ToTem ASCO abstract draft

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ToTem: a Phase Ib trial of temisirolimus with gemcitabine and cisplatin

Background: a combination of gemcitabine (G) and cisplatin (C) is a standard-of-care, systemic anti-cancer therapy regimen for neoadjuvant treatment of muscle-invasive and palliative treatment of advanced bladder cancer (BC). There is a pressing need for more effective chemotherapy regimens, but there have been no significant improvements on this regimen for more than a decade. mTOR is a rational target for treatment of bladder cancer, as abnormalities are commonly observed in mTOR's upstream activators or downstream effectors, within the PI3K/Akt/mTOR signaling pathway. We have therefore performed a Phase Ib trial, combining escalating doses of the mTOR inhibitor, temsirolimus (T) with GC.
Methods: following regulatory and ethical approvals, eligible patients with advanced malignancy were treated with escalating doses of intravenous (IV) temsirolimus (T) in combination with fixed doses of IV GC, in a 21-day cycle. Previous unpublished data suggest a possible interaction between G and T. We therefore pursued a cautious dose escalation strategy, as in the table below, as a precaution against excessive toxicity.

Cohort	Cisplatin (Day 1)	Gemcitabine (Day 1, 8)	Temsirolimus				
			D1	D2	D8	D9	D15
1	70 mg/m^2	1000 mg/m^2					10mg
2	70 mg/m^2	1000 mg/m^2			10mg		10mg
3a	70 mg/m^2	1000 mg/m^2	10mg		10mg		10mg
3b	70 mg/m^2	1000 mg/m^2		10mg		10mg	10mg

Results: 14 patients have been treated, at 4 dose schedules in 2 UK centres. There have been no treatment-related deaths or SUSARs. There were 14 SAEs, of which 4 were SARs, in 10 individuals, 7 of whom had received IMP. Addition of 10mg T on days 15, then 8 and 15 was tolerated, but DLTs were encountered when administering three 10mg doses of T, both on days 1, 8 and 15 (neutropenia; hypokalaemia) and days 2, 9 and 15 (febrile neutropenia; rash).
Conclusions: it has not been feasible to add three, weekly doses of T to GC, even at low T doses, in the patient group tested, because of predominantly haematological toxicity. Forthcoming pharmacokinetic analyses will inform a planned amendment to the scheduling of T in combination with GC

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