Maintenance therapy with trofosfamide, idarubicin and etoposide in patients with rhabdomyosarcoma and other high-risk soft tissue sarcomas (CWS-2007-HR): a multicentre, open-label, randomised controlled phase 3 trial

Ewa Koscielniak,[a,b,*] Gustaf Ljungman,[c] Bernarda Kazanowska,[d] Felix Niggli,[e] Monika Sparber-Sauer,[a,b] Rupert Handgretinger,[f] Martin Zimmermann,[g] Joachim Boos,[h] Bernd Blank,[a] Erika Hallmen,[a] Irene Teichert von Lüttichau,[i] Irene Schmid,[j] Birgit Fröhlich,[k] Hermann L. Müller,[l] Wolfgang Behnisch,[m] Ruth Ladenstein,[n,d] Monika Scheer,[o] Christian Vokuhl,[p] Thekla von Kalle,[q] Claudia Blattmann,[a,b] Stefan Bielack,[a,r] and Thomas Klingebiel[s]

[a]Klinikum Stuttgart, Olgahospital, Pediatrics 5 (Oncology, Hematology, Immunology), Stuttgart, Germany
[b]University of Tübingen, Medical Faculty, Germany
[c]Department of Women's and Children's Health, Pediatric Oncology, Uppsala University, Uppsala, Sweden
[d]Department of Pediatric Hematology/Oncology and BMT, University of Wroclaw, Wroclaw, Poland
[e]Department of Pediatric Oncology, University Children's Hospital, Zurich, Switzerland
[f]Hospital for Children and Adolescents, Department of Pediatric Hematology and Oncology, University of Tübingen, Tübingen, Germany
[g]Department of Pediatric Hematology and Oncology, Medical School, Hannover, Germany
[h]Medical Faculty, University of Münster, Albert-Schweitzer-Campus Münster, Germany
[i]Children's Hospital, Hospital Schwabing, Hospital Rechts der Isar, Technical University München, Germany
[j]Dr. von Hauner Children's Hospital, Department of Pediatrics, Division of Pediatric Hematology and Oncology, University Hospital Munich, Ludwig Maximilian University München, Germany
[k]Department of Pediatric Hematology and Oncology, University Hospital Münster, University of Münster, Germany
[l]University Children's Hospital, Department of Pediatrics and Pediatric Hematology/Oncology, Klinikum Oldenburg AöR, Carl von Ossietzky University, Oldenburg, Germany
[m]Department of Pediatric Oncology, Hematology, Immunology and Pulmonology, Heidelberg University Hospital, Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany
[n]St Anna Children's Hospital, Children's Cancer Research Institute, Department of Studies and Statistics for Integrated Research and Projects and Medical University of Vienna, Paediatric Department, Vienna, Austria
[o]Department of Pediatric Oncology and Hematology, Charité-Universitätsmedizin, Berlin, Germany
[p]Section of Pediatric Pathology, Department of Pathology, University Bonn, Germany
[q]Institute of Radiology Olgahospital, Zentrum für Kinder-, Jugend und Frauenmedizin, Klinikum Stuttgart, Stuttgart, Germany
[r]University Hospital Muenster, Department for Children and Adolescents, Department of Pediatric Hematology and Oncology, Muenster, Germany
[s]University Hospital Frankfurt, Department for Children and Adolescents, Goethe University, Frankfurt am Main, Germany

eClinicalMedicine
2024;78: 102957
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.102957

Summary

Background Rhabdomyosarcoma and other soft tissue sarcomas (STS) with high-risk features are still associated with an unsatisfactory outcome. We evaluated the efficacy of oral maintenance therapy added at the end of standard therapy in patients with high-risk rhabdomyosarcoma and STS.

Methods CWS-2007-HR was a multicentre, open-label, randomised controlled, phase 3 trial done at 87 centers in 5 countries. Eligible patients were those aged 6 months to 21 years with non-metastatic incompletely resected embryonal rhabdomyosarcoma occurring in unfavourable sites with unfavourable age (≥10 years) and/or tumour size (>5 cm); all non-metastatic alveolar rhabdomyosarcoma and those with any non-metastatic rhabdomyosarcoma with nodal involvement. A further group was also eligible: patients with non-metastatic undifferentiated sarcoma, extraskeletal Ewing sarcoma and primary unresected synovial sarcoma. Patients in complete remission at the end of standard therapy (nine cycles of ifosfamide, vincristine with doxorubicine or dactinomycin, and surgery or radiotherapy, or both) were randomised to either stop treatment (S-arm) or to receive oral maintenance therapy (M-arm) with eight 10-day courses (25 weeks) of trofosfamide (2 × 75 mg/m^2/day)

*Corresponding author. Klinikum Stuttgart, Olgahospital, Zentrum für Kinder-, Jugend- und Frauenmedizin, Pediatrics 5 (Oncology, Hematology, Immunology), Stuttgart, Germany.
E-mail addresses: e.koscielniak@klinikum-stuttgart.de, ewa.koscielniak@uni-tuebingen.de (E. Koscielniak).

and idarubicin (1 × 5 mg/m^2/day 1,4,7,10) alternating with trofosfamide and etoposide (2 × 25 mg/m^2/day). The primary outcome was event-free survival (EFS) and the secondary outcome was overall survival (OS) in the intent-to treat population. This trial is registered at ClinicalTrials.gov, NCT00876031, and, EudraCT 2007-0001478-10.

Findings Between July 1st, 2009 and June 30th, 2019, 195 patients were randomly assigned to the M-arm (n = 96) or S-arm (n = 99). In the intent-to-treat population, with a median follow-up of 5.2 years (IQR 3.9–6.1) for surviving patients, the 3-year EFS in the M-arm was 66.9% (95% CI 58.1–77.2) versus 75.6% (67.6–84.6) in the S-arm (hazard ratio, (HR) 1.62, 95% CI 0.98–2.69, p = 0.06). 3-year OS was 82.8% (95% CI 75.4–90.8) in the M-arm versus 84.7% (95% CI 77.8–92.1) in the S-arm (HR 1.55, 95% CI 0.84–2.89, p = 0.17). Grade 3–4 adverse events were haematological in 66% of patients, febrile infections in 6%, gastrointestinal in 10%, and sensory neuropathy in 1%.

Interpretation The addition of 25 weeks of oral maintenance therapy with trofosfamide, etoposide and idarubicin after standard therapy does not improve EFS and OS in patients with high-risk rhabdomyosarcoma and other STS.

Funding Deutsche Kinderkrebsstiftung Grant No.DKS 2009.09, DKS 2012.06, DKS 2015.13, DKS 2018.10 and DKS 2021.04.

