

Innovations in Clinical Trial Design in the Era of Molecular Profiling

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Abstract

Historically, cancer has been studied, and therapeutic agents have been evaluated based on organ site, clinical staging, and histology. The science of molecular profiling has expanded our knowledge of cancer at the cellular and molecular level such that numerous subtypes are being described based on biomarker expression and genetic mutations rather than traditional classifications of the disease. Drug development has experienced a concomitant revolution in response to this knowledge with many new targeted therapeutic agents becoming available, and this has necessitated an evolution in clinical trial design. The traditional, large phase II and phase III adjuvant trial models need to be replaced with smaller, shorter, and more focused trials. These trials need to be more efficient and adaptive in order to quickly assess the efficacy of new agents and develop new companion diagnostics. We are now seeing a substantial shift from the traditional multiphase trial model to an increase in phase II adjuvant and neoadjuvant trials in earlier-stage disease incorporating surrogate endpoints for long-term survival to assess efficacy of therapeutic agents in shorter time frames. New trial designs have emerged with capabilities to assess more efficiently multiple disease types, multiple molecular subtypes, and multiple agents simultaneously, and regulatory agencies have responded by outlining new pathways for accelerated drug approval that can help bring effective targeted therapeutic agents to the clinic more quickly for patients in need.

Key words Biomarkers, Clinical trial, Design, Endpoints, Neoadjuvant therapy, Tumor

1 Introduction

In the field of oncology, the traditional process for determining which drugs will benefit patients is both long and expensive. It is estimated to take 10–15 years and cost over two billion dollars for a promising therapy to reach the marketplace [1, 2]. This process is composed of a series of clinical trials beginning with the assessment of drug safety and dosing (Phase I), establishment of efficacy and indications (Phase II), and testing for superiority over current standard of care treatment regimens (Phase III). Historically, cancer has been studied and therapeutic agents have been evaluated

based on organ site and clinical staging. Despite the fact that our best opportunity to cure cancer occurs in its earliest stages, most early oncology drug development begins in the metastatic setting. However, therapeutic benefit in the metastatic setting doesn't necessarily translate to benefit in the adjuvant setting for primary tumors, and a lack of benefit in the metastatic setting could also miss efficacy potential in earlier stages of disease [1].

Traditional clinical trial structure usually addresses a single therapeutic question in a large population of patients with disease in a defined organ site and focuses on reducing false-positive and false-negative results. These trials are usually comparative and look for superiority of an experimental therapy over a concurrently accrued control group with a primary endpoint of overall survival. Enhanced efficacy in any patient subgroup is determined only retrospectively, and survival data take many years to accrue. In the past, these types of trials were acceptable because there were limited therapies available, and cancer within an organ site was thought to be a homogeneous disease. However, the last two decades have brought a literal explosion in our knowledge of cancer at the cellular and molecular level such that numerous subtypes are being described based on biomarker expression and genetic mutations that transcend traditional classifications of the disease [3–5]. Drug development has experienced a concomitant revolution in response to this knowledge. Focus has shifted from general cytotoxic agents to the development of targeted agents that interfere with cancer cell growth and survival more selectively and potentially protect normal tissues to a greater extent. While improved molecular characterization of cancer presents great prospects for a future of truly individualized therapy, these advances are dividing cancer into smaller and smaller subpopulations and create situations where patient selection is based on underpinning molecular alterations rather than organ site, which present significant challenges for evaluating new therapies. The abundance of newly identified molecular targets and therapeutic agents means we no longer have the luxury of focusing on a limited number of therapies to evaluate going forward but must instead replace the traditional, large phase II and phase III adjuvant trial models with smaller, shorter, and more focused trials in the neoadjuvant, adjuvant, and metastatic setting. These trials need to be more efficient and adaptive in order to quickly assess the efficacy of new agents and develop new companion diagnostics when appropriate without the burden of the current regulatory structure of multiple sequential trials and long evaluation periods. The goal of these trials should be to deliver effective therapies to patients with narrowly defined disease subtypes. We are now seeing a substantial shift from the traditional multiphase trial model to an increase in phase II neoadjuvant trials in earlier-stage disease incorporating surrogate endpoints for long-term survival

to assess efficacy of therapeutic agents. In this chapter, we will describe recent innovations in clinical trial design and endpoint assessment that are moving the field of oncology toward achieving these goals.

2 Innovations in Clinical Trial Endpoints

2.1 *Traditional Clinical Trial Endpoints*

Establishing the efficacy of a therapeutic agent is the most important goal of oncology drug development. Traditional gold standard endpoints are overall survival (OS), i.e., the time from diagnosis to death, and progression-free survival (PFS), a shorter endpoint related more directly to quality of life [6] (Table 1). For years, response rate (RR) as determined by tumor volume changes from imaging studies, and physical exams have been what investigators and patients have used to measure efficacy of a drug. For a variety of reasons, tumor RR is not the best endpoint, and it is not generally accepted in obtaining regulatory approval for a therapy. Instead, the more stringent measurement of overall survival (OS) as a “defining” endpoint reflects what is considered most indicative of clinical benefit (Table 1).

