TIP#5

The current standard of care after progression on frontline combination therapy is VEGFR-targeted monotherapy.

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.

- Tivozanib is a potent, highly selective VEGFR TKI that inhibits all 3 VEGFRs (VEGFR-1, -2, and -3).

- There is limited data to guide treatment sequencing after frontline immunotherapy.

- Renal cell carcinoma (RCC) is the eighth most common cancer in the United States.

**Rationale for Tivozanib and Nivolumab Combination Therapy**

- The addition of nivolumab, an anti-programmed death 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, thus potentially 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 and the anti-PD-1 antibody nivolumab may allow it to be used more readily as a combination therapy with an immune checkpoint inhibitor (ICI).
  - These mechanisms may act synergistically to inhibit the immune response that mediates antitumor activity.

- In the TiNivo phase 1/2 clinical trial (NCT03136627), treatment with tivozanib monotherapy was safe and efficacious in patients with advanced RCC.

- 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.

**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.

**Study Sites**

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

**Summary**

- Immuno-oncology combinations have become the standard of care in the first-line treatment of advanced RCC, and few data exist on sequencing treatment after prior immunotherapy combination regimens.

- Tivozanib is a potent and selective VEGFR inhibitor associated with 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 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.

**Study Sites by Region**

**Endpoints**

- **Table 1. Study Endpoints**

**References**


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.