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ORIGINAL REPORT

Methotrexate, Doxorubicin, and Cisplatin (MAP) Plus Maintenance Pegylated Interferon Alfa-2b Versus MAP Alone in Patients With Resectable High-Grade Osteosarcoma and Good Histologic Response to Preoperative MAP: First Results of the EURAMOS-1 Good Response Randomized Controlled Trial

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Trial unit staff at the Medical Research Council Clinical Trials Unit of University College London, Children's Oncology Group, Cooperative Osteosarcoma Study Group, Scandinavian Sarcoma Group, EURAMOS Intergroup Safety Desk, and Quality of Life Coordinating Centre were central to the trial design, trial conduct, data analysis, data interpretation, and development of this report. S.S.B., G.J., J.M.H., T.B.-B., and M.R.S. accessed raw data. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

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ABSTRACT

Purpose
EURAMOS-1, an international randomized controlled trial, investigated maintenance therapy with pegylated interferon alfa-2b (IFN-α-2b) in patients whose osteosarcoma showed good histologic response (good response) to induction chemotherapy.

Patients and Methods
At diagnosis, patients age ≤ 40 years with resectable high-grade osteosarcoma were registered. Eligibility after surgery for good response random assignment included ≥ two cycles of preoperative MAP (methotrexate, doxorubicin, and cisplatin), macroscopically complete surgery of primary tumor, < 10% viable tumor, and no disease progression. These patients were randomly assigned to four additional cycles MAP with or without IFN-α-2b (0.5 to 1.0 μg/kg per week subcutaneously, after chemotherapy until 2 years postregistration). Outcome measures were event-free survival (EFS; primary) and overall survival and toxicity (secondary).

Results
Good response was reported in 1,041 of 2,260 registered patients; 716 consented to random assignment (MAP, n = 359; MAP plus IFN-α-2b, n = 357), with baseline characteristics balanced by arm. A total of 271 of 357 started IFN-α-2b; 105 stopped early, and 38 continued to receive treatment at data freeze. Refusal and toxicity were the main reasons for never starting IFN-α-2b and for stopping prematurely, respectively. Median IFN-α-2b duration, if started, was 67 weeks. A total of 133 of 268 patients who started IFN-α-2b and provided toxicity information reported grade ≥ 3 toxicity during IFN-α-2b treatment. With median follow-up of 44 months, 3-year EFS for all 716 randomly assigned patients was 76% (95% CI, 72% to 79%); 174 EFS events were reported (MAP, n = 93; MAP plus IFN-α-2b, n = 81). Hazard ratio was 0.83 (95% CI, 0.61 to 1.12; $P = .214$) from an adjusted Cox model.

Conclusion
At the preplanned analysis time, MAP plus IFN-α-2b was not statistically different from MAP alone. A considerable proportion of patients never started IFN-α-2b or stopped prematurely. Long-term follow-up for events and survival continues.

INTRODUCTION

Osteosarcoma is the most frequent primary sarcoma of bone, primarily diagnosed in adolescents and young adults; however, it is rare overall, with only two to three affected individuals per million person-years. Most recent regimens have included several weeks of preoperative chemotherapy, followed by surgery and several months postoperative chemotherapy.[1] Reported outcomes have been similar internationally and have shown little improvement over previous decades.[2,3] Histologic response to preoperative chemotherapy is an important prognostic factor. A good histologic response is usually classified as < 10% viable tumor in the resected specimen. Good responders have had better 5-year survival than poor responders (75% to 80% *v* 45% to 55%).[1,4]

Four international osteosarcoma groups with a history of successfully conducted clinical trials[5-9] formed the European and American Osteosarcoma Study Group (EURAMOS)[10,11]: the Children's Oncology Group (COG), Cooperative Osteosarcoma Study Group (COSS), European Osteosarcoma Intergroup (EOI), and Scandinavian Sarcoma Group (SSG). The EURAMOS-1 trial established large-scale multinational cooperation in clinical trials for osteosarcoma.[11] MAP (methotrexate, doxorubicin, and cisplatin) chemotherapy was accepted as standard.[8,12] Intensified salvage chemotherapy was investigated in poor responders. On the basis of preclinical and clinical evidence,[13] we decided to investigate the value of maintenance treatment with interferon alfa (IFN-α) in good responders.

Maintenance treatment is well established in acute lymphoblastic leukemia[14] and is being investigated in sarcomas.[15] IFN-α has antiproliferative, differentiation-inducing, apoptotic, and antiangiogenic properties, and its clinical activity has been demonstrated in several cancers, including as postchemotherapy maintenance.[13,16-19] It has been associated with activity against osteosarcomas (some of which have expressed IFN-α/β receptor[20]) in vitro, in animal models, and in patients with metastatic disease.[13] Most notably, single-institution treatment of 89 consecutive patients with semipurified leukocyte IFN-α as the only adjuvant treatment after surgery resulted in 10-year metastasis-free and sarcoma-specific survival rates of 39% and 43%, respectively.[21] On the basis of this rationale, we aimed to test IFN-α as maintenance treatment in osteosarcoma.[13] The objective of our random assignment was to examine whether addition of a pegylated formulation of interferon alfa-2b (IFN-α-2b) as maintenance therapy after postoperative MAP would improve outcomes, with event-free survival (EFS) as the primary outcome measure.

