Ipilimumab + nivolumab in people with rare variant renal cell carcinoma refractory to nivolumab alone: Part 2 of UNISON (ANZUP 1602) nivolumab then ipilimumab + nivolumab in advanced non-clear cell renal cell carcinoma

C. Conduit[1], G Kichendasse[2], C A Harris[3,4], H Gurney[5], T Ferguson[6], F Parnis[7], J C Goh[8], M F Morris[9], C Underhill[10,11], D W Pook[12], I D Davis[1,13,14], F Roncolato[1,15,16], M L Harrison[17], S Begbie[18], A M Joshua[19], E Link[20], E J Hovey[21] and C Gedye[22] on behalf of the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP)

1. Australian and New Zealand Urogenital and Prostate Cancer Trials Group, (ANZUP), Sydney, NSW, Australia, 2. South Oncology Clinical Research Unit, Bedford Park, SA, Australia, 3. St George Hospital Cancer Care Centre, Kogarah, NSW, Australia, 4. University of New South Wales, Kensington, NSW, Australia, Macquarie University, Sydney, NSW, Australia, 6. Royal Perth Hospital, Perth, WA, Australia, 7. Ashford Cancer Centre, North Adelaide, SA, Australia, 8. Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia, 9. Sunshine Coast University Hospital, Birtinya, QLD, Australia, 10. Border Medical Oncology Research Unit, Albury Wodonga Regional Cancer Centre, 11. Rural Medical School, Albury Campus, University of New South Wales, Albury-Wodonga, NSW, Australia, 12. Monash Health, Melbourne, VIC, Australia, 13. Eastern Health Clinical School, Monash University, Box Hill, VIC, Australia, 14. Eastern Health, Melbourne, VIC, Australia, 15. NHMRC Clinical Trials Centre, University of Sydney, Camperdown, NSW, Australia, 16. Macarthur Cancer Therapy Centre, Campbelltown, NSW, Australia, 17. Royal Prince Alfred Hospital, Hunters Hill, NSW, Australia, 18. North Coast Cancer Institute, Port Macquarie Base Hospital, Port Macquarie, NSW, Australia, 19. St Vincent's Hospital Sydney Darlinghurst NSW, Australia, 20. Centre for Biostatistics and Clinical Trials (BaCT), Peter MacCallum Cancer Centre, Melbourne, VIC, Australia, 21 Prince of Wales Hospital, Sydney, NSW, Australia, 22. Calvary Mater Newcastle, Waratah, NSW, Australia.

1. Background and rationale

- UNISoN is an open-label, two-part sequential multicentre phase 2 clinical trial evaluating the sequential addition of ipilimumab to nivolumab in metastatic rare variant, non-clear cell renal cell carcinomas (nccRCC) progressing on nivolumab monotherapy.
- **Aim:** To determine the effectiveness of adding ipilimumab to nivolumab in metastatic nccRCC refractory to nivolumab monotherapy.
- **Target population:** Locally advanced or metastatic nccRCC not amenable to curative treatment; any nccRCC histology permitted, provided if >50% non-clear component in diagnostic sample.
- Interim results arising from UNISoN have previously been reported, including:
  - Part 1 (nivolumab monotherapy) – ASCO GU 2021.
    - Objective tumour response rate (OTRR) of 17%.
    - 6-month progression-free survival (PFS) of 45%.
  - Part 2 (sequential ipilimumab/nivolumab in nivolumab refractory tumours) at a median of 20.3 months follow-up – ASCO AM 2021
    - OTRR of 10%.
    - Median PFS 2.6 months (95% confidence interval [CI] 2.2-3.8 months).
    - PFS6 25% (95% CI 13-39).
- Here we report the final planned analysis of UNISoN.

2. Study Design, Schema, Population

Design: open-label, two-part sequential multicentre phase 2 clinical trial evaluating sequential ipilimumab plus nivolumab in metastatic non-clear cell renal cell carcinomas refractory to nivolumab monotherapy.
Sample size: To detect OTRR 30% in Part 2 (α=0.05, β=0.2); assumed ~55% of participants eligible for inclusion (n=48).
Population: 83 evaluable participants enrolled to UNISoN Part 1, representative of nccRCC subtypes; 41 were enrolled to Part 2, including type 1 (n=4, 10%) and type 2 papillary (n=13, 32%), chromophobe (n=8, 20%) RCC. Median age 63 years (range 54-70). ECOG 0 (n=25, 61%).
The 41 participants enrolled to UNISoN Part 2 were followed for a median of 22 months (16-30).

