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EURAMOS-1, an international randomised study for osteosarcoma: results from pre-randomisation treatment†

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Background: Four international study groups undertook a large study in resectable osteosarcoma, which included two randomised controlled trials, to determine the effect on survival of changing post-operative chemotherapy based on histological response.

Patients and methods: Patients with resectable osteosarcoma aged ≤40 years were treated with the MAP regimen, comprising pre-operatively of two 5-week cycles of cisplatin 120 mg/m^2, doxorubicin 75 mg/m^2, methotrexate 12 g/m^2 × 2 (MAP) and post-operatively two further cycles of MAP and two cycles of just MA. Patients were randomised after surgery. Those with ≥10% viable tumour in the resected specimen received MAP or MAP with ifosfamide and etoposide. Those with <10% viable tumour were allocated to MAP or MAP followed by pegylated interferon. Longitudinal evaluation of quality of life was undertaken.

Results: Recruitment was completed to the largest osteosarcoma study to date in 75 months. Commencing March 2005, 2260 patients were registered from 326 centres across 17 countries. About 1334 of 2260 registered patients (59%) were randomised. Pre-operative chemotherapy was completed according to protocol in 94%. Grade 3–4 neutropenia affected 83%

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of cycles and 59% were complicated by infection. There were three (0.13%) deaths related to pre-operative chemotherapy. At definitive surgery, 50% of patients had at least 90% necrosis in the resected specimen.

Conclusions: New models of collaboration are required to successfully conduct trials to improve outcomes of patients with rare cancers; EURAMOS-1 demonstrates achievability. Considerable regulatory, financial and operational challenges must be overcome to develop similar studies in the future.The trial is registered as NCT00134030 and ISRCTN 67613327.

Key words: osteosarcoma, randomised controlled trial, trial conduct, international collaboration

introduction

Osteosarcoma is the commonest primary bone cancer affecting young people with an overall age-standardised incidence rate of 5.2 cases/million [1]. Cure of osteosarcoma in a proportion of patients was consistently reported first in the 1970s, achieved through the combination of surgical extirpation of the primary tumour with multi-drug chemotherapy. The results were further improved during the next decade, but since then, no clinically significant advances have been made in survival, although more patients access combination chemotherapy within and outside trials.

In 2001, four clinical study groups agreed to collaborate to conduct osteosarcoma studies more rapidly. EURAMOS (European and American Osteosarcoma Studies) was formed from the Children's Oncology Group (COG), Cooperative Osteosarcoma Study Group (COSS) of the German Society for Pediatric Oncology and Hematology (GPOH), European Osteosarcoma Intergroup (EOI) and Scandinavian Sarcoma Group (SSG).

The EURAMOS group aimed to improve outcomes in osteosarcoma, principally through large international, collaborative randomised, controlled trials (RCTs). Additional objectives were to facilitate biological research in osteosarcoma, more rapidly identify new therapeutic approaches and develop a common understanding and methodologies for staging, pathology and other aspects of disease management [2].

The first study, EURAMOS-1, began recruitment in 2005 and closed registration in June 2011. Good histological response, assessed in the resected tumour, has been associated with improved survival [3–5]. Therefore, this study addressed separate treatment questions based on histological response. EURAMOS-1 was notable for addressing randomised questions in a rare cancer on an unprecedented scale and for launching at a time of profound change to European legislation related to trial regulation and governance [6]. We describe the study, its population and the initial treatment of 2260 registered patients.

methods

patients

We designed a clinical trial to include patients with newly diagnosed localised or metastatic osteosarcoma (see supplementary Material, available at *Annals of Oncology* online) of the extremity or axial skeleton deemed to be suitable for complete resection of all disease sites. Patients were aged ≤40 years at diagnostic biopsy and had to both register on the study and start chemotherapy within 30 days after diagnostic biopsy. Patients required adequate bone marrow function (neutrophils $\geq 0.5 \times 10^9$/l or WBC $\geq 3 \times 10^9$/l; platelet count $>100 \times 10^9$/l); renal function (glomerular filtration rate ≥70 ml/min/1.73 m^2); liver function (bilirubin ≤1.5 × upper limit of normal); cardiac function (shortening fraction ≥28% or ejection fraction ≥50%) and performance status (Karnofsky score ≥60; WHO performance status ≤2; or Lansky score ≥60%). Standard staging and organ function investigations were undertaken.

