SUB-urothelial DUrvalumab-zirconium to investigatE local and systemic distribution of durvalumab when injected in the sub-urothelium: SUBDUE-3 (ANZUP 2402)

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Introduction

- Durvalumab is a monoclonal antibody that inhibits binding of PD-L1. Sub-urothelial injection of durvalumab offers a novel therapeutic strategy for bladder cancer.
- The SUBDUE-1 Phase Ib dose escalation study, presented at ASCO 2022, evaluated sub-urothelial durvalumab in patients undergoing radical cystectomy for bladder cancer. The study demonstrated safety, tolerability, and preliminary evidence of tumor microenvironment immunomodulation, with no treatment-related adverse events.
- Prior to initiating Phase 2 trials in patients with NMIBC, it is crucial to determine the extent of durvalumab's local retention in the bladder wall versus systemic distribution
- The SUBDUE-3 study will investigate the local and systemic biodistribution of ^{89}Zr-durvalumab following sub-urothelial injection, providing critical insights into its pharmacokinetics.
- This research will contribute to the understanding and further development of sub-urothelial immunotherapy as a potential treatment for patients with bladder cancer.

Study Schema

Design:

- Investigator initiated
- Open label non-randomised phase 0 clinical trial
- Single centre in Australia

Target Population:

Patients with either MIBC or HR-NMIBC scheduled for radical cystectomy.

Sample Size:

1-3 participants

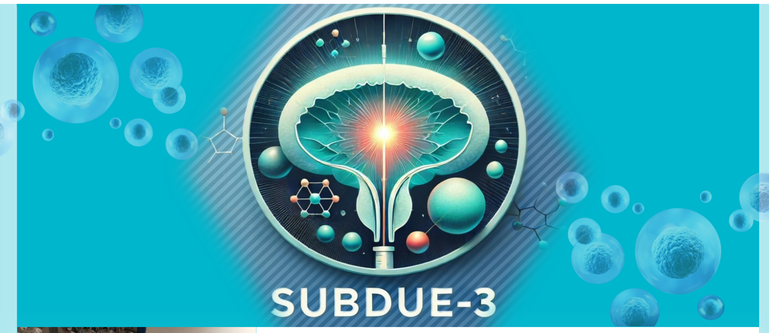
Eligibility

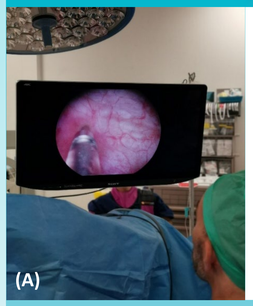
Inclusion:

- Age ≥18 years
- MIBC or HR-NMIBC (T1, high-grade Ta, carcinoma in situ) scheduled for radical cystectomy
- ECOG performance status of <2
- Life expectancy of ≥6 months
- Adequate organ and marrow function
- Negative pregnancy test for female pre-menopausal patients

Exclusion:

- Concurrent cancer therapy with overlapping biological intent (neo-adjuvant chemotherapy permitted)
- Unresolved Grade ≥2 toxicity from previous cancer treatments
- Major surgery within 28 days prior to durvalumab
- History of allogeneic organ transplantation, active or prior autoimmune disorders, history of primary immunodeficiency, active infections, use of immuno-suppressive medication within 14 days before durvalumab administration
- Receipt of a live attenuated vaccine within 30 days before or after durvalumab treatment.
- Pregnant or breastfeeding females





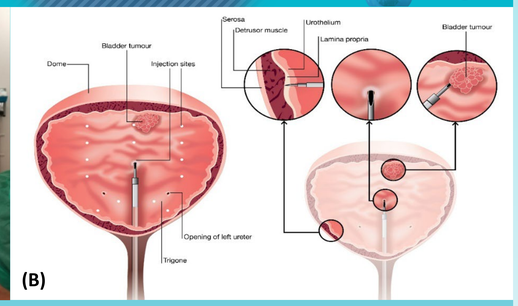


Figure 1: Sub-urothelial injection of durvalumab, with: (A) Cystoscopic view of injection of durvalumab into bladder, and: (B) Diagram illustrating injection method and locations; note (B) is a diagrammatic representation only – not all injection sites are shown.

Endpoints

Primary:

- Visual and semi-quantitative assessment using PET-CT scans over multiple timepoints to assess local (bladder wall) and systemic (liver, kidney, lung, bone marrow) distribution.

