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

Proposer's name and Group	J Whelan and S Strauss, London Sarcoma Service, UCLH
Short title	Randomised phase II study of ridaforolimus (mTOR inhibitor) vs ridaforolimus and dalotuzumab (IGFR-1 antibody) in osteosarcoma
Summary diagram	(See end of document)
Patient group **(Summary only)**	Recurrent or refractory osteosarcoma
Main eligibility criteria **(Summary only)**	<u>Inclusion</u> • histologically confirmed osteosarcoma • Recurrent/refractory disease for whom no curative treatment exists. • Patients must have received methotrexate, adriamycin, cisplatin and ifosfamide chemotherapy. • Age > 12 years • ECOG Performance Status 0-1 • Measurable disease by RECIST criteria • Normal organ function <u>Exclusion</u> • No prior IGFR1 inhibitors • No prior mTOR inhibitors • Clinically Significant unrelated disease • Uncontrolled diabetes • Symptomatic brain metastases • Other malignant disease within 5 years • Pregnancy, breastfeeding
Control treatment **(Name, administration route, duration)**	none
Research treatment(s) **(Name, administration route, duration)**	Doses to be determined from results of current phase I study of the combination: *Ridaforolimus (mTOR inhibitor):*

	Dalotuzumab (IGFR-1 inhibitor): Continue until disease progression or unacceptable toxicity.
Current knowledge **(Known safety data and known activity data)**	**Ridaforolimus:** well documented safety profile from phase II and phase III clinical trials. Main toxicities are stomatitis, and myelosuppression. **Activity**: RECIST confirmed responses observed in patients with recurrent/ metastatic osteosarcoma on phase II clinical trial (Mita, et al. Proc ASCO, 2008). Results from placebo-controlled randomised phase III study of maintenance therapy in metastatic sarcoma are awaited. This study included a small cohort of patients with osteosarcoma. **Dalotuzumab**: Safety from phase I and phase 2 studies. Well tolerated. Most common toxicity is 10% incidence of hyperglycaemia. No clinical activity studies performed as single agent in osteosarcoma. **Ridaforolimus + dalotuzumab:** Currently in phase I in advanced malignancy (www.clinicaltrials.gov/ NCT00730379). DLT and MTD to be established.
Rationale **(250 words max)**	Osteosarcoma is a rare primary malignancy of bone. Adjuvant chemotherapy increases cure rates over those achieved with surgery alone from <20% to between 60-70%. The limits of conventional chemotherapy in achieving cure have now been reached as judged by the very limited improvement in survival rates over the past two decades. Thus new therapeutic targeted agents are required. The insulin growth factor (IGF) system may play an important role in osteosarcoma. IGF levels are at their highest in adolescence when the incidence of osteosarcoma peaks and numerous studies have shown that OS cell lines and tumors express the IGF-1R, depend upon IGF-I ligand for growth and survival, and are growth inhibited with IGF-1R blockade. Early clinical trials using IGFR-1 antibodies have demonstrated anti-tumour action in patients with sarcomas. Results from phase II studies that included patients with osteosarcoma are awaited. The mTOR pathway, which can be activated by IGF1-R signaling (as well as other mechanisms of PI3K activation) also appears to play a significant role in sarcoma growth and the phase II trials of ridaforolimus have demonstrated very encouraging efficacy in bone sarcomas. There is pre-clincal evidence to suggest that tumour cells may develop resistance to mTOR blockade via feedback activation of Akt, thereby attenuating anti-tumour effects. Pre-treatment with IGFR-inhibitors which block this feedback activation may enhance the effect of mTOR inhibition or may overcome the

	resistance of some tumours to mTOR inhibitors. There is therefore a good rationale for combining these two agents. Patients with recurrent or refractory osteosarcoma after treatment with the known active chemotherapy agents have a poor prognosis. These patients will be treated with the study drugs to establish whether there is sufficient clinical activity to consider how they may be added to adjuvant chemotherapy.	
Hypothesis **(50 words max)**	IGFR and mTOR signalling are known to be active in osteosarcoma. What is the activity of mTOR inhibition against osteosarcoma? Does the combination of ridaforolimus and dalotuzumab have additional clinical activity in patients with osteosarcoma with acceptable toxicity?	
Trial design		Phase I
		non-randomised Phase II, specify:
	X	randomised phase II, specify:
		Phase III
Blinding		Single blinding possible
		Double blinding possible
	X	No blinding possible
Primary outcome measure	Overall Response Rate (RECIST),	
Secondary outcome measures	Progression Free Survival , Overall survival, PET response, biologic response	
Control arm event rate	____ % events at ____ years	
Accrual duration		
Accrual rate / year		
Accrual total target	50	
Total trial duration		
Need for international collaboration	yes	
Potential sub-studies	x	Biology / translation :eg: PD, PK, PET, circulating tumour DNA

		Qualify of life
		Other, specify:

Summary diagram

(Insert picture below or on next page)