NOX66 Plus Low Dose Carboplatin - a Phase 1 Safety and Signaling Study

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BACKGROUND

NOX66 is under development as a sensitizer of chemotherapy and radiotherapy across a range of tumour types. The active ingredient, idronoxil, has been well studied, with *in vitro* evidence of increased cytotoxicity of agents including cisplatin, carboplatin, paclitaxel, gemcitabine, toptecan, doxorubicin and captothecin. The mode of action of idronoxil is summarized below (Figure 1).

Early phase studies of an IV formulation showed that idronoxil has a short half-life, with significant and rapid Phase 2 metabolism to inactive conjugates. It was concluded that for idronoxil to have maximum effect that it must be administered in a manner to allow constant availability of active drug to the cells (high bioavailability of active drug . A phase 2 study of IV idronoxil (dose 2 days per week) in combination with cisplatin or paclitaxel in patients with ovarian cancers showed efficacy signals in some patients, however a Phase 3 study of oral idronoxil in combination with carboplatin was terminated early due to slow recruitment and lack of efficacy. The rapid and complete metabolism of idronoxil is believed to be a primary reason for lack the results seen.

NOX66 has been developed to specifically address the challenges of phase 2 metabolism and allow active (unconjugated) idronoxil to bind ENOX2. Formulation in a fatty acid environment is proposed to protect idronoxil from complete metabolism, modifying the release of idronoxil within the body. Furthermore, rectal delivery allows the bypassing of first pass metabolism, further protecting from complete conjugation of idronoxil.

A first in man study of NOX66 as a monotherapy and in combination with carboplatin at both low dose (AUC4) and standard dose (AUC6) is ongoing, with last patient visit scheduled for April 2018. We have previously reported that during the administration of NOX66 as monotherapy, no patients (n=15) experienced an adverse event considered related to NOX66.

Here we present data from the administration of NOX66 in combination with low dose

STUDY DESIGN & OVERVIEW

- ♦ End Stage, metastatic disease (no further therapy options) with solid tumours of type: breast, head and neck, lung, prostate and ovarian.
- ♦ Each patient undertakes 3 sequential phases of treatment:
  - Monotherapy: 21 day cycle where NOX66 is administered for daily for 14 days,
  - **Low Dose Carboplatin (reported here): 3 x 28 day cycles; NOX66 is administered Day 1-7, IV carboplatin (AUC4) Day 2**
  - High Dose Carboplatin: 3 x 28 day cycles; NOX66 is administered Day 1-7, IV carboplatin (AUC6) Day 2
- ♦ 19 Patients recruited, 18 patients received at least one dose of NOX66 (safety population)
- ♦ Preliminary response on CT images by investigator per RECIST 1.1 following completion of low dose and high dose carboplatin

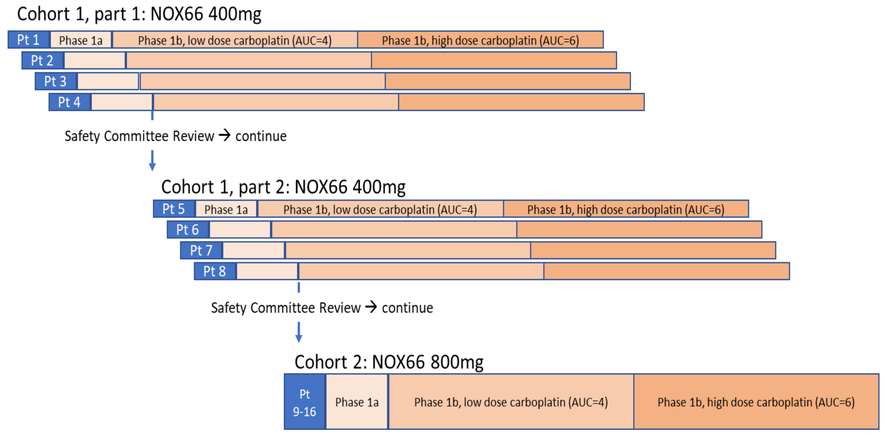
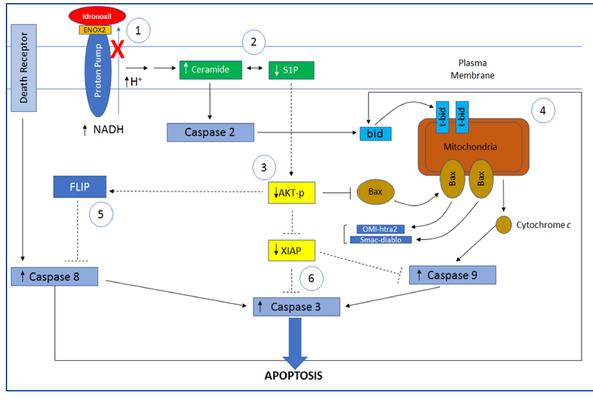


Figure 1. Putative biochemical pathway associated with Idronoxil



Cascade of events in Figure 1 is as follows:

1. Idronoxil binds to ENOX2 → inhibition of the trans membrane electron pump → accumulation of proton ions .
2. Accumulation of protons disrupts sphingomyelin pathway → blockage of ceramide conversion to S1P → ↓S1P and ↑Ceramide .
3. ↓S1P → ↓PI3K, ↓Akt, ↓XIAP and ↑ Caspase 2.
4. ↓Akt → ↓NF-κB → up regulation of the intrinsic (mitochondrial) pathway of apoptosis, via ↑Caspase 9 and ↑Caspase 3, → cell death.
5. ↓Akt → inhibition of FLIP → ↑Caspase 8 (activated via the Death Receptor on the Protein Membrane) → ↑Caspase 3 → apoptosis.
6. ↓XIAP prevents down regulation of Caspase 9 and Caspase 3, supporting apoptosis.

