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# TiNivo: Tivozanib Combined With Nivolumab: Safety and Efficacy in Patients With Metastatic Renal Cell Carcinoma (mRCC)


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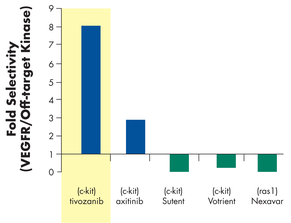
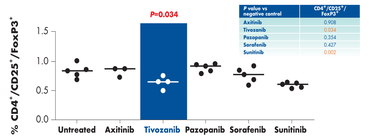
## Introduction

- Metastatic renal cell carcinoma (mRCC) treatment has been revolutionized over the past decade with antiangiogenic tyrosine kinase inhibitors (TKIs) and immunotherapy[1]
- Vascular endothelial growth factor (VEGF) pathway inhibitory agents have become an mRCC standard-of-care treatment[2]
- Tivozanib is a highly potent and selective VEGF receptor TKI inhibitor (VEGFR TKI) with a long half-life that is approved by the European Commission for the treatment of patients with mRCC[3-7]
- Tivozanib has a favorable adverse event (AE) profile because of the unique selectivity of tivozanib (**Figure 1**) that leads to minimal off-target toxicities, making it the ideal candidate for combination therapy with nivolumab, a programmed cell death protein-1 (PD-1) immune checkpoint inhibitor
- A mechanism of synergy between VEGFR and PD-1 inhibition exists, as VEGFR TKIs have been shown to modulate antitumor immunity[8]
  - Tivozanib enhances PD-1 activity through regulatory T-cell reduction (**Figure 2**)[9]

### Figure 1. Selectivity of tivozanib compared with other VEGF TKIs




### Figure 2. 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.

- Nivolumab has been associated with improved overall survival in patients with mRCC treated past the first line and is approved for previously treated patients with mRCC[7]
  - We previously demonstrated promising efficacy for tivozanib in combination with nivolumab in the phase 1b/2 TiNivo trial (NCT03136627),[10] and now present updated results for the full maximum tolerated dose (MTD) cohort

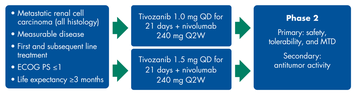
### *Study Objectives*

- Determine the safety and tolerability 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 1b/2, open-label, multicenter, dose-escalation study of tivozanib in combination with nivolumab in patients with mRCC (**Figure 3**)

### Figure 3. 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)
  - No prior exposure to tivozanib or nivolumab
  - ECOG PS ≤1
  - Life expectancy ≥3 months
- Phase 1b consisted of 6 patients
  - Tivozanib 1.0 mg QD + nivolumab 240 mg Q2W (n=3) and tivozanib 1.5 mg QD + nivolumab 240 mg Q2W (n=3)
  - No patient experienced a DLT in cycle 1, and MTD was determined to be full-dose tivozanib (1.5 mg QD + nivolumab 240 mg Q2W)
- Following MTD determination, a phase 2 expansion cohort of MTD-enrolled patients was added to further evaluate safety, tolerability, and efficacy
- 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 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

- In the phase 2 expansion, 22 additional patients were enrolled at MTD, resulting in N=25 for this cohort
- Baseline patient characteristics for all 25 patients are described in **Table 1**
  - Two patients received prior immunotherapy (anti-PD-L1), all other prior therapy was sunitinib or pazopanib

### Table 1. Baseline patient characteristics in all enrolled patients

| | Patients (N=25) |
|---|---|
| **Median age, y (range)** | 64 (37-75) |
| **Sex, n (%)** | |
| Male | 19 (76) |
| Female | 6 (24) |
| **Prior therapy, n (%)** | |
| 0 | 12 (48) |
| 1 | 11 (44) |
| 2+ | 2 (8) |
| **ECOG PS, n (%)** | |
| 0 | 15 (60) |
| 1 | 10 (40) |
| **IMDC, n (%)** | |
| Favorable | 7 (28) |
| Intermediate | 17 (68) |
| Poor | 1 (4) |

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

### *Safety*

- 15 (60%) patients experienced ≥1 treatment-related grade 3/4 AE (**Table 2**)
  - Excluding uncomplicated hypertension, the treatment-related grade 3/4 AE rate was 44%
  - 3 (12%) patients required a tivozanib dose reduction (nivolumab dose reductions were not permitted)
  - 3 (12%) patients discontinued treatment due to AEs