Secondary:

- Characterisation of pattern of distribution of ^{89}Zr-durvalumab in the bladder wall using visual and semi-quantitative PET parameters.
- Biodistribution kinetics of bladder and systemic organs (liver, kidney, lung, bone marrow).
- Comparison to the dosimetry in similar cohorts receiving systemic ^{89}Zr-durvalumab will be undertaken, where comparable data is available.
- Pharmacokinetic analysis of blood samples to determine radiation levels.
- Adverse events will be recorded using NCI CTCAE criteria.
- Participant and study staff radiation dose measurements will be undertaken.

Hypothesis and Aim

- Locally administered immunotherapy may offer a novel therapeutic approach by adding a distinct mode of anti-cancer activity while potentially reducing the risk of systemic immune-related adverse events.
- The use of sub-urothelial durvalumab is envisioned as an alternative or complementary therapy to intravesical BCG or chemotherapy in the HR-NMIBC treatment setting.
- The primary aim of this study is to evaluate the local and systemic distribution of radiolabeled ^{89}Zr-durvalumab following sub-urothelial injection

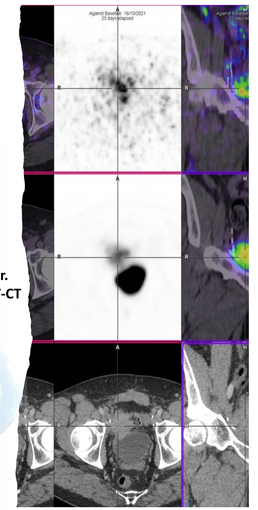


Figure 3: PET-CT imaging of the bladder. Images of Zirconium-girentuximab PET-CT for illustration only

Methods

25mls of sub-urothelial ^{89}Zr-durvalumab constituted as:

(A) **37 Megabecquerels (MBq) in 4mg of Durvalumab in 4mls of 0.9% saline**

combined with

(B) **21mg of Durvalumab in 21 mls of 0.9% saline**

- Injected in 1mL aliquots across 25 locations (25 × 1 mL injections) throughout the bladder using a 5Fr BoNee® needle via 22Fr rigid cystoscope at a general anaesthetic cystoscopy performed 2 weeks pre-cystectomy
- Injections are distributed in a grid-like pattern (including the trigone) to achieve bladder-wide distribution. Where tumor is present, durvalumab is injected at the base.
- After injection, PET imaging will be performed at several time points over 7 days. At each imaging time point, blood sampling will be undertaken to evaluate the systemic bioavailability of ^{89}Zr-durvalumab using a gamma counter. *See Figure 1 and Figure 2.*

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The SUB-urothelial DUrvalumab InjEction-1 (SUBDUE-1) trial: first-in-human trial in patients with bladder cancer

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First published: 12 March 2024 | https://doi.org/10.1111/bju.16325 | Citations: 2

1 Enrolment

2 Sub-urothelial injection of ^{89}Zr-Durvalumab

3 PET imaging and blood PK samples:

1-3 hours
24 hours
72 hours
5-7 days

Figure 2: SUBDUE-3 Study Schema

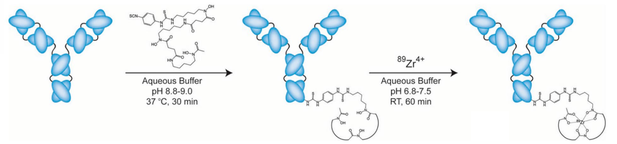

Figure 4: The Bioconjugation and Radiosynthesis of ^{89}Zr-DFO-labeled Antibodies

Conclusions

- SUBDUE-3 is currently open and recruiting in Australia with a one-year recruitment strategy expected to finish recruiting in 2025.
- In SUBDUE-3, ^{89}Zr-durvalumab will be administered by sub-urothelial injection and PET imaging will be performed at varying time points to analyse local and systemic distribution.
- Dosimetric analyses will determine the distribution and radiation dose of ^{89}Zr-durvalumab both within the bladder and systemically, providing critical insights for future therapeutic strategies in bladder cancer treatment.
- This will contribute to the understanding and further development of sub-urothelial immunotherapy as a potential treatment for patients with bladder cancer.

This study is being conducted by the Australian and New Zealand Urogenital and Prostate Trials Group Ltd (ANZUP) in collaboration with South Metropolitan Health Service, Western Australia and the University of Western Australia. ANZUP is supported by the Australian Government through a Cancer Australia infrastructure Grant.

We thank all trial participants and their families, principal investigators, co-investigators, and study coordinators for their commitment to this trial.

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