ABS #2585

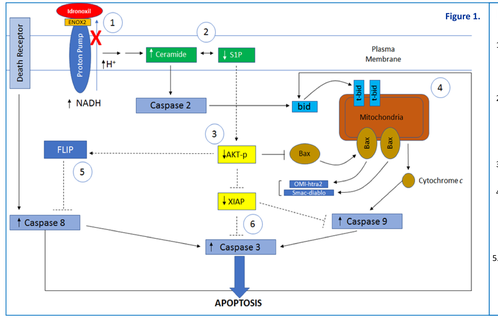
A phase 1 study of NOX66 in combination with carboplatin in patients with end stage solid tumours

Paul L. de Souza, Marinella Messina, Ian Minns, Mikheil Shavdia, Nana Chikhladze, Graham Kelly

BACKGROUND

NOX66 – a novel formulation of the isoflavonoid idronoxil in a lipophilic base – is being investigated as an enhancer of chemotherapy and radiotherapy. While the mode of action of idronoxil (outlined in Figure 1) suggests a direct cytotoxic effect as a monotherapy, research has focused on using lower doses of idronoxil to enhance the effect of standard therapies. *In vitro* studies of Phenoxodiol (previous nomenclature for idronoxil) with platinum based therapies has shown up to 2000 fold increase in the cytotoxic effects and reversal of pre-existing resistance [1-4]; and reduces the dose necessary to obtain antitumoural effect. In xenograft models of range tissues types, Idronoxil enhances the cytotoxic effects of carboplatin and other antineoplastics [7-9]. Preliminary evidence suggests that idronoxil may also stimulate an immune response via a NK cell pathway[10]– this may provide a complimentary effect to chemotherapy treatments and support the effects of radiotherapy both at the sites of irradiation and in tumours not irradiated.

Figure 1.



Putative Biochemical Pathway Associated with Idronoxil

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 →

NOX66 has been formulated to extend the effective half life of idronoxil with studies in rats indicating that half life of the parent idronoxil is increased from < 60 min when administered orally to > 6h when administered rectally as NOX66[11]. The low bioavailability due to short half life, and extensive Phase 2 metabolism of idronoxil when administered orally has been identified as a reason for the failure of idronoxil in an historical Phase 3 trial.

REFERENCES

1. Aguero, MF, et al. Phenoxodiol Inhibits Growth of Metastatic Prostate Cancer Cells. The Prostate. 2010, Vol. 70, pp. 1211-1221.
2. Herst P, Davis JE, Neeson P et al. The anti-cancer drug, phenoxodiol, kills primary myeloid and lymphoid leukemic blasts and rapidly proliferating T cells. *Haematologica*. 2009, Vols. 94(7):928-934.
3. Sapi, E., Alvero, A.B, Chen, W. et al. Resistance of ovarian carcinoma cells to docetaxel is XIAP dependent and reversible by phenoxodiol. Oncol Res. 2004, Vols. 14(11-12): 567-78.
4. Mor G, Chen W, Sapi E, et al. Phenoxodiol a chemosensitizer in taxotere-resistant ovarian cancer cells. Proc Amer Assoc Cancer Res . 2004, Vol. 45 Abstract 4885.
5. Morre DJ, Dick S, Bosneaga et al. tNOX (ENOX2) Target for Chemosensitization-Low-Dose Responses in the Hormetic Concentration Range. Am J Pharmacol Toxicol . 2008, Vols. 3 (1): 19-29 .
6. Li Y, Huang X, Huang Z, Feng J. Phenoxodiol enhances the antitumor activity of gemcitabine in gallbladder cancer through suppressing Akt/mTOR pathway. Cell Biochem Biophys. 2014, Vols. 70(2):1337-42.
7. Alvero, AB, et al. Phenoxodiol-Topotecan Co-administration Exhibit Significant Anti-tumour Activity Without Major Adverse Side Effects. Cancer Biol Ther. 2007, Vols. 6(4): 612-617.
8. Yao, C, et al. Co-administration Phenoxodiol With Doxorubicin Synergistically Inhibit the Activity of Sphingosine Kinase-1 (SphK1), a Potential Oncogene of Osteosarcoma, to Suppress Osteosarcoma Cell Growth Both in vivo and in vitro. Molec Onc. 2012, Vols. 6:392-404.
9. McPherson RA, Galettis PT, de Souza PL. Enhancement of the activity of phenoxodiol by cisplatin in prostate cancer cells. Br J Cancer. 2009, Vols. 24,100(4):649-55.
10. Georgaki, S, et al. Phenoxodiol, an Anticancer Isoflavone, Induces Immunomodulatory Effects in vitro and in vivo. *Molec Onc*. 2009, Vol. 13(98), pp. 3929-3938.
11.Data on File

