic review was performed using clinical trials from four data sources: i) ClinicalTrials.gov; ii) PubMed; iii) Clinicaltrialsregister.eu; and iv) American Society of Clinical Oncology. The search terms included: '(Ewing sarcoma OR Ewing family of tumors) AND (phase II OR phase I/II)'. Overall, 465 trials were identified and 64 were included in the present study, of which, 37 had published results. The highest objective response rate came from irinotecan-based chemotherapy. Currently, the majority of targeted therapy has failed to demonstrate any activity except for regorafenib. Trials using anti-angiogenesis small molecular tyrosine kinase inhibitors (aaTKIs) are currently ongoing with promising early results. For immunotherapy, anti-insulin like growth factor 1 receptor antibody demonstrated disappointing activity. The best outcome came from irinotecan-based regimens. Targeted therapy with aaTKIs is worthy of further investigation, with immunotherapy is not recommended for off-label use.

Introduction

Ewing sarcoma (EWS) is a small-round-blue-cell tumor that is derived from primordial mesenchymal stem cells, which often originate from the bone marrow (1). The incidence of EWS is one case in one million people in the US (1). The current standard first-line chemotherapy for EWS includes vincristine, doxorubicin, cyclophosphamide (VDC), ifosfamide and etoposide (IE), also termed VDC/IE (2,3), or vincristine, ifosfamide, doxorubicin and etoposide (VIDE) (4). The use of these chemotherapy regimens has resulted in the 5-year survival rate increasing from 59 to 78% in children and young adolescents, and from 20 to 60% in adults (5). However, there is currently no standardized second-line treatment for recurrent or refractory EWS. Various methods, including classical cytotoxic agents, targeted therapy, such as anti-angiogenesis small molecular tyrosine kinase inhibitors (aaTKIs), and immunotherapy, such as check-point inhibitors, have been tested in these progressed cases. Unfortunately, the prognosis for these patients remains poor (5,6). The majority of phase I trials for these methods have demonstrated acceptable safety profiles, but have failed to reach the primary endpoint in the phase II trials. In the last two decades, only one phase II trial testing these new drugs has progressed to phase III; however, there is no published data available. Until now, there has not been a standard second-line regimen following progression from the first-line treatment. As a rare disease with a number of different treatment options, it can be time-consuming for doctors to obtain useful information. In the present study, the outcomes of various treatment regimens for relapsed or refractor Ewing sarcoma, the optimal sequence of drugs following VDC/IE or VIDE treatment, and the promising management techniques expected in future trials were investigated. The records of phase II and phase I/II clinical trials in the last 15 years were reviewed according to PRISMA methodology (7).

Materials and methods

Searching strategy. Four data sources were initially searched using the following search terms: i) (Condition or disease 'Ewing sarcoma' OR 'Ewing family of tumors') AND (phase 'Phase 2') AND (study start from '01/01/2003' to '10/01/2018') on ClinicalTrials.gov; ii) ('Ewing sarcoma' OR 'Ewing family of tumors') AND ('Phase 2' OR 'Phase II') AND (date-publication '2003:2018') on PubMed; iii) ('Ewing sarcoma' OR 'Ewing family of tumors') AND (trial phase 'Phase two') AND (data range '2003-01-01' to '2018-10-01') on Clinicaltrialsregister.eu (EudraCT); and iv) 'Ewing sarcoma' in the abstracts available on the American Society of Clinical

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Abbreviations: EWS, Ewing sarcoma; NCT, ClinicalTrials.gov; EudraCT, Clinicaltrialsregister.eu; ASCO, American Society of Clinical Oncology; ORR, objective response rate; aaTKIs, anti-angiogenesis small molecular tyrosine kinase inhibitors; IGF-1R, anti-insulin-like growth factor 1 receptor; VDC, vincristine, doxorubicin, cyclophosphamide; IE, ifosfamide and etoposide; ICE, ifosfamide, cisplatin and etoposide; RECIST, response evaluation criteria in solid tumors; IT, irinotecan/temozolomide; CR, complete response; PR, partial response; PFS, progression free survival

Key words: Ewing sarcoma, phase II, recurrent, refractory

Oncology (ASCO) website. The final search was performed on October 15, 2018. As there were no phase III trials with published results available using the aforementioned search strategy, only phase II trials were included in the present study. There was only one phase III trial identified that is currently recruiting, which opened in April 2018 (no. NCT03495921); a multicenter, 1:1 randomized phase III study of intradermal autologous Vigil immunotherapy in combination with irinotecan and temozolomide.

