

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

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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 or more lesions able to be assessed for response (by RECIST).

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

ENDPOINTS:



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

- Investigate if NOX66 will sensitise tumours to palliative radiation therapy
 - Measured by RECIST and pain scores
 - Dose confirmation for future trials
 - Plasma idronoxil levels
 - Changes in PSA

- Levels of ceramide, S1P, ENOX2 in blood – look for correlation
- miRNA – early investigation in relation to Abscopal response

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

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 - providing response information at the sites of irradiation as well as sites distant to RT (a potential abscopal response), PSA levels and pain evaluation.

Dose Escalation:

Up to three doses of NOX66 (400mg, 800mg, 1200mg) will be investigated in escalating dose cohorts (cohorts 1-3, respectively).

Each cohort will be reviewed by a Data Safety Monitoring Committee comprising each site PI, an independent medical oncologist and a medical monitor representing the sponsor company. following the completion of NOX66 therapy within the cohort (4th patient, Day 15).

Provided no acute safety signals are noted, the next cohort shall commence at the escalated dose.

Following the Week 6 Scan for patient 12 (cohort 3) a determination of dose for cohort 4 will be made.

Cohort 1 – Patients 1-4



2 week safety review, NOX66 dose modification → Cohort 2 – Patients 5-8



2 week safety review, NOX66 dose modification → Cohort 3 – Patients 9-12



6 week safety and response review, NOX66 dose confirmation → Cohort 4 – Patients 13-24

Study Progress

Recruitment commenced in March 2018, at eleven centres in Australia (5), New Zealand (1) and Georgia (5).

At the time of writing, 9 of 24 patients have been recruited, with Cohort 3 currently ongoing.

Cohort 1:

Four patients were dosed with 400mg NOX66 and RT. All patients completed the 15-day treatment phase. Adverse Events noted during this phase included: Following DSMC review, the study was approved to continue to cohort 2 with dose escalation.

Adverse event	Severity	Relationship to NOX66
Dry Mouth	Grade 1 /	Possibly related
Fatigue	Grade 1 /	Possibly related

Cohort 2:

Four patients were dosed with 800mg NOX66 and RT. All patients completed the 15-day treatment phase. Adverse Events noted during this phase included:

Adverse event	Severity	Relationship to NOX66
Mucositis oral	Grade 1 /	Possibly related

Following DSMC review, the study was approved to continue to cohort 3 with dose escalation. One patient within this cohort has withdrawn from follow up due to need to commence further therapy for his cancer care. This patient will be replaced within the study to allow ongoing assessment of the 800mg dose.

Cohort 3:

Currently one patient has been dosed with 1200mg NOX66 and RT, with treatment completed. No Adverse events have been noted to date.



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