PATIENTS AND METHODS

Setting

EURAMOS-1 was an open-label phase III randomized controlled trial (RCT) for patients with localized or metastatic high-grade osteosarcoma considered suitable for complete surgical resection. Eligibility for registration has been described previously.[10,11] Key criteria were localized or metastatic high-grade osteosarcoma of an extremity or the axial skeleton (with exception of craniofacial sites), with all disease sites potentially amenable to complete surgical resection, and age ≤ 40 years.

All patients received induction MAP followed by surgery of the primary. Thereafter, patients age ≥ 5 years who had completed two cycles of induction MAP, had undergone macroscopically complete resection of their primary tumor, had < 10% viable tumor on histologic response assessment, and had no evidence of disease progression were eligible for the good response random assignment. Histologic response assessment was conducted locally before random assignment and later confirmed by a trial reference pathologist. Random assignment had to be performed < 35 days after surgery. Patients age < 5 years at potential random assignment were excluded from random assignment because of reports of neurologic complications in young children receiving IFN-α for other diseases.[22] Participants and/or their legal guardians, as appropriate, provided written informed consent to registration and random assignment. Regulatory and ethics approvals were obtained according to national requirements.

Trial Treatments and Procedures

Induction MAP (weeks 1 to 10) comprised two 5-week cycles of doxorubicin 75 mg/m^2 of body-surface area, cisplatin 120 mg/m^2, and methotrexate 12 g/m^2, followed by surgery of the primary in week 11. Doxorubicin and cisplatin were administered in weeks 1 and 6 and methotrexate in weeks 4 ,5, 9, and 10 (Fig 1, treatment scheme; Data Supplement). Up to two additional doses of methotrexate were permitted preoperatively if surgery had to be delayed. The protocol (Data Supplement) contained detailed guidance on mandatory tests and requirements for each treatment cycle, supportive care, and dose adjustments. If present, primary metastases were to be surgically removed in weeks 11 to 20.

After histologic assessment of the resected tumor, consenting patients were randomly assigned in a one-to-one ratio to four postoperative cycles of MAP (weeks 12 to 29; cisplatin omitted in last two cycles) or to the same regimen followed by maintenance pegylated IFN-α-2b (Fig 1). Treatment allocation was performed using concealed permuted blocks with three stratification factors: trial group (COG, COSS, EOI, or SSG), location of tumor (proximal femur or proximal humerus *v* other limb *v* axial skeleton), and presence of metastases (no *v* yes or possible). Lung metastases, detected by spiral computed tomography scanning, were considered certain if there were three or more lesions ≥ 5 mm in maximum diameter or a single lesion ≥ 1 cm. Scans of patients registering metastatic disease with fewer or smaller lesions were classified as possible metastatic disease. Patients were randomly assigned centrally through the Medical Research Council Clinical Trials Unit (COSS, EOI, and SSG) or COG.

Subcutaneous IFN-α-2b was planned weekly from week 30 to 104 at 0.5 μg/kg per week (maximum, 50 μg) for 4 weeks and increased to 1.0 μg/kg per week (maximum, 100 μg) thereafter if no flu-like symptoms worse than Common Toxicity Criteria for Adverse Events (version 3.0)[23] grade 2 or other toxicities worse than grade 1 were experienced.

Assessments

During MAP treatment, clinical and toxicity assessments were performed before each drug administration. During IFN-α-2b, patients were monitored twice per week for 8 weeks and once or twice per month thereafter. Adverse events were graded according to the Common Toxicity Criteria for Adverse Events (version 3.0)[23] and reported centrally as the maximum grade during pre- and postoperative chemotherapy and maximum grade per 3-month period during IFN-α-2b. Toxicity was assessed in each patient until trial treatment was stopped. Late toxicity throughout follow-up was collected at COSS, EOI, and SSG.

All patients were assessed for local and distant recurrence at predefined intervals by physical examination and radiography of the chest and primary site. Radiographically detected relapse was also imaged by computed tomography, magnetic resonance imaging, and/or bone scans and, if appropriate, confirmed by histology. Patients were observed regularly for ≥ 5 years after treatment (Data Supplement).

Statistical Analyses

The primary outcome measure was EFS, defined as time from random assignment until a first event (local recurrence, new metastatic disease, progression of primary metastatic disease, secondary malignancy, or death) or censoring at last contact. Secondary outcome measures included: overall survival (OS; time from random assignment until death resulting from any cause or last contact), short- and long-term toxicities, and quality of life, which will be the topic of separate analyses.

