The addition of nivolumab, an anti-programmed cell death protein 1 (anti–PD-1) antibody, to tivozanib is a treatment strategy of interest. In a phase 3 clinical trial (NCT02627963), treatment with tivozanib monotherapy was safe and efficacious in patients with advanced RCC.

The VEGFR Pathway and Tivozanib

The current standard of care after progression on frontline combination immunotherapy is VEGFR-targeted monotherapy. There is limited data to guide treatment sequencing after frontline immunotherapy combinations. Renal cell carcinoma (RCC) is the eighth most common cancer in the United States. Early-stage disease can commonly be asymptomatic, and 16% of patients present with metastatic RCC.

Tivozanib in combination with nivolumab demonstrated promising antitumor efficacy and a tolerable adverse event (AE) profile. The selectivity and favorable tolerability of the VEGFR TKI tivozanib may allow it to be used more readily as a combination therapy with immunotherapy.

Study Rationale

The VEGF pathway plays a critical role in angiogenesis, which is an essential process in endothelial cell proliferation, migration, and survival in cancer.

Tivozanib is a potent, highly selective VEGF-TK that inhibits all 3 VEGF receptors (VEGFR-1, -2, and -3).

It is a phase 2 clinical trial (NCT02279953), treatment with tivozanib monotherapy was safe and efficacious in patients with advanced RCC. On March 15, 2021, researchers were granted US Food and Drug Administration approval and is indicated for the treatment of adult patients with relapsed or refractory advanced RCC following 1 or 2 prior systemic therapies.

Rationale for Tivozanib and Nivolumab Combination Therapy

The inclusion of immunotherapy, an oncoprogrammed cell death strategy, likely to be a treatment strategy of interest because—Tivozanib has been shown to reduce production of regulatory T cells; thus, facilitating immune-mediated responses—Nivolumab blocks the immune checkpoint protein PD-1 from interacting with programmed death ligand 1.

— The selectivity and favorable tolerability of the VEGFR TKI tivozanib may allow it to be used more readily as a combination therapy with an immunotherapeutic checkpoint inhibitor (IC)

— These mechanisms may eat synergistically to reduce inhibition of the immune response that mediates antitumor activity.

— The TKI–phase 1/2 clinical trial (NCT03033824) in patients with RCC who received treatment with tivozanib alone, tivozanib in combination with nivolumab demonstrated promising efficacy and tolerable adverse event (AE) profile.

— An objective response rate (ORR) of 36% (95% CI, 26.7-45.1%) was observed, with a disease control rate of 94% (95% CI, 83.8-98.7%) with median progression-free survival (PFS) of 18.9 months (95% CI, 16.4 months-not reached).

— In a subset of patients who received prior treatment for RCC, 6% ORR with tivozanib and nivolumab combination was 62% and median PFS was not reached (Figure 1).

— 20% patients experienced ≥1 grade 3/4 treatment–related AE, with the most common being hypertension (n=3 [1.3%]).

— Previous data from separate studies have shown that tivozanib alone, nivolumab alone, and nivolumab in previously treated patients resulted in an ORR of 16% and 25% (Figure 1A) and PFS of 11.0 and 6.4 months (Figure 1B), respectively.

— These results further support investigation in the phase 3 trial TIN4-c, which is evaluating tivozanib in combination with nivolumab or nivolumab in the treatment of advanced RCC that has progressed following 1 or 2 lines of therapy including IC.

Endpoints

Study endpoints are shown in Table 1.

Table 1. Study Endpoints

Primary endpoints

Patient-assessed blinded independent radiological review (and PFS based on review by RECIST v1.1) ORR measured by the CRITC

Secondary endpoints

CR (from screening until death [the 1L setting])

ORR measured by CRITC

DOR (from screening until death [the 1L setting])

Safety and tolerability (from screening to follow-up visit [≥30 days after last dose of study drug])

Exploratory endpoints

HRQOL by FKSI-DRS and EORTC QLQ-C30

Table 2. Key Inclusion and Exclusion Criteria

Inclusion criteria

Age ≥18 years

Histologically or cytologically confirmed RCC with clear cell component

Radiographic disease progression following ≥1 lines of therapy in the metastatic setting

Patients may have received treatment with IC and RCC therapies

Exclusion criteria

Patients must have recovered from the AEs of prior therapy or returned to baseline

History of uncontrolled hypertension

History of uncontrolled diabetes

Active, serious, or uncontrolled cardiovascular disease

Interference with the administration of the combination

If used, the combination must be discontinued

Interference with the administration of the combination

OS (from screening until death [≈42 months])

Secondary endpoints

ECOG PS 0-1

Combination therapy (n=163)

Monotherapy (n=103)

Figure 2. Study Design of TiNivo-2

tivozanib-eligible patients with advanced RCC that has progressed after 1 to 2 lines of therapy including IC.

The study was 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. Tivozanib-3 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 the TKI–VEGFR target in combination with IC.

Tivozanib is an active and selective VEGFR inhibitor with demonstrated single-agent activity and a favorable toxicity profile.

Because of tivozanib’s effect on reducing regulatory T cells, it may have a synergistic effect on the tumor microenvironment when combined with an IC such as nivolumab.

In the phase 1/2 TiNivo clinical trial, tivozanib combination therapy with nivolumab has demonstrated enhanced efficacy and a tolerable toxicity profile in patients with treatment-naive and pretreated advanced RCC.

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