Diagnostic biopsies were to be examined by local institutional pathologists and reviewed by each study group's reference pathologists.

study design

Figure 1 shows the design with randomisation defined by histological response in the primary tumour after pre-operative chemotherapy. Response classification was dichotomised: ≥90% necrosis (good response); <90% necrosis (poor response). Registered patients were offered randomisation when also had: completed two courses of cisplatin and doxorubicin pre-operatively; completed ≥2 (but ≤6) courses of methotrexate pre-surgery; recovered fully from prior therapy; no disease progression; undergone complete macroscopic resection of the primary tumour and undergone complete removal of all metastatic disease or this was planned and deemed feasible. Patients with good histological response had to be ≥5 years due to concerns of age-related toxicity from interferon [7]. Data collection including registration characteristics and reports on pre-operative chemotherapy, surgery and pathology had to be received by the randomising data centre. Consent was obtained according to national regulations. Supp_Appendix_B (supplementary Material, available at *Annals of Oncology* online) describes the study organisation.

treatment

Chemotherapy for the control arm (Figure 2) was based on the standard described in the previous largest RCT for osteosarcoma [8]. Pre-operative treatment comprised methotrexate 12 g/m^2 (M), doxorubicin 75 mg/m^2 (Adriamycin, A) and cisplatin 120 mg/m^2 (P). Preferred schedules were 48-h infusion for doxorubicin and either 72-h infusion or two 4-h infusions on separate days for cisplatin. Methotrexate was given over 4 h and folinic acid rescue commenced at 24 h. Surgery was scheduled after two cycles of MAP, i.e., 10 weeks after starting chemotherapy.

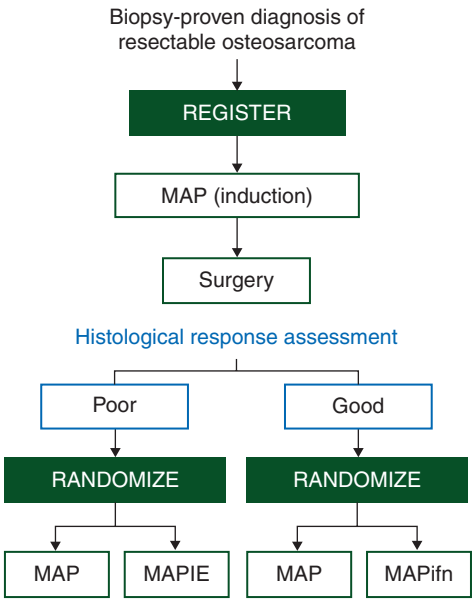

Figure 1. EURAMOS-1 study design.

