Title: *Endothelin Receptor Antagonist for Anti-Vascular Endothelial Growth Factor signaling pathway inhibitor Induced hypertension and/or proteinuria*

Author: Jaya Kala, MD

Affiliation: Division of Renal Diseases and Hypertension, University of Texas Health Science Center, Houston, Texas

Background: Anti-angiogenic drugs targeting VEGF (bevacizumab) and its receptors (sunitinib, sorafenib, pazopanib, axitinib) are standard treatment for renal cell, non–small cell lung, colorectal carcinoma, and gastrointestinal stromal tumors. However, VEGF signaling pathway inhibitors (VSPIs) frequently cause hypertension and proteinuria leading to dose interruption or discontinuation. Proposed mechanisms include reduced nitric oxide and prostacyclin production, increased endothelin-1 (ET-1), microvascular rarefaction, renin–angiotensin activation, oxidative stress, and arterial stiffness. Sunitinib-induced hypertension is partially reversed by ETA/ETB antagonism with macitentan, supporting an ET-1–driven "preeclampsia-like syndrome." Current management (ACEi, ARBs, CCBs, diuretics, β-blockers) is nonspecific. These therapies are nonspecific and do not target the underlying endothelin-1 (ET-1)–driven pathophysiology. We propose the use of Aprocitentan, an endothelin receptor antagonist, approved by FDA for uncontrolled hypertension, to treat hypertension and or proteinuria caused by VSPI.

Methods: We extracted data from patients who were referred to Onco-nephrology clinic for uncontrolled hypertension and or proteinuria while on VSPI agents. Among patients who were referred, 4 patients were started on Aprocicentan (while continuing their other antihypertensives). The patients are currently being closely followed for hypertension, proteinuria, cancer treatment and prognosis.

Results: Of the 4 patients who were started on treatment with Aprocicentan, two patients showed response with improved proteinuria, and all patients showed improvement in their hypertension. Due to hyperkalemia, three patients had to stop their ACEi. Three patients continued VSPI treatment while on Aprocicentan, except one who had TMA on kidney biopsy.

Conclusion: Our limited data set indicates feasibility of using Aprocitentan, to specifically target the underlying ET-1 pathophysiology of VSPI-induced hypertension and proteinuria. Use of Aprocicentan allows for continuation of VSPI cancer treatment while taking care of hypertension and proteinuria.

Patient	Cancer type	VSPI drug	Initial protein (g/g Cr)	Treatment duration of aprocicentan at follow up (f/u) in months	f/u protein (g/g Cr)	Initial blood pressure (BP)	f/u BP	Biopsy for proteinuria	Able to continue VSPI agent for cancer
1	Papillary thyroid cancer	Lenvima	9	9	0.98	141/74	130/80	IgA nephropathy	Yes
2	Renal cell carcinoma	Lenvima	0.5	1	pending	161/93	125/65	Not done	Yes
3	Hepatocellular carcinoma	Bevacizumab	5	4	Pending	151/77	115/55	Thrombotic microangiopathy (TMA)	switched
4	Renal cell carcinoma	Lenvima	1	2	0.3	151/76	147/79	Not done	Yes