Eligibility criteria. After the initial screening, the following eligibility criteria were used in further investigation: i) Patients had recurrent disease or their cancer was deemed refractory to previous first-line chemotherapy (VDC/IE or VIDE); ii) trials focused on EWS patients, or had one EWS stratum; iii) antitumor activity was assessed using a primary or secondary endpoint; and iv) language was limited to English. The aforementioned four data sources were searched sequentially. Finally, duplications among or inside each database were removed.

Data collection and analysis. The systematic search in each database was performed by two different individuals. Disagreements were resolved by discussion. The following information was extracted from each trial: i) General information, including date, identification number, principle investigators and centers; ii) drug information, including name and dose; iii) trial design, including phase, randomization, population, study status and statistical design; iv) participant enrollment, including the estimated and effective enrollment in each stage (for multiple-stage design), age, mean time from initial diagnosis to protocol enrollment and prior lines of systemic anticancer therapy; and v) endpoints, including the criteria of response, patients evaluated for efficacy, response rate and survival rate. Response to therapy was recorded as complete response, partial response, stable disease and progression of disease. The objective response rate (ORR) was defined as the rate of complete response and partial response. The records of phase II and phase I/II clinical trials in the last 15 years were reviewed according to PRISMA methodology (7).

Interventions were classified into four groups: i) Classical cytotoxic chemotherapy, either alone or in combination with other cytotoxic drugs; ii) targeted therapy, including TKIs that target different molecules or pathways, either alone or in combination with cytotoxic drugs; iii) immunotherapy, including monoclonal antibodies, immune checkpoint blockade and antitumor viruses, either alone or in combination with the previous two groups; and iv) other therapy. For phase I/II trials, only participants in the phase II part were analyzed.

Results

Study selection. Overall, 465 trials were identified following the initial screening (Fig. 1). The first step involved an eligibility assessment, and 343 trials were excluded for the following reasons: i) The studies were not phase II clinical trials (n=156), that is, they were phase I clinical trials (n=55), retrospective clinical trials (n=6), case reports (n=12), literature reviews or meta-analyses (n=49), preclinical studies (n=33) or papers presenting methodologies (n=1); ii) non-interested enrollment (n=76), including trials for patients with chemo-naïve metastatic disease (n=57) and trials for other diseases (n=19); iii) there was no EWS stratum available (n=79); iv) endpoints were used that did not include the antitumor activity of the drugs (n=25), including local control of radiotherapy (n=6), engraftment (n=2) and toxicity (n=17); and v) others (n=6), including one trial that closed before enrolling any participants and five trials that were reported in languages other than English.

The second step involved the removal of duplications (n=59). Duplicate trials were removed sequentially in order of ClinicalTrials.gov (n=1), PubMed (n=22), EudraCT (n=14) and ASCO (n=22). One trial was registered twice on ClinicalTrials.gov (no. NCT00154388 and NCT00031915) with the final result was reported in one paper (8). Finally, 64 trials were included in the present study (Fig. 1). *Study characteristics*. The general characteristics of the 64 trials included in the present study are summarized in Table I. They were classified into four groups: Chemotherapy (n=27), targeted therapy (n=17), immunotherapy (n=17) and stem cell transplantation (n=3; Fig. 2). Of the 64 trials, 37 were completed (at least EWS stratum was completed) and had published results with an abstract (n=10) or full-text (n=27) available. The ORR was assessed in 36 trials, which were then further analyzed.

Results of trials with published final reports. There were 19 trials enrolled that used chemotherapeutic agents (Table II). The best ORR results (>15%) were identified in the following trials: Irinotecan with an ORR of 71 (9) or 38% (10); ifosfamide, cisplatin and etoposide (ICE), 51% (11); cisplatin and etoposide, 18% (12); and trabectedin, 15% (13) and docetaxel, 15% (14).

There were eight trials that used targeted therapy in the present study and six drugs were assessed. The majority of these trials did not reach their primary endpoints in phase I and failed to enter phase II (Table III). Only one trial using regorafenib demonstrated a clinical response, with an ORR of 11% (15).

There were nine trials enrolled in the present study that used immunotherapy, in which IGF-1R was administrated as monotherapy (n=6) or in combination with temsirolimus (n=3). The best result was identified in the combination group (ORR, 29%) (16). However, all the other eight trials revealed a poor ORR of ≤15%. Five of the nine trials closed before entering phase II due to a lack of efficacy (Table IV).