STUDY DESIGN

This first-in-man study was performed in the Eastern European country of Georgia. The study consisted of 2 cohorts of 8 patients, allocated 1 of 2 doses of NOX66 – 400mg or 800mg. Patients with end stage breast, prostate, lung, ovarian or head and neck cancers were eligible for inclusion. Key inclusion / exclusion criteria are shown in Table 1. Each patient was scheduled to receive up to 27 weeks of treatment as follows:

- **Monotherapy: 1 x 21-day treatment cycle, NOX66 administered daily for days 1-14**
- **Low Dose Carboplatin (Cycles 1-3): 3 x 28-day treatment cycles, carboplatin AUC4 administered on day 2, NOX66 administered daily for days 1-7**
- **Standard Dose Carboplatin (Cycles 4-6): 3 x 28-day treatment cycles, carboplatin AUC6 administered on day 2, NOX66 administered daily for days 1-7**

Safety assessments were conducted following enrolment of 4 patients and 8 patients prior to continuation of recruitment (Figure 2) and ongoing throughout the study. Patients with tumours suitable for measurement by RECIST criteria were assessed by radiological scans at the commencement of Cycles 3 and 6. A protocol amendment, requiring patients to be suitable for assessment by RECIST criteria was incorporated during recruitment, with additional patients recruited to compensate for those who could not be assessed.

Figure 2.

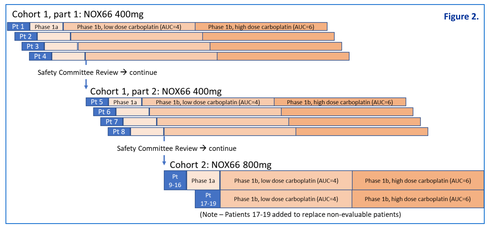


Table 1.

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 RESULTS

Nineteen Caucasian patients (12 Female and 7 male) with median age 61—64 years were recruited into the trial between 17 March 2017 and 26 October 2017, with eighteen patients receiving at least one dose of NOX66. Results are presented in the following tables:

Table 2: All Adverse events occurring during monotherapy and during combination therapy.

Table 3: Response to treatment and Adverse events ≥ Grade 3 severity per patient.

Table 4: Overall response to treatment per RECIST by dose cohort and combination cycle.

Table 2.

