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Original Article

A phase II trial of nivolumab followed by ipilimumab and nivolumab in advanced non-clear-cell renal cell carcinoma

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Objective

To evaluate the efficacy of sequential treatment with ipilimumab and nivolumab following progression on nivolumab monotherapy in individuals with advanced, non-clear-cell renal cell carcinoma (nccRCC).

Materials and Methods

UNISoN (ANZUP1602; NCT03177239) was an open-label, single-arm, phase 2 clinical trial that recruited adults with immunotherapy-naïve, advanced nccRCC. Participants received nivolumab 240 mg i.v. two-weekly for up to 12 months (Part 1), followed by sequential addition of ipilimumab 1 mg/kg three-weekly for four doses to nivolumab if disease progression occurred during treatment (Part 2). The primary endpoint was objective tumour response rate (OTRR) and secondary endpoints included duration of response (DOR), progression-free (PFS) and overall survival (OS), and toxicity (treatment-related adverse events).

Results

A total of 83 participants were eligible for Part 1, including people with papillary (37/83, 45%), chromophobe (15/83, 18%) and other nccRCC subtypes (31/83, 37%); 41 participants enrolled in Part 2. The median (range) follow-up was 22 (16–30) months. In Part 1, the OTRR was 16.9% (95% confidence interval [CI] 9.5–26.7), the median DOR was 20.7 months (95% CI 3.7-not reached) and the median PFS was 4.0 months (95% CI 3.6–7.4). Treatment-related adverse events were reported in 71% of participants; 19% were grade 3 or 4. For participants who enrolled in Part 2, the OTRR was 10%; the median DOR was 13.5 months (95% CI 4.8–19.7) and the median PFS 2.6 months (95% CI 2.2–3.8). Treatment-related adverse events occurred in 80% of these participants; 49% had grade 3, 4 or 5. The median OS was 24 months (95% CI 16–28) from time of enrolment in Part 1.

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Conclusions

Nivolumab monotherapy had a modest effect overall, with a few participants experiencing a long DOR. Sequential combination immunotherapy by addition of ipilimumab in the context of disease progression to nivolumab in nccRCC is not supported by this study, with only a minority of participants benefiting from this strategy.

Keywords

carcinoma, renal cell, immunotherapy, kidney neoplasms, clinical trial

Introduction

Despite increasing treatment options for individuals diagnosed with advanced clear-cell RCC (ccRCC), there is a paucity of effective systemic treatments for individuals with rare variant or non-clear-cell (nccRCC) histologies. Immunotherapy has changed the treatment landscape of ccRCC, improving landmark median overall survival (OS) to more than 4 years for individuals with International Metastatic RCC Database Consortium (IMDC) intermediate-/poor-risk disease [1]. However, people with nccRCC were excluded from most large, practice-changing trials in RCC [2–5], with worldwide access barriers being a pervasive issue, resulting in significant inequity and, in turn, short survival for many [6].

In the absence of prospective trials, clinicians treating nccRCC patients have historically extrapolated from trials of ccRCC or relied on retrospective datasets [7–11]. nccRCC comprises a biologically and clinically heterogeneous group of neoplasms, and it is difficult to generalize results because of differences among nccRCC histological subtypes [12–14]. There is however a strong biological rationale for the use of immune checkpoint inhibitors [15], with multiple trials evaluating immunotherapy strategies in patients with nccRCC [16–21].

UNISoN (ANZUP 1602), an open-label, single-arm, two-part sequential, multi-centre, phase 2 clinical trial, evaluated a novel strategy involving the sequential addition of ipilimumab, a humanized cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody, to nivolumab, an anti-programmed cell death-1 (PD1) monoclonal antibody, in people with advanced nccRCC progressing on nivolumab monotherapy (NCT03177239). A sequential design was chosen in preference to an upfront combination approach, for two reasons: (1) so that intensified treatment could be directed to those most likely to require it, sparing others from unnecessary potential treatment-related toxicity, and (2) to reduce cost associated with treatment and improve the likelihood of securing government reimbursement for ongoing supply of the drug(s), if the trial was successful. There are currently no subsidized anti-cancer therapies for this population in Australia and financial toxicity is a concern for patients and health systems [22].

