TiNivo-2: A Phase 3, Randomized, Controlled, Multicenter, Open-Label Study to Compare Tivozanib in Combination With Nivolumab to Tivozanib Monotherapy in Patients With Renal Cell Carcinoma Following 1 or 2 Lines of Therapy in Which at Least One Line Has an Immune Checkpoint Inhibitor

TPS405

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Background

- Renal cell carcinoma (RCC) is the eighth most common cancer in the United States.[1] Early-stage disease can commonly be asymptomatic, and 16% of patients present with metastatic RCC[1]
- In the past decade, treatment options have been transformed with the advent of antiangiogenic small-molecule vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) in combination with checkpoint inhibitor immunotherapy[2]
- There is limited data to guide treatment sequencing after frontline immunotherapy combinations
- The current standard of care after progression on frontline combination immunotherapy is VEGFR-targeted monotherapy[2]

Study Rationale

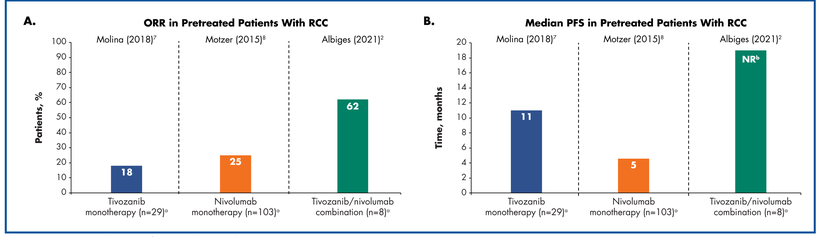
The VEGFR Pathway and Tivozanib

- The VEGFR pathway plays a critical role in angiogenesis, which is an essential process in endothelial cell proliferation, migration, and survival in cancer[3]
- Tivozanib is a potent, highly selective VEGFR TKI that inhibits all 3 VEGFRs (VEGFR-1, -2, and -3)[2]
- In a phase 3 clinical trial (NCT02627963), treatment with tivozanib monotherapy was safe and efficacious in patients with advanced RCC[4]
- On March 10, 2021, tivozanib was granted US Food and Drug Administration approval and is indicated for the treatment of adult patients with relapsed or refractory advanced RCC following ≥2 prior systemic therapies[5]

Rationale for Tivozanib and Nivolumab Combination Therapy

- The addition of nivolumab, an anti-programmed cell death protein 1 (anti–PD-1) antibody, to tivozanib is a treatment strategy of interest because:
  - Tivozanib has been shown to reduce production of regulatory T cells,[6] thus potentially facilitating immune-mediated responses
  - Nivolumab blocks the immune checkpoint protein PD-1 from interacting with programmed death ligand 1[2]
  - The selectivity and favorable tolerability of the VEGFR TKI tivozanib[2] may allow it to be used more readily as a combination therapy with an immune checkpoint inhibitor (ICI)
  - These mechanisms may act synergistically to remove inhibition of the immune response that mediates antitumor activity[2]
- In the TiNivo phase 1/2 clinical trial (NCT03136627) in patients with RCC who were treatment naive or who received prior therapy, tivozanib in combination with nivolumab demonstrated promising antitumor efficacy and a tolerable adverse event (AE) profile[2]
  - An objective response rate (ORR) of 56% (95% CI, 36.5%-75.5%) was observed, with a disease control rate of 96% (n=24) and median progression-free survival (PFS) of 18.9 months (95% CI, 16.4 months-not reached)[2]
  - In a subanalysis of patients who received prior treatment for RCC, the ORR with tivozanib and nivolumab combination therapy was 62% (**Figure 1A**) and median PFS was not reached (**Figure 1B**)[2]
  - 20 patients (80%) experienced ≥1 grade 3/4 treatment-related AE, with the most common being hypertension (n=13 [52%])[2]
  - Previous data from separate studies have shown that tivozanib or nivolumab monotherapy in previously treated patients resulted in an ORR of 18% and 25% (**Figure 1A**) and PFS of 11.0 and 4.6 months (**Figure 1B**), respectively[7,8]
- These results support further investigation in the phase 3 trial TiNivo-2, which is evaluating tivozanib in combination with nivolumab vs tivozanib monotherapy in patients with advanced RCC that has progressed following 1-2 lines of therapy including an ICI

Figure 1. Antitumor Activity in Pretreated Patients. (A) ORR was higher with tivozanib/nivolumab combination therapy than with either single agent alone; (B) PFS was longer with tivozanib/nivolumab combination therapy than with either monotherapy alone



ORR, objective response rate; PFS, progression-free survival; RCC, renal cell carcinoma.
[a] Data from separate studies.
[b] The tivozanib/nivolumab combination arm did not reach the limits of PFS during the trial, which followed up patients for 19 months.