Keywords: Rhabdomyosarcoma; Soft tissue sarcoma; Maintenance therapy

Research in context

Evidence before this study

We searched PubMed for articles published in English and German between January 1st 1990 and June 30th 2024 using the terms "rhabdomyosarcoma or soft tissue sarcoma and maintenance or metronomic therapy and randomised clinical trial". We found one randomised phase 3 trial that investigated the effect of maintenance chemotherapy added at the end of standard multimodal therapy on outcome. This study shows that maintenance chemotherapy with cyclophosphamide and vinorelbine improves overall survival by 13% in patients with high-risk rhabdomyosarcoma who are in complete remission after standard multimodal therapy. In addition, we found 14 papers describing maintenance therapy in rhabdomyosarcoma and/or other soft tissue sarcomas (STS) that evaluated maintenance therapy in a non-randomised way, added at the end of first-line therapy or in relapse in patients with localised and metastatic tumours. Two of them showed no improvement in prognosis with the addition of cyclophosphamide and vinorelbine maintenance in very high-risk (alveolar type with involved lymph nodes) and metastatic rhabdomyosarcoma, and in one recently published study the effect remained unclear. Seven papers were published by the CWS group (Cooperative Weichteilsarkomstudiengruppe), the second European paediatric soft tissue sarcoma study group, along with the European pediatric Soft tissue sarcoma Study Group (EpSSG), to conduct international trials in all types of STS. Five of these trials showed that maintenance therapy with vinblastine and cyclophosphamide or oral maintenance therapy with trofosfamide, idarubicin and etoposide had a beneficial effect on survival in patients with localised and metastatic rhabdomyosarcoma and other STS such as extraskeletal Ewing sarcoma and undifferentiated sarcoma.

Added value of this study

CWS-2007-HR shows that prolonging treatment with oral idarubicin, trofosfamide and etoposide in patients with high-risk rhabdomyosarcoma and other STS in complete remission after multimodal standard therapy does not improve prognosis.

Moreover, CWS-2007-HR was, to the best of our knowledge, the first randomised trial of maintenance therapy to include second malignancies as an event and highlights the importance of assessing late effects when increasing the burden of chemotherapy.

As both negative and positive trial results are needed to refine and further develop scientific theories and hypotheses, this study provides valuable information on the treatment of these rare tumours and may help to plan future research in this area.

Implications of all the available evidence

The goal of eradicating minimal residual disease in patients with rhabdomyosarcoma and other high-risk STS who are in complete remission after standard multimodal therapy by prolonging therapy with low-dose maintenance therapy requires further studies to improve risk-adapted patient stratification based on biomarkers such as ctDNA. In addition, innovative biology-based therapeutic approaches that go beyond conventional chemotherapeutic agents to avoid the increase in cumulative doses of chemotherapy and the associated severe late effects are also warranted since the risk of late effects due to maintenance therapy is one of the most important factors in long-term outcomes and remains to be determined.

Introduction

Soft tissue sarcomas (STS) comprise approximately 7.4% of all pediatric malignancies, with rhabdomyosarcoma being the most common STS in children (https://www.kinderkrebsregister.de). Since the 1970s, collaborative pediatric groups have developed multimodal therapeutic strategies and optimized the risk adapted therapy stratification. These efforts have improved the 5-year overall survival of paediatric patients with rhabdomyosarcoma to approximately 70%.[1–3] Unfortunately, cure rates have stagnated since the 1990s despite dose intensification of standard drugs such as alkylators and anthracyclines, the inclusion of alternative drugs and the use of high-dose chemotherapy with hematopoietic stem cell rescue.[4–9] Most of these conventional chemotherapy regimens are based on the cyclic administration of drugs near or at the maximum tolerated dose. Another type of therapy, called metronomic or maintenance therapy, based on the frequent administration of low doses of drugs, began to gain interest about 20 years ago after its efficacy was demonstrated in the mouse model.[10,11] The Cooperative Weichteilsarkomstudiengruppe (CWS) first investigated maintenance therapy in patients with metastatic rhabdomyosarcoma and other STS in a non-randomised way, comparing a three-drug maintenance therapy: trofosfamide, idarubicin and etoposide with high-dose chemotherapy. This study showed significant benefit in OS for maintenance therapy.[9] Based on these promising results, we initiated a randomised trial, CWS-2007-HR, to evaluate whether the addition of oral maintenance therapy (with trofosfamide, idarubicin, and etoposide) to standard therapy in patients with localised rhabdomyosarcoma, defined as high risk and very high risk according to the CWS stratification and other high risk STS would improve survival.

Methods

Study design and participants

CWS-2007-HR was an investigator-initiated, international, multicentre, open-label, phase 3, randomised trial conducted in 87 pediatric oncology centers in five countries (Austria, Germany, Poland, Sweden, and Switzerland).

Based on the standard diagnostic work up, each patient was assigned to a risk adapted stratification based on six prognostic factors according to the CWS-stratification system (Appendix Table A1). Patients were eligible (primary assessment for eligibility) for inclusion in the CWS-2007-HR if they met the following criteria: 1. age >6 months <21 years at the time of randomisation, 2. embryonal rhabdomyosarcoma N0, M0, Intergroup Rhabdomyosarcoma Studies (IRS) clinical group II or III, tumour size >5 cm and/or age ≥10 years, in unfavorable primary sites and all N1 (high-risk rhabdomyosarcoma group); 3. alveolar rhabdomyosarcoma, IRS group II or III, N0/N1, (very-high-risk rhabdomyosarcoma group); 4. localised undifferentiated sarcoma, extraskeletal Ewing sarcoma (EES), any N, size and IRS group and synovial sarcoma, IRS group III, (high-risk STS group). Patients with these characteristics who were in complete clinical response or had minimal residual structure (defined as residual radiological abnormality that cannot be defined as residual tumor according to imaging assessment criteria, cannot be removed without significant risk to the patient, i.e. paramenigeal site and should not normally be the reason for not terminating the standard therapy) at the end of standard therapy on imaging studies were eligible (second assessment for eligibility) for randomisation: to stop treatment (S-arm) or to receive maintenance therapy (M-arm). Central radiological review was offered and recommended when local radiologists were uncertain about tumour status at the end of standard therapy. All diagnoses were confirmed by central pathology review. Molecular confirmation by FISH (*FOXO1* break) and/or RT-PCR (*FOXO1::PAX3/7, PAX3::NCOA1/2, EWS::FLI1, EWS::ERG, SYT::SSX1/2*) was recommended but not mandatory. Sex was reported as defined at birth and confirmed by self-report. Key exclusion criteria were pregnancy or lactation and other medical condition precluding treatment with protocol therapy i.e. HIV infection. Patients were removed from the study only if they withdrew consent or did not comply with study procedures. Data from the start of patient enrollment in the SoTiSaR (a Registry for STS in children, adolescents and young adults) through the end of standard therapy were collected and analyzed at the CWS International Study Center in Stuttgart, Germany. The data of the randomised patients were collected by the responsible investigators via the EDC web-based documentation system "Marvin". The trial was conducted in accordance with the Helsinki Declaration and Good Clinical Practice guidelines. The central ethics approval for the CWS-2007-HR was granted by the Ethics Review Boards of the University of Tübingen (293/2007 AMG1). All participating centers were required to obtain written approval from their local authorities and ethics committees and written informed consent from patients, their parents or legal guardians.