DEMOGRAPHICS	COHORT 1 (n=8)	COHORT 2 (n=11)
Median Age	61	64
Gender:		
F	5 (62.50%)	7 (63.63%)
M	3 (37.50%)	4 (36.36%)
Ethnicity:		
Caucasian	8 (100%)	8 (100%)
Other	0 (0%)	0 (0%)
Tumour Type:		
Breast	3 (37.50%)	4 (36.36%)
Head and Neck	0 (0%)	0 (0%)
Prostate	1 (12.5%)	2 (18.18%)
Lung	3 (37.50%)	2 (18.18%)
Ovarian	1 (12.5%)	2 (18.18%)

RESULTS - Low Dose Carboplatin

Of the eighteen patients commencing Low Dose (AUC4) therapy in combination with NOX66

- ♦ 8 patients received NOX66 400mg, 10 patients received NOX66 800mg
- ♦ 13 patients completed 3 cycles of combination therapy - these patients continue in the study, receiving up to 3 cycles of High Dose Carboplatin (AUC6)
- ♦ 13 patients were evaluable for radiological assessment of response following third dose of carboplatin (9-12 weeks from baseline)
  - ⇒ Of the these, 12 showed stable disease compared with baseline, with one patient (800mg NOX66, prostate cancer) showing a partial response and one patient with progressive disease (800mg NOX66, lung cancer).
- ♦ No patient discontinuations were due to NOX66 administration (either adverse events or practical issues). Reasons for discontinuation were: due to patient decision (n=3) and due to SAE (n=1)(see Table 1)

Table 1. Summary Adverse Events and Response 3 month post therapy

	Patient	Tumour Type	ADVERSE EVENTS		Response
			PT TERM	SEVERITY [a]	(RECISTv1.1)
COHORT 1 (400mg nOX66)	1	Ovarian	Nausea	Grade 1 / Mild	SD
	2	Lung	Back pain	Grade 2 / Mod	WD
			Back pain	Grade 3 / Severe[#]	
	3	Lung	Pulmonary embolism	Grade 1 / Mild	SD
			Embolism arterial	Grade 1 / Mild	
	4	Lung	None	NA	WD
	5	Breast	Hydrothorax	Grade 2 / Mod	NE
			Pericarditis	Grade 2 / Mod	
			WBC counts increased	Grade 1 / Mild	
	6	Breast	Hypocalcaemia	Grade 2 / Mod	SD
			Pulmonary fibrosis	Grade 1 / Mild	
	7	Breast	Asthenia	Grade 2 / Mod	NE
			Neuropathy peripheral	Grade 1 / Mild	
	8	Prostate	None	NA	SD
COHORT 2 (800 mg NOX66)	9	Prostate	Fatigue G1	Grade 1 / Mild	SD
	11	Ovarian	Neutropenia	Grade 1 / Mild	PR
	12	Ovarian	Infusion related reaction	Grade 3 / Severe[^#]	SD
	13	Lung	None	NA	PD
	14	Breast	Anemia	Grade 2 / Mod*	SD
			Anemia	Grade 1 / Mild	
	15	Lung	Anemia	Grade 2 / Mod	ND
			hypocalcemia	Grade 2 / Mod	
	16	Breast	None	NA	WD
	17	Breast	None	NA	SD
	18	Breast	None	NA	SD
	19	Breast	None	NA	SD

[a] *NCTCAE v4.03;* *possibly related to NOX66; [#]led to withdrawal; ^Serious;

- ♦ Total of 19 Adverse events were reported by 11 patients during this phase of study (Table 1).
  - ⇒ One adverse event (Grade 2 anaemia, breast cancer), receiving 800mg NOX66 was considered possibly related to NOX66. This event resolved while continuing therapy
  - ⇒ Two (2) events led to withdrawal, one was a serious.

CONCLUSIONS

This interim analysis shows that, in patients with End-Stage Metastatic Cancer of varying primary origin, NOX66 in combination with low dose (AUC4) carboplatin is well tolerated, with no Serious Adverse Events or patient withdrawals considered related to NOX66 therapy.

Furthermore, efficacy signals –from evaluable patients during this phase of the study - provides support for further investigation of NOX66 combined with low dose carboplatin as a therapeutic option for patients with solid tumours.

The study is continuing to the NOX66 / high dose carboplatin phase, with last patient visit scheduled for May 2018. Final results, including relationship to prior therapy and disease progression at study entry, will be reported soon after.

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