

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

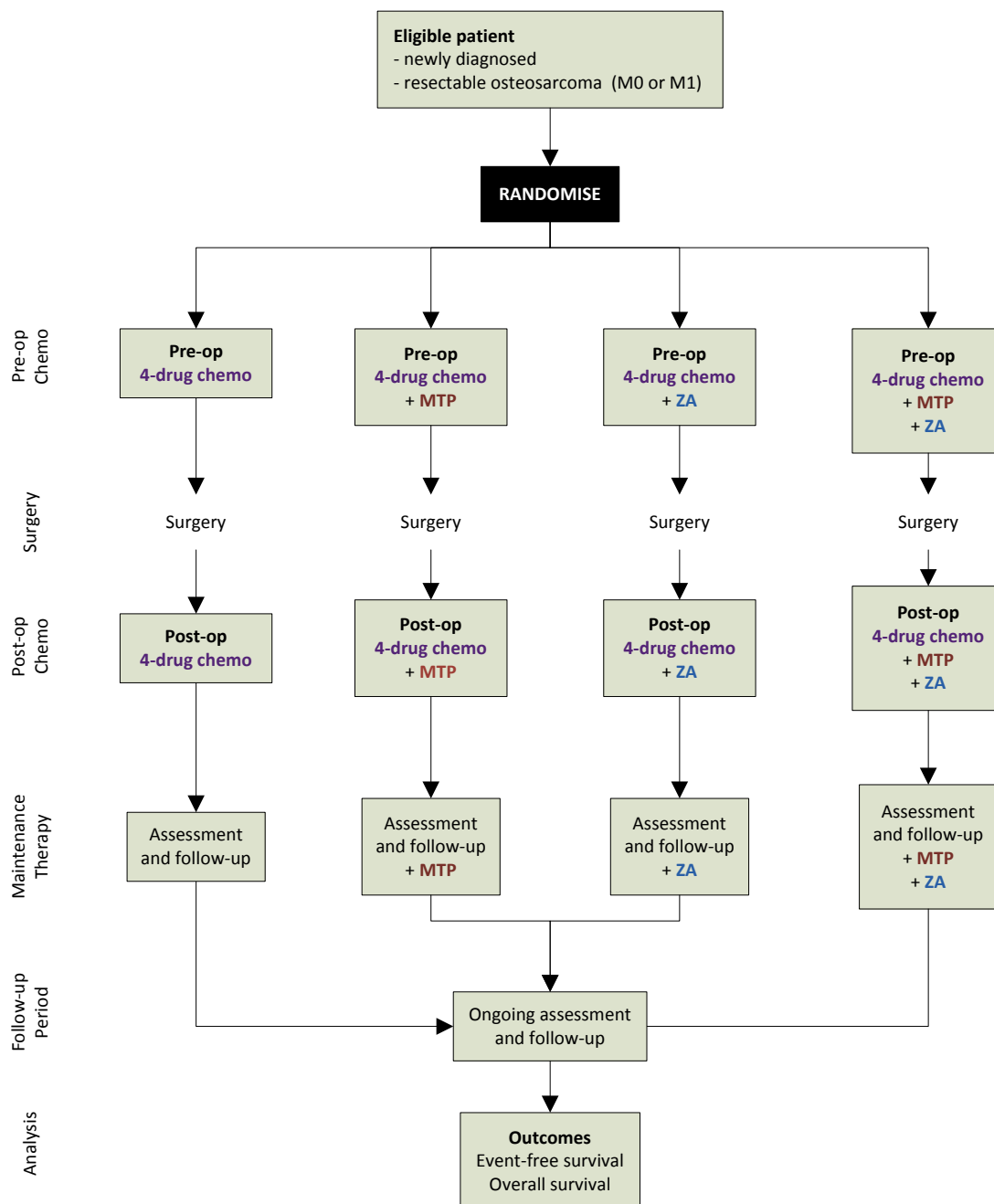
Proposers' names	Whelan, Bielack, Smeland, Sydes
Short title	[F] Multi-Arm Multi-Stage trial of mifamurtide (MTP) and zoledronic acid with 4-drug chemotherapy for osteosarcoma
Summary diagram	(See end of document)
Patient group (Summary only)	High grade osteosarcoma of the extremity or axial skeleton
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)	Neo-adjuvant chemotherapy with doxorubicin, cisplatin and high-dose methotrexate plus ifosfamide
Research treatment(s) (Name, administration route, duration)	<ol style="list-style-type: none"> 1. Addition of mifamurtide 2. Addition of zoledronic acid
Current knowledge (Known safety data and known activity data)	<ol style="list-style-type: none"> 1. Mifamurtide has shown results in the AOST-0133 trial which warrant further investigation. The safety data are well-reported. There is some preliminary evidence that MTP and ifosfamide may work synergistically and, therefore, this will be part of standard treatment. 2. Zoledronic acid is being assessed in many cancer sites which are at risk of bone disease and is included in the ongoing SFCE trial. The drug may have direct anti-tumour effects as well as bone-protecting effects. The toxicities are well-reported, but include instances of osteonecrosis of the jaw (ONJ).
Rationale (250 words max)	<ol style="list-style-type: none"> 1. The role of mifamurtide is considered worthy of further study by healthcare providers and there is a need to collect further high quality information on the use of this drug in order to assess its role. A hazard ratio of 0.67 would be targeted as a clinically relevant advantage that would justify changing to this treatment