Randomisation and masking

Randomisation was stratified according to risk groups (Stratum A encompassed high-risk rhabdomyosarcoma, Stratum B encompassed very-high-risk rhabdomyosarcoma and high-risk STS). To reduce possible imbalances in the number of treatment assignments, a permuted block design was used. Randomisation had to occur within 30 days of the end of standard therapy, defined as the date of the last intervention, i.e. chemotherapy cycle, surgery (i.e. second-look biopsy if needed), the end of radiotherapy if given after the last chemotherapy cycle, or the date of the last diagnostic procedure confirming remission status. If randomised

to the M-arm, maintenance therapy should start within 35 days after the last standard therapy day. Random allocation was performed at the study center in Stuttgart using randomisation lists generated by CenTrial GmbH, an inter-university consortium for conducting clinical trials, using Randomiser software generated at the Institute of Statistics, University of Graz. A random assignment number allocated to each patient was provided to the respective investigators via FAX. The study was open-label, and treatment allocation was not masked to the patients or the investigators.

Procedures

Patients with rhabdomyosarcoma and high-risk STS i.e. undifferentiated sarcoma, EES and primary unresected synovial sarcoma were registered in the CWS-Register SoTiSaR (approved by the Ethics Review Board of the University of Tübingen 158/2009B02) and treated according to the CWS-Guidance with standard therapy (consisted of nine cycles of ifosfamide, vincristine, dactinomycin with or without doxorubicin, and surgery or radiotherapy, or both). The CWS-Guidance treatment plans (Figures A1 and A2) and the description of the staging procedure and chemotherapy regimens are provided in the Appendix.

The trial design and treatment summary after randomisation is shown in Figure A3 (Appendix). Maintenance therapy (M-arm) consisted of eight 10-day courses of trofosfamide (2×75 mg/m^2/day) and idarubicin (1×5 mg/m^2/day 1,4,7,10) alternating with trofosfamide and etoposide (2×25 mg/m^2/day) p.o. Detailed recommendations for performing oral maintenance therapy (i.e. dose adjustment depending on age and haematological parameters) were provided in the protocol. Parents and/or patients should have kept a daily record of tablet intake (and any deviations) in a study diary, which should have been presented to the doctor at each visit. Adverse events were monitored at least weekly and were assessed according to National Cancer Institute Common Toxicity Criteria, version 3, (description of toxicity evaluation—Appendix). All patients were monitored for possible tumour recurrence with ultrasound and MRI scans every 3 months and chest CT scans (every 6 months) during the first and second year, every 6 months (MRI) and annually (chest CT) during the third to fifth year.

Outcomes

The primary outcome was event-free survival (EFS) and the secondary outcome was overall survival (OS) of the intent to-treat population (ITT). EFS was calculated as the time between the date of randomisation and the first event or the date of the last patient contact. Event was defined as relapse of disease (local, metastatic, or combined), second malignancy, and death of any cause. OS was defined as time from randomisation to death or last follow up for surviving patients.

Statistical analysis

The sample size for randomisation was calculated based on the estimates for the primary endpoint, i.e. EFS. Based on the results of previous studies, the probability of a 3-year EFS was estimated to be 60%. In order to detect an increase of 15%, resulting in a hazard ratio of 0.56, 297 patients would have to be randomised (2-sided alpha = 5%, power 80%) with 97 expected events. The sample size was calculated using PASS 2000. It was expected to take 6 years to enroll all participants, with a follow-up period of 3 years after the last patient randomisation. Given the significantly lower recruitment rate and number of events at 6 years, the recruitment period was extended to 9 years in consensus with the Independent Data Monitoring Committee (IDMC) with 3 years of follow-up, resulting in a sample size of 196 patients and 113 events (two-tailed alpha 0.05, power 85%).[12] The underlying 3-year EFS and hazard ratio (HR) have not been changed (HR 0.56). Having a sequential design according to Wald the trial shall be stopped, if the observed number of adverse events (defined in protocol) exceeds 4.95 + 0.186× number of the recruited patients. Patient accrual ended on June 30th 2019, and data collected up to June 30th 2022 were analysed. Clinical variables and their frequency distributions were compared by the χ^2-Test or by the Fisher's exact-test. Primary and secondary outcomes (EFS and OS) were analyzed using the Kaplan–Meier method. CIs for the Kaplan–Meier estimator were stated at the 95% level. Patients who had not experienced an event at their last contact were considered censored. Survival curves were compared by the log-rank test (Mantel–Haenszel Test) at an alpha level of 0.05 (5%). HRs for the treatment effect and variables considered as potential risk factors were estimated with Cox's regression method for EFS and OS, and 95% CIs were calculated according to Wald's method. No adjustments were made for multiplicity. The main analyses were conducted according to the ITT principle, including patients in each group to which they were assigned, whether or not they actually received the allocated treatment. Additional descriptive analyses were performed in the per-protocol (PP) population, defined as patients who received their assigned treatment and an as-treated approach (patients treated with maintenance therapy versus patients who did not receive maintenance therapy, regardless of their randomisation arm). Median follow-up was estimated with a reverse Kaplan–Meier estimator according to Schemper and Smith. Statistical analyses were performed using R 3.02 (Bell Laboratories, Murray Hill, NJ, USA) software packages. A two-sided p value less than 0.05 was considered significant. The IDMC annually supervised the study progress, monitored safety and efficacy and recommended continuing randomisation as planned. This trial is registered at ClinicalTrials.gov. NCT00876031 and EudraCT 2007-0001478-10.