Conflicting results from the same regimen. Although the participants were strictly limited to recurrent or refractory EWS, conflicting results were observed for the same drug or regimen. For trabectedin, a promising result was reported in an ASCO abstract (13) with an ORR of 15%, whereas in 2012 another trial revealed no response (ORR, 0%) (17). The same dose and response criteria were used in each trial. A similar phenomenon was identified in irinotecan, where the ORR varied from 0 (18), to 38 (10), to 71% (9). All three trials utilized the World Health Organization criteria to assess objective response rates (ORR). However, different

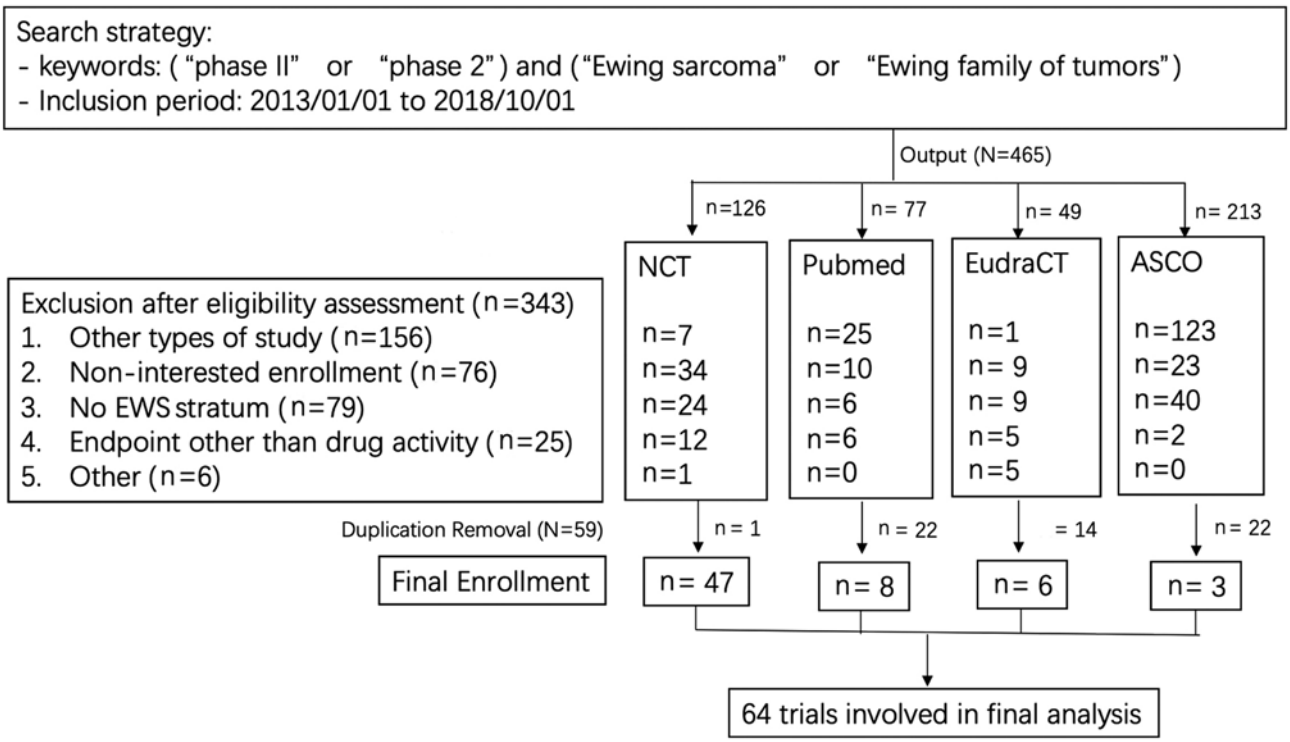

Figure 1. Flowchart diagram of the data selection steps. NCT, United States National Library of Medicine, ClinicalTrials.gov; EudraCT, European Clinical Trials Database, Clinicaltrialsregister.eu; ASCO, American Society of Clinical Oncology; EWS, Ewing sarcoma.

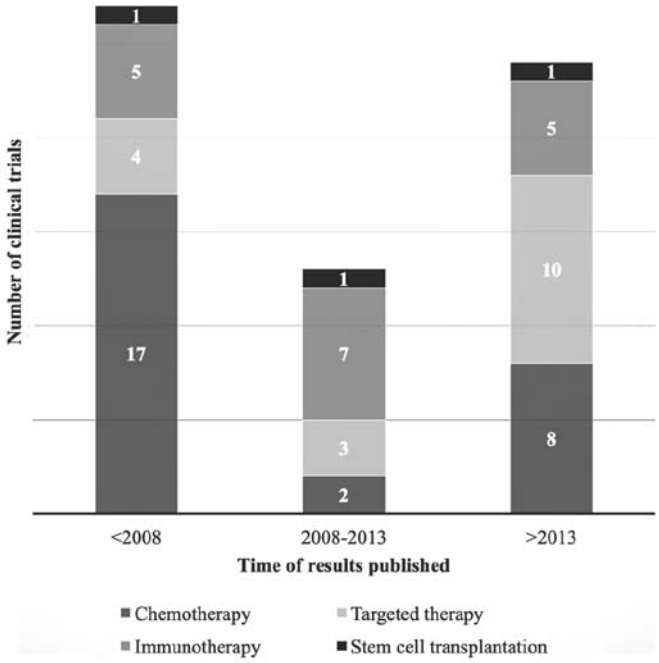

Figure 2. Type of intervention in different time periods in the 64 trials included in present study.

