THE LANCET Oncology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Marina NM, Smeland S, Bielack SS, et al. Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): an open-label, international, randomised controlled trial. *Lancet Oncol* 2016; published online Aug 25. http://dx.doi.org/10.1016/S1470-2045(16)30214-5.

SUPPLEMENTARY APPENDIX

Randomised Phase III Comparison of MAPIE vs MAP in patients with a Poor Response to pre-operative chemotherapy for newly-diagnosed high-grade osteosarcoma: results from the EURAMOS-1 trial

TABLE OF CONTENTS

=== SUPPLEMENTAL TABLES ===

Table S1: Poor Responders randomisations, by country

Country	Number of randomised poor responders
USA	281
Germany	123
UK	72
Netherlands	26
Canada	18
Norway	17
Belgium	16
Switzerland	14
Austria	13
Sweden	9
Australia	8
Hungary	8
Denmark	4
Czech Republic	3
Finland	3
New Zealand	2
Ireland	1
Total	**618**

Table S2: Reasons for non-randomisation, for patients with poor histological response

Reason patient was not randomised	N	Percent
No consent	204	46.2%
Progression (local or distant)	111	25.1%
Late histology	45	10.2%
Wrong preoperative CT	31	7.0%
Other*	17	3.8%
No removal of metastases/ unresectable disease	16	3.6%
Not recovered from prior therapy	7	1.6%
Change of diagnosis	6	1.4%
Incomplete resection of primary tumour	5	1.1%
Total	**442**	**100%**

*Other reasons for non-randomisation were:

- not able to randomise within 35 days after definitive surgery (5 patients)
- patient choice (2 patients)
- physician choice (1 patient)
- site was too late to randomise the patient (2 patients)
- patient was registered as non-metastatic but actually had a metastatic disease. This was a stratification factor and it was not possible to amend it after registration (1 patient)
- surgery delayed (1 patient)
- unable to tolerate methotrexate (2 patients)
- uncertain radiological response to induction chemotherapy (1 patient)
- disagreement between local and central histology resulted in 3rd opinion on pathology which is likely to be non-randomisation due to late histology but not explicitly stated (1 patient),
- no response to induction chemotherapy (1 patient)

Table S3: Details of second malignancies

Second malignancy	ICD-O code	Time to SMN from randomisation	Received postoperative dose on trial	Number of doses on trial	Cytogenetic abnormality
MAP arm					
Acute myeloid leukemia	99203	1·2 years	MTX: 87·4 g/m^2 DOX: 295 mg/m^2 DDP: 224 mg/m^2	8 doses 4 doses 2 doses	
Myelodysplastic syndrome	99873	3.9 years	MTX: 76·5 g/m^2 DOX: 293 mg/m^2 DDP: 240 mg/m^2	7 doses 4 doses 2 doses	Monosomy 7
Squamous cell carcinoma	80703	6·4 years	MTX: 66·7 g/m^2 DOX: 300 mg/m^2 DDP: 242 mg/m^2	8 doses 4 doses 2 doses	
MAPIE arm					
Acute myeloid leukemia	9891-3	0·9 years	MTX: 61·5 g/m^2 DOX: 229 mg/m^2 DDP: 247 mg/m^2 I: 49·2 g/m^2 E: 1·4 g/m^2	5 doses 3 doses 2 doses 4 doses 3 doses	inv 11, 11q23 abnormality, chromosome 7
Acute myeloid leukemia	99203	1·2 years	MTX: 12·5 g/m^2 DOX: 75 mg/m^2 DDP: 118 mg/m^2 I: 0 g/m^2 E: 0 g/m^2	1 dose 1 dose 1 dose 0 doses 0 doses	t(9;11) 11q23
Acute myeloid leukemia	99203	2·4 years	MTX: 102·4 g/m^2 DOX: 318 mg/m^2 DDP: 220 mg/m^2 I: 61·0 g/m^2 E: 1·5 g/m^2	8 doses 4 doses 2 doses 5 doses 3 doses	
Acute myeloid leukemia	99203	3 years	MTX: 68·9 g/m^2 DOX: 298 mg/m^2 DDP: 239 mg/m^2 I: 51·5 g/m^2 E: 1·3 g/m^2	6 doses 4 doses 2 doses 5 doses 3 doses	Monosomy 7
Acute myeloid leukemia	99203	5·2 years	MTX: 12 g/m^2 DOX: 104 mg/m^2 DDP: 120 mg/m^2 I: 11·5 g/m^2 E: 0·36 g/m^2	1 dose 2 doses 1 dose 1 dose 1 dose	
Acute myeloid leukemia	99203	5·6 years	MTX: 94·1 g/m^2 DOX: 302 mg/m^2 DDP: 240 mg/m^2 I: 59·8 g/m^2 E: 1·5 g/m^2	8 doses 4 doses 4 doses 21 doses 15 doses	deletion Y chromosome
Ewing sarcoma (conventional osteosarcoma-osteoblastic, at diagnosis)	92603	5·7 years	MTX: 100 g/m^2 DOX: 304 mg/m^2 DDP: 241 mg/m^2 I: 60·5 g/m^2 E: 1·5 g/m^2	8 doses 4 doses 2 doses 5 doses 3 doses	t(6; 11; 22)-mediated EWSR1 gene rearrangement
Myelodysplasia	99873	2·1 years	MTX: 85·6 g/m^2 DOX: 147 mg/m^2 DDP: 113 mg/m^2 I: 14·0 g/m^2 E: 0·29 g/m^2	8 doses 4 doses 2 doses 6 doses 3 doses	
Myelodysplastic syndrome	99893	2·8 years	MTX: 71·0 g/m^2 DOX: 288 mg/m^2 DDP: 232 mg/m^2 I: 50·8 g/m^2 E: 0·98 g/m^2	6 doses 4doses 2 doses 5 doses 3 doses	
Thyroid carcinoma	80003	7·8 years	MTX: 92·5 g/m^2 DOX: 295 mg/m^2 DDP: 231 mg/m^2 I: 59·6 g/m^2 E: 1·5 g/m^2	8 doses 4 doses 2 doses 5 doses 3 doses	

