# Overview of Tivozanib (Tivo) Safety in Patients with Metastatic Renal Cell Carcinoma (mRCC)

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## Objective of this Retrospective Analysis

**To evaluate the safety profile of 2L+ tivozanib (tivo) monotherapy in patients with mRCC that had progressed after prior treatment with at least one contemporary systemic VEGFR-TKI- or ICI-based mono or combination therapy by comparing the incidence of adverse events (AEs) in two separate Phase 3 studies.**

## Conclusions

- **Tivozanib showed a manageable safety profile as monotherapy** across the two Phase 3 studies included in the analysis (TIVO-3 and TiNivo-2)
- **Adverse events were generally consistent with the known safety profile of tivozanib** and the disease state under study
- **The most common ≥Grade 3 treatment-related AE was hypertension** (incidence approximately 21% in each study and clinically manageable)
- **All other ≥Grade 3 AEs occurred with single digit % incidence**
- **Incidences of all-cause ≥Grade 3 events** and serious adverse events (SAEs), as well as some treatment-related events (e.g., decreased appetite, asthenia, dysphonia, stomatitis) **were lower in TiNivo-2,** likely because this study enrolled patients receiving earlier lines of treatment
- This is consistent with **TIVO-3 inclusion of patients that were more heavily pre-treated than those in TiNivo-2**

## Methods and Limitations

- This analysis was a comparison of the incidence of safety events in two independent study cohorts
- Each cohort comprised the safety population of the tivo monotherapy arm of one study: TIVO-3 (N=173) or TiNivo-2 (N=171)[3,4]
- Both Phase 3 randomized studies enrolled patients with mRCC (permitted prior lines of systemic therapies were described in the entry criteria for each study and are summarized in Figures 1 and 2)
- All-cause and treatment-related AEs, Grade ≥3 AEs, and serious events (SAEs) from both studies were included in the analysis
- The primary limitation this investigation is that it is a retrospective analysis of two separate clinical studies

**Acknowledgements**
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**References**

1. FOTIVDA® (tivozanib) Prescribing Information. 2024; 2. Rathmell WK, et al. J Clin Oncol. 2022; 40:2957–2995; 3. Rini et al., Lancet Oncol 2020; 21: 95–104; 4. Choueiri TK, et al. Lancet 2024; 404:1309–1320; 5. OPDIVO® (nivolumab) Prescribing Information. 2024.

## Background of this Review

- Tivo is a potent and highly selective oral VEGF-TKI designed to optimize VEGF blockade and minimize off-target toxicities. Tivo has been evaluated in two Phase 3 randomized studies:
- TIVO-3 (Figure 1) compared tivo monotherapy with sorafenib monotherapy in patients with mRCC that has progressed after 2 or 3 systemic therapies. This study led to the approval of tivo for the treatment of patients with relapsed or refractory mRCC following ≥2 prior systemic therapies[1,2,3]
- TiNivo-2 (Figure 2) randomized patients with mRCC who had previous exposure to an ICI to tivo alone at 1.34 mg, or at 0.89 mg in combination with the ICI nivolumab (nivo) as 2L or 3L therapy[4,5]
- TiNivo-2 did not demonstrate benefit of adding nivo to tivo after prior ICI exposure, but clinically meaningful outcomes were observed with tivo as a second-line (2L) and third-line (3L) treatment following ICI therapy:[4]

2L (median PFS):
**Tivo+Nivo:** 7.3 months (95% CI 5.4–9.3)
**tivo** 9.2 months (95% CI 7.4–10.0)

**HR 1.15 (0.82–1.62); p=0.43**

3L (median PFS):
**Tivo+Nivo:** 4.8 months (95% CI 3.2–7.5)
**tivo:** 5.5 months (95% CI 2.9–7.4)

**HR 0.97 (0.65–1.45); p=0.89**

## Design of the Two Phase 3 Studies

**Figure 1. TIVO-3 Study Design**

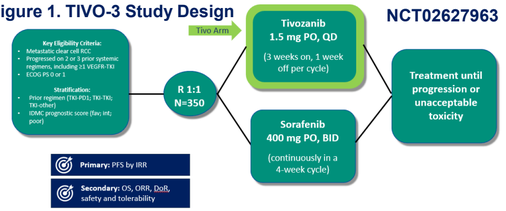
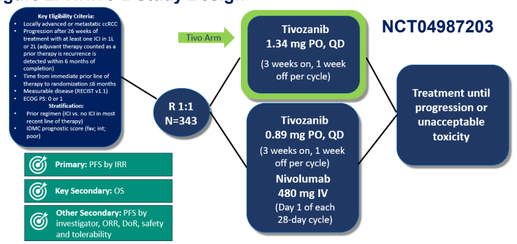



**Figure 2. TiNivo-2 Study Design**




## Baseline Demographics and Disease Characteristics

**Table 1. Baseline Demographics**

| Parameter | TIVO-3 ITT (N=175) | TiNivo-2 ITT (N=172) |
|---|---|---|
| **Median Age yrs, (range)** | 62 (34-88) | 63 (33-82) |
| **Sex, Male, n (%)** | 126 (72) | 134 (78) |
| **Race, n (%)** | | |
| White | 165 (94) | 107 (62) |
| Asian | 2 (1) | 0 |
| Black | 0 | 8 (5) |
| Other or Not Reported | 8 (5) | 57 (33) |
| **ECOG PS 0-1. N (%)** | 175 (100) | 172 (100) |
| **IDMC Risk Category, n (%)** | | |
| Favorable | 33 (19) | 31 (18) |
| Intermediate | 109 (62) | 113 (66) |
| Poor | 32 (18) | 28 (16) |

