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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] On March 2021, tivozanib was 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 (5.6 vs. 3.9 months, hazard ratio 0.73, p=0.016) and higher objective response rate (18 vs. 8%) than sorafenib. Treatment-related adverse events with tivozanib were common (84%) but manageable with Grade 3 or higher adverse events occurring in less than 5% except hypertension (20%). Treatment-related adverse effects led to dose interruptions in 48% and dose reductions in 24%.

PQI Process:

- Verify dosage: the recommended starting dose of tivozanib is 1.34 mg orally once daily, with or without food for 21 days followed by 7 days off treatment for a 28-day cycle[4]
- Dose interruptions and/or dose reduction may be needed to manage adverse reactions (see below)[3,4]
    - First and only dose reduction: tivozanib 0.89 mg daily for 21 days followed by 7 days off for a 28-day cycle
- Dose reductions required for patients with moderate hepatic impairment (Tbili >1.5-3 times ULN with any AST)
- Monitor thyroid levels at baseline and every 2-3 months
- Check pregnancy status in females of reproductive potential
- Review patient medication list for possible drug-drug interactions
    - Strong CYP3A4 inducer: avoid concomitant use of strong CYP3A inducers with tivozanib[4]

Dose Modifications for Adverse Reactions

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

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
- 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. The Lancet Oncology 21:95-104, 2020.
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. Fotivda® (tivozanib) [prescribing information].