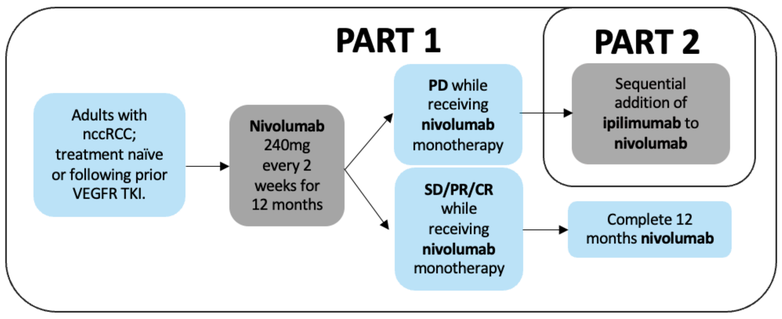


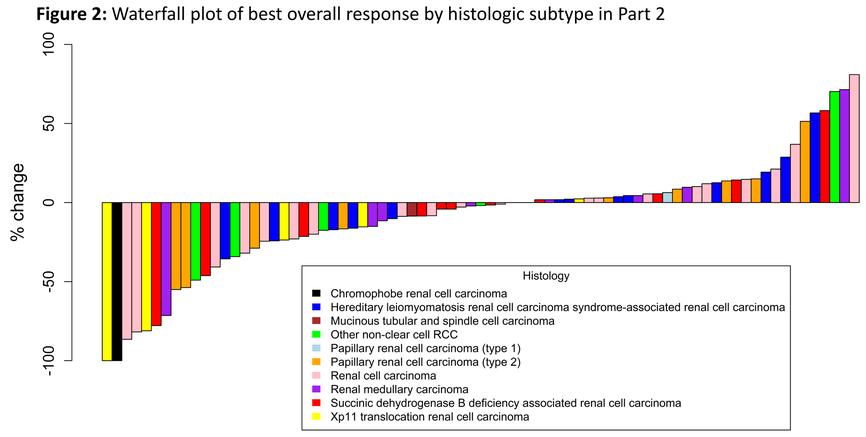
Figure 1: Study Schema. nccRCC = non-clear cell renal cell carcinoma, VEGFR TKI = vascular endothelial growth factor receptor tyrosine kinase inhibitor, PD = progressive disease (as assessed by Response Evaluation Criteria in Solid Tumours [RECIST]), SD = stable disease, PR = partial response, CR = complete response

3. Study Endpoints

- **Primary Objectives:** OTRR for nivolumab monotherapy in Part 1 and sequential addition of ipilimumab to nivolumab in Part 2.
- **Secondary Objectives:** PFS, duration of response, time to treatment discontinuation, immune-related OTRR (irOTRR), immune-related disease control rate (irDCR), overall survival (OS), immune-related adverse events (irAE) and toxicity.
- **Translational/Exploratory Objectives:** association between clinical outcomes and biomarkers, including immune-related biomarkers, in nccRCC.

4. Results

Figure 2: Waterfall plot of best overall response by histologic subtype in Part 2



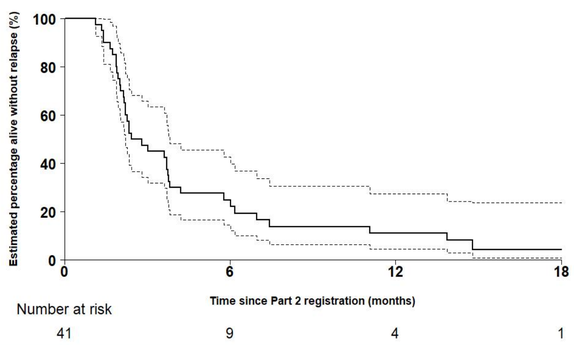
A) Primary endpoint: Objective Tumour Response Rate in Part 2

- 33 (79%) participants were evaluable; 6 participants died prior to evaluation, and 2 participants were either too unwell or withdrew consent.
- OTRR = 12% (all partial responses), clinical benefit rate = 48%.
- Responses did not clearly correspond to histologic subtype (see Figure 2).

