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ABSTRACT

Purpose: The phase III, open-label, prospective, multicenter, randomized Ewing 2008R1 trial (EudraCT2008-003658-13) was conducted in 12 countries to evaluate the effect of zoledronic acid (ZOL) maintenance therapy compared with no add-on regarding event-free survival (EFS, primary endpoint) and overall survival (OS) in standard-risk Ewing sarcoma (EWS).

Patients and Methods: Eligible patients had localized EWS with either good histologic response to induction chemotherapy and/or small tumors (<200 mL). Patients received six cycles of VIDE induction and eight cycles of VAI (male) or eight cycles of VAC (female) consolidation. ZOL treatment started parallel to the sixth consolidation cycle. Randomization was stratified by tumor site (pelvis/other). The two-sided adaptive inverse–normal four-stage design (planned sample size 448 patients, significance level 5%, power 80%) was changed after the first interim analysis using the Müller–Schäfer method.

Results: Between April 2010 and November 2018, 284 patients were randomized (142 ZOL/142 no add-on). With a median follow-up of 3.9 years, EFS was not significantly different between ZOL and no add-on group in the adaptive design (HR, 0.74; 95% CI, 0.43–1.28, $P = 0.27$, intention-to-treat). Three-year EFS rates were 84.0% (95% CI, 77.7%–90.8%) for ZOL vs. 81.7% (95% CI, 75.2%–88.8%) for no add-on. Results were similar in the per-protocol collective. OS was not different between groups. The 3-year OS was 92.8% (95% CI, 88.4%–97.5%) for ZOL and 94.6% (95% CI, 90.9%–98.6%) for no add-on. Noticeable more renal, neurologic, and gastrointestinal toxicities were observed for ZOL ($P < 0.05$). Severe renal toxicities occurred more often in the ZOL arm ($P = 0.003$).

Conclusions: In patients with standard-risk localized EWS, there is no additional benefit from maintenance treatment with ZOL.

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Translational Relevance

The international multicenter Ewing 2008R1 trial is the first study to investigate the value of zoledronic acid (ZOL) as additional maintenance therapy versus no add-on treatment in patients with localized Ewing sarcoma in a randomized setting. Add-on ZOL was not superior to conventional chemotherapy alone with respect to event-free survival (EFS) and overall survival (OS). More toxicities were observed in the experimental arm, especially more renal toxicities (grade ≥3).

In patients with standard-risk localized Ewing sarcoma, there is no additional benefit from maintenance treatment with ZOL. Standard treatment demonstrated an excellent outcome in this group of patients with a 3-year EFS of 81% and a 5-year OS of 89%.

Introduction

For more than 40 years, national and international groups have addressed their efforts to optimize treatment strategies to improve long-term survival rates in patients with Ewing sarcoma (EWS; ref. 1). Results from previous trials indicated that progress in EWS therapy had reached a plateau, with long-term survival rates stagnating at around 75% for patients without overt metastases at diagnosis (2, 3). The North American Children's Oncology Group found that, in patients with localized disease, a dose-compressed treatment regimen administered every 2 weeks (2-weekly) resulted in a higher 5-year event-free survival (EFS) rate of 73% compared to a 5-year EFS rate of 65% when the treatment was administered at 3-week intervals (3-weekly) (2). The EuroEWING99 trial used a dose-intense vincristine, ifosfamide, doxorubicin, and etoposide backbone induction regimen, and showed a 3-year EFS of about 75% (3).

To further improve EFS, the Ewing 2008R1 trial evaluated the bisphosphonate zoledronic acid (ZOL) as an addition to the standard treatment in patients with localized EWS. Nitrogen-containing bisphosphonates (N-BP) such as ZOL are potent inhibitors of bone resorption *in vivo* by inhibiting farnesyl diphosphate synthase, a key enzyme of the mevalonate pathway. N-BP have been shown to inhibit angiogenesis *in vitro* and *in vivo* (4) and to lower serum levels of proangiogenic vascular endothelial growth factor and platelet-derived growth factor in cancer patients (4, 5). N-BP are widely used in the treatment of bone metastases in patients with breast cancer, multiple myeloma, and prostate cancer (5). Tumor cells homing in bone tissue may disrupt physiologic bone structure by release of cytokines that activate osteoclasts and foster resorption of the bone matrix resulting in the release of cytokines that further promote tumor cell proliferation. Bisphosphonates targeting osteoclasts have been used successfully to break this vicious cycle in carcinoma (6). A similar effect was demonstrated in preclinical EWS and osteosarcoma models (7, 8). The bone microenvironment is an important pathogenic factor in EWS, and ZOL treatment has been shown to stop the feedback loop between EWS-induced osteolytic bone lesions and release of EWS-stimulating growth factors (9). *In vitro* and *in vivo* data have also demonstrated a direct antitumor activity of ZOL against EWS cells (9, 10). ZOL inhibited the development of EWS bone metastases in a TC71 mouse xenograft model (11) and also inhibited the dissemination of spontaneous lung metastases from a primary EWS tumor *in vivo* (10).

The Ewing 2008R1 trial therefore aimed to evaluate the effect of ZOL maintenance therapy on EFS (primary endpoint) and overall survival (OS) from randomization in favorable standard-risk EWS.

Patients and Methods

Study design

The Ewing 2008R1 trial was an international, phase III, open-label, multicenter, randomized, and controlled trial of international study groups in patients with standard-risk localized EWS comparing two maintenance regimens in a parallel-group design: add-on therapy with zoledronic acid and without add-on therapy. Standard-risk localized EWS was defined as patients with a good histopathologic response (<10% viable tumor cells after induction therapy) and/or patients with a small initial tumor volume (<200 mL) who either underwent complete surgery at the time of diagnosis or received primary or preoperative radiotherapy (Supplementary Fig. S1).