Methods

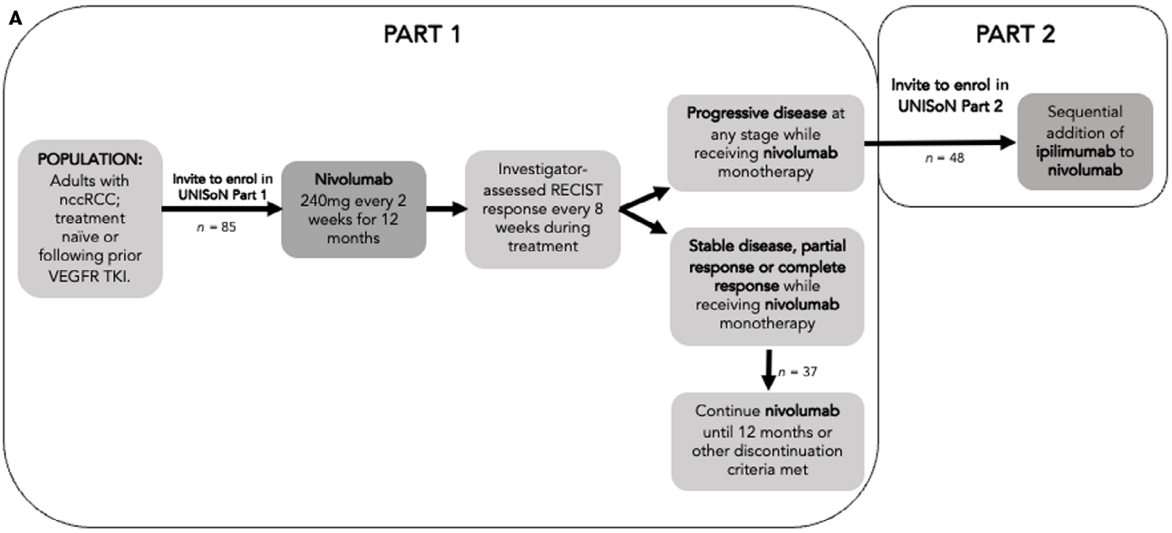
Participants

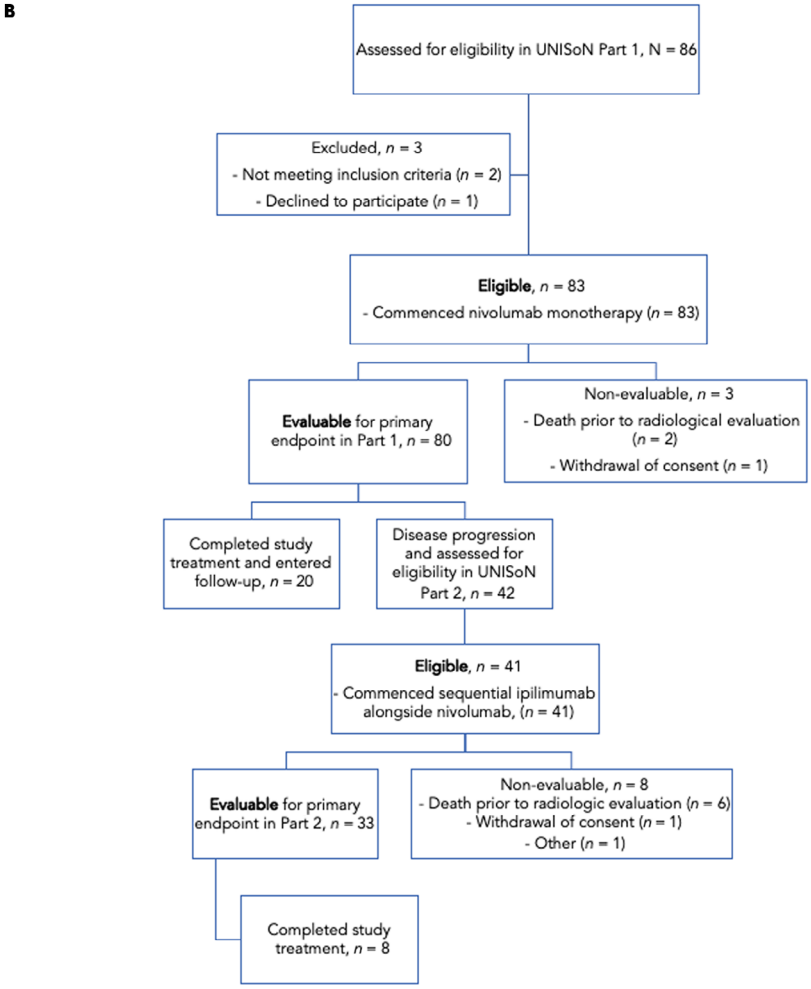
Eligible participants were aged ≥18 years with locally advanced or metastatic nccRCC not amenable to curative treatment. Any nccRCC histology was permitted if a non-clear component of >50% was present in the diagnostic sample. Prior treatment with other systemic therapy including tyrosine kinase inhibitors and/or radiotherapy was permitted. Participants required an Eastern Cooperative Oncology Group performance status score of ≤1 (at screening for Part 1, and at enrolment in Part 2, where applicable) and measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Key exclusion criteria were inadequate organ function, untreated central nervous system metastases, existing autoimmune disease requiring systemic treatment within the past 2 years, or other conditions requiring systemic corticosteroids within 14 days of enrolment. Prior treatment with T-cell co-stimulating or immune checkpoint therapies was not permitted. Full criteria are listed online (NCT03177239).