Total ifosfamide dose includes doses at 14g/m^2/cycle and 9g/m^2/cycle.

Table S4: Comparison of second malignancy between MAPIE and MAP arms

	Main event **Second malignancy**	**Competing event** **Any other type of event** (local recurrence, new metastases, progression of existing metastases, death or a combination of events)
Cox model*	**Cause-specific HR (95%CI)**	**Cause-specific HR (95%CI)**
Treatment MAPIE vs MAP	3·24 (0·87-12·06), p=0·079	0·92 (0·73-1·15) p=0·46
Fine-Gray model+	**Sub-distribution HR (95%CI)**	**Sub-distribution HR (95%CI)**
Treatment MAPIE vs MAP	3·21 (0·87-11·85) p=0·081	0·91 (0·73-1·15) p=0·43

*proportionality of hazards tested: for the main event p=0·99, for the competing event p=0·0006
+proportionality not violated, tested with Schoenfeld-like residuals graph

Table S5: Subgroups analyses, Restricted Mean Survival Time by arm, with difference, 95%CI, number of patients and events

Exploratory subgroups	Restricted Mean Survival Time (months)				MAP		MAPIE	
	MAP	MAPIE	Difference (95% CI)	p-value	patients	events	patients	events
Gender								
Male	40·7	42·3	1·6 (-4·3; 7·6)	0·59	174	94	191	97
Female	46·6	47·0	0·4 (-6·2; 7·1)	0·90	136	59	117	57
Age*								
Child	45·0	50·6	5·6 (-2·9; 14·1)	0·20	91	43	77	30
Adolescent	41·2	42·2	1·0 (-5·8; 7·8)	0·77	126	65	156	81
Adult	44·6	40·8	-3·7 (-11·8; 4·4)	0·37	93	45	75	43
Site & location								
Proximal femur/humerus	31·3	37·0	5·7 (-7·3; 18·7)	0·39	43	28	34	22
Other limb site	44·9	45·5	0·6 (-3·7; 4·8)	0·80	253	120	257	121
Axial skeleton	n/a	n/a	n/a	n/a	14	5	17	11
Metastases status								
Non metastatic¥	46·66	46·71	0·05 (-4·7; 4·8)	0·98	265	118	276	129
Metastatic	23·1	26·6	3·5 (-7·6; 14·5)	0·54	45	35	32	25
Lung metastases								
No¥	45·9	46·3	0·4 (-4·2; 5·0)	0·86	272	124	280	132
Yes	23·8	29·0	5·2 (-6·3; 16·8)	0·37	38	29	28	22
Extra pulmonary metastases								
No	43·7	45·2	1·5 (-2·9; 5·9)	0·50	302	147	299	147
Yes	n/a	n/a	n/a	n/a	8	6	9	7

¥possible metastases were combined with no metastases
*age:
- **Child**: male 0–12 yrs; female 0–11 yrs;
- **Adolescent**: male 13–17 yrs; female 12–16 yrs;
- **Adult**: male 18 yrs or older; female 17 yrs or older