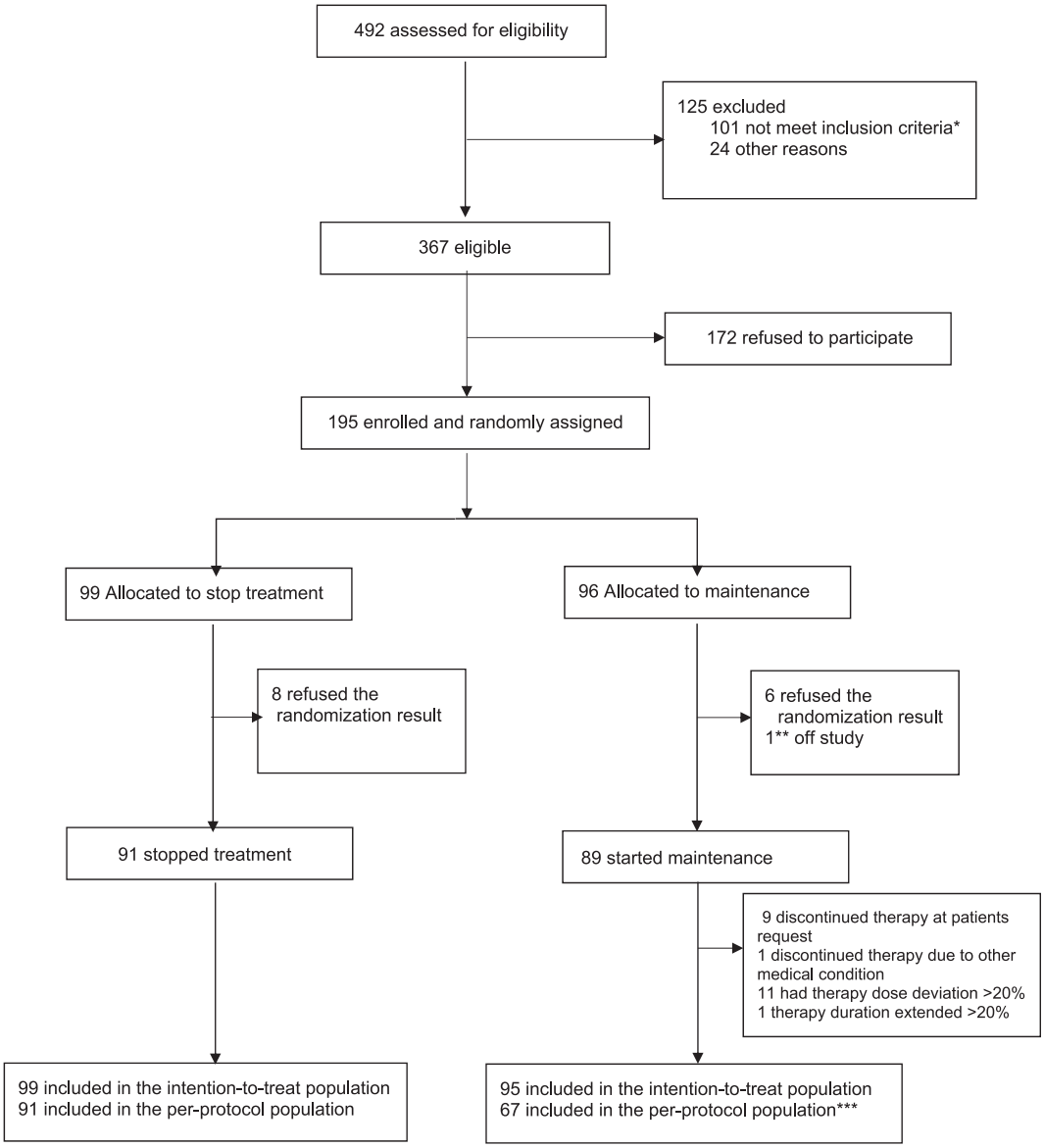

Fig. 1: Consort diagram. *60 no complete remission at end of standard therapy, 25 medical reasons: cardiac or renal dysfunction, tube feeding, no swallowing reflex, 16 major deviations from standard therapy. **Due to major violation of inclusion criteriaidentified after randomisation. ***Protocol patients were defined as those who received at least 80% of the cumulative planned doses of maintenance therapy within the indications for dose changes as described in the protocol and within a maximum extension of 20% compared to the prescribed protocol duration.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between July 1st, 2009 and June 30th, 2019, 492 patients were assessed for eligibility at the end of the standard therapy. 367 met the inclusion criteria and 195 were randomised: 99 to the S-arm and 96 to the M-arm (Fig. 1). One patient was subsequently found not to meet the eligibility criteria and was withdrawn from the study. Due to parental refusal of the randomisation results, six patients assigned to the M-arm did not start treatment. They were included in the ITT and excluded from the PP analysis. Randomisation results were rejected by the parents of eight patients randomised to discontinue treatment. Five of them received maintenance therapy. All eight patients were included in the ITT analysis but

excluded from the PP analysis. The six patients assigned to the M-arm who did not receive maintenance therapy were analyzed in the as-treated approach along with patients who did not receive maintenance therapy while assigned to the S-arm, and vice versa, five patients assigned to the S-arm who received maintenance therapy were analyzed along with patients assigned to the M-arm who received maintenance therapy. Data on treatment delivery and adherence, dose and duration modulations were available for 89 patients (Appendix Table 3A).

Baseline characteristics of patients in the two treatment groups are shown in Table 1 and of the eligible but non-randomised patients in Table A2 (Appendix). At the time of data cutoff (June 30th, 2022), median follow-up for surviving patients was 5.2 years (IQR 3.9–6.1). In the ITT population, the 3-year EFS was 75.6% (95% CI 67.6–84.6) in the S-arm versus 66.9% (95% CI 58.1–77.2) in the M-arm, (HR 1.62, 95% CI 0.98–2.69, p = 0.06). The 3-year OS was 84.7% (95% CI 77.8–92.1) in the S-arm versus 82.8% (95% CI 75.4–90.8) in the M-arm (HR 1.55, 95% CI 0.84–2.89, p = 0.17) Fig. 2. 158 patients met criteria for PP analysis. 3-year EFS was 74.6% (95% CI 66.1–84.1) in the S-arm versus 70.1% (95% CI 59.9–82.0) in the M-arm, (HR 1.27, 95% CI 0.72–2.24 p = 0.40). 3-year OS was 84.4% (95% CI 77.2–92.3) in the S-arm versus 83.4% (95% CI 74.9–92.9) for patients in the M arm (HR 1.29, 95% CI 0.64–2.61, p = 0.48). The analysis of the as-treated population showed a 3-year EFS of 69.5% (95% CI 60.7–79.6) in patients who received maintenance therapy versus 73.1% (95% CI 64.7–82.5) in those who did not (HR 1.15, 95% CI (0.89–1.89, p = 0.60). The 3-year OS was 85.7% (95% CI 78.9–93.2) in patients who received maintenance therapy versus 82.2% (95% CI 74.9–90.3) in those who did not (HR 1.06 95% CI 0.87–1.96, p = 0.86), Fig. 2. In the ITT population, 54 (27%) patients relapsed with a similar distribution of local and metastatic events in the two arms (Table 2). Combined relapses were slightly more common in the M-arm (8 versus 2), but three out of eight occurred in patients who did not receive maintenance therapy. The median time to relapse (TTR) calculated from the date of randomisation was 6.3 months (IQR 3.2–12.6) in the S-arm and 8.2 months (IQR 6.2–15.2) in the M-arm. Nine patients had second malignancy as their first event, three in the S-arm and six in the M-arm, four of which were the latest events (4–10 years after randomisation). Details on second malignancy by treatment arm are shown in Table A4 (Appendix). 42 (21%) patients died: 24 (25%) in the M-arm and 18 (18%) in the S-arm. All deaths except four: two in the M-arm (one due to second acute myeloid leukemia (AML) and one unclear sudden death at the day of randomisation) and two in the S-arm, both due to second malignancies (AML and osteosarcoma) were due to tumour recurrence. Adverse event data are summarised in Table 3. The majority of adverse events were mild (grade 1–2.). The most common grade 3–4 adverse events were leucopenia (59, 66%) and neutropenia (55, 61%). Grade 3 infection was reported in 7 (8%) patients. No treatment related serious adverse events (including hospitalisation) occurred. An exploratory subgroup analysis in the ITT population, showed for patients with rhabdomyosarcoma only the 3-year EFS of 74.3% (95% CI 64.7–85.3) in the S-arm versus 65.4% (95% CI 55.0–77.7) in the M-arm (HR 1.58, 95% CI 0.87–2.88, p = 0.13) and the 3-year OS was 83.2% (95% CI 74.5–92.8) in the S-arm versus 74.6% (95% CI 64.3–86.4) in the M-arm (HR 1.32, 95% CI 0.66–2.75, p = 0.46). In the "as treated" rhabdomyosarcoma population, 3-year EFS was 70.5% (95% CI 60.4–82.2) in patients who did not receive maintenance therapy versus 71.3% (95% CI 59.7–85.2) in those who did (HR 1.1 95% CI, 0.57–2.08, p = 0.79). The 3-year OS was 79.2% (95% CI 70.0–89.5) in patients who did not receive maintenance therapy versus 85.6% (95% CI 76.2–96.1) in patients who did receive maintenance therapy (HR 0.75, 95% CI 0.33–1.69, p = 0.49).

