Pre-ESMO POV: Efficient Clinical Trial and Approval Strategies in Oncology

A PRECISION PERSPECTIVE

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A Pre-ESMO POV: Efficient Clinical Trial and Approval Strategies in Oncology

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Background

As the oncology community heads to the European Society of Medical Oncology (ESMO) conference in Munich, the oncology development advancements and novel approvals we've seen in just a year's time are undoubtedly top-of-mind. Innovative science has brought great opportunity to the highly complex hematologic treatment arena; it has also created the need for sophisticated translation and clinical strategies to navigate/streamline the time to market.

The unprecedented acceleration in oncology research and development, coupled with the expansion of expedited approval programs, has led to a significant increase in the number of novel oncology drug approvals. The approval of the first immune checkpoint inhibitor, ipilimumab (Yervoy®), in 2011 represented a turning point in cancer therapy.[1] Rather than acting directly on tumours to inhibit or destroy them, immune checkpoint inhibitors act on the key molecules that govern the complex interactions between tumours and the immune system. Their success has revitalised interest in immunotherapy as an evolving treatment modality using immunotherapeutics designed to overcome the mechanisms exploited by tumours to evade immune destruction.

In August 2017, the accelerated approval of tisagenlecleucel (Kymriah™), a chimeric antigen receptor (CAR) T-cell therapy, changed the landscape again.[2] This paradigm-shifting immunocellular therapy became the first therapy based on *in vitro* gene transfer to reach the market in relapsed pediatric acute lymphocytic leukemia. More recently, the US Food and Drug Administration (FDA) cleared a second CAR T-cell therapy, axicabtagene ciloleucel (Yescarta™), for patients with large B-cell lymphomas whose cancer has progressed after receiving at least 2 prior treatment regimens.[3]

Because they are engineered from a patient's own T cells, CAR T-cell therapies are very expensive to develop and deliver. According to the most recent study released by the Tufts Center for the Study of

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[1] National Cancer Institute. FDA approval for ipilimumab. https://www.cancer.gov/about-cancer/treatment/drugs/fda-ipilimumab. Updated July 3, 2013. Accessed November 16, 2017.
[2] US Food and Drug Administration. FDA approval brings first gene therapy to the United States. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm. Published August 30, 2017. Accessed November 16, 2017.
[3] US Food and Drug Administration. FDA approved CAR T-cell therapy to treat adults with certain types of large B-cell lymphoma. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm581216.htm. Published October 18, 2017. Accessed November 16, 2017.

Drug Development, the average cost to develop and gain marketing approval for a new drug is nearly $2.6 billion, based on[4]:

- Estimated average out-of-pocket costs: $1.395 billion
- Time costs (or expected returns that investors forego while a drug is in development): $1.163 billion
- Expenses incurred for product development efforts that did not reach fruition: $42 million

(Note: Factors that contribute to higher out-of-pocket costs include increased clinical trial complexity, larger clinical trial sizes, changes in protocol design, and testing on comparator drugs. The median development time was nearly a decade.)

With the high cost and lengthy time to market, and the unique challenges that come with developing precision medicines, small and mid-sized biotech and pharmaceutical companies need to consider new, more efficient approaches to drug development. Working with a multifaceted team of basic scientists, clinical trial development expert oncologists and hematologists, biostatisticians, and clinical trial operations experts with experience in optimising worldwide trial execution can mean the difference between success and starting over from scratch.

Strategies for Efficient Clinical Trials and Approvals

Over the years, we have learned that preclinical planning experience, up-to-date clinical design knowledge, and deep trial performance expertise can be combined for efficient and faster market approval, and help reduce development costs. But, what does this mean? As a prologue to our upcoming quarterly newsletter on this topic, here are 4 key factors to consider in the accelerated molecule-to-market approach.

1. **Identify the right patients.**
   Selecting the patients most likely to respond to an investigative therapy enables smaller study populations and saves time and money. Measuring the right patient population improves the likelihood of achieving statistically significant response rates in a shorter time frame. Adaptive trial designs enable one or more aspects of the study to be modified as the trial progresses. By combining clinical outcome and biomarker assessments, drug developers gain improved early insight into the effect of a therapeutic, and can move quickly from proof-of-concept to potential approval with a much smaller number of participants compared with conventional study designs.

