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)

T Niazi[1,5], SM McBride[11,5], S Williams[2,5], ID Davis[3,5,19,20], MR Stockler[4,5], AJ Martin[4,5], HT Chung[21], FT Roncolato[4,5,18], A Ebacher[22], E Khoo[5,12], J Martin[5,16], TS Lim[5,17], S Hughes [5,7], D Pryor[5,8], J Catto[9], P Kelly[5,10], LG Rezaei[12], SC Morgan[5,13], R Rendon[14], CJ Sweeney[5,15], on behalf of the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP)

1. Jewish General Hospital, McGill University, Montreal, QC, Canada, 2. Peter MacCallum Cancer Centre, Melbourne, Vic, Australia, 3. Eastern Health Clinical School, Monash University, Box Hill, Vic, Australia, 4. NHMRC Clinical Trials Centre, University of Sydney, Camperdown, NSW, Australia, 5. Australian and New Zealand Urogenital and Prostate Cancer Trials Group, (ANZUP), Sydney, NSW, Australia, 6. Chris O'Brien Lifehouse, Camperdown, NSW, Australia, 7. Guy's and St. Thomas' Hospital NHS Trust, London, United Kingdom, 8. Princess Alexandra Hospital, WA, Australia, 9. Academic Urology Unit, University of Sheffield, Sheffield, United Kingdom, 10. Bon Secours Radiotherapy Cork, in partnership with UPMC Hillman Cancer Centre, Cork, Ireland, 11. Memorial Sloan Kettering Cancer Center, New York, NY, United States of America, 12. Icon Cancer Centre, Gold Coast University Hospital, QLD, Australia, 13. The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada, 14. Nova Scotia Health Authority and Dalhousie University, Halifax, NS, Canada, 15. South Australian Immunogenomics Cancer Institute, University of Adelaide, SA, Australia, 16. Calvary Mater Newcastle, Waratah, NSW, Australia, 17. Fiona Stanley Hospital, Murdoch, WA, Australia, 18. Macarthur Cancer Therapy Centre, Campbelltown, NSW, Australia, 19. Monash University, Melbourne, Australia, 20. Eastern Health, Melbourne, Australia, 21. Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, ON, Canada, 22. Centre Hospitalier Universitaire de Sherbrooke, Canada.

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 people with very high-risk localized prostate cancer, or with very high risk features and persistent PSA after radical prostatectomy.
- 15% of patients with very high-risk localized prostate cancer have an MFS event with 5 years of potentially curative treatment with standard ADT (testosterone suppression) plus definitive or salvage radiation.
- Darolutamide is a novel antagonist of the androgen receptor with favorable tolerability and negligible penetration of the blood-brain barrier and improves the OS of people when added to standard ADT in incurable settings.

2. Aim

To determine the effectiveness of adding darolutamide to ADT and radiation therapy in patients with very high-risk prostate cancer:

- Primary definitive radiation therapy; or
- Post-prostatectomy

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:

- Accrual over 3 years;
- 4 years of additional follow-up;
- 2-sided alpha of 5%;
- 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

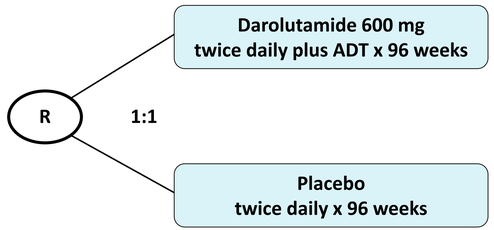
5. Study Schema

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 of 85% in the control group and 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

Country	# Sites activated *(incl satellite)*	# Participants randomized
Australia	32	502
Canada	19	232
New Zealand	3	42
US	19	50
Ireland	9	24
UK	10	31
Global total	91	881

Enrolment opened

31 March 2020

Current enrolment

881 participants randomized*

100 sites planned to be activated in 6 countries

91 sites (including satellite sites) currently open & recruiting across Australia, NZ, Canada, USA, Ireland & UK*

**(as at 31 January 2023)*

Acknowledgements

We thank the trial participants, principal investigators, co-investigators, and study coordinators at all participating centers for their commitment to this trial.

Abstract # TPS396

ClinicalTrials.gov Identifier: NCT04136353

Web site: https://anzup.org.au/clinical-trial/dasl-hicap-trial

For all trial enquiries: dasl.study@sydney.edu.au

#DASLHiCaP @ANZUPtrials

SCAN ME

In collaboration with:

Funding provided by:

This ANZUP investigator-initiated study is being led by ANZUP in collaboration with the NHMRC Clinical Trials Centre, Canadian Cancer Trials Group, Cancer Trials Ireland, Memorial Sloan Kettering Cancer Center, and the Prostate Cancer Clinical Trials Consortium. We thank Bayer AG for their financial support and study drug.

ANZUP receives valuable infrastructure support from the Australian Government through Cancer Australia.