Analysis by other clinical variables of known prognostic value, such as sex, age, histology (alveolar rhabdomyosarcoma, other rhabdomyosarcoma, HR-STS) tumour invasiveness, site and size, nodal involvement and IRS group, in the ITT population showed no significant difference in any subgroup with an exception in patients with tumour size ≤5 cm, IRS group I + II, primary site HN and N0 status. For OS, a difference was observed only in patients with tumour size ≤5 cm in favour of the S-arm (Appendix Figure A4).

Discussion

This international randomised phase 3 trial evaluated the efficacy of oral maintenance therapy given in children, adolescents, and young adults ≤21 years of age with localised, high-risk rhabdomyosarcoma and STS who were in complete clinical remission after standard therapy. EFS and OS were not significantly different in the M-arm compared to the S-arm arm in the ITT and PP analyses. This clearly indicates that extending treatment by adding this form of oral maintenance therapy with trofosfamide, idarubicin and etoposide did not improve outcome in the study population. The EFS and OS results of the as-treated analysis, supported the lack of any beneficial effect of maintenance therapy on outcome. Subgroup analysis by histological entity (rhabdomyosarcoma, other STS) in the ITT population showed similar results.

Low-dose maintenance therapy, which is thought to have different mechanisms of action than intensive chemotherapy, theoretically has the potential to eradicate minimal residual disease, leading to improved EFS, or at least to delay relapse, possibly leading to improved OS, as later relapses have been shown to translate into better post-relapse survival.[13] Our study however, showed no improvement in either of these outcomes.

The EpSSG RMS 2005 study, which evaluated the role of 6 months of cyclophosphamide and vinorelbine

maintenance in high-risk rhabdomyosarcoma patients, showed improved OS but not EFS in the ITT analysis and improved both outcomes in the PP analysis.[14] In previous CWS studies, TTR was shown to be predictive of OS.[13] The median TTR in CWS-2007-HR and in RMS 2005 was >6 < 12 months in both arms suggesting that TTR was unlikely to be a factor influencing OS in either study. Interestingly, the EFS and OS of patients without maintenance therapy in our study (74% and 83%) were almost identical to the DFS and OS of patients with maintenance therapy in the RMS 2005 study (77% and 86%). In fact, the outcome in both arms were much better than expected when the CWS-2007-HR study was designed based on the results of the CWS-96 study. This is probably due to the general improvement in diagnostic and therapeutic standards, as the intensive chemotherapy and radiotherapy used in the patients enrolled in the CWS-2007-HR trial (according to the CWS-Guidance) were even reduced compared to CWS-96 and to the fact that only patients who had a complete clinical response were eligible for randomisation.[5,15]

There are some similarities and some differences between our study and the RMS 2005 trial. The eligibility criteria for patients with rhabdomyosarcoma were almost identical in both trials, with the exception of patients with alveolar rhabdomyosarcoma and nodal involvement, who were not eligible in RMS 2005 in contrast to CWS-2007-HR, as was the standard intensive chemotherapy with IVA prior to maintenance therapy. In RMS 2005, standard therapy were randomised (IVA versus IVADO), but there was no difference in outcome between these two arms.[16] The recommendation for irradiation for patients with rhabdomyosarcoma was also identical in the CWS-Guidance and RMS 2005.[14,15]

The main differences were in the eligibility of patients with EES, undifferentiated sarcoma, and high-risk synovial sarcoma in the CWS-2007-HR, the definitions of outcomes and the composition of the maintenance therapy. The inclusion of patients with other high-risk STS was based on the experience of the previous CWS studies with very good results when these patients were treated in a similar way to those with high-risk rhabdomyosarcoma, and some evidence that they may benefit from maintenance therapy.[3,9,17] The primary outcome was disease-free survival (DFS) in the RMS 2005 study and EFS in the CWS-2007-HR study, where second malignancy was also considered an event. The drugs, dosage, and route of administration were also different: RMS 2005 maintenance therapy consisted of an alkylator and vinca alkaloid, and the CWS-2007-HR regimen consisted of an alkylator (trofosfamide), topoisomerase inhibitor (etoposide), and an anthracycline (idarubicin) and was administered per os. Trofosfamide (mainly metabolised to ifosfamide) has been shown to have antiangiogenic

Characteristic	Standard-Arm n = 99	Maintenance-Arm n = 95
	n (%)	n (%)
Sex		
Male	61 (61%)	55 (57%)
Female	38 (38%)	40 (43%)
Age		
≤10	61 (62)	55 (58)
>10	38 (38)	40 (42)
Tumour Size		
≤5 cm	34 (34)	33 (35)
>5 cm	60 (61)	61 (64)
Missing values	5 (5)	1 (1)
Histology		
eRMS	44 (47)	41 (44)
RMS spindle cell	2	1
RMS not other specified	1	0
aRMS	25 (25)	29 (31)
FOXO1 fusion positive	8 (8)	14 (15)
PAX3	4 (4)	11 (12)
PAX7	4 (4)	3 (3)
Fusion negative	3 (3)	3 (3)
Not known	14 (14)	12 (13)
HR-STS[a]	27 (27)	24 (25)
Tumour Site[b]		
HN-PM	35 (35)	31 (33)
HN-nPM	14 (14)	12 (13)
GU-BP	9 (9)	9 (9)
GU-nBP	4 (4)	4 (4)
ORB	0 (0)	0 (0)
EXT	24 (24)	21 (22)
OTH	13 (13)	18 (19)
Tumor invasiveness[c]		
T1	37 (37)	39 (41)
T2	55 (56)	50 (53)
TX	7 (7)	6 (6)
Regional lymph node involvement[d]		
N0	71 (72)	66 (69)
N1	23 (23)	25 (26)
NX	5 (5)	4 (4)
IRS clinical group[e]		
I	5 (5)	2 (2)
II	13 (13)	13 (14)
III	80 (81)	80 (84)
Missing values	1 (1)	0 (0)

[a]HR-STS: non-metastatic undifferentiated sarcoma, extraskeletal Ewing sarcoma and primary unresected synovial sarcoma. [b]HN-PM- Head/Neck-Parameningeal, HN-nPM–Head/Neck-non Parameningeal, GU-BP- Genitourinary-Bladder/Prostate, GU-nBP- Genitourinary-non Bladder/Prostate, ORB- Orbita, EXT- Extremity, OTH other. [c]T1, localised to the organ or tissue of origin; T2, extending beyond the organ or tissue of origin; TX, insufficient information about the primary tumour. [d]N0, no evidence of lymph node involvement, N1, evidence of lymph node involvement, NX, no information about lymph node involvement. [e]IRS clinical group, Intergroup Rhabdomyosarcoma Study Grouping after primary surgery/biopsy; IRS I, complete resection at first surgery; IRS II, microscopic residual disease after initial surgery; IRS III, biopsy or initial macroscopic residual disease after initial surgery.

