Combination therapy with Avelumab and Cabozantinib in patients with newly diagnosed metastatic clear cell renal cell carcinoma

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Abstract #334

Introduction

Immune therapy combinations are now standard first-line therapy for patients with metastatic clear cell renal cell carcinoma (mccRCC). Cabozantinib modulates key components of the immune system such as decreasing regulatory T-cells and increasing T-effector cell populations and is approved for treatment of mRCC.

We hypothesize that Avelumab + Cabozantinib will be safe and show clinical activity in mccRCC.

Methods

Phase I clinical trial using a 3+3 design with three planned dose cohorts: Cabozantinib 20mg/day, 40mg/day and 60mg/day + Avelumab (10mg/kg q2weeks for up to 12 cycles) in each arm.

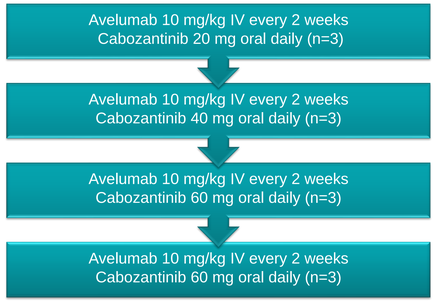
There were an additional 3 patients included in the final dose cohort as a confirmation of the RP2D.

- **Primary endpoint**: safety and identification of the recommended phase II dose (RP2D).
- **Secondary endpoints:** objective response rate (ORR) and radiographic progression free survival (PFS).

No dose modifications were allowed for Avelumab but dose delays were permitted. Dose reductions were allowed for Cabozantinib. RECIST 1.1 was used to determine ORR. **Treatment beyond progression was allowed.**

Data lock on 09 October 2020

Figure 1: Flow diagram of dose escalation



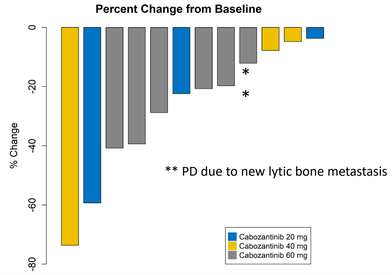
- **Inclusion criteria:**
  - Male or female subject aged ≥ 18 years.
  - Histologically proven clear cell renal carcinoma
  - Measureable disease by RECIST 1.1
  - ECOG Score 0-2
- **Exclusion criteria:**
  - Current use of immunosuppressive medication or active autoimmune disease
  - Prior systemic treatment for mccRCC
  - Subjects with a diagnosis of deep vein thrombosis (DVT) or incidentally detected asymptomatic PE on routine scans are excluded unless treated and clinically stable for at least 2 weeks before first dose.

Results

Table 1: Demographics of patients

Characteristics	Number of patients (%)
Median age [range], year	66.5 [47-81]
Male sex	7 (58)
White race	12 (100)
Clear cell subtype	12 (100)
IMDC prognostic risk	
• Favorable	3 (25)
• Intermediate	7 (58)
• Poor	2 (17)
Number of organs with metastases	
• 1	0 (0)
• ≥2	12 (100)
Prior systemic therapies	0 (0)
Prior nephrectomy	5 (42)
VTE history	4 (33)

Figure 2: Best responses in target lesions



Results

Table 2: Incidence of Treatment Related Adverse Events Grade 3 or Higher

Side effects	Cabo 20mg (N=3)	Cabo 40mg (N=3)	Cabo 60mg (N=6)	Total N=12 (%)
Acute Kidney Injury			1	1/12 (8.3)
ALT Increase			1	1/12 (8.3)
AST Increase			1	1/12 (8.3)
Anemia		1		1/12 (8.3)
Diarrhea		1	2	3/12 (25)
Fatigue			1	1/12 (8.3)
Hypertension	1			1/12 (8.3)
Hypokalemia			1	1/12 (8.3)
Palmar-Plantar Erythrodysesthesia			1	1/12 (8.3)
Rash Maculopapular		1		1/12 (8.3)
DVT/PE		1	3	4/12 (33.3)

- Four SAE's related to study treatment were observed, thromboembolism, after the DLT period.
- Immune related adverse events (irAE) occurred in six patients (50%) and included hypothyroidism, colitis, nephritis, allergic rhinitis and rash.
- AE's are tabulated if related to either cabozantinib or avelumab

Table 3: Dose reduction in each cohort

Cohort	Dose reduction, n (%)	Final dose, median
Cabozantinib 20 mg	0	20 mg
Cabozantinib 40 mg	1 (33%)	40 mg
Cabozantinib 60 mg	5 (83%)	30 mg
Total	6 (50%)	30 mg

- No dose limiting toxicities were observed in any cohort.
- Six patients required dose reductions of cabozantinib after the DLT period: one in the 40mg cohort and five in 60mg cohort, most frequently due to oral mucositis and hand foot syndrome.
- One patient discontinued Avelumab due to irAE (nephritis).
- No patients discontinued Cabozantinib due to toxicity.

Results

Figure 3: Treatment duration

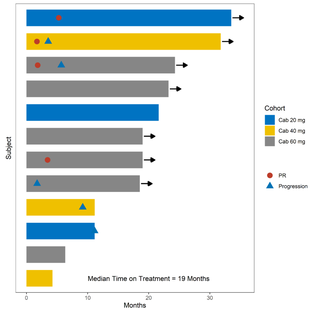
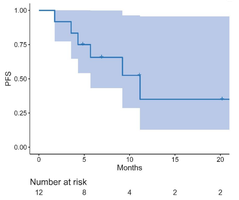


Figure 4: PFS



Median PFS: 11.3 Months

Table 4: Best response

Complete response	0 (0%)
Partial response	4 (33%)
Stable disease	7 (58%)
Progressive disease	1 (8%)

- ORR was 33% and clinical benefit rate was 92%.
- One patient experienced progression on first scan, but remained on the protocol and reached PR at 7 months.

Conclusions

- Avelumab + Cabozantinib in mccRCC is safe with promising clinical activity
- No dose limiting toxicities were observed with this combination
- irAE frequency is consistent with Avelumab therapy for mccRCC

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