Building Effective Biomarker Plans: The Questions to Ask *BEFORE* You Write Your Letter of Intent

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Effective Integration of Biomarker Studies in CTEP Trials

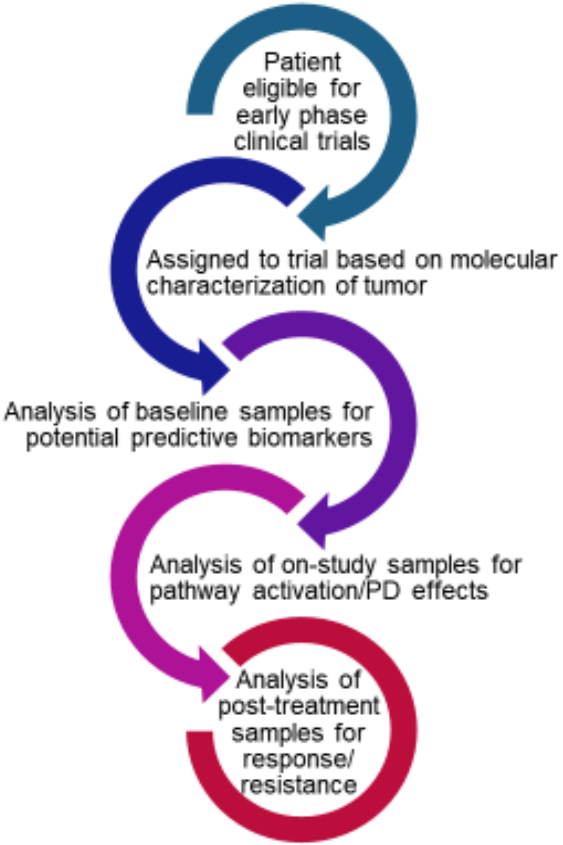
Fit-for-Purpose Biomarker Assays

Biomarker Review Committee

National Clinical Laboratory Network

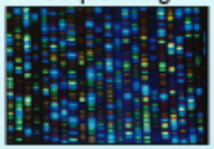
Cancer Immune Monitoring and Analysis Centers

CIMAC-CIDC
Immuno-Oncology Biomarkers Network

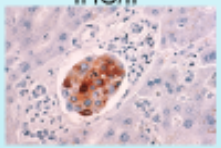


Translational Research with Trial Samples

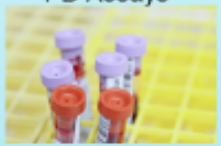
Sequencing



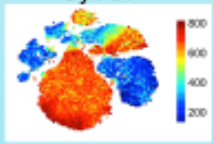
IHC/IF



PD Assays



CyTOF



The questions to ask BEFORE you write your LOI…

Question 1: What is the trial?

- Is this phase 1 or phase 2?
- What is the primary objective and the clinical endpoint?
- What is the medical setting (will usually be advanced disease...all-comers? organ-specific?).
- Will the patients get surgery or not?

- These decisions will impose an initial set of constraints on the type, number and timing of specimens that you can collect.

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REALITY CHECK:

- Beware of biomarker plans that are so burdensome or complex that they compromise accrual or delay reaching the primary objective.
- You will NOT be able to address every scientific question of interest.

Question 2: Which is MORE important?

- Understanding how the drug is working (or not working)?

OR

- Understanding what group of patients is more likely to benefit?

Pharmacodynamics: What do you know?

- Will it be feasible to collect serial samples for measurement in the medical setting of your trial?
  - Can the effect be followed in blood, or are tissue samples required?
- Do you have any idea what the right time points will be?
- What is the magnitude of the drug effect that you can expect on the analyte you are measuring as the indicator?

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REALITY CHECK:

If you are at square one on all of these points, developing a reliable PD assay will take on the order of several months or even several years, perhaps longer than you want to wait to start your trial. And it may not be cost-effective for a single trial.

Pharmacodynamics: Conversation with the lab

- How large an effect size can the existing assay detect? Is it reasonable to expect such an effect size in your trial?
- Will the sampling strategies necessary for the PD assay be feasible in your trial?
  - “Archival” ≠ biopsy or resection, FFPE ≠ frozen
- How do the selected time points align with the other procedures the patients will need to undergo?
- Is the analyte stable enough for the samples to be stored (how?) and batched, or is real-time analysis required?

Predictive Biomarker: What do you know?

- What do you know about the baseline distribution of the biomarker in the targeted patient population?
  - Too rare? Too prevalent? Highly variable?
- Do you know anything about the distribution of the biomarker in patients who have been treated with the agent for whom you have outcome information?
- Can prospective-retrospective studies be planned to acquire information?

Predictive Biomarker: Should you use it for eligibility?