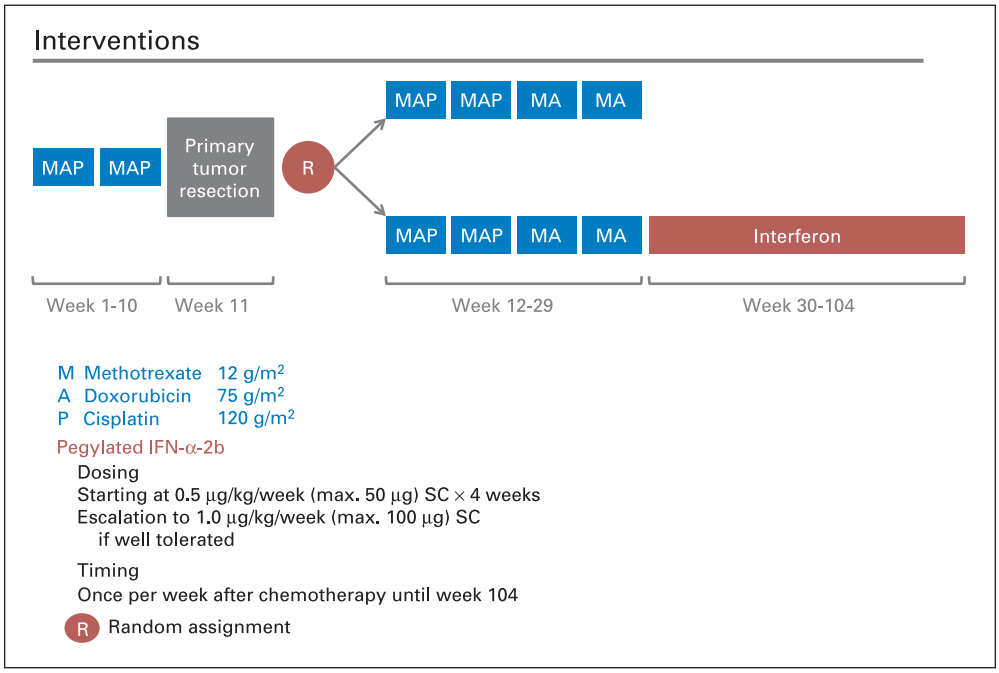

Fig 1. Treatment scheme. IFN-α-2b, interferon alfa-2b; MA, methotrexate, doxorubicin; MAP, methotrexate, doxorubicin, and cisplatin; R, random assignment; SC, subcutaneously.

To detect absolute improvements of 10% from 70% to 80% in 3-year EFS (hazard ratio [HR], 0.63 in favor of IFN-α-2b) with two-sided 5% significance level and 80% power required ≥ 147 EFS events.[24] The same applied to an improvement in 5-year OS from 70% to 80%, requiring ≥ 147 deaths in the longer term. The initial plan to register 1,400 patients (to randomly assign 1,260 [good responders, n = 567; poor responders, n = 693]) was revised to approximately 2,000 patients because of a lower randomization rate and relatively fewer poor responders than anticipated.[11] Interim data were reviewed annually by an independent data monitoring committee and could have been reported early if either $P \leq .001$ for EFS[25,26] or severe IFN safety issues were identified.

A prespecified subgroup of patients with localized disease comprised those without definitive metastases at registration. To detect a 10% improvement from 75% to 85% in 3-year EFS and 5-year OS (HR, 0.56) with two-sided 5% significance and 80% power required 98 events.

The primary analysis used intention-to-treat principles. The Kaplan-Meier method was used to estimate survival functions, log-rank tests for differences between survival curves, and Cox models (adjusted for stratification factors) to estimate treatment effects, with suitability checked by tests for proportionality of hazards. All comparisons were expressed relative to control, with HR < 1 favoring IFN-α-2b. Consistency of treatment effect was examined using the interaction test (χ^2 test for heterogeneity) in subgroups defined posthoc: sex, age, site of disease, location on bone, lung metastases, nonlung metastases, and histologic subtype. Median follow-up was calculated using reverse censoring on death.

In a prespecified exploratory analysis, EFS was computed from 23 weeks after starting postoperative chemotherapy, excluding patients who experienced progression before the expected start of IFN-α-2b. IFN-α-2b dose was summarized only for patients who could have completed and reported completing IFN-α-2b by the data freeze (patients registered before November 15, 2010). Analyses were performed using Stata software (versions 12.1 and 13.1; Stata, College Station, TX).

RESULTS

Patients

Between April 2005 and June 2011, 2,260 patients were registered from > 300 sites in 17 European, North American, and Australasian countries. The data were frozen on February 15, 2013, because the event target was reached. A total of 1,041 patients were good responders, and 716 (69%) from 246 trial sites were randomly assigned (MAP, n = 359; MAP plus IFN-α-2b, n = 357; Fig 2). COG, COSS, EOI, and SSG randomly assigned 300, 206, 161, and 49 patients, respectively. Table 1 lists registration characteristics for these randomly assigned patients. Median age was 14 years (interquartile range [IQR], 11 to 16), and 421 (59%) were male; 630 (88%) had localized disease, and 86 (12%) had primary metastases; of these, 66 had lung-only, 15 had extrapulmonary-only, and five had both lung and extrapulmonary metastases.

Median follow-up was 44 months (IQR, 28 to 58) for MAP and 44 months (IQR, 29 to 58) for MAP plus IFN-α-2b. Twenty patients (6%) in each arm were permanently lost to follow-up. For patients last reported as alive, 94% were seen < 14 months before data freeze.

Treatment

Postoperative MAP. Postoperative MAP was delivered similarly in both treatment arms. Median standardized postoperative dose of methotrexate was 95 g/m^2 (target, 96g/m^2); doxorubicin, 298 mg/m^2 (target, 300 mg/m^2); and cisplatin, 239 mg/m^2 (target, 240 mg/^{2}; Data Supplement).

