ACCELERATING DRUG DISCOVERY AND DEVELOPMENT USING GENOMICS

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Despite the continuing advancements in the treatment of cancer and the introduction of new therapies, responses still vary from patient to patient. In many cases, this variation remains unexplained, making it difficult to predict who will respond. For instance, immunotherapies targeting cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and the PD-1 ligand (PD-L1) result in favorable responses in subsets of patients among considerable numbers of non-responders, highlighting the need for predictive biomarkers. Specific molecular characteristics are also crucial for identifying patients likely to respond to treatment with small molecule inhibitors, such as alectinib and crizotinib in ALK-positive non-small cell lung cancer (NSCLC), or osimertinib in EGFR T790M positive NSCLC.

The response of a tumor to a therapy, including immunotherapies, depends on a number of individual factors such as the expression of proteins on the tumor cells, the tumor microenvironment, tumor mutational burden (TMB), and the production of neo-antigens, which arise as a result of tumor-specific mutations. Genomics-based biomarkers that predict the response of specific therapies to patient-specific tumor variations are not easy to find: not only does the right biomarker have to be identified, but the therapy in question also has to show clinical benefit. Furthermore, there is pressure to identify predictive biomarkers by the end of Phase I studies to select the correct patients to enroll in subsequent phases.

Despite these challenges, finding the right biomarkers can reduce development time, accelerate failure of unsafe or inactive compounds, and reduce average development costs for approved compounds. Ultimately, predictive biomarkers can lead to better outcomes for cancer patients by identifying those who will respond to a particular therapy, avoiding unnecessary treatment of those who will not and also lowering treatment costs.

This white paper discusses studies investigating predictive biomarkers for clinical response to immunotherapies targeting PD-1/PD-L1 and the use of biomarkers identified in pre-clinical studies to accelerate development of small molecule inhibitors of the fibroblast growth factor (FGF)/FGF receptor (FGFR). The potential of next-generation sequencing (NGS) for predicting tumor neo-antigens that can be targeted using immunotherapy is also explored.
Predicting Clinical Response to PD-1 Checkpoint Inhibition

PD-1 and its ligands, PD-L1 and PD-L2, contribute to the suppression of T cell function and restriction of tumor cell killing. PD-1 is found in many cell types, and high PD-1 expression has been associated with poor prognosis in a number of cancer types, including NSCLC, malignant melanoma and colorectal cancer (CRC). Inhibition of the interaction between PD-1 and its ligands has been shown to result in anti-tumor activity, and antibodies directed against both PD-1 and PD-L1 have been developed for clinical applications.

The extent of tumor neo-antigenic burden has been linked to PD-1/PD-L1 clinical response, but the challenges associated with neo-antigen discovery have resulted in a more intense focus on efficiently stratifying patients by other methods.

With the understanding that TMB impacts response to immunotherapies, a recent study by Chalmers et al. aimed to characterize the distribution of TMB and the subset of patients with high TMB in a number of different cancers using comprehensive genomic profiling (CGP). The group analyzed 100,000 patient genomes, 62,150 of which were assessed for both TMB and microsatellite instability (MSI). Of this subset of patients, 4,328 had high TMB and 699 had both MSI and high TMB. Although MSI generally occurred as a subset of TMB (Figure 1), the co-occurrence of the two phenotypes was highly dependent on cancer type: in gastrointestinal cancers, MSI and TMB almost always co-occurred. In addition, Chalmers et al. found that the majority of patients with MSI also had high TMB. The study concluded that CGP is an accurate and cost-effective method of assessing whole exome mutational burden, which identified many cancer types that might benefit from immunotherapy.

![Figure 1. The relationship between tumor mutational burden and microsatellite instability in 62,150 patients samples from various types of cancer](image-url)
Complementing these results, George et al., reported that the number of patients with metastatic CRC who could potentially benefit from anti-PD-1/anti-PD-L1 therapy positively correlated with TMB. Importantly, the study assessed MSI and TMB, as opposed to MSI assessment alone: almost a quarter of patients without MSI had high TMB, but these patients would remain unidentified using only MSI assessment.5

**Predicting Clinical Response to FGF/FGFR Signaling Inhibition**

Abnormal FGF/FGFR signaling has been shown to play a role in tumor cell growth, survival, migration and angiogenesis. FGFR-activating mutations, gene amplifications and translocations have been found in different cancers,8 such as breast, bladder and gastric, making FGFR an attractive target for biomarker studies.