Study Protocol and Procedures

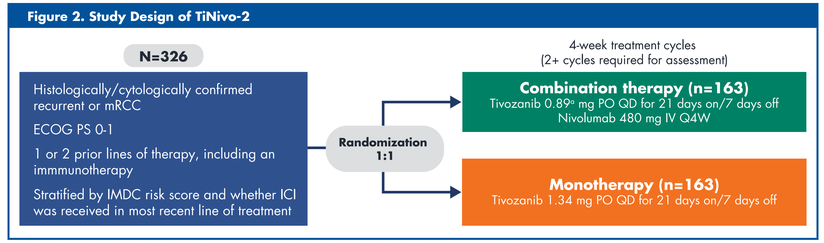
Objective

- To compare the efficacy and safety of tivozanib and nivolumab combination therapy with those of tivozanib monotherapy in patients with advanced RCC that has progressed following 1 to 2 lines of therapy including an ICI

Study Design

- This is a phase 3, randomized, controlled, multicenter, open-label, global, clinical trial (NCT04987203)
- Approximately 326 patients will be randomized 1:1 to receive tivozanib in combination with nivolumab or tivozanib monotherapy (**Figure 2**)

Figure 2. Study Design of TiNivo-2



[a]Protocol amendment in February 2022 reduced dose of tivozanib from 1.34 to 0.89 mg when combined with nivolumab. This amendment was not the result of any clinical outcomes seen in the conduct of the TiNivo-2 trial, which has enrolled 2 patients thus far. The growing body of evidence in combination trials suggest that the risk-benefit may be optimized at a reduced dose in the combination.
1L, first line; 2L, second line; ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic RCC Database Consortium; IV, intravenous; mRCC, metastatic renal cell carcinoma; PO, orally; Q4W, every 4 weeks; QD, once daily; TKI, tyrosine kinase inhibitor.

Endpoints

- Study endpoints are shown in **Table 1**

Table 1. Study Endpoints

Primary endpoints
PFS assessed by blinded independent radiological review (until PD [≈30 months] as measured by RECIST v1.1)
Secondary endpoints
OS (from screening until death [≈42 months])
ORR (measured as CR+PR; from screening until PD [≈30 months] as measured by RECIST v1.1)
DOR (from screening until PD or death [≈30 months])
Safety and tolerability (from screening to follow-up visit [30 days after last dose ±7 days])
Exploratory endpoints
HRQOL by FKSI-DRS and EORTC QLQ-C30
PK of tivozanib

CR, complete response; DOR, duration of response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; FKSI-DRS, Functional Assessment of Cancer Therapy–Kidney Symptom Index Disease-Related Symptoms; HRQOL, health-related quality of life; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

Enrollment Criteria

- Key enrollment criteria are shown in **Table 2**

Table 2. Key Inclusion and Exclusion Criteria

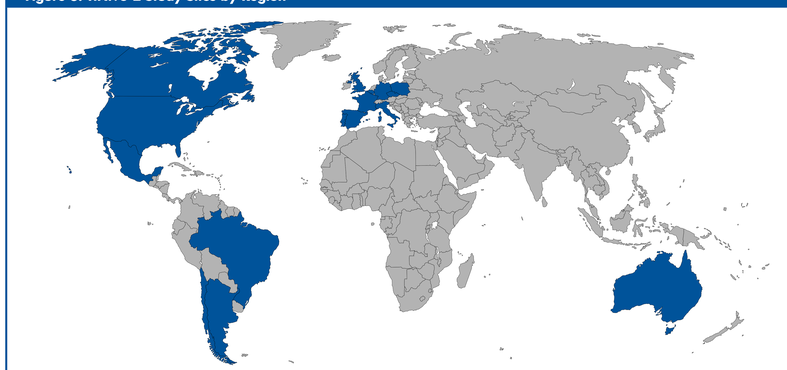
Inclusion criteria	Exclusion criteria
Age ≥18 years	Prior treatment with tivozanib
Histologically or cytologically confirmed RCC with a clear cell component	>1 prior line of therapy with an ICI in the metastatic setting
Radiographic disease progression during or following ≥6 weeks of treatment with an ICI for locally advanced or mRCC with a clear cell component either in 1L or 2L setting	>2 prior lines of therapy in the advanced or metastatic setting
Patients must have recovered from the AEs of prior therapy or returned to baseline	History of life-threatening toxicity related to prior immune therapy
Measurable disease per RECIST v1.1	Active, known, or suspected autoimmune disease
ECOG PS 0-1	Known CNS metastases other than stable, treated brain metastases
	Uncontrolled hypertension: systolic BP >150 mm Hg or diastolic BP >100 mm Hg while receiving ≥2 antihypertensive medications

1L, first line; 2L, second line; AE, adverse event; BP, blood pressure; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; mRCC, metastatic renal cell carcinoma; mTOR, mechanistic target of rapamycin; RECIST, Response Evaluation Criteria in Solid Tumors.

Study Sites

- The study is actively enrolling and expected to be conducted in approximately 200 sites across the United States, Argentina, Australia, Belgium, Brazil, Canada, Chile, Czech Republic, France, Germany, Italy, Mexico, Poland, Portugal, Spain, and United Kingdom (**Figure 3**)

Figure 3. TiNivo-2 Study Sites by Region



Summary

- Immunotherapy combinations have become the standard of care in the 1L treatment of advanced RCC, and few data exist on sequencing treatment after prior immunotherapy combination regimens[2]
- Tivozanib is a potent and selective VEGFR inhibitor with demonstrated single-agent activity and a favorable toxicity profile[4]
- Because of tivozanib's effect on reducing regulatory T cells,[6] it may have a synergistic effect on the tumor microenvironment when combined with an ICI such as nivolumab
- In the phase 1/2 TiNivo clinical trial, tivozanib combination therapy with nivolumab has demonstrated enhanced efficacy and a tolerable safety profile in patients with treatment-naive and pretreated advanced RCC[2]

This phase 3 study (NCT04987203) will compare the efficacy and tolerability profile of tivozanib and nivolumab combination therapy vs that of tivozanib monotherapy in patients with advanced RCC that progressed after 1L or 2L treatment following an ICI

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