IFN-α-2b

Of 357 patients randomly assigned to MAP plus IFN-α-2b, 82 (23%) reported not starting; information was missing for four (1%). The most common reason for not starting was treatment refusal (78%; Fig 2). Of the 357 patients, 271 (76%) started IFN-α-2b at median 23 weeks after random assignment. At data freeze, 128 (47%) of these 271 patients reported completing protocol treatment, 105 (39%) of 271 reported stopping early, and 38 (14%) of 271 reported still receiving

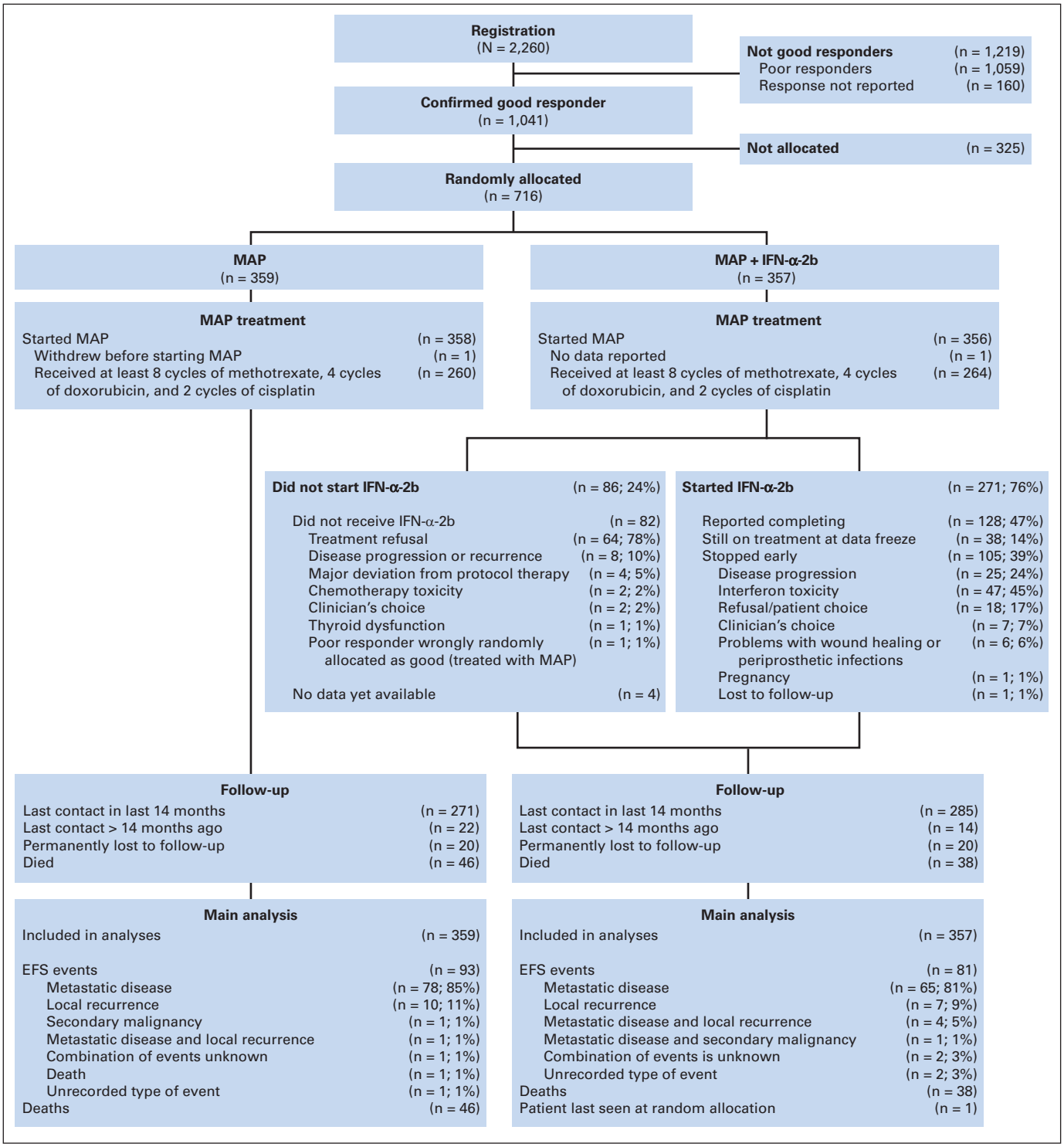

Fig 2. CONSORT diagram. EFS, event-free survival; IFN-α-2b, interferon alfa-2b; MAP, methotrexate, doxorubicin, and cisplatin.

treatment. Reported reasons for early termination were: toxicity (n = 47; 45%), osteosarcoma progression (n = 25; 24%), refusal or patient choice (n = 18; 17%), clinician decision (n = 7; 7%), problems with wound healing or periprosthetic infections (n = 6; 6%), and other reasons (pregnancy, n = 1; lost, n = 1; Fig 2). Of the 271 patients, 132 (49%) required IFN-α-2b dose reductions or delays. The target cumulative IFN-α-2b dose was 72 μg/kg. In 319 patients who could have completed IFN-α-2b by the data freeze, the observed median dose was 25.8 μg/kg (IQR, 0.5 to 60.0). Of these 319 patients, 240 reported starting IFN-α-2b; among these 240, median dose was 40.0 μg/kg (IQR, 14.5 to 65.0; Data Supplement). Median duration of therapy was 67 weeks (IQR, 25 to 75).