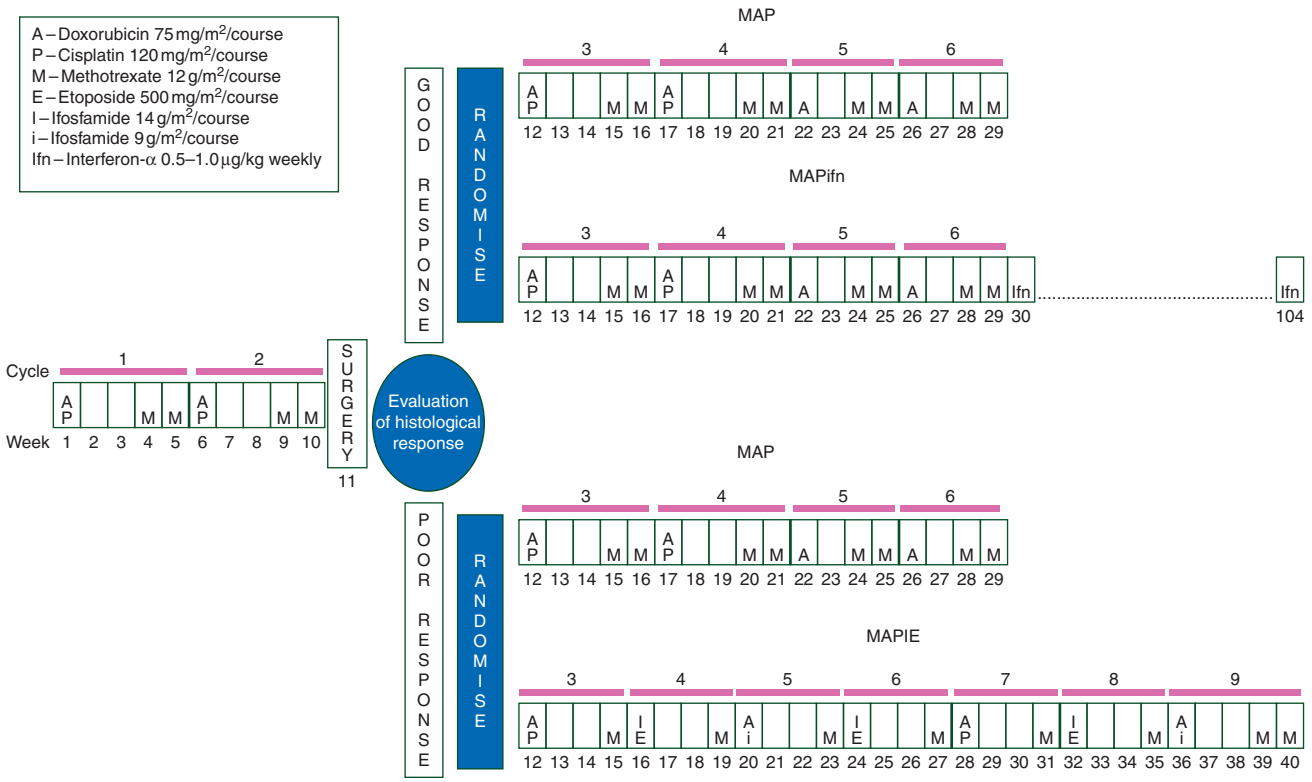

Figure 2. EURAMOS-1 treatment schedule.

Eligible, consenting patients with good histological response were randomised to complete six cycles of MAP or MAP followed by maintenance pegylated interferon α-2b (Ifn; Merck) at 0.5–1.0 μg/kg/week to 24 months after starting chemotherapy. Eligible, consenting patients with poor histological response were randomised to continue standard chemotherapy with MAP or to MAP/IE over 28 weeks, a schedule designed to deliver the same total doses as post-operative MAP with additional ifosfamide and etoposide (IE), agents previously demonstrating activity in osteosarcoma [9]. Ifosfamide 3000 mg/m^2 ×3 days, total dose 9 g/m^2, was given with doxorubicin in cycles designated as Ai, and at 2800 mg/m^2 ×5 days, total dose 14 g/m^2, with etoposide 100 mg/m^2 ×5 days, designated IE cycles.

The protocol detailed dose modifications to account for toxicity for all treatments. Granulocyte growth factors were recommended but not mandated. Dexrazoxane could be used at investigators' discretion for reduced cardiac function remaining in the normal range; this applied throughout in North America but was withdrawn by the European Medicines Agency in 2011.

Response assessment was required to determine suitability for surgery and to exclude progression (see supplementary Material, available at *Annals of Oncology* online).

quality-of-life evaluation

Quality of life (QL) was assessed using self- and parent-completed questionnaires to determine short- and long-term impacts. For patients ≥16 years, QL was assessed using EORTC QLQ-C30 questionnaire [10]. Patients <16 years in COG centres answered the generic PedsQL questionnaire, and in Europe, PEDQOL [11, 12]. The initial QL assessment was at week 5, then 3 months after definitive surgery, at 18 months and 3 years after commencing therapy.

outcome measures

The primary outcome measure was event-free survival (EFS), defined as time from randomisation to the first of: detection of local recurrence or metastases, progression of metastatic disease, detection of secondary malignancy or death from any cause. EFS was chosen because prevention of first recurrence is the principal goal of adjuvant treatment of osteosarcoma, given the low rate of survival after first recurrence. Furthermore, treatment of recurrence is heterogeneous; treatment guidance for relapse accompanied the protocol, but sites' existing standard practice was accepted. Secondary outcome measures were overall survival (OS), toxicity and QL. Toxicity was assessed using CTCAE version 3.0 [13].

