DASL-HiCaP: Darolutamide Augments Standard Therapy for Localized Very High-Risk Cancer of the Prostate (ANZUP1801). A randomized phase 3 double-blind, placebo-controlled trial of adding darolutamide to androgen deprivation therapy and definitive or salvage radiation.

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Background: Radiation therapy (RT), plus androgen deprivation therapy (ADT)with a luteinizing hormone releasing hormone analogue (LHRHA), is standard of care for men with very high-risk localized prostate cancer (PC), or with very high-risk features and persistent PSA after radical prostatectomy (RP). Despite this, incurable distant metastases develop within 5 years in 15% of men with very high-risk features. Darolutamide is a structurally distinct oral androgen receptor antagonist with low blood-brain-barrier penetration, a demonstrated favorable safety profile and low potential for drug-drug interactions. Our aim is to determine the efficacy of adding darolutamide to ADT and RT in the setting of either primary definitive therapy, or adjuvant therapy for very high-risk PC.

Methods: This study is a randomized (1:1) phase III placebo-controlled, double-blind trial for men planned for RT who have very high-risk localized PC; or very high-risk features with PSA persistence or rise within one year following RP. The trial will be stratified by: RP; use of adjuvant docetaxel; pelvic nodal involvement. 1100 participants will be randomized to darolutamide 600 mg or placebo twice daily for 96 weeks. Participants will receive LHRHA for 96 weeks, plus RT starting week8-24 from randomisation. Participants are allowed nonsteroidal antiandrogen (up to90 days) in addition to LHRHA up until randomisation. Early treatment with up to 6cycles of docetaxel completed at least 4 weeks prior to RT is permitted. The primary endpoint is metastasis-free survival (ICECaP-validated), with secondary endpoints overall survival, PC-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 recurrence. Tertiary endpoints include incremental cost-effectiveness, and identification of prognostic and/or predictive biomarkers of treatment response, safety and resistance to study treatment.

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