The randomized R1 trial was a component of the Ewing 2008 study (ClinicalTrials.gov: NCT00987636, EudraCT: 2008–003658–13), which recruited patients with localized or metastatic EWS at diagnosis. This trial was conducted in 120 pediatric and adult oncology centers in 12 countries. Representativeness of study participants is described in Supplementary Table S1. The trial was approved by the appropriate ethics committees in line with the legislation in each country. The studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Eligibility criteria

Inclusion criteria were a localized, biopsy-proven EWS of bone or soft tissue and classified as standard-risk disease. Further criteria were age ≥4 and <50 years, Lansky or Karnofsky score >50%, hemoglobin >8 g/dL (transfusion allowed), platelets >80,000/μL (transfusion allowed), white blood count >2000/μL, cardiac values left ventricular ejection fraction >40%, and shortening fraction >28%. Registration

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and start of chemotherapy had to be within 45 days of diagnostic biopsy or surgery. Exclusion criteria were more than one cycle of chemotherapy prior to registration, second malignancy, pregnancy or lactation, concurrent treatment within any other clinical trial, or any other medical, psychiatric, or social condition incompatible with protocol treatment. There were 501 patients who withdrew from the study because they did not meet the inclusion or exclusion criteria, or for other reasons. The diagnosis of EWS was based on morphologic and immunophenotypic criteria and, whenever possible, on molecular confirmation of EWSR1 rearrangement by FISH or RT-PCR. A review by the reference pathologist was recommended before random assignment for all patients without molecular confirmation of the diagnosis.

Written informed consent was obtained from all patients and/or their parents/guardians before enrollment. Additional informed consent for randomization was obtained after six courses of vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) induction.

Pretreatment evaluation

Patients underwent physical examination, a diagnostic chest CT, technetium skeletal scintigraphy or 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET-CT), and bone marrow aspirations and biopsies. Primary tumor volume was measured by MRI or CT, as appropriate. Renal function was assessed by tubular phosphate reabsorption and glomerular filtration rate.

Treatment

Induction chemotherapy consisted of six chemotherapy courses with the combination of VIDE (12, 13). Local therapy was tailored to patient and tumor characteristics and included surgery with complete surgical removal wherever feasible after VIDE cycle 6, primary radiotherapy, or a combination of both (Supplementary Fig. S1). Consolidation chemotherapy consisted of eight cycles of chemotherapy composed of vincristine and actinomycin D (VA) plus cyclophosphamide (VAC) for females or VA plus ifosfamide (VAI) for males. Patients randomized to ZOL add-on received ZOL at 28-day intervals starting at cycle 6 of VAC/VAI consolidation chemotherapy (parallel to VAC/VAI cycles, 21-day intervals allowed) for a maximum of nine cycles. Patients <18 years received ZOL 0.05 mg/kg body weight (BW) by i.v. infusion for 30 to 60 minutes. In patients ≥18 years, ZOL was dosed according to BW (>40 kg: 4 mg; 20–40 kg: 2 mg).

Randomization

Randomization was performed centrally by the Ewing headquarters after six VIDE courses. Written informed consent for randomization was obtained following the induction therapy. Within the consent, the study patients and/or their parents/guardians were given the opportunity to express any objections to the randomization process. In patients who underwent surgery for local control, randomization was performed after evaluation of the histologic response. The randomization was balanced and stratified according to tumor origin (pelvis vs. other) using block randomization (blocksize of four). The randomization envelopes and lists were prepared by the Institute of Biostatistics and Clinical Research, Muenster. No blinding was performed.

Endpoints and assessments

The primary endpoint was EFS, defined as the time from randomization to the date of the first event assessed by the investigator (progression, relapse, secondary malignancy, or death, whichever occurred first). Follow-up was scheduled every 3 months during the first 3 years, every 6 months during years 4 and 5, and then annually, regardless of treatment compliance. Secondary efficacy endpoint was overall survival (OS) from randomization, considering deaths from all causes. Central imaging review of tumor volume and response and central pathologic review of resection specimens were not performed. Compliance with treatment and toxicity were monitored. All chemotherapy doses were recorded, as well as the reasons for dose reduction or delay. Further secondary endpoints were acute toxicities related to chemotherapy. They were assessed after each course using a list of selected items from the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and Bearman's criteria for sinusoidal obstruction syndrome. A free text area was available for the documentation of other acute toxicities. A modified list was used to evaluate toxicities after radiotherapy, using Radiation Therapy Oncology Group classification.

For each toxicity item, the analysis was based on the maximum grade observed over the entire consolidation/maintenance treatment period by combining toxicities reported on consolidation (VAI/VAC) and add-on treatment forms. Toxicities from radiotherapy were not considered. Grade 4 hematologic toxicities and grade ≥3 nonhematologic toxicities were classified as severe.

Statistical analysis

The study was designed to ensure 80% power to detect a difference between the add-on and the no add-on arms in the primary endpoint EFS from randomization [expected 3-year EFS: 80% vs. 70%, hazard ratio (HR) 0.626] within an adaptive design with two-sided significance level 5%. Initially, a two-sided equally spaced four-stage group-sequential design with O'Brien & Fleming boundaries (14) using log-rank tests was planned and changed to an adaptive design using the inverse–normal combination function (15, 16). Assuming exponentially distributed event times, accrual time of 5 years, follow-up time of 2 years, and 5% dropouts, the initial target sample size was 448 patients to observe 146 events. With support from the independent data-monitoring committee, randomization was stopped after the first interim analysis. The observed effect was in favor of no add-on, and the conditional power was low to obtain a significant result in the remaining stages (Supplementary Statistics S1). The required number of events could not be achieved in a reasonable additional time due to lower event rates and recruitment numbers as assumed and because the trial lasted already longer than planned. Based on data of the first interim analysis (March 2017), the design was changed to perform one additional final analysis using the conditional error rejection probability method (ref. 17; Supplementary Statistics S1). This is the final analysis based on the data as of June 2019.