Table 1. Patient Characteristics at Registration

Characteristic	MAP (n = 359) No.	MAP (n = 359) %	MAP Plus IFN-α-2b (n = 357) No.	MAP Plus IFN-α-2b (n = 357) %	Total (N = 716) No.	Total (N = 716) %
Sex						
Male	211	59	210	59	421	59
Female	148	41	147	41	295	41
Age at registration, years						
< 5	0	0	1	0	1	0
5-9	58	16	44	12	102	14
10-19	275	77	288	81	563	79
20-29	22	6	17	5	39	5
> 30	4	1	7	2	11	2
Median	14		14		14	
IQR	11-16		12-16		11-16	
Site of tumor						
Femur	179	50	191	54	370	52
Tibia	113	31	102	29	215	30
Fibula	14	4	20	6	34	5
Humerus	36	10	33	9	69	10
Radius	5	1	5	1	10	1
Ulna	2	1	0	0	2	0
Scapula/clavicle	2	1	1	0	3	0
Pelvis/sacrum	5	1	5	1	10	1
Rib	3	1	0	0	3	0
Location of tumor						
Proximal	156	43	150	42	306	43
Diaphysis	13	4	12	3	25	3
Distal	180	50	189	53	369	52
NA (not long bone)	10	3	6	2	16	2
Pathologic fracture at diagnosis						
No	321	90	308	86	629	88
Yes	37	10	49	14	86	12
Missing	1	NA	0	NA	1	NA
Lung metastases						
No	295	82	288	81	583	81
Possible*	29	8	33	9	62	9
Yes	35	10	36	10	71	10
Other metastases						
No	343	96	348	97	691	97
Possible*	3	1	2	1	5	1
Yes	13	4	7	2	20	3
WHO 2002 classification of osteosarcoma[27]						
Conventional	320	90	322	92	642	91
Telangiectatic	25	7	20	6	45	6
Small cell	2	1	1	0	3	0
High-grade surface	3	1	5	1	8	1
Other	4	1	2	1	6	1
Missing	5	NA	7	NA	12	NA

Abbreviations: IFN-α2b, interferon alfa-2b; IQR, interquartile range; MAP, methotrexate, doxorubicin, and cisplatin; NA, not applicable;
*Possible metastases were collected only by Cooperative Osteosarcoma Study Group, European Osteosarcoma Intergroup, and Scandinavian Sarcoma Group.

Efficacy

EFS at 3 years for all 716 randomly assigned patients was 76% (95% CI, 72% to 79%). A total of 174 events were reported (MAP, n = 93; MAP plus IFN-α-2b, n = 81; Fig 2). In both arms, patients' first events mostly included metastases (MAP, n = 79; MAP plus IFN-α-2b, n = 70). Local recurrence was involved in 22 of the 174 first events (MAP, n = 11; MAP plus IFN-α-2b, n = 11). Of these, 17 were isolated local recurrences, and five were combined with distant metastases. One secondary malignancy (acute myeloid leukemia) was reported as a first event (MAP-alone arm). Type of first event was not reported for three patients (MAP, n = 1; MAP plus IFN-α-2b, n = 2).

Treatment effect for IFN-α-2b was estimated as HR of 0.83 (95% CI, 0.61 to 1.12; $P = .214$). Rates of 3-year EFS for MAP and MAP plus IFN-α-2b were 74% (95% CI, 69% to 79%) and 77% (95% CI, 72% to 81%), respectively (Fig 3A).

In 630 patients with localized disease, 135 EFS events were reported (MAP, n = 72; MAP plus IFN-α-2b, n = 63). The estimated treatment effect was consistent with the whole trial population (HR, 0.83; 95% CI, 0.59 to 1.17; $P = .284$); 3-year EFS estimates were 77% (95% CI, 71% to 82%) and 80% (95% CI, 75% to 84%) for MAP and MAP plus IFN-α-2b, respectively.

A total of 84 deaths were reported (MAP, n = 46; MAP plus IFN-α-2b, n = 38; Fig 3B). This early estimate of survival had an HR of 0.77 (95% CI, 0.50 to 1.19); 5-year OS was 81% (95% CI, 74% to 86%) for MAP and 84% (95% CI, 78% to 88%) for MAP plus IFN-α-2b. Follow-up continues for survival.

Toxicity

The toxicity of preoperative chemotherapy has previously been reported.[11] During postoperative MAP, toxicity was mostly hematologic and did not differ by arm (Data Supplement). One patient died as a result of toxicity (cardiomyopathy); worst toxicity was grade 4 for 628 (88%) and grade 3 for 59 (8%) of 716 patients.

With regard to IFN-α-2b, toxicity data were reported for 268 of 271 patients who started IFN-α-2b. No fatal toxicities were reported (Table 2). The worst toxicity during IFN-α-2b was grade 4 for 32 (12%) of 268 patients (primarily hematologic [n = 26] or left ventricular systolic dysfunction [LVSD; n = 4]); grade 3 was worst toxicity for 101 (38%) and grade 1 to 2 for 105 (39%) of 268 patients. Three suspected unexpected serious adverse reactions related to IFN-α-2b were reported: two new cases of LVSD and one knee joint effusion.

From routinely collected long-term toxicity data, seven (4%) of 193 patients receiving MAP and eight (4%) of 199 patients receiving MAP plus IFN-α-2b reported grade 3 to 4 LVSD (Data Supplement). One additional grade 4 LVSD was reported as a serious adverse event during follow-up.

Exploratory Analyses

Exploratory subgroup analyses found no evidence of heterogeneity in treatment effect (Fig 3C; Data Supplement). An exploratory EFS analysis (Fig 3D) separated patients allocated to MAP plus IFN-α-2b who started IFN-α-2b from those who did not start and compared them with patients allocated to MAP. Patients who did not start their allocated IFN-α-2b seemed to do worse than patients not allocated to IFN-α-2b. The exploratory analysis of EFS computed from 23 weeks after start of postoperative chemotherapy included 702 patients who had not previously experienced progression. HR was 0.83 (95% CI, 0.61 to 1.12), similar to the overall EFS estimate.

