Tivozanib Combined With Nivolumab: Phase Ib/II Study in Metastatic Renal Cell Carcinoma

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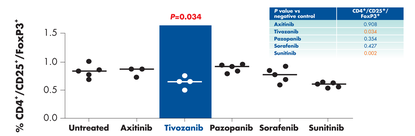
Introduction

- The treatment of metastatic renal cell carcinoma (mRCC) has been revolutionized over the past decade with the advent of novel antiangiogenic drugs, particularly tyrosine kinase inhibitors (TKIs), and most recently immunotherapy[1]
- Inhibitors of the vascular endothelial growth factor (VEGF) pathway have become the standard of care for the treatment of patients with mRCC[2]
- Tivozanib is a novel and highly potent VEGF receptor TKI inhibitor (VEGFR TKI) that has demonstrated antitumor efficacy[3,7]
  - The unique selectivity of tivozanib leads to minimal off-target toxicities and thus a favorable adverse event (AE) profile
- VEGFR TKIs have also been shown to modulate antitumor immunity, providing a mechanism of synergy between VEGFR and programmed cell death protein-1 (PD-1) inhibition[8]
  - Tivozanib enhances PD-1 activity through regulatory T-cell reduction (**Figure 1**)[9]

Figure 1. Tivozanib significantly reduces regulatory T-cell production[9]



Influence on regulatory T cells
Sixteen hours after the last TKI application, splenocytes were isolated and CD4+/CD25+/FoxP3+ regulatory T cells were analyzed by flow cytometry.
Results
Only tivozanib and (as described before) sunitinib significantly reduced the percentage of regulatory T cells.

- The PD-1 immune checkpoint inhibitor nivolumab has been associated with improved overall survival in patients with mRCC treated past the first line[7]
- Due to the specificity of tivozanib and its preferable AE profile, tivozanib is an ideal candidate for combination therapy

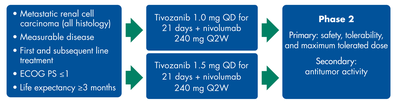
Study Objectives

- Determine the safety, tolerability, and maximum tolerated dose (MTD) of tivozanib in combination with nivolumab in patients with mRCC
- Assess preliminary antineoplastic activity of tivozanib and nivolumab in combination in patients with mRCC

Methods

- TiNivo is a phase Ib/II, open-label, multicenter, dose-escalation study of tivozanib in combination with nivolumab in patients with mRCC (**Figure 2**)

Figure 2. TiNivo study design



ECOG PS, Eastern Cooperative Oncology Group performance status; Q2W, every 2 weeks; QD, once daily.

- Key inclusion criteria include the following:
  - Patients aged ≥18 years
  - Histologically documented RCC with a clear cell component (phase 2 cohort)
  - mRCC with measurable or evaluable disease by Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) criteria
  - No prior exposure to tivozanib or nivolumab
  - ECOG PS ≤1
  - Life expectancy ≥3 months
- Patients received tivozanib QD for 21 days, followed by a 7-day rest period (1 cycle=4 weeks), and nivolumab intravenously 240 mg Q2W
- Dose escalation was dependent on the number of patients experiencing a dose-limiting toxicity (DLT) during cycle 1 and was used to determine MTD
- Following MTD determination, a phase 2 expansion cohort of MTD-enrolled patients was added to further evaluate safety, tolerability, and preliminary antineoplastic activity
- Assessments were as follows:
  - Toxicity was graded via National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03
  - Response assessment using RECIST v1.1 criteria with computed tomography and/or magnetic resonance imaging scans was performed every 2 cycles (8 weeks)
  - Overall objective response rate, progression-free survival, and duration of disease stabilization were calculated

Results

- Phase Ib consisted of 6 patients
  - Tivozanib 1.0 mg/d + nivolumab 240 mg (n=3)
  - Tivozanib 1.5 mg/d + nivolumab 240 mg (n=3)
- No patient in phase Ib experienced a DLT in cycle 1, and MTD was determined to be full-dose tivozanib 1.5 mg/d + nivolumab 240 mg
- In the phase II expansion cohort, 21 patients were enrolled at MTD
  - In total, 6 patients discontinued tivozanib and 7 patients discontinued nivolumab
  - There was 1 dose reduction for tivozanib (cycle 6) and a total of 17 dose interruptions
- Baseline patient characteristics for all 27 patients are described in **Table 1**

Table 1. Baseline patient characteristics in all enrolled patients

	Patients (N=27)
Median age, y (range)	63 (37-75)
Sex, n (%)	
Male	20 (74)
Prior therapy, n (%)	
0	12 (44)
1	13 (48)
2	2 (8)
ECOG PS, n (%)	
0	18 (66.7)
1	9 (33.3)

