Activity of Cabozantinib (XL184) in Patients With Metastatic, Refractory Renal Cell Carcinoma (RCC)

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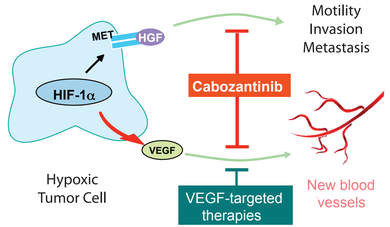
INTRODUCTION

- Cabozantinib is a dual inhibitor of MET and VEGFR2
- MET and VEGFR cooperate to drive tumor angiogenesis, invasion, and metastasis[1]
- Upregulation of MET is associated with the ability of tumors to evade antiangiogenic treatment[1]

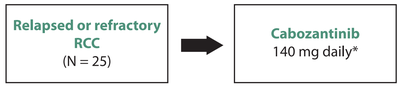
Figure 1. Rationale for Dual MET/VEGFR2 Inhibition in Tumors



- Functional defects in the tumor suppressor von Hippel Lindau gene (*VHL*) are present in over 70–90% of sporadic and 100% of hereditary clear cell RCC tumors[2–4]
- *VHL* loss results in up-regulation of VEGF secretion and increased HGF-driven invasiveness[2]
- Knockdown of MET expression by multiple shRNAs preferentially inhibits the viability of RCC *VHL*$^{-/-}$ cells[5]
- A retrospective review[6] of 1056 consecutively enrolled patients (from 12 centers) treated with initial anti-vascular endothelial growth factor (VEGF) demonstrated:
  - 272 (26%) of these patients had primary refractory disease with PD as a best response
  - Median overall survival (OS) in patients with PD versus without PD was 6.8 versus 29 months ($P < 0.0001$), respectively

METHODS

Figure 2. Study Design: Multi-Institutional Study



*Corresponds to 175 mg salt form

Study Endpoints

- Safety and tolerability of cabozantinib
- Antitumor activity of cabozantinib

Key Study Eligibility Criteria

- Karnofsky Performance Status (≥70) / ECOG 0–1
- Histologically-confirmed RCC (with clear cell components) with metastases
- Refractory or progressed following standard therapies
- Measurable disease per mRECIST

Assessments

- Safety
- Tumor assessments per mRECIST 1.0 using CT/MRI at baseline and q8w thereafter
- Pharmacokinetic and pharmacogenetic sampling

RESULTS

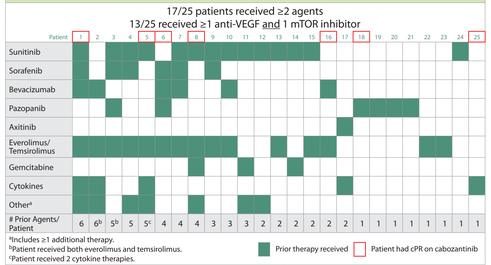
- This is an analysis of preliminary results from an ongoing study

Table 1. Demographics and Baseline Characteristics (N = 25)

Median age, years (range)	61 (41–79)
Sex, n	
Male	21
Female	4
ECOG PS, n (%)	
0	17 (68)
1	8 (32)
Measurable disease, n (%)	25 (100)
Median number of prior agents	2
Prior systemic agents, n (%)	
1	8 (32)
2	6 (24)
3	3 (12)
≥4	8 (32)
Prior anticancer therapies, n (%)	
Prior anti-VEGF therapy	22 (88)
Prior mTOR inhibitor therapy	15 (60)
Prior cytokine therapy	5 (20)
Prior chemotherapy	3 (12)
Bone metastases[a], n (%)	4 (16)

[a]1/4 patients with bone metastases at baseline was followed by bone scan.

Table 2. Prior Systemic Agents by Patient

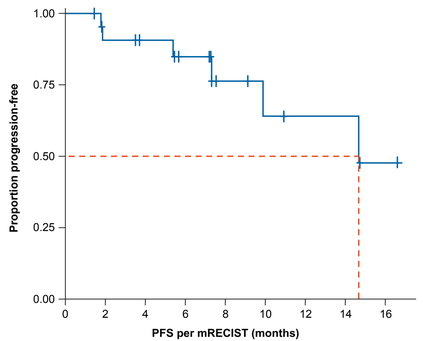


[a]Includes ≥1 additional therapy.
[b]Patient received both everolimus and temsirolimus.
[c]Patient received 2 cytokine therapies.

Table 3. Patient Disposition

Summary of treatment status, n	**25**
Active, n (%)	10 (40)
Treatment discontinuation, n (%)	15 (60)
Primary reason for discontinuation, n (%)	
Progressive disease	6 (24)
Adverse event	7 (28)
Subject request	2 (8)

Figure 3. Progression-Free Survival (N = 25)



Median PFS (months)	PFS (95% CI)	# Events
14.7	(7.3, –)	6

Table 4. Summary of Response

mRECIST response evaluable, n	**25[a]**
Best overall response, n (%)	
Confirmed partial response	7 (28)
Stable disease	13 (52)
Progressive disease	1 (4)
Week 16 DCR[b], n (%)	18 (72)

[a]No post-baseline tumor assessments available for 4 patients.
[b]Disease control rate (DCR) defined as PR + SD at week 16.

