Abstract #E43: Nivolumab plus cabozantinib in patients with non-clear cell renal cell carcinoma: Results of a phase 2 trial

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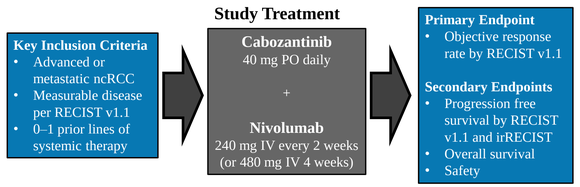
INTRODUCTION

- Kidney cancer represents many different malignancies, varying in pathobiology and sensitivity to approved systemic agents with clear cell RCC comprising 60–80% of cases and are dependent on vascular endothelial growth factor (VEGF) signaling.[1]
- Other subtypes are collectively grouped as non-clear cell RCC (ncRCC) but constitute a diverse mixture of heterogeneous malignancies.
- Cabozantinib plus nivolumab (CaboNivo) improved objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) over sunitinib in a phase 3 trial for metastatic clear cell renal cell carcinoma (ccRCC) (NCT03141177).[2]
- We report the results of a phase 2 trial of CaboNivo in patients with ncRCC

METHODS

This is a single institution, phase II study (ClinicalTrials.gov identifier: NCT03635892) of cabozantinib in combination with nivolumab in patients with advanced or metastatic ncRCC, who did not receive prior PD-1/PD-L1-targeted treatment.



- Cohort 1 included patients with papillary, unclassified, or translocation-associated RCC; Cohort 2 included patients with chromophobe RCC.
- Cohort 1 was a single-stage design that met its primary endpoint(N=20) and was expanded to produce more precise estimates of ORR (total N=40). Cohort 2 was a Simon two-stage design that closed early.
- Histopathology was prospectively reviewed at MSKCC and retrospectively reviewed/confirmed by a dedicated GU Pathologist (YC). Papillary included unclassified with papillary features, high grade/type 1 papillary, and FH-deficient/type 2 papillary.
- Correlative analyses by next-generation sequencing were performed.

RESULTS

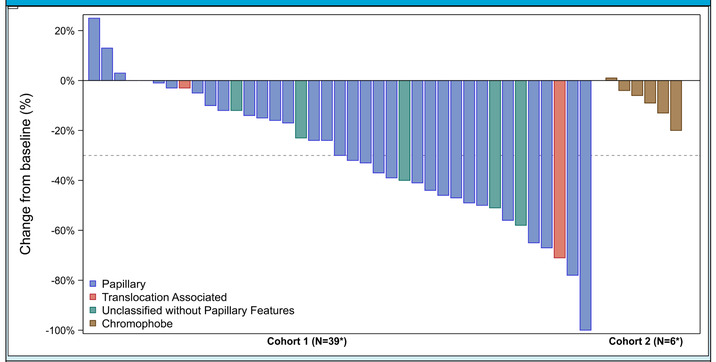
- A total of 47 patients were treated; 40 in Cohort 1 and 7 in Cohort 2 with a median follow up time of 13.1 months (range 2.2 – 28.6) (**Table 1**).
- ORR for Cohort 1 was 48% (95% CI 31.5–63.9) and no objective responses were seen in the 7 patients in Cohort 2 with chromophobe histology (**Figure 1; Table 2**).
- Among patients with papillary histology, objective response was seen in 15 of 32 (47%, 95% CI: 29-65). Response was seen in 3 of 6 patients with unclassified RCC and 1 of 2 patients with translocation-associated RCC (**Figure 1**).
- Cohort 1: Median PFS was 12.5 months (95% CI 6.3–16.4) and median OS was 28 months (95% CI 16.3–NE) (**Figure 2**).
- Grade 3/4 treatment-related adverse events were observed in 32% of patients. Cabozantinib and nivolumab were discontinued due to toxicity in 13% and 17% of patients, respectively. (**Table 3; Table 4**)
- 5/6 patients with NF2 mutations and 4/5 patients with FH mutations had an objective response, while 1/6 patients with SETD2 mutations had an objective response (**Figure 3**).

