PD2-2**The Role of Molecular Targeting Therapy for Metastatic Renal Cell Cancer - Working Toward Individual Treatment – Overview for Sorafenib**

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Sorafenib, a multikinase inhibitor, inhibits both tyrosine (such as VEGFR and PDGFRb) and serine/threonine-specific kinases (such as c-Raf). Two phase I studies established a suggest phase II dose of 400mg twice daily orally on a continuous basis, although another suggested that higher doses were possible. Subsequently a randomized discontinuation design trial showed that continuing sorafenib after stable disease delayed renal cancer progression. This observation was further expounded in the TARGETrial, where patients with renal clear cell carcinoma of low or intermediate MSK risk and who had failed one prior therapy within 8 months were randomized in a blinded fashion to either sorafenib 400mg BID or placebo. The result was a doubling in median progression-free survival from 12 to 24 weeks for sorafenib over placebo. Importantly, further follow up on the trial demonstrates the first evidence of an overall survival advantage (3.5 months) for a VEGF targeted drug in RCC, establishing a key therapeutic tenet in the disease. The major side effects of sorafenib are hypertension, diarrhea, diffuse skin rash and hand-foot syndrome. While PFS in first line sorafenib compared to interferon-alpha was not significantly different, sorafenib did demonstrate an improved QOL over the low dose cytokine treatment. Sorafenib has been combined with a variety of agents including interferon-alpha, bevacuzimab and temsirolimus and further trials in this area are moving forward. Dose escalation of sorafenib may provide a therapeutic advantage in selected patients but this requires further evaluation. Sorafenib will also be evaluated in the adjuvant setting for high risk surgically resected renal cancer in several major studies recently opened.

PD2-3**Towards Optimal Management of Metastatic Renal Cell Carcinoma: an Update on the Role of Sunitinib as First-line Treatment**

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Recent advances in the understanding of the pathogenesis of renal cell carcinoma (RCC) have contributed to the development of novel targeted therapies. One such agent is sunitinib malate (SUTENT[®]), an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, KIT, RET and FLT3 with demonstrated antitumor and anti-angiogenic activity.

In an independent analysis of pooled data from two phase II trials of sunitinib in cytokine-refractory metastatic RCC (mRCC; N=168),^{1,2} the objective response rate (ORR) was 45% (95% CI: 39-54),³ Median progression-free survival (PFS) was 8.4 months (95% CI: 7.9-10.7) and median overall survival (OS) was 19.9 months (95% CI: 14.2-29.6)³

A subsequent randomized phase III trial compared sunitinib and interferon-alfa (IFN- α) in patients with untreated mRCC (N=750).⁴ The ORR (Independent Central Review) was 39% in the sunitinib group and 8% in the IFN- α group (P<0.000001). Median PFS in the sunitinib and IFN- α groups was 11.0 months (95% CI: 10.7-13.4) and 5.1 months (95% CI: 3.9-5.6), respectively.⁵

Baseline features that significantly predicted PFS during sunitinib treatment were hemoglobin, ECOG performance status, time from diagnosis to treatment, corrected calcium level and LDH.⁵ Importantly, the benefit of sunitinib with respect to PFS extended across all Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic risk factor groups.⁵ Most sunitinib-related adverse events were ameliorated by dose interruption or modification and treatment was discontinued in less than 10% of patients because of adverse events.⁴

Sunitinib is now considered the reference standard for first-line treatment of mRCC, demonstrating significant improvement in ORR and PFS, compared with IFN- α , with acceptable safety.

References 1. Motzer RJ, et al. *J Clin Oncol* 2006;24:16-24. 2. Motzer RJ, et al. *JAMA* 2006;295:2516-24. 3. Rosenberg JE, et al. *J Clin Oncol* 2007;25(Suppl 18S):Abstract 5095 (poster presentation). 4. Motzer RJ et al. *New Eng J Med* 2007;356:115-24. 5. Motzer RJ, et al. *J Clin Oncol* 2007;25(Suppl 18S):Abstract 5024 (oral presentation).