DISCUSSION

We investigated maintenance pegylated IFN-α-2b for patients whose resectable osteosarcomas showed good histologic response to MAP

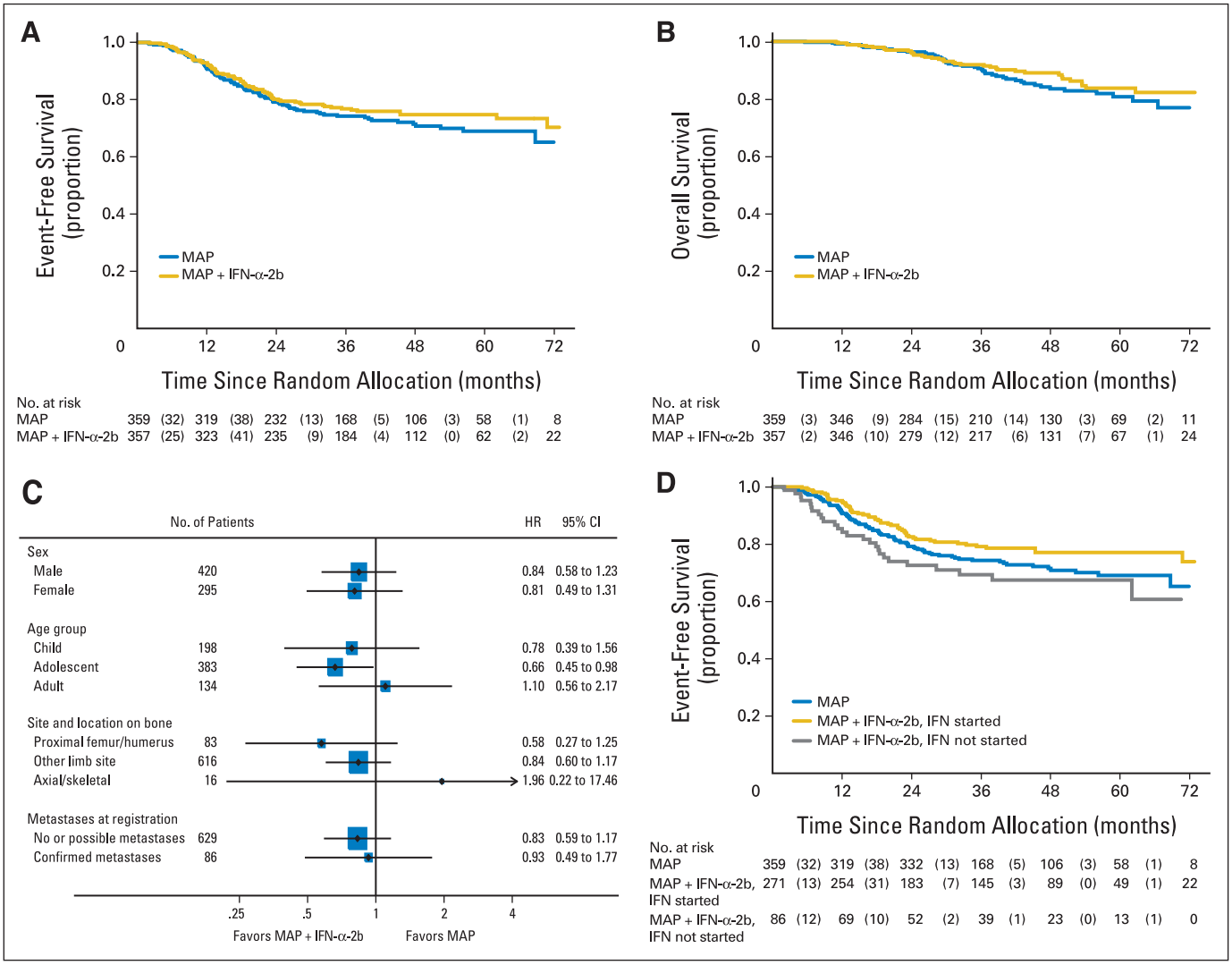

Fig 3. (A) Event-free survival; (B) overall survival; (C) exploratory subgroup analysis; (D) exploratory comparison. Nos. in parentheses in risk tables of parts A, B, and D indicate No. of patients who had an event during the specified time period. HR, hazard ratio. IFN-α-2b, interferon alfa-2b; MAP, methotrexate, doxorubicin, and cisplatin.

induction chemotherapy. The point estimate of treatment effect showed improved EFS and OS. However, neither was statistically significant, and the CIs were consistent with no effect. No change in practice is indicated by these data.

We were able to ask this question, as well as a parallel question concerning chemotherapy intensification in patients whose osteosarcomas had poor histologic response, only because of the cooperative efforts of four multi-institutional groups.[10,11] This will provide a framework for future trials.

With an age range up to 40 years and inclusion of patients with resectable axial and/or primary metastatic disease, our study had broader eligibility than many others. However, all patients had their primary tumors resected, and all of these had shown a good response to chemotherapy. The observed 3-year EFS of 76% for the 716 randomly assigned patients meeting our eligibility criteria is in the range of those previously observed for good responders.[4,9,12,28] Approximately four fifths of first events were exclusively metastatic, and there was no suggestion of an altered distribution of type of event by treatment arm.