ALL ADVERSE EVENTS	Cohort 1 (400mg)				Cohort 2 (800mg)				Total	
	Monotherapy (A) n=8		Combination Therapy (B) n=8		Monotherapy (A) n=7		Combination Therapy (B) n=10		n=18	
PT Term	n	%	n	%	n	%	n	%	n	%
ALL	1	12.50%	7	87.50%	1	14.29%	8	80.00%	15	83.33%
Anaemia	0	0.00%	1	12.50%	1	14.29%	3	30.00%	5	27.78%
Iron deficiency anaemia	0	0.00%	1	12.50%	0	0.00%	1	10.00%	2	11.11%
Neutropenia	0	0.00%	1	12.50%	0	0.00%	2	20.00%	3	16.67%
Pericarditis	1	12.50%	0	0.00%	0	0.00%	0	0.00%	1	5.56%
Abdominal pain upper	0	0.00%	1	12.50%	0	0.00%	0	0.00%	1	5.56%
Diarrhoea	0	0.00%	1	12.50%	0	0.00%	0	0.00%	1	5.56%
Flatulence	0	0.00%	1	12.50%	0	0.00%	0	0.00%	1	5.56%
Gastrointestinal haemorrhage	0	0.00%	0	0.00%	0	0.00%	1	10.00%	1	5.56%
Nausea	0	0.00%	1	12.50%	0	0.00%	0	0.00%	1	5.56%
Asthenia	0	0.00%	1	12.50%	0	0.00%	0	0.00%	1	5.56%
Fatigue	0	0.00%	0	0.00%	0	0.00%	1	10.00%	1	5.56%
Sudden death	0	0.00%	1	12.50%	0	0.00%	0	0.00%	1	5.56%
Infusion related reaction	0	0.00%	0	0.00%	0	0.00%	1	10.00%	1	5.56%
Platelet count decreased	0	0.00%	0	0.00%	0	0.00%	1	10.00%	1	5.56%
White blood cell count increased	0	0.00%	1	12.50%	0	0.00%	0	0.00%	1	5.56%
Hypoalbuminaemia	0	0.00%	0	0.00%	0	0.00%	1	10.00%	1	5.56%
Hypocalcaemia	0	0.00%	1	12.50%	0	0.00%	2	20.00%	3	16.67%
Back pain	0	0.00%	1	12.50%	0	0.00%	0	0.00%	1	5.56%
Altered state of consciousness	0	0.00%	0	0.00%	0	0.00%	1	10.00%	1	5.56%
Coma	0	0.00%	0	0.00%	0	0.00%	1	10.00%	1	5.56%
Neuropathy peripheral	0	0.00%	1	12.50%	0	0.00%	0	0.00%	1	5.56%
Hydrothorax	1	12.50%	0	0.00%	0	0.00%	0	0.00%	1	5.56%
Pulmonary embolism	0	0.00%	1	12.50%	0	0.00%	0	0.00%	1	5.56%
Pulmonary fibrosis	0	0.00%	1	12.50%	0	0.00%	0	0.00%	1	5.56%
Embolism arterial	0	0.00%	1	12.50%	0	0.00%	0	0.00%	1	5.56%

DEMOGRAPHICS

	COHORT 1 (n=8)	COHORT 2 (n=11)
Median Age	61	64
Median Weight	79.3	76
Gender		
F	5 (62.50%)	7(63.64%)
M	3 (37.50%)	4 (36.36%)
Ethnicity		
Caucasian	8 (100.0%)	11 (100.0%)
Disease stage		
Metastatic	8 (100.0%)	10 (90.91%)
Locally advanced		1(9.09%)

Table 4. Overall Response (RECIST v1.1)

Dose cohort	Assessment[a] Time point	Partial Response	Stable Disease	Progressive Disease
Cohort 1	**Cycle 3B**	**0 (0.0)**	**4 (100.0)**	**0 (0.0)**
	Cycle 6B	**0 (0.0)**	**1 (50.0)**	**1 (50.0)**
Cohort 2	**Cycle 3B**	**0 (0.0)**	**7 (77.8)**	**2 (22.2)**
	Cycle 6B	**1 (16.7)**	**4 (66.7)**	**1 (16.7)**

Two patients had non-measurable target lesions at Screening and have been excluded.
[a]*Assessed at the start of the cycle*

CONCLUSION

- **NOX66 has been observed to be well tolerated in patients with end stage tumours in combination with carboplatin, with no severe or serious adverse events attributed to NOX66 use.**
- **Preliminary signals for response to treatment, combined with the observed safety profile, suggest further investigations using NOX66 800mg in combination with platinum based therapy.**

