

CONCEPT C: Concept Sheet for a Potential Trial Addressing an Unresolved Issue in Osteosarcoma

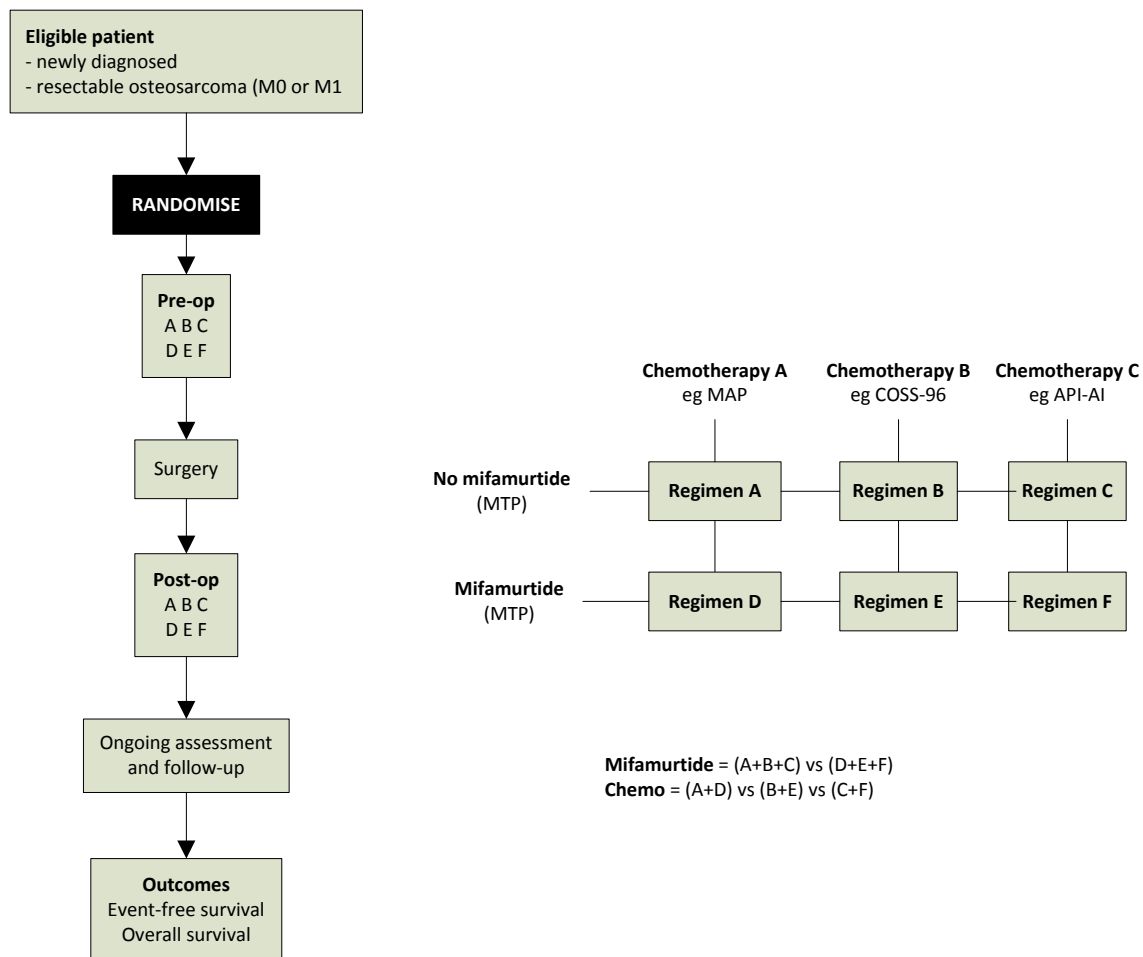
Proposers' names	Whelan, Bielack, Smeland, Sydes
Short title	[C] Randomised controlled factorial trial of combining standard chemotherapy regimens with or without MTP for osteosarcoma
Summary diagram	(See end of document)
Patient group (Summary only)	High grade osteosarcoma of the extremity or axial skeleton
Main eligibility criteria (Summary only)	<p><i>As per EURAMOS-1</i></p> <ol style="list-style-type: none"> 1. Histologically proven high grade osteosarcoma of the extremity or axial skeleton (including from second malignancies) 2. Resectable disease 3. Age up to 40 years 4. Registration within 30 days of diagnostic biopsy 5. Start chemotherapy within 30 days of diagnostic biopsy 6. Adequate neutrophils, platelets, GFR, bilirubin and cardiac function 7. Adequate performance status
Control treatment (Name, administration route, duration)	1. Neo-adjuvant 3-drug MAP (doxorubicin, cisplatin and high dose methotrexate) chemotherapy (as per AOST-0133 and EURAMOS-1). No mifamurtide
Research treatment(s) (Name, administration route, duration)	<ol style="list-style-type: none"> 2. Neo-adjuvant 3-drug MAP (doxorubicin, cisplatin and high dose methotrexate) chemotherapy (as per AOST-0133 and EURAMOS-1). Plus mifamurtide (for 36 weeks) from the start of chemotherapy. 3. 4-drug ifosfamide-containing chemotherapy (eg COSS-96) doxorubin, cisplatin, high-dose methotrexate and ifosfamide). No mifamurtide. 4. 4-drug ifosfamide-containing chemotherapy (eg COSS-96) doxorubin, cisplatin, high-dose methotrexate and ifosfamide). Plus mifamurtide (for 36 weeks) from the start of chemotherapy. 5. 3-drug non-methotrexate chemotherapy (eg API-AI: doxorubin, cisplatin and ifosfamide). No mifamurtide. 6. 3-drug non-methotrexate chemotherapy (eg API-AI: doxorubin, cisplatin and ifosfamide). Plus mifamurtide (for 36 weeks) from the start of chemotherapy.
Current knowledge (Known safety data and known	Mifamurtide is the only licensed drug for use in osteosarcoma and may become part of standard practice. The safety data are

