

**EXECUTIVE SUMMARY**  
**Thoracic Malignancies Steering Committee**  
**Clinical Trials Planning Meeting**  
**Strategies for Integrating Biomarkers into Clinical Development of New Therapies for Lung Cancer**  
**A Joint NCI Thoracic Malignancies Steering Committee - FDA Workshop**  
**February 2-3, 2012**

**Meeting Co-chairs:** Fred R. Hirsch, Claudio Dansky Ullmann, Shakun Malik  
**TMSC Co-chairs:** David Harpole, Mark Socinski, William Sause

**Introduction**

The National Cancer Institute (NCI) Thoracic Malignancies Steering Committee (TMSC) and the Food and Drug Administration (FDA) convened a Clinical Trials Planning Meeting to develop Strategies for Integrating Biomarkers into Clinical Development of New Therapies for Lung Cancer on February 2-3, 2012 in Bethesda, MD. Meeting attendees included TMSC members, clinicians, clinical trials experts, biostatisticians, translational scientists, health-related quality of life scientists, patient advocates, and NCI staff.

The objectives and goals of the meeting were to:

1. To bring together leading academicians, clinicians, industry and government representatives to identify challenges and potential solutions in the clinical development of novel targeted therapies for lung cancer
2. Achieve initial consensus for a high priority biomarker-driven clinical trial proposal to be initiated through the NCI TMSC
3. Published summary report from the meeting.

**Background**

Though there has been intensive effort to develop effective drugs for treatment of lung cancer there has been underwhelming success in phase III trials in unselected patients. A new tack is needed to overcome the insufficiencies of the current approach. The community has been addressing these issues in a number of forums in recent years including:

- 2004: FDA initiated its critical path initiative encouraging innovative trial designs to accelerate translation of biomedical discoveries into therapy
- 2005: PHARMA formed the Adaptive Design Working Group
- 2006: FDA Focus on Biomarker Development and streamlining clinical trials
- 2007: EMA issued a Reflection Paper on Methodological Issues in Confirmatory Clinical trials Planned with Adaptive Design
- 2010: FDA released guidance on Adaptive Design trials for Drugs and Diagnostics
- 2010: IOM Report Calls for Better Phase 2 Trial Designs

A number of key issues are important to address to make a fundamental change in how we approach developing new and effective therapies for lung cancer.

- New trials that use molecular targeting approaches must grapple with the statistical trial design issues of small sample sizes and the need to develop biomarkers preclinically and subsequent incorporation into phase I testing.
- A more rapid development strategy is needed that incorporates the heterogeneity of lung cancer and the need for multiple biomarkers for patient selection and response to therapy.
- Combinations of new drugs along with several accompanying biomarkers are likely scenarios in the near term.
- The questions around how to use other endpoints other than survival, such as Progression Free Survival (PFS), will need to be addressed.

The meeting approached these core issues in three sessions over a day and a half. The first session addressed trial design challenges in the era of biomarker-based trials including issues of statistical design, one drug/one biomarker vs. multiple drugs/multiple biomarkers, adaptive designs and the inherent regulatory issues from a variety of perspectives.

The second session tackled drug and biomarker co-development in lung cancer including biomarker development and validation, transitioning markers from research to CLIA lab settings and how the FDA approaches companion diagnostic tests on a regulatory level. The second session also included a more in depth look at what has worked and not worked in recent trials. Angiogenesis inhibitors, EGFR, and molecular profiling were all discussed along with perspectives from patient advocates and community oncology.

The third and final session was focused on next steps in the development of future lung cancer trials. The session primarily focused on specific therapies or disease states including adjuvant and neo-adjuvant therapies, combined modalities, advanced disease approaches, pharmacogenomic driven trials and the difficulties of emerging resistance to targeted therapies.

### **Consensus and Recommendations**

- A collaborative effort is absolutely key to make needed progress in research and treatment of patients with lung cancer. The collaboration must have participants from Academia, FDA, NCI and Industry. Communications between the FDA and lung cancer research community is key to enhancing successful agent and maker development and implementation. NCI should continue to facilitate interactions between all stakeholders.
- Biomarkers identification and validation needs to be thoroughly defined earlier in testing at preclinical stages and must continue development in clinical trials
- Finding a suitable short term endpoints to effectively mirror survival and shorten trial times, such as Progression Free Survival (PFS) is a critical need but depends on the endpoint having sufficient magnitude of clinical benefit, which must be both statistically

significant and clinically relevant.

- Validated Patient Reported Outcomes ( PROs) or other Quality of Life (QOL) tools need to be further developed and tested in clinical trials
- Exploration of innovative trial designs, adaptive designs and earlier end points need to continue, but it is important that they remain relevant to the clinical questions being asked.
- Patient enrollment in clinical trials without biomarkers is no longer considered an optimal approach.
- Tissue collection is feasible and needed in the majority of patients, however, the difficulties in doing so in community settings should be addressed.
- Accrual remains a central issue to successful trial implementation and accrual needs to be improved across the board.
- Multiple molecular assays and panels can be successfully approved through regulatory processes, but each component must be properly validated.

### **Proposed**

At the conclusion of the day and half meeting, there was general agreement that given the complexities of developing new drugs in concert with markers that it would be useful to develop master protocols templates for different stages of lung cancer that could form an agreed upon foundation for clinical trial design and implementation.

- Early stage disease
- Adjuvant
- Neo-adjuvant
- Stage III
- Advanced and metastatic

**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.**