Using Patient-Initiated Study Participation in the Development of Evidence for Personalized Cancer Therapy

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Need for Considering New Trial Strategies

• On average only ¼ of cancer patients receiving an approved cancer drug regimen will gain a significant benefit from that treatment.

• Despite this lack of effectiveness of current therapies, they are considered “standards of care.”

• The ¾ of patients receiving these approved therapies with minimal benefit often suffer toxicities, and always have the consequence of delayed effective therapy.

• A significant component of this reality stems from the fact that many approved first line therapies were evaluated years to decades ago assuming a relative homogeneity in patient subtypes.
New Powerful Tools Can Detect Patient Subpopulations with Different Responses

- Recently developed powerful genomic and molecular tools can sub-classify tumors
- Traditional biomarkers (e.g., for receptors- HER2) and emerging molecular markers now can allow identification of tumor subtypes from genome wide molecular analyses
- These subpopulations may have different prognoses and responses to therapy
Post-Approval Non-Responder Studies

• A prospective study of a marketed drug, in which genomic data from biospecimens are used to identify biomarkers predictive of clinical outcomes.

• Objective is to identify biomarkers that reliably predict patients unlikely to benefit, and to use such data to support revision of the approved drug label and a change in standard of care.

• Many investigational drugs in clinical trials now are accompanied by molecular signatures that identify responder sub-populations.
Opportunity to Identify Subpopulations of Responders/Non-Responders

- Many investigational drugs in clinical trials now are accompanied by molecular signatures that identify responder sub-populations

- Powerful opportunity to identify sub-populations of patients not responding to existing approved cancer treatment regimens
  - Avoid delays in effective therapy
  - Opportunity to receive new selective therapies not added onto existing non-selective regimens
  - Avoid costs and toxicities of drugs with unlikely benefit
Sage Bionetworks Non-Responder Project

- Studies are being planned to identify predictive markers of non-response to standard of care cancer therapies
- Several candidate tumors have been proposed for study, with an initial pilot in AML. These include lung cancer, breast cancer, ovarian cancer, and multiple myeloma
Patient-Initiated Study Participation

• A model in which patients are engaged and recruited directly by the sponsor of an IRB-approved study, and patients in turn drive the participation of their physicians and other health care providers to facilitate collection of required data and/or tissue samples.
Why Consider Patient-Initiated Study Participation?

- Potential benefits from trials/cohort studies enabling patient-initiated study participation:
  - Large patient sample sizes
  - Participation and robust patient consents
  - Long term scalability
Goal of the Panel

• Take a specific example of patient-initiated study participation in the setting of metastatic non-small cell lung cancer

• Examine study design and related considerations, with special attention to:
  a) Feasibility of designing a prospective study featuring patient-initiated participation
  b) Evidentiary standards and other factors influencing how actionable resulting data would be to support regulatory approval of label changes
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* Views expressed are the author’s professional views and not necessarily those of the U.S. FDA
Trial Design Principles

- Study design should have the ability to address the primary study objective

- Study objective(s) should be clearly laid out, e.g., identify molecular signatures associated with non-response to chemotherapy

- Study results, depending on the study design, should be interpretable
Study Designs Commonly Seen

• Prospective adequate & well-controlled
  – Placebo-control, active-control, add-on
  – May be stratified by biomarker status

• Prospective (adaptive) enrichment

• Retrospective case-control with single-arm

• The proposal: prospective cohort with defined predictor(s) to identify non-responder
Potential Explanations of Treatment Effect Seen in an Approved Drug

• Variability within clinical expectation of a homogeneous patient population

• Variability due to heterogeneity at molecular, genomic or genetic level that is either prognostic and/or predictive of therapy
Scientific Consideration of Post-Approval Non-Responder Study with Patient Initiated Study Participation

- A prospective study of a marketed drug with biospecimens prospectively collected following patient consents
- Use genomic data to identify biomarkers that can reliably predict patients unlikely to benefit
- Such data may be considered to support revision of the approved drug label and a change in standard of care
- The sponsorship should be different from those industry-sponsored trials with appropriate governance structure, in principle, with no financial and scientific conflict of interests
- The study should be attentive to potential bias due to patient accrual, trial conduct and analysis interpretation if restrict label only in patient subset
Regulatory Considerations
Post-Marketing Study to Justify Label Revision

• Level of scientific rigor differs depending on study design

• Single arm study can address association of biomarker and clinical outcome, absent of comparative evidence

• Efficacy vs toxicity may bear different evidential criteria
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Principles of the SAGE Non-Responder Project

- The treatment under investigation should have substantial response and non-response rates (>20 percent in either group).