irinotecan administration strategies were utilized in these three trials, from 50 mg/m^2/dose for 5 days, repeated every 3 weeks; to 20 mg/m^2/dose for 5 days per week for 2 weeks, repeated every 4 weeks; to 16 mg/m^2/dose for 5 days per week for 2 weeks, repeated every 3 weeks. The combination of cixutumumab and temsirolimus was administered with the same variations, and an ORR of 12% (or 29% if a regression of 20-30% was recorded as minor response) was reported in adults in 2012 (16), 15% in adults in 2013 (19) and 0% in children and young adults in 2015 (20). The same dose of cixutumumab was used in the three trials, with the only difference being a lower dose of temsirolimus of 8-10 mg/m^2 (equivalent to an adult flat dose of 14 mg) in children and young adults, compared with a 25 mg flat dose in adults. Furthermore, over half of the adults required a decreased dose amount due to toxicity levels, and 29% of them required a second reduction (19).

Risk of bias

Selection bias. The mean time from the initial diagnosis to recurrence or progression varied from 19 to 43 months (21,22). With available data, almost all participants had more than two lines of prior systemic anticancer therapy, except in the cisplatin/etoposide trial (12) and in one of the cixutumumab trials (16). The median prior line of systemic therapy varied among trials (range 1-6).

Detection bias. In the 36 trials that reported their results and used ORR as an endpoint, response evaluation criteria in solid tumors (RECIST) was the most commonly used criteria (27 trials), including 13 that used RECIST version 1.1 (23), nine that used RECIST version 1.0 (24), four that used a non-specific version of RECIST and one that used RECIST version 1.1 and the World Health Organization (WHO) criteria (25,26) at the same time and observed no difference in the outcome from different criteria. For the remaining nine trials, seven used the WHO criteria alone, one used the Choi criteria (27) and one was not available.

Publication bias. According to the registration system, two trials started enrolling participants 10 years ago; however, no published results were available. One trial investigated exatecan (no. NCT00055952), which started in January 2003, and the other investigated hematopoietic stem cell transplantations (no. NCT00998361), which started in June 2009. There was no specific reason given for the unpublished results (Table V).

Location bias and language bias. Trials registered in the domestic clinical trials registration system were not screened. There were five trials registered in languages other than English, which were then excluded.

Time lag bias. Several trials assessing new drugs are still ongoing and the results have not yet been reported, including targeted therapy (aaTKIs, PI3K/mTOR and poly(ADP-ribose) polymerase) and immunotherapy (checkpoint blockade, oncolytic virus; Table V).

Multiple publication bias. Duplicated studies were identified and removed following abstract and/or full text screening.

Discussion

The present study investigated what can be learned from prospective phase II trials, and what can be expected from ongoing clinical trials. A comprehensive systematic review was performed with the aim of determining the optimal sequence of drugs following the use of VDC/IE or VIDE.

Cytotoxic chemotherapy. New drugs and regimens have been investigated more recently, but the most promising results still came from chemotherapy (e.g., irinotecan) based on available data. In addition to phase II trials (9,10,18), retrospective studies have provided more evidence on irinotecan/temozolomide (IT), which had ORRs as high as 34, 68 and 55% (28,29), and a median time to progression of 5.5 (30) and 3.0 months (29). At first, two patients showed an initial response but relapsed following withdrawal of the drug for 5 and 6 months, respectively (28). After recommencing the same IT regimen, the two patients achieved a second PR; one that lasted for at least another 15 cycles and the other another 22 cycles (28). On the basis of the success of IT, more clinicians use it as the first choice of treatment following the failure of VDC/IE or VIDE.

