Activity of Tivozanib in Non-Clear Cell Renal Cell Carcinoma (nccRCC): Subgroup Analysis From a Phase 2 Randomized Discontinuation Trial

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Background

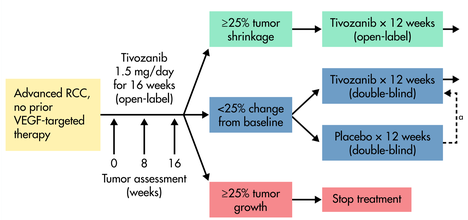
- NccRCC belongs to a heterogenous group of tumors that includes papillary, chromophobe, and collecting duct[1]
- Due to the rarity and poor molecular characterization of nccRCC, there is an underrepresentation in clinical trials evaluating patients with this type of RCC; because of this, patients are often treated with non-tailored therapies[1]
- Tivozanib is a potent and highly selective vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor with a long half-life[2,3]
- Tivozanib is approved by the US Food and Drug Administration for treatment of patients with relapsed/refractory (R/R) advanced RCC following ≥2 prior systemic therapies[4]
- Here, we present a subgroup analysis using data on patients with nccRCC from a phase 2 randomized discontinuation trial of tivozanib for the treatment of advanced RCC. The objective of this analysis was to evaluate the efficacy and safety of tivozanib in this population.

Methods

Study Design

- Using data from a phase 2 randomized discontinuation trial of tivozanib (NCT00502307), patients included in these analyses were adults (aged ≥18 years) who had histologically or cytologically confirmed recurrent or metastatic nccRCC that was not amenable to surgery, a Karnofsky performance status ≥70%, a lack of prespecified laboratory and hematologic abnormalities, and had received ≤1 prior systemic treatment not including a VEGF-targeted therapy (**Figure 1**)
- Patients were excluded from study participation if they had central nervous system malignancies, clinically symptomatic metastases, or clinically significant cardiovascular disease ≤3 months before entering the study

Figure 1. Study Design



RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.
[a] Patients with progression during the double-blind phase were unblinded; those receiving placebo were allowed to restart tivozanib.
All patients were unblinded after 12 weeks of double-blind treatment.

- In this randomized discontinuation scheme, enrolled patients received open-label tivozanib 1.5 mg orally once daily for 3 weeks followed by 1 week off for 4 cycles (for a total of 16 weeks)
- Tumor assessments were performed every 2 cycles, and response was determined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- After the 16-week open-label period, the sum of the longest diameters of target lesions was compared with baseline, and a 25% cutoff for response or progression (modified RECIST), as assessed by the investigators (INV), was used for assigning treatment for the next 12 weeks:
  - Patients with ≥25% tumor shrinkage continued taking open-label tivozanib, whereas patients with ≥25% tumor growth stopped treatment
  - Patients with a <25% change in tumor size (shrinkage or growth) were randomly assigned 1:1 in a double-blind manner to receive either tivozanib or a placebo for the next 12 weeks
- Patients were unblinded for documented progressive disease (PD) at any time during the randomization phase, and those receiving placebo were permitted to restart tivozanib. At completion of the 12-week randomization phase, all patients were unblinded and permitted to resume or continue receiving long-term open-label tivozanib.
- Retrospective subgroup analyses evaluated efficacy (objective response rate [ORR] at 16 weeks by INV assessment, best ORR, and progression-free survival [PFS] by independent radiographic review [IRR]) by all nccRCC histology and by nccRCC histological subtype (papillary, chromophobe, collecting duct, mixed/unclassified)
- Treatment-related adverse events (TRAEs) are presented for the total nccRCC histological subgroup

Statistical Analysis

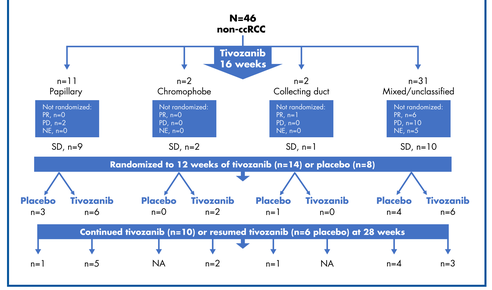
- For the primary analysis, unconfirmed INV-assessed ORR at week 16 following the open-label phase was summarized for all treated patients, and best unconfirmed and confirmed ORRs at any point during the study period were reported for patients continuously treated with tivozanib. The Kaplan-Meier (KM) method was used to estimate the median PFS.
- For analysis of PFS, patients who discontinued treatment without PD or death were censored at their last assessment, and patients who were randomized to receive placebo were censored at the time of randomization

