Denosumab and pembrolizumab in advanced clear cell renal carcinoma: KeyPAD (ANZUP 1601)

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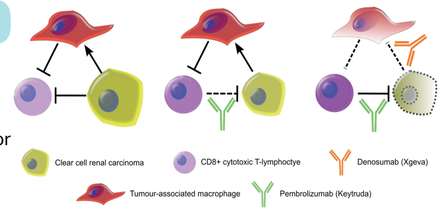
1. Background and Rationale

- Anti-PD1 immune checkpoint inhibitors (ICI) help some people with clear cell renal cell carcinoma (ccRCC).
- Inhibition of Receptor Activator of Nuclear Factor κB Ligand (RANKL) signalling may potentiate ICI
- Expression of RANKL, RANK and OPG are associated with prognosis in ccRCC



2. Hypothesis and Aim

- RANKL inhibition will increase the activity of ICI in people with advanced pre-treated ccRCC
- To determine the activity and safety of the RANKL inhibitor denosumab (D) with pembrolizumab (P) in people with pretreated advanced ccRCC

3. Study Design

Design:
- Single arm, multi-centre, phase 2 clinical trial.

Target Population:
- metastatic or unresectable ccRCC;
- progression on or after vascular endothelial growth factor receptor inhibitor (VEGFR TKI);
- no prior treatment with and ICI or D.

Sample Size:
- 70 participants provide 90% power with a 1-sided type 1 error rate of 10% to distinguish the observed OTRR from benchmarks of 25% vs 40% using Simon's 2-stage minimax design with an allowance of 9% for ineligibility and/or inevaluability.

4. Study Schema

Eligibility

Advanced or metastatic ccRCC
Target lesion(s) by RECIST 1.1
ECOG PS 0-2
Progression after VEGFR TKI
No previous immunotherapy
No significant autoimmune disease
Adequate organ function
Tumour sample available (archival or recent biopsy)

Intervention

Pembrolizumab 200mg IV every 3 weeks
+
Denosumab 120mg SC days 1, 8, 22 then every 3 weeks

Treatment until disease progression, prohibitive toxicity or to a maximum of 2 years treatment duration.

Objectives

Primary:
Objective tumour response rate (OTR) per RECIST 1.1

Secondary:
Median progression free survival (mPFS)
PFS at 6 months (PFS6)
Duration of response (DOR)
Adverse events (AE)

Tertiary:
Biomarkers

5. Results

Participant Characteristics		N=58
Age (median, range)		67 (60-72)
Gender – no. (%)	Female	11 (19)
	Male	47 (81)
ECOG – no. (%)	0	30 (52)
	1	27 (47)
	2	1 (2)
Stage at diagnosis – no. (%)	Stage I	8 (14)
	Stage II	9 (16)
	Stage III	24 (42)
	Stage IV	16 (28)
MSKCC prognostic risk group – no. (%)	Favourable	40 (70)
	Intermediate	12 (21)
	Poor	5 (9)
	Not reported	1 (2)
IMDC prognostic risk group – no. (%)	Favourable	42 (72)
	Intermediate	10 (17)
	Poor	6 (10)
Prior nephrectomy – no. (%)		51 (88)
Sites of metastases – no. (%)	Lung	38 (66)
	Lymph nodes	29 (50)
	Bone	23 (40)
	Liver	14 (24)
	Kidney	12 (22)
	Brain	0
	Other	16 (28)
Prior systemic therapy – no. (%)	1	49 (84)
	2	7 (12)
	>2	2 (4)
Prior systemic therapy – no. (%)	Sunitinib	30 (52)
	Pazopanib	29 (50)
	Axitinib	5 (7)
	Everolimus	3 (5)
	Sorafenib	3 (5)
	Cabozantinib	1 (2)
	Other*	2 (4)

Primary Endpoint	N=58	
OTRR N=58*		95% CI
PR	18 (31%)	20 – 45
SD	15 (26%)	15 – 39
PD	24 (42%)	29 – 55

*N=1 missing

Participant Outcomes

59 participants were recruited from Dec 2017 – Jul 2022.

Median follow-up was 40 months.

OTRR 31% (all partial; 95%CI 20-45%)

PFS6 53% (95% CI, 39-65%)

Median Progression-Free Survival (PFS) was 7.5 months

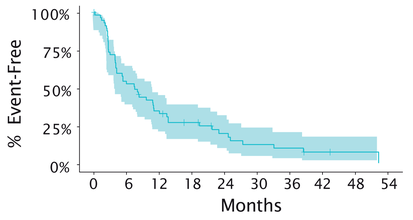
Median Duration of Response (DOR) was 17 months

Immune related adverse events grade ≥ 3 were reported in 20% of participants; treatment was discontinued for toxicity in 22%.

One participant suffered G3 osteonecrosis of the jaw; one G3 hypocalcaemia.

One participant died of myositis, attributed to study treatment.

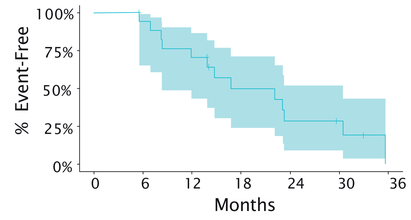
Progression Free Survival (PFS)



Number at risk (number censored)

58(0) 30(1) 19(2) 13(4) 8(6) 5(6) 4(6) 2(7) 1(8) 0(8)

Duration of Response (RECIST)



Number at risk (number censored)

18(0) 16(1) 12(1) 7(3) 4(3) 3(4) 0(5)

D + P versus prior clinical trials of anti-PD1 ICI in VEGFR TKI refractory advanced ccRCC

Clinical trial	OTRR (%)	mPFS (months)	PFS6 (%)
KeyPAD	31	7.5	53
Checkmate-025	25	4.6	38
NIVOREN	21	3.7	35
TITAN	17	3.7	38
NORA	20	5.3	46
NCT01354431 0.3mg/kg	20	2.7	30
NCT01354431 2mg/kg	22	4.0	30
NCT01354431 10mg/kg	20	4.2	40
NIVES	17	5.6	42
MEDI0680	24	3.6	36
WITNESS	28	5.3	44

6. Conclusions

- D + P is safe in people with VEGFR TKI refractory ccRCC.
- The primary endpoint of OTRR was not met.
- Compared to other trials of anti-PD1 ICI in people with ccRCC progressing after VEGFR TKI, D + P shows encouraging activity in median PFS and in PFS6, a now recognised useful surrogate of ICI benefit.
- Further studies combining RANKL inhibitors such as denosumab with ICI in ccRCC are warranted.

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