Cancer Letters 387 (2017) 121–126

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

Mini-review

Precision oncology: A new era of cancer clinical trials

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ARTICLE INFO

Keywords:
Clinical trial
Oncology
Biomarker-based design
Adaptive design

ABSTRACT

Traditionally, site of disease and anatomic staging have been used to define patient populations to be studied in individual cancer clinical trials. In the past decade, however, oncology has become increasingly understood on a cellular and molecular level, with many cancer subtypes being described as a function of biomarkers or tumor genetic mutations. With these changes in the science of oncology have come changes to the way we design and perform clinical trials. Increasingly common are trials tailored to detect enhanced efficacy in a patient subpopulation, e.g. patients with a known biomarker value or whose tumors harbor a specific genetic mutation. Here, we provide an overview of traditional and newer biomarker-based trial designs, and highlight lessons learned through implementation of several ongoing and recently completed trials.

Background

Traditionally, site of disease and anatomic staging have been used to define patient populations to be studied in individual cancer clinical trials. In the past decade, however, oncology has become increasingly understood on a cellular and molecular level, with many cancer subtypes being described as a function of biomarkers or tumor genetic mutations. In parallel, cancer therapeutic research has largely shifted from a focus on cytotoxic agents to newer drugs that act through inhibiting cancer cell growth and survival mechanisms while protecting healthy cells to the extent possible. More recently, therapies that serve to unleash the patient's own immune response to fight cancer cells are being discovered and tested in cancer clinical trials. Examples of approved targeted agents include panitumumab and cetuximab, now indicated for treatment of advanced colorectal cancer patients with KRAS wild-type tumors [1,2]; erlotinib, afatinib, and gefitinib, targeting EGFR mutations in patients with advanced non-small-cell lung cancer [3,4]; and ceritinib [5] and crizotinib [6], tyrosine kinase inhibitors targeting ALK mutations. Newly approved immunotherapies include nivolumab [7] and pembrolizumab [8].

With these changes in the science of oncology have come changes to the way we design and perform clinical trials. Increasingly common are trials tailored to detect enhanced efficacy in a patient subpopulation, e.g. patients with a known biomarker value or whose tumors harbor a specific genetic mutation. Classes of biomarker-based designs such as enrichment, stratified, and strategy designs have been previously discussed from a methodological perspective [9,10]. In this review, we first provide a brief overview of these classes of designs along with newer biomarker based design strategies for multiple tumor types/multiple molecular profiles. We then highlight several recently completed and current biomarker-driven trials, with emphasis given to relevant practical considerations and lessons learned in their implementation.

Biomarker-based design overview

Biomarker-based designs can be broadly classified according to the number of disease types, molecular groups, and targeted therapies they include. Table 1 lists several biomarker-based trials categorized by common features. Earlier biomarker-based designs typically assessed a single targeted therapy in a single disease type with 1 or 2 molecular groups. These include **enrichment, marker-stratified, and marker strategy designs**. The **marker-enriched or "targeted" design** (Fig. 1a) was first described by Simon and Maitournam [11–13], although an enriched trial was previously used to study the safety and efficacy of trastuzumab in women with HER2 positive breast cancer and led to its regulatory approval in this setting [14]. In this design, only patients positive for a particular biomarker are randomized to experimental versus control treatments. Examples of enrichment trials in practice include N9831 [15] and TOGA [16]. While enriched designs traditionally include randomization to targeted versus non-targeted treatments, historically, some targeted agents have been approved on the basis of enriched single-arm trials. One example is crizotinib for the treatment of non-small cell lung cancer in 2011; others include ceritinib and alectinib [17]. The related **adaptive enrichment design** includes a mid-trial adaptation based on interim analysis results [18]. This design

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http://dx.doi.org/10.1016/j.canlet.2016.03.015
0304-3835/

Table 1
Types of biomarker-based designs, classifications, and examples.