Table 1: Patient Characteristics

	Cohort 1 (N=40)	Cohort 2 (N=7)
Age at diagnosis (years) – median (range)	57 (33, 78)	54 (46, 68)
Sex		
Male	28 (70%)	3 (43%)
Female	12 (30%)	4 (57%)
Histology		
Papillary*	32 (80%)	-
Unclassified without papillary features†	6 (15%)	
Translocation-Associated	2 (5%)	-
Chromophobe†	-	7 (100%)
Karnofsky performance status		
90	29 (73%)	5 (71%)
80	11 (27%)	2 (29%)
IMDC risk classification		
Favorable	8 (20%)	3 (43%)
Intermediate	27 (67%)	3 (43%)
Poor	5 (13%)	1 (14%)
MSKCC risk classification		
Good	8 (20%)	2 (29%)
Intermediate	24 (60%)	4 (57%)
Poor	8 (20%)	1 (14%)
Prior nephrectomy	27 (67%)	7 (100%)
Prior systemic therapy‡	14 (35%)	2 (29%)
VEGF inhibitor	10 (25%)	2 (29%)
mTOR inhibitor	8 (20%)	0 (0%)
Chemotherapy	2 (5%)	0 (0%)
Number of sites of disease at treatment – median (range)	2 (1, 7)	2 (1, 3)
Location of metastasis		
Lymph node	31 (78%)	2 (29%)
Lung	18 (45%)	2 (29%)
Bone	12 (30%)	2 (29%)
Retroperitoneum/peritoneum	10 (25%)	4 (57%)
Liver	8 (20%)	2 (29%)

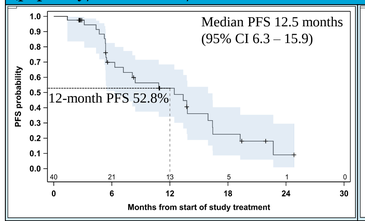
*Includes 16 unclassified with papillary features, 11 high grade/type 1 papillary and 5 FH-deficient/type 2 papillary.
†Sarcomatoid features were found in one unclassified without papillary features and one chromophobe.
‡Ten patients in Cohort 1 received prior combination therapy; 1 patient received erlotinib, and 1 patient received crizotinib.

Figure 1. Maximum change in target lesions by histology

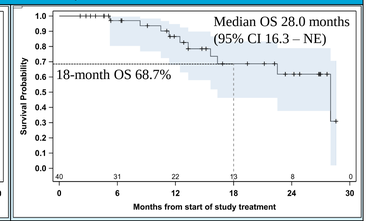


*Two patients with rapid clinical progression had unevaluable lesions are excluded from the plot.

Figure 2. PFS by RECIST and OS Kaplan-Meier Curves of Cohort 1 (papillary/unclassified/translocation-associated RCC)



Progression-free survival, RECIST 1.1. There were 22 PFS events (20 progressions and 2 deaths with no progression). Median PFS is 12.5 months (95% CI: 6.30, 15.9). The PFS estimate is 52.8% (95% CI: 34.1, 68.5) at 12 months.



Overall survival. There were 10 deaths in this 40 patient cohort. Median OS is 28.0 months (95% CI: 16.3, NE). The OS estimate is 68.7% (95% CI: 46.3, 83.3) at 18 months. Median follow-up time for survivors is 13.1 months (range: 2.2, 28.6).

Table 3. Drug exposure in combined cohort 1 & 2

Median treatment duration, months (95% CI)*	11.0 (7.8, 21.1)
Treatment-related AE of any grade	41 (87%)
Treatment-related AE of grade 3 or 4	15 (32%)
Treatment-related AE leading to discontinuation of either study drug	10 (21%)
Treatment-related AE leading to discontinuation of both study drugs	4 (9%)
Cabozantinib	
Median treatment duration, months (95% CI)	9.1 (7.4, 21.1)
Dose reduction	37 (79%)
Discontinuation for AE	8 (17%)
Nivolumab	
Median treatment duration, months (95% CI)	10.6 (6.0, 18.8)
Discontinuation for AE	6 (13%)

In the combined cohort of 47 patients, 27 discontinued cabozantinib, 28 discontinued nivolumab, and 20 continue one or both therapies at the time of data cutoff.
*On either cabozantinib or nivolumab

