The following questions will be addressed in Breakout Sessions 1 A&B - Predictive Assays
Group A leaders: Drs. Birrer, McShane and Williams
Group B leaders: Drs. Barlow, Carbone and Hamilton

Morning sessions

- What defines clinical utility for this type of assay?
- What type of evidence is needed to demonstrate clinical utility?
- What would be an appropriate endpoint?

Afternoon sessions

- How can the needed evidence be obtained?
- What could NCI do to facilitate demonstration of clinical utility?

Multiple facets of "predictive" assay

- Class 1: Patients with a positive assay result benefit from a new therapy relative to another available therapy, whereas patients with negative assay result do not benefit from the new therapy relative to other therapy
- Class 2: The assay result identifies patients for whom a given therapy has (or may have) activity
- Class 3: The assay result identifies patients who are, versus who are not, likely to benefit from a wide class of treatments (e.g., adjuvant chemotherapy)
- Class 4: Patients with a positive assay result benefit from the new therapy relative to standard therapy

- **Evidence generation**
  - Types of evidence
    - Type 1: Preponderance of anecdotal evidence or striking serendipitous findings
    - Type 2: Databases – large academic centers, health systems, insurers
    - Type 3: General retrospective
      - Discovery example: P2G, exceptional cases approach
      - Consistent signal across multiple retrospective studies: Example of KRAS in advanced colorectal cancer
    - Type 4: Prospective-retrospective studies
    - Type 5: Prospective trials
      - 5A: Non-randomized
        - Example: Mutation guided screening platforms (coordinated single-arm phase II trials)
      - 5B: Randomized
        - Example (phase II): NCI MPACT trial
        - Example (phase III): Prospective trial designed to validate a marker-based test (e.g., TAILORx, RxPONDER, MINDACT)

- **Initial questions for consideration of clinical utility for a predictive assay**
  - Is there a clearly identifiable patient population with unmet need that could be addressed by this assay?
  - Is the assay well-defined?

    - What are the specific clinical management decisions that could be informed by the assay?
    - Will the assay fill a completely unmet need (e.g., identify patients likely to benefit from a novel targeted therapy), or is it proposed as a better alternative to an existing assay or approach for making a specific clinical management decision (e.g., marker-based risk score to replace collection of clinico-pathologic variables)?
    - Is it likely that changes in clinical management directed by the assay would have a favorable benefit to risk balance?
    - Should clinical utility be viewed solely from perspective of individual patient or from a societal perspective as well?
    - Additional considerations for certain classes of predictive assay
        - Class 2: Is clinical utility discussion relevant, or are these predictive assays only an intermediate step toward class 1, 3, or 4 assays?
        - Class 4: Is the goal to establish clinical utility of the assay or to establish efficacy of the therapy
- What type of evidence is needed?
    - Analytical performance
    - Clinical (predictive) performance
    - When, if ever, is each type of evidence (above, "background"), sufficient to support a clinical utility claim?
    - Evidence needed to justify investigational use (to generate type 5 evidence): mutation profiling clinical trial
    - How to handle modifications to assays or clinical decisions they guide resulting from evidence emerging during the evidence generation phase?
- How can the needed evidence be obtained?
- What can NCI do to facilitate demonstration of clinical utility?

BACKGROUND READING

The BRAF/vemurafinib and ALK/crizotinib cases will be used as examples in these breakout discussions. Please look at the following documents before the workshop.

CDER/FDA Summary Review for Zelboraf in conjunction with cobas 4800 V600 Mutation Test
http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202429Orig1s000SumR.pdf

FDA Summary of Safety and Effectiveness Data for cobas 4800 BRAF V600 Mutation Test
http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110020b.pdf

FDA approval of Zelboraf in conjunction with cobas 4800 BRAF V600 Mutation Test
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm268301.htm

Prescribing information for ZELBORAF (vemurafenib)
http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202429s000lbl.pdf

CDER/FDA Summary Review for XALKORI (crizotinib) for treatment of ALK+ advanced NSCLC
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202570Orig1s000SumR.pdf

To prepare for the discussion of trial design, please see manuscripts (*1-3*) below.

Please familiarize yourself with the lung biomarker literature in citations *(4-9)*.

Citations (*10-14)* are additional suggested reading.

1. B. Freidlin, L. M. McShane, E. L. Korn, Randomized clinical trials with biomarkers: design issues. *Journal of the National Cancer Institute* **102**, 152 (Feb 3, 2010).
2. B. Freidlin, L. M. McShane, M. Y. Polley, E. L. Korn, Randomized phase II trial designs with biomarkers. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **30**, 3304 (Sep 10, 2012).
3. L. M. McShane, D. F. Hayes, Publication of tumor marker research results: the necessity for complete and transparent reporting. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **30**, 4223 (Dec 1, 2012).
4. M. Fukuoka *et al.*, Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **29**, 2866 (Jul 20, 2011).
5. E. L. Kwak *et al.*, Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *The New England journal of medicine* **363**, 1693 (Oct 28, 2010).
6. J. O. Lee *et al.*, Anaplastic lymphoma kinase translocation: a predictive biomarker of pemetrexed in patients with non-small cell lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer* **6**, 1474 (Sep, 2011).
7. A. T. Shaw *et al.*, Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. *The lancet oncology* **12**, 1004 (Oct, 2011).
8. W. Brugger *et al.*, Prospective molecular marker analyses of EGFR and KRAS from a randomized, placebo-controlled study of erlotinib maintenance therapy in advanced non-small-cell lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **29**, 4113 (Nov 1, 2011).
9. J. Y. Douillard *et al.*, Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **28**, 744 (Feb 10, 2010).
10. K. B. Dahlman *et al.*, BRAF(L597) mutations in melanoma are associated with sensitivity to MEK inhibitors. *Cancer discovery* **2**, 791 (Sep, 2012).
11. J. S. de Bono, A. Ashworth, Translating cancer research into targeted therapeutics. *Nature* **467**, 543 (Sep 30, 2010).
12. L. A. Garraway, J. Baselga, Whole-genome sequencing and cancer therapy: is too much ever enough? *Cancer discovery* **2**, 766 (Sep, 2012).
13. R. M. Simon, S. Paik, D. F. Hayes, Use of archived specimens in evaluation of prognostic and predictive biomarkers. *Journal of the National Cancer Institute* **101**, 1446 (Nov 4, 2009).
14. J. S. Welch *et al.*, Use of whole-genome sequencing to diagnose a cryptic fusion oncogene. *JAMA : the journal of the American Medical Association* **305**, 1577 (Apr 20, 2011).