Table 1
Definitions of traditional clinical trial endpoints and surrogate endpoints used in neoadjuvant trials [6, 7]

Endpoint Name	Definition
Overall survival (OS)	Time from randomization until death from any cause
Disease-free survival (DFS)	Time from randomization until recurrence of tumor or death from any cause
Objective response rate (ORR)	Proportion of patients with tumor size reduction (sum of partial + complete responses)
Time to progression (TTP)	Time from randomization until objective tumor progression
Progression-free survival (PFS)	Time from randomization until objective tumor progression or death from any cause
Event-free survival (EFS)	Time from randomization to (a) progression of disease that precludes surgery, (b) local or distant recurrence, or (c) death from any cause
Pathological complete response (pCR)	The absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected (breast) specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy
Residual cancer burden (RCB)	A continuous variable measurement derived from primary tumor dimensions, cellularity of the tumor bed, and axillary nodal burden at the time of surgery

While OS is frequently utilized by the US Food and Drug Administration (FDA) as a major endpoint in the drug approval process, it presents significant problems for assessment of targeted therapeutics [8]. Phase II and III studies can often take one or more years to accrue adequately large numbers of patients. Additional years must pass, usually three or more, before the appropriate numbers of patients live out the natural course of their disease. This prolonged time frame required to assess OS is one reason that it may not be the most practical primary endpoint for phase II studies. OS is also affected by the use of subsequent lines of therapies as well as improvements in supportive care that may obscure the effects of a particular therapeutic agent during the assessment period. Moreover, prolonged time courses add to the cost of clinical trials as one gets further along in drug development. With the tremendous costs of bringing novel agents to market, pharmaceutical manufacturers have reduced incentive to evaluate novel risky therapies, particularly for targeted agents where only a small portion of the patient population may be responsive and biomarkers to identify those patients may not be well defined. Finally, judging a therapy by OS alone ignores reduction of symptoms and improvements in the quality of life.

Based on all the drawbacks of using the traditional OS endpoint, clinicians also utilize alternative measurement endpoints that are reached earlier in the treatment course and may be more meaningful to the patient. Newer clinical trials are incorporating quality-of-life (QOL) measurements such as the “Lung Cancer Symptom Scale” which is a subjective QOL questionnaire filled out by patients and nurses that reports subjective symptoms, in addition to the standard measurements of response rate and overall survival.

Endpoints such as time to progression (TTP), which is the time from randomization to the time of progressive disease, may be used as a surrogate for OS, particularly in clinical trials including patients that have received prior treatment or have inoperable or metastatic disease. TTP and progression-free survival (PFS) (Table 1) have been correlated with OS in patients with rectal cancer [9]. These endpoints offer several advantages over traditional OS in clinical trial design. Both TTP and PFS permit smaller sample sizes and shorter study durations – (e.g., months as compared to years). TTP and PFS do not require demonstration of tumor mass shrinkage and thus are useful in trials designed to evaluate cytostatic agents that arrest growth but do not shrink the tumor. Lastly, TTP and PFS can be measured in real time after a single line of therapy, and when these measures are used, the designation of a response is not confounded by subsequent events. The disadvantage of TTP and PFS, as compared to OS, in clinical trials is the requirement for costly, frequent, and careful imaging assessment for progression [10, 11].

2.2 RECIST Criteria

Since 2000, the Response Evaluation Criteria in Solid Tumors (RECIST) criteria have been used to assess therapeutic response [12] (Table 2). These criteria are based on the premise that tumor shrinkage reflects a positive outcome of antineoplastic therapy. Utilizing two-dimensional CT and/or MRI imaging data, tumor response rate is categorized as complete response, partial response, stable, or progressive disease based on the extent and duration of tumor shrinkage (Table 2). As an example, the drug sorafenib, a multiple tyrosine kinase inhibitor, was approved for use in patients with advanced hepatocellular carcinoma (HCC) [14, 15]. The use of sorafenib was found to prolong survival in patients with HCC by 3 months and was associated with a 31% increase in OS at 1 year. Nevertheless, the RECIST response rate was only 2% [14]. The same drug has been studied in patients with advanced renal cell cancer [16]. The response rate was only 10%, but this constituted a significant prolongation in survival that led to FDA approval of this agent in advanced renal cell cancer.