sample size calculations

We assumed 70% 3-year EFS on MAP for good response and 45% for poor response, timed from randomisation. Each sample size was based on 5% two-sided significance level and 80% power. The Good Response randomisation needed 147 EFS events to detect improved 3-year EFS from 70% to 80%, i.e., hazard ratio (HR) = 0·63 [14]. Five-year survival was estimated as 70% so long-term analyses for survival were planned for when 147 deaths are reported, for the same relative and absolute improvements. For poor response, 378 events were targeted to detect improved 3-year EFS and 5-year OS from 45% to 55% (HR = 0·75).

We anticipated 45% (567) randomised patients would have good response and 55% (693) poor response [8]. We planned to register ∼1400 patients over 3.5 years to randomise 1260, assuming 10% non-randomisation for ineligibility or non-consent. The observed non-randomisation rate was higher and the registration target was increased to ∼2000 patients.

statistical analysis

This paper describes the full, registered patient population, including all patients who signed the informed consent documents, up to the point of surgery. Standard descriptive statistics are used.

results

study participants

Between April 2005 and June 2011, 2260 patients from 326 sites in seventeen countries were registered (supplementary Figures S1 and S2, available at *Annals of Oncology* online); 1164 (52%) COG, 520 (23%) COSS, 457 (20%) EOI and 119 (5%) SSG. The majority of patients were aged 10–19 with localised tumours of the lower limb (Table 1) and conventional type osteosarcoma on histology (Table 2). Males comprised 59% (1330/2260) of the cohort; 355 (16%) had definite metastases, 161 (7%) possible and 1722 (77%) no metastases. Of 355 patients with definite metastases, 273 (77%) had lung mets only, 54 (15%) other mets only, 22 (6%) both lung and other and 5 (1%) definite-lung and possible other mets. Of 161 patients with possible metastases, 144 (89%) had possible lung metastases, 11 (7%) possible other mets and 6 (4%) both. Table 1 shows baseline characteristics.

The eligibility criteria spanned children and adults ≤40 years old. We estimated accrual as a proportion of expected age-related osteosarcoma incidence osteosarcoma to address whether participation was equally likely within the study age range. In all groups, the proportion recruited from the estimated population fell from age ≥ 15yrs in females and 19yrs in males, such that ~1/3 of potentially eligible patients were not registered (supplementary Figure S3, available at *Annals of Oncology* online). Figure 3 shows the CONSORT diagram.

randomisation

Randomisation was offered to eligible registered patients with reported histological response. For those with reported good response, 69% (716/1040) accepted the relevant randomisation and for poor response, 58% (617/1059); one patient with good response was erroneously randomised to the poor response cohort and allocated MAP. The overall randomisation rate was 64% (1334/2100) for patients with known histological response.

There was some variability in proportion randomised between groups: COSS 363/520 (70%), SSG 82/119 (69%), EOI 276/457 (60%) and COG 613/1164 (53%) (supplementary Table S2, available at *Annals of Oncology* online). Patients aged 20–29 years were less frequently randomised (106/199, 53%) than those 5–19 years (1194/1995, 60%) or >30 years (32/53, 60%). The main reason recorded for non-randomisation was absence of consent (413/2260, 18%). Progression prior to surgery was recorded in 176 patients (8%). Eighty-eight patients (4%) could not be randomised because of late reporting of histology and 67 (3%) for incorrect pre-operative chemotherapy. Patient characteristics for randomised and non-randomised patients and by histological response are shown in Table 1.

histology

Diagnosis was confirmed by reference pathologists in 2160/2209 (98%) of registered patients (Table 2). The commonest histological subtype was conventional (92%, 2033/2209), followed by telangiectatic (4%, 96/2209), small cell (1%, 14/2209) and high-grade surface (1%, 29/2209). Thirty-one patients were deemed ineligible post-registration based on reference histological review of the biopsy. Biopsy details remain unavailable for 51 patients (2%). In 1917 patients with reference pathologist assessment of both diagnostic biopsy and resected specimen, the classification was different for 75 (4%) patients. Of these, 36/75 were re-classified as different subtypes of osteosarcoma, 15/75 as conventional, 13/75 as telangiectatic, 6/75 as high-grade surface osteosarcoma and 5/75 were ineligible.