Survival rates (EFS and OS) were estimated using the Kaplan–Meier method with 95% pointwise confidence intervals (CI) using log transformation. Median and 25% to 75% quantiles (Q25–Q75) of follow-up were estimated using the reverse Kaplan–Meier method. The HR and 95% CI for EFS and OS were estimated in Cox regressions (18). Proportional hazard assumption was checked by using the ZPH diagnostics and tests based on the weighted Schoenfeld residuals.

The primary efficacy analysis was performed in the full analysis set according to the intention-to-treat principle (i.e., according to patients' randomly assigned treatments). Sensitivity analyses (e.g., to account for randomization strata) were performed using multivariable Cox regression models including the treatment effect and adjusting for the stratum primary tumor origin (pelvis/other) and for sex and age (years). Analyses were repeated in the per-protocol and safety collective (as-treated). Subgroup analyses were performed for these variables by first calculating the treatment differences for EFS and OS within each subgroup and comparing the groups via log-rank tests. Whether there was a different treatment effect between subgroup categories was

examined using a Wald test for the interaction term in a Cox model containing the treatment and subgroup variable and their interaction. Additionally, competing risk approaches were used for EFS to estimate the effect of treatment on the cumulative incidence (19), subdistribution hazard (20), and cause-specific hazard (21) of each competing event: locoregional recurrence/local progress, new metastases/metastatic progress, combined relapse/-progress, secondary malignancy, and death. Cumulative incidence was estimated using the Aalen–Johansen estimator (19). Gray's K-sample test was applied to compare the cumulative incidence of the corresponding event type. Safety analyses were performed on the safety set (as-treated population). The proportion of patients with specific toxicity (renal, gut, etc.) or severe toxicity was compared using the Fisher exact test. Data preparation and unadjusted analysis were performed using SAS software, Version 9.4 TS1M7 of the SAS System for Windows. Adaptive analyses were performed using ADDPLAN v6.1.1 and R v3.6.0 (RRID:SCR_001905) using the package "rpact" v2.0.1. The adaptive design provides confirmatory results, whereas all other P values and confidence limits were two-sided and intended to be exploratory, not confirmatory. Therefore, no adjustment for multiplicity was made. Exploratory P values ≤ 0.05 were considered to be statistically noticeable. All analyses were performed according to the ICH-E9 guideline and reported according to the CONSORT statement.

Data availability

The data obtained in the course of this study are not publicly available due to legal restrictions and data protection reasons. However, selected data can be made available on GitHub (RRID: SCR_002630) upon justified request to the corresponding author. The clinical trial protocol, amendments (Supplementary Data S1), and synopsis are attached as supplementary data.

Results

Patients

Between October 2009 and June 2019, 1,421 patients, enrolled in 120 centers from 12 countries, were assessed for eligibility (**Fig. 1**). Of 474 potentially eligible R1 patients, 173 were not enrolled in the randomized trial because of patient/parent refusal ($n = 88$), physician refusal ($n = 31$), organizational reason ($n = 21$), other reasons ($n = 20$), medical contraindication ($n = 7$), progression of disease ($n = 4$), and in two patients for unknown reasons. Seventeen patients were pending for randomization and four patients died before randomization. Thus, 284 patients were randomized between April 2010 and November 2018: 142 to the ZOL add-on arm and 142 to the no add-on arm. Patient characteristics of the randomized patients were similar to those of the nonrandomized patients (Supplementary Table S2). Patients who entered the study after stopping randomization were included in a registry. Of the 142 patients allocated to the ZOL add-on arm, 19 patients did not receive the randomized treatment, whereas one patient randomized to no add-on received ZOL because of physician choice/clinical decision. These 20 patients were included in the respective treatment group of the safety set, as they were treated, but excluded in the per-protocol analysis. For the definition of per-protocol set, other major protocol violations leading to exclusion and treatment details of excluded patients, see **Fig. 1**; Supplementary Data S2, and Supplementary Table S3.

The median age at registration was 13.7 years (range, 4.2–49.3 years). The baseline characteristics were well balanced between arms (**Table 1**). Median follow-up from randomization was 3.9 years (Q25–Q75 2.1–5.4, maximum 8.9 years) and similar between treatment groups (Supplementary Figs. S2 and S3).

Efficacy

A total of 52 events were reported (22 in the ZOL add-on arm, 30 in the no add-on arm): 13 local progressions or local relapses, 26 new metastases, eight combined relapses and progressions, five secondary malignancies, and no death as first event (**Table 2**). The confirmatory efficacy analysis using the adaptive design did not show a significant difference in the primary endpoint, EFS from randomization, between treatment arms (ITT, Supplementary Statistics S1). The HR for the comparison of ZOL add-on versus no add-on was 0.74 (95% CI, 0.42–1.28, $P = 0.27$ LR-test) in the full analysis set. The EFS rates at 3 and 5 years were 84.0% (95% CI, 77.7%–90.8%) and 81.4% (95% CI, 74.5%–89.0%) in the add-on arm compared with 81.7% (95% CI, 75.2%–88.8%) and 74.4% (95% CI, 66.3%–83.4%) in the no add-on arm (**Fig. 2A**). The treatment effect was similar in the multivariable sensitivity analysis adjusted for primary tumor origin, sex, and age, as well as in the analyses conducted in the per-protocol and safety set. In the subgroup analysis, there was no difference in treatment effect within the categories of sex, age, and primary tumor origin (**Fig. 2B**). When considering the different types of first events in the competing risk approach, the cumulative incidence for local recurrence or progress was lower for ZOL add-on in comparison with no add-on (subdistribution-HR 0.3; 95% CI, 0.08–1.08, $P = 0.05$; Supplementary Fig. S4; Supplementary Table S4).