There are a number of reasons why RECIST-defined response rates are an inadequate endpoint for efficacy in many clinical trials. First, tumor cytotoxicity may not result in rapid shrinkage, especially in tumors that induce large amounts of stroma (rather than cellular elements that may “die” with chemotherapy). Second, RECIST categories are broad and thus somewhat imprecise: a tumor that shrinks 29% and a tumor that grows 19% are both considered stable disease, while these two responses are clearly different [13]. Third, despite imaging advances there are issues with scanning variability and resolution, particularly with lesions <1 cm, that can significantly affect accuracy. Lastly, RECIST criteria cannot be used in tumors that localize or metastasize to the bone since these lesions do not shrink, making it difficult in the assessment of diseases such as prostate cancer, as well as in many hematologic malignancies that cannot be measured with tumor size.

Table 2
Summary of RECIST response criteria [13]

Stage	Definition
Complete response (CR)	Complete resolution of the tumor for at least 4 weeks
Partial response (PR)	Greater than 30% reduction in tumor sustained for at least 4 weeks
Progressive disease (PD)	At least 20% increase in tumor size with no CR, PR or SD documented before the increase of disease
Stable disease (SD)	Neither PR or PD criteria are met

2.3 Surrogate Endpoints for Long-Term Survival in Neoadjuvant Trials

The concept of achieving greater therapeutic benefit from introducing agents earlier in the disease process has led to an increase in the number of phase II trials in the neoadjuvant setting in early-stage cancers. A critical principle of neoadjuvant clinical trials is that tumor response serves as a surrogate endpoint for, and is strongly correlated with long-term patient survival.

2.3.1 Pathological Complete Response (pCR)

One measure of tumor response that is uniquely available in the neoadjuvant trial setting is pathologic(al) complete response (pCR). pCR is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy [7] (Table 1). A number of studies and meta-analyses have shown that pCR is associated with long-term survival, and it has been adopted as a primary endpoint in neoadjuvant trials, particularly in breast cancer [17–25]. Some of these studies have shown that pCR predicts long-term outcome more effectively in various breast cancer subtypes rather than the disease as a whole [24, 25]. However, there is some controversy as to whether sufficient evidence exists to confidently use pCR as a surrogate endpoint to recommend or reject a treatment for general clinical use [26]. Some of these concerns have been based on inconsistent definitions of pCR regarding the presence of nodal metastasis, residual in situ carcinoma, and residual cellularity [22, 23], as well as some seemingly contradictory results for therapeutic regimens tested in the adjuvant vs. neoadjuvant setting [1]. While these concerns are legitimate, more precise criteria for pCR have been accepted as the current standard, and many studies do show promising correlations between pCR and EFS and OS on the individual patient level. Future studies with more homogeneous tumor subtypes where there are potentially greater differences in pCR rates between treatment arms may help to determine more definitively the strength of the relationship between pCR and long-term outcomes [27].

2.3.2 Residual Cancer Burden (RCB)

A second endpoint that has been more recently developed for assessment of response to neoadjuvant therapy is residual cancer burden (RCB). RCB is a pathology-based, continuous variable measurement derived from primary tumor dimensions, cellularity of the tumor bed, and axillary nodal burden in breast cancer [28]. It was developed out of a need to assess more effectively the spectrum of residual disease (RD) found in surgical specimens, which can range from pCR to therapeutic resistance. Each of the components of the RCB index has prognostic significance, and as a result, the RCB endpoint is strongly prognostic and represents the range of residual disease seen in a treated population. RCB can also be divided into four classes (RCB 0-RCB III) that associate with prognosis. Extensive RD (RCB III) associates with poor prognosis,

whereas patients in category 0 or I (pCR or minimal RD) have very similar 5-year prognosis and represent a pool of patients that benefit from neoadjuvant therapy [28].

The component measurements of RCB were found to be highly reproducible among pathologists over a large number of specimens [29], and the methods for assessment of RCB components could readily be incorporated into routine pathologic review with no increase in patient care cost. An RCB calculation program is freely available online: (http://www.mdanderson.org/breast-cancer_RCB). While RCB calculation currently may not be a routine analysis parameter for neoadjuvant studies, it is an endpoint for the I-SPY 2 TRIAL described in Subheading 3.

3 Innovations in Clinical Trial Design in the Era of Molecular Profiling

3.1 Neoadjuvant Use of Pertuzumab Under FDA Guidelines for Accelerated Approval

In 2012, the US Food and Drug Administration published “Guidance for Industry. Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval” [7]. These guidelines provide two pathways for drug approval in the neoadjuvant setting for breast cancer. The first is to perform a single randomized trial where all patients are treated neoadjuvantly, but a sufficient number of patients are accrued to demonstrate agent superiority for both the pCR and longer-term event-free survival (EFS) endpoints. When all patients have been accrued and the pCR endpoint has been successfully achieved, the pharmaceutical company can file for accelerated approval. Full approval would follow at the 3-year EFS endpoint if superiority of the new agent is demonstrated. If superior EFS is not observed, accelerated approval will be withdrawn. A second pathway is to conduct a neoadjuvant trial for the pCR assessment and simultaneously begin a confirmatory adjuvant trial for long-term survival. If a successful pCR endpoint is achieved in the neoadjuvant trial, accelerated approval is considered only when accrual is complete for the confirmatory trial [30].

