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Positive Quality Intervention: Tivozanib (Fotivda®) for Relapsed or Refractory Advanced Renal Cell Carcinoma

Description: The purpose of this PQI is to review the clinical considerations around the use of tivozanib (Fotivda®) for patients with relapsed or refractory advanced renal cell carcinoma.

Background: Tivozanib is a small molecule that inhibits the phosphorylation of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, and VEGFR-3.[1] Tivozanib is approved by the FDA for the treatment of advanced or metastatic renal cell carcinoma in patients who have previously received two or more prior systemic therapies based on the phase III trial TIVO-3.[2,3]

With a median follow-up of 19 months, patients treated with tivozanib had a significantly longer median progression-free survival (PFS) (5.6 vs. 3.9 months; hazard ratio [HR] 0.73, p=0.02) and a higher objective response rate (18% vs. 8%) compared to sorafenib.[2] In the updated results with extended follow-up (data cutoff: May 24, 2021), the investigator-assessed PFS hazard ratio favored tivozanib over sorafenib (HR, 0.624; 95% confidence interval [CI], 0.49-0.79, p<0.0001).[4] Longer-term progression-free survival rates at 12, 36, and 48 months were also higher with tivozanib. The median overall survival (OS) was not significantly different between the groups (16.4 vs. 19.1 months; HR, 0.89 (95% CI, 0.7-1.114, p=0.3533).[4] However, median OS was significantly improved with tivozanib (48.3 months) compared to sorafenib (32.8 months) in patients achieving 12-month PFS (HR, 0.45; 95% CI, 0.22-0.91, p=0.0221).

Treatment-related adverse events with tivozanib were common (84%) but manageable, with Grade 3 or higher adverse events attributed to VEGFR TKI class effects reported in 46% of patients, including hypertension (20%), diarrhea, fatigue, asthenia, rash, and palmar-plantar erythrodysesthesia.[2,4,5] Tivozanib-related dose reductions occurred in 50% of patients, dose interruptions in 25%, and treatment discontinuations in 21%, with a median time to these events being 81 days, 85 days, and 114 days, respectively.[5]

PQI Process:

- Verify dosage: The recommended starting dose of tivozanib is 1.34 mg by mouth once daily, with or without food, for 21 days on treatment followed by 7 days off treatment for a 28-day cycle[6]
- Dose interruptions and/or dose reduction may be needed to manage adverse reactions (see below)
    - First and only dose reduction: tivozanib 0.89 mg daily by mouth once daily for 21 days on treatment followed by 7 days off treatment for a 28-day cycle[6]
- Dose reductions are recommended for patients with moderate hepatic impairment (Tbili >1.5-3 times ULN with any AST)[6]
- Monitor thyroid levels at baseline and every 2-3 months[6]
- Ensure blood pressure is controlled prior to initiation and monitor throughout treatment
- Closely monitor patients at increased risk for venous thromboembolic events
- Check pregnancy status in females of reproductive potential
- Review patient medication list for possible drug-drug interactions/allergies
    - Strong CYP3A4 inducer: avoid concomitant use of strong CYP3A inducers with tivozanib
    - Contains RD&C Yellow No.5 (tartrazine)
- Hold for at least 24 days before elective surgery; do not administer for 2 weeks following major surgery[6]

Dose Modifications for Adverse Reactions[6]

Adverse Reaction	Severity	Dose Modifications
Hypertension	Grade 3	• Hold for Grade 3 that persists despite optimal antihypertensive therapy • Resume at reduced dose when hypertension is controlled at less than or equal to Grade 2
	Grade 4 or Hypertensive Crisis	• Permanently discontinue
Cardiac Failure	Grade 3	• Hold until improves to Grade 0 to 1 or baseline • Resume at a reduced dose or discontinue depending on the severity and persistence of adverse reaction
	Grade 4	• Permanently discontinue
Thromboembolic Events	Any Grade	• Permanently discontinue
Hemorrhagic Events	Grade 3 or 4	• Permanently discontinue
Proteinuria	2 grams or greater proteinuria in 24 hours	• Hold until ≤ to 2 grams of proteinuria per 24 hours • Resume at a reduced dose • Permanently discontinue for nephrotic syndrome
Reverse Posterior Leukoencephalopathy Syndrome	Any Grade	• Permanently discontinue
Other Adverse Reactions	Persistent or intolerable Grade 2 or 3 adverse reaction Grade 4 laboratory abnormality	• Withhold until improves to Grade 0 to 1 or baseline • Resume at reduced dose
	Grade 4 adverse reaction	• Permanently discontinue

Dose Modifications and Timing of Adverse Events:[5]

Tivozanib-Emergent Adverse Event	Dose Modification Rate, %	Median Time to Onset, days (range)	Median Duration, days (range)
Hypertension	20	17 (11-35)	29 (7-66)
Diarrhea	18	58 (27-127)	15 (3-57)
Asthenia/Fatigue	24	29 (11-74)	90 (28-...)
Nausea/Vomiting	25	54 (14-107)	15 (3-71)
Rash	18	110 (39-294)	51 (14-...)
Hand-foot syndrome	14	40 (29-71)	62 (26-...)

Patient-Centered Activities:

- Provide Oral Chemotherapy Education (OCE) Sheet and review with patient
- Consider providing Treatment Support Kit (TSK)
- Instruct patient to monitor blood pressure at home and report any increases from baseline
- Ensure that the patient has access to loperamide to use as needed for diarrhea and to call the provider if loperamide does not control diarrhea
- Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for one month after the last dose
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. Eskens, Ferry ALM, et al. "Biologic and clinical activity of tivozanib (AV-951, KRN-951), a selective inhibitor of VEGF receptor-1,-2, and-3 tyrosine kinases, in a 4-week-on, 2-week-off schedule in patients with advanced solid tumors." *Clinical Cancer Research* 17.22 (2011): 7156-7163.
2. Rini BI, Pal SK, Escudier BJ, et al. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study. *Lancet Oncol.* 2020;21(1):95-104. doi:10.1016/S1470-2045(19)30735-1
3. Chang E, Weinstock C, Zhang L, et al: FDA Approval Summary: Tivozanib for Relapsed or Refractory Renal Cell Carcinoma. Clinical Cancer Research, 2021.
4. Beckermann KE, Asnis-Alibozek AG, Atkins MB, et al. Long-Term Survival in Patients With Relapsed/Refractory Advanced Renal Cell Carcinoma Treated With Tivozanib: Analysis of the Phase III TIVO-3 Trial. *Oncologist*. 2024;29(3):254-262.
5. Zengin ZB, Pal SK, McDermott DF, et al. Temporal Characteristics of Adverse Events of Tivozanib and Sorafenib in Previously Treated Kidney Cancer. *Clin Genitourin Cancer.* 2022;20(6):553-557.
6. Fotivda® (tivozanib) [prescribing information].