Targeted therapy. As for targeted therapy, classical agents arising from leukemia regimens, such as imatinib or dasatinib, did not exhibit any activity in patients with EWS. Only regorafenib, which has a stronger anti-angiogenesis effect, demonstrated promising clinical activity in patients with EWS. Further trials for other types of aaTKI, including pazopanib, cabozantinib and apatinib, which have shown some activity in other types of sarcoma (31-33), are ongoing and the results of which are anticipated. For patients who were refractory to first-line chemotherapy, pazopanib was reported to be effective in a set of case series (34-37). Early results from the cabozantinib trial (no. NCT02243605) in patients with EWS look promising, and an ORR of 28.1% in 32 patients was observed, as well as a high tumor burden reduction rate of 71% (38). For apatinib, which is also a strong aaTKI (39), an ORR of 70% (7/10) was observed in an off-label set of patients with EWS (33). Based on these data, it was concluded that aaTKIs require further investigation.

Except for monotherapy, preclinical studies have demonstrated the synergistic antiproliferative and pro-apoptotic activity of irinotecan or topotecan and aaTKIs *in vitro*, and the improvement of the *in vivo* anticancer activity on angiogenesis, endothelial and cancer cells, such as pancreatic (40) and ovarian cancer cells (41). Based on the non-overlapped adverse effects of irinotecan (42,43) and aaTKIs (44,45), these studies suggested a possible translation of this combination into the clinic. A phase I study of axitinib and irinotecan combined with 5-fluorouracil and leucovorin in patients with advanced colorectal cancer described an acceptable toxicity profile (46). Another phase I trial that used a triplet combination of pazopanib, irinotecan and cetuximab in patients with refractory metastatic colorectal cancer also provided evidence for a manageable safety profile (47).

Table I. Basic characteristics in the 64 trials involved in the present study.

Classification	Number of trials
Data available	
Results published	37
No results available	26
Terminated by researcher	1
Phase	
I/II	14
II	50
Intervention	
Chemotherapy	27
Targeted therapy	17
Immunotherapy	17
Stem cell transplantation	3
Strategy	
Monotherapy	40
Combination	24
Route of administration	
Oral	14
Intravenous	41
Oral and intravenous	9
Centers involved in each trial	
Single	7
Multiple	57
Targeted population	
EWS only	16
Sarcoma	26
Solid tumor	16
All types of cancer	6

Table II. Trials that included classical cytotoxic chemotherapy.

A, Alkylating agents

Author, year	Intervention	Disease type	Phase	Time from diagnosis to enrollment	Prior lines of systemic therapy	Version of response criteria	No. of patients evaluated[a]	Mean age, years	ORR in patients with EWS, %	(Refs.)
Owens *et al*, 2013	Cisplatin and etoposide	EWS	III	20.4 months	1	RECIST 1.1 WHO	38	19	18	(12)
Beaty *et al*, 2010	Oxaliplatin	Solid tumor	II	NA	2	RECIST 1.0	124 (10)	11[b]	0	(58)
Van Winkle *et al*, 2005	ICE	Sarcoma	I	NA	NA	WHO	97 (22)	11.4[b]	51[b]	(11)
Jones *et al*, 2014	PM00104	EWS	II	43.3 months	4	RECIST 1.1	16	23	0	(22)
Minard-Colin *et al*, 2012	Vinorelbine and cyclophosphamide	Sarcoma	II	19 months	≥2	WHO	117 (15)	12[b]	13	(21)
Baruchel *et al*, 2012	Trabectedin	Sarcoma	II	NA	NA	RECIST 1.0	40 (10)	NA	0	(17)
Dileo *et al*, 2007	Trabectedin	EWS	NA	NA	NA	RECIST, non-specific	20	NA	15	(13)
Subbiah *et al*, 2018	Lurbinectedin	Solid tumor	II	NA	≥2	RECIST 1.1	350 (28)	33	14	(59)
Michelagnoli *et al*, 2015	Treosulfan	EWS	I	NA	2	RECIST 1.1	14	19	0	(60)

B, Plant alkaloids

Author, year	Intervention	Disease type	Phase	Time from diagnosis to enrollment	Prior lines of systemic therapy	Version of response criteria	No. of patients evaluated[a]	Mean age, years	ORR in patients with EWS, %	(Refs.)
Bomgaars *et al*, 2007	Irinotecan	Solid tumor	III	NA	NA	WHO	161 (16)	NA	0	(18)
Dumont *et al*, 2011	Irinotecan	Sarcoma	II	NA	2	NA	38 (7)	48[b]	71	(9)
Bisogno *et al*, 2006	Irinotecan	Soft tissue sarcoma	II	NA	2	WHO	32 (13)	10[b]	38	(10)
Hawkins *et al*, 2006	Topotecan	Solid tumor	NA	NA	2	WHO	55 (20)	NA	10	(61)
Fox *et al*, 2012	Docetaxel and gemcitabine	Sarcoma	I	NA	NA	RECIST 1.1	53 (14)	43	14	(62)
Zwerdling *et al*, 2006	Docetaxel	Solid tumor	I	NA	2	WHO	160 (20)	13[b]	15	(14)
Jacobs *et al*, 2010	Ixabepilone	Solid tumor	II	NA	NA	RECIST 1.0	61 (9)	13[b]	0	(63)