Figure 4. Example of a Radiographic Response in an RCC Patient With Sarcomatoid Differentiation Who was Pretreated With a VEGFR Inhibitor and an mTOR Inhibitor

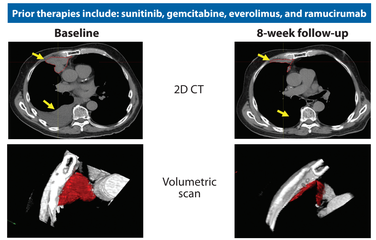
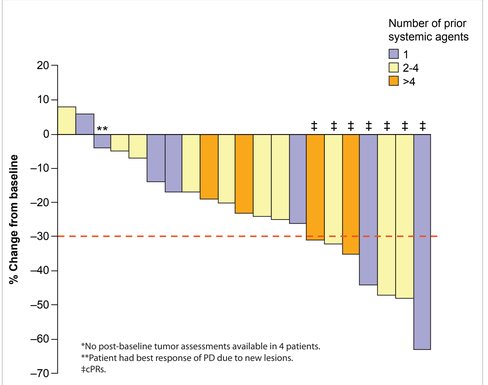
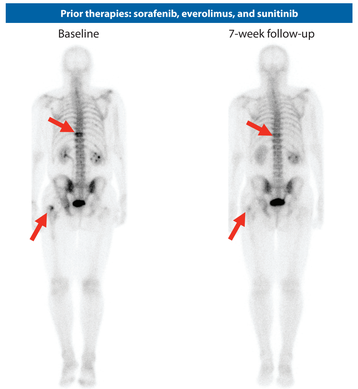


Figure 5. Best Response in Patients With ≥1 Post-Baseline Scan (n = 21)*



*No post-baseline tumor assessments available in 4 patients.
**Patient had best response of PD due to new lesions.
‡cPRs.

Figure 6. Example of Partial Bone Scan Resolution in a Symptomatic Patient With Predominantly Osteolytic Bone Metastases



Symptom Alleviation in Patients With Bone Pain

- Patient showing resolution of bone lesions on bone scan (Figure 6) also substantially reduced narcotic use by 7 weeks and continued on reduced narcotics until week 25
- A second patient with bone metastases and pain at baseline (rated 5/10) reported complete resolution of pain by 4 weeks and remains pain free as of 73 weeks on study

Table 5. Most Frequently Reported Adverse Events Regardless of Causality (N = 25)

Adverse Event[a]	All Grades, n (%)	Grade ≥3, n (%)
Fatigue[b]	20 (80)	4 (16)
Diarrhea[b]	16 (64)	3 (12)
Hypophosphatemia[c]	14 (56)	9 (36)
Hypomagnesemia[c]	10 (40)	0
Hypothyroidism[c]	10 (40)	0
Nausea	10 (40)	0
Proteinuria	9 (36)	2 (8)
Vomiting	9 (36)	1 (4)
Hyponatremia[d]	8 (32)	5 (20)
Palmar-plantar erythrodysesthesia[b]	8 (32)	1 (4)
Dyspnea	8 (32)	0

[a]MedDRA v. 14.1 Preferred Terms (converted to US spelling), CTCAE v. 3.0 grading; n = number of patients with the event.
[b]Groupings of Preferred Terms related to a particular medical condition.
[c]Did not result in a dose reduction nor in discontinuation. Two subjects were dose interrupted due to hypophosphatemia.
[d]Resulted in dose reduction in one patient.

- No related Grade 5 events reported

SUMMARY

- Dual targeting of MET and VEGFR2 with cabozantinib demonstrates encouraging activity in this heavily pretreated (median 2 prior systemic agents) RCC population
  - Median PFS of 14.7 months
  - 7 patients (28%) with confirmed PRs
  - Only one patient (4% rate of PD) showed evidence of primary refractory disease
  - 19/21 patients (90%) with ≥1 post-baseline scan experienced tumor regression
  - Reduction of bone lesions on bone scan observed accompanied by symptom improvement
- The safety profile of cabozantinib was comparable to that seen with other VEGFR TKIs
- Further evaluation of cabozantinib in RCC is planned

REFERENCES

1. Aftab and McDonald. *Clin Transl Oncol*. 2011;13(10):703–9.
2. Rini, et al. *J Clin Oncol*. 2008;27(19):3225–34.
3. Nickerson, et al. *Clin Cancer Res*. 2008;14(15):4726–34.
4. Rechsteiner, et al, *Canc Res*. 2011;71(16): 5500–11.
5. Bommi-Reddy, et al. *Proc Natl Acad Sci U S A*. 2008;105(43):16484–9.
6. Heng, et al. *Ann Oncol*. 2011 Nov 5. (Epub ahead of print)

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Poster available for download at www.exelixis.com.