Pertuzumab, a humanized monoclonal antibody that binds the dimerization domain of the HER2 receptor, was awarded accelerated approval in September of 2013 and was the first targeted agent to achieve this landmark approval under the FDA’s 2012 draft guidance. Approval of the drug for neoadjuvant use was granted based on several lines of evidence. The first was that pertuzumab had gained approval for use in advanced breast cancer based on results of the phase III CLEOPATRA trial. CLEOPATRA was a randomized control trial for metastatic breast cancer patients that demonstrated significant improvement in PFS and OS in patients treated with pertuzumab added to trastuzumab/docetaxel over a placebo/trastuzumab/docetaxel control arm [31]. Additional evidence came out of

two phase II neoadjuvant trials, NeoSphere, and TRYPHAENA. The NeoSphere trial accrued just over 400 patients with Stage II/III HER2+ breast cancer. The patients were randomized to receive one of four regimens: pertuzumab/trastuzumab/docetaxel, trastuzumab/docetaxel, pertuzumab/trastuzumab, or pertuzumab/docetaxel. Significantly higher pCR rates were seen in the pertuzumab/trastuzumab/docetaxel arm over the trastuzumab/docetaxel arm (39.3% vs. 21.5%, respectively) [32]. The TRYPHAENA trial was designed mainly as a cardiac safety study incorporating pertuzumab into various standard of care regimens for Stage II/III HER2+ breast cancers [33]. Though there was no control arm in this trial, the pCR rates achieved in three treatment arms of this study exceeded those of NeoSphere [30]. The final critical step toward meeting the requirements for accelerated approval of pertuzumab was achieved when the phase III adjuvant trial, APHINITY, completed enrollment of 3800 patients in August 2013. The APHINITY trial is a double-blind, placebo-controlled study in which patients are allowed to receive any standard chemotherapy regimen and are then randomized to receive either pertuzumab or placebo. The primary endpoint is invasive DFS. Results are not yet known but will move toward a definitive determination of whether DFS is improved with the addition of adjuvant pertuzumab and possibly lead to full approval for its use in the neoadjuvant setting [30].

The goal of neoadjuvant therapy trials is to increase the pace at which potentially beneficial agents become available for use. Accelerated approval can provide access to therapies with solid evidence of improved response, while long-term survival data are awaited. It is not necessarily meant to change the standard of care for patients, particularly in the absence of evidence for long-term outcome improvement, but it may be challenging for some oncologists to pass on an opportunity to provide a beneficial agent such as pertuzumab to their high-risk HER2+ patients. Others may choose not to provide a drug approved under these guidelines simply because long-term outcome data are missing [30].

Regardless, the accelerated approval of pertuzumab establishes a new paradigm for a pathway to make promising new drugs available to patients more quickly and cheaply. This new pipeline opens the door for many new additional trials and drugs to be approved using this approach, and not just in breast cancer [30]. In the last 5 years, several new clinical trials with innovative designs have been implemented to work toward the goals of neoadjuvant therapy in the era of molecular profiling: assessment of multiple drugs for activity in various molecular subtypes of disease in an efficient and cost-effective manner.

3.2 New Clinical Trial Designs

In many respects, the concepts of patient stratification and biomarker-based design in clinical trials have been in use for many years (reviewed in [34, 35]). These early designs are gradually

being replaced by newer designs that include multiple therapeutic agents, multiple molecular groups, and even multiple disease types [35]. Among these new designs are the basket trial and platform (or umbrella) trials. Some of these trials also incorporate adaptive elements based on Bayesian statistics that make them even more innovative and efficient [5].

3.2.1 Basket Trials

The concept of the basket trial is based on the hypothesis that the presence of a molecular aberration in a tumor predicts response to a particular targeted therapy independent of other factors such as tissue of origin, disease stage, and histopathology. Basket trials generally include multiple tumor types, and a master protocol is implemented to screen patients for selected molecular alterations that are actionable therapeutic targets involved in tumorigenesis, tumor growth, or metastasis. Patients are then assigned to the appropriate sub-protocol corresponding to an identified molecular alteration in their tumor (Fig. 1a). This type of trial is becoming more attractive because it provides an opportunity to look at very rare mutations and rare disease types as well as mutations that are difficult to study in the context of a single disease [36].

