Bipolar androgen therapy (BAT) for nonmetastatic castration-resistant (M0 CRPC) prostate cancer progressing on darolutamide: Working Out M0 BAT (WOMBAT; ANZUP 2201)

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1. Background and Rationale

ADT in combination with androgen receptor pathway inhibitors (ARPI), such as darolutamide, is an effective treatment for metastatic prostate cancer. However, long-term androgen blockade is associated with significant metabolic sequalae, and treatment resistance will eventually develop with subsequent cancer progression.[1]

Mechanisms of treatment resistance include amplification of the androgen receptor (AR), overexpression of AR variants, aberrant AR activity, and autocrine/paracrine androgen synthesis in tumour cells.[2]

Bipolar androgen therapy (BAT) involves cycling between supra-physiological and castrate levels of testosterone.[3] Studies suggest BAT may restore the sensitivity of prostate cancer to ARPI treatment.[4,5]

We hypothesise that the addition intermittent darolutamide to BAT will maximise the oscillation between supraphysiologic testosterone conditions while counteracting some of the negative metabolic consequences of androgen blockade.

2. Study Design

Aim:

To determine the utility of adding BAT to ADT and intermittent darolutamide in people with M0 CRPC progressing on ADT and continuous darolutamide.

Design:

Single arm, multi-centre, phase 2 clinical trial.

Target Population:

- M0 CRPC on conventional imaging
- Previous PET-only M1 HSPC that is M0 at CRPC and study screening permitted if >18 months from initiation of darolutamide
- SBRT to PET-only metastases permitted prior to screening if lesions no longer visible on baseline imaging for study

Sample Size:

- Based on ARAMIS[1] trial outcomes, 69 participants are needed to determine if the treatment could increase the proportion of participants who have not died and are metastases free (MFS) at 6 months from 61.3% to 71.7%
- This corresponds to a median MFS from 8.5 to 12.5 months and a hazard ratio of ~0.68, with a one-sided type I error of α=10% and 80% power.
- Futility analysis planned after 41 participants are enrolled

3. Study Schema

Key Inclusion Criteria:

- Histologically confirmed prostate adenocarcinoma
- ECOG performance status 0-1
- PSA progression while on darolutamide despite castrate serum testosterone (<1.7nmol/L)
- PSA >1 ng/mL

Key Exclusion Criteria:

- Neuroendocrine or small cell prostate cancer
- M1 disease on CT/WBBS
- Significant cardiac or thrombotic disease

Interventions:

Six-week cycles

Day 1: Testosterone enanthate

Days 29-56: darolutamide

Ongoing ADT

Primary Objective:

MFS on conventional imaging (RECIST / PCWG3)

Secondary Objectives:

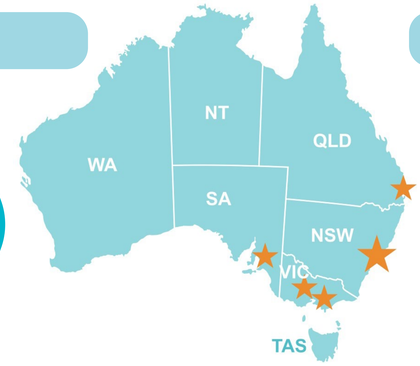
- Safety and tolerability
- Health-related Quality of Life (EORTC QLQ-C30, EORTC QLQ-PR25)
- PSA response rate
- Time to PSA progression
- Metabolic effects (Serum PINP, plasma CTX, bone densitometry)

Tertiary Objective:

Exploratory biomarker analysis to assess associations of outcomes with cell-free DNA alterations, AR-V7 status and circulating tumour DNA methylation changes.

4. Progress

- **8 centres enrolling patients**
- **1 active participant.**
- **1 in screening**
- **Recruitment is ongoing**



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For more information scan this QR code:

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