Study Treatment

Nivolumab was administered at 240 mg i.v. over the course of 30 min every 14 days, for a maximum of 12 months, unless there was evidence of disease progression or unacceptable toxicity, of if death or other discontinuation criteria occurred sooner. If a participant experienced disease progression before 12 months, they were invited to enrol in Part 2 of UNISoN, where up to four cycles of ipilimumab (1 mg/kg i.v. every 21 days) was added to nivolumab (240 mg i.v. every 21 days; Fig. 1A). If participants experienced at least stable disease following combination of ipilimumab and nivolumab, they continued nivolumab 240 mg i.v. every 14 days for a maximum of 12 months (inclusive of treatment in Part 1), whereupon participants entered follow-up. Compassionate treatment off-study with a further 12 months of nivolumab was allowed. No dose reductions were permitted. Dose delays for adverse events were allowed, however, if the delay was ≥8 weeks, treatment was permanently discontinued.

Fig. 1 Trial design **(A)** and CONSORT diagram **(B)**. nccRCC, non-clear-cell renal cell carcinoma, RECIST, Response Evaluation Criteria in Solid Tumours; TKI, tyrosine kinase inhibitors; VEGFR, vascular endothelial growth factor.





Trial Oversight

UNISoN was an investigator-initiated trial, designed by the authors as members of the Australian and New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group (Sponsor), coordinated by the Centre for Biostatistics and Clinical Trials (BaCT), and approved by the North Sydney Local Health District Health Research Ethics Committee. All participants provided written informed consent. An independent data and safety monitoring committee (IMDC) reviewed efficacy and safety. Drug supply and funding were provided by Bristol-Myers Squibb, who had no direct input into study conduct, data collection/analysis, or manuscript preparation.

Endpoints and Assessments

The primary endpoint of UNISoN was objective tumour response rate (OTRR), defined as the percentage of participants with a confirmed partial or complete response per investigator-assessed RECIST in Part 1 and Part 2. Secondary endpoints included duration of response (DOR), progression-free survival (PFS), OS, adverse events, and time to treatment discontinuation in Parts 1 and 2. Translational exploratory endpoints, including associations between clinical outcomes and biomarkers, will be reported separately.

Disease assessments included CT or MRI of the brain, chest, abdomen and pelvis at baseline, continuing every 8 weeks until progression or treatment discontinuation, and then every 12 weeks during follow-up. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Participants were permitted to continue treatment after progression if specific eligibility criteria were met. Treatment beyond 12 months was available through compassionate access for up to an additional 12 months.

Statistical Considerations and Analyses

We estimated that recruitment of 85 eligible participants in Part 1 of UNISoN would allow enrolment of approximately 48 participants (55%) in Part 2 after disease progression, allowing for 80% power to detect a clinically relevant OTRR of 30% from sequential ipilimumab and nivolumab, and to reject the null hypothesis of a clinically non-relevant OTRR of 15% (one-sided $\alpha = 0.05$).

Time-to-event endpoints were estimated using the Kaplan–Meier method, accompanied by medians, rates and two-sided 95% CIs. Binary endpoints of treatment activity are presented as proportions with CIs. All adverse events and serious adverse events were tabulated according to worst grade.

Results

Participants and Treatments

Between November 2017 and September 2019, a total of 86 participants enrolled at 19 sites across Australia. Of these, 83 (97%) were eligible and received nivolumab; one participant withdrew consent prior to commencing study treatment, and two participants were ineligible following central review of imaging (Fig. 1B). Of the eligible participants, histological subtypes included papillary type 2 (23/83, 28%), chromophobe (15/83, 18%), papillary type 1 (14/83, 17%), sarcomatoid RCC (6/83, 7%), Xp11 translocation (5/83, 6%), hereditary leiomyomatosis syndrome-associated RCC (5/83, 6%), or other histologies (7/83, 8%). Participant characteristics were representative of a population with advanced nccRCC (Table 1). Eleven participants (13%) received tyrosine kinase inhibitor therapy before enrolment, including agents targeting vascular endothelial growth factor, MET and/or ERK; 15 participants (18%) received radiotherapy. The majority had previously undergone surgery (53/83, 64%).

The median time to treatment discontinuation for participants in Part 1 was 5.1 months (95% CI 3.6–8.3). Twenty participants (24%) completed 12 months of nivolumab monotherapy without progression or toxicity and entered survival follow-up. The primary reason for discontinuation of treatment in Part 1 was disease progression (45/83, 54%), with 41 participants (49%) enrolling in UNISoN Part 2 following disease progression. In Part 2, the median time to treatment discontinuation was 2.1 months (95% CI 1.8–2.8); 10% (95% CI 3–21) continued study treatment 6 months from treatment commencement.