Design types	Number of disease types within a single protocol	Number of molecular profiles	Number of targeted therapies	Design features	Real-world example trials
Enrichment or targeted	1	1 (e.g. marker positive only)	>1	- Strong biologic rationale that marker negative patients are unlikely to benefit - Reliable assay - Statistical efficiency (i.e. reduced sample size requirements) - Recommended for rare prevalence markers and rare diseases	- N9831 - TOGA
Marker-stratified or marker-by-treatment interaction	1	>1 (e.g. marker positive and marker negative)	>1	- Insufficient evidence of a biomarker's ability to predict treatment effect to justify exclusion of a subpopulation from randomization	- INTEREST - MARVEL
Modified marker strategy	>1	>1	>1	- Typically used in settings with one or more approved therapies, and the interest is in identifying marker subgroups that may have the most benefit - Overlap between the marker based and the non-marker based arms can result in large sample size - Similar to a marker strategy design, except that it includes multiple molecular profiles matched with multiple targeted agents - Can include multiple tumor types - Tests for overall strategy, and not for individual marker-treatment pair	- SHIVA - M-PACT
Umbrella	1	>1	>1	- Existence of national network of clinical sites doing molecularly targeted clinical trials using a common genomic screening platform - Flexible design for the adding/dropping of subtrials based on new emerging data - Use of central clinical laboratory for molecular profiling for a large cohort of patients - Can be logistically complex to set up and implement - Careful statistical consideration needed when adding new or removing existing subtrials	- FOCUS4 - LUNG-MAP - ALCHEMIST
Bayesian biomarker-adaptive	1 (with adaptive randomization)	>1	>1, one per molecular subtype	- Strong scientific rationale, and preliminary evidence for the molecular marker-drug pairing - Reliable assay, with rapid turn-around times - Short term, reliable endpoint to make the adaptation meaningful - Sufficient infrastructure set up and real time data availability	- BATTLE - I-SPY2
Basket	>1	>1	>1, one per molecular subtype	- Strong scientific rationale for the molecular marker-drug pairing - Reliable assay - Availability of a sufficient number of drugs targeting multiple pathways - Single protocol for multiple disease cohorts - Assess for signals of efficacy for each individual marker-drug pairing, and sometimes within each disease cohort - Statistical design principles not well established	- NCI-MATCH

initially randomizes an unselected patient population to experimental versus control treatment, and if the experimental treatment effect reaches a futility threshold in the marker-negative group at an interim analysis, accrual of marker-negative patients is terminated and the remaining sample size re-allocated to marker-positive patients. The **marker-stratified design or marker-by-treatment interaction** (Fig. 1b) is a reasonable alternative when there is insufficient evidence of a biomarker's ability to predict treatment effect to justify exclusion of a subpopulation from randomization [19]. In this design, all patients are randomized to experimental versus control treatments; however, patients are first stratified by marker status and then randomized to a treatment arm within their given marker cohort. Examples of stratified trials in practice include INTEREST [20] and MARVEL [21]. The **marker strategy design** (Fig. 1c) has been used when the specific objective of a clinical trial is to validate the biomarker in the treatment decision-making process [19,22,23]. In this design, patients are screened for biomarkers and then randomized to a treatment strategy that takes biomarker status into account (often a targeted therapy) versus a treatment that ignores the biomarker (often standard of care). As proposed, the strategy design typically evaluates only one marker, limiting its use in practice.

Newer biomarker-based designs expand on the earlier ones by including multiple targeted therapies, multiple disease types, and/or multiple molecular groups. These include **modified strategy designs, umbrella trials, Bayesian biomarker-adaptive designs**, and **basket trials**. A **modified strategy design** (Fig. 1d) is similar to a marker strategy design, except that it includes multiple targeted molecular profiles, thereby accommodating a more heterogeneous patient population. In this framework, the final analysis compares the marker-based strategy arm versus the non-marker-based strategy arm (i.e. conventional, physician-directed) across all profiles. Examples of modified strategy designs include SHIVA [24,25] and M-PACT [26].