Chemosensitization of Carboplatin by NOX66

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BACKGROUND

The experimental anti-cancer drug Idronoxil is a first-in-class inhibitor of the oncogene external NADH oxidase Type 2 (ENOX2). ENOX2 maintains the trans-membrane electron potential of the cancer cell plasma membrane, with loss of that potential disrupting a wide range of functions of the plasma membrane. Inhibition of sphingosine kinase is a major outcome, resulting in loss of a range of pro-survival signalling pathways, notably PI3K and Akt, and consequent loss of function of DNA repair enzymes including PARP 1 and topoisomerases 1 and 2.

Since 2001, idronoxil has been under development as a chemo-sensitiser, utilising its ability to block repair of DNA damage, seeking to convert sub-lethal drug-induced damage into unrepairable, lethal damage. In vitro and in vivo (mouse xenografts), idronoxil sensitises by typically 2000-fold the cytotoxic effects of standard cytotoxic drugs including cisplatin, carboplatin, paclitaxel, gemcitabine, toptecan, doxorubicin and captothecin.

Despite earlier clinical studies of oral and intravenous dosage formulations of idronoxil showing that the drug had significant pharmacokinetic problems including a relatively short half-life (45 minutes) and being subject to extensive Phase 2 metabolism, idronoxil was taken into Phase 2 and Phase 3 studies as a sensitiser of carboplatin in patients with carboplatin-refractory ovarian cancer, with the Phase 3 study abandoned in 2009 due to lack of efficacy. Subsequent understanding of the MoU of idronoxil suggests that (i) optimal biological effect requires constant rather than intermittent presence of the drug, and (ii) that idronoxil Phase 2 metabolites are irreversibly inactive in terms of anti-cancer activity.

NOX66 is a novel dosage formulation of idronoxil designed to protect the drug from Phase 2 metabolism and to extend its half-life (from 45 minutes to > 8 hours).

Here we describe the design of the first-in-human study of NOX66 as a monotherapy and in combination with carboplatin in patients with end-stage solid tumours.

STUDY OVERVIEW

This s a Phase I open label, 2 -step dose escalation study of NOX66, a suppository formulation, in patients with refractory solid tumours.

- Tumours selected for 5 phenotypes: breast, head and neck, lung, prostate and ovarian.
- The study comprises 2 stages of assessment:
  - Monotherapy: a single 21 day cycle where NOX66 is administered for daily for 14 days, with idronoxil levels measured throughout
  - Combination therapy: Up to 6 x 28 day cycles where NOX66 is administered 1 day prior to IV carboplatin and continues for 7 consecutive days. Patients start on low dose (AUC4) carboplatin for 3 cycles and progress to standard dose (AUC6) for a further 3 cycles, following safety and initial efficacy assessment.
- Total 16 evaluable patients: n=8 allocated to 400mg NOX66 dosage Cohort 1;n=8 allocated to 800mg dosage Cohort
- Patient assessed for safety parameters
- Preliminary response on CT images by investigator per RECIST 1.1 at 3 months (Cycle 3) and 6 months (end cycle 6)

STUDY OBJECTIVES

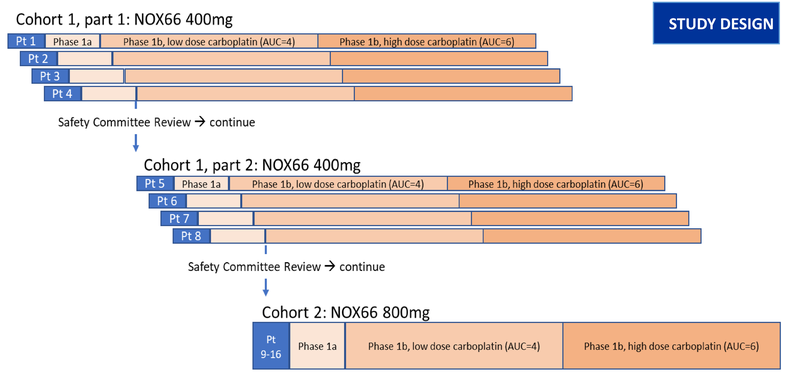
The primary objectives of this study are to determine:

- tolerability, adverse event profile, maximum tolerated dose (MTD), and dose-limiting toxicities (DLTs) of NOX66 in patients with refractory solid tumours, both as a single agent and in combination with carboplatin
- The ability of NOX66 to combine with a standard dosage of carboplatin to produce a meaningful anti-cancer effect in solid tumours considered to be refractory to cytotoxic chemotherapy
- The abilioty of NOX66 to combine with dosage of carboplatin two-thirds of the standard dosage to produce a meaningful anti-cancer effect in solid tumours considered to be refractory to cytotoxic chemotherapy.

