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Darolutamide with androgen deprivation therapy (ADT) and definitive or salvage locoregional radiation therapy (RT) for localised, very high-risk prostate cancer: Interim analysis of an international, placebo-controlled, randomised phase 3 trial (DASL-HiCaP; ANZUP1801)

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Background

We evaluated the addition of darolutamide to standard of care ADT and RT for very high-risk localised or biochemically persistent/recurrent prostate cancer within 1 year after radical prostatectomy (RP).

Methods

Participants (pts) were prescribed an LHRH analog for 96 weeks plus RT to prostate/prostate bed and pelvic nodes and randomised 1:1 to darolutamide 600 mg vs placebo, twice daily for 96 weeks. The primary endpoint was metastasis-free survival based on conventional imaging with CT and/or technetium bone scan (MFS-CI, as per ICECaP surrogacy for OS). PSA-progression free survival (PFS), prostate cancer specific survival (PCSS), and overall survival (OS) were secondary endpoints. The protocol specified a single interim analysis after 87 MFS-CI events, with IDSMC review for external disclosure if the 2-sided, stratified log-rank p-value for MFS-CI was <0.012.

Results

We randomised 1,106 pts from 30APR20 to 09AUG23 with median age 71 (IQR 65-75), pelvic nodal involvement on CT in 29%, Gleason score 9-10 in 73%, and prior RP in 15%. Median follow-up was 3.8 years (IQR 3.3 to 4.5). MFS-CI was longer amongst those assigned darolutamide vs placebo: 4-year MFS-CI 95% vs 88%, hazard ratio 0.42 (95% CI 0.27 to 0.66), 27 vs 63 events, p=0.0001. PSA-PFS, PCSS, and OS are shown below. The proportions of pts experiencing grade ≥2 of the following AE clusters of special interest (darolutamide vs placebo) were: fatigue/asthenia (14% vs 10%), hypertension (7% vs 9%), fractures (2% vs 3%), and cardiac (3% vs 3%). Any AE grade ≥3 was experienced by 43% vs 36% of pts, respectively.

Conclusions

Darolutamide significantly improved MFS-CI when added to ADT and loco-regional RT for very high-risk localised, or biochemically persistent/recurrent prostate cancer. Follow-up is ongoing to confirm the surrogacy of MFS-CI for OS.

	DarolutamideN=553 events (event-free at 4y)	PlaceboN=553 events (event-free at 4y)	Hazard ratio (95% CI)
MFS	27 (95%)	63 (88%)	0.42 (0.27 to 0.66)
PSA-PFS	46 (91%)	95 (83%)	0.47 (0.33 to 0.67)
PCSS	4 (99%)	7 (99%)	0.58 (0.17 to 1.97)
OS	21 (97%)	24 (95%)	0.88 (0.49 to 1.59)

Clinical trial identification

NCT04136353.

Legal entity responsible for the study

The Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP).