Efficacy

Treatment response data were available for 80 participants (80/83, 96%) in Part 1; two participants died prior to evaluation, and one withdrew consent. Tumour reduction was observed in 41/83 participants (49%) and the investigator-assessed OTRR was 17.5% (95% CI 10–27). Three participants (4%) experienced a complete response and 11 (14%) experienced a partial response (Table 2 and Fig. 2A), with numerical differences seen between histological subtypes (Table S1). Of the 27 (27/80, 34%) participants who experienced progressive disease as their best overall response, three (3/13, 23%) had papillary type 1, 10 (10/23, 43%) had papillary type 2 and four (4/13, 31%) had chromophobe histology, with the remaining 10 having other rare subtypes (Fig. 2B,C).

After a median 29 months' (95% CI 28–33) follow-up in Part 1, the median PFS was 4 months (95% CI 3.6–7.4) and the 12-month PFS rate was 30% (95% CI 21–40; Fig. 3A). The median DOR for responding participants was

Table 1 Baseline characteristics of the participant population.

Characteristic		Part 1, *n* = 83
Median (range) age, years		64 (21–88)
Sex, *n* (%)	Male	57 (69)
	Female	26 (31)
ECOG performance status, *n* (%)	0	51 (61)
	1	32 (39)
Synchronous or metachronous diagnosis, *n* (%)	Disease recurrence after prior curative-intent nephrectomy	41 (49)
	Synchronous diagnosis of metastatic disease	42 (51)
Previous VEGFR-targeted or other systemic therapy, *n* (%)		11 (13)
Histological subtype, *n* (%)	Papillary, type 1	14 (17)
	Papillary, type 2	23 (28)
	Chromophobe	15 (18)
	RCC, not otherwise specified	8 (10)
	Sarcomatoid RCC	6 (7)
	Hereditary leiomyomatosis and renal cell cancer	5 (6)
	Xp11 translocation	5 (6)
	Renal medullary carcinoma	2 (2)
	Succinate dehydrogenase-associated	1 (1)
	Mucinous tubular spindle cell carcinoma	1 (1)
	Other (papillary RCC [type undetermined], spindled and epithelioid morphology, collecting duct carcinoma)	3 (4)

ECOG, Eastern Cooperative Oncology Group; VEGFR, vascular endothelial growth factor receptor.

Table 2 Objective response rate, best overall response and duration of response.

Endpoint		Part 1 (*n* = 83)	Part 2 (*n* = 41)
Confirmed objective response, % (95% CI)		16.9 (9.5–26.7)	10 (3–23)
Confirmed best overall response, *n* (%)	Complete response	3 (4)	0 (0)
	Partial response	11 (13)	4 (10)
	Stable disease	39 (47)	12 (29)
	Progressive disease	27 (34)	17 (41)
	Unable to determine or not reported	3 (4)	8 (20)
Duration of response	Median, months (95% CI)	20.7 (3.71–NR)	N/A*
	6-month, % (95% CI)	79 (47–93)	
	12-month, % (95% CI)	71 (41–88)	
	18-month, % (95% CI)	57 (28–78)	

*N/A, not applicable; NR, not reached. *Duration of response in Part 2 was not assessed as treatment information post-study could not be reliably assessed.*

20.7 months (95% CI 3.7–not reached), with 57% (95% CI 28–78) of participants continuing to respond after 18 months (Table 2). The median OS of participants in Part 1 was 24 months (95% CI 16–28). At 6 months from registration, 79% (95% CI 69–87) were alive; 65% (95% CI 54–74) were alive at 12 months (Fig. 3D).

In Part 2, 80% of participants (33/41) were evaluable for response, with eight participants excluded from efficacy analysis; six died prior to evaluation, one withdrew consent and one was too unwell to undergo evaluation. The OTRR was 10% (95% CI 3–23), all partial responses (Table 2). After a median follow-up of 22 months (95% CI 16–30) from registration in Part 2, the median PFS was 2.6 months (95% CI 2.2–3.8; Fig. 3B). Twenty-five percent (95% CI 13–39) of participants were free from progression or death at 6 months. The median OS for this cohort was 10 months (95% CI 6–17); 67% (95% CI 50–80) were alive at 6 months (Fig. 3E).

Safety

Treatment-related adverse events of any grade occurred in 59 participants (59/83, 71%) during Part 1 treatment, with 20 (24%) experiencing grade 3 or 4 adverse events (Table 3). The most common grade 3 or 4 adverse events included elevated lipase (13/83, 16%), elevated amylase (4/83, 5%) and colitis (2/83, 2%). The most common adverse events of any grade were fatigue (24/83, 29%), rash (17/83, 20%), nausea (12/83, 15%) and hypothyroidism (10/83, 12%). While in follow-up, one (1/83, 1%) participant experienced a grade 4 reduction in left ventricular ejection fraction, which was considered possibly related to nivolumab. Treatment-related adverse events leading to discontinuation occurred in 9.6% of participants (8/83). No deaths were attributable to treatment.