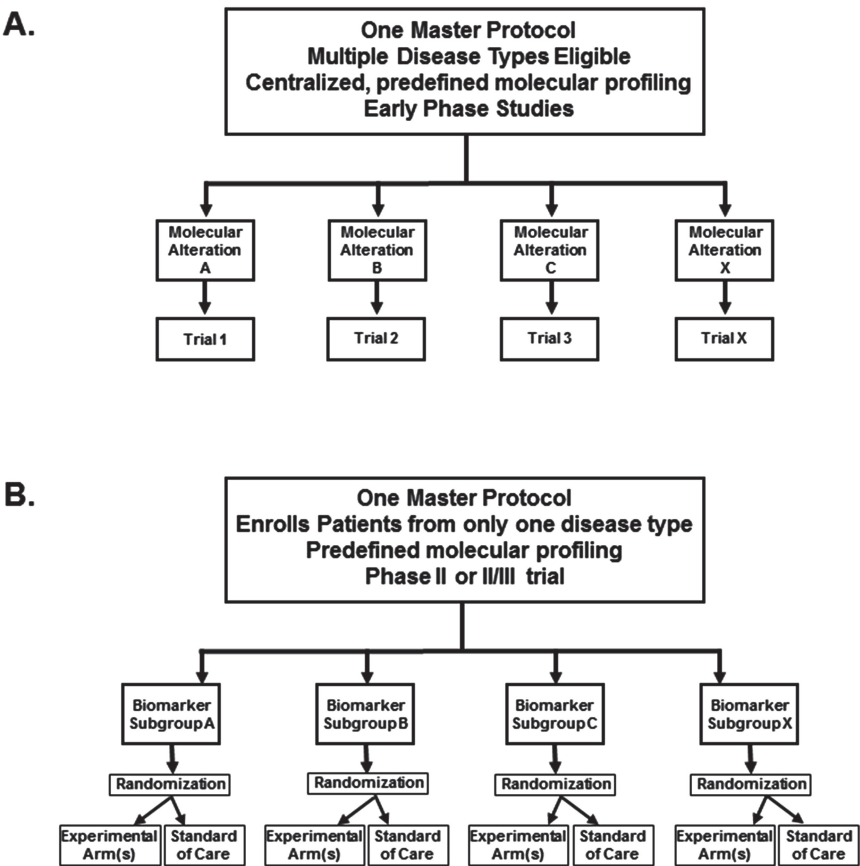


Fig. 1 Diagrams for basket trials and platform trial formats. (a) Basket trial; (b) platform trial

The CUSTOM (Molecular Profiling and Targeted Therapy for Advanced Thoracic Malignancies) trial was the first completed basket trial that evaluated response to multiple targeted therapies against specific molecular aberrations for multiple tumor histologic types simultaneously. It was designed to identify biomarkers in, and to evaluate five targeted therapies in patients grouped by molecular markers and tumor type in advanced non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and thymic malignancies [37]. The drugs included in the trial were erlotinib (EGFR mutations); MK2206, an AKT inhibitor (PIK3CA, AKT1, and PTEN mutations); the MEK inhibitor selumetinib (KRAS, HRAS, NRAS, and BRAF mutations); lapatinib (HER2 mutations); and sunitinib (KIT and PDGFRA mutations). The intent was to evaluate each drug in all three tumor types for a total of 15 arms, but the trial ultimately only enrolled 45 of 257 patients with actionable mutations, with over half of those being NSCLC tumors in the erlotinib and selumetinib arms. This was largely due to the low incidence of the targeted mutations in specific tumor types. The trial did surpass their response goal of 40% in the erlotinib arm of the trial with an ORR of 60% (9/15 PR), but the ORR in selumetinib arm was only 11% (1/9 PR). These results were consistent with other clinical trial data for these agents and demonstrated the potential capability to identify compounds of high and low activity in small cohorts of patients with selected molecular alterations using this type of trial design [37].

Two currently accruing basket trials, the ASCO-sponsored Targeted Agent and Profiling Utilization Registry (TAPUR) trial and the National Cancer Institute-Molecular Analysis for Therapy Choice (NCI-MATCH) trial, greatly expand the scope and size of the CUSTOM trial design. The TAPUR trial began accruing patients in March 2016 and has a screening goal of over 1000 patients in a 3-year time frame. It aims to address two common issues in precision medicine: lack of access to FDA-approved drugs for off-label use and the lack of safety and efficacy data for these agents. TAPUR will address these issues by making these FDA-approved drugs available to patients at no charge and creating a registry to record and make key clinical outcomes freely available [38]. The trial is open to patients with advanced solid tumors, multiple myeloma, and non-Hodgkin's lymphoma and will evaluate 10–15 drugs in cohorts of up to 35 patients that will be defined by tumor type, genomic alteration, and drug. The TAPUR trial allows for therapy matching when the prescribed molecular tests used for patient selection were completed in any CAP-/CLIA-accredited laboratory. The primary endpoint is OR or stable disease for 16 weeks.