Regarding the secondary endpoint, OS from randomization, we did not observe a statistically noticeable benefit of ZOL: 25 deaths were reported (13 in the add-on arm, 12 in the no add-on arm), leading to an HR of 1.08 (95% CI, 0.49–2.37, $P = 0.84$). OS rates for add-on versus no add-on were 92.8% (95% CI, 88.4%–97.5%) vs. 94.6% (95% CI, 90.9%–98.6%) at 3 years and 87.3% (95% CI, 80.7%–94.5%) vs. 89.6% (95% CI, 83.7%–95.9%) at 5 years, respectively (**Table 2**; **Fig. 2C**). The cause of death was cancer in 23 cases (add-on 11 cases, no add-on 12 cases). In the add-on arm, one patient died of secondary malignancy and one patient died of pneumonia (Supplementary Table S5).

Toxicities

All patients developed hematologic toxicity (**Fig. 3A**). A higher number of renal, neurologic, and gastrointestinal toxicities of all grades were observed during consolidation and maintenance therapy in the add-on arm ($P < 0.05$), and infections and skin toxicity were more pronounced in the add-on arm (**Fig. 3B**). Of the documented severe toxicities, only renal toxicities occurred more frequently in the add-on arm ($P = 0.003$; **Fig. 3C**).

Details of the maximal toxicity grades are given in Supplementary Table S6.

Discussion

This is the first randomized trial to address the role of ZOL in patients with EWS with localized disease. We did not demonstrate a statistically significant improvement in EFS with the ZOL add-on arm as maintenance. The trial was made possible through the close cooperation of multiple European countries and centers, and centers outside Europe, predominantly in Australia.

The rationale of the trial was based on the bone tropism of EWS metastases, shared with common cancers such as the lung, breast, and prostate. A benefit was observed from maintenance treatment with ZOL in breast, lung, and prostate cancers in earlier trials (5), supporting the design of our protocol. In prostate cancer, however, more

Figure 1.
CONSORT flow chart. For definition of the per-protocol set, major protocol violations leading to exclusion, and treatment details of excluded patients, see Supplementary Box S2 and Supplementary Table S3. Informed consent for randomization was obtained from patients just before randomization, after induction therapy, and not at study inclusion.

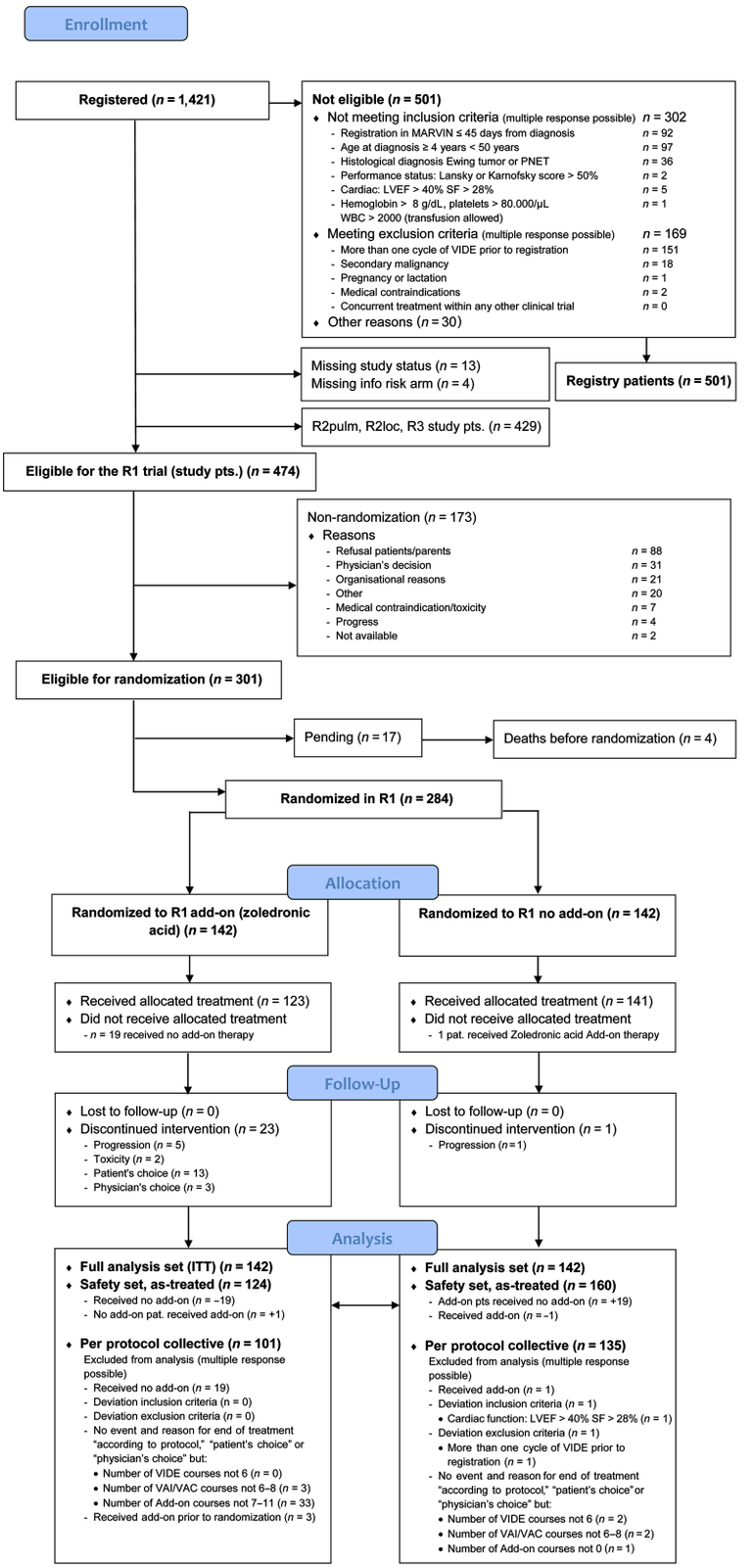

Table 1. Patient and tumor baseline characteristics.