activity data)	<p>well-reported.</p> <p>There are many potential regimens for chemotherapy. These have been used in individual trials but have not been compared directly, nor widely used in the context of mifamurtide. The activity and safety of these regimens (without mifamurtide) has been published.</p>								
Rationale (250 words max)	<p>There are many chemotherapy regimens considered standard around the world but the best regimen is not widely agreed. A standard of care in EURAMOS-1 is MAP (methotrexate, doxorubicin and cisplatin). Several regimens have published encouraging results and may warrant further investigation. These regimens should be compared in a definitive trial to assess which agent has the greater activity, particularly in the context of consistent use of mifamurtide, and short-term and long-term safety data can be prospectively collected (eg cardiac function, hearing loss, nephrotoxicity, fertility). Only be direct randomised comparison of these agents will the best approach be decided for the future.</p>								
Hypothesis (50 words max)	<p>One of the chemotherapy regimens will be shown better than the others given the totality of long-term efficacy and safety data.</p>								
Trial design	<table border="1"> <tr> <td data-bbox="536 969 608 1037"></td> <td data-bbox="608 969 1380 1037">Phase I</td> </tr> <tr> <td data-bbox="536 1037 608 1104"></td> <td data-bbox="608 1037 1380 1104">non-randomised Phase II, specify: _____</td> </tr> <tr> <td data-bbox="536 1104 608 1171"></td> <td data-bbox="608 1104 1380 1171">randomised phase II, specify: _____</td> </tr> <tr> <td data-bbox="536 1171 608 1245">X</td> <td data-bbox="608 1171 1380 1245">Phase III -- factorial</td> </tr> </table>		Phase I		non-randomised Phase II, specify: _____		randomised phase II, specify: _____	X	Phase III -- factorial
	Phase I								
	non-randomised Phase II, specify: _____								
	randomised phase II, specify: _____								
X	Phase III -- factorial								
Blinding	<table border="1"> <tr> <td data-bbox="536 1245 608 1312"></td> <td data-bbox="608 1245 1380 1312">Single blinding possible</td> </tr> <tr> <td data-bbox="536 1312 608 1379"></td> <td data-bbox="608 1312 1380 1379">Double blinding possible</td> </tr> <tr> <td data-bbox="536 1379 608 1451">X</td> <td data-bbox="608 1379 1380 1451">No blinding possible</td> </tr> </table>		Single blinding possible		Double blinding possible	X	No blinding possible		
	Single blinding possible								
	Double blinding possible								
X	No blinding possible								
Primary outcome measure	<p>Event-free survival (disease progression or death from any cause)</p>								
Secondary outcome measures	<p>Overall survival</p> <p>Toxicity</p> <p>Quality of life</p> <p>Acceptance of randomisation</p>								
Control arm event rate	<p>60 % EFS at 3 years</p> <p><i>(EURAMOS-1 assumes Good Responders have EFS of 70% at 3 years and Poor Responders have EFS of 45% at 3 years. If, like EURAMOS-1, 55% of patients are good responders, 3-year EFS will be about 60%)</i></p>								