- The disease must have clear, robust definitions of response and non-response that are clinically important. (A non-response biomarker should have the potential to change clinical practice.)

- Routine clinical management of the disease guarantees access to high quality tissue specimens.

- The non-response group should ideally be defined as patients refractory to treatment rather than those who respond then relapse early.
NSCLC Study Objectives

• Determine the feasibility of patient-initiated study enrollment
• Determine success rate for collection of evaluable normal tissue and tumor specimens
• Identify molecular signatures associated with non-response to chemotherapy
• Develop data to support regulatory approval of drug label change
NSCLC Study Design

- Single arm, prospective registry
- Metastatic NSCLC appropriate for first-line platinum-based doublet chemotherapy
- Core needle biopsy feasible and safe
- Measurable disease by RECIST criteria
- Estimated rate of non-response: 50%
- Collect OS
NSCLC Study Schema

1. Patient awareness of study via web, advocacy organizations, physician, other
2. Patient/physician initiates request for study enrollment; informed consent obtained
3. Patient referred to regional center for biopsy and specimen acquisition
4. Patient returns to care of local oncologist, treated with platinum-based chemotherapy for 3 cycles then assessed for response/non-response
5. Clinical data submission by physician
NSCLC Study Schema

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Clinical data submission by physician

Specimen Repository

CLIA lab
Research lab
Data analysis
Data repository

Conference on Clinical Cancer Research
Using Patient-Initiated Study Participation in the Development of Evidence for Personalized Cancer Therapy

Laurie Fenton Ambrose
President & CEO
Lung Cancer Alliance
Feasibility of Patient-Initiated Study Participation: Patient Perspective

• Yes, it is feasible. Patients and families can be highly motivated to accelerate research into discoveries.

• Paper reflects examples including LCA’s own experience with the lung cancer community vis-à-vis “Give A Scan.”

• Give A Scan goal -- to accelerate imaging research and software development so imaging can be a more accurate “quantitative biomarker” and thus expedite improvements in the early diagnosis and treatment of lung cancer.
Principles That Guided Give A Scan

- Database should be made available to all researchers.
- Patient privacy would be maintained at highest level possible.
- Patients should bear no cost.
- LCA would neither buy nor sell scans or data.
- LCA would not be directly involved in research.
- Patients would be advised upfront that research may lead to commercialization.
- Governance practices and policies observed – Advisory Board created.
Translate Experience to Non-Responder Project Using Patient-Initiated Study Participation for NSCLC

- Would patients be willing to donate specimens? Yes.
- Can principles be established to guide the study process? Yes.
- Are there additional challenges? Yes.
- Can they be overcome? Yes.
Patient Considerations and Challenges

• Timing will influence patients’ receptivity to messages about study participation.
• At diagnosis -- very difficult time to ask patients to consider this.
• Only way to acquire tumor tissue is biopsy or surgery.
• Most patients are not being biopsied as standard of care at this stage (rather being diagnosed by CT scans or PET/CT to assess tumor growth over time).
• Surgery is not an option in these patients.
• Overall challenging time to discuss study that has risk, might cause harm, and could potentially cost money.
How to Maximize the Opportunity to Collect Tumor Tissue

• Cover the cost of the biopsy and genetic assays for the tumor.

• Encourage CMS to cover new tools, such as Electromagnetic Navigation Bronchoscopy (ENB) that help facilitate biopsies and can reach peripheral tumors bronchoscopes cannot.

• Partner with researchers who are recruiting individuals at high risk for lung cancer for CT screening.
  – Maximizing potential of diagnosing early stage operable lung cancer.
  – Patients already amendable to study participation.
  – Patients have more time to process and digest information.
  – Patients are more motivated to participate.
Comment About Lung Cancer Community

• The lung cancer community recognizes that very little is being done to sufficiently support them.