Pathological assessment of histological response to pre-operative chemotherapy was available for 1975/2012 patients; 979 reported a good response and 996 a poor response. The response rate of good histological response to MAP was 50% overall, ranging from 46% (433/949) COG, to 53% COSS (265/499), 53% SSG (58/110) and 54% EOI (223/417).

chemotherapy

Ninety-four percent registered patients (2123/2248) completed two cycles of MAP pre-operatively. Median received pre-operative dose for doxorubicin was 149 mg/m^2 (target 150 mg/m^2), 239 mg/m^2 cisplatin (target 240 mg/m^2) and 46.8 g/m^2 high-dose methotrexate (target 48 g/m^2). Median time from registration in EURAMOS-1 to starting chemotherapy was 0 days [interquartile range (IQR) -2; 0]. Median time from start of chemotherapy to surgery was 82 days (IQR 76; 90). Median time from surgery to starting post-operative chemotherapy for randomised patients was 18 days (IQR 14; 24).

The pre-operative toxicities reported were as expected. Table 3 shows the worst reported toxicity. CTCAE grade 3–4 toxicity was common: 1863/2234 (83%) neutropenia; 1292/2237 (58%) infective complications; 1122/2238 (50%) thrombocytopenia; 544/1989 (27%) mucositis; grade 1 or 2 mucositis was reported in a further 21% (427/1989) and 28% (557/1989), respectively. Severe renal, neurological and left ventricular dysfunctions were uncommon.

There were three treatment-related deaths (3/2260, 0.13%) during the pre-operative period, two from infective complications and one from toxic epidermal necrolysis secondary to methotrexate.

surgery

The amputation rate, including rotationplasty, was 17% (346/2054), ranging from 16% (169/1045, COG) to 19% (22/114, SSG) (Table 4). Macroscopic clearance of the primary tumour was reported in 99% (2035/2051). There were three post-operative deaths: one patient died from embolic complications on the third post-operative day, a second from pneumonia with respiratory failure on day 29 and a third from infection complicated by multisystem failure 48 days after surgery.

data completeness and follow-up

Long-term event data were sought in all patients, regardless of randomisation. In 15 February 2013, 1455/1566 (93%) had data within the previous 14 months; death and loss to follow-up were reported in 526/2260 and 168/2260 patients, respectively. Long-term event data from the full cohort, including second malignancy data, will be reported with further follow-up.

discussion

Osteosarcoma therapy was revolutionised by the introduction of adjuvant combination chemotherapy, in the 1970s, but has

