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


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 treatment. With median follow-up of 44 months, 3-year EFS for all 716 randomized patients was 76% (95% CI, 72% to 79%); 174 EFS events were reported (MAP, n = 81; 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.

J Clin Oncol 33. © 2015 by American Society of Clinical Oncology
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. Reported outcomes have been similar internationally and have shown little improvement over previous decades. 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% vs 45% to 55%).

Four international osteosarcoma groups with a history of successfully conducted clinical trials formed the European and American Osteosarcoma Study Group (EURAMOS), 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. MAP (methotrexate, doxorubicin, and cisplatin) chemotherapy was accepted as standard. Intensified salvage chemotherapy was investigated in poor responders. On the basis of preclinical and clinical evidence, 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 and is being investigated in sarcomas. IFN-α has anti-proliferative, differentiation-inducing, apoptotic, and antiangiogenic properties, and its clinical activity has been demonstrated in several cancers, including as postchemotherapy maintenance. It has been associated with activity against osteosarcomas (some of which have expressed IFN-α/β receptor) in vitro, in animal models, and in patients with metastatic disease. 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. On the basis of this rationale, we aimed to test IFN-α as maintenance treatment in osteosarcoma. 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.
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. 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 ≤ .001 for EFS25,26 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 favoring IFN-α-2b. Consistency of treatment effect was examined using the interaction test (χ² 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 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/m² (target, 96 g/m²); doxorubicin, 298 mg/m² (target, 300 mg/m²); and cisplatin, 239 mg/m² (target, 240 mg/m²; 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...
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).

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**Efficacy**

EFS at 3 years for 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; 3-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. 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.
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 expected7 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/m² 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

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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.

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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 muralid tripeptide phosphatidylethanolamine (HR, 0.80; 95% CI, 0.62 to 1.0), 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, but smaller than our 0.63 target.

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.

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. 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, 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.

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.

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

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<th>%*</th>
<th>No.</th>
<th>%*</th>
<th>No.</th>
<th>%*</th>
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<th>%*</th>
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**Other notable serious AEs and toxicities**

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<td>Flu-like syndrome</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>12</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain (muscle)</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain (head/headache)</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>12</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

**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 alpha 2b; LVSD, left ventricular systolic dysfunction; NA, not applicable.

*Based on No. of patients reporting each type of toxicity. tRoutinely collected on CRF. †Spontaneously reported on CRF or as serious AE. §Or grade 1 to 2 neutrophils.

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

Supported by governmental, nongovernmental, scientific, and charitable body funders in each participating country, with additional funding for pan-European trial coordination. Peglated interferon-alfa-2b was provided by Merck, which reviewed this report. EURAMOS-1 was supported by multiple national and international governmental agencies and cancer charities, including the National Cancer Institute, which provided funding to the Children’s Oncology Group (North America, Australasia, and Switzerland); the European Science Foundation under the EUROCORES Program European Clinical Trials through Contract No. ERASC-2003-980409 from the European Commission, DG Research, FP6 (Reference No. MM/NG/EMRC/0202); St Anna Kinderkrebsforschung (Austria); Fonds National de la Recherche Scientifique and Fonds voor Wetenschappelijk Onderzoek-Vlaanderen (Belgium); Parents Organisation (Czech Republic); Danish Medical Research Council (Denmark); Academy of Finland (Finland); Deutsche Forschungsgemeinschaft (Ref No. BI 1045/1-1 & 1-2), Deutsche Krebshilfe (Reference No. 50-2723-Bi2), and Federal Ministry of Education and Research (Reference No. BMBF 01KN1105; Germany); Semmelweis Foundation (Hungary); Council for Medical Research (the Netherlands); Research Council of Norway (Norway); Scandinavian Sarcoma Group (Sweden); Swiss Paediatric Oncology Group (Switzerland); Cancer Research UK (Reference No. CRUK/05/013), Medical Research Council, National Institute for Health Research at University College London Hospitals, and Biomedical Research Centre (United Kingdom).
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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

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

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Acknowledgment

We acknowledge the input of Mahesh K.B. Parmar, James Pickering, Nicola Joffe, Anne Holliday, Karen Sanders, Monique Tomiczek, Beth May, Matthias Kevric, Benjamin Sorg, Doojden Villaluna, Caroline Wang, Martha Perisougou, Leonardo Trani, Jenny Potratz, Dorothie Carrle, Miriam Wilhelm, Katja Zils, and Carmen Teske.


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