The NCI-MATCH trial is complementary to the TAPUR trial in that they both aim to elucidate beneficial uses for targeted therapies. The trial opened in August 2015 to patients with advanced solid tumors and lymphoma with a goal that 25% of patients enrolled have rare tumor types. Ten treatment arms were initially

available and included drugs that were FDA-approved for a cancer indication or were being tested experimentally and had evidence for effectiveness against tumors with a specific molecular alteration. The trial design allows for arms to be added or dropped over time. Next-generation sequencing is used to screen tumors for actionable genetic abnormalities, and patients are then assigned to an appropriate treatment arm if a drug is available [39]. Unlike the TAPUR trial, NCI-MATCH requires testing to be performed by one of four predetermined CAP/CLIA laboratories. In November 2015, the NCI-MATCH trial paused for a planned interim analysis upon reaching the benchmark of enrolling 500 patients for mutation screening in just 3 months. This enrollment rate was about five times higher than expected and reflects a need for these types of avenues to provide access and opportunities to treat patients with limited options. The interim analysis revealed that the match rate of mutations to a targeted therapy was approximately 9%, which is close to the 10% rate projected in the original design. However, it was also noted that the actual mutation prevalence rates found were much lower than expected based on estimates from TCGA and other databases [39, 40].

Over half (19/33) of patients enrolled to treatment arms of the trial had rare tumor types. It was found that not all matched patients were enrolled in a treatment arm of the trial for a variety of reasons. One is that the turnaround time for sequencing results was up to 48 days in some cases, and this often left the door open for changes in health status that affected eligibility. Another issue that is impacting NCI-MATCH is the requirement that all patients must have molecular profiling done at specific molecular labs and requires prospective molecular analysis. With these requirements, there have been issues with adequate biopsy sample quantity and quality [41]. The trial reopened in May 2016 with 24 treatment arms available for cohorts of up to 35 patients and a fourfold increase in laboratory capacity that is anticipated to deliver sequencing results in less than 2 weeks after biopsy [39]. It should be noted that while there is some minor duplication in the evaluable actionable mutations between NCI-MATCH and TAPUR, there is very little overlap in the targeted agents matched to them. In the NCI-MATCH trial, patients are allowed to switch to a second treatment arm if their first treatment proves ineffective and they have a second actionable mutation; those who fail to match to the complement of open trial arms at the time of screening can be notified if an appropriate therapeutic agent for any identified mutations is brought into the trial.

These trials are an important step in challenging the traditional dogma of treating cancers based on organ site, stage, and tumor histology and are beginning to focus more on patient- and tumor-specific biology. They are generating significant interest in the medical community by bringing precision medicine into clinical

trials using hypothesis-driven strategies and designs. The use of master protocols for screening patients for genetic abnormalities and matching to targeted therapies is a very efficient method to deliver experimental therapy in the age of molecular profiling. However, this type of trial design raises questions about what is truly learned from these trials and how that information can be used going forward. While tumor biology is an important, if not the most important consideration when assessing targeted therapeutic options, tumor histology still plays a role in the potential of identifying actionable targets, as illustrated in the CUSTOM trial [37]. The individual protocols incorporated into these basket trials accrue only a small number of patients with mixed tumor types, some of which will be inherently more responsive to certain therapies than others. A protocol could be deemed successful based on % ORR, but many tumor types within that cohort could have no response at all. Because population sizes are small, accurately estimating response rates for individual tumor types isn't possible and does not forge a clear path forward [5]. Ultimately, these trials, with their large screening populations, provide valuable molecular biomarker prevalence data and, for many new targeted therapies, can point to a potential target population for additional phase II analysis of efficacy in a rational manner.

3.2.2 Platform Trials

In contrast to a basket trial, a platform trial is designed to test multiple therapies in a single disease type (Fig. 1b). They often use a master protocol to identify various molecular subgroups of interest within the population, and some therapies may be restricted to certain molecular subgroups. Once assigned to a biomarker subgroup, patients are then randomized to receive either standard of care therapy (control) or one of several targeted agents. Because they focus on a single disease type, all therapeutic agents included in a platform trial can share a common control arm which significantly reduces the number of enrolled patients required to have adequate statistical power [4]. This makes the platform trial much more time- and cost-efficient than traditional trial structures. Platform trials can also be designed as a “standing trial” where experimental arms can be added and dropped over time, and the trial can remain open to accrual for an undetermined time frame in a continual screening process [4].