Table 3

	Pt #	Tumour Type	PRIOR THERAPY TYPE	PRIOR THERAPY Name	THERAPY 1 cycle Monotherapy (A) 6 cycle Combination (B) CYCLE COMPLN	RESPONSE RECISTV1.1* REASON NON COMPLN	CYCLE 3	CYCLE 6	SEVERE AEs and SAEs (Grade 3[#] or above) AE (PT term)	REL NOX66	REL CPLATIN
COHORT 1 (400 mg)	1	Ovarian	Chemo Surgery	Carboplatin/Paclitaxel Omentectomy/Hysterectomy	1A, 3B, 6B	NA	SD	SD	Nil	NA	NA
	2	Lung	Chemo	Cisplatin/Gemcitabine Paclitaxel/Docetaxel	1A, 2B	PD	ND	ND	Back pain	Unlikely/ UR	Unlikely/UR
	3	Lung	Chemo	Cisplatin/Etoposide	1A, 3B, 5Bd7	WD Pt decision	SD	ND	Abdominal Pain upper	Unlikely/ UR	Unlikely/UR
	4	Lung		Cisplatin/Gemcitabine	1A, 1Bd15	WD Pt decision	ND	ND	Nil	NA	NA
	5	Breast	Chemo Surgery	Docetaxel Epirubicin/Cyclophosphamide/5-flurouracil Mastectomy (R)	1A, 3B, 6B	NA	NE	NE	Iron deficiency Anemia	Unlikely/ UR	Unlikely/UR
	6	Breast	Chemo Hormonal Surgery	Capecitabine/Docetaxel Epirubicin/Cyclophosphamide/5-flurouracil Anastrozole Mastectomy	1A, 3B, 6Bd1	PD	SD	PD	Nil	NA	NA
	7	Breast	Chemo Hormonal Surgery	Epirubicin/Cyclophosphamide/5-flurouracil Cisplatin/Gemcitabine/Docetaxel Navelbine Letrozole Mastectomy	1A, 3B, 6B	NA	NE	NE	Nil	NA	NA
	8	Prostate	Opiate analgesic	Zoldex	1A, 3B, 5B	SAE	SD	NA	Sudden Death	Unlikely/ UR[#]	Possibly [#]
COHORT 2 (800 mg)	9	Prostate	Chemo Hormonal	Docetaxel Elgard (Lesuprorelin acetate) Abiraterone	1A, 3B, 6B	NA	SD	SD	Nil	NA	NA
	10	Prostate	Chemo Hormonal Surgery Other	Docetaxel Enzalumatide/Bicalumatide Radical Prostectomy/Lymphadectomy surgical castration Zoledonic Acid	1A, 3B, 6B	NA	PD	PD	Nil	NA	NA
	11	Ovarian	Chemo Surgery	Carboplatin/Paclitaxel Omentectomy w partial proctectomy Hysterectomy/ iliac lymphadectomy	1A, 3B, 6B	NA	SD	SD	Anaemia	Unlikely/ UR	Possibly
	12	Ovarian		Carboplatin/Paclitaxel Omentectomy / iliac Lymphadectomy Hysterectomy/ Lymphadectomy Colectomy Ileorectal anastomosis	1A, 3Bd2	SAE	SD	ND	Infusion related reaction	Unlikely/ UR	Certain
	13	Lung	Chemo RT	Carboplatin/Gemcitabine/Navelbine Docetaxel 66 Gy	1A, 2Bd15	SAE	PD	ND	Gastrointestinal Haemorrage (Death)	Unlikely/ UR	Unlikely/UR
	14	Breast	Chemo Surgery RT	Epirubicin/Cyclophosphamide/5-flurouracil Cisplatin/Docetaxel/Navelbine Mastectomy Regional lymph nodes (40Gy)	1A, 3B	PD Pt decision	SD	ND	Nil	NA	NA
	15	Lung	Chemo	Carboplatin/Gemcitabine	1A, 2Bd7	SAE	ND	ND	1. Altered State consciousness 2. Coma (Death)	Unlikely/ UR Unlikely/ UR	Unlikely/UR Unlikely/UR
	16	Breast	Chemo	Capecitabine/Docetaxel/ Methotrexate 5-flurouracil	Not dosed	WD Pt decision	NA	NA	Nil	NA	NA
	17	Breast	Chemo Hormonal Surgery	Carboplatin/Cisplatin/ Paclitaxel/Docetaxel/Navelbine Anastrozole Mastectomy Omentectomy / iliac Lymphadectomy Hysterectomy/ Lymphadectomy Colectomy ileorectal anastomosis	3B, 6B	NA	SD	PR	Nil	NA	NA
	18	Breast	Chemo Hormonal	Epirubicin/Cyclophosphamide/5-flurouracil Docetaxel Fulvestrant	3B, 6B	NA	SD	SD	Neutropenia	Unlikely/ UR	Likely
	19	Breast	Chemo Hormonal	Carboplatin Docetaxel/Capecitabine Epirubicin/Cyclophosphamide Navelbine Anastrozole Exemestrone	3B, 6B	NA	SD	SD	Nil	NA	NA

** Assessed by the site Investigator; # NCI CTCAE v 4.03 ; ≠ In the opinion of the site Investigator; no autopsy conducted (per family wishes) for definitive cause of death.*

Contact: Ian.Minns@noxopharm.com