Table 4. Treatment-related adverse events in combined cohort 1 & 2

Adverse Event	All grades	Grade 3/4
Fatigue	27 (57)	0 (0)
Palmar-plantar erythrodysesthesia syndrome	27 (57)	2 (4)
Diarrhea	25 (53)	3 (6)
Hypertension	18 (38)	6 (13)
Dry mouth	17 (36)	0 (0)
Nausea	14 (30)	1 (2)
Mucositis oral	13 (28)	0 (0)
Hoarseness	12 (26)	0 (0)
Constipation	10 (21)	0 (0)
Dry skin	10 (21)	0 (0)
Dyspnea	10 (21)	0 (0)
Headache	10 (21)	0 (0)
Cough	9 (19)	0 (0)
Gastroesophageal reflux disease	9 (19)	0 (0)
Arthralgia	8 (17)	0 (0)
Pruritus	8 (17)	0 (0)
Rash maculo-papular	8 (17)	0 (0)

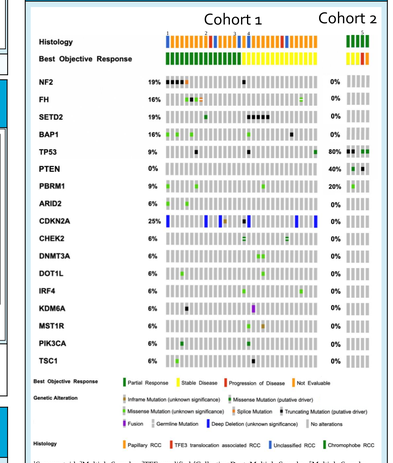
Treatment-related adverse events occurring with at least 15% all-grade frequency are shown.

Table 2: Summary of Efficacy Outcomes

	Cohort 1 (N=40)	Cohort 2 (N=7)
Objective response rate (95% CI)	48% (31.5, 63.9)	0% (0, 41.0)
Best response – n (%)		
Partial response	19 (48%)	0 (0%)
Stable disease	20 (50%)	5 (71%)
Progressive disease	1 (3%)	1 (14%)
Not Evaluable	0 (0%)	1 (14%)
Disease control rate (95% CI)	98% (86.8, 99.9)	71% (29.0, 96.3)
Clinical benefit rate (95% CI)	58% (40.9, 73.0)	29% (3.7, 71.0)
Median progression-free survival, months (95% CI)	12.5 (6.3, 15.9)	*
Median duration of response, months (95% CI)	13.6 (9.7, 19.8)	†

Objective response includes patients with a complete or partial response. Clinical benefit includes patients with objective response or stable disease (SD) for at least 24 weeks. Disease control includes patients with any response or SD on study.
*Not calculated for Cohort 2; †No responders in Cohort 2

Figure 3: Targeted Exome Sequencing



[1]Sarcomatoid [2]Multiple Samples [3]FFE-amplified [4]Collecting Duct; Multiple Samples [5]Multiple Samples

Targeted exome sequencing by MSK-IMPACT of Cohort 1 (N=32) and Cohort 2 (N=5).

KEY TAKEAWAYS/CONCLUSIONS

- Cabozantinib + Nivolumab showed promising efficacy in metastatic non-clear cell RCC patients with papillary, unclassified, or translocation-associated histologies.
- Adverse events in non-clear cell RCC were consistent with the observed adverse-event profile of this combination in ccRCC.
- Genomic studies highlight the heterogeneity of non-clear cell RCC and warrant further study as predictors of response to systemic therapy.

References

1. Linehan WM. Genetic basis of kidney cancer: Role of genomics for the development of disease-based therapeutics. Genome Res 2012;22:2089-2100.

2. Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2021;384:829-841.

Conflicts of Interest
Dr. Lee has consulting or advisory roles with Amgen, Bristol Myers Squibb, EMD Serono, Eisai, Exelixis, Merck, and Pfizer; travel, accommodations, expenses from Calithera Biosciences, Eisai; and research funding from Bristol Myers Squibb, Calithera, Eisai, Eli Lilly, Exelixis, Merck, and Pfizer.

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