	<p>(but a hazard ratio of 0.75 would be considered).</p> <p>2. Zoledronic acid is an interesting agent that shows activity in many bone diseases and is, therefore, of potential use in patients with osteosarcoma. A hazard ratio of 0.67 would be targeted as a clinically relevant advantage that would justify changing to this treatment (but a hazard ratio of 0.75 would be considered).</p> <p>3. The trial would use novel multi-arm multi-stage methods. The 3-drug chemotherapy arm would be considered the control arm. In a series of intermediate analyses, each of the 3 research arms would be compared pairwise with only the control arms. Recruitment would be stopped early to any research arm that is not showing sufficient relative activity (lack-of-benefit analyses); follow-up would, of course, continue and all arms would be included in the final comparisons. By using this adaptive design, limited resources for trials become focused on the most encouraging arms. This approach has been used successfully in other cancers eg prostate, ovarian. This is not a factorial design. No assumptions are made about the presence of any interactions. Research arms that are better than the control arm would be directly compared at the end of the trial.</p>								
Hypothesis (50 words max)	The addition of mifamurtide or zoledronic acid may each improve outcomes for patients with osteosarcoma. Mifamurtide may work better in the context of ifosfamide-containing chemotherapy.								
Trial design	<table border="1"> <tr> <td></td> <td>Phase I</td> </tr> <tr> <td></td> <td>non-randomised Phase II, specify: _____</td> </tr> <tr> <td></td> <td>randomised phase II, specify: _____</td> </tr> <tr> <td>X</td> <td>Phase III == MAMS design</td> </tr> </table>		Phase I		non-randomised Phase II, specify: _____		randomised phase II, specify: _____	X	Phase III == MAMS design
	Phase I								
	non-randomised Phase II, specify: _____								
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X	Phase III == MAMS design								
Blinding	<table border="1"> <tr> <td></td> <td>Single blinding possible</td> </tr> <tr> <td></td> <td>Double blinding possible</td> </tr> <tr> <td>X</td> <td>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	Event-free survival (disease progression or death from any cause) (Overall survival)								
Secondary outcome measures	Overall survival Toxicity Quality of life Acceptance of randomisation								

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> <p>(60 % survival at 5 years)</p>	
Target difference	HR=0.67 is used for sample size calculations	
Accrual duration	4.2 to 6.4 years (depending on the target difference) (could set maximum duration of 5 years)	
Accrual rate / year	<p>400 patients per year internationally</p> <p><i>(EURAMOS-1 is registering 400 patients per year)</i></p>	
Accrual total target	<p>1688-2573 patients</p> <p>(Depending on accrual rate and the number of arms recruiting)</p> <p><i>(EURAMOS-1 will register 2000 patients)</i></p>	
Total trial duration	<p>4.2 to 6.4 years (depending on accrual rate and how many arms stop recruitment early)</p> <p>(Note: a hazard ratio of 0.75 would take 2 to 3 years longer)</p>	
Need for international collaboration	<p>This efficient trial will answer two of the most important questions for patients with osteosarcoma in an relatively short period. The results would change practice. However, the number of patients required and the rate of accrual required are high in order to obtain the efficiencies offered. No one country or group could attain the necessary rate of accrual alone. Therefore, these questions could all be addressed only with broad, enthusiastic and committed collaboration.</p>	
Potential sub-studies	X	Biology / translation
	X	Qualify of life
		Other, specify:
Strengths	<ul style="list-style-type: none"> • Uses efficient multi-arm multi-stage (MAMS) methods to address the questions • Answers two important questions: use of MTP, use of bisphosphonates • If a single trial to answer one of these questions takes 4 to 5 years (initiation, recruitment, treatment, analysis, publication) , then answering all three questions separately would take 12 to 15 years. This study promptly addresses all of these questions and 	