**Table 2. Baseline Disease Characteristics**

| Parameter | TIVO-3 ITT (N=175) | TiNivo-2 ITT (N=172) |
|---|---|---|
| **Pathology, n (%)** | | |
| Clear Cell | 165 (94) | 157 (91) |
| Clear cell component | 9 (5) | 14 (8) |
| Other | 1 (1) | 1 (1) |
| **Prior Treatment, n (%)** | | |
| >1 line (any therapy) | 175 (100) | 172 (100) |
| 1 line | 0 | 105 (61) |
| ≥2 lines | 175 (100) | 67 (39) |
| any ICI | 47 (27) | 172 (100) |
| no VEGFR-TKI | 0 | 53 (31) |
| any VEGFR-TKI | 175 (100) | 118 (69) |
| 1 VEGFR-TKI | - | 101 (59) |
| 2 VEGFR-TKI | 79 (45) | 18 (11) |
| VEGFR-TKI+ICI | 47 (27) | 66 (38) |
| VEGFR-TKI + other agent | 49 (28) | 4 (2) |

Study populations were generally consistent with respect to baseline demographics and disease characteristics (Table 1, Table 2). Cohorts differed primarily in terms of prior treatment.

## Adverse Events – Overview

**Table 3. TEAE Overview**

| Parameter | TIVO-3 SAFETY (N=173)[a] | TiNivo-2 SAFETY (N=171)[b] |
|---|---|---|
| **Median duration of treatment, months (range)** | **6.5 (0.1 – 37.0)** | **7.4 (0.1 – 17.9)** |
| **Any TEAE, n (%)** | **171 (99)** | **167 (98)** |
| Any Grade ≥ 3 event | 131 (76) | 103 (60) |
| Any serious event (SAE) | 75 (43) | 64 (37) |
| Event leading to dose reduction | 44 (25) | 38 (22) |
| Event leading to dose interruption | 87 (50) | 93 (54) |
| Event leading to treatment withdrawal | 37 (21) | 33 (19) |
| **Any Tivozanib-related Event, n (%)** | 146 (84) | 144 (84) |
| Any Grade ≥ 3 tivozanib-related event | 79 (46) | 60 (35) |
| Any tivozanib-related SAE | 21 (12) | 15 (9) |
| Death due to tivozanib-related event | 0 | 1 (1) |

a. Median follow-up for TIVO-3 19.0 months (95% CI 15.0−23.4)
b. Median follow-up for TiNivo-2 12.0 months (95% CI 11.5–12.8)

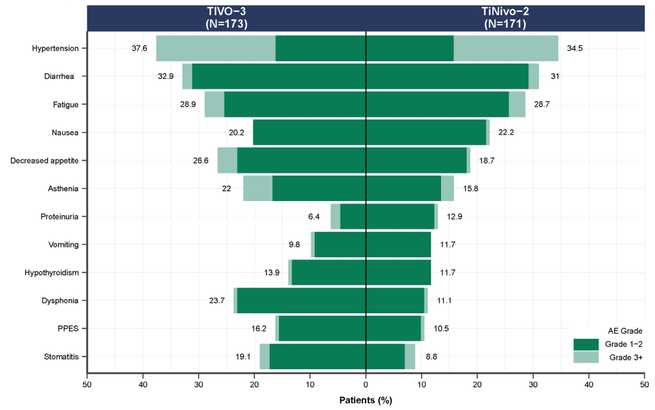
## Treatment Emergent Adverse Events

**Table 4. All Cause Grade ≥3 Events with Overall Incidence ≥2%**

| Preferred Term, n (%) | TIVO-3 SAFETY (N=173) | TiNivo-2 SAFETY (N=171) |
|---|---|---|
| Hypertension | 37 (21) | 38 (22) |
| Asthenia | 13 (8) | 8 (5) |
| Fatigue | 8 (5) | 8 (5) |
| Decreased appetite | 8 (5) | 4 (2) |
| Weight decreased | 4 (2) | 5 (3) |
| Anemia | 4 (2) | 3 (2) |
| Back pain | 3 (2) | 5 (3) |
| Dyspnea | 5 (3) | 2 (1) |
| Arthralgia | 3 (2) | 4 (2) |
| Diarrhea | 3 (2) | 4 (2) |

- There was consistency between the studies in the incidence of all-cause TEAEs, as well events leading to death or treatment modification (Table 3)
- Consistent with the greater proportion of patients with more advanced disease in TIVO-3, the incidence of all-cause SAEs and ≥Grade 3 TEAEs was higher in this study than in TiNivo-2 (Table 4)

**Figure 3. Most Common >10% Tivozanib-Related AEs (Any Grade)**




The overall pattern of AEs was generally consistent between studies and reflective of both the known safety profile of Tivozanib and the population of patients with advanced renal cancer (Table 3, Figure 3).

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