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/vemurafenib 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](http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202429Orig1s000SumR.pdf)


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