Accelerate the Development of Highly Effective and Safe Anti-Cancer Agents in the Era of Precision Medicine

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Over the past 5 years, there has been an explosion in the pace of drug discovery, development, and approval of novel molecularly targeted therapies, immunotherapies, and diagnostics in oncology. To provide a better resource for expert advice, the FDA Office of Hematology and Oncology (OHOP) was recently restructured to reflect disease-specific offices that align more closely with academic medical centers. In addition, the FDA Scientific Liaison Program was recently launched to increase outreach to key stakeholders, including those from government, patient groups, and academia.

Drug approval pathways are also evolving to reflect changes in clinical research. Traditional approval pathways are based on improvement in a direct measure of clinical benefit: longer life, better life, or established surrogate. By comparison, accelerated approval pathways are based on improvements in surrogate endpoints such as overall response rate (ORR) and progression-free survival (PFS), which reasonably predict clinical benefit over available therapy. Accelerated pathways launched in 1992, during the human immunodeficiency virus (HIV) crisis, when viral load was used as a surrogate endpoint of clinical efficacy. At present, accelerated approval pathways are used frequently to facilitate the approval of new therapies in oncology. Post-marketing studies are needed to confirm the clinical benefit in the real-world practice setting.

**Breakthrough Therapies**

In 2012, the FDA established the ‘breakthrough therapy’ designation for drugs that show a substantial improvement over available therapy, based on preliminary clinical evidence, for serious life-threatening diseases. To date, approximately 40% of breakthrough therapy requests have been for oncology products, and one-third of these have been granted. Of 9 new molecular agents approved for oncology indications in 2014, 5 were designated as breakthrough therapies. The pace of breakthrough therapy designations in oncology has continued throughout 2015.

Examples of breakthrough therapy designations that were granted and subsequently approved in non-small cell lung cancer (NSCLC):

- Ceritinib for crizotinib-refractory ALK-positive NSCLC, based on data from an expansion cohort in phase I
- Pembrolizumab for PDL1-positive second-line NSCLC, based on data from an expansion cohort “validation set” in phase I
- Nivolumab for non-squamous NSCLC, following a 3.5-month review

The breakthrough therapy designation has ushered in a new spirit of “all hands on deck,” aligning key FDA review teams comprised of clinical, statistics, manufacturing, pharmacology, and toxicology experts to prioritize their review of potentially transformative therapies. The new designation has also optimized communications between the FDA and drug manufacturers. However, the breakthrough therapy designation has also given rise to many questions: What is the ideal threshold for granting a breakthrough therapy designation? What constitutes ‘available’ therapy? How late in the drug development process is too late for a breakthrough therapy designation request? On what basis should the FDA rescind a breakthrough therapy? Answering these questions will be an ongoing challenge for the FDA and drug manufacturers.

**Next-Generation Oncology Trials**

Another recent shift in oncology clinical trials involves a move away from larger trials enrolling all-comers toward trials focused on a smaller enriched patient population, such as patients with ALK-mutated NSCLC. However, as the prevalence of desired molecular signatures (e.g., driver oncogene mutations) becomes lower, better screening approaches will be needed to identify potential treatment candidates.

Large trials employing master protocols are also emerging. The master ‘umbrella’ protocol is designed to evaluate the impact of different
drugs on different mutations in a single type of cancer. For instance, the recent BATTLE-1 and BATTLE-2 trials employed an umbrella protocol in lung cancer, as did the I-SPY2 trial in breast cancer.\textsuperscript{1,2} By comparison, the master ‘basket’ protocol is designed to evaluate the effect of one or more drugs on a single mutation in a variety of cancer types. Recent ‘basket’ examples include imatinib trials, trials of BRAF-mutated cancers, and the National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) study.\textsuperscript{3}

Another emerging model for oncology clinical trials involves novel public-private partnerships. The Lung Master Protocol (Lung-MAP study) trial is a collaboration between the FDA, NCI, National Institutes of Health (NIH), and the Friends of Cancer Research.\textsuperscript{4} Patients with squamous NSCLC undergo broad biomarker screening and, based on their individual molecular profiles (e.g., PI3K, CDK4/6, FGFR), are assigned to different treatment cohorts. With the approval of new therapies and discontinued development of others, the Lung-MAP protocol has been modified to reflect best practices in NSCLC treatment.

In the future, master protocols may incorporate more comprehensive genomic and proteomic profiling techniques and increasingly complex drug combinations. Additional guidance from the FDA, institutional review boards, and drug safety monitoring boards will be needed to shape best practices for protocol implementation.

**Evolving Companion Diagnostic Paradigm**

‘Companion diagnostics’ describes tests that are essential for safe and effective drug use. At present, the FDA lists 22 pairs of drugs and companion diagnostics approved in oncology. As an example, pembrolizumab was recently approved with a companion diagnostic that identifies patients with PD-L1-positive NSCLC. The PD-L1 companion diagnostic is required for pembrolizumab use as part of the drug indication. By comparison, ‘complementary diagnostics’ describe non-essential tests that may be useful to identify patients who are more or less likely to benefit from specific therapies. As an example, nivolumab was also recently approved for the treatment of patients with advanced NSCLC, but with no specific PD-L1 eligibility requirement and without the requirement of a companion diagnostic. However, some evidence suggests that patients with PD-L1 overexpression will achieve a better response to nivolumab treatment.

**Novel Endpoints**

Traditional oncology endpoints have a range of advantages and limitations (Table 1). A recent meta-analysis of 14 trials of advanced NSCLC therapies showed a strong correlation between ORR and PFS, but found no association between ORR and OS or between PFS and OS.\textsuperscript{5} These findings highlight the challenges of measuring the benefit of therapy in settings with high crossover rates and longer survival after progression. New approaches are emerging to evaluate the potential clinical benefit of investigational therapies. Waterfall plots of response, swimmer plots of treatment duration, and spider plots of changes in tumor burden are examples of emerging tools designed to capture response metrics in oncology trials.

**Summary**

Through better understanding of the underlying pathogenesis of malignancy, there have been revolutions in the rational development of therapies manipulating key pathways for the preservation of oncogenesis. Novel innovations and programs such as breakthrough therapy designation and accelerated drug approval pathways are increasingly utilized to expedite access of highly safe and effective therapies to patients. As the drug-development paradigm shifts to a more patient-centered model, looming challenges in the continued development of oncology drugs and diagnostics remain.

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### Table 1. Characteristics of Traditional Oncology Endpoints

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<tr>
<th>Overall Response Rate</th>
<th>Progression-Free Survival</th>
<th>Overall Survival</th>
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<tr>
<td>• Quick to measure with fewer patients</td>
<td>• Accounts for stable disease</td>
<td>• Objective</td>
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<tr>
<td>• Can be assessed in single-arm trials</td>
<td>• Potentially limited by ascertainment bias</td>
<td>• Requires longer studies with longer follow-up</td>
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<tr>
<td>• Binary endpoint (yes/no)</td>
<td>• Magnitude is important</td>
<td>• Confounded by crossover and subsequent therapies</td>
</tr>
<tr>
<td>• Does not capture stable disease</td>
<td>• Cannot be assessed in single-arm trials</td>
<td>• Cannot be assessed in single-arm trials</td>
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**References**


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