Table 1: **Baseline characteristics of ITT patients by treatment group.**

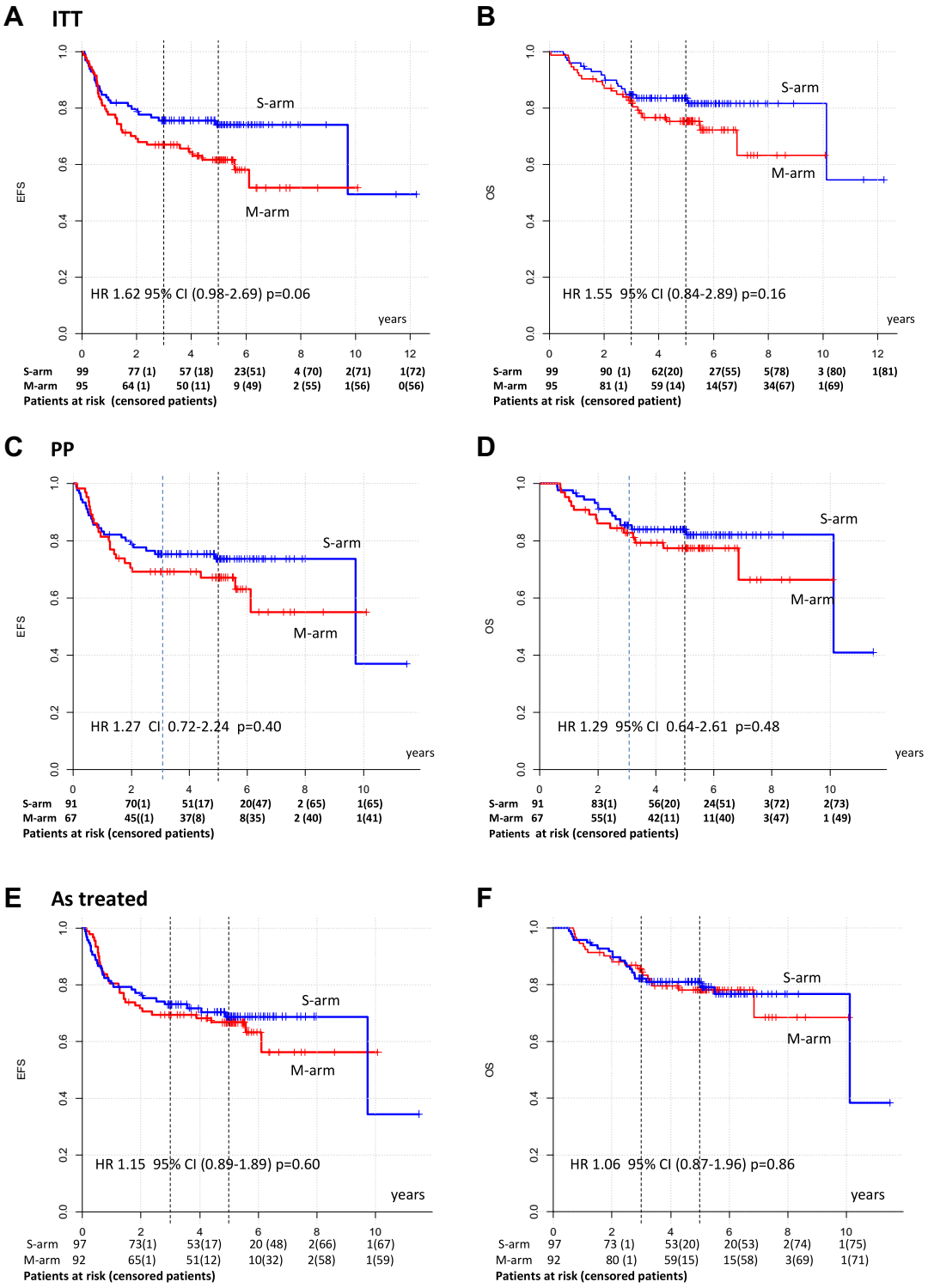

Fig. 2: Kaplan–Meier estimates of (A) Event-free survival (EFS) and (B) Overall survival (OS) in the ITT population, C and D in the PP population and E and F in as-treated patients. The vertical dotted lines mark the 3 and 5 year intervals. HR, Hazard Ratio; 95% CI, 95% confidence interval.

Events	Standard-Arm n = 99	Maintenance-Arm n = 95
	n (%)	n (%)
Total events	27 (27)	36 (38)
Local and locoregional relapse	13 (13)	13 (14)
Metastatic relapse	8 (8)	9 (9)
Combined relapse	2 (2)	8 (8)
Second malignancy	3 (3)	6 (6)
Type unknown	1 (1)	0 (0)
Alive	81 (82)	71 (75)
Dead	18 (18)	24 (25)
Death of primary disease	16 (16)	22 (23)
Death of other causes	2[b] (2)	2[a] (2)

[a]One death due to second malignancy (acute myeloid leukemia), one after unclear seizure on the day of randomisation and acute encephalopathy. [b]Two deaths due to second malignancies (acute myeloid leukemia and osteosarcoma).

Table 2: **First events by randomised group.**

effects and activity against resting tumour stem cells and has been used successfully in adult patients with sarcomas.[18–22] The combination of alkylating agents with anthracylines and etoposide is among the most effective in paediatric STS even though it failed to improve prognosis when used as intensive first-line therapy in patients with rhabdomyosarcoma.[6,23–25] There may be several reasons for the negative result seen in this study. Ineffectiveness of the drugs used is unlikely given the large amount of clinical and preclinical data supporting their activity in STS. Similarly, the duration of therapy, which is known to affect survival, was identical in our study and in RMS 2005.[26] One of the reasons may be the selection of eligible patients based on imaging criteria alone, which is not very accurate in assessing residual tumour burden and may be the cause of the heterogeneity of the CWS-2007-HR and RMS 2005 populations, as there was no central radiological review in either study. 30–40% of patients with high-risk rhabdomyosarcoma in radiologically complete remission at the end of standard therapy, who were eligible for our study and RMS 2005, relapse in the first 6–18 months after standard therapy, probably due to residual tumour cells. The remaining 60–70% are cured without further therapy.[8] Therefore, it is evident that a more accurate prediction of the risk of recurrence at the end of standard therapy is urgently needed. Circulating tumour DNA (ctDNA) testing has started to be used to enroll ctDNA-positive patients at high risk of recurrence into randomised trials.[27] We believe that the evaluation of ctDNA in patients with STS could provide a more precise definition of patients at risk at the end of standard therapy, improve the eligibility criteria for future studies of maintenance therapy and the assessment of its role in prognosis.[28] This could save the 60–70% of patients cured with standard therapy from unnecessary further therapy. It is also possible that further improvements in the prognosis may only be possible with innovative therapeutic approaches beyond conventional cytotoxic agents. Although maintenance therapy relies on the administration of drugs at low doses, the cumulative doses administered may be comparable to those of conventional regimens and may be associated with severe late sequelae.[11] Nine patients (six with embryonal rhabdomyosarcoma) had second malignancy as a first event in the present study, three in the S arm (3%) and six in the M arm (6%). This results in an overall rate of 4.6% in this high-risk group of patients, which is only slightly higher than the second malignancy rate reported for all rhabdomyosarcoma risk groups.[15] However, the risk of late effects due to maintenance therapy is one of the most important factors in long-term outcomes and remains to be determined.

