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NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer Panel

NCCN Panel for Kidney Cancer – Submission Request for Tivozanib for Subsequent Therapy

On behalf of Aveo Oncology, please accept this request to consider tivozanib as subsequent therapy for advanced kidney cancer based on FDA approval[1], pivotal Phase III TIVO-3 trial[2,3], and other clinical data.[4]

Changes Requested on page "Principles of Systemic Therapy" (KID-C 1 of 2): **"Subsequent Therapy"**

- **Preferred regimen**: please add tivozanib (category 1)
- **Suggested footnote:** Tivozanib pivotal study included patients who received two or more prior systemic therapies and was stratified by prior therapy including prior immunotherapy.

FDA approval: Tivozanib (FOTIVDA®) is approved for the treatment of adult patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies.[1]

Clinical Rationale: Tivozanib received FDA approval[1] for patients with RCC who relapsed or are refractory. The pivotal Phase III TIVO-3 trial demonstrated improvement in progression-free survival (PFS) and overall response rate (ORR) in heavily pretreated patients. Importantly, TIVO-3 is the first Phase III study to include patients who received prior checkpoint inhibition (CPI).[2,3] Tivozanib has also demonstrated activity in other subsequent settings.[4] Tivozanib provides an effective subsequent option with a tolerable safety profile that is highly relevant due to the increasing adoption of CPI for frontline therapy.

Literature: Summary of results from the pivotal TIVO-3 and study 902 are as follows:

	TIVO-3[2,3]	902 crossover[4]
Design	Phase III RCT (N=350) versus sorafenib	Phase II (161)
Patients	Prior systemic therapies: 2 (62%) or 3 (38%); including prior CPI	After sorafenib (71%) or more (29%)
PFS	**HR 0.73 (95%CI 0.56-0.95; *P*=0.016), mPFS 5.6 v 3.9 mo** • **Prior CPI: HR 0.55 (95% CI 0.32-0.94), mPFS 7.3 v 5.1 mo**	11.0 mo
ORR	**18% vs 8%** • **Prior CPI: 24.4% vs 6.8%**	ORR: 18% Stable disease: 52%
OS	HR 0.97 (95% CI 0.75-1.24) medians 16.4 vs 19.2 mo • Prior CPI: HR 0.84 (95% CI 0.50-1.40)	22 mo

Bold: statistically significant.

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TIVO-3 Phase III trial[2,3] - The pivotal Phase III multicenter, randomized, controlled, open-label, TIVO-3 trial enrolled 350 patients with metastatic renal cell carcinoma (RCC) and at least two previous systemic treatments; 27% patients received prior checkpoint inhibition and all patients received prior VEGF TKI. At a median follow-up of 19 months, TIVO-3 met its primary endpoint of PFS improvement over sorafenib (HR: 0.73 *P*=0.016); the PFS and ORR benefit favored tivozanib in subgroups and was notable in the most relevant predefined subgroups of patients who received prior checkpoint inhibition (PFS HR: 0.55; ORR: 24.4% vs 6.8%,) and two prior TKIs (PFS HR: 0.57; ORR 15.2% vs 7.5%). ORR was also higher with tivozanib. Consistent with other VEGF TKI versus VEGF TKI studies in RCC, no significant difference was found for overall survival in the intention-to-treated population.

Study 902 crossover of Phase III TIVO-1 trial[4] – In this open-label crossover extension study, 161 patients were previously randomized to sorafenib in the Phase III TIVO-1, and then crossed over to tivozanib after independent documentation of disease progression. Median progression-free survival from the start of tivozanib treatment was 11.0 months; median overall survival was 21.6 months. Overall response rate was 18% and stable disease rate was 52%. Duration of response was 15.2 and 12.7 months, respectively. The ORR, PFS, and OS were consistent with cabozantinib and axitinib results in the METEOR and AXIS pivotal trials.

Safety – In the pivotal trial,[2] grade 3 or 4 treatment-related adverse events were reported in 46% of patients in the tivozanib arm and 55% in the sorafenib arm. Dose reductions due to adverse events were less frequent with tivozanib (24%) than sorafenib (38%). Adverse reactions leading to permanent discontinuation were also less for patients treated with tivozanib (8% vs. 15%). The most frequent grade 3 or 4 adverse event with tivozanib was hypertension (20%). No treatment-related deaths occurred.[2]

Sincerely Yours,

Michael N Needle

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Michael Needle, M.D.

Chief Medical Officer

Enclosed References:

1. FOTIVDA (tivozanib) [Prescribing Information]. Boston, MA. Aveo Oncology; 2021.
2. **TIVO-3**: Rini BI, et al. Lancet Oncol. 2020 Jan;21(1):95-104.
3. **TIVO-3 OS update**: Pal, SK, et al. Eur Urol. 2020 Sep 13;S0302-2838(20)30624-2.
4. **902 Study**: Molina AM, et al. 2018. Eur J Cancer. 94:87-94.