C, Antimetabolites

Author, year	Intervention	Disease type	Phase	Time from diagnosis to enrollment	Prior lines of systemic therapy	Version of response criteria	No. of patients evaluated[a]	Mean age, years	ORR in patients with EWS, %	(Refs.)
DuBois *et al*, 2009	Cytarabine	EWS	II	21.8 months	NA	RECIST 1.0	10	20	0	(64)
Warwick *et al*, 2013	Pemetrexed	Solid tumor	II	NA	NA	RECIST 1.0	66 (10)	11[b]	0	(65)

Table II. Continued.

D, Antitumor antibiotics

Author, year	Intervention	Disease type	Phase	Time from diagnosis to enrollment	Prior lines of systemic therapy	Version of response criteria	No. of patients evaluated[a]	Mean age, years	ORR in patients with EWS, %	(Refs.)
Grohar *et al*, 2017	Mithramycin	EWS	II	NA	4	RECIST 1.1	6	NA	0	(66)

[a]Participants with other diseases were included, the number of all patients evaluated was given for the whole trial with the number of EWS stratum shown in parentheses; [b]Numbers for the whole population, including those patients with EWS. ORR, objective response rate; EWS, Ewing sarcoma; RECIST, response evaluation criteria in solid tumors; WHO, World Health Organization; NA, not available; ICE, ifosfamide, carboplatin, etoposide.

Table III. Trials that included targeted therapy.

Author, year	Intervention	Major targets	Disease type	Phase	Prior lines of systemic therapy	Version of response criteria	No. of patients evaluated[a]	Mean age, years	ORR in EWS, %	(Refs.)
Chao *et al*, 2010[c]	Imatinib	BCR-ABL, c-kit and PDGFR	Sarcoma	I	NA	RECIST 1.0	7 (5)	33	0	(67)
Bond *et al*, 2008[c]	Imatinib	BCR-ABL, c-kit and PDGFR	Solid tumor	II	2	RECIST 1.0	71 (24)	16[b]	4	(68)
Chugh *et al*, 2009[c]	Imatinib	BCR-ABL, c-kit and PDGFR	Sarcoma	II	NA	RECIST, non-specific	185 (13)	Adult >10 years	0	(8)
Schuetze *et al*, 2016[c]	Dasatinib	BCR-ABL, Src family, c-kit, ephrin receptor, and PDGFR	Solid tumor	II	3	Choi	200 (17)	55[b]	6	(56)
Choy *et al*, 2014[c]	Olaparib	PARP	EWS	II	5	RECIST 1.1	12	30.5	0	(69)
University of Oxford, 2016[d]	Linsitinib	IGF-1R	EWS	II	NA	RECIST, non-specific	15	Adult	0	(70)
Children's Oncology Group, 2015[d]	Alisertib	Aurora A kinase	All cancer	II	NA	RECIST 1.0	118 (10)	14	0	(71)
Attia *et al*, 2017[c]	Regorafenib	RET, VEGFR1, VEGFR2, VEGFR3, c-kit, PDGFR	Solid tumor	II	NA	RECIST 1.1	28	32	11	(15)

Time from diagnosis to enrollment was not available. [a]When participants with other diseases were included, the number of all patients evaluated was given for the whole trial, with the number of EWS stratum shown in parentheses; [b]Numbers for the whole population, including those patients with EWS; [c]Year of publication; [d]Year the trial ended, but no data published. ORR, objective response rate; EWS, Ewing sarcoma; BCR-ABL, Philadelphia chromosome; c-kit, KIT proto-oncogene, receptor tyrosine kinase; NA, not available; RECIST, response evaluation criteria in solid tumors; PDGFR, platelet-derived growth factor receptor; PARP, poly(ADP-ribose) polymerase; IGF-1R, insulin like growth factor 1 receptor; RET, ret proto-oncogene; VEGFR, vascular endothelial growth factor receptor.

Table IV. Trials that included immunotherapy with published results.