Toxicity observed during preoperative MAP was as expected[7] and did not differ by allocation. Death related to toxicity during postoperative MAP was limited to one case of cardiomyopathy. Nevertheless, most patients reported grade 4 toxicities, mostly hematologic, attesting to the treatment burden of osteosarcoma chemotherapy. As expected,[13,29] toxicities observed during IFN-α-2b were mainly grade 1 to 2. However, grade 3 and 4 toxicities were reported for one half of patients who started IFN-α-2b, mostly hematologic. Several patients developed signs of cardiac failure during IFN-α-2b. Although we cannot exclude a contribution from IFN-α-2b to this complication, we note these patients had previously received doxorubicin 450 mg/m^2 and that a similar number of control-arm patients also developed LVSD. Given the high cumulative anthracycline dose, the overall incidence of severe clinical cardiac toxicity in this mainly adolescent population receiving a high cumulative anthracycline dose by continuous infusion, rather than as a bolus, does not seem excessive.[30]

The point estimates of the HR favored IFN-α-2b maintenance for both EFS and OS, but the CIs were consistent with no effect. The

Table 2. Worst-Grade Toxicities Reported During IFN-α2b Treatment

Toxicity	Worst Grade 0 No.	0 %*	1-2 No.	1-2 %*	3 No.	3 %*	4 No.	4 %*
Any	30	11	105	39	101	38	32	12
Routinely collected toxicities†								
Neutrophils	72	38	39	21	65	34	14	7
Leucocytes	76	29	158	59	25	9	7	3
Platelets	142	53	112	42	6	2	6	2
Mood alteration (depression)	193	75	55	21	8	3	1	0
Fever	156	59	107	40	1	0	1	0
Hemoglobin	131	49	127	48	8	3	0	0
Fatigue	134	50	129	49	3	1	0	0
Cardiac arrhythmia	243	96	7	3	3	1	0	0
Rigor/chills	202	75	64	24	2	1	0	0
Vomiting	236	89	28	11	2	1	0	0
Diarrhea	239	90	25	9	2	1	0	0
Bilirubin	245	92	18	7	2	1	0	0
Weight loss	231	87	35	13	1	0	0	0
Thyroid dysfunction	242	92	20	8	1	0	0	0
Creatinine	250	94	15	6	1	0	0	0
Mucositis	174	94	12	6	0	0	0	0
Other notable serious AEs and toxicities‡								
LVSD	NA	NA	1	0	2	1	4	2
Amylase	NA	NA	0	0	0	0	1	0
Mood alteration (agitation)	NA	NA	0	0	0	0	1	0
Infection (normal neutrophils)§	NA	NA	2	1	6	2	0	0
Flu-like syndrome	NA	NA	12	5	0	0	0	0
Pain (muscle)	NA	NA	4	2	4	2	0	0
Pain (head/headache)	NA	NA	12	5	0	0	0	0
Pain (extremity/limb)	NA	NA	5	2	0	0	0	0

NOTE. Includes all routinely collected toxicities and any other toxicities with reported incidence in ≥ five patients of any grade or of grade ≥ 4 in one patient.

Abbreviations: AE, adverse event; CRF, case report form; IFN-α2b, interferon alfa-2b; LVSD, left ventricular systolic dysfunction; NA, not applicable.

*Based on No. of patients reporting each type of toxicity.

†Routinely collected on CRF.

‡Spontaneously reported on CRF or as serious AE.

§Or grade 1 to 2 neutrophils.

observed effect size for EFS (HR, 0.83; 95% CI, 0.61 to 1.12) was similar to that reported for another biologic agent, liposomal muramyl tripeptide phosphatidylethanolamine (HR, 0.80; 95% CI, 0.62 to 1.0),[8] but smaller than our 0.63 target.

The interpretation of our findings is limited, because approximately one quarter of patients allocated to IFN-α-2b never started it. Furthermore, not all patients continued IFN-α-2b after having started; only 128 of 357 patients reported completing the planned protocol treatment. These issues of initiation and adherence arose even though neither the dose nor schedule of IFN-α-2b nor the duration of treatment was unusual,[16,18,19,31] and a pegylated preparation was expected to result in fewer adverse effects.[13,16]

One may speculate why the attrition rate for IFN-α-2b was high. Patient choice was the most common reason for non–random assignment and for never starting IFN-α-2b among allocated patients and a common reason for its premature termination. We assume that both previous exposure to 29 protocol weeks of chemotherapy and awareness of a favorable prognosis for good responders affected compliance. A recent RCT of IFN-α maintenance for relapsed lymphoma faced similar abandonment problems. Those researchers concluded that it was not clear whether the absence of a demonstrable advantage reflected a lack of intrinsic activity or indicated the inability to administer an adequate dose of IFN to patients for sustained periods.[32]

At first glance, our observations might call for an as-treated analysis comparing those who initiated IFN-α-2b against the control arm. However, patients allocated to IFN-α-2b who never started the drug fared worse than patients never allocated to receive IFN-α-2b in the first place, for reasons that are currently obscure.

Would a treatment effect have become more obvious if the chosen IFN-α-2b dose had been higher or the treatment period longer? Even in melanoma, where many RCTs of IFN have been performed, evidence supporting a specific IFN dose, duration, or formulation and identification of subsets of patients beyond those with detectable residual disease most likely to benefit remain debatable issues, with no RCT showing additional benefit for treatment extending beyond 12 to 18 months.[19,33] For osteosarcoma, such evidence is completely absent. The timing of IFN-α-2b therapy is similarly uncertain. Although IFN-α may enhance the sensitivity of osteosarcomas to selected chemotherapeutic agents,[34] there are no data demonstrating that IFN-α-2b can be safely administered concurrently with MAP and no data indicating that it would be more efficacious.