Results

Baseline Characteristics

- Of the 272 patients enrolled in this study, 46 (16.9%) had nccRCC pathology and were included in this analysis
- The nccRCC population comprised patients with the following subtypes: papillary (n=11 [4%]), chromophobe (n=2 [0.7%]), collecting duct (n=2 [0.7%]), and mixed/unclassified (n=31 [11.4%]) (**Figure 2**)

Figure 2. Patient Disposition for Phase 2 Tivozanib Study



ccRCC, clear cell renal cell carcinoma; NA, not applicable; NE, not evaluable; PR, partial response; PD, progressive disease; SD, stable disease.

- Patients were predominantly male, and the median age was 53.6 years. Two-thirds of patients with nccRCC presented with ≥T3 disease at diagnosis, and 50% had de novo metastatic disease. Only 26% received prior systemic treatment, which was primarily interferon (IFN) therapy (**Table 1**).

Table 1. Patient Demographics

Characteristic, n (%)	nccRCC (N=46)
Male	34 (74)
Age, median (range), years	53.6 (26-75)
Race	
White	38 (83)
Asian	8 (17)
Extent of disease at diagnosis	
≥T3	31 (67)
N+	20 (43)
M+	23 (50)
Prior nephrectomy	24 (52)
Number of prior lines of systemic treatment, median (range)	0 (0-1)
Prior systemic treatment	12 (26)
IFN	11 (24)
Investigational treatment (± IFN)	3 (6)

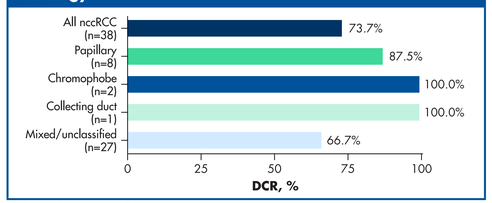
ECOG PS, Eastern Cooperative Oncology Group performance status.
Data cutoff of May 24, 2021. Bold-faced numbers indicate values ≥15% INV LT-PFS at 36 months.

- Patients received a mean 9.4 (median 7, range, 1-25) cycles of tivozanib (or placebo for the 8 patients randomized to placebo after 16 weeks tivozanib); the corresponding mean time on treatment was 8.36 months (median 6.27 months)

Efficacy of tivozanib

- The ORR at 16 weeks (prior to randomization) in all treated patients with nccRCC was 15.2% (**Table 2**)
- The best unconfirmed ORR (at any time point) in patients with nccRCC continuously treated with tivozanib was 31.6%, and the best confirmed ORR was 21.1%
- When analyzed by nccRCC histologic subset, the best unconfirmed ORR ranged from 22.6% to 100.0%, and the best confirmed ORR ranged from 14.8% to 100.0%
- There was a trend toward lower ORRs in patients with mixed/unclassified nccRCC histological subtypes compared with patients with other nccRCC subtypes (**Table 2**)
- Of note, 5 of 12 patients experienced a confirmed or unconfirmed PR as best response at >16 weeks from tivozanib initiation
- The median time to best response was 23.2 weeks (mean, 26.7 weeks) for confirmed responses, and the median time to any response (confirmed and unconfirmed) was 19.1 weeks (mean, 27.2 weeks)
- The observed disease control rate (DCR) was 74% in all patients with nccRCC continuously treated with tivozanib, and ranged from 67% to 100% by individual nccRCC histological subset (**Figure 3**)

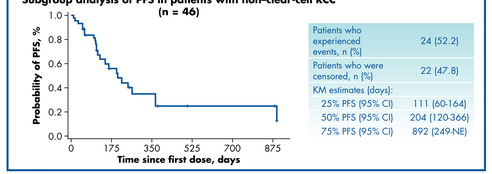
Figure 3. DCR (CR+PR+SD as Best Response[a]) by nccRCC Histology



[a] Patients continuously treated with tivozanib.

- The median PFS was 6.7 months or 204 (95% CI, 120-366) days for all patients with nccRCC (**Figure 4**)

Figure 4. Progression-Free Survival



KM, Kaplan-Meier.