- If you do…
  - You may increase the likelihood of positive trial result for the drug
  - You may spare patients from toxicity who are unlikely to benefit from treatment

Predictive Biomarker: Should you use it for eligibility?

- If you don't…
  - You will likely improve accrual,
  - You will reduce the expense and logistical complexity of the trial,
  - You may detect off-target effects of the drug,
  - You may detect a strong prognostic effect of the biomarker,

  - **You will not lock the development program into a specific assay,**
  - **You can assess clinical sensitivity and specificity of the biomarker.**

Predictive Biomarker: What should the cutpoint be?

- Further development of the biomarker assay as a diagnostic device requires information on both marker negative and marker positive subpopulations in order to establish clinical sensitivity and specificity.

KNOW THIS: as soon as positive results are reported for a trial in which a predictive biomarker was used to select the patients for enrollment, the more difficult it becomes to enroll "marker negative" patients in subsequent trials

--even if the chosen biomarker may not be optimal,

--even if the assay is only available from one laboratory in the entire country,

--even if the cutpoint is entirely provisional.

Prioritization

- **Integral biomarkers:** Are essential for conducting the study. Must be performed on all the participants to address the trial's primary objective.
- **Integrated biomarkers:** Address the highest priority biomarker question in the trial.
- **Exploratory biomarkers:** Do not meet the criteria for either integral or integrated biomarkers.

- For both integral and integrated biomarkers, CTEP approval to include them in the biomarker plan requires scientific/technical review and a source of funding.

Integral Biomarkers: Considerations

- Is it feasible in this medical setting?
  - Is the prevalence of the biomarker high enough?
  - What will the turn-around time for the testing be?
- Where will the testing be done?
  - Will a CLIA-certified laboratory be needed?
  - Will central testing be needed (up front or confirmatory)?
  - Will it require an IDE?
- How will it be paid for?

Understand CLIA

- Will the biomarker results be reported to the patient or their physician at any time, on or off study?
  - If so, the test will need to be performed in a CLIA-certified laboratory,
  - And if it is a brand-new LDT, the lab will need time to validate it.

- If the test result is correlative and will not become part of the patient's medical record the lab need not be CLIA-certified.
  - But it should be *CLIA-like* in many of its procedures.

Understand IDEs

- Will an investigational biomarker assay be used as part of the trial to determine eligibility or assign treatment? Will the use of this device pose a significant risk to participants?
  - CDRH may require laboratory monitoring plan or submission of application for an IDE (Investigational Device Exemption)

- Does not apply to
  - Biomarker assays used as part of standard diagnostic routine or performed using FDA cleared or approved IVDs as indicated
  - Information in the patient's existing medical record at the time they enter the trial

- Significant risk here refers to risk from use of the biomarker test, not the drug. If the result of the biomarker test was wrong…
  - Would the patient forego alternative treatments known to be of benefit?
  - Would the patient suffer any known detriment from treatment on the trial?

Integrated Biomarkers in Early Phase Trials

- Clearly identified as part of the clinical trial from the outset
- Ideally performed on all the trial participants or on a pre-defined subset such as an expansion cohort
- Intended to:
  - Address the highest priority scientific question in the trial
  - Identify or validate assays or biomarkers planned for use in future trials.
- Should be based on sufficient preliminary data to ensure scientifically valid results from the trial, and have demonstrated reproducible analytic qualities.

Familiar example: PK studies

You should expect to publish the results.

The integrated biomarker should drive specimen collection

- Will biopsies be feasible? Will paired biopsies be feasible…at the time points of interest? Can sample collections be aligned with visits for other procedures (e.g. stagings) to reduce burdens on the patient?
- Can the pre-analytic requirements be met in a multi-center trial?
- Remember: there is only so much tissue! (And not every core will be usable.)
- **If there is only enough sample to perform ONE biomarker assay, the integrated assay is that one.**

Assay Analytical Validation: “Fit-for-Purpose”

- What role will the biomarker play in the drug development process or what will be its clinical use?
- Does the assay measure what it is intended to measure?
- Can the assay be performed on the types of specimens available?
- Is the assay analytic performance acceptable *for the context in which the biomarker will be used*?
  - If there is a signal in the data, will the assay have the necessary sensitivity/precision/dynamic range to detect it over the noise?

All laboratories are not alike!

- A CLIA-certified clinical lab may have limited time for adapting an assay for your trial
- A translational research lab focused on pre-clinical models may have very limited experience with human specimens
- A PD laboratory program
  - Need NOT be CLIA-certified, but
  - Should have strict "CLIA-like" controls for materials, procedures and documentation
  - Should be capable of using pre-clinical systems for modeling
  - Should have extensive experience performing assays on human samples from trials

Two Keys to Success

- Prioritize
- Talk with your laboratory colleagues early and often

QUESTIONS?

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www.cancer.gov/espanol