Author, year	Intervention	Disease type	Study design	Time from diagnosis to enrollment, months	Prior lines of systemic therapy	Version of response criteria	No. of patients evaluated[a]	Mean age, years	ORR in EWS, %	(Refs.)
Juergens *et al*, 2011	Figitumab	EWS	2-stage	NA	3	RECIST 1.1	106	18	14	(72)
Tap *et al*, 2012	Ganitumab	Sarcoma	1-stage	NA	≥3	RECIST 1.0	38 (22)	29	5	(73)
Pappo *et al*, 2011	R1507	Sarcoma	2-stage	16.7	NA	WHO	317 (115)	25[b]	10	(74)
Anderson *et al*, 2016	Robatumumab	Sarcoma	2-stage	NA	NA	RECIST, non-specific	219 (84)	20[b]	7	(75)
Malempati *et al*, 2012	Cixutumumab (IMC-A12)	Solid tumor	2-stage	NA	1	RECIST, non-specific	45 (35)	15[b]	9	(76)
Schoffski *et al*, 2013	Cixutumumab (IMC-A12)	Sarcoma	2-stage	20.3	≥3	RECIST 1.0	113 (17)	27	6	(77)
Naing *et al*, 2012	Cixutumumab and temsirolimus	Sarcoma	2-stage	NA	6	RECIST 1.0	20 (17)	24[b]	12 (29)[c]	(16)
Wagner *et al*, 2015	Cixutumumab and temsirolimus	Sarcoma	2-stage	NA	NA	RECIST 1.1	46 (11)	18[d]	0	(20)
Schwartz *et al*, 2013	Cixutumumab and temsirolimus	Sarcoma	2-stage	NA	2	RECIST 1.1	174 (27)	38[b]	15	(19)

[a]When participants with other diseases were included, the number of all patients evaluated was provided for the whole trial, with the number of EWS stratum shown in parentheses; [b]Numbers for the whole population, including EWS; [c]Overall, three patients exhibited 20-30% regression. Although these patients failed to reach the criteria for partial response, they were still recorded as responders in the original literature and the ORR was reported as 29%; [d]Only children or young adults were enrolled in the trial. ORR, objective response rate; EWS, Ewing sarcoma; RECIST, response evaluation criteria in solid tumors; WHO, World Health Organization; NA, not available.

Based on this evidence, trials have been designed that use IT in combination with aaTKIs to maximize antitumor activity (no. NCT03416517).

Immunotherapy. Immunotherapy based on anti-insulin-like growth factor 1 receptor (IGF-1R) antibody was somewhat disappointing. Preclinical studies have revealed the IGF-1R pathway as promising new targets for EWS (48,49) and these observations have led to several clinical studies. However, given the non-optimal results from these trials, almost all health providers have stopped further investigation on IGF-1R antibody. Efforts have been made to look for biomarkers and narrow down the population who may benefit from the use of IGF-1R antibody. A multi-center study classified patients into different subtypes based on IGF-1R expression via immunohistochemistry (19), but there was no overall effect on outcome. Although in patients with EWS who were IGF-1R-negative had improved median PFS, it may be explained by the less aggressive biological behavior rather than real response to therapy.

Another type of immunotherapy with checkpoint blockade remains ongoing. Tumor mutation burden is considered an important factor for immune checkpoint blockade therapy (50,51). However, from the view of biological nature and genomic landscape, EWS does not belong to hyper-mutated tumors with a mutation frequency of <10 mutation/Mb (52), and only EWS-ETS gene rearrangements were identified in the majority of tumors (53,54). The role of the immune checkpoint blockade remains to be defined by well-designed clinical trials.

Limitations. The time to recurrence is the most important prognostic factor for patients with recurrent EWS. Patients who relapsed >2 years from the initial diagnosis had a 5-year survival of 30%, compared with 7% for patients that relapsed within 2 years (5,6). Patients in different trials experienced recurrence at different time points and may impact final oncological outcomes.

Different criteria have been used to assess drug response. The WHO criteria, RECIST 1.0 (a simplified version of the WHO criteria) and its newer version, RECIST 1.1, continue to be based on changes in tumor size. All these three criteria have a similar evaluation power for solid tumors (25,55). In the 37 trials with published results that were investigated in the present study, 36 used at least one of the three aforementioned criteria and provided a fair comparison among the trials. In the dasatinib trial (56), the Choi criteria were selected as the tumor response criteria, which the authors believed was associated with improved outcome in patients with gastrointestinal stromal tumors that were treated with TKIs (57). The significant differences observed between the Choi and RECIST criteria were due to the addition of change in tumor density in computed tomography scans and a smaller magnitude of change in tumor size to score response. From that point, more responses were scored using the Choi criteria, although only one partial response was recorded in all 17 participants with EWS (56).