- Overall, 8 patients with SD after treatment with tivozanib for 16 weeks were randomized to 12 weeks of placebo, which may have resulted in PD prior to unblinding and resumption of treatment with tivozanib

Safety and tolerability of tivozanib

- Hypertension, dysphonia, asthenia, diarrhea, fatigue, and rash were the most common TRAEs (≥5% incidence; **Table 3**)
- Duodenal ulcer hemorrhage and hyperbilirubinemia were the only grade 4 TRAEs, each occurring once in a single patient. No grade 5 TRAEs occurred.
- Across all patients with nccRCC, 1 TRAE led to discontinuation (ulcer hemorrhage)

Table 3. Most Common (≥5% Incidence) Treatment-Related Adverse Events[a]

TRAE, n (%)	All grades	Grade 1	Grade 2	Grade 3
Hypertension	21 (46)	10 (22)	9 (20)	2 (4)
Dysphonia	7 (15)	7 (15)	NA	NA
Asthenia	6 (13)	2 (4)	3 (7)	1 (2)
Diarrhea	5 (11)	4 (9)	NA	1 (2)
Fatigue	4 (9)	3 (7)	1 (2)	NA
Rash	3 (7)	1 (2)	2 (4)	NA

TRAE, treatment-related adverse event.
[a] No grade 5 TRAEs occurred during this study. Two grade 4 TRAEs (duodenal ulcer hemorrhage, hyperbilirubinemia) occurred once in a single patient

Conclusions

- This retrospective analysis demonstrated the promising activity of tivozanib in nccRCC, which was observed across papillary, chromophobe, collecting duct, and mixed/unclassified RCC histologies
  - The ORR (best ORR, 31.6%; confirmed ORR, 21.1%) and median PFS of 6.7 months were comparable to those reported in other trials in patients with nccRCC, such as the ASPEN trial of everolimus vs sunitinib (ORR, 9% vs 18% and median PFS, 5.6 vs 8.3 months, respectively)[5]
- Tivozanib was generally well tolerated, with grade 1/2 hypertension being the most common TRAE, only 2 grade 4 TRAEs being reported, and 1 TRAE leading to discontinuation of treatment

Tivozanib was found to be efficacious and well tolerated in patients with advanced nccRCC, potentially adding another treatment option for a patient population that has experienced limited responses with existing therapies[1,2,3]

Table 2. ORR at Week 16 and Best Response by INV

ORR at week 16, n (%)	All nccRCC, (n=46)	Papillary, (n=11)	Chromophobe, (n=2)	Collecting duct, (n=2)	Mixed/unclassified, (n=31)
PR	7 (15.2)	0	0	1 (50.0)	6 (19.4)
SD	22 (47.8)	9 (81.8)	2 (100.0)	1 (50.0)	10 (32.3)
PD	12 (26.1)	2 (18.2)	0	0	10 (32.3)
NE	5 (10.9)	0	0	0	5 (16.1)
Best ORR[a] with tivozanib, n (%)	**All nccRCC, (n=38)**	**Papillary, (n=8)**	**Chromophobe, (n=2)**	**Collecting duct, (n=1)**	**Mixed/unclassified, (n=27)**
PR	12 (31.6)	3 (37.5)	1 (50.0)	1 (100.0)	7 (22.6)
SD	16 (42.1)	4 (50.0)	1 (50.0)	0	11 (40.7)
PD	6 (15.8)	1 (12.5)	0	0	5 (18.5)
NE	4 (10.5)	0	0	0	4 (14.8)
Best confirmed ORR with tivozanib, n (%)	**All nccRCC, (n=38)**	**Papillary, (n=8)**	**Chromophobe, (n=2)**	**Collecting duct, (n=1)**	**Mixed/unclassified, (n=27)**
PR	8 (21.1)	2 (25.0)	1 (50.0)	1 (100.0)	4 (14.8)
SD	20 (52.6)	5 (62.5)	1 (50.0)	0	14 (51.9)
PD	6 (15.8)	1 (12.5)	0	0	5 (18.5)
NE	4 (10.5)	0	0	0	4 (14.8)

INV, investigator; nccRCC, non-clear cell renal cell carcinoma; NE, not evaluable; ORR, objective response rate; PD, progressive disease; SD, stable disease.
[a] Includes unconfirmed PR.

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