	<p>will save 7 to 11 years.</p> <ul style="list-style-type: none">• Randomisation performed before treatment starts• Arms diverge quickly after randomisation• Designed as a 4-arm trial: does not assume that there are no interactions• Focuses resources on the arms showing the most promise• High chance of being allocated to a research arm (say, 3/5) which would likely appeal to patients
Limitations	<ul style="list-style-type: none">• Requires agreement on which chemo regimens to use – assumes the use of ifosfamide• Does not address what is the optimal start time of MTP nor ZA• Does not address the optimal duration of MTP nor ZAs• Requires a good collaboration, likely ~400 patients / year to provide answer in reasonable timeframe• Innovative methods might be off-putting to any more conservative researchers

Summary diagram



Scenario 1: 400 patients per year, no arms stop early; HR=0.67

Start with 4 arms - drop none - 2:1:1:1:1:1:1 ratio
 HR=0.67

N-STAGE TRIAL DESIGN version 2.1.0, 28 August 2009

A sample size program for n-stage trial designs by Friederike Barthel & Patrick Royston, based on Royston, Barthel, Parmar and Oskooei (2009)

OPERATING CHARACTERISTICS

DESIGN FOR 4 STAGES

NOTE: I-OUTCOME AND D-OUTCOME ARE IDENTICAL

MEDIAN SURVIVAL TIME: 4.1 TIME UNITS

	Alpha(1S)	Power	HR H0	HR H1	Crit. HR	Length*	Time
STAGE 1	0.5000	0.942	1.000	0.670	1.000	2.192	2.192
STAGE 2	0.3000	0.941	1.000	0.670	0.912	0.695	2.887
STAGE 3	0.1000	0.940	1.000	0.670	0.844	1.051	3.938
STAGE 4	0.0250	0.901	1.000	0.670	0.794	0.550	4.488
Overall**	0.0207	0.841				4.488	

Note: patient accrual stopped at time 5.000

* Length (duration of each stage) is expressed in one year periods

** Correlations between hazard ratios estimated internally by the program

SAMPLE SIZE AND NUMBER OF EVENTS

	-----STAGE 1-----			-----STAGE 2-----		
	Overall	Control	Exper.	Overall	Control	Exper.
Arms	4	1	3	4	1	3
Acc. rate	400	160	240	400	160	240
Patients*	877	351	526	1155	462	693
Events**	121	58	63	202	97	105

	-----STAGE 3-----			-----STAGE 4-----		
	Overall	Control	Exper.	Overall	Control	Exper.
Arms	4	1	3	4	1	3
Acc. rate	400	160	240	400	160	240
Patients*	1575	630	945	1795	718	1077
Events**	357	171	186	453	216	237

.5 patients allocated to each E arm for every 1 to control arm.

* Patients are cumulative across stages

** Events are cumulative across stages, but are only displayed for those arms to which patients are still being recruited

** Events are for the same outcome at all 4 stages

Scenario 2: 400 patients per year, some arms stop early; HR=0.67

Start with 4 arms - drop some - 2:1:1:1:1:1:1 ratio
HR=0.67

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OPERATING CHARACTERISTICS

DESIGN FOR 4 STAGES

NOTE: I-OUTCOME AND D-OUTCOME ARE IDENTICAL

MEDIAN SURVIVAL TIME: 4.1 TIME UNITS

	Alpha(1S)	Power	HR H0	HR H1	Crit. HR	Length*	Time
STAGE 1	0.5000	0.942	1.000	0.670	1.000	2.192	2.192
STAGE 2	0.3000	0.941	1.000	0.670	0.912	0.671	2.863
STAGE 3	0.1000	0.941	1.000	0.670	0.844	0.925	3.788
STAGE 4	0.0250	0.900	1.000	0.670	0.794	0.434	4.222
Overall**	0.0207	0.841				4.222	

Note: patient accrual stopped at time 5.000

* Length (duration of each stage) is expressed in one year periods

** Correlations between hazard ratios estimated internally by the program

SAMPLE SIZE AND NUMBER OF EVENTS

	-----STAGE 1-----			-----STAGE 2-----		
	Overall	Control	Exper.	Overall	Control	Exper.
Arms	4	1	3	3	1	2
Acc. rate	400	160	240	400	200	200
Patients*	877	351	526	1145	485	660
Events**	121	58	63	167	97	70

	-----STAGE 3-----			-----STAGE 4-----		
	Overall	Control	Exper.	Overall	Control	Exper.
Arms	2	1	1	2	1	1
Acc. rate	400	267	133	400	267	133
Patients*	1516	732	784	1688	847	841
Events**	234	172	62	294	216	78

.5 patients allocated to each E arm for every 1 to control arm.

