National Cancer Institute

Genitourinary Cancers Steering Committee's Bladder Cancer Task Force

Clinical Trials Planning Meeting (CTPM)

Novel Therapeutics for Non-Muscle Invasive Bladder Cancer

NIH Campus, Bethesda, Maryland, March 26-27, 2015

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Introduction

The NCI Bladder Cancer Task Force convened a Clinical Trials Planning Meeting (CTPM) Workshop focused on Novel Therapeutics for Non-Muscle Invasive Bladder Cancer (NMIBC). This meeting was held on NIH campus in Bethesda, Maryland, on March 26th and 27th, 2015. Meeting attendees included a broad and multi-disciplinary group of clinical and research stakeholders composed of leaders from NCI, Food and Drug Administration (FDA), National Clinical Trials Network (NCTN), and the pharmaceutical and biotech industry. There were approximately 96 attendees at the meeting. Most of the attendees were included on discussion panels for each of the three sessions, reflecting their expertise with the subject matter.

The meeting goals and objectives were to:

1. Create a collaborative environment in which the greater bladder research community can pursue future optimally designed novel clinical trials focused on the theme of molecular targeted and immune-based therapies in NMIBC
2. Frame the clinical and translational questions that are of highest priority
3. Develop two clinical trial designs focusing on immunotherapy and molecular targeted therapy
4. Publish summary report from the meeting

The meeting was organized in five sessions over two days. The introductory session covered an overview of the state-of-the-art, opportunities, and challenges of Non-muscle-invasive bladder cancer. Session 1 addressed key genetic targets and relevant pathways for intervention in bladder cancer. Session 2 addressed the immunobiology of checkpoint blockade, identified

mechanisms and therapies relevant to bladder cancer, and challenges in the non-muscle-invasive space. This session was followed by an overview and panel discussion on regulatory perspective on novel therapeutics for NMIBC. Session 3 addressed clinical trial designs, tumor acquisition, embedded companion diagnostics, and trial requirements and infrastructure challenges that are unique for clinical trials in NMIBC. A panel discussion relative to logistical issues and collaboration among NCTN groups followed this session. The subsequent final sessions focused on designing two clinical trials respectively based on immunotherapy and molecular targeted therapy, and on take home messages from the meeting.

Background and Summary of Discussions Leading to Recommendations:

NMIBC comprises the most common stages/subsets of bladder cancer, and is a significant unmet need in bladder cancer. Despite a fast growing field of novel drug trials in metastatic bladder cancer, therapeutic progress and trial activity have been limited in the NMIBC space due to a number of challenges.

Despite successful development and implementation of large Phase II and Phase III trials in bladder and upper tract cancers, there are no active and accruing trials in the NMIBC space within the NCTN. Furthermore, there has been only one new FDA approved drug (Valrubicin) in any bladder cancer disease state since 1998.

Although genomic-based data for bladder cancer are increasingly available, translating these discoveries into practice changing treatment is yet to come.

Recently, major efforts in defining the genomic characteristics of NMIBC have been achieved. Aligned with these data is the growing number of targeted therapy agents approved and/or in development in other organ site cancers and the multiple similarities of bladder cancer with molecular subtypes in these other cancers. Additionally, although bladder cancer is one of the more immunogenic tumors seen in man, some tumors have the ability to attenuate or eliminate host immune responses.

Immunology-based clinical trial in patients with NMIBC

Consensus and recommendations

Based on the development and demonstration of profound efficacy with more favorable side effect profiles of recently developed immunotherapy agents, especially immune checkpoint inhibitors, immunotherapy has become a critical approach to the therapy of multiple malignancies. The focus of CTPM session 2 was to leverage current immunotherapy clinical and translational data from bladder and other malignancies to produce optimal clinical trial designs to evaluate immunotherapy approaches in NMIBC patients.

Given the wide array of immune checkpoint inhibitor and agonist therapies currently being tested for safety and initial efficacy in multiple ongoing clinical trials, a broad multi-arm phase Ib trial design was proposed in patients with NMIBC who have recurred after induction BCG (BCG failure patients) to test the safety of immune therapies as monotherapy (including PD-1 or PD-L1 checkpoint inhibitors), in combination with intravesical BCG, and in combination with external beam radiation therapy. It was considered that due to a high risk for serious adverse events in a BCG-relapsing NMIBC population, combined immune checkpoint blockade (i.e. anti-CTLA-4 therapy plus anti-PD-1 or anti-PD-L1 therapy) in combination with intravesical BCG should not be pursued at this time. The study design is meant to represent all rational immune therapy targets suitable for combination with BCG for which phase I clinical trial with available safety data are documented. The exact number of arms will be dictated by sponsor interest and safety data as it emerges. A short phase I lead-in design is anticipated in each arm. The immunotherapy agent of interest will not be dose reduced. If dose limiting toxicity is encountered amongst the first 6 patients in a study arm, an additional 6 patients may be enrolled at 1/3rd dose BCG. It is anticipated that adequate number of CIS-only as well as Ta/T1 patients will be included within each arm in order to ensure an adequate number of patients in each arm such that confidence interval estimates of the 6-month relapse free survival rate within NMIBC patient subsets will be of value in making decisions about subsequent phase II/III registration trial designs (i.e. Ta/T1 compared to CIS-only). Lastly, the study is envisioned as utilizing a flexible randomization strategy. In such a design, arms can be added in or taken out throughout the life cycle of the trial based on emerging safety data or new target identification.

Molecularly targeted clinical trial in patients with NMIBC

Consensus and recommendations

The molecular target demonstrating the most promise for intervention at this time in NMIBC is the fibroblast growth factor receptor 3 (FGFR3), a gene that is frequently mutated in this disease state. The high recurrence rate of NMIBC leads to significant morbidity and health care spending due to the need for frequent cystoscopic monitoring and operative intervention. Therefore, an effective oral agent to reduce the recurrence of NMIBC would be of high value.

Testing FGFR3 targeted agents in NMIBC requires careful balancing of risks and benefits when considering trial designs, as these agents are currently being investigated as systemic agents and do not have intravesical formulations. Studies to demonstrate anti-tumor activity are required to determine whether systemic administration of FGFR3 inhibitors can lead to anticancer effects on tumors in the lining of the bladder. These pilot studies would provide the rationale for larger “adjuvant” or post-transurethral resection studies.

One study design using a “marker lesion” was heavily discussed at the meeting. This design, restricted to patients with low grade tumors in order to minimize risk, requires that a small (≤1cm) non-invasive appearing tumor is left in place, in order to determine the ablative effect of therapy while systemic therapy is administered. However, these studies have some risk to patients in that a small tumor is left in place for a period of time. To minimize this risk, any remaining tumor is removed after 2-3 months of treatment, a period that has been demonstrated to be safe.

An alternative approach is the phase 0 “window of opportunity” trial, which takes advantage of the interval between identification of recurrent tumor on office cystoscopy, and the operative transurethral resection, usually performed several weeks later. The investigational agent is given for a defined, relatively short, period of time, and the anti-tumor activity is evaluated at transurethral resection. This approach also allows assessment of anti-tumor ablative activity of an experimental agent.
While the marker lesion design has been shown to be safe, there is a theoretical risk of progression during the interval of treatment (shown to be <1%). Therefore, a majority of the participants felt that a window-of-opportunity study would be a more acceptable approach. Concepts are under development to test FGFR3 inhibitors using this study design.

This Executive Summary presents the consensus arising from the CTPM. These recommendations are not meant to address all clinical contexts, but rather represent priorities for publicly funded clinical research.