Trial Design: Safety of NOX66 in Combination with Palliative Dose Radiotherapy - A Phase 1 Dose Escalation Study

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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). Inhibition of ENOX2 in tumour cells can cause a cascade of events which ultimately promote cell apoptosis and prevent DNA repair in damaged cells.[1-4] It has further been shown *in vitro* that inhibiting Sphingolipid metabolism, which can be achieved through ENOX2 inhibition, can enhance the effect of radiation in causing cell injury and death.[5-6]

NOX66, a novel formulation containing Idronoxil as an active ingredient and designed for rectal administration, is under clinical investigation in combination with chemotherapy and radiotherapy. It is hypothesised that NOX66, through delivery of Idronoxil to tumour cells and inhibition of ENOX2, may enhance the effects of radiotherapy in target tumours and provide improved efficacy in irradiated tumours. Furthermore, the Idronoxil-ENOX2 interaction may facilitate the stimulation of an abscopal response within non-irradiated tumour cells due to the direct pro-apotosis effects of Idronoxil. Here we describe the design of the 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
At least two lesions, one of which is measurable and one which is suitable for radiation therapy
Ongoing androgen deprivation therapy with luteinizing hormone-releasing hormone (LHRH) agonist or antagonist
ECOG Performance status 0-2
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 (eg.

Study Objectives

Primary

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

Secondaries

- 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

Exploratory

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

Study Methodology

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

- Cohort 1 (n=4): NOX66 400mg
- Cohort 2 (n=4): NOX66 800mg (subject to dose escalation criteria being met)
- Cohort 3 (n=4): NOX66 1200mg (subject to dose escalation criteria being met)
- Cohort 4 (n=12): NOX66 dose to be determined from assessment of cohorts 1-3

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

Baseline: Tumour assessment scan using CT/MRI, screening laboratory assessments (including PSA levels), and pain assessment (Brief Pain Inventory-Short Form)

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

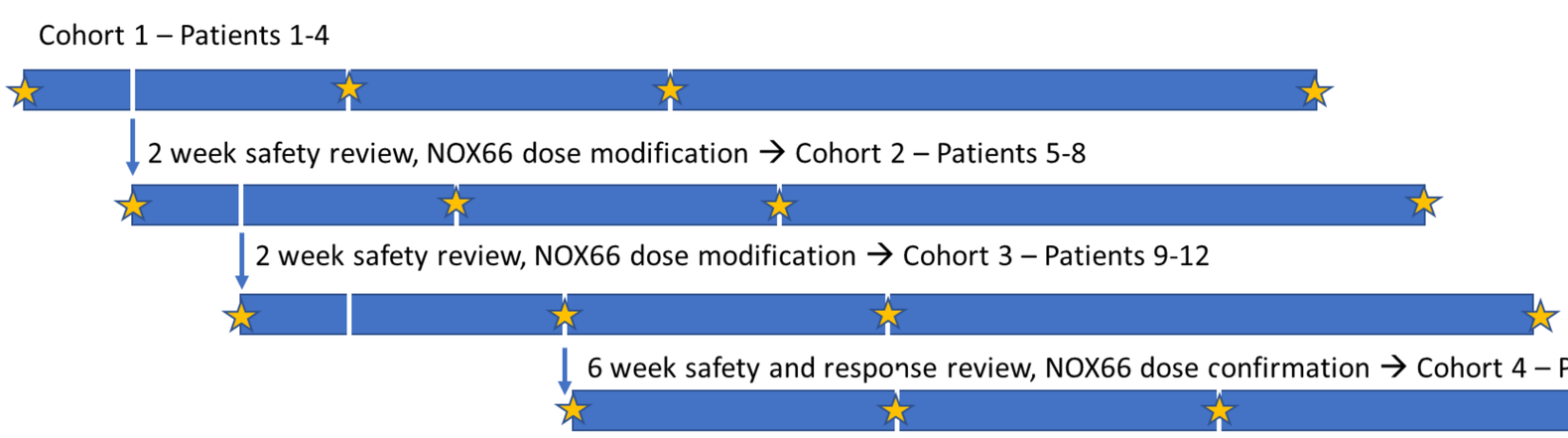
Day 2-8: Lesions selected for irradiation will receive palliative dose (20Gy) radiation therapy in 5 fractionated doses over 7 days (no radiation therapy on weekends).

Week 6: Initial follow up scan using CT/MRI, follow up laboratory assessments (including PSA levels), and pain assessment

Week 12: Second follow up scan using CT/MRI, follow up laboratory assessments (including PSA levels), and pain assessment

Week 24: third follow up scan using CT/MRI, follow up laboratory assessments (including PSA levels), and pain assessment

Patients will continue to be followed up after 24 weeks at the discretion of the investigator.



Dose Escalation:

Each of Cohorts 1-3 will be reviewed 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

References

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Study Locations

The Study is being conducted at Radiation Oncology Centres in NSW and Queensland

Acknowledgement

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NOXOPHARM

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