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

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1. Background and rationale

- Definitive radiation therapy (RT), plus androgen deprivation therapy (ADT) with a luteinising hormone releasing hormone analogue (LHRHA) for at least one year, is standard of care for men with very high-risk localised prostate cancer, or with very high risk features and persistent PSA after radical prostatectomy.
- Incurable distant metastases develop within 5 years in approximately 15% of men with very high risk features.
- Darolutamide is a novel antagonist of the androgen receptor with favourable tolerability due to 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: Randomised (1:1) phase III placebo-controlled, double-blind trial

Target Population: Participants with either very high-risk localised 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 75-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

Primary

Metastasis free survival (metastasis 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

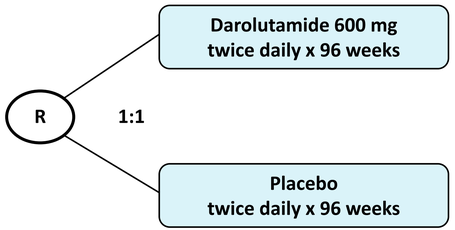
- Incremental cost-effectiveness
- Identify molecular imaging biomarkers that are prognostic and/or predictive of response to treatment, safety and resistance to study treatment

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

- Metastasis-free survival *(primary)*
- 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
- Incremental cost-effectiveness
- Prognostic/predictive biomarkers

Statistical analysis

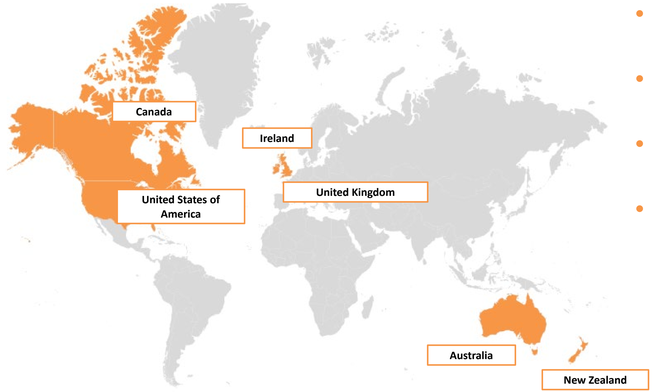
1100 participants:

- 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 LN involvement (yes or no)

6. Study Progress



- 6 countries engaged in start-up activities
- 100 sites enlisted to commence recruitment
- International face to face Investigator Meeting held
- Participant accrual to commence Q1 2020

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In collaboration with

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