SUB-urothelial Durvalumab InjEction – 1 (**SUBDUE-1**) – Results from the first nine urothelial cancer patients using a dose-escalation schedule

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Background:

- The sub-urothelial administration of checkpoint inhibitors has not been reported.
- This approach could be safer and/or more efficacious than systemic delivery for patients with non-muscle-invasive bladder cancer (NMIBC).
- A potential role for sub-urothelial durvalumab injection in the management of bladder cancer was first mooted by Prof Hayne in mid-2018.
- The idea was developed by ANZUP through the bladder concept development process leading to the SUBDUE-1 trial.
- Following necessary Human Research Ethics Committee and governance approvals, the first sub-urothelial durvalumab injection was performed on 16 December 2019 (Figure 1).

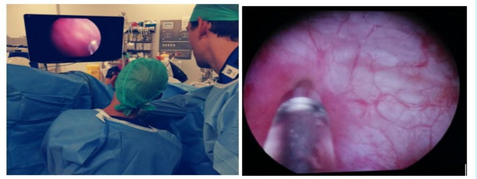
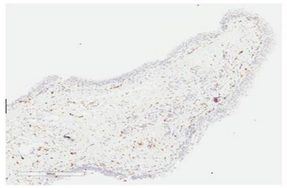


Figure 1: First patient receiving sub-urothelial durvalumab injection

Methods:

- This phase 1b study employed a 3+3 dose-escalation design to explore tolerability, safety and immunological impact of sub-urothelial durvalumab, a programmed death-ligand 1 (PDL1) monoclonal antibody. Durvalumab inhibits signalling mediated by PD-L1.
- Eligible participants had high risk NMIBC or MIBC without prior chemotherapy or immune checkpoint inhibition (BCG allowed) and were planned for cystectomy.
- Participants received 25, 75 or 150mg durvalumab diluted in 25mL normal saline injected into the sub-urothelium at 25 locations (25x1mL injections), at least 2 weeks prior to radical cystectomy.
- Systematic four quadrant cold cup bladder biopsies were taken immediately prior to durvalumab injection and immediately prior to scheduled cystectomy.
- Tumour, if present, was biopsied before and after injection and bladder maps recorded.
- International Prostate Symptom Index (IPSS) and O'Leary symptom score at various time points, and adverse events (AE) as per CTCAE (Version 4) were recorded. Immunohistochemistry for CD3, CD8, CD68 and CD168 was carried out (Figure 2).
- Relative changes in immune cell counts (RCI) on bladder biopsy for each IHC marker are reported (value > 1.0 designating an increase post-durvalumab) (example figure 2)



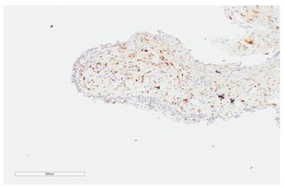


Figure 2: showing comparison of bladder biopsies from the same location on the left anterior bladder wall a) pre- and b) post- injection with durvalumab. CD168 immunohistochemistry shows an increase in CD168-positive cells.

Results:

- Nine participants were recruited; eight male (89%), 1 female; mean age 72 years (range 56 – 82).
- No dose-limiting toxicities were observed.
- No evidence of treatment-related effect on IPSS or O'Leary Symptom scores was seen. Fourteen AEs were reported by six (67%) patients: 10 were Grade 1, 3 Grade 2, 1 Grade 3.
- None were considered immune- or treatment-related by investigators. Transient elevation of peri-operative thyroid stimulating hormone was seen in two subjects, which normalised without intervention.
- No hepatitis was seen.
- All patients underwent planned cystectomy. RCI of different immune populations was calculated (Table 1, Figure 3).
- Visible tumour was present in only 4 patients limiting interpretation of RCI. RCI varied significantly between cell types (p = 0.008*).
- RCI numerically increased by dose but did not reach statistical significance (p = 0.076**). A numeric increase in monocytes was seen, most marked at the 150mg dose.

	CD3	CD8	CD68	CD168	p=0.008
25mg	1.14	1.10	1.16	0.95	
75mg	0.86	0.86	1.44	1.48	
150mg	1.48	1.15	1.92	1.56	
p=0.076					

Table 1: Mean RCI of different immune populations by dose of sub-urothelial durvalumab

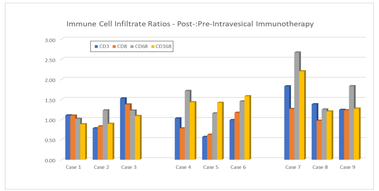


Figure 3: relative changes in Immune cell counts (RCI) after durvalumab injection in individual patients

Conclusion and discussion:

- Sub-urothelial injection of durvalumab was safe at all three dose levels without any drug-related adverse events
- Immunological studies showed differential effects on immune cells with the macrophage population most affected.
- All 9 patients proceeded to cystectomy as scheduled, recovered well and are alive without evidence of disease recurrence.
- A complete pathological response was achieved in one patient with refractory CIS unresponsive to BCG and gemcitabine. Pre-durvalumab biopsies confirmed persistent disease with a subsequent complete response to durvalumab 150mg sub-urothelial injection. No bladder CIS was detectable on either repeat matched cold cup biopsies or on the whole mount cystectomy specimen.
- SUBDUE-1 has outperformed expectations, demonstrating sub-urothelial durvalumab injection to be feasible and safe without immune-related adverse events.
- Immune infiltrate changes varied significantly between immune cell types with a trend to increased macrophage infiltration that warrants future study.
- Further studies investigating the role of 150mg sub-urothelial durvalumab in the management of NMIBC are planned.

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This study is being conducted by the Australian and New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group Ltd. ANZUP is supported by the Australian Government through Cancer Australia.
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