CLINICAL INVESTIGATION

Targeted therapies in oncology: perspectives on trial designs and practical considerations

"Overall, the need remains for development of a flexible design paradigm that incorporates both prospective identification of biomarkers that are predictive of treatment effect and on-study validation of such markers and their thresholds, which continue to be typically performed in separate studies in an *ad hoc* fashion."

Keywords: clinical trial design • oncology • targeted therapies

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Historical paradigm & advent of targeted therapies

New oncologic therapies have traditionally been studied in a sequence of clinical trials intended to assess safety (Phase I), efficacy (Phase II) and improvement over the standard of care (Phase III) in homogeneous patient populations, that is, those with same-stage disease of a specific organ system. However, as cancer has become increasingly understood on the molecular level, therapeutic research has largely shifted from a focus on cytotoxic agents to newer targeted drugs that inhibit specific cancer cell growth and survival mechanisms, for example, cell growth signaling, tumor blood vessel development, immune-response enhancement, etc. Here, we focus on trials of targeted therapies thought to be most effective in certain patient subpopulations, such as those with a known biomarker value or genetic tumor mutation. For example, panitumumab and cetuximab have been indicated as treatment options for advanced colorectal cancer patients with *KRAS* wild-type (but not *KRAS* mutant) tumors, and targeted therapies directed toward epidermal growth factor receptor mutation and anaplastic lymphoma kinase rearrangement have improved outcomes in a subset of patients with advanced non-small-cell lung cancer [1–5].

Trial design options for therapies targeting patient subsets

This new paradigm for the treatment of cancer has produced a parallel need for new trial designs to study these treatments, and to identify the patient populations or molecularly defined subpopulations who benefit. In the past decade, a number of biomarker-based design solutions have been proposed, which can be broadly classified on several levels. First, the developmental pathway for clinical trials for targeted therapies is as follows: 'Phase I' trials, where the marker and treatment are studied together in normal versus tumor tissue, the assay validated and any relevant marker positivity thresholds selected; Phase II trials, where interest lies in identifying and possibly validating a marker-based subpopulation where efficacy of a targeted therapy is most promising; and Phase III trials, which are generally powered for a randomized treatment comparison with the current standard of care in the population identified and believed to benefit from earlier Phase II studies [6]. Marker-based trial designs may further be classified as retrospective (i.e., evaluation of the marker-treatment-outcome relationship after the prospective trial has been completed, sometimes in an *ad hoc* manner) or prospective (i.e., formal incorporation of marker detection or predictiveness in the design considerations, such as in calculations of sample size), where the latter is considered the gold standard for evaluation and validation of [Marker A + Drug A] type combinations. A third classification of biomarker designs is a purely statistical one – frequentist or 'classical' designs versus Bayesian designs, where differences between the two approaches lie

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primarily in the methods for hypothesis testing and use of prior information or historical data. Some well-cited specific biomarker-based trial designs from the literature are described below, with emphasis given to prospective and Phase II–III designs where validation or subsequent use of a predictive biomarker is of most interest.

> "Furthermore, there is a need for more rigorous methodology and improved approaches for biomarker threshold selection (i.e., classification of patients as marker-'positive' vs marker-'negative') when naturally continuous biomarkers are utilized."

Most existing biomarker-based designs utilize either a retrospective analyses of the biomarker, and/or rely on a dichotomous marker and/or previously defined marker threshold. Freidlin & Simon (2005) proposed a two-stage 'adaptive signature design', where a set of genes sufficiently predictive of treatment efficacy among patients enrolled during the first stage of a Phase III trial is subsequently used to classify the remaining patients as 'sensitive' or 'not sensitive' in the second stage [7]. This design was subsequently expanded to incorporate cross-validation [8]. Other proposed marker-based designs similarly do not affect treatment of patients' on-study, though one such design by Jiang, Freidlin & Simon (2009) does include retrospective identification of a continuous marker threshold [9]. Of those biomarker-based designs that could be considered 'adaptive' designs (i.e., allowing for interim changes or restrictions to accrual to marker-defined subpopulations), most assume that dichotomizing thresholds for marker(s) of interest have already been established [10–14]. This is true even of most Bayesian adaptive designs [13–16], such as BATTLE [13] and I-SPY2 [14], where initial stratification of patients according to dichotomous biomarker status was performed, and adaptations such as alteration of randomization probabilities, and adding and dropping of arms within a marker-based comparison were incorporated for clinical decision making. Most recently, large 'basket' or 'umbrella' trials such as the National Cancer Institute's Molecular Analysis for Therapy Choice (NCI MATCH) [17] study and the Lung Cancer Master Protocol (Lung-MAP) [18] have gained popularity, where numerous parallel sub-protocols are designed to evaluate targeted therapies in their respective molecular target populations, often across histologies.

Statistical issues, clinical relevance & logistics

In the setting of Phase I trials of targeted agents, focus has shifted from simple safety analyses and determination of the maximum tolerated dose to more complex investigations including preliminary efficacy signals in marker-based subpopulations and biomarker threshold determination as co-aims. In both Phase I and II studies, where short trial duration is often required for feasibility, a common issue is whether to use a traditional clinical endpoint (e.g., tumor response) or a biomarker-based endpoint (e.g., circulating levels in blood) as the primary endpoint for assessing targeted drug activity. While the latter endpoint type is typically faster to observe and easier to measure, clinical endpoints are more relevant to patient outcomes in the long term. Critical to the use of patient biomarkers in clinical trials, either as a per-patient screening tool prior to treatment arm assignment or as a study-wide decision tool (e.g., in interim analyses for accrual restriction or enrichment), is a reliable assay with a relatively fast turnaround time. For biomarkers that have already been validated with a specified threshold separating marker-positive from marker-negative patients, a related practical concern is prevalence (of marker-positives) in the population, as this determines the number of patients required to be screened in order to enroll a certain number of patients to a biomarker-enriched trial. Enriched trials have other inherent weaknesses, including inability to validate the biomarker (i.e., testing for a statistically significant treatment arm by marker status interaction effect), and the potential of precluding the (perhaps unexpected) finding that marker-negative patients also benefit from the study treatment [19,20]. This underscores the advantages of maintaining randomized, 'all-comers' (unselected) designs in Phase II biomarker-based trials, where randomization between the experimental targeted treatment and standard of care or placebo occurs for both marker groups, and where a formal test of the predictiveness of the biomarker (i.e., detection of a significant marker-by-treatment interaction effect) remains feasible. Indeed, even if a strong efficacy signal is identified within an enriched, single-arm targeted study (such as a cohort within NCI MATCH), this promising signal could be driven by the prognostic profile of the patients who happened to enroll more than the effect of the targeted therapy. Distinguishing a drug's intended effect from chance enrollment or cohort features requires a randomized study. Thus, the use of a randomized, unselected design in the Phase II setting is recommended, where validation of both the predictiveness (and perhaps threshold) of the biomarker and the population likely to benefit from the targeted therapy can be assessed.

Summary

Overall, the need remains for development of a flexible design paradigm that incorporates both prospective identification of biomarkers that are predictive of treatment effect and on-study validation of such markers and their thresholds, which continue to be typically

performed in separate studies in an *ad hoc* fashion. Furthermore, there is a need for more rigorous methodology and improved approaches for biomarker threshold selection (i.e., classification of patients as marker-'positive' vs marker-'negative') when naturally continuous biomarkers are utilized. In this current era of stratified medicine and targeted therapeutics, systematic evaluation and development of new design strategies, both for early phase and definitive trials, is necessary for the proper validation of tailored treatments.

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