Collins M, Wilhelm M, Conyers R, et al: Benefits and adverse events in younger versus older patients receiving neoadjuvant chemotherapy for osteosarcoma: findings from a meta-analysis. J Clin Oncol 31:2303-2312, 2013

Positive RMST difference MAPIE-MAP presents a longer mean time to first event for MAPIE patients

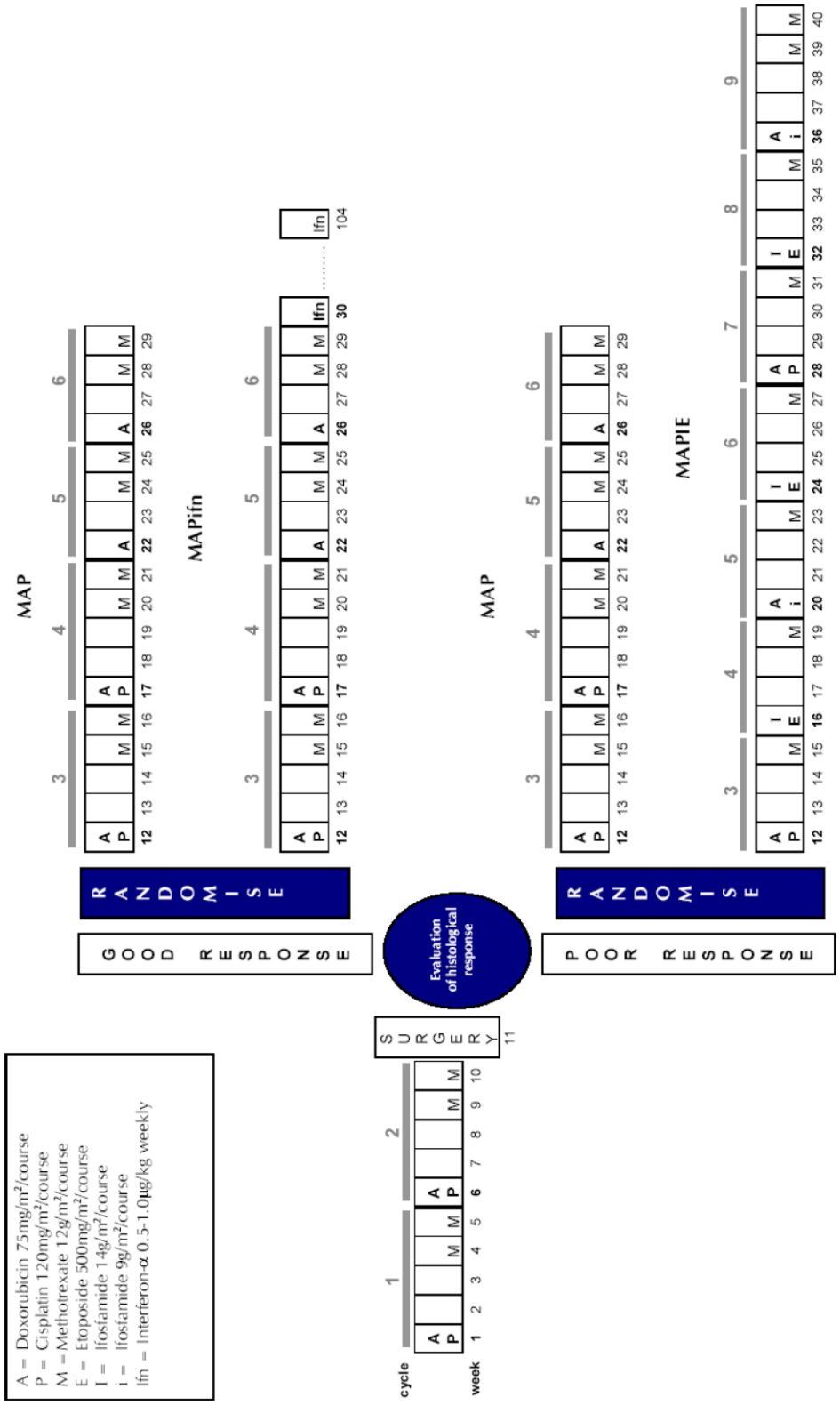
Table S6: Less common postoperative treatment toxicities by allocated treatment, grade 3 and 4.

