Precision Medicine Clinical Trials: Defining New Treatment Strategies

Brandy M. Heckman-Stoddard and Judith J. Smith

Objectives: *To discuss the role of clinical trials in the changing landscape of cancer care resulting in individualized cancer treatment plans including a discussion of several innovative randomized studies designed to evaluate multiple targeted therapies in molecularly defined subsets of individuals.*

Data Sources: *Medical and nursing literature, research articles, and clinicaltrials.gov.*

Conclusion: *Recent advancements in cancer biomarkers and biomedical technology have begun to transform fundamentals of cancer therapeutics and clinical trials through innovative* adaptive *trial designs. The goal of these studies is to learn not only if a drug is safe and effective but also how it is best delivered and who will derive the most benefit.*

Implications for Nursing Practice: *Implementation of clinical trials in the cancer biomarker era requires knowledge, skills, and expertise related to the use of biomarkers and molecularly defined processes underlying a malignancy, as well as an understanding of associated ethical, legal, and social issues to provide competent, safe, and effective health care and patient communication.*

Key Words: *Precision medicine, clinical trial, adaptive design, biomarker, molecular targets, research ethics*

Precision medicine is an approach to deliver optimal patient outcomes by integrating clinical and molecular patient data to understand the biological basis of the disease.[1] This approach guides selection of the most appropriate targeted therapy based on distinctive patient characteristics and unique molecular features of a malignancy. The aim of this

Brandy M. Heckman-Stoddard, PhD, MPH: *Division of Cancer Prevention, National Cancer Institute, Bethesda, MD.* Judith J. Smith, MSN, RN, AOCN®: *Division of Cancer Prevention, National Cancer Institute, Bethesda, MD.*

Address correspondence to Judith J. Smith, MSN, RN, AOCN®, National Cancer Institute, 9609 Medical Center Drive, Room 5E-206, MSC 9781, Bethesda, MD 20892-9781. e-mail: judiths@mail.nih.gov

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strategy is to optimize patient outcomes, while providing more favorable safety profiles than traditional population-based cancer chemotherapy.

Clinical trials are the means by which investigational agents, devices, or biologics, such as chemotherapy agents, blood products, or gene therapies are scientifically evaluated in human volunteers for safety and efficacy. Typically, candidate therapeutic agents progress through a carefully regulated and lengthy multi-phase clinical trial process before receiving US Food and Drug Administration (FDA) approval. Moving forward, significant modifications to current clinical trial designs will be necessary to progress toward a more personalized approach. *Adaptive* trial design is an example of an innovative accelerated effort for evaluating targeted therapies. This design allows researchers to analyze accumulating study data at prospective interim time points and to alter the course of an individual's study plan or the trial itself.[2] Common types of trial adaptations are listed in Table 1.[2] This article will describe adaptive design, and present examples of studies currently being conducted using this novel approach, as well as discuss ways in which genomic and biomarker research advances precision medicine.

Adaptive Design Trials

Adaptive design trials have the ability to answer multiple questions in a single trial structure.[2,3] The paradigm in oncology is shifting to use trials to learn not only if a drug is safe and effective but also how it is best delivered and who will derive the most benefit. Adaptive trials use a strategy in which results of an interim analysis can influence the treatment arms offered to patients subsequently enrolled. Below we discuss two adaptive clinical trials programs as examples.

TABLE 1.
The Most-Common Types of Adaptive Settings in Modern Clinical Trials

Stopping early (or late, that is, extending accrual) with a conclusion of either superiority or futility
Adaptively assigning doses to more efficiently assess the dose-outcome relationship
Dropping arms or doses
Seamless phases of drug development within a single trial
Changing the proportion of patients randomized to each arm
Adaptively homing in on an indication or responder population
Adding arms or doses
Changing accrual rate

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I-SPY

I-SPY 1 (ClinicalTrials.gov numbers: NCT00043017) is a neoadjuvant trial of women with locally advanced breast cancer, which are assessed for estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 (HER2), and Mammaprint (Agendia, Irvine, CA), a 70-gene predictive signature of distant recurrence prior to treatment (or randomization).[4,5] The trial evaluates molecular biomarkers of treatment response and breast imaging to guide "adaptive" (ie, subsequent optimal treatments) randomization. Initial studies were used to develop and validate optimal metrics of treatment response in I-SPY1.

In I-SPY 1, chemotherapy was administered before surgery, and biomarkers were compared with tumor response on the basis of magnetic resonance imaging (MRI), pathologic residual disease at the time of surgical excision, and 3-year disease-free survival. The study found that pathologic complete response (pCR), defined as no invasive tumor present in either the breast or axillary lymph nodes, differed by molecular subset; hormone receptor-positive/HER2-negative carcinomas were associated with the lowest pCR (9%) and hormone receptor-negative/HER2-positive had the highest pCR (45%).[4] I-SPY 1 also indicated that pCR was predictive of recurrence free survival within a molecular subset.[4] The study showed that MRI volume was the best predictor of residual disease after chemotherapy.[5] This study established the infrastructure to integrate biomarkers and imaging with shared methods and real-time access to study data which will be leveraged for I-SPY 2.

I-SPY 2 (investigation of serial studies to predict your therapeutic response with imaging and molecular analysis 2) (ClinicalTrials.gov numbers: NCT01042379) is an adaptive design trial using Bayesian statistics comparing novel drugs in combination with standard chemotherapy with the efficacy of standard therapy alone. The trials schema is shown in Figure 1. Acceptability criteria for novel drugs include: compatibility with taxane therapy and for HER2-directed therapy, comparability with taxane plus trastuzumab; rationale for efficacy in breast cancer; targeting key pathways/molecules in breast cancer: HER2, insulin-like growth factor receptor (IGFR),