Safety

- 14 (51.9%) patients experienced ≥1 grade 3/4 AE of any cause (**Table 2**)

Table 2. All-causality treatment-emergent AEs; all-grade (AEs in ≥10% of patients) and grade 3 or 4 (all AEs)

	All grade	Grade 3/4
AE, n (%)	**Patients (N=27)**	
Any AE	27 (100)	14 (51.9)
Hypertension	14 (51.8)	4 (14.8)
Arthralgia	10 (37.0)	0
Asthenia	10 (37.0)	0
Dysphonia	10 (37.0)	0
Mucosal inflammation	9 (33.3)	0
Decreased appetite	8 (29.6)	0
Diarrhea	8 (29.6)	0
Dry skin	6 (22.2)	0
Headache	6 (22.2)	0
Myalgia	6 (22.2)	0
Nausea	6 (22.2)	0
Pruritus	6 (22.2)	0
Hypothyroidism	5 (18.5)	0
Palmar-plantar erythrodysesthesia syndrome	5 (18.5)	2 (7.4)
Back pain	4 (14.8)	0
Dry mouth	4 (14.8)	0
Constipation	3 (11.1)	0
Hypophosphatemia	3 (11.1)	1 (3.7)
Muscle spasms	3 (11.1)	0
Rash	3 (11.1)	1 (3.7)
Vomiting	3 (11.1)	0
Increased ALT	2 (7.4)	1 (3.7)
Increased amylase	2 (7.4)	2 (7.4)
Increased AST	2 (7.4)	1 (3.7)
Increased lipase	2 (7.4)	1 (3.7)
ACS	1 (3.7)	1 (3.7)
Hyperglycemia	1 (3.7)	1 (3.7)
Sarcoidosis	1 (3.7)	1 (3.7)

Note: Highlighted AEs indicate possible immune-related AEs.
ACS, acute coronary syndrome; ALT, alanine aminotransferase increased; AST, aspartate aminotransferase increased.

Preliminary Antineoplastic Activity

- Preliminary efficacy was assessed in the 14 patients who started therapy at the MTD and had ≥2 treatment scans (ie, were on treatment for ≥4 months; **Table 4**; **Figure 3**; **Figure 4**)
  - Of the patients evaluated for efficacy, 11 of 14 are undergoing treatment, including 3 patients in cycle 8 with a partial response (PR) (**Figure 4**)

Table 3. Response to treatment in patients receiving the full treatment dose with ≥2 treatment scans

Best overall response, n (%)	Patients (n=14)
CR	0
PR	9 (64.3)[a]
SD	5 (35.7)[b]
Progressive disease	0
Objective response rate (CR + PR)	9/14 (64.3)
Disease control rate (CR + PR + SD)	14/14 (100)

CR, complete response; SD, stable disease.
[a]Includes 5 patients with an unconfirmed response.
[b]Includes 2 patients with an unconfirmed response.

Figure 3. Change in tumor size by prior treatment

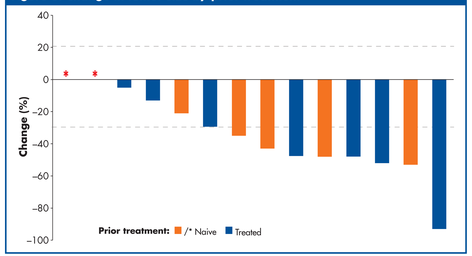
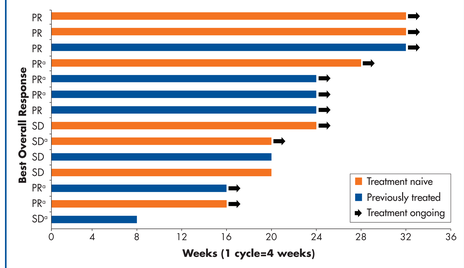
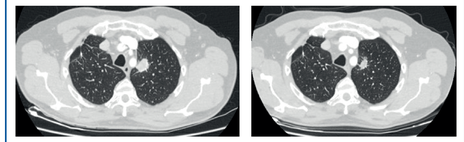


Figure 4. Response and treatment duration



*Unconfirmed response.

Figure 5. Patient scan at baseline and at week 8 of treatment



Baseline Week 8

Conclusions

- The specificity of tivozanib led to a promising AE profile of full-dose tivozanib combined with full-dose nivolumab
- Safety data were favorable, with 52% of patients experiencing grade 3/4 AEs
  - The most common AE was hypertension
  - Minimal off-target AEs were observed, likely due to the high specificity of tivozanib
- Although preliminary, the 64% objective response rate and 100% disease control rate in patients receiving the MTD suggest promising antitumor efficacy; 11 of 14 patients remain on therapy
- Overall, these results demonstrate very promising efficacy for tivozanib in combination with immune checkpoint inhibitors

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