Toxicity	MAP (n=301)				MAPIE (n=298)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	N	%	N	%	N	%	N	%
Anorexia	2	1%	0	0%	2	1%	0	0%
Dehydration	3	1%	0	0%	1	0%	0	0%
Haemorrhage pulmonary - nose	2	1%	0	0%	2	1%	0	0%
Wound complication, non-infectious	2	1%	0	0%	2	1%	0	0%
Fatigue	1	0%	0	0%	2	1%	0	0%
Fracture	2	1%	0	0%	1	0%	0	0%
Liver dysfunction	2	1%	0	0%	0	0%	1	0%
Syndromes – other	1	0%	0	0%	2	1%	0	0%
Aphasia or dysarthria	2	1%	0	0%	0	0%	0	0%
Colitis	1	0%	0	0%	1	0%	0	0%
Constipation	2	1%	0	0%	0	0%	0	0%
Device/prosthesis	1	0%	0	0%	1	0%	0	0%
DVT/Thrombosis/Embolism	1	0%	1	0%	0	0%	0	0%
Hypotension	1	0%	0	0%	0	0%	1	0%
Lipase	0	0%	0	0%	1	0%	1	0%
Renal/genitourinary - other (specify)	0	0%	0	0%	0	0%	2	1%
Syncope (fainting)	0	0%	0	0%	2	1%	0	0%
Weight loss	1	0%	0	0%	1	0%	0	0%
Blood/bone marrow - other (specify)	0	0%	1	0%	0	0%	0	0%
Bone marrow, other (infarction)	0	0%	1	0%	0	0%	0	0%
Decubitus	0	0%	1	0%	0	0%	0	0%
Dermatology/skin - other (specify)	1	0%	0	0%	0	0%	0	0%
Dyspnoea	0	0%	0	0%	1	0%	0	0%
Dystonic reaction	1	0%	0	0%	0	0%	0	0%
Hemiparesis	1	0%	0	0%	0	0%	0	0%
Infection of the prosthesis	0	0%	0	0%	1	0%	0	0%
Infection with normal ANC - blood	0	0%	0	0%	1	0%	0	0%
Joint-effusion	0	0%	0	0%	1	0%	0	0%
Musculoskeletal - other (post-operative	0	0%	0	0%	1	0%	0	0%
Neuropathy: cranial - CN II	0	0%	1	0%	0	0%	0	0%
Pancreatitis	1	0%	0	0%	0	0%	0	0%
Pneumonia (metapneumo virus)	0	0%	0	0%	1	0%	0	0%
Prolonged QTc	1	0%	0	0%	0	0%	0	0%
Supraventricular tachycardia	0	0%	0	0%	1	0%	0	0%
Ventricular arrhythmia - ventricular fibrillation	0	0%	1	0%	0	0%	0	0%

Note: This table supplements Table 3. This includes only adverse events that were reported spontaneously by sites.

=== SUPPLEMENTAL FIGURES ===

Figure S1: Treatment schedule



*Cisplatin and doxorubicin were administered at the same doses as given pre-operatively. Ifosfamide (high-dose) when combined with etoposide (3 post-operative cycles) was administered at 2.8g/m^2/day with mesna uroprotection (560 mg/m^2/dose) over 4 hours and etoposide at 100mg/m^2/day over 1 hour administered daily x 5 days. Two additional cycles of ifosfamide (standard dose) 3g/m^2/day with mesna uroprotection (600mg/m^2) daily for 3 days combined with standard doxorubicin. Growth factor support starting at least 24 hours was recommended after IE and DOX, I cycles, according to local practice e.g. filgrastim 5µg/kg or PEG-filgrastim 6mg subcutaneously.

=== SUPPLEMENTAL LISTS ===

List S1: EURAMOS-1 Investigators And Participants

EURAMOS-1: A randomised trial of the European and American Osteosarcoma Study Group to optimize treatment strategies for resectable osteosarcoma based on histological response to pre-operative chemotherapy is published in name of all the following collaborators:

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Viktoria Samuelsson	Statistician
Anna Bladtröm	Statistician
Thor Alvegård	TMG Member: Data Manager Supervisor
Jeanette Ceberg	Monitor
Christina Danewid	Monitor
Mercedes Marotta	Data Systems Engineer
Mona Malström	CRF Designer