Characteristics	Full analysis set (intention-to-treat)			Per-protocol set		Safety set (as-treated)	
	Total *N* = 284	Add-on *N* = 142	No add-on *N* = 142	Add-on *N* = 101	No add-on *N* = 135	Add-on *N* = 124	No add-on *N* = 160
Sex, No. (%)							
Male	158 (56%)	82 (58%)	76 (54%)	56 (55%)	72 (53%)	71 (57%)	87 (54%)
Female	126 (44%)	60 (42%)	66 (46%)	45 (45%)	63 (47%)	53 (43%)	73 (46%)
Age, y							
Median (range)	13.7 (4.2–49.3)	13.4 (4.3–49.3)	13.9 (4.2–45.7)	12.0 (4.3–48.5)	14.1 (4.3–45.7)	12.9 (4.3–49.3)	14.2 (4.2–45.7)
Follow-up since randomization, y							
Median duration (rev KM Est, Q25–Q75)	3.9 (2.4–5.4)	3.8 (2.3–5.7)	4.1 (2.4–5.3)	4.0 (2.7–5.9)	4.1 (2.5– 5.3)	3.9 (2.5–5.7)	3.9 (2.3–5.3)
Range (min – max)	0–8.9	0–8.9	0.3–8.4	0.6–8.9	0.3–8.4	0.2–8.9	0–8.4
Primary tumor origin 1, No. (%)							
Pelvis	41 (14%)	20 (14%)	21 (15%)	11 (11%)	21 (16%)	16 (13%)	25 (16%)
No Pelvis	243 (86%)	122 (86%)	121 (85%)	90 (89%)	114 (84%)	108 (87%)	135 (84%)
Primary tumor origin 2, No. (%)							
Soft tissue	42 (15%)	24 (17%)	18 (13%)	17 (17%)	17 (13%)	20 (16%)	22 (14%)
Bone	242 (85%)	118 (83%)	124 (87%)	84 (83%)	118 (87%)	104 (84%)	138 (86%)
Primary tumor site, No. (%)							
Pelvis	41 (14%)	20 (14%)	21 (15%)	11 (11%)	21 (16%)	16 (13%)	25 (16%)
Abdomen	3 (1%)	2 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	2 (1%)
Spine	32 (11%)	13 (41%)	19 (13%)	10 (10%)	18 (13%)	13 (10%)	19 (12%)
Chest	54 (19%)	27 (19%)	27 (19%)	18 (18%)	25 (19%)	24 (19%)	30 (19%)
Head/neck	21 (7%)	12 (8%)	9 (6%)	9 (9%)	9 (7%)	10 (8%)	11 (7%)
Upper extremity	37 (13%)	21 (15%)	16 (11%)	17 (17%)	16 (12%)	19 (26%)	18 (11%)
Lower extremity	96 (34%)	47 (33%)	49 (35%)	35 (35%)	45 (33%)	41 (33%)	55 (34%)
Primary tumor volume, No. (%)							
<200 mL	214 (76%)	104 (74%)	110 (77%)	73 (73%)	106 (79%)	86 (70%)	128 (80%)
≥200 mL	69 (24%)	37 (26%)	32 (23%)	27 (27%)	29 (21%)	37 (30%)	32 (20%)
Missing data or not applicable	1	1		1		1	
Local treatment of primary tumor (planned or completed) at the date of randomization							
Resection after chemotherapy alone: any tumor volume and good histologic response	212 (75%)	103 (73%)	109 (77%)	72 (71%)	104 (77%)	88 (71%)	124 (78%)
Resection after chemotherapy and early radiotherapy: tumor volume at diagnosis <200 mL and good histologic response	7 (2%)	6 (4%)	1 (1%)	5 (5%)	1 (1%)	6 (5%)	1 (1%)
Resection at diagnosis: tumor volume at diagnosis <200 mL	29 (10%)	15 (11%)	14 (10%)	12 (12%)	14 (10%)	13 (10%)	16 (10%)
Radiotherapy alone (tumor unresectable): tumor volume at diagnosis <200 mL and at least partial clinical response, excluding progressive disease	32 (11%)	17 (12%)	15 (11%)	11 (11%)	13 (10%)	16 (13%)	16 (10%)
Other	4 (1%)	1 (1%)	3 (2%)	1 (1%)	3 (2%)	1 (1%)	3 (2%)
Clinical response of primary tumor to initial chemotherapy at the date of randomization							
Complete or partial remission	267 (95%)	131 (94%)	136 (96%)	90 (92%)	129 (96%)	113 (93%)	154 (97%)
Stable disease	13 (5%)	8 (6%)	5 (4%)	8 (8%)	5 (4%)	8 (7%)	5 (3%)
Missing data or not applicable	4	3	1	3	1	3	1

Note: Median and quantiles of follow-up were estimated using the reverse Kaplan–Meier method. Due to rounding of the values, the percentages do not always add up to exactly 100%.

Abbreviations: Add-on, zoledronic acid; rev KM Est, reverse Kaplan–Meier estimator; Q25, 25% quantile; Q75, 75% quantile.

recent multimodal approaches have not confirmed the data from these initial reports (22). Reasons for the lack of benefit of ZOL in EWS remain speculative. Homing mechanisms in the premetastatic mesenchymal niche may differ by cancer type and may contribute to a response to ZOL in some cancers and to a lack of response in others. An important factor in this context is the pattern of time to relapse. In contrast to EWS and osteosarcoma, where relapse occurs relatively early and in most patients within 36 months after diagnosis, relapse in

Table 2. Results of efficacy analysis in terms of progression-free survival and overall survival.