Table 1. Baseline characteristics at registration

Response	Randomised				Not randomised						Overall	
	Good		Poor		Good		Poor		Not known			
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Sex												
Male	421	59	365	59	190	59	264	60	90	56	1330	59
Female	295	41	253	41	134	41	178	40	70	44	930	41
Missing	0	n/a	0	n/a	0	n/a	0	n/a	0	n/a	0	n/a
Age at registration												
0–4	1	0	1	0	6	2	3	1	0	0	11	0
5–9	102	14	94	15	48	15	45	10	21	13	310	14
10–14	305	43	217	35	130	40	167	38	59	37	878	39
15–19	258	36	218	35	113	35	166	38	54	34	809	36
20–24	28	4	52	8	19	6	37	8	17	11	153	7
25–29	11	2	15	2	5	2	10	2	5	3	46	2
30–34	1	0	9	1	3	1	5	1	1	1	19	1
35–39	10	1	11	2	0	0	7	2	2	1	30	1
40	0	0	1	0	0	0	2	0	1	1	4	0
Median (quartiles)	14 (11, 16)		14 (11, 17)		14 (11, 16)		15 (12, 17)		15 (11, 17)		14 (11, 17)	
Min–max	4–38		4–40		4–32		4–40		5–40		4–40	
Missing	0	n/a	0	n/a	0	n/a	0	n/a	0	n/a	0	n/a
Site and location												
Proximal femur or humerus	83	12	77	13	44	14	68	16	21	14	293	13
Other limb site	617	86	508	82	265	84	340	78	107	70	1837	82
Axial or skeletal	16	2	31	5	7	2	30	7	24	16	108	5
Missing	0	n/a	2	n/a	8	n/a	4	n/a	8	n/a	22	n/a
Pathological fracture												
No at diagnosis	629	88	545	89	272	86	387	88	131	86	1964	88
Yes at diagnosis	86	12	69	11	44	14	52	12	22	14	273	12
Missing	1	n/a	4	n/a	8	n/a	3	n/a	7	n/a	23	n/a
Localised disease												
Yes (no mets)	567	79	491	80	239	76	324	74	101	66	1722	77
Possible mets	63	9	48	8	19	6	26	6	5	3	161	7
No (yes mets)	86	12	76	12	58	18	88	20	47	31	355	16
Missing	0	n/a	3	n/a	8	n/a	4	n/a	7	n/a	22	n/a
Lung metastases												
No	583	81	505	82	247	78	340	77	107	70	1782	80
Possibly	62	9	46	7	16	5	26	6	6	4	156	7
Yes	71	10	64	10	53	17	73	17	40	26	301	13
Missing	0	n/a	3	n/a	8	n/a	3	n/a	7	n/a	21	n/a
Other metastases												
No	691	97	590	96	304	97	414	95	141	92	2140	96
Possibly	5	1	8	1	4	1	2	0	3	2	22	1
Yes	20	3	18	3	7	2	22	5	9	6	76	3
Missing	0	n/a	2	n/a	9	n/a	4	n/a	7	n/a	22	n/a
Duration of symptoms (days)												
Median (quartiles)	8 (4, 13)		8 (4, 14)		8 (4, 12)		10 (6, 16)		9 (6, 16)		8 (4, 14)	
Min–max	0–78		0–312		0–104		0–260		0–104		0–312	
Missing	85	n/a	68	n/a	43	n/a	59	n/a	30	n/a	285	n/a
Group												
COG	300	42	313	51	180	56	256	58	115	72	1164	52
COSS	206	29	157	25	60	19	78	18	19	12	520	23
EOI	161	22	115	19	73	23	89	20	19	12	457	20
SSG	49	7	33	5	11	3	19	4	7	4	119	5
Total	716	100	618	100	324	100	442	100	160	100	2260	100

Table 2. Pathology at diagnostic biopsy and surgery

	Diagnostic biopsy		Resected specimen	
	N	%	*N*	%
Data available				
Yes	2209	98	2012	89
No	51	2	248	11
Type of pathologist				
Reference	2160	98	1951	97
Local only	49	2	61	3
Histology				
Conventional	2033	92	1832	93
Telangiectatic	96	4	90	5
Small cell	14	1	7	0
High-grade surface	29	1	28	1
Secondary	0	0	0	0
Unclassified osteosarcoma	2	0	1	0
Ineligible	31	1	15	1
Not assessable	0	0	2	0
Info missing from the form	4	n/a	37	n/a
Excision of tumour				
Marginal	n/a	n/a	264	13
Wide	n/a	n/a	1474	74
Radical	n/a	n/a	222	11
Intra-lesional	n/a	n/a	26	1
Not known	n/a	n/a	19	1
Info missing from the form	n/a	n/a	7	n/a
Histological response				
Good (<10% viable tumour)	n/a	n/a	979	50
Poor (≥10% viable tumour)	n/a	n/a	996	50
Info missing from the form	n/a	n/a	37	n/a
Total	2209	100	2012	100

improved little since. The cost of seeking cure is exceptionally high as patients receive particularly complex and toxic chemotherapy regimens, plus disabling surgery. The single new treatment which has emerged, mifamurtide (MTP-PE), has been the subject of considerable controversy and its availability varies internationally, due to disagreements about interpretation of the available clinical data and cost.

