**Genitourinary Steering Committee (GUSC) Renal Cancer Task Force (TF)**
**Clinical Trials Planning Meeting (CTPM)**
**Advanced Renal Cell Cancer - Improving First Line Treatment**
**February 16-17, 2013**

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## Introduction/Meeting Description

The National Cancer Institute (NCI) Genitourinary Cancer Steering Committee (GUSC) convened a Clinical Trials Planning Meeting for the Advanced Renal Cell Cancer on February 16-17, 2013 in Orlando, FL. The meeting attendees included GUSC members, renal cancer clinicians, clinical trials experts, biostatisticians, translational scientists, basic scientists, patient advocates and NCI staff.

The goals of the meeting were to focus the Renal Task Force to review data that has defined the use of targeted therapy in renal cell carcinoma (RCC), and frame the clinical and translational questions that are of highest priority. The specific task will be to fully develop two specific clinical trials that meet the clinical and translational goals of advancing the initial care of advanced RCC patients. The meeting goals and objectives included: 1) reviewing of the clinical trials and translational data with VEGF-targeted and mTOR-therapy for patients with advanced RCC; 2) define priority questions for initial therapy in advanced RCC patients; 3) develop two clinical trial designs that would address the priority questions¸ and; 4) define important translational questions that should be addressed in association with these clinical trials.

Deliverables included: 1) developing a consensus statement for publication on current standards of care for advanced RCC; 2) finalize two ready-to-implement clinical trials in RCC patients; 3) establish a list of translational priorities, including mechanisms of resistance and identification of patient subsets, and; 4) outline the translational objectives that would be addressed within the context of the developed clinical trials.

## Background/Importance of Research Topic/Disease/Limitations

The rationale for the meeting was the use of targeted therapy and new therapeutic agents in management of advanced renal cell carcinoma (ARCC). There is hope that with this now deeper molecular understanding of the oncogenic pathways in RCC, particularly clear cell RCC (ccRCC), enhanced therapeutic targeting of these pathways will lead to meaningful clinical benefit. Agents discussed prior to the meeting included the vascular endothelial growth factor (VEGF)-targeted agents sunitinib, sorafenib, pazopanib, axitinib and bevacizumab, and the mammalian target of rapamycin (mTOR)-targeted agents temsirolimus and everolimus

The availability of multiple new drugs for therapeutic use in RCC has generated a long list of crucial clinical questions that remain unanswered. Among them are questions regarding optimal sequencing of therapies, the potential benefit of combining targeted therapies, and the feasibility of combining targeted and conventional therapies. Along with these clinical questions are translational questions that will drive future clinical trials including definition of the mechanisms of resistance to targeted therapy and identification of molecular or histopathologic subsets of tumors for particular treatment approaches.

## Frontline Trial Design

### Biomarkers

Lactate dehydrogenase **(**LDH) is a known prognostic factor in mRCC, with recent supportive evidence from the phase 3 global ARCC trial studying temsirolimus versus IFN-alpha in first-line treatment of poor-risk mRCC. Additionally, LDH may serve as a predictive factor for response to targeted therapy, particularly with mTOR inhibition. Preclinical data has established that mTOR regulates both anaerobic glycolysis as well as hypoxia inducible factor (HIF) activation in tumors. Accordingly, the rationale for LDH being a predictive factor is that LDH is a marker of anaerobic glycolysis, is increased in tissue injury, hypoxia and necrosis, and its translation is regulated by HIF. LDH may predict for tumor aggressiveness as well as for specific pathway activation. Therefore, the hypothesis for a proposed frontline study is that elevated baseline LDH will be predictive of overall survival (OS) in patients treated with mTOR inhibition.

Biomarkers of response to anti-angiogenic therapy have not been well characterized. However, data from the phase 2 and phase 3 trials with pazopanib suggest that high interleukin-6 (IL-6) levels are associated with worse prognosis but conversely with greater relative OS benefit from pazopanib (ref: Tran et al 2012). IL-6 is therefore another potentially important biomarker that may be predictive of response to targeted therapy.

