

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

Proposer's name	Richard Gorlick, Rob Goldsby, Neyssa Marina
Short title	[D] A four arm, phase 3 randomized trial of methotrexate, adriamycin and cisplatin (MAP) versus MAP with MTP-PE versus MAP with zoledronic acid versus MAP with MTP-PE and zoledronic acid for newly diagnosed, localized osteosarcoma in children, adolescents and young adults.
Summary diagram	(See end of document)
Patient group (Summary only)	Newly diagnosed, localized osteosarcoma
Main eligibility criteria (Summary only)	<p>Patients with newly diagnosed, high grade, biopsy proven, localized osteosarcoma. Patients must have normal organ function.</p> <p>Patients must have adequate cardiac function. Patients must have normal renal function as defined by a creatinine <1.5 X normal for age and a GFR > 100 ml/min/1.73 m². Patients must have adequate liver function and performance status. Informed written consent according to institutional guidelines must be obtained prior to entry on study. The treating physician and the patient or patient's family must be committed to resection of the primary site following completion of the induction phase of treatment.</p> <p>The Following Patients Are Not Eligible For This Study. Patients with osteosarcoma that arises in areas of Paget's disease. Patients who have received previous chemotherapy or radiation therapy. Pregnant or breast-feeding women will not be entered on this study due to the risks of fetal toxicities and teratogenic effects of doxorubicin and methotrexate in humans and of dexrazoxane in animals. Patients with known HIV infection are excluded from the study. HIV testing is not required for study entry. Patients with osteosarcoma of the jaw. Patients with extra-osseous osteosarcoma.</p>
Control treatment (Name, administration route, duration)	<p>1) MAP as per EURAMOS1</p> <p>C = cisplatin 60 mg/m²/d x 2 days, A = adriamycin 37.5 mg/m²/d X 2 days</p> <p>M = methotrexate 12 grams/m² with leukovorin rescue</p>
Research treatment(s) (Name, administration route, duration)	<p>Three experimental arms</p> <p>2) MAP + MTP-PE MTP-PE 2 mg/m²</p> <p>3) MAP + ZA</p> <p>ZA = zoledronic acid: dose administered iv over at least 15 minutes</p>

	4) MAP + ZA + MTP-PE	
Current knowledge (Known safety data and known activity data)	Phase 1/2 dose escalation study of zoledronate in newly diagnosed patients in combination with ifosfamide/etoposide and MAP chemotherapy in patients with newly diagnosed metastatic osteosarcoma underway in COG	
Rationale (250 words max)	<p>We propose a randomized phase III trial comparing standard chemotherapy to standard therapy with and without MTP-PE with and without zoledronic acid. This will be a weighted randomization with fewer patients being randomized to the standard therapy alone arm. The need to include the standard therapy alone arm is to ensure that the outcome of this group is comparable to similarly treated historical control and verify that there has not been temporal drift in survival. We will analyze the histologic response and EFS with and without zoledronic acid. We will assess the utility and value of sampling bone resorption markers and determine if they have utility in predicting response. We will include an evaluation of PET scanning and look to see if there are any long-term consequences of zoledronic acid on the maintenance of endoprosthesis health.</p> <p>The goal would be to prepare this study to start as soon as the current study, AOST0331, closes. The strengths of this proposal relates to the known availability of the agent, the known safety profile of the agent (and we will know the MTD when combined with osteosarcoma based chemotherapy), and the substantial preclinical data demonstrating direct anti-cancer and, more importantly, anti-osteosarcoma activity of zoledronic acid. If zoledronic acid proves to provide a benefit and the toxicity is low as expected, it would be incorporated into the backbone of future investigations.</p>	
Hypothesis (50 words max)	<ul style="list-style-type: none"> -Examine whether the addition of MTP-PE with and without zoledronic improves event free survival and overall survival in patients with newly diagnosed, localized osteosarcoma compared to those treated with MAP chemotherapy alone. -To assess the histologic response in patients with osteosarcoma treated with standard chemotherapy with MTP-PE and zoledronic acid versus patients treated with standard chemotherapy alone. -To determine incidence of elevated bone resorption markers (especially urinary n-telopeptide) at baseline and evaluate if there is a change with therapy (analyzed at baseline, end of induction (pre-op), and end of therapy). -To evaluate if zoledronic acid reduces long-term complications of limb salvage surgery. 	
Trial design		Phase I

		non-randomised Phase II, specify: _____
		randomised phase II, specify: _____
	X	Phase III
Blinding		Single blinding possible
		Double blinding possible
	X	No blinding possible
Primary outcome measure	Survival	
Secondary outcome measures	Histologic response, biochemical markers, surgical complications	
Control arm event rate	40 % events at 5 years	
Accrual duration		
Accrual rate / year	150 year/COG alone	
Accrual total target		
Total trial duration		
Need for international collaboration		
Potential sub-studies	X	Biology / translation
	X	Qualify of life
		Other, specify:
Strengths	Feasibility and Safety Data Available, will address outstanding MTP-PE uncertainty	
Limitations	Will MTP-PE be possible to randomise, re-addresses some prior questions	

Summary diagram

Treatment schema

Standard Arm

Week	1	4	5	6	9	10	Primary site surgery	12	15	16	17	20	21	22	24	25	26	28	29
Biopsy	C/A	M	M	C/A	M	M		C/A	M	M	C/A	M	M	A	M	M	A	M	M

Experimental Arms

Week	1	4	5	6	9	10	Primary site surgery	12	15	16	17	20	21	22	24	25	26	28	29
Biopsy	C/A	M	M	C/A	M	M		C/A	M	M	C/A	M	M	A	M	M	A	M	M

MTP-PE TWICE A WEEK (week12-23)	MTP-PE ONCE A WEEK (week 24 -36)
---	--

Week	1	4	5	6	9	10	Primary site surgery	12	15	16	17	20	21	22	24	25	26	28	29
Biopsy	C/A-ZA	M	M	C/A-ZA	M	M		C/A-ZA	M	M	C/A-ZA	M	M	A-ZA	M	M	A-ZA	M	M

MTP-PE TWICE A WEEK (week12-23)	MTP-PE ONCE A WEEK (week 24 -36)
---	--

C = cisplatin60 mg/m2/d x2 days, A = adriamycin 37.5 mg/m2/d X 2 days with dexrazoxane 375 mg/m2 before each dose
 M = methotrexate 12 grams/m2 with leukovorin rescue, ZA = zoledronic acid:dose administered iv over at least 15 minutes
 MTP-PE 2 mg/m2