Outcome	Full analysis set (intention-to-treat)		Per-protocol set[a]		Safety set (as-treated)[b]	
	No add-on $N = 142$	Add-on $N = 142$	No add-on $N = 135$	Add-on $N = 101$	No add-on $N = 160$	Add-on $N = 124$
EFS since randomization						
Number and type of events	30	22	28	14	34	18
Estimates						
3-y EFS (KM est, 95% CI)	81.7 (75.2–88.8%)	84.0 (77.7–90.8%)	82.5 (75.9–89.6%)	86.9 (80.2–94.1%)	80.8 (74.5–87.7%)	85.5 (79.0–92.4%)
5-y EFS (KM est, 95% CI)	74.4 (66.3–83.4%)	81.4 (74.5–89.0%)	74.8 (66.6–84.0%)	83.5 (75.7–92.0%)	74.0 (66.3–82.5%)	82.6 (75.4–90.5%)
HR of event (95% CI)[c]	Ref.	0.74 (0.42–1.28) $P = 0.2719$	Ref.	0.65 (0.34–1.23) $P = 0.1794$	Ref.	0.64 (0.36–1.14) $P = 0.1278$
Result of the confirmatory analysis, adaptive design[d]	-	Not significant	-	-	-	-
Multivariable HR of event (95% CI)[e]	Ref.	0.74 (0.42–1.28) $P = 0.2834$	Ref.	0.76 (0.39–1.47) $P = 0.4125$	Ref.	0.68 (0.38–1.22) $P = 0.1955$
Type of first event						
Locoregional recurrence/local progress	10	3	9	3	10	3
New metastases/metastatic progress	13	13	12	6	17	9
Combined relapse/progress	6	2	6	2	6	2
Secondary malignancy	1	4	1	3	1	4
Death as first reported event	0	0	0	0	0	0
Overall Survival since randomization						
Number of deaths	12	13	10	9	14	11
Survival Estimates						
3-y OS (KM Est, 95% CI)	94.6 (90.9–98.6%)	92.8 (88.4–97.5%)	96.0 (92.7–99.5%)	93.2 (88.2–98.6%)	93.9 (90.1–97.8%)	93.6 (89.1–98.3%)
5-y OS (KM Est, 95% CI)	89.6 (83.7–95.9%)	87.3 (80.7–94.5%)	90.8 (84.9–97.0%)	87.4 (79.7–95.9%)	89.2 (83.5–95.2%)	87.6 (80.6–95.2%)
HR of death (95% CI)[c]	Ref.	1.08 (0.49–2.37) $P = 0.8445$	Ref.	1.16 (0.47–2.86) $P = 0.7441$	Ref.	0.95 (0.43–2.10) $P = 0.9003$
Multivariable HR of event (95% CI)[e]	Ref.	1.08 (0.49–2.36) $P = 0.8556$	Ref.	1.24 (0.50–3.10) $P = 0.6460$	Ref.	0.97 (0.44–2.15) $P = 0.9382$
Cause of death[f]						
Due to cancer	12	11	10	7	14	9
Secondary malignancy	0	1	0	1	0	1
Other cause (pneumonia)	0	1	0	1	0	1

Abbreviations: Add-on, zoledronic acid; EFS, event-free survival; HR, hazard ratio; KM Est, Kaplan–Meier estimate; OS, overall survival; Ref., reference.

[a]Per protocol: Excluding 48 patients (seven in the no add-on arm, 41 in the add-on arm) with major protocol deviation (**Fig. 1**; Supplementary Table S3; Supplementary Box S2).

[b]Safety set (as-treated): Patients were analyzed regarding the treatment they actually received. One patient randomized to no add-on received zoledronic acid, and 19 patients randomized to add-on did not receive zoledronic acid (**Fig. 1**).

[c]Hazard ratios with their 95% confidence intervals are estimated in Cox regression models including only the treatment effect as covariable. *P* values are from univariate two-sided log-rank tests. Proportional hazard assumption was checked by using the ZPH diagnostics and tests based on the weighted Schoenfeld residuals.

[d]The specification of the statistical adaptive design, the design change, and the detailed results of the interim analysis and final analysis are in Supplementary Statistics S1.

[e]HR with their 95% CI and Wald *P* values are estimated in Cox regression models including the treatment effect, primary tumor origin (pelvis/no pelvis), sex, and age (years) as covariables.

[f]Treatment details of patients who died from other causes than cancer are in Supplementary Table S5.