One approach to identify pharmacodynamic and predictive biomarkers in this pathway is exemplified by a study from Perera and colleagues.9 This group screened a large number of cancer cell lines with two small-molecule FGFR inhibitors, erdafitinib (JNJ-42756493) and a related compound, JNJ-42541707, to identify those cell lines that were sensitive to the compounds. The cancer cell lines used included those exhibiting gene amplifications, deletions, mutations or overexpression, or biomarker pathway mutations or overexpression. Perera et al. studied the molecular characteristics of the cell lines and observed that FGFR1, 2 and 4 overexpression and FGFR1 and 2 amplifications predict sensitivity to the small-molecule FGFR inhibitors, while KRAS and BRAF mutations and RAS/RAF pathway mutations predict resistance (Figure 2).9

![Figure 2. FGFR1, 2 and 4 overexpression predict sensitivity to JNJ-42541707](image)

*Figure 2. FGFR1, 2 and 4 overexpression predict sensitivity to JNJ-42541707*
Following this study, FGFR1 and 2 amplifications, and other FGF/FGFR aberrations, were associated with clinical responses to erdafitinib. In a Phase I dose-escalation study in patients with advanced solid tumors, erdafitinib achieved clinical responses, demonstrated pharmacodynamic biomarker activity and had a manageable safety profile. Of a total 59 evaluable patients in the study, 23 harbored FGFR1–4 or FGF3/4 amplifications, mutations or translocations that are predicted to constitutively activate the FGF/FGFR signaling pathway. Supporting the findings of the genomics study performed by Perera et al. detailed above, no responses were observed in 36 patients with unknown or no known FGFR alterations.⁸

Interestingly, not all the genomic aberrations responded equally to erdafitinib; a patient with an FGFR3 translocation had a prolonged and deep response, which enticed the investigators back into the laboratory to reinvestigate the effect of inhibition with erdafitinib on genetic translocation. They observed that cells overexpressing several of the translocations were very sensitive to erdafitinib.¹⁰ Further clinical studies are being carried out to tease apart the response of patients with each of the aberrations to the FGFR inhibitor. Results from these experiments and the first clinical trial enabled enrollment of biomarker-selected patients with metastatic or unresectable urothelial cancer harboring FGFR gene alterations in a Phase II trial of erdafitinib.¹¹

The Future of Genomics in Drug Discovery and Development

A large percentage of the mutations found in tumor cells are not shared across patient populations and are therefore considered to be patient-specific.¹² Development of personalized immunotherapies targeting specific neo-antigens has been largely restricted by the cost and limitations of techniques available, along with a lack of understanding surrounding the nature of individual neo-antigens. However, recent proof of concept studies show that neo-antigens can be safely and rapidly identified for potential clinical use.¹³,¹⁴

Owing to the advancements in precision medicine, NGS, a high-throughput sequencing technology, is now a highly effective and accessible method of capturing a large amount of genetic information. NGS can be used to identify appropriate therapies already clinically available, by directing treatment decisions based on the presence or absence of genetic features that predict clinical response to therapy. Several companies are now offering such services directly to clinicians.

One can envision using NGS of a patient’s tumor to identify neo-antigens to make new compounds so the individual immune system can recognize and target the tumor for destruction. Concurrently, a bespoke blood-based test could be developed to screen for those specific mutations to monitor the efficacy of the compound, alerting the physician if treatment becomes ineffective to enable a rapid medication switch.

Despite current knowledge and technologies driving advancements in the field of oncology, and specifically immunotherapy, further insights into the functionality of cancer can be gained from integrating data from several approaches. Building on their expertise in RNA, exome and whole genome sequencing, Covance is seeking to combine these tools with others such as mass spectrometry (informing on the proteomics of cancer) to further identify and validate patient-specific neo-antigens presented on the surface of tumor cells to be determined and evaluated as biomarkers.¹⁵ Harnessing the power of biomarkers will reduce the time it takes for therapies to reach the patients most likely to benefit.
At Covance, we have formed partnerships with leading cancer centers and academic institutions, and can support complex drug development challenges with a variety of technologies, including NGS. Using NGS, we can characterize specific mutations, overall mutational burden and potentially patient-specific neo-antigens that may serve as a target for individualized immunotherapies on a shorter timescale than has been previously possible.

References