Name	Role
Ole Sten Nielsen	National Co-ordinator: Denmark
Maija Tarkkanen	National Co-ordinator: Finland
Oskar Johansson	National Co-ordinator: Iceland
Mikael Eriksson	National Co-ordinator: Sweden
	Oncology panel
Thomas Wiebe	Oncology Panel
Åke Jakobson	Oncology Panel
Maija Tarkkanen	Oncology Panel
Ole Steen Nielsen	Oncology Panel
Tom Böhling*	Pathology review panel
Lars-Gunnar Kindblom*	Pathology review panel
Henryk Domanski	Pathology review panel
Bodil Bjerkehagen	Pathology review panel
Johan Wejde	Pathology review panel
Ola Myklebost	Biological Studies panel
Nils Mandahl	Biological Studies panel
Sakari Knuutila	Biological Studies panel
Otte Brosjö	Surgical panel
Ingeborg Taksdal*	Radiology panel
Veli Söderlund	Radiology panel
Øyvind Bruland	Radiotherapy panel
Linda Werner-Hartman	Statistics panel
Tor Skärby	Pharmacy panel

S1.5. Members of EURAMOS Intergroup Safety Desk (EISD)

Trude Butterfaß-Bahloul	TMG Member: Clinical Research Associate SAE, Safety Desk Manager
Heidi Oellers	TMG Member: Monitoring/Auditing
Marc Urban	TMG Member: Monitoring/Auditing
Karl-Friedrich Lukat	Clinical Research Associate SAE, Safety Desk Manager
Melanie Langeleist	Safety Desk Assistant
Dorothee Hülser	Safety Desk Assistant
Gudrun Würthwein	Data Management of Safety Database
Sonja Baier	Data Management of Safety Database
Attyla Drabik	Safety Desk Manager
Charlotte Young	Safety Desk Manager
Kirsten Werner	Safety Desk Manager
Andrea Paneitz	Safety Desk Manager
Ruth Wagner	Safety Desk Manager
Eva Grünewald	Safety Desk Manager
Christiana Rohde-Osei	Safety Desk Assistant
Kerstin Hovestadt	Safety Desk Assistant
Linus Lauterbach	Safety Desk Assistant

S1.6 Members Of Quality Of Life Coordinating Centre

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

List S1.7: Expert Panels

Oncology Panel

The oncology panels of each group checked the protocol for content, consistency and accuracy on all topics surrounding study medication. Members of each group's oncology panel were appointed to represent the group in the TMG and the TSC. Some groups offered or required consultation with named members of the oncology panel on issues surrounding chemotherapy.

Pathology review panel

The purpose of the Pathology Review Panel was to ensure that the histopathological criteria for admission to the trial and histological response to chemotherapy were assessed in a timely and consistent fashion for all trial groups participating in EURAMOS 1. Each of the participating groups formed a pathology sub-panel. Together, these form the pathology panel of the EURAMOS 1 trial. Each of the 4 collaborating groups named one representative pathologist to represent their group in intergroup discussions. These four elected one pathologist to represent pathology in the Trial Management Committee.

Pathology review was to be undertaken for all patients within the trial. Both the diagnostic biopsy and the resection specimen histology were to be reviewed by a study pathologist. The process of pathology review is detailed in the protocol.

Biological Studies panel

Parallel biological studies were performed in selected groups for this trial lead by the biological studies panel. The biological studies panel were responsible for the development of protocols within their trial group and for ensuring the use of uniform methodologies between groups to allow data comparability.

Surgical panel

The surgical panel issued guidance surrounding tumour resection and reconstruction. Some groups offered or required consultation with members of the surgical panel prior to tumour surgery.

Radiology panel

The radiology panel issued guidance surrounding imaging of the primary tumour and of metastatic disease. Members of the panel assisted in determining metastatic status. Review of thorax CT scans was undertaken by members of the trial management group in conjunction with a panel radiologist. Central review of chest CT scans was requested for patients registered as having (possible) metastatic disease and fulfilling the following criteria: no lesion greater than 1 cm or less than 3 lesions of any size.

Radiotherapy panel

The radiotherapy panel issued guidance surrounding radiotherapy for insufficient margins or inoperable relapse. Some groups offered or required consultation with members of the radiotherapy panel prior to irradiating a specific patient.

Statistics panel

The statistics panel was involved in all aspects of trial design, data storage and management, and evaluation.

List S2: Independent Members Of Independent Trial Oversight Committees

(a) Independent Data Monitoring Committee

Name	Role
Barry Hancock	Chair: Sheffield, UK
Gerald Gilchrist	Member: Minnesota, USA
Otilia Dalesio	Member: Amsterdam, NL
Peter Høglund	Member: Lund, Sweden

(b) Trial Steering Committee

Name	Role
Stefano Ferrari	Chair: Bologna, Italy
Joseph Mirro	Member: Memphis, USA
Hans Strander	Member: Stockholm, Sweden
Robert Souhami	Member: London, UK