Key secondary objectives are:

- to characterise some key pharmacokinetic features of NOX66
- to assess potential biomarkers of idronoxil biologic activity

STUDY DESIGN



KEY Inclusion criteria	KEY Exclusion criteria
Histologically confirmed locally or metastatic advanced solid tumours	Tumour involvement Central Nervous System
At least 1 measurable lesion on CT or MRI scan	Patients who are breastfeeding or pregnant
ECOG performance scale of 0-1	Clinically significant uncontrolled cardiac disease or myocardial infarction within last 12 months; QTc of >470 msec on screening ECG
Adequate heamatologic, hepatic and renal function	Uncontrolled infection or systemic disease
Minimum life expectancy of 12 weeks	Any major surgery, radiotherapy, immunotherapy within the last 21 days (palliative radiation > 2 weeks permitted
Fertile patients agree to use of effective contraception during study and 90 days after last dose of NOX66	No concurrent chemotherapy or biologic therapy; chemotherapy with delayed toxicity within last 4 weeks
	History solid organ transplant
	Known unsuitability for treatment with carboplatin or suppository use

STUDY STATUS (as at 1st September 2017)

DEMOGRAPHICS

		COHORT 1 (n=8)	COHORT 2 (n=6)
Median Age		61	64
Gender			
	F	5 (62.50%)	3 (50.00%)
	M	3 (37.50%)	3 (50.00%)
Ethnicity			
	Caucasian	8 (100.0%)	6 (100.0%)

ENROLLED PATIENT STATUS ON STUDY

	Pt	Tumour Type	Monotherapy (21 day cycle) Phase 1a Status	Combination Therapy (28 day cycles) Phase 1b Status	Response#(Cycle 3) Target Lesion RECIST 1.1 criteria	Adverse Events (Phase 1B) ALL	Severity*	Related to NOX66
COHORT 1	1	Ovarian	Complete	Ongoing - Cycle 6	Stable Disease Stable disease (Cycle 6)	Nausea	Grade 1/mild	UR
	2	Lung	Complete	Withdrawn (pt decision)	ND	NIL		
	3	Lung	Complete	Ongoing - Cycle 4	Stable Disease	Pulmonary embolism Arterial embolism	Grade 1/mild Grade 1/mild	UR
	4	Lung	Complete	Withdrawn	Progressive Disease			
	5	Breast	Complete	Ongoing - Cycle 4	Stable Disease	Exudative pericarditis Bilateral hydrothorax WBC elevation	Grade 1/mild Grade 2/mod Grade 2/mod	UR
	6	Breast	Complete	Ongoing - Cycle 4	Stable Disease	Hypocalcaemia	Grade 2/mod	UR
	7	Breast	Complete	Ongoing - Cycle 4	Stable Disease	Asthenia Peripheral neuropathy	Grade 2/mod Grade 1/mild	UR
	8	Prostate	Complete	Ongoing - Cycle 3	ND	NIL		
COHORT 2	9	Prostate	Complete	Ongoing - Cycle 1	ND	NIL		
	10	Prostate	Complete	Ongoing - Cycle 1	ND	NIL		
	11	Ovarian	Complete	Ongoing - Cycle 1	ND	NIL		
	12	Ovarian	Complete	Ongoing - Cycle 1	ND	NIL		
	13	Lung	Ongoing	NA	ND	NIL		
	14	Breast	Ongoing	NA	ND	NIL		
	15	Prostate	Ongoing	NA	ND	NIL		
	16	Pre-screen						
						No DLTs at 400 mg and 800 mg NOX66 dose		

*# First response assessment by Investigator; * NCTCAE v4.03 ; ND=Not Determined; UR= unrelated*

SUMMARY

- 15/16 patients recruited to date, with enrolment to complete in Sept 2017.
- NOX66 well tolerated as monotherapy and in combination with carboplatin
- Cohort 2 continuing enrolment with expectation of to complete by September 2017
- Additional patients may be replaced to allow up to 16 evaluable patients. These patients will be enrolled at the highest tolerated dose. Currently n=2
- Study completion expected in April—May 2018 and final analysis thereafter

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