2. **Use biomarkers.**
   There is substantial momentum behind the prudent use of biomarkers. From 2006 to 2015, drug

[4] DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. *J Health* Econ. 2016;47:20-33.

applications with biomarkers demonstrated a higher likelihood of approval across all phases of development.[5] Of the 39 oncology drugs approved by the FDA from 2011 to 2015, 15 included biomarker evidence.[6] Incorporating biomarker strategies into clinical trial design enables researchers to identify responders, optimise doses, and analyze results for further study, facilitating regulatory review and efficiently maximising return on investment. It is also important to consider the downstream regulatory implications of a biomarker that could be used clinically to select and follow patients receiving these newer therapies.

3. **Focus on a manageable safety profile.**
   Safety is critical for both approval and efficient movement forward of the experimental therapy to demonstration of efficacy. Many of the immune therapies that have been approved or are near approval have well-defined and manageable toxicities that have not hindered their development. Clinical manageability is the key to defining the safety profile. If safety issues cannot be managed in the clinic, special attention and diligence are required to develop methods that allow the safe administration of the product under development. One example of this approach is the frequent use of Actemra® (tocilizumab) anti-IL-6 therapy to treat the cytokine release syndrome often associated with CAR T-cell therapy.[7]

   With novel therapies, including biologics and immune therapies, clinical management is often better approached with a focus on the optimal biologic dose (OBD) rather than the maximum tolerated dose (MTD) commonly used in the past with small molecules. Defining an OBD, which is often well below the MTD, is a much better strategy for most novel therapies than pushing to toxicity. There have been many cases where OBD demonstrated safety and efficacy, while higher doses have shown higher toxicity and, sometimes, lower efficacy.

4. **Maximise the potential to demonstrate efficacy.**
   Two elements must be synchronised to demonstrate efficacy. First, the therapeutic product must be able to perform the necessary physiologic tasks as designed. The development process must be carefully designed and executed to minimise inadvertent or any other risks of failure. The data at the end of the study is the currency that leads to approval, acceptance, and use. In today's regulatory environment, attaining approval requires much more complex planning to minimise the risk of failure and maximise the accumulated data to support safety and efficacy. We have seen promising products shelved as failures due to risks built into the study design during development.

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[5] BIO, Biomedtracker, Amplion. Clinical development success rates 2006-2015. https://www.bio.org/bio-industry-analysis-published-reports. Accessed November 16, 2017.
[6] Asabere A, Bastian A. A decade of oncology drug development: FDA-approved drug trends between 2005 and 2015. *J Clin Oncol*. 2015;33(Suppl 15):e17788.
[7] Bonifant CL, Jackson HJ, Brentjens RJ, Curran KJ. Toxicity and management in CAR-T cell therapy. *Mol Ther Oncolytics*. 2016;3:16011.

Such failures can now be recognised and mitigated. Efficient thinking and planning must begin during the candidate selection process and continue throughout the development program.

Fundamentally, drug developers must demonstrate the essential elements of manageable safety and efficacy that outweigh toxicity, proving a positive risk-to-benefit ratio for the selected population of patients to be treated. This sounds simple, but it requires a lot of profound planning, execution, and flexibility.

Our upcoming newsletter series will expand on each of these 4 factors. All include a common thread: collaboration between scientists and clinical operations teams.

Real-world Examples

A closer look at the recent approvals of tisagenlecleucel and axicabtagene ciloleucel, as well as the approval of venetoclax (Venclexta™) for patients with chronic lymphocytic leukemia, reveals that the strategies we've outlined work not only in principle, but in practice.

Tisagenlecleucel was granted Breakthrough Therapy Designation by the FDA in April 2017 based on data from the JULIET study; it received marketing approval in August 2017 based on the results of the pivotal open-label, multicenter, single-arm phase 2 ELIANA trial, the first pediatric global CAR T-cell therapy registration trial. Notably, approval was based on a study of only 63 pediatric patients with relapsed/refractory acute lymphoblastic leukemia (ALL). Results showed 83 percent of patients who received treatment with tisagenlecleucel achieved complete remission (CR) or CR with incomplete blood count recovery (CRi) within 3 months of infusion. In addition, no minimal residual disease (MRD) was common.[8] Even with significant but manageable toxicity and a small number of subjects, this overall response rate was compelling enough to lead to accelerated approval.

Axicabtagene ciloleucel received approval approximately 2 years from initiation of the company's phase 1 trial, ZUMA-1. A closer look at ZUMA