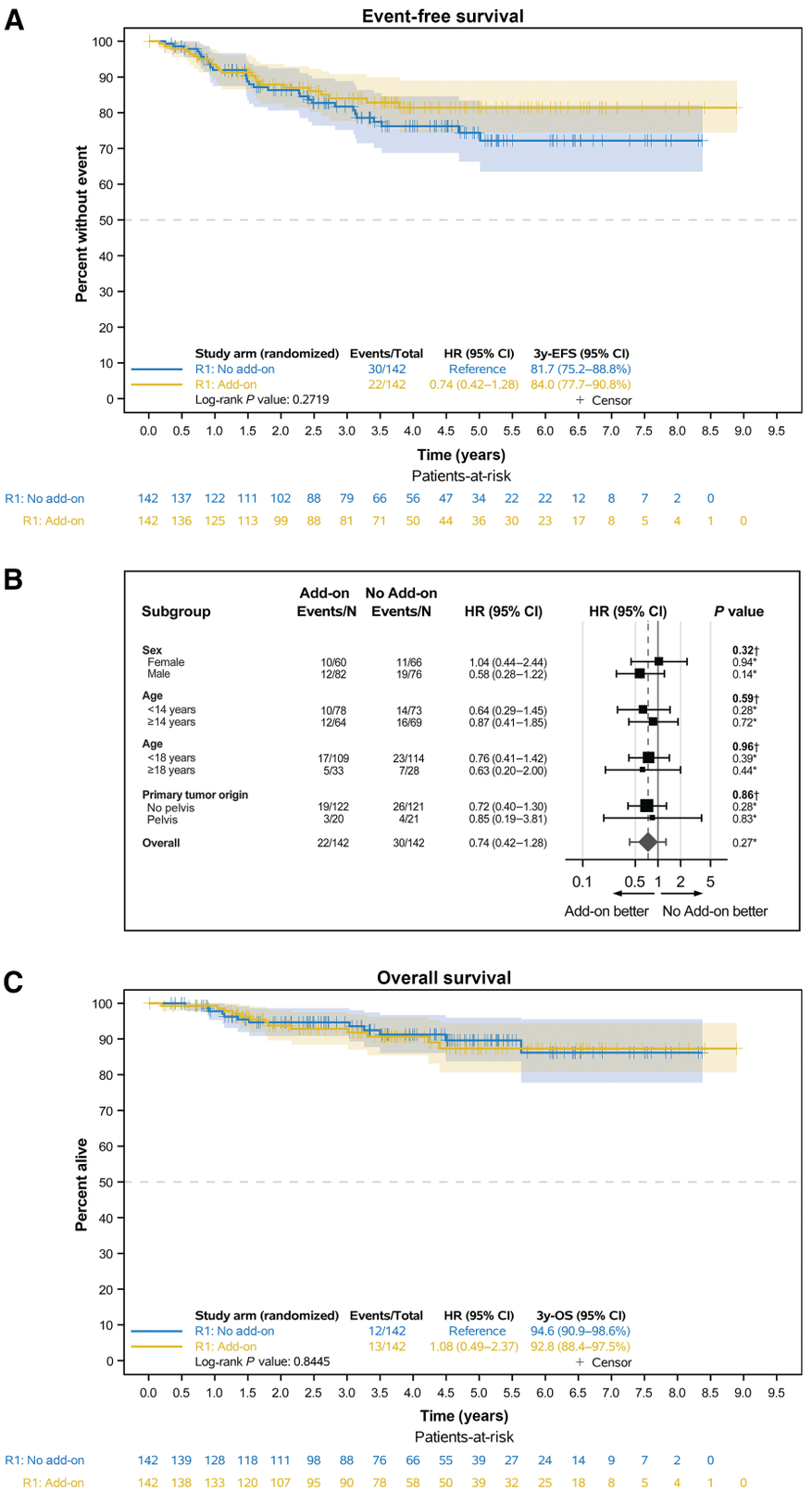

Figure 2.

EFS (**A** and **B**) and OS (**C**). **A,** Kaplan–Meier curves with pointwise 95% confidence limits (log-transformed) of EFS by treatment group in the full analysis set (intention-to-treat). At the time of this analysis (cutoff date June 30, 2019), 52 events were reported: 22 in the add-on group and 30 in the no add-on group. **B,** Forest plot of EFS from randomization in the full analysis set (ITT) according to subgroups including all randomized patients. The hazard ratios (HR) for the comparison of add-on vs. no add-on were estimated in Cox proportional hazard models within each subgroup. The *P* values were obtained from two-sided log-rank tests comparing both treatment groups within each subgroup category (*), or from Wald tests for the treatment and subgroup interaction term from a Cox regression model which includes the covariates treatment group, the respective subgroup, and the interaction term of both (†). **C,** Kaplan–Meier curves with pointwise 95% confidence limits (log-transformed) of overall survival from randomization by treatment group in the full analysis set (ITT).

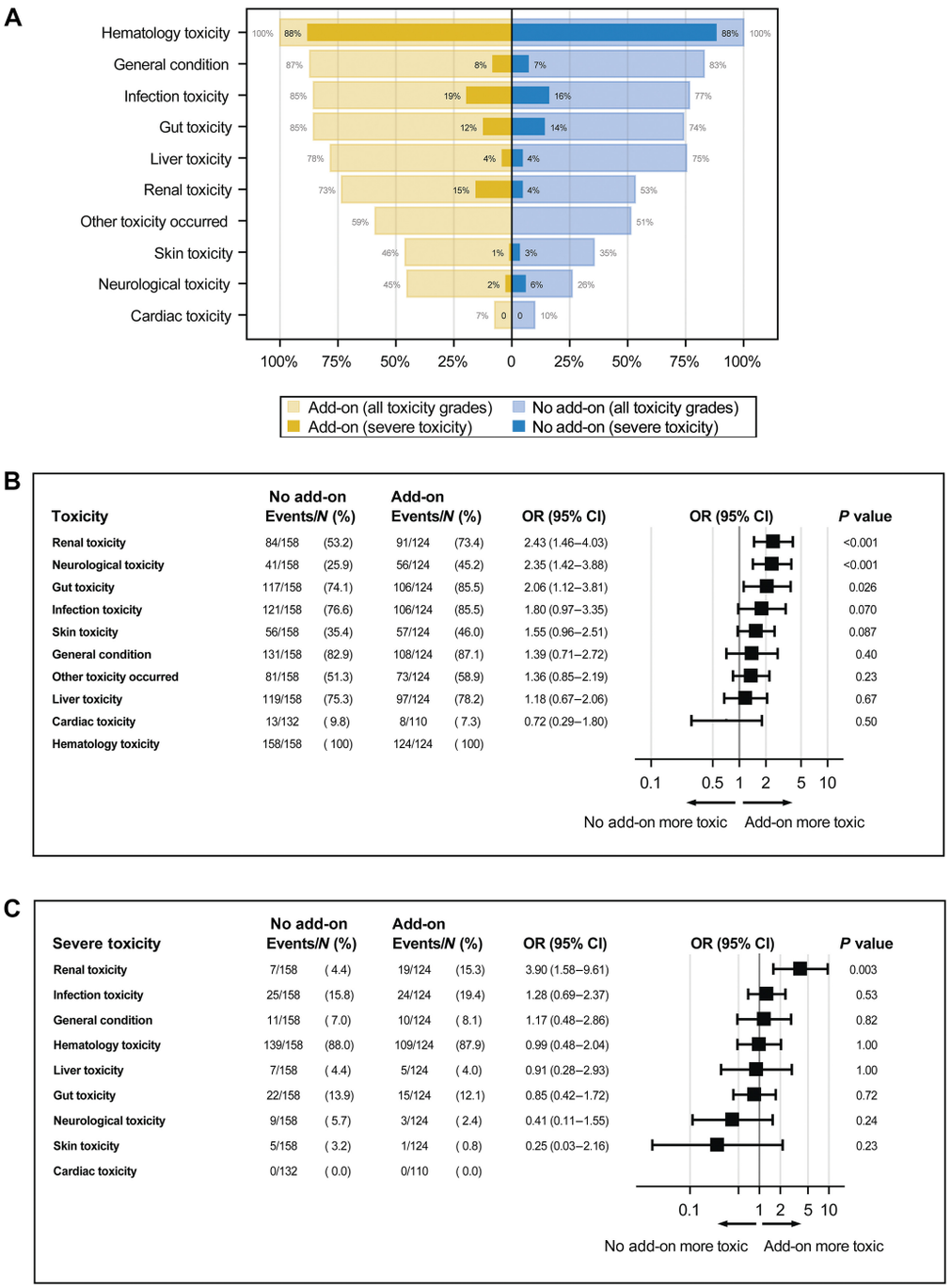

Figure 3.