Was the good responder cohort, with its relatively low recurrence risk, ideal to observe effects of IFN-α-2b? Good responders generally have a lower burden of micrometastatic residual disease (because of chemosensitivity of their osteosarcomas) than poor responders, and IFN may work best in such a context of minimal residual disease. This is exemplified by adjuvant data from melanoma, where IFN activity was confined to a subpopulation with microscopic nodal disease.[19,35]

In conclusion, our collaborative group completed a large prospective RCT in a rare condition within a reasonable timespan. Although the point estimates for EFS and OS favored the intervention—maintenance with pegylated IFN-α-2b—the CIs of the HRs included 1, and we conclude no difference; the observed effect size for EFS was smaller than targeted. A considerable proportion of patients allocated to IFN-α-2b never started or did not complete treatment with the drug, which complicates interpretation of the efficacy data. Reported toxicity in patients who started IFN-α-2b did not seem excessive.

Although we have reached the target number of EFS events, ongoing follow-up of patients is crucial and will permit the planned analysis of OS. The current EFS results, reported at the protocol-defined analytic end point, do not support the routine use of IFN-α-2b maintenance after standard chemotherapy for osteosarcoma.

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Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

cisplatin: an inorganic platinum agent (cis-diamminedichloroplatinum) with antineoplastic activity. Cisplatin forms highly reactive, charged, platinum complexes, which bind to nucleophilic groups such as GC-rich sites in DNA, inducing intrastrand and interstrand DNA cross-links as well as DNA-protein cross-links. These cross-links result in apoptosis and cell growth inhibition. Carboplatin and oxaliplatin are other members of this class.

Cox proportional hazards regression model: a statistical model for regression analysis of censored survival data, examining the relationship of censored survival distribution to one or more covariates. This model produces a baseline survival curve, covariate coefficient estimates with their standard errors, risk ratios, 95% CIs, and significance levels.

IFN-α-2b (interferon-alfa-2b): recombinant interferon alfa that is commercially prepared from a bacterial fermentation of *E. coli* bearing an expression vector containing the interferon alfa-2b (*IFN-α-2b*) gene from human leukocytes.

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Methotrexate, Doxorubicin, and Cisplatin (MAP) Plus Maintenance Pegylated Interferon Alfa-2b Versus MAP Alone in Patients With Resectable High-Grade Osteosarcoma and Good Histologic Response to Preoperative MAP: First Results of the EURAMOS-1 Good Response Randomized Controlled Trial

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(*) Group representative

A4. Scandinavian Sarcoma Group (SSG)

Norway. Oslo University Hospital (Dr Kirsten Sundby Hall); Bergen University Hospital (Dr Odd Monge); Trondheim University Hospital (Dr Erling Moe).

Sweden. Umeå University Hospital (Dr Ulf Hjalmars (Children)Dr Beatrice Malmer, Dr Kjell Johansson (Children)); Linköping University Hospital (Dr Najme Wall, Dr Maria Östlund, Dr Mikael Behrendtz); Gothenburg Sahlgrenska University Hospital (Dr Lina Hansson, Dr Gustaf Österlundh (Children), Dr Monika Sender, Dr Katarina Engström,); Lund University Hospital, Oncologic dept. (Dr Mikael Eriksson, Dr Lars Hjorth (Children)); Akademiska sjukhuset, Uppsala University Hospital (Dr Ingela Turesson, Dr Gustaf Ljungman (Children)); Karolinska University Hospital, Stockholm (Dr Elisabet Lidbrink, Dr Cecilia Petersen (Children), Dr Mikael Szeps, Dr Annika Folin, Dr Christina Linder-Stragliotto, Dr Jonas Karlén (Children), Dr Åke Jacobson (Children)).

Finland. Tampere University Hospital (Dr Tuula Lehtinen); Helsinki University Central Hospital (Dr Maija Tarkkanen); Turku University Hospital (Dr Paula Lindholm).

Denmark. Aarhus University Hospital (Dr Akmal Safwat (Adult), Dr Ole Steen Nielsen, Dr Henrik Hasle (Children)); Copenhagen Rigshospital (Dr Catherine Rechnitzer).

SSG Panel Representatives and Additional Contributors

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A5. Members of Independent Oversight Committees

Independent Data Monitoring Committee:
Barry Hancock, Chair: Sheffield, United Kingdom
Gerald Gilchrist, Member: Minnesota, United States
Otilia Dalesio, Member: Amsterdam, the Netherlands
Peter Høglund, Member: Lund, Sweden
Trial Steering Committee:
Stefano Ferrari, Chair: Bologna, Italy
Joseph Mirro, Member: Memphis, United States
Hans Strander, Member: Stockholm, Sweden
Robert Souhami, Member: London, United Kingdom

A6. Members of EURAMOS Intergroup Safety Desk (EISD)

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Heidi Oellers, TMG Member: Monitoring/Auditing
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Eva Grünewald: Safety Desk Manager
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B7. Members of Quality of Life Coordinating Centre

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Andreas Wiener, TMG Member: Quality of Life Panel
Katja Baust: Psychotherapist
Carmen Teske: Study Documentation
Karina Riemenschneider: Secretary