Based on the LDH and IL-6 biomarker data, along with current findings that the Heng criteria are prognostic for survival but not predictive for response, objectives for this concept were created. The primary objectives are to determine whether the progression free survival (PFS) of anti-angiogenic tyrosine kinase inhibition (TKI) is superior to mTOR inhibition in the front line setting for intermediate or poor risk patients with ARCC, and to confirm whether LDH and IL-6 are predictive of PFS with TKI versus mTOR therapy. Other objectives include evaluating overall survival in the two groups and identification of subgroups of patients who may derive differential benefit from TKI vs mTOR inhibitor therapy based on biomarkers. Other correlative endpoints include examination of plasma markers for intrinsic and acquired resistance to each agent, as well as baseline tissue analysis for gene expression, proteomic profiling and sequence data.

The proposed scheme for the frontline design is a phase III study with approximately 500 patients with newly diagnosed metastatic intermediate or poor risk ccRCC. Patients will be randomized 1:1 between TKI and mTOR inhibitor therapy. Patients would remain on study until progression by RECIST criteria version 1.1. The primary endpoints are PFS and predictive value of LDH and IL-6. Although biomarkers are integral to the study, they would not impact treatment assignment (They would be measured at baseline). Proposed biomarker measurements include pretreatment, progression, and last timepoint prior to progression.

## Neoadjuvant/Presurgical Trial Design

Advantages of presurgical design include selection of patients most likely to benefit from surgery. Additionally, there can be assessment of interaction between therapy and tumor microenvironment through a randomized design. This study design's eligibility criteria would include patients with primary in place, good-intermediate risk with no liver metastases. The randomization would be after core biopsies to confirm clear cell histology and would be between PD-1 antibody and TKI. After this presurgical

therapy, there would be a nephrectomy followed by continuation of the same therapy if good initial response or stable disease, or crossover to other arm if upfront progression was recorded.

The primary efficacy objectives would be to explore whether anti-PD1 antibody provides superior PFS compared to a single agent TKI. The secondary correlative objectives would be related to specific endothelial subpopulations, suppressive immune cells and myeloid cells in stroma, PD1 antibody, genomic information and circulating cytokines and angiogenesis factors. The goals of the secondary objectives are to better understand mechanisms of treatment response and resistance, and identify candidate biomarkers of prognosis and response.

Challenges include tissue handling/consistent SOPs, validating antibodies and developing tools to accurately identify and quantitate markers of interest. Additional challenges include identifying the extent of genomic diversity and how this diversity influences tumor behavior and understanding the mechanisms contributing to genomic heterogeneity

A variety of study designs was proposed. Considerations included testing presurgical paradigm in patients with localized vs metastatic disease, and the use of approved vs. novel agents. Primary end points considered included primary tumor response vs metastatic tumor response vs molecular response. In the end, it was decided that the overarching goal of the trial concept should be to identify predictive biomarkers for novel compounds and the field was narrowed down to 3 trial concepts: 1) TKI + rational agent to overcome TKI resistance; 2) mTOR inhibitor + PD1 antibody (3 arms), or; 3) TKI + PD1 antibody. The final study design was a randomized phase II study comparing a PD-1 blocking agent with a PD-1 blocking agent plus a TKI, with progression free survival as a primary endpoint, and durable tumor response as a secondary endpoint. The sample size would be approximately 130 patients. The advisory committee recommended that robust tissue based data be generated from prior presurgical studies using TKIs to support the rationale for the current study design.

**Consensus**

The studies being designed must address an important clinical question. Other studies (RECORD-3 recapitulation, BATON) need to have results made available before proceeding. Preliminary data appropriate to the studies in question should be generated to bolster the rationale and study design. There was also a consensus that a study in poor-risk patients may allow biomarker testing and change the standard treatment paradigm in that group. The value of including intermediate risk group patients needed to be more than adding accrual number to justify their inclusion in the First Line Study proposal.

In the case of the presurgical study, formal collaborations with industry for PD-1 and PD-L1 antibodies have to be confirmed.

**Recommendations**

- Further defining priority questions for initial therapy in advanced RCC patients
- Further developing two clinical trial designs that would address the priority questions
- Define important translational questions that should be addressed in association with these clinical trials.

**References/Literature**


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