Some current standing platform trials also include Bayesian adaptive design elements that make them more efficient and unique. Incorporation of these adaptive statistical analysis methods allows for information to be assimilated as it is collected and can affect the future course of the trial. The use of a Bayesian approach can reveal that the answer to a question addressed in the trial has been reached with a sufficient certainty. The effectiveness of a given therapy in a certain biomarker subgroup may suggest it needs to be dropped or its randomization probability altered [5]. One

excellent example of an adaptive design platform trial is the I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2).

The I-SPY 2 TRIAL is a multicenter, adaptive design phase II trial of neoadjuvant therapy for high-risk breast cancer (BC) that evaluates multiple new agents added to standard of care therapy for effects on pathological complete response (pCR) rates in various HR/HER2 molecular subtypes. The goal of the trial is to identify improved treatment modalities for subsets of patients based on the molecular characteristics of their disease [4] (Table 3). Regimens that show a high Bayesian predictive probability of being more effective than standard therapy will graduate from the trial in that particular biomarker signature(s). Regimens will be dropped if they show a low probability of improved efficacy across all biomarker signatures. New drugs will enter as others complete their evaluation. The general I-SPY 2 TRIAL structure is shown in Fig. 2. The primary endpoint is pCR at the time of surgery. The trial uses a Bayesian adaptive randomization algorithm to assign patients to either control therapy or one of several arms available to their particular biomarker subtype. As patients complete surgery and response data is reported, the randomization algorithms are updated, and the randomization probabilities are adjusted for the various biomarker signature/drug combinations. When patients enroll in the trial, they are screened for HR, HER2, and

Table 3
Patient biomarker subtype categories and biomarker signatures evaluated in the I-SPY 2 TRIAL [4]

Biomarker signatures eligible for graduation	Breast cancer biomarker subtypes defined in I-SPY 2 TRIAL (HR, HER2, MP)								Estimated prevalence (%)
	+,+,+	+,+,-	+, -, +	+, -, -	- , +, +	- , +, -	- , -, +	- , -, -	
All	YES	YES	YES	YES	YES	YES	YES	YES	100
HR+	YES	YES	YES	YES	NO	NO	NO	NO	49
HR-	NO	NO	NO	NO	YES	YES	YES	YES	51
HER2+	YES	YES	NO	NO	YES	YES	NO	NO	37
HER2-	NO	NO	YES	YES	NO	NO	YES	YES	63
MP+	YES	NO	YES	NO	YES	NO	YES	NO	48
HR-/HER2-	NO	NO	NO	NO	NO	NO	YES	YES	34
HR-/HER2+	NO	NO	NO	NO	YES	YES	NO	NO	17
HR+/HER2-	NO	NO	YES	YES	NO	NO	NO	NO	29
HR+/HER2+	YES	YES	NO	NO	NO	NO	NO	NO	20

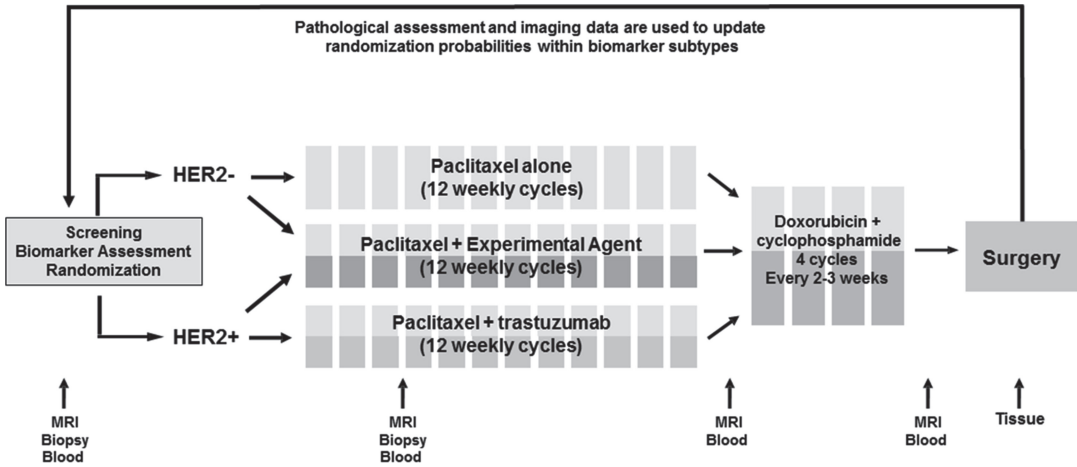


Fig. 2 Schema for the ISPY-2 TRIAL, an adaptive design standing platform trial. Following biomarker assessment, patients are randomized to 12 weekly cycles of paclitaxel alone (HER2-), paclitaxel + trastuzumab (HER2+), or paclitaxel + an experimental agent followed by 4 cycles of doxorubicin + cyclophosphamide prior to surgery. Imaging data and blood samples are collected at enrollment, week 3, 13, and prior to surgery. Tissue samples are collected at enrollment, week 3 and surgery. Pathological assessment and imaging data are used to update the randomization and treatment effect probabilities for each biomarker subtype as the trial progresses

MammaPrint status and assigned to 1 of 8 biomarker subtype categories (Table 3). All available therapies are evaluated for effectiveness in their particular biomarker category, and patients are likely to be assigned to treatment arms that are performing better for their biomarker signature [5].