Adverse event	Grade 1–2	Grade 3	Grade 4
	n (%)	n (%)	n (%)
Hematological toxicity			
Anaemia	52 (59)	11 (12)	0
Leukopenia	26 (29)	41 (46)	18 (20)
Neutropenia	22 (25)	35 (40)	20 (23)
Thrombocytopenia	15 (17)	5 (6)	1 (1)
Non–haematological toxicity			
Cardiac			
Arrythmia	1 (1)	–	–
Infection	43 (49)	7 (6)	–
Fever	24 (27)	–	–
Nephrotoxicity	52 (59)	–	–
Neurology	9 (10)	1 (1)	–
Nausea or vomiting	81 (92)	6 (7)	1 (1)
Gastrointestinal	48 (54)	3 (3)	–
Allergy	1 (1)	–	–
Dermatological	14 (16)	–	–
Other[b]	3 (3)	–	–

[a]Highest severity per patient; toxicities counted once per patient. [b]Other: Fatigue, Dyspnoea.

Table 3: **Adverse events reported in 88 patients during maintenance therapy.**[a]

In the recently published randomised COG trial ARST1431, investigating the addition of temsirolimus to chemotherapy in patients with intermediate risk rhabdomyosarcoma, maintenance therapy with cyclophosphamide and vinorelbine was used as part of the backbone regimen in both arms, based on the encouraging results of the RMS 2005 trial, but its overall impact on prognosis remained unclear, highlighting the fact that further studies are needed to establish the role of maintenance therapy in the treatment of patients with rhabdomyosarcoma.[29] The main limitation of this study is related to the well-known obstacles associated with conducting randomised trials in rare tumours in children such as a lower than expected recruitment rate leading to an extension of the recruitment period.[29,30] There were several reasons for the low recruitment

rate, including a high proportion of eligible patients who were not randomised, mainly due to parental refusal or physician decision. A major hurdle has also been the new EU regulation, the EU Clinical Trials Directive 2001/20/EC (EU CTD), which caused several participating countries to delay the start of the trial.[30] Many other randomised trials of pediatric malignancies have faced similar recruitment problems.[14,31] Another limitation is that the randomisation was not blinded, which may introduce a risk of bias. However, blinding the randomisation between three oral chemotherapeutic agents and placebo in a trial conducted primarily in a paediatric population seemed both unethical and unfeasible. In conclusion, CWS-2007-HR as the first randomised trial of oral maintenance therapy in patients with high-risk rhabdomyosarcoma and other high-risk STS has shown that prolonging treatment with idarubicin, trofosfamide and etoposide in patients in complete remission after multimodal standard therapy does not improve survival. Our study provides valuable information on the treatment of these rare tumours and may help to refine hypotheses and plan future research in this area. Further studies with improved risk-adapted patient stratification based on biomarkers such as ctDNA and innovative biology-based therapeutic approaches are warranted.

Contributors

EK and TK conceptualised the CWS-2007-HR study, wrote the study protocol and the first and final draft of the manuscript and secured funding for the trial and were also involved in recruitment and treatment of participants. JB contributed to the conceptualization of the study, methodolgy and supervision and review and editing of the manuscript. GL,BK, FN and RL secured and were responsible for the conducting the study in their countries. BB and MZ verified the underlying data and performed all statistical analyses. EH accessed and verified the data. RH, ITL, IS, BF, HLM, WB, MS,CB,SB, MSS were involved in the recruitment and treatment of participants.MSS and MS also contributed to the methodology and the management of the study. CV performed the reference histopathology and TK the imaging analysis. All authors had access to data reported in this study. All authors participated in the analysis and interpretation of results and were involved in review and editing of the final draft.

Data sharing statement

Individual participant data are not publicly available since this was requirement not anticipated in the study protocol. Deidentified data (patient characteristics and outcomes) will be made available to other researchers on request, subject to approval of a formal written data access request, from the time of publication until 2 years after publication. Trial documentation, including the protocol, is available on request from the corresponding author. Data recipients are required to enter into a formal data sharing agreement. Requests are reviewed by the Trial Steering Committee for scientific merit and ethical considerations, including patient consent. The ethics committee that originally approved the trial should also approve any use of the data that is not covered by the consent forms already collected.

Declaration of interests

MS-S has acted as consultant and advisory board member for Roche, Bayer and Swedish Orphan Biovitrum and received a grant from Bayer to support a research project on NTKR positive tumours. ITvL has received an institutional grant from GlaxoSmithKline Research&Development Limited as a sponsor of a phase 1 study.

IS has received travel and advisory board support from Astra Zeneca and Fennec. ThK has received travel support from the Deutsche Gesellschaft für Kinderheilkunde (DGKJ), consultancy fees for participation in advisory boards and lectures from the DKMS (Deutsche Knochenmarkspenderdatei). SB has received consultancy fees from Y-mAbs, MAP Biopharam, SERB SAS and Atheneum Partners GmbH, fees for expert testimony from Zschimmer & Schwarz Mohsdorf GmbH & Co. KG and travel support from the European Society for Medical Oncology.

Acknowledgements

We thank all patients, parents, national and international investigators and data managers who participated in the study, and Dr. Mary Morgan, a native speaking colleague, for review of the manuscript. We are particularly indebted to Professor Jörn Treuner, former Chairman of the CWS Group, for his leading role in conducting previous CWS studies, the results of which provided the basis for the design of this trial.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102957.

References

1 Pappo AS, Shapiro DN, Crist WM, Maurer HM. Biology and therapy of pediatric rhabdomyosarcoma. *J Clin Oncol*. 1995;13(8):2123–2139. https://doi.org/10.1200/JCO.1995.13.8.2123.
2 Stevens MC, Rey A, Bouvet N, et al. Treatment of nonmetastatic rhabdomyosarcoma in childhood and adolescence: third study of the international society of paediatric oncology–SIOP malignant mesenchymal tumor 89. *J Clin Oncol*. 2005;23(12):2618–2628. https://doi.org/10.1200/JCO.2005.08.130.
3 Koscielniak E, Harms D, Henze G, et al. Results of treatment for soft tissue sarcoma in childhood and adolescence: a final report of the German Cooperative Soft Tissue Sarcoma Study CWS-86. *J Clin Oncol*. 1999;17(12):3706–3719. https://doi.org/10.1200/JCO.1999.17.12.3706.
4 Oberlin O, Rey A, Sanchez de Toledo J, et al. Randomized comparison of intensified six-drug versus standard three-drug chemotherapy for high-risk nonmetastatic rhabdomyosarcoma and other chemotherapy-sensitive childhood soft tissue sarcomas: long-term results from the International Society of Pediatric Oncology MMT95 study. *J Clin Oncol*. 2012;30(20):2457–2465. https://doi.org/10.1200/JCO.2011.40.3287.
5 Sparber-Sauer M, Ferrari A, Kosztyla D, et al. Long-term results from the multicentric European randomized phase 3 trial CWS/RMS-96 for localized high-risk soft tissue sarcoma in children, adolescents, and young adults. *Pediatr Blood Cancer*. 2022;69(9):e29691. https://doi.org/10.1002/pbc.29691.
6 Crist WM, Anderson JR, Meza JL, et al. Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. *J Clin Oncol*. 2001;19(12):3091–3102. https://doi.org/10.1200/JCO.2001.19.12.3091.
7 Arndt CA, Stoner JA, Hawkins DS, et al. Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamide for intermediate-risk rhabdomyosarcoma: children's oncology group study D9803. *J Clin Oncol*. 2009;27(31):5182–5188. https://doi.org/10.1200/JCO.2009.22.3768.
8 Arndt CAS, Bisogno G, Koscielniak E. Fifty years of rhabdomyosarcoma studies on both sides of the pond and lessons learned. *Cancer Treat Rev*. 2018;68:94–101. https://doi.org/10.1016/j.ctrv.2018.06.013.
9 Klingebiel T, Boos J, Beske F, et al. Treatment of children with metastatic soft tissue sarcoma with oral maintenance compared to high dose chemotherapy: report of the HD CWS-96 trial. *Pediatr Blood Cancer*. 2008;50(4):739–745. https://doi.org/10.1002/pbc.21494.
10 Browder T, Butterfield CE, Kraling BM, et al. Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. *Cancer Res*. 2000;60(7):1878–1886.
11 Andre N, Carre M, Pasquier E. Metronomics: towards personalized chemotherapy? *Nat Rev Clin Oncol*. 2014;11(7):413–431. https://doi.org/10.1038/nrclinonc.2014.89.