In Part 2, during treatment or follow-up, 33 participants (33/41, 80%) experienced treatment-related adverse events of any

Fig. 2 Best change from baseline in target lesions in **(A)** Part 1 nivolumab alone and **(B)** ipilimumab + nivolumab Part 2; **(C)** Swimmers' plot demonstrating response to treatment in UNISoN Part 1 and 2. Note: Three patients in Part 1 and eight patients in Part 2 were not evaluable. RECIST, Response Evaluation Criteria in Solid Tumours.

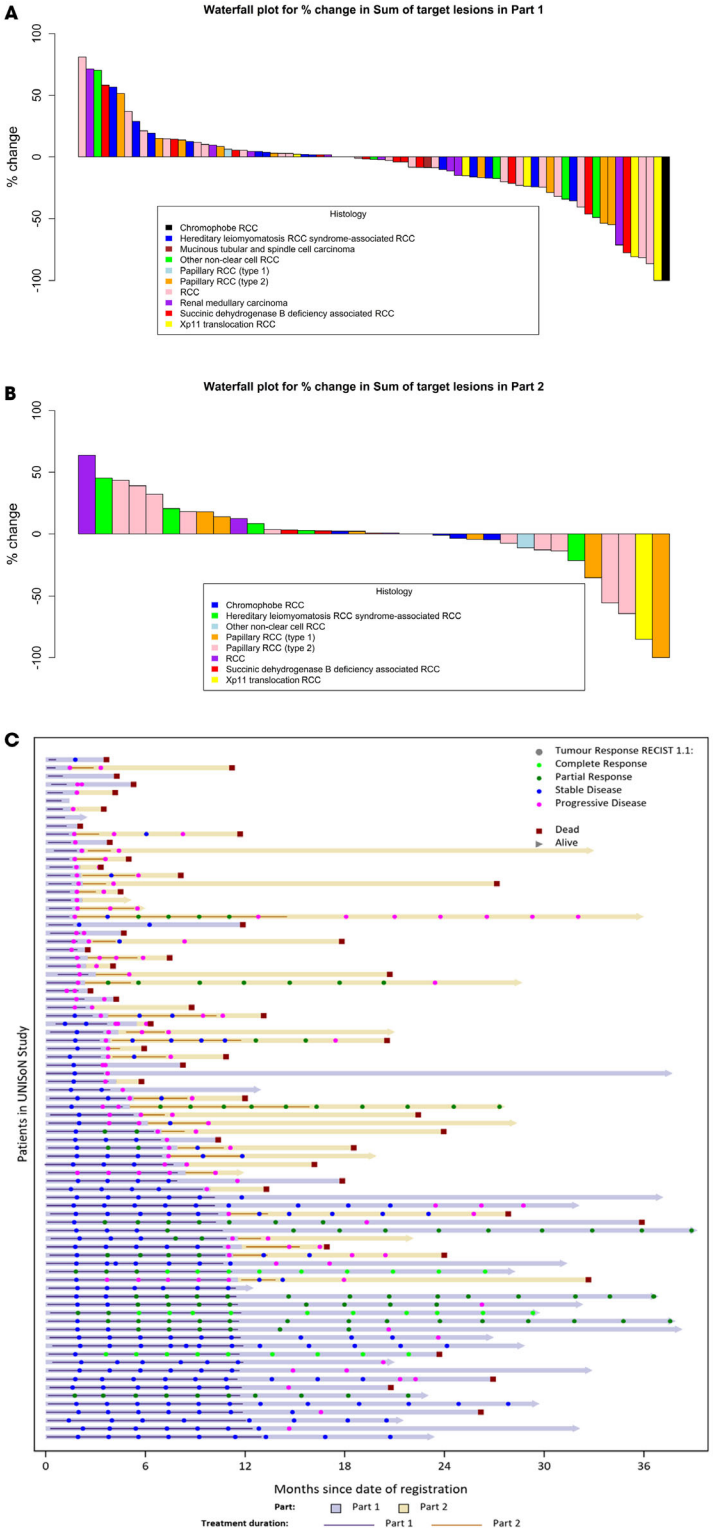
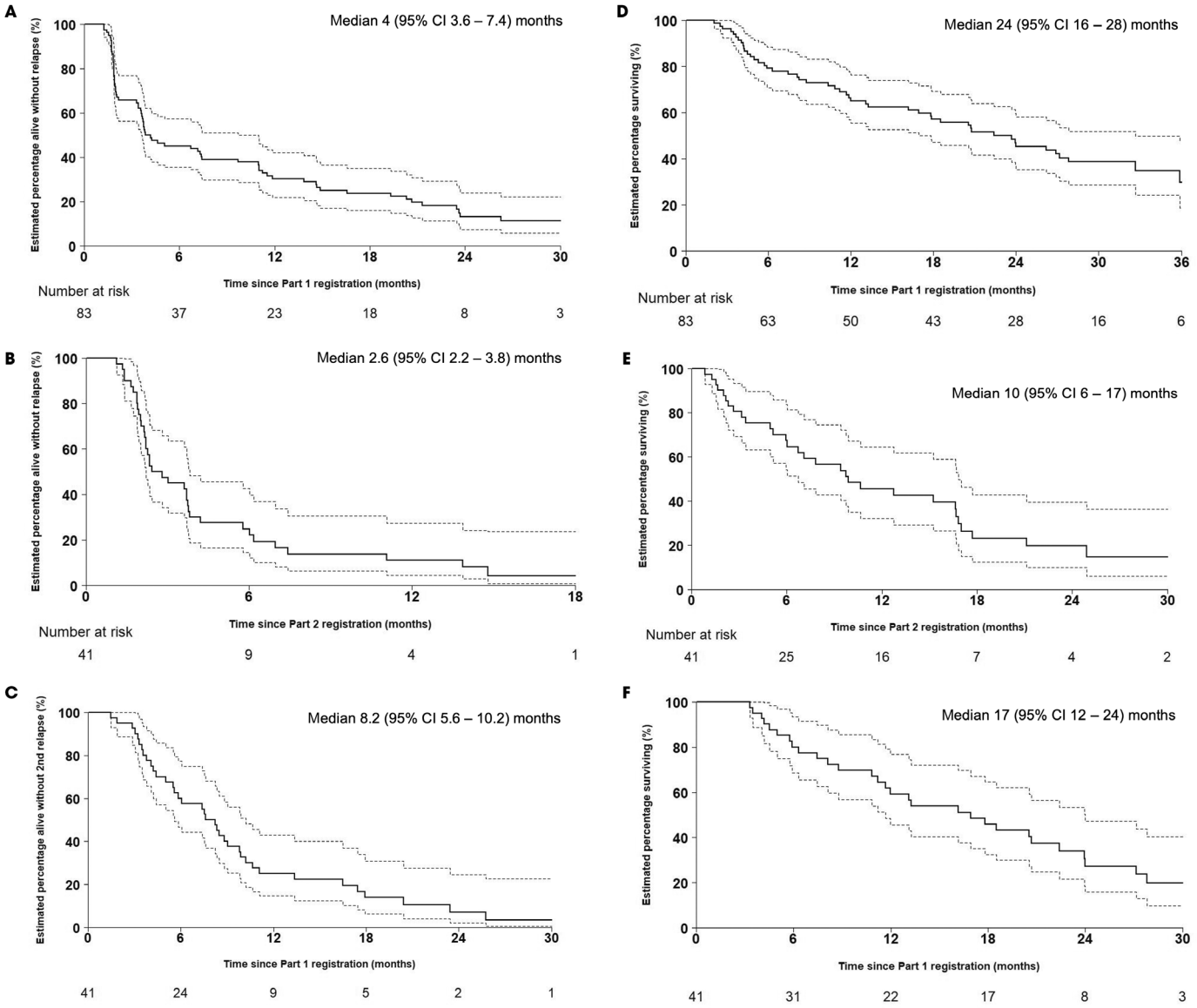