During the course of the trial, therapies are evaluated for effectiveness in each of ten possible biomarker signatures (Table 3), which represent various subsets of the eight biomarker categories to which patients are assigned. The goal of the trial is to pair therapies with biomarker signatures where they are most effective. The Bayesian algorithm calculates probabilities for each signature that a given therapy will be successful in a 300-patient, randomized, neo-adjuvant phase III trial. These probabilities are based on all data available in the trial, including pCR and MRI data collected during treatment. A drug will “graduate” from the I-SPY 2 TRIAL when this probability reaches 85% for any 1 of the 10 possible biomarker signatures. Accrual to that treatment arm stops when this is achieved. Graduation of a drug from the trial is made public only after all patients in that treatment arm and concurrent control patients have completed surgery and the final prediction probabilities are calculated. The maximum number of patients that can be assigned to a treatment arm is capped at 120. A therapy can be dropped for futility when the probability for phase III success drops below 10% for all 10 signatures [5].

To date, four experimental agents have graduated from the I-SPY 2 TRIAL: (1) the PARP inhibitor veliparib (+ carboplatin) in HR-/HER2- cancers [42]; (2) neratinib (N), a pan-ERBB

family inhibitor in the HR-/HER2+ signature [43]; (3) MK2206, an AKT inhibitor in all HER2+ and all HR- and HR-/HER2+ signatures; and (4) trastuzumab-DM1 (T-DM1) + pertuzumab (anti-HER2 agents + tubulin inhibitor) in HER2+, HR+/HER2+, and HR-/HER2+ patients. Currently accruing treatment arms include ganitumab (IGF-1R inhibitor) + metformin, ganetespib (HSP90 inhibitor), pembrolizumab (PD-1, immune checkpoint inhibitor), and talazoparib (PARP inhibitor) + irinotecan. In June 2016, the trial reached a major landmark with the randomization of 1000 patients.

One important feature of the I-SPY 2 TRIAL is that it incorporates broad-based genomic and proteomic profiling analyses to identify markers predictive for therapeutic response. Because of the neoadjuvant design of I-SPY 2, clinical outcome is assessed in roughly 6 months (pCR at time of surgery) after enrollment and provides a tremendous opportunity for predictive marker analysis that could graduate to FDA approval as a companion diagnostic upon validation. Our lab serves as the protein biomarker engine for the I-SPY2 TRIAL, and we have developed and incorporated a robust laser capture microdissection (LCM) and reverse phase protein microarray (RPPA)- based workflow for broadscale protein/phosphoprotein biomarker analysis of pretreatment biopsy specimens for patients enrolled in the trial.

4 Conclusions

We hope to leave the reader with several thoughts going forward. In the last two decades, the landscape of our knowledge of tumor biology has changed dramatically, and the pathways to obtaining drug approval need to evolve in response to these dramatic changes. Trial design ideally must be hypothesis driven, biomarker guided, and individualized based on the biology of tumors. In the future, it is imperative to design studies that match a therapy with a specific molecular correlate of response: e.g., a companion diagnostic. Techniques such as genomic microarrays, RPPA analysis, DNA mutation studies, and even IHC are very important in identifying drug-targeted pathways. Targeted therapy, by definition, treats a pathologic signaling pathway that drives the cancer. The responsibility falls to clinical trial designers to use this information to predict which surrogates or molecular endpoints can be used to stratify patients. In the past, patients were stratified by histology alone. In the future, DNA mutations in a particular gene, RNA transcript profiles, or proteomic profiles including the activation state or phosphorylation of a protein in the target signaling pathway will constitute a “multi-omic” systems biology-based view of cancer biology and patient stratification and selection [44–46]. Stratification of patients using molecular profiling will increase the likelihood of response while sparing toxicity without treatment benefit.

Molecular stratification may allow drugs with significant activity to be detected in small populations, obviating the time delay to accrue and study large populations of patients. Ideally, the oncologist of the future will not treat patients based on their specific organ category of disease, i.e., adenocarcinoma of the breast. Instead, they will treat the molecular pathway defect itself, which may be independent of histology.

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