DASL-HiCaP: Darolutamide Augments Standard Therapy for Localized Very High-Risk Cancer of the Prostate – a randomized phase 3 double-blind, placebo-controlled trial of adding darolutamide to androgen deprivation therapy and definitive or salvage radiation in very high risk, clinically localized prostate cancer (ANZUP 1801)

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1. Background and rationale

- Definitive radiation therapy (RT), plus androgen deprivation therapy (ADT) with a luteinizing hormone releasing hormone analog (LHRHA) for at least one year, is standard of care for patients with very high-risk localized prostate cancer, or with very high risk features and persistent PSA after radical prostatectomy.
- Incurable distant metastases on conventional scans develop within 5 years in approximately 15% of patients whose cancers are very high risk.
- Darolutamide is a novel antagonist of the androgen receptor with favorable tolerability and negligible penetration of the blood-brain barrier.

2. Aim

To determine the effectiveness of adding darolutamide to ADT and radiation therapy in either the primary definitive setting or very high-risk postoperative setting.

3. Study Design

Design: Randomized (1:1) phase III placebo-controlled, double-blind trial.

Target Population:

- Participants with either very high-risk localized prostate cancer, or very high-risk features with PSA persistence or rise within one year following radical prostatectomy, suitable for RT.

Sample Size:

- 1100 participants, followed until 130 events gives 80% power to detect a 40% reduction in the hazard for metastasis or death (improvement in 5-year metastasis-free survival (MFS) from 85.0% to 90.7%) assuming: accrual over 3 years; 4 years of additional follow-up;
- a two-sided alpha of 5%; an allowance for up to 3% non-adherence and 10% loss to follow-up; and,
- an interim analysis after approximately 67% of the required number of events.

4. Study Objectives

To determine the effect of adding darolutamide to ADT and radiation therapy on:

Primary

Metastasis free survival: metastasis on conventional imaging or death from any cause

Secondary

- Overall survival (death from any cause)
- Prostate cancer-specific survival
- PSA-progression free survival
- Time to subsequent hormonal therapy (restart or change to treat recurrence/progression)
- Time to castration-resistance (PCWG3 criteria)
- Frequency and severity of adverse events (CTCAE v5.0)
- Health related quality of life (EORTC QLQ-C30, QLQ-PR25, EQ-5D-5L)
- Fear of cancer recurrence (FCR)

Tertiary/Correlative

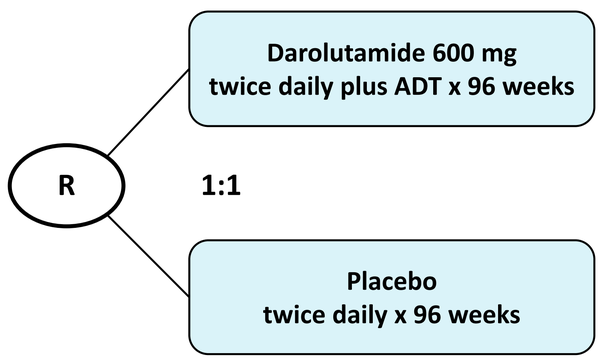
- Incremental cost-effectiveness
- Identify molecular and imaging biomarkers that are prognostic and/or predictive of benefit from treatment, safety and resistance to study treatment

5. Study Schema

All participants are also treated concurrently with an LHRHA for 96 weeks post randomization, plus RT starting at week 8-24 post randomization.

Eligibility

- Very high-risk localized prostate cancer to be treated with definitive radiation, or Very high-risk features + PSA persistence/rise within 12 months following radical prostatectomy (RP) to be treated with post RP radiation
- Suitable for EBRT with or without brachytherapy
- CT/MRI and bone scan negative for distant metastases (allow pelvic LN)



Endpoints

Primary

- Metastasis-free survival

Secondary

- Overall survival
- Prostate cancer-specific survival
- PSA-progression free survival
- Time to subsequent hormonal therapy
- Time to castration-resistance
- Frequency and severity of adverse events
- Health-related quality of life
- Fear of cancer recurrence

Exploratory

- Incremental cost-effectiveness
- Prognostic/predictive biomarkers

Statistical analysis

1100 participants:

- 3 years accrual + at least 4 years of additional follow up (until 130 events recorded)
- 80% power to detect 40% reduction in the hazard for metastasis or death
- Assuming MFS rate at 5 years: 85% in the control group; 90.7% darolutamide group, allowing for interim analysis and missing data

Stratification

1. Previous radical prostatectomy (yes or no)
2. Planned docetaxel use (yes or no)
3. Clinical or pathological pelvic lymph node involvement (yes or no)

6. Study Progress

Enrollment opened

31 March 2020

Current enrollment

530 participants randomized*

100 sites planned to be activated in 6 countries

56 sites currently open & recruiting across Australia, NZ, Canada, USA, Ireland & UK*

**(as at 10 May 2022)*

Country	# Sites activated	# Participants randomized
Australia	28	347
Canada	10	106
New Zealand	3	30
US	6	30
Ireland	5	11
UK	4	6
Global total	56	530

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SCAN ME

ClinicalTrials.gov Identifier: **NCT04136353**

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#DASLHiCaP

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