B) Secondary endpoint: Progression-Free Survival in Part 2

- 6-month PFS 25% (95% CI 13-39) (see Figure 3).
- 12-month PFS 11% (95% CI 4-23%).

Figure 3: Kaplan-Meier PFS in Part 2; grey dotted lines represent CI



C) Secondary endpoint: Overall Survival in Parts 1 and 2

- In Part 1/2, mOS was 24 months (95% CI 16-28) (see Figure 4).
  - 12-month OS 65% (54-74%).
- Participants progressing to Part 2 experienced shorter OS: mOS 10 months (95% CI 6-17) (see Figure 5).

D) Secondary endpoint: Median duration of response in Part 1

- The median duration of response was 20.7 months (95% CI 3.71-NR).
- Of the participants who experienced CR/PR (n=14), 47% (95% CI 21-69) remained in response at 18-months.

E) Secondary endpoint: Median time on treatment

- In Part 2, the median time on treatment was 2.1 months (95% CI 2.2-3.8).
- Median number of cycles of ipilimumab plus nivolumab was 3 (range 1-24)

F) Secondary endpoint: Adverse events (AE) in Part 2 (assessed by CTCAE)

- 33/41 (80%) participants experienced an AE; n=15 G3, n=5 G4-5.
- The most common AEs included diarrhoea/colitis (n=11; n=4 G3) and rash (n=4).
- One participant experienced G5 pneumonitis attributed to study treatment.

Figure 4: Kaplan-Meier OS in Part 1/2

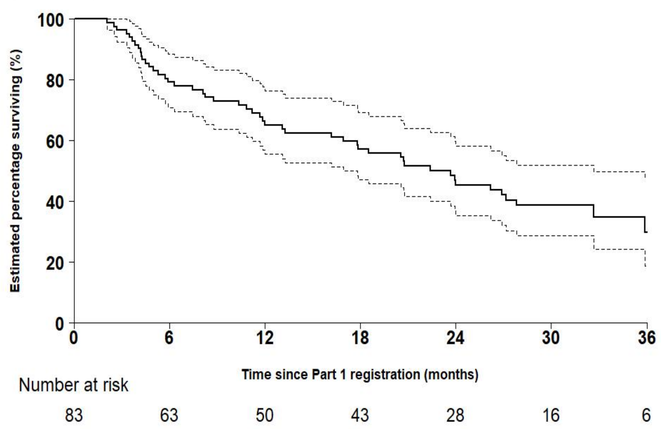
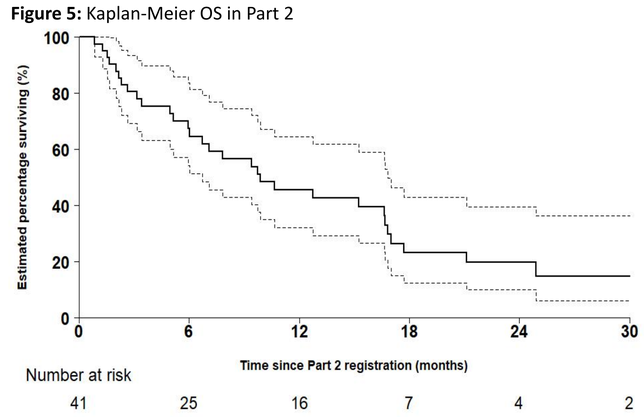


Figure 5: Kaplan-Meier OS in Part 2



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5. Summary

The primary endpoint of the UNISoN study was not met as a minority of participants benefited from treatment with ipilimumab and nivolumab after failure of nivolumab monotherapy. Whilst some participants did derive meaningful benefit from this approach, novel biomarkers of response are required to guide intensification of therapy at the outset and explore other strategies. Translational research within UNISoN continues.

SCAN ME

ClinicalTrials.gov Identifier: **NCT03177239**
Website: **www.anzup.org.au**
For all trial enquiries: trials@anzup.org.au

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@DrCraigGedye

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