Acute toxicities. **A,** The butterfly plot showing the proportion of patients experiencing acute toxicity, whatever the grade (light yellow for add-on and light blue for no add-on arm) and severe toxicity (dark yellow for add-on and dark blue for no add-on arm) according to treatment group (as-treated, safety set). The forest plots display the number of toxicities and the odds ratio of acute toxicity (**B**), whatever the grade, or of severe toxicity (**C**) in patients who received add-on therapy relative to patients who received no add-on therapy. *P* values are from Fisher exact tests. Toxicity items are ordered by descending odds ratios. This as-treated analysis was performed on the safety set (124 add-on and 160 no add-on patients). No documentation of toxicities was available for two patients who were randomized to add-on but did not receive add-on. Patients with missing data for a specific toxicity evaluation were excluded for this toxicity. Acute chemotherapy-related toxicity was assessed after each course, using a list of selected items from the NCI-CTC-v3.0. A free text area was available to document other toxicities. The toxicity items were then pooled by category: hematologic toxicity, infection or fever, gut toxicity, skin toxicity, renal toxicity, liver toxicity, neurologic toxicity, cardiac toxicity, and general condition. Details are provided in Supplementary Table S6. For each toxicity item, the analysis is based on the maximum grade observed over the whole consolidation/maintenance treatment duration (combining toxicities reported on consolidation (VAI/VAC) and add-on treatment forms). Toxicities from radiotherapy were not regarded. Grade 4 hematologic toxicities and grade ≥3 nonhematologic toxicities were classified as severe toxicities.

carcinomas emerges often decades later as bone metastasis. Similar results to this study were seen in the OS2006 trial, which demonstrated no improvement in outcome from adding ZOL in patients with osteosarcoma (23). Preclinical models demonstrated an effect of ZOL on the development of soft-tissue metastases (i.e., pulmonary metastases in combination with alkylating agents). As cumulative renal toxicity was predictable from the toxicity profile of ZOL (24) and alkylating agents (25), the trial design scheduled only three cycles with combined treatment. Whether an extended period of combined treatment would have changed results is unknown, and it is likely that cumulative toxicity would be significant. Furthermore, the young age of the patients may play a role. In breast cancer, the benefit from ZOL was more prominent in postmenopausal women. It is well known that hormone status is a major factor, besides physical activity and nutrition, and that menopause significantly changes bone metabolism. We demonstrated an excellent response to the backbone treatment, and this may ameliorate the effect of ZOL. Ancillary studies on the biomaterial collected prospectively in the trial may contribute to a deeper understanding of why ZOL did not improve survival.

Our findings may also have been limited by the dropout of eligible patients to randomization. The main reason for nonrandomization was patient/parent refusal. Of note, consent for randomization was not obtained at inclusion but after induction therapy. A similar effect was reported from the EURAMOS group where approximately 25% of patients allocated to the add-on treatment with IFNα2b never started the treatment and only 35% completed the treatment as per protocol (26). Patient characteristics of the randomized patients were similar to those of the nonrandomized patients (Supplementary Table S2). Following the advice of the independent data monitoring committee, the trial was discontinued before reaching the initially planned sample size, as the conditional power in first interim analysis was low to obtain a significant difference in EFS in the remaining stages with a higher number of patients (Supplementary Statistics S1). The trial database was closed in June 2019, achieving a maximal follow-up of 8.9 years. Due to the legal regulations, patients could not be followed up with the study thereafter.

Toxicity related to ZOL was noticeably greater than without add-on, particularly renal toxicity but also neurologic and gut toxicities. No patient had a treatment-related death as the first event. Given the relatively short follow-up, we have limited information on late effects data. So far, we have observed five second malignancies, and four occurred in the ZOL arm. The Euro Ewing 2012 trial randomized the VIDE-VAI/VAC regimen (arm A) and compressed VDC/IE, modified from the regimen of the Children's Oncology Group (ref. 2; arm B, ref. 27). Here, the outcome was in favor of arm B with more non-disease–related events reported in arm A (27). Results of the second randomization regarding the efficacy of ZOL are pending and are awaited with interest.

Ewing 2008R1 achieved EFS rates at 3 and 5 years after randomization of 84.0% and 81.4% and OS rates of >93% at 3 and >87% at 5 years. The overall results were better than expected based on the results of the Euro-EWING99-R1 trial. The improved survival compared with the very similar Euro-EWING99-R1 trial may be attributed to the sex-specific maintenance that was introduced with cyclophosphamide for females and ifosfamide for males. The sex-specific maintenance had been introduced as results from the randomized Euro-EWING99-R1 trial showed that cyclophosphamide (VAC) can replace ifosfamide (VAI) in standard-risk Ewing sarcoma (3). However, some interaction in terms of efficacy was seen between treatment and sex, with males showing better response to VAI (28).

In conclusion, the Ewing 2008R1 trial demonstrated excellent outcomes for standard-risk localized EWS patients with good histopathologic response and/or initial tumor volume <200 mL, and the result of the ZOL randomization does not support the use of bisphosphonates for these localized EWS patients. Of note, the survival improved remarkably in the past years.

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Note

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