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Disclosure

I.D. Davis: Financial Interests, Personal, Full or part-time Employment, Professor of Medicine and Head of Eastern Health Clinical School: Monash University; Financial Interests, Personal, Full or part-time Employment, Professor of Medicine; Head, Eastern Health Clinical School; medical oncologist: Eastern Health; Financial Interests, Institutional, Local PI, Institutional support for clinical research: Movember Foundation, Merck/MSD, Bristol-Myers Squibb, Exelixis, Astellas, Pfizer, AstraZeneca, Roche/Genentech, Eisai, Bayer, Johnson & Johnson/Janssen, Ipsen, Seagen, Amgen, BioNTech SE; Financial Interests, Institutional, Local PI, EPI-7386-CS-010 trial: ESSA Pharma; Non-Financial Interests, Member of Board of Directors, Director and Chair; unremunerated: ANZUP Cancer Trials Group; Non-Financial Interests, Advisory Role, All honoraria and payments are made directly to ANZUP Cancer Trials Group with no pass-through payment: Roche, Telix Therapeutics, AstraZeneca, Bayer, Astellas, MSD; Non-Financial Interests, Member: ASCO, Clinical Oncology Society of Australia, Medical Oncology Group of Australia, American Association for Cancer Research, Australian Academy of Health and Medical Sciences, Australian Society for Medical Research. S. McBride: Financial Interests, Personal, Advisory Board: Bayer, Pfizer. J. Martin: Financial Interests, Personal, Advisory Board: Astellas; Financial Interests, Personal, Officer, Chief Medical Officer: SeeTreat; Financial Interests, Personal, Stocks/Shares: GenesisCare, SeeTreat, MarginClear; Financial Interests, Institutional, Research Grant, Research grant for a clinical trial in oesophageal cancer: Varian. S. Hughes: Financial Interests, Personal, Invited Speaker, Ran an education seminar on prostate cancer for trainees at 2 national events: P3 2024 meeting; P3 2025 meeting: Bayer; Financial Interests, Personal, Invited Speaker, Co-Chair/organiser for the Annual PROSPECT Prostate and Bladder Cancer Meeting: 2024; 2025: Astellas; Financial Interests, Personal, Invited Speaker, Gave a talk on the prostate cancer diagnostic pathway to Janssen staff: 2025: Janssen; Financial Interests, Personal, Invited Speaker, Panel member at an educational webinar on PSMA Lutetium: 2025: Novartis; Financial Interests, Institutional, Other, Unrestricted grant to run an webinar and a multidisciplinary training day on the management of advanced bladder cancer: 2025 (Astellas had no input to the content): Astellas; Financial Interests, Personal, Full or part-time Employment, I'm the Clinical Lead for Radiotherapy and chair the SABR multidisciplinary meeting: The London Clinic (Charity); Financial Interests, Personal, Ownership Interest, I'm co-founder and co-CEO of The Learning Lab - a Digi-tech company: The Learning Lab; Non-Financial Interests, Other, Member of the Education Council; Course leader for various international education activities: ASCO. D. Pryor: Financial Interests, Personal, Invited Speaker, Educational Meeting Speaker March 2023: Bayer; Financial Interests, Personal, Invited Speaker, Educational meeting speaker November 2021: AstraZeneca; Financial Interests, Personal, Full or part-time Employment, Part time visiting medical officer for private health care provider: Icon Cancer Care. P.J. Kelly: Financial Interests, Personal, Invited Speaker, Delivered a talk on bone health in prostate cancer June 2024: Amgen; Financial Interests, Personal, Advisory Board, Medical opinions for defence council in medicolegal cases: States Claims Agency, Ireland; Financial Interests, Personal, Advisory Board, Barrigel ad board Estro 2025: Teleflex; Financial Interests, Personal, Other, Advisory contract: Boston Scientific; Financial Interests, Personal, Other, Travel support to attend ESTRO annual meeting 2025: Accord; Financial Interests, Personal, Other, Travel support to attend GU ASCO Meeting 2025: Pfizer. S. 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Sweeney: Financial Interests, Personal, Advisory Board, Consultancy: Genentech_Roche, Bayer, Astellas, Pfizer; Financial Interests, Personal, Other, Consultancy: Janssen, Novartis, Amgen; Financial Interests, Personal, Advisory Board, Consultant: Advancell; Financial Interests, Personal, Advisory Board, Advisory Boards: BMS; Financial Interests, Personal, Stocks/Shares, Consultant reimbursement receiving < 1% of company total stocks: Advancell; Financial Interests, Personal, Stocks/Shares, University of Adelaide has established a company in Australia with me and a colleague as co-founders with the UoA patent related to parthenolide and related derivatives protecting people from damaging effect of non-therapeutic radiation. The drug will be developed with focus on preventing civilians and military personnel from acute radiation syndrome from nuclear accidents or attacks. There is no cancer related indication.: Parthera; Financial Interests, Institutional, Advisory Board, Abiraterone plus cabozantinib: Exelixis; Financial Interests, Personal, Other, No royalties or licensing fees. Please see details of stock in shell company as University of Adelaide spin out company called Parthera with plans to out license UoA parthenolide non-therapeutic radiation protectant patent to Parthera. I am named on the patent. There is no cancer related indication: University of Adelaide; Financial Interests, Institutional, Research Grant: Bayer, Janssen, Astellas, Pfizer, Dendreon, Sanofi. All other authors have declared no conflicts of interest.