While many studies have been undertaken for osteosarcoma, they are often characterised by being non-randomised or, if randomised, by their long accrual periods [15–18]. This was the background against which we joined together to attempt to develop new paradigms for treating this disease.

The EURAMOS group chose to undertake a large cohort study, embedding two randomised comparisons as our first collaboration [6]. The two questions chosen for this first study stratified post-operative treatment according to the histologically assessed response to pre-operative chemotherapy. It assessed maintenance therapy in patients with a better prognosis (Good Response) [19] and intensification in patients with poorer prognosis (Poor Response) [9, 20–22]. These important questions were amenable to a relatively simple trial design. However, the agents chosen highlight the paucity of new or investigational products appropriate to include in phase III trials.

EURAMOS-1 has been successfully executed. The study was developed through a commitment to collaboration between four

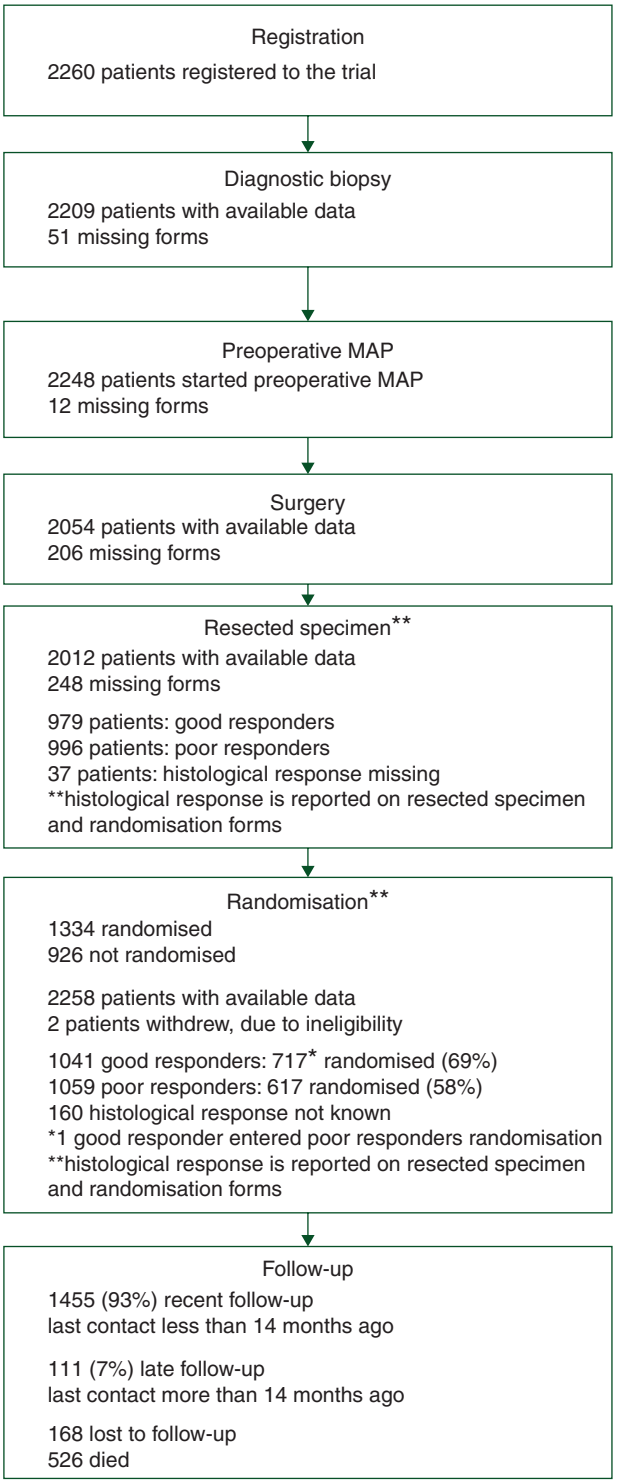

Figure 3. EURAMOS-1 CONSORT diagram.

well-established study groups. With 1334 patients with resectable osteosarcoma randomised, it doubled the size of the previous largest RCT in this population and accrual was completed in around 6 years. Other indicators of quality and safety for a trial on this scale are reassuring. Concordance with protocol chemotherapy was excellent. Toxicities were consistent with previous experience of these agents. The treatment-related death