Abundant trials assessing new drugs are still ongoing and no results have been reported yet (Table V). Although classical targeted drugs such as imatinib and IGF-1R antibody demonstrated no activity in patients with EWS, aaTKIs appear more

Table V. Trials with unpublished results.

A, Chemotherapy (n=8)

NCT identifier	EudraCT identifier	Phase	Start date	Disease type	Intervention
00055952	NA	II	March, 2003	Sarcoma	Exatecan (analogue of camptothecin)
03275818	2016-002464-14	II	September, 2017	Solid tumor	Nab-paclitaxel
03245450	2016-003352-67	I/II	August, 2017	Sarcoma	Eribulin and irinotecan
03441360	2018-001282-17	II	February, 2018	Sarcoma	Eribulin
02945800	NA	II	October, 2016	Sarcoma	Nab-paclitaxel and gemcitabine
01962103	2013-000144-26	I/II	October, 2013	Sarcoma	Nab-paclitaxel
03359005	NA	II	December, 2017	EWS	Irinotecan, temozolomide, vincristine
NA	2014-000259-99	II	August, 2014	EWS	TC/IT/GD/IFOS: Cyclophosphamide, topotecan, irinotecan, temozolomide, gemcitabine, docetaxel, ifosfamide

B, Target (n=9)

NCT identifier	EudraCT identifier	Phase	Start date	Disease type	Intervention
02243605	NA	II	September, 2014	Sarcoma	Cabozantinib
03458728	NA	I/II	March, 2018	Solid tumor	Copanlisib
03416517	NA	II	January, 2018	EWS	Anlotinib and irinotecan
03245151	NA	I/II	November, 2017	Solid tumor	Lanvatinib and everolimus
00788125	NA	I/II	September, 2008	Solid tumor	D-ICE: Dasatinib, ifosfamide, carboplatin and etoposide
02116777	NA	I/II	May, 2014	All Cancer types	Talazoparib and temozolomide
02574728	NA	II	June, 2015	All Cancer types	Sirolimus and metronomic chemo (celecoxib, etoposide and cyclophosphamide)
01956669	2013-003595-12	II	September, 2013	Solid tumor	Pazopanib (votrient)
02712905	2017-001710-28	I/II	May, 2016	All Cancer types	INCB059872 (FAD-directed inhibitor of LSD1)

C, Immunotherapy (n=6)

NCT identifier	EudraCT identifier	Phase	Start date	Disease type	Intervention
01492673	NA	II	December, 2011	Solid tumor	Cyclophosphamide, topotecan, bevacizumab
0503295	NA	II	July, 2007	Sarcoma	Reolysin (unmodified oncolytic reovirus)
02511132	NA	IIb	May, 2017	EWS	Vigil (immunotherapy utilizing genetically modified tumor cells), irinotecan and temozolomide
02304458	2014-005674-11	I/II	February, 2015	Solid tumor	Nivolumab with or without ipilimumab
02541604	2014-004697-41	I/II	November, 2015	Solid tumor	MPDL3280A (atezolizumab)
NA	2006-004040-10	I/II	May, 2017	Sarcoma	Sunitinib and nivolumab

D, Stem cell transplant (n=3)

NCT identifier	EudraCT identifier	Phase	Start date	Disease type	Intervention
NA	2015-002584-41	II	October, 2016	Solid tumor	TREO/MEL chemotherapy and aPBSCT
00998361	NA	II	June, 2009	Sarcoma	Hematopoietic stem cell transplantation from HLA compatible donor
02100891	NA	II	April, 2014	Solid tumor	Haploidentical transplant and donor natural killer cells

NCT, ClinicalTrials.gov; EudraCT, Clinicaltrialsregister.eu; NA, not available; EWS, Ewing sarcoma; FAD, flavin adenine dinucleotide; LSD1, lysine-specific demethylase 1; TREO/MEL, treosulfan/melphalan; aPBSCT, autologous peripheral blood stem cell transplantation; HLA, human leukocyte antigen; NA, not applicable.

promising from the early revealed data, either as monotherapy or in combination with cytotoxic drugs. Therefore, more evidence is required to draw a robust conclusion for the new drugs.

Although abundant new drugs for targeted therapy and immunotherapy have been tested in the last 15 years, the best response came from traditional cytotoxic chemotherapy, particularly irinotecan-based regimens. Targeted therapy with

aaTKIs either alone or in combination with chemotherapy require further investigation. Currently, immunotherapy is not recommended for off-label use.

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Availability of data and materials

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Authors' contributions

JX and LX performed the systematic search. XS and SD reviewed the original phase 2 trial studies. WG designed the study. XT designed the data extraction sheet and final tables, provided supportive data from COG and ESMO meetings and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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