Fig. 3 Progression-free survival per investigator assessment in **(A)** Part 1, nivolumab alone, **(B)** ipilimumab + nivolumab in Part 2 and **(C)** free from second progression for those who had ipilimumab + nivolumab. Overall survival in **(D)** Part 1, nivolumab alone, **(E)** Part 2 ipilimumab + nivolumab and **(F)** Part 1 and 2 for those who had ipilimumab + nivolumab.



grade, with 20 (49%) experiencing grade 3, 4 or 5 adverse events (Table 3). The most common grade 3 or 4 adverse events were diarrhoea or colitis (4/41, 10%), and elevated lipase (3/41, 7%). One treatment-related death (2%) due to pneumonitis was recorded during follow-up after treatment cessation.

Discussion

Immune checkpoint immunotherapy is beneficial for many people with ccRCC, but less is known about the role of immunotherapy in people with RCC of variant histology. The trade-off between efficacy and toxicity of sequential vs. upfront combination immunotherapy is unclear in RCC (and other cancers) and pragmatic approaches to improving access to effective anti-cancer therapies are needed worldwide. The UNISoN study aimed to address these questions with a sequential immunotherapy trial design for people with nccRCC.

Nivolumab monotherapy shows encouraging anti-tumour activity in a population with advanced nccRCC of any histology, with 17% of participants in our cohort experiencing an objective response and 67% deriving clinical benefit. Importantly, UNISoN recruited a high proportion of participants with non-papillary nccRCC histology including

Table 3 High-grade immune-related adverse events or immune-related adverse events occurring in 5% or more of participants during treatment and follow-up.

		Part 1			Part 2		
		Any grade, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)	Any grade, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)
Any adverse event		59 (71)	15 (18)	5 (6)	33 (80)	15 (37)	4 (10)
Skin and subcutaneous tissue disorders	Any	31 (37)	1 (1)	0 (0)	9 (22)	2 (5)	0 (0)
	Rash	17 (20)	1 (1)	0 (0)	4 (10)	2 (5)	0 (0)
	Pruritus	10 (12)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	Dry skin	8 (10)	0 (0)	0 (0)	3 (7)	0 (0)	0 (0)
General disorders and administration site conditions	Any	30 (36)	0 (0)	0 (0)	3 (7)	0 (0)	0 (0)
	Fatigue	24 (29)	0 (0)	0 (0)	3 (7)	0 (0)	0 (0)
	Infusion-related reaction	6 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders	Any	27 (33)	3 (4)	1 (1)	15 (37)	4 (10)	0 (0)
	Nausea	12 (15)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
	Diarrhoea	8 (10)	0 (0)	0 (0)	6 (15)	1 (2)	0 (0)
	Colitis	3 (4)	2 (2)	0 (0)	5 (12)	3 (7)	0 (0)
Respiratory, thoracic and mediastinal disorders	Any	6 (7)	0 (0)	0 (0)	4 (10)	4 (10)	0 (0)
	Pneumonitis*	1 (1)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
Investigations	Lipase increased	19 (23)	8 (10)	5 (6)	7 (17)	3 (7)	2 (5)
	Serum amylase increased	5 (6)	2 (2)	2 (2)	1 (2)	1 (2)	0 (0)
	Creatinine increased	5 (6)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)
	Alanine aminotransferase increased	2 (2)	1 (1)	0 (0)	2 (4)	0 (0)	0 (0)
	Aspartate aminotransferase increased	2 (2)	1 (1)	0 (0)	2 (4)	0 (0)	0 (0)
	Alkaline phosphatase increased	1 (1)	1 (1)	0 (0)	1 (2)	0 (0)	0 (0)
Metabolism and nutrition disorders	Hyperglycaemia	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Blood and lymphatic system disorders	Anaemia	2 (2)	1 (1)	0 (0)	1 (2)	1 (2)	0 (0)
Endocrine disorders	Any	14 (17)	2 (2)	0 (0)	7 (17)	1 (2)	1 (2)
	Hypothyroidism	10 (12)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)
	Hyperthyroidism	5 (6)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)
	Hypophysitis	1 (1)	1 (1)	0 (0)	1 (2)	1 (2)	0 (0)
	Adrenal insufficiency	3 (4)	1 (1)	0 (0)	3 (6)	0 (0)	1 (2)

**One grade 5 toxicity occurred during follow-up in Part 2, with one participant developing pneumonitis and dying from respiratory failure despite intensive immunosuppressive therapy.*

almost 20% with chromophobe RCC. Responses were observed across most nccRCC histologies, including 16% (2/13) of participants with type 1 papillary RCC and 13% (3/23) with type 2 papillary RCC.

Whilst nivolumab offered a clinically meaningful median DOR in participants who experienced a response, many participants had a short PFS, suggesting nccRCC often demonstrates primary or acquired resistance to PD1-targeted immunotherapy, and highlighting the clinical and molecular heterogeneity of these neoplasms. Our results are in keeping with contemporary studies of PD1 inhibition recruiting during a similar period to UNISoN [16,18]. Notably, in the Checkmate 374 study evaluating nivolumab, 32% of participants (14/44) received prior therapy, which represents a slightly different population to UNISoN, in which only 13% were exposed to prior systemic treatment. The duration of study treatment in UNISoN was restricted to 12 months for pragmatic reasons, however, most eligible participants continued treatment beyond this period, which was supported by the manufacturer. The optimal duration of successful anti-PD1 immunotherapy remains unknown in nccRCC and other malignancies.