Table 3. Worst pre-operative MAP toxicity

Worst toxicity grade with pre-operative MAP	Randomised				Not randomised						Overall	
	Good		Poor		Good		Poor		Not known			
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Grade 0	7	1	10	2	4	1	3	1	8	5	32	1
Grade 1	12	2	8	1	5	2	9	2	5	3	39	2
Grade 2	19	3	40	6	9	3	18	4	9	6	95	4
Grade 3	109	15	79	13	36	11	79	18	28	18	331	15
Grade 4	569	79	480	78	267	82	331	75	95	59	1742	77
Grade 5	0	0	0	0	1	0	0	0	2	1	3	0
Not assessed	0	n/a	1	n/a	1	n/a	1	n/a	1	n/a	4	n/a
Not reported on CRF	0	n/a	0	n/a	1	n/a	1	n/a	12	n/a	14	n/a
Total	716	100	618	100	324	100	442	100	160	100	2260	100

Three deaths were treatment-related (two from infective complications and one from toxic epidermal necrolysis secondary to methotrexate) and three occurred after surgery.
Percentages exclude the 'not assessed' and 'not reported' rows.
Excludes three deaths occurred after surgery. Of those patients, one Good Responder had worst toxicity of grade 1; one poor responder had worst toxicity of grade 3 and one person with unknown histological response had a worst toxicity of grade 4.

Table 4. Surgical details

Data source	Total	
	N	%
Surgical data		
Received	2054	91
Not received	206	9
Pathological fracture at surgery		
No	1881	92
Yes	169	8
Missing on surgery form	4	n/a
Surgical procedure		
Amputation	213	10
Disarticulation	30	1
Rotationplasty	103	5
Resection + reconstruction	1571	77
Resection only	91	4
Other	45	2
Missing	1	n/a
Macroscopic clearance achieved		
Yes	2035	99
No, despite surgery	16	1
Missing	3	n/a
Total	2054	100

rate of 0.18% from pre-operative chemotherapy is at the lower end of the range previously reported.

In other areas, the study has highlighted where improvement is needed. This was the first publicly-funded pan-European clinical trial to be activated after European countries implemented the European Clinical Trials Directive, which created new challenges [23]. There were limits to the accessibility of the trial for osteosarcoma patients. We were unable to open EURAMOS-1 in some countries that wished to participate either because of regulatory constraints or insufficient funding. Moreover, even though we used age eligibility criteria which allowed inclusion of all patients aged <40 years, the proportion of potentially eligible patients fell with increasing age beginning from late teenage years, a phenomenon consistent with accrual rates seen for other cancers in young adults [24, 25].

The feasibility of delivering intensive chemotherapy for a rare cancer in multiple centres within a Good Clinical Practice framework is amply demonstrated here. However, it is also clear that the treatment burden of MAP is exceptionally high, reflected in levels of grade 3–4 haematological and non-haematological toxicity. While the link between increased toxicity and improved survival from osteosarcoma remains to be unravelled [26], future approaches must look to reduce this burden as well as improve efficacy.

At the time of trial planning, few data were available to guide a sample size calculation to accurately estimate randomisation rates and these were markedly lower than expected, which contributed to a decision to expand registration targets from 1400 to over 2000. Information collected on reasons for non-randomisation has been relatively non-informative but anecdotally, young people expressed a reluctance to risk allocation to experimental treatments that were substantially longer than the standard MAP schedule. Further investigation of this important area is needed [27]. Greater patient involvement at the design stage may help in the future.

First results of the Good Response randomisation have been presented orally [28], with a clear demonstration that large-scale practice-changing randomised, controlled trials can be undertaken in rare cancers by extending the traditional boundaries of collaboration. From EURAMOS-1, we are growing a wider collaboration with groups willing to work together. A successor study has not yet emerged despite willingness by investigators and other trials groups joining the collaboration to face the

formidable regulatory and financial challenges which must be overcome. The absence of testable new innovations in this disease is a cause for major concern and even more apparent now we have established a successful test platform.

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participation

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disclosure

The authors have declared no conflicts of interest.

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