	(60 % survival at 5 years)
Target difference	HR=0.80 is used for sample size calculations of chemo regimens HR=0.71 is used for sample size calculations of MTP
Accrual duration	4.5 years
Accrual rate / year	400 patients per year
Accrual total target	1757 patients for chemo comparison 774 patients for MTP comparison i.e. chemo comparison requires <i>many</i> more patients, meaning that the MTP comparison could be optional for some patients or that there would be additional power for subgroup analyses/interactions
Total trial duration	7 years
Need for international collaboration	Defining an internationally agreed standard chemotherapy for patients with osteosarcoma requires broad global input in order to have generaliseable and widely acceptable results. The role of MTP could be confirmed
Potential sub-studies	X Biology / translation
	X Qualify of life
	Other, specify:
Strengths	<ul style="list-style-type: none"> • Assesses the role of MTP • Defines the standard of care for future internationally collaborative trials • Randomisation performed before treatment starts • Arms diverge quickly after randomisation • Provides trials groups standard regimen to exposure by other groups • Broad accrual leads to internally acceptable results • MTP comparison well powered
Limitations	<ul style="list-style-type: none"> • Standard factorial trials ignore interactions. Powering for interactions greatly increases the number of patients required. • Requires agreement on which chemo regimens to use and which of those is considered “standard” • Does not address other promising agents

• Limited power for interactions of chemotherapy * MTP

Summary diagram



3-way chemo comparison: 400 patients per year; HR=0.80, power=80%

Chemo regimens (all without MTP) - superiority - 3-arm (factorial across MTP)
 HR=0.80 - assume MAP+MTP = standard as this is the known combination

ART - ANALYSIS OF RESOURCES FOR TRIALS (version 1.0.7, 19 October 2009)

A sample size program by Abdel Babiker, Patrick Royston & Friederike Barthel,
 MRC Clinical Trials Unit, London NW1 2DA, UK.

Type of trial	Superiority - time-to-event outcome
Statistical test assumed	Unweighted logrank test (local)
Number of groups	3
Allocation ratio	Equal group sizes
Global test	
Total number of periods	7
Length of each period	One year
Survival probs per period (group 1)	0.843 0.711 0.600 0.506 0.427 0.360 0.304
Survival probs per period (group 2)	0.873 0.762 0.665 0.580 0.506 0.442 0.385
Survival probs per period (group 3)	0.873 0.762 0.665 0.580 0.506 0.442 0.385
Number of recruitment periods	5
Number of follow-up periods	2
Method of accrual	Uniform
Recruitment period-weights	1 1 1 1 1 0 0
Hazard ratios as entered (groups 1, 2, 3)	1, .8, .8
Hazard ratios per period (group 1)	1.000 1.000 1.000 1.000 1.000 1.000 1.000
Hazard ratios per period (group 2)	0.800 0.800 0.800 0.800 0.800 0.800 0.800
Hazard ratios per period (group 3)	0.800 0.800 0.800 0.800 0.800 0.800 0.800
Alpha	0.050 (two-sided)
Power (designed)	0.800
Total sample size (calculated)	1757
Expected total number of events	830

Values given below apply to each group at the end of the trial

Unadjusted event probs (groups 1, 2, 3)	0.696, 0.615, 0.615
Unadjusted loss to follow-up probs	0.000, 0.000, 0.000
Unadjusted cross-over probabilities	0.000, 0.000, 0.000
*Expected numbers of events per group	306, 263, 263
Expected proportions with event	0.521, 0.448, 0.448
Expected proportions lost to follow-up	0.000, 0.000, 0.000
Expected proportions with cross-over	0.000, 0.000, 0.000

* Rounded to next whole number of events above the exact expected number

2-way MTP comparison: 400 patients per year; HR=0.70, power=90%

MTP - superiority - 2-arm (factorial across chemo)
HR=0.71 (as per the AOST-0133)

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MRC Clinical Trials Unit, London NW1 2DA, UK.

Type of trial	Superiority - time-to-event outcome
Statistical test assumed	Unweighted logrank test (local)
Number of groups	2
Allocation ratio	Equal group sizes
Total number of periods	7
Length of each period	One year
Survival probs per period (group 1)	0.843 0.711 0.600 0.506 0.427 0.360 0.304
Survival probs per period (group 2)	0.886 0.785 0.696 0.617 0.546 0.484 0.429
Number of recruitment periods	5
Number of follow-up periods	2
Method of accrual	Uniform
Recruitment period-weights	1 1 1 1 1 0 0
Hazard ratios as entered (groups 1,2)	1, .71
Hazard ratios per period (group 1)	1.000 1.000 1.000 1.000 1.000 1.000 1.000
Hazard ratios per period (group 2)	0.710 0.710 0.710 0.710 0.710 0.710 0.710
Alpha	0.050 (two-sided)
Power (designed)	0.900
Total sample size (calculated)	774
Expected total number of events	361

Values given below apply to each group at the end of the trial

Unadjusted event probs (groups 1,2)	0.696, 0.571
Unadjusted loss to follow-up probs	0.000, 0.000
Unadjusted cross-over probabilities	0.000, 0.000

*Expected numbers of events per group	202, 159
Expected proportions with event	0.521, 0.411
Expected proportions lost to follow-up	0.000, 0.000
Expected proportions with cross-over	0.000, 0.000

* Rounded to next whole number of events above the exact expected number