Trial in Progress: NOX66 in combination with Palliative Radiotherapy in patients with CRPC – a Phase 1 safety and dose finding study

Dr Isabell Vocks[1], Dr Anne Capp[2]
([1]Noxopharm Limited, [2]Genesis CancerCare Newcastle)

Background

The naturally occurring isoflavone, genistein, has been investigated for its potential chemo-protective and anti-cancer activity, with multiple pharmacological properties being identified including direct induction of apoptosis and prevention of cell repair and growth. These findings led to the development of isoflavonoids - molecules based on the chemical structure of genistein - designed to enhance the chemotherapeutic and antineoplastic effects. One of these compounds - idronoxil - has been shown *in vitro* to sensitize multiple cancer cell lines to common chemotherapies, in some cases by up to 2000 fold. Recent *in vitro* studies have shown sensitization of prostate cancer cells to the effects of radiotherapy. Furthermore, evidence suggests that idronoxil may stimulate an increase in NK cell activity - it is theorised that an immunostimulatory effect may support an abscopal response in patients being treated with radiotherapy. A previous Phase 3 study of idronoxil in ovarian cancer, however, failed to show improved efficacy when compared with standard chemotherapy alone. It is believed that this lack of efficacy was due to the rapid metabolism and elimination of idronoxil.

NOX66, a novel formulation of idronoxil as an active ingredient and designed for rectal administration, is under clinical investigation in combination with chemotherapy and radiotherapy. NOX66 is designed to protect idronoxil from rapid metabolism and elimination, allowing for therapeutic levels of idronoxil to remain in the body. A Phase 1 study of NOX66 as monotherapy and in combination with chemotherapy (carboplatin) has been completed, showing NOX66 to be suitably tolerated.

Here we describe the design of, and provide preliminary safety data for, a first-in-human study of NOX66 in combination with radiotherapy in patients with late-stage prostate cancer, investigating the safety of three dose levels of NOX66.

Study Title: NOX66 and Palliative Radiotherapy in Patients with Late-Stage Prostate Cancer - A Phase 1b Proof of Concept and Dose Confirmation Study
ClinicalTrials.gov Identifier: NCT03307629

KEY Inclusion criteria
Histologically confirmed prostate cancer and/or PSA of >100 ng/mL at original diagnosis.
Metastatic disease evidenced by either CT/MRI imaging or bone scan.
Objective evidence of disease progression.
Eligible to receive palliative radiation therapy for management of disease.
One symptomatic lesions suitable for Radiation Therapy.
KEY Exclusion criteria
Tumour involvement of the central nervous system.
Concurrent systemic chemotherapy or biological therapy.
Any situation where the use of suppository therapy is contra-indicated or impractical.

Study Methodology

Objectives

Primary

- Safety and tolerance of NOX66 in escalating dose cohorts, in combination with palliative radiotherapy

Secondaries

- Investigate if NOX66 will sensitize tumours to palliative radiation therapy
  - Measure by RECIST and **pain scores**
- Dose confirmation for future trials
- Plasma idronoxil levels
- Changes in PSA
- Review of CT/MRI scans by Radiation Oncology Expert Committee –assessment of observable and/or symptomatic changes from baseline over time

A total of 24 patients will be recruited into the trial, in four cohorts.

The Study will involve treatment with NOX66 and radiation therapy as follows:

Day 1-15: NOX66 will be administered rectally (one, two or three suppositories daily, depending on cohort allocation)

Day 2-8: Lesions selected for irradiation will receive palliative dose (20Gy) radiation therapy in 5 fractionated doses over 7 days.

Safety Monitoring (SAEs and severity of all AEs, treatment discontinuation) will be assessed throughout the study, with safety in the treatment phase of the study (Days 1-15) providing evidence for dose escalation. Efficacy signals will be monitored through assessment of CT scans), PSA levels and pain evaluation.

Dose Escalation

- Patient follow up for 24 weeks
- Tumour assessment at baseline, 6 weeks, 12 weeks, 24 weeks

Study Progress—Results

Recruitment commenced in March 2018, at eleven centres in Australia (5), New Zealand (1) and Georgia (5).
At the time of writing, 14 of 24 patients have been recruited, Cohort 3 has been completed and 2 replacement patients for Cohort 2 have been included. Results in table 1 show patient data of 9 patients with dataset available to this date.

Table 1

		Efficacy							Safety		
Patient	Cohort	Baseline PSA	6-week PSA (ng/ml)	12-week PSA (ng/ml)	24-week PSA (ng/ml)	RECIST assessment at 6 weeks	RECIST assessment at 12 weeks	RECIST assessment at 24 weeks	Adverse Events > Grade 2	Related to NOX66	Related to RT
01	1/400 mg	2044	2593	2117	1945	SD	SD	SD	NIL	NA	NA
02	1/400 mg	67.7	87.4	100	624.1	SD	SD	NE	NIL	NA	NA
03	1/400 mg	315	183	370	819	SD	SD	SD	NIL	NA	NA
04	1/400 mg	350	550	610	1600	PD	NE	PD	NIL	NA	NA
05	2/800 mg	440	ND	947	ND	ND	PD	Deceased	Aneamia, Hypophosphatemia, Desease Progression	UR	UR
06	2/800 mg	150	Deceased	ND	ND	ND	ND	ND	Vomiting, Nausea, Decreased lymphocyte count, Hypocalcemia, Death	UR	UR
07	2/800 mg	15.5	6	5.2	2.2	SD	PR	PR	NIL	NA	NA
08	2/800 mg	152	143	ND	ND	ND	Deceased	ND	Death	UR	UR
09	3/1200 mg	80.5	42.5	17.3	TBD	PR	PR	TBD	NIL	NA	NA

Safety: Up to this date at least 5 patients experienced one or more Adverse Events (AE)s. Three of the overall AEs were considered possibly related (PR) to NOX66 and these were mild (Grade 1). All severe AEs were considered unrelated to either NOX66 or RT, and were due to progressive disease, as shown in Table 1.

Preliminary efficacy: Of the 9 evaluable patients receiving one dose of NOX66, Patient 07 in Cohort 2 (800 mg) showed Partial Response in the overall RECIST analysis for week 24. This patient's PSA decreased > 75 % at week 12 and week 24. Patient 09 in Cohort 3 (1200 mg) showed Partial Response in overall RECIST analysis for week 12. The PSA decreased > 75% at week 12.

NOXOPHARM

This study is sponsored and fully funded by Noxopharm Limited