* Patients are cumulative across stages

** Events are cumulative across stages, but are only displayed for those arms to which patients are still being recruited

** Events are for the same outcome at all 4 stages

Scenario 3: 400 patients per year, no arms stop early; HR=0.75

Start with 4 arms - drop none - 2:1:1:1:1:1:1:1 ratio
HR=0.75

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OPERATING CHARACTERISTICS

DESIGN FOR 4 STAGES

NOTE: I-OUTCOME AND D-OUTCOME ARE IDENTICAL

MEDIAN SURVIVAL TIME: 4.1 TIME UNITS

	Alpha(1S)	Power	HR H0	HR H1	Crit. HR	Length*	Time
STAGE 1	0.5000	0.940	1.000	0.750	1.000	2.982	2.982
STAGE 2	0.3000	0.941	1.000	0.750	0.934	1.045	4.027
STAGE 3	0.1000	0.940	1.000	0.750	0.883	1.558	5.585
STAGE 4	0.0250	0.900	1.000	0.750	0.845	0.849	6.434
Overall**	0.0204	0.839				6.434	

Note: patient accrual stopped at time 8.000

* Length (duration of each stage) is expressed in one year periods

** Correlations between hazard ratios estimated internally by the program

SAMPLE SIZE AND NUMBER OF EVENTS

	-----STAGE 1-----			-----STAGE 2-----		
	Overall	Control	Exper.	Overall	Control	Exper.
Arms	4	1	3	4	1	3
Acc. rate	400	160	240	400	160	240
Patients*	1193	477	716	1610	644	966
Events**	226	103	123	391	178	213

	-----STAGE 3-----			-----STAGE 4-----		
	Overall	Control	Exper.	Overall	Control	Exper.
Arms	4	1	3	4	1	3
Acc. rate	400	160	240	400	160	240
Patients*	2234	894	1340	2573	1029	1544
Events**	701	317	384	896	404	492

.5 patients allocated to each E arm for every 1 to control arm.

* Patients are cumulative across stages

** Events are cumulative across stages, but are only displayed for those arms to which patients are still being recruited

** Events are for the same outcome at all 4 stages

Scenario 4: 400 patients per year, some arms stop early; I=EFS (HR=0.67), D=survival (HR=0.75)

N-STAGE TRIAL DESIGN

version 2.1.0, 28 August 2009

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OPERATING CHARACTERISTICS

DESIGN FOR 4 STAGES

MEDIAN SURVIVAL TIME (I-OUTCOME): 4.1 TIME UNITS

MEDIAN SURVIVAL TIME (D-OUTCOME): 6.8 TIME UNITS

	Alpha(1S)	Power	HR H0	HR H1	Crit. HR	Length*	Time
STAGE 1	0.5000	0.942	1.000	0.670	1.000	2.192	2.192
STAGE 2	0.3000	0.941	1.000	0.670	0.912	0.695	2.887
STAGE 3	0.1000	0.940	1.000	0.670	0.844	1.051	3.938
STAGE 4	0.0250	0.900	1.000	0.750	0.845	4.067	8.005
Overall I**	0.0080	0.809				8.005	
Lowest	0.0020	0.793					
Highest	0.0250	0.900					
I-stages	0.0809	0.881					

Note: patient accrual stopped at time 8.000

* Length (duration of each stage) is expressed in one year periods

** Correlations between hazard ratios estimated internally by the program assuming corhr(), correlation between hazard ratios on I & D, is 0.60

SAMPLE SIZE AND NUMBER OF EVENTS

	-----STAGE 1-----			-----STAGE 2-----		
	Overall	Control	Exper.	Overall	Control	Exper.
Arms	4	1	3	4	1	3
Acc. rate	400	160	240	400	160	240
Patients*	877	351	526	1155	462	693
Events**	121	58	63	202	97	105

	-----STAGE 3-----			-----STAGE 4-----		
	Overall	Control	Exper.	Overall	Control	Exper.
Arms	4	1	3	4	1	3
Acc. rate	400	160	240	400	160	240
Patients*	1575	630	945	3200	1280	1920
Events**	357	171	186	892	406	486

.5 patients allocated to each E arm for every 1 to control arm.

* Patients are cumulative across stages

** Events are cumulative across stages, but are only displayed for those arms to which patients are still being recruited

** Events are for I-outcome at stages 1 to 3, D-outcome at stage 4