### Table 2. Treatment-related AEs of all grades (AEs in ≥20% of patients) and grade 3 or 4 (all AEs)

| | All grades | Grade 3/4 |
|---|---|---|
| | Patients (N=25) | |
| **Total, n (%)** | 25 (100) | 15 (60) |
| **Gastrointestinal disorders, n (%)** | 18 (72) | 0 |
| Diarrhea | 11 (44) | 0 |
| Stomatitis | 8 (32) | 0 |
| Dry mouth | 5 (20) | 0 |
| **General disorders, n (%)** | 18 (72) | 1 (4) |
| Asthenia | 15 (60) | 0 |
| Fatigue | 2 (8) | 1 (4) |
| **Skin and subcutaneous disorders, n (%)** | 17 (68) | 3 (12) |
| Pruritus | 9 (36) | 0 |
| Dry skin | 7 (28) | 0 |
| Palmar-plantar erythrodysesthesia syndrome | 7 (28) | 2 (8) |
| Rash | 4 (16) | 1 (4) |
| **Musculoskeletal disorders, n (%)** | 15 (60) | 1 (4) |
| Arthralgia | 10 (40) | 0 |
| Myalgia | 8 (32) | 0 |
| Myositis | 2 (8) | 1 (4) |
| **Vascular disorders, n (%)** | 15 (60) | 11 (44) |
| Hypertension | 15 (60) | 10 (40) |
| Malignant hypertension | 2 (8) | 2 (8) |
| **Respiratory disorders, n (%)** | 11 (44) | 0 |
| Dysphonia | 10 (40) | 0 |
| **Investigations, n (%)** | 10 (40) | 5 (20) |
| ALT increased | 3 (12) | 1 (4) |
| AST increased | 3 (12) | 1 (4) |
| Blood alkaline phosphatase increased | 1 (4) | 1 (4) |
| Gamma-glutamyl transferase increased | 1 (4) | 1 (4) |
| Amylase increased | 2 (8) | 1 (4.0) |
| Lipase increased | 1 (4) | 1 (4.0) |
| **Metabolism and nutritional disorders, n (%)** | 10 (40) | 0 |
| Decreased appetite | 7 (28) | 0 |
| **Endocrine disorders, n (%)** | 7 (28) | 0 |
| Hypothyroidism | 7 (28) | 0 |
| **Cardiac disorders** | 3 (12) | 1 (4) |
| Acute coronary syndrome | 1 (4) | 1 (4) |

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

### *Efficacy*

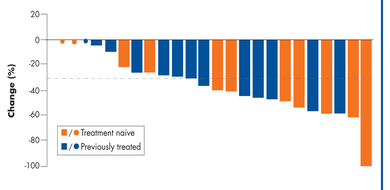
- Efficacy was assessed in the 25 patients who started therapy at the MTD (**Table 3** and **Figure 4**)
  - Patients had an **objective response rate (ORR) of 56%** with a **disease control rate of 96%**
  - **18 patients (72%) had tumor shrinkage ≥25% so far**, and **1 patient had a complete response**
  - Median time to best response was 16 weeks
  - ORR was comparable in treatment-naive and previously treated patients
- 13 of 25 patients (52%) are still on treatment (**Figure 5**)

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

| Best overall response, n (%) | Patients (N=25) |
|---|---|
| **CR** | **1 (4)** |
| PR | 13 (52) |
| SD | 10 (40) |
| PD | 1 (4) |
| **ORR (CR + PR)** | **14/25 (56)** |
| **Disease control rate (CR + PR + SD)** | **24/25 (96)** |

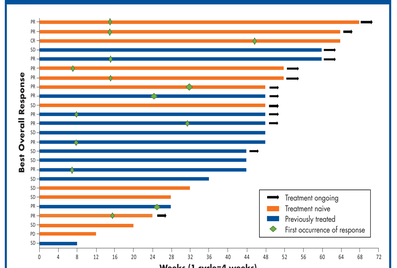
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

### Figure 4. Change in tumor size by prior treatment




One additional patient had progressive disease as best response due to appearance of new lesions in the first scan.

### Figure 5. Response and treatment duration




## Conclusions

- In TiNivo, the tivozanib and nivolumab combination regimen showed promising antitumor efficacy, with most patients having disease control for ≥48 weeks
  - A high rate of disease control was observed, including a patient with a complete response
- The combination regimen showed a favorable AE profile with minimal off-target effects, likely due to the high specificity of tivozanib
  - The most common grade 3/4 AE was uncomplicated hypertension, an on-target effect
  - Notably, grade 3/4 fatigue, diarrhea, and elevations of hepatic enzymes were low, as predicted by single-agent experience with tivozanib
  - A low discontinuation rate and a small number of dose reductions due to AEs were observed
- At the time of this interim analysis, 13 patients remain on treatment
- Plans are underway for an additional randomized trial

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