12 Lachin JM. Introduction to sample size determination and power analysis for clinical trials. *Control Clin Trials*. 1981;2(2):93–113. https://doi.org/10.1016/0197-2456(81)90001-5.

13 Mattke AC, Bailey EJ, Schuck A, et al. Does the time-point of relapse influence outcome in pediatric rhabdomyosarcomas? *Pediatr Blood Cancer*. 2009;52(7):772–776. https://doi.org/10.1002/pbc.21906.

14 Bisogno G, De Salvo GL, Bergeron C, et al. Vinorelbine and continuous low-dose cyclophosphamide as maintenance chemotherapy in patients with high-risk rhabdomyosarcoma (RMS 2005): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2019;20(11):1566–1575. https://doi.org/10.1016/S1470-2045(19)30617-5.

15 Koscielniak E, Timmermann B, Munter M, et al. Which patients with rhabdomyosarcoma need radiotherapy? Analysis of the radiotherapy strategies of the CWS-96 and CWS-2002P studies and SoTiSaR registry. *J Clin Oncol*. 2023;41(31):4916–4926. https://doi.org/10.1200/JCO.22.02673.

16 Bisogno G, Jenney M, Bergeron C, et al. Addition of dose-intensified doxorubicin to standard chemotherapy for rhabdomyosarcoma (EpSSG RMS 2005): a multicentre, open-label, randomised controlled, phase 3 trial. *Lancet Oncol*. 2018;19(8):1061–1071. https://doi.org/10.1016/S1470-2045(18)30337-1.

17 Koscielniak E, Sparber-Sauer M, Scheer M, et al. Extraskeletal Ewing sarcoma in children, adolescents, and young adults. An analysis of three prospective studies of the Cooperative Weichteilsarkomstudiengruppe (CWS). *Pediatr Blood Cancer*. 2021;68(10):e29145. https://doi.org/10.1002/pbc.29145.

18 Wagner A, Hempel G, Boos J. Trofosfamide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the oral treatment of cancer. *Anticancer Drugs*. 1997;8(5):419–431.

19 Stolting S, Klink T, Bela C, Engels C, Wagner T. Metronomic scheduling of trofosfamide chemotherapy in human NSCLC xenografts highly increases therapeutic efficacy compared to conventional scheduling by inhibition of angiogenesis. *Int J Clin Pharmacol Ther*. 2004;42(11):652–653. https://doi.org/10.5414/cpp42652.

20 Blomqvist C, Wiklund T, Pajunen M, Virolainen M, Elomaa I. Oral trofosfamide: an active drug in the treatment of soft-tissue sarcoma. *Cancer Chemother Pharmacol*. 1995;36(3):263–265. https://doi.org/10.1007/BF00685858.

21 Hartmann JT, Kopp HG, Gruenwald V, et al. Randomised phase II trial of trofosfamide vs. doxorubicin in elderly patients with untreated metastatic soft-tissue sarcoma. *Eur J Cancer*. 2020;124:152–160. https://doi.org/10.1016/j.ejca.2019.10.016.

22 Raciborska A, Bilska K, Rodriguez-Galindo C. Maintenance treatment with trofosfamide in patients with primary bone ewing sarcoma - single center experience. *Dev Period Med*. 2019;23(1):39–44. https://doi.org/10.34763/devperiodmed.20192301.3944.

23 Dantonello TM, Int-Veen C, Harms D, et al. Cooperative trial CWS-91 for localized soft tissue sarcoma in children, adolescents, and young adults. *J Clin Oncol*. 2009;27(9):1446–1455. https://doi.org/10.1200/JCO.2007.15.0466.

24 Breitfeld PP, Lyden E, Raney RB, et al. Ifosfamide and etoposide are superior to vincristine and melphalan for pediatric metastatic rhabdomyosarcoma when administered with irradiation and combination chemotherapy: a report from the Intergroup Rhabdomyosarcoma Study Group. *J Pediatr Hematol Oncol*. 2001;23(4):225–233. https://doi.org/10.1097/00043426-200105000-00010.

25 Soft Tissue Sarcoma Committee of the Children's Oncology Group, Lager JJ, Lyden ER, et al. Pooled analysis of phase II window studies in children with contemporary high-risk metastatic rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. *J Clin Oncol*. 2006;24(21):3415–3422. https://doi.org/10.1200/JCO.2005.01.9497.

26 Bisogno G, Hawkins DS. An unresolved issue in rhabdomyosarcoma treatment: the duration of chemotherapy. *Pediatr Blood Cancer*. 2020;67(5):e28174. https://doi.org/10.1002/pbc.28174.

27 Kasi PM, Fehringer G, Taniguchi H, et al. Impact of circulating tumor DNA-based detection of molecular residual disease on the conduct and design of clinical trials for solid tumors. *JCO Precis Oncol*. 2022;6:e2100181. https://doi.org/10.1200/PO.21.00181.

28 Abbou S, Klega K, Tsuji J, et al. Circulating tumor DNA is prognostic in intermediate-risk rhabdomyosarcoma: a report from the children's oncology group. *J Clin Oncol*. 2023;41(13):2382–2393. https://doi.org/10.1200/JCO.22.00409.

29 Gupta AA, Xue W, Harrison DJ, et al. Addition of temsirolimus to chemotherapy in children, adolescents, and young adults with intermediate-risk rhabdomyosarcoma (ARST1431): a randomised, open-label, phase 3 trial from the Children's Oncology Group. *Lancet Oncol*. 2024;25(7):912–921. https://doi.org/10.1016/S1470-2045(24)00255-9.

30 Pritchard-Jones K, Europe S. Clinical trials for children with cancer in Europe - still a long way from harmonisation: a report from SIOP Europe. *Eur J Cancer*. 2008;44(15):2106–2111. https://doi.org/10.1016/j.ejca.2008.07.026.

31 Dirksen U, Brennan B, Le Deley MC, et al. High-dose chemotherapy compared with standard chemotherapy and lung radiation in ewing sarcoma with pulmonary metastases: results of the European ewing tumour working initiative of national groups, 99 trial and EWING 2008. *J Clin Oncol*. 2019;37(34):3192–3202. https://doi.org/10.1200/JCO.19.00915.