• They know that little if any research has been funded.

• They are angry.

• They want to do what they can to advance better outcomes – and if approached at the right time – with the right plan of engagement I believe they would participate.
Using Patient-Initiated Study Participation in the Development of Evidence for Personalized Cancer Therapy

Jamie Freedman
Vice President, R&D
GlaxoSmithKline
Patient-Initiated Samples

“An open-label, trial with a marketed drug, in which genomic data from biospecimens will identify biomarkers predictive of clinical outcome”

Patients motivated to provide their tissues in the context of a clinical trial to better define how a drug should be used to treat future patients with the same disease.
Sample Collection

• Blood
  – Easily accessible, but limited information about actual disease (unless germline)
    • Pharmacogenomics
    • Proteomics
    • Circulating nucleic acids (surrogate for tumor)

• Tumor
  – Variable feasibility (depending on location)
  – Extensive information about disease
  – Predictive biomarkers
Predictive Biomarkers

• Aberrant drug target(s)
  – Activating mutation, amplification
  – Overexpression, methylation

• Aberrant pathways
  – Gene expression profiles (microarrays)
  – Proteomic profiles

• Polymorphisms
  – Single nucleotide, tandem repeats
Sample Storage

Frozen tumor
- Snap frozen
  - Via liquid nitrogen (≈-80°C)
  - Isopentene (≈-50°C)
  - In vial on dry ice
- OCT (optimal cutting temp medium) then liq N2

Fresh tumor
- RNA later; protein later

Fixed tumor
- FFPE
- Other fixatives

Pros/Cons
- Storage at -80°C or colder; good preservation of nucleic acids; crush/freeze artifacts impact morphology
- OCT preserves morphology and histological assessments; can interfere with other assays
- RNA/protein later maintains integrity of RNA and protein for extraction only
- FFPE usual fixative; good for histology; IHC; impacts some assays by cross linking
- Specialized
Incoming tissue samples to Central Lab

To be tested for inclusion criteria or other protocol specified testing

Accessioned/Labeled at central lab

Sent to Biomarker/AP lab

H&E performed

Sections tested/resulted

Stained sections stored at AP Lab

Untested samples returned to Central Lab for Storage

Sample Storage (no inclusion criteria)

Accessioned/Labeled at Central Lab

Samples stored at Central Lab and in DB

Within 24 hours (for active studies)

Request to prepare samples

1. Preparation and shipment of samples (no microtomy required at Central Lab).
   --AND/OR--
   2. Microtomy of specific blocks and subsequent shipment.

Additional slides cut per protocol (if needed)

Block sent back to site

Incoming sample from site

Within 24 hours (for samples without valid holds)

Accessioned/Labeled at Central Lab

Samples stored at Central Lab and in DB

Block return request received from site

Bulk shipped samples may not be accessioned in 24 hours due to volume of samples.
Patient Protection

- Informed consents for open-access of patient data
- Patient privacy/protection
  - HIPAA
  - Anonymous coding
  - Double de-identification
  - Genetic Information Non-Discrimination Act
    - http://www.ginahelp.org/
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Clinical Information

Clinical Research
• Electronic Case Report Forms
  – Structured
  – Controlled vocabularies
  – Regulatory Standards
• Validated
• CDISC

Clinical Care
• Electronic Health Records
  – Largely unstructured
  – Free text
  – Health care standards
• Unmonitored
• HL7
Biomedical Research Integrated Domain Group (BRIDG)

NCI eCRFs and ASCO CORE use BRIDG to connect research and care

Clinical Document Architecture

LOINC

SNOMED

LOINC

MedDRA

eCTD

= Vocabulary

= Standard

= Model

= Document Standard, or Architecture
Patient-initiated Study Portal

(Army of Women – Health of Women Study)
NSCLC non-responder project

Research Environment
- SNPArray Data
- Expression Array Data
- Patient Samples

Clinical Care Environment
- Clinical Data
- Radiological Data

caBIG® Applications
- caTissue
- caArray

API

caBIG® Services to Local System
- Tolven
- caExchange - Hub

(ISPY-2/caBIG infrastructure)