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Review

Optimal design of trials to demonstrate the utility of genomically-guided therapy: Putting Precision Cancer Medicine to the test

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ABSTRACT

The new age of Precision Cancer Medicine, with specific biomarkers being used to direct targeted agents, generally concerns only a subset of patients within a certain histopathologically defined tumor type. This paradigm is challenged by the need to perform widespread molecular screening in certified laboratories, with results available to clinicians within reasonable timeframe. Tumor heterogeneity and clonal evolution must be considered in the decision making process. Adaptive and innovative clinical trial designs exploring predictive algorithms and reconsideration of traditional efficacy endpoints are required to rapidly translate scientific discoveries into patient care. Furthermore, international collaboration in cancer research and open discussions on the availability of investigational agents will likely redefine the drug development and approval process in the coming years.

1. Introduction

With the development and clinical use of molecularly targeted agents, it soon became clear that only selected patient populations derive benefit from such therapies. Precision Cancer Medicine (PCM) has emerged from the accumulated evidence on matching targeted agents with tumor molecular aberrations (Hoelder et al., 2012). Drugs designed to

Abbreviations: CSC, Cancer stem cell; COSMIC, Catalogue of Somatic Mutations in Cancer; CTC, Circulating tumor cell; ctDNA, Circulating tumor DNA; CRC, Colorectal cancer; DCR, Disease control rate; EMA, European Medicines Agency; FDA, Food and Drug Administration; GIST, Gastrointestinal stromal cell tumor; ICGC, International Cancer Genome Consortium; IDE, Investigational Device Exemption; NCI, National Cancer Institute; NSCLC, Non-small cell lung cancer; OS, Overall survival; PCM, Precision Cancer Medicine; PFS, Progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TCGA, The Cancer Genome Atlas; TTG, Time to tumor growth; TGR, Tumor growth rate; WIN, Worldwide Innovative Networking.

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interact with a specific target, and especially those that used predictive biomarkers, were able to produce the highest relative improvement in response rate and survival (Ocana et al., 2013). Current knowledge gathered from large-scale collaborative sequencing projects such as the Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC), in addition to publicly available resources such as the cBioPortal for Cancer Genomics and the Catalogue of Somatic Mutations in Cancer (COSMIC) have facilitated our understanding of the genetic interpatient tumor heterogeneity in multiple cancers subtypes (Dienstmann et al., 2013a).

However, recent studies have also described striking intrapatient intratumor heterogeneity and how clonal evolution under treatment pressure may represent major challenges to PCM, questioning the value of a single needle biopsy or surgical excision to accurately capture the complete genomic landscape of a patient's cancer (Bedard et al., 2013; Gerlinger et al., 2014). Moreover, with few exceptions, most druggable genomic aberrations are present only in small to moderate proportions of patients, further emphasizing multicenter collaboration in early drug development as critical for successful clinical trial enrollment. Nevertheless, we believe that the described heterogeneity in genomic profiles, in particular, applies to bystander mutations and that true tumor-driving events are usually present in the majority of subclones from the primary tumor as well as the metastatic lesions (Yap et al., 2012). Therefore, regimens that target genomic alterations with high variant frequencies are expected to provide substantial tumor responses. As clinical responses to targeted agents are consistently abrogated by the development of drug resistance, we see repeated tumor biopsies of progressing lesions and/or characterization of circulating markers (tumor cells, tumor DNA) as a key component of patient's care, allowing identification of mechanisms of resistance and potentially guiding alternative treatment options with investigational agents (Dienstmann et al., 2013a). Clinical trial designs for cancer diagnostics and therapeutics must take into consideration these rate-limiting steps in order to efficiently and dynamically incorporate genomic data and assess the value of matching profiled patients to specific interventions or targeted therapies. Here, we discuss some of the challenges to rapidly translate scientific discoveries to effective drug development programs and present clinical trial frameworks to test PCM with novel efficacy endpoints. Of note, our objective is to present key concepts on this topic, knowing that most innovative trial designs in fact combine these ideas and take advantage of adaptive flexible models for successful proof-of-concept.

2. Biomarker – drug co-development

Clinical trial design in the era of PCM is dictated by the type of biomarker being testing or developed (Yap et al., 2010). Predictive biomarkers inform the investigator of potential anti-tumor activity of a given therapy. Prognostic biomarkers provide information on the risk of relapse, disease progression or death. Pharmacogenomic biomarkers inform how patients respond to a drug with respect to toxicity or efficacy. Analytical validity, clinical validity and clinical utility of biomarkers need to be established during the development process. Analytical validation means confirming that the test measures with adequate sensitivity and specificity what it claims to measure. Clinical validity of a biomarker refers to how well the test works in identifying patients who will or will not respond or present toxicity to a given therapy. Finally, clinical utility means that measuring the biomarker and using it for decision-making is beneficial to patients relative to the standard of care (Simon and Roychowdhury, 2013).

Co-development of biomarkers and drugs is essential for the success of genomically-guided therapies, but this strategy raises many technical and sometimes ethical issues. First, the main objectives of the trial are not only to assess the safety and efficacy of the drug, but also to investigate the performance of the diagnostic in that specific therapeutic context. Therefore, timing and alignment of the development processes, which rely on a coordinated preclinical assessment of potential biomarkers, are crucial steps for effective clinical translation. For example, this knowledge guides the decision of whether to recruit marker-negative patients (i.e., those that are not expected to benefit from the drug) in the trial. In addition to robust and validated diagnostic assays, the pharmacological properties of the drug should be assessed before clinical testing. These include pharmacokinetics/pharmacodynamics modeling, definition of readouts of pathway inhibition and the most appropriate drug scheduling for achievement of biological effects. Importantly, specific genomic variants that are expected to predict sensitivity should be functionally validated. For non-hotspot gene alterations it may be difficult to know whether they are involved in deregulating a particular pathway and what is the potency of the drug in this context. Systems biology and experimental models relating genomic events to drug effectiveness are needed before variants of unproven biological significance are utilized for clinical decision-making regarding therapies. Of note, even when the diagnostic assay is validated, the gene alteration is a known driver event in a particular tumor type and a potent selective drug is available, there is no guarantee of success in a different context – the higher efficacy of vemurafenib and dabrafenib in $BRAF^{V600E}$ melanoma as compared to colorectal cancer (CRC) is a clear example (Dienstmann et al., 2013a).

The turnaround time for results of biomarker tests, particularly clinical next-generation sequencing, is an important consideration for patients undergoing molecular profiling, especially in the metastatic setting when treatment decisions have to be made in a short timeframe. As an alternative to the traditional approach of centralized biomarker analysis just before considering the inclusion of the patient in a trial, we favor the alternative strategy of local prescreening at academic institutions while patients are still receiving standard treatment for advanced disease. This approach is time and tissue saving, increasing the chances of patient recruitment in early clinical trials, although the financial burden of prescreening tests is transferred from trial sponsors to health care providers (Rodon et al., 2012). All these issues have to be taken into consideration during the design of clinical trials that incorporate biomarkers.