2015 Strategic Priorities

Thoracic Malignancy Steering Committee (TMSC)

Lung cancer remains the deadliest cancer in the world despite the progress that has been made with the approval of targeted and immunotherapies. With 5-year survival at a dismal 17% across all stages, there is dire need to conduct clinical research via innovative trial designs that are biomarker driven with clinically meaningful endpoints for this patient population.

The Thoracic Malignancy Steering Committee (TMSC) has been in existence for 5 years and has reviewed a robust portfolio of clinical trials in lung cancer. Most notably has been the initiation of two novel paradigm-shifting trials in biomarker-driven molecularly targeted therapies that were a direct result of the Joint FDA-NCI Clinical Trials Planning Meeting in February 2012. These trials, ALCHEMIST (randomized phase III adjuvant therapy) and LungMAP (A stepwise rapid evaluation of potential novel agents in stage IV non-small cell lung cancer (NSCLC)) are directing lung cancer care into an era of personalized medicine. These trials are based on platforms of tissue acquisition with molecular testing.

At the recent face-to-face meeting in Santa Monica in February 2015, the steering committee highlighted accomplishments and set goals for the next several years; notably to increase awareness of trial development in mesothelioma, small cell lung cancer (SCLC) and thymoma, as well as focusing on enhanced integration of the SPORE and PO1 investigators on the committee into clinical trial design. In fact, there have been two recent meetings concerning the "State of the Science" for investigations into novel therapies for SCLC. Moreover, the TMSC is in the process of forming a working group of experts in mesothelioma, an unmet need in the community that is unlikely to be filled by industry. Below are a summary of the directions the TMSC plans to emphasize over the next few years.

1) **Innovative clinical trials that facilitate rapid development of immunotherapies and novel targeted agents for newly defined subsets in thoracic malignancies.**

   Immunotherapy has become another pillar in treatment of advanced malignancy in addition to chemotherapy and radiation and may have a role in earlier stages of disease, either alone or in combination with existing treatments. Unfortunately, existing biomarker selection has been only minimally successful in identifying patients most likely to benefit from these agents, leaving an opportunity to use the strength in collaboration between basic/translational scientists and lung cancer clinicians from the TMSC to develop a new series of trials:

   a. Examine potential synergies between various immunotherapy agents in patients with advanced NSCLC.

   b. Evaluate tumor tissue for development of new biomarkers of agent activity and tumor response.

   c. Examine any role for these agents in the NSCLC adjuvant setting in resectable disease and as part of multimodality therapy for stage III disease as well as in other thoracic malignancies (mesothelioma, SCLC).

2) **The rapid testing of new agents and strategies for the treatment of small cell lung cancer (SCLC) through innovative, real world trial designs that recognize the aggressive and widely metastatic nature of the disease and consequent patient disability.**

   Little change has occurred in the treatment of SCLC over the past 25 years. Advances in genomic/genetic profiling have identified potential targets for therapy in significant subsets of patients. A concerted effort of the TMSC is focused on SCLC, with development of a structure for rapid evaluation of these targeted therapies. A SCLC workshop was conducted at Memorial Sloan Kettering in April 2015 followed by a meeting at the NCI in May 2015. The focus of these meetings was on ways to understand the biology of SCLC with an emphasis on developing the best preclinical models and innovative trial designs.

   It was noted that the trials conducted so far in extensive disease with add-ons to the standard cisplatin/etoposide regimen have not yielded positive results. Investigators familiar with the

disease feel that a major impediment to progress is the clinical reality that these patients frequently present with severely compromised performance status and need to be treated quickly. As such, they are frequently excluded from trials despite the fact that SCLC responds well to the initial chemo/radiotherapy, usually accompanied by marked improvements in performance status followed within months by rapid disease progression. Alternative trial designs, such as the use of maintenance therapy with eligibility criteria based upon clinical condition after initial chemotherapy, are considered to be of high priority for trial design. A potential approach would have multiple arms with various agents, including immunotherapy, with an option to add on arms when new drugs become available.

3) **Exploration of neoadjuvant therapy for localized, resectable NSCLC, both as a method to potentially improve outcome as well as a way to evaluate the biological efficacy of new therapies.**

The use of short duration induction trials in patients with resectable NSCLC creates an opportunity to obtain pre-therapy and post-therapy tumor tissue for the rapid development/assessment of potential activity of new agents as well as the evaluation of potential biomarkers of clinical response for a variety of targeted therapies or immunotherapy agents. This paradigm was also a priority of the 2012 FDA-NCI meeting.

4) **Rapid testing to determine the optimal role in terms of both efficacy and toxicity of new radiation approaches including protons, image-guided radiation therapy, stereotactic body radiation therapy (SBRT), etc.**

There are now subsets of patients with NSCLC who are observed to have an extensive survival after first and second line therapy. SBRT is a safe and effective local control modality that needs to be examined for its potential in controlling these metastatic lesions in patient with stage IV lung cancer and possibly prolonging survival or even offering a curative local approach with minimal morbidity. It will be critical to define the number and extent of oligometastatic lesions in order to identify a true subset of patients most likely to benefit. Prospective randomized

trials will be required to test the incremental value of local therapy added to systemic therapy, in order to overcome the inherent selection bias of such trials enrolling a patient population especially likely to do well independent of interventions pursued. In addition, trials are being developed to examine the efficacy of novel radiation techniques such as proton beam therapy. For both SBRT and proton beam therapy trials, overall survival should be the primary endpoint of choice, in light of the potential for post-treatment scarring to render the area around the treated lesion(s) uninterpretable.