Fewer participants were eligible for Part 2 than expected, due to higher rates of primary resistance, and often rapid disease progression. Additionally, owing to early disease progression on ipilimumab, fewer individuals were also evaluable in efficacy analyses, resulting in underpowering of the primary endpoint. The response rate to sequential addition of ipilimumab in Part 2 was lower than projected, and the trial did not meet its primary endpoint. Other studies with a similar design to UNISoN have shown that the sequential strategy is frequently not reliable [23,24]. However, the response rate observed in UNISoN is consistent with studies of ipilimumab in second-line treatment settings in ccRCC and other malignancies following anti-PD1 resistance [25,26]. It remains unclear whether second-line ipilimumab following

initial anti-PD1 resistance accurately estimates the activity of CTLA-4 inhibition, however, upfront doublet immunotherapy combinations have yielded suboptimal outcomes for many individuals in both the nccRCC and ccRCC settings [17,19].

In a study of upfront ipilimumab/nivolumab that enrolled a similar proportion of participants with papillary nccRCC to that enrolled in UNISoN, only 20% experienced OTRR, with a higher likelihood of response if sarcomatoid features were present or tumour PDL1 expression was >1% [17]. Other studies using this approach are yet to report.

Whilst UNISoN is an important trial designed to address the significant unmet needs that exist within nccRCC, various other trials have reported and continue to shape the standard of care. Small-molecule inhibitors in nccRCC have demonstrated some efficacy [27–32] (Table S2) and have entered clinical practice guidelines [33,34]. Pertinently, however, combination approaches combining PD1-based immunotherapy with these small-molecule inhibitors, such as cabozantinib [20,35] or lenvatinib [21], offer higher response rates than either agent alone, and suggest that orthogonal mechanism combinations may be pragmatic in people with advanced nccRCC. Both studies showed few responses in chromophobe RCC, highlighting a particular histology of unmet need. Other novel approaches are under investigation.

No new safety signals were observed in participants from our study. Higher rates of toxicity were expected and observed from combination ipilimumab/nivolumab than with nivolumab alone. However, the oncology community is generally familiar with the development and management of common immunotherapy toxicities from use in both genitourinary and other malignancies, notwithstanding the importance of ongoing education and specialized input, when required [36]. Unfortunately, it is difficult to discern whether toxicities emerging during sequential treatment with ipilimumab related to prior or concurrent administration of nivolumab in this trial.

As a rare group of malignancies, international collaboration is required to enact change for individuals diagnosed with this condition [37]. International, multi-centre trials, and a focus on translational research and tissue biobanks to identify molecular drivers and other predictive biomarkers to support treatment decisions for this heterogeneous population are needed. Translational studies of biospecimens kindly donated by UNISoN participants will contribute to this effort.

Our study was limited by its single-arm design; however, no standard of care was available, and there was strong impetus to evaluate immunotherapy strategies based on pre-clinical and retrospective evidence. With higher-than-expected rates of rapid progression in both Part 1 and 2, a high proportion of non-evaluable participants meant our primary endpoint was underpowered. Reliance on RECIST to determine treatment failure in Part 1 may have delayed enrolment of participants in Part 2, which may have limited our ability to test the potential benefit of sequential ipilimumab. A higher proportion of patients in Part 1 progressed after several months of therapy, meaning that some of those enrolling in Part 2 had very short treatment durations, which may have made assessment of DOR in Part 2 unreliable. Additionally, inclusion of a minority of individuals with prior exposure to targeted therapies may have hampered responses to immunotherapy; however, there is minimal data to suggest sequencing is important in nccRCC, and for a condition where there are no locally funded systemic treatments, it was considered unethical to actively exclude these people from enrolment.

In conclusion, UNISoN demonstrates efficacy of nivolumab monotherapy in some people with advanced nccRCC and suggests additional benefit from ipilimumab in a minority of patients. However, the study failed to meet its primary endpoint and the sequential approach of addition of ipilimumab to nivolumab upon progression cannot currently be recommended. Contemporaneous studies demonstrate efficacy of combining immunotherapy and targeted therapy, although as always, more effective therapies and actionable predictive biomarkers to direct treatments and sequencing are required. Ongoing research into clinicopathological and molecular factors that might predict treatment benefit will be important when considering therapeutic combinations for nccRCC. Future clinical trials in advanced RCC should consider how best to assess activity in various types of nccRCC.

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Disclosure of Interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. Ciara Conduit: honoraria (AstraZeneca, Limbic). Ian D. Davis: participation on data safety monitoring board/advisory boards, including Ipsen (advisory board; unpaid), MSD (RCC virtual advisory board; unpaid), Merck/Pfizer (APAC GU advisory board; unpaid), Merck/Pfizer (avelumab

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Abbreviations: ccRCC, clear-cell RCC; CTLA-4, cytotoxic T-lymphocyte antigen-4; DOR, duration of response; IMDC, International Metastatic RCC Database Consortium; OS, overall survival; PD1, programmed cell death-1; PFS, progression-free survival; nccRCC, non-clear-cell RCC; OTRR, objective tumour response rate.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Best overall response per RECIST v1.1 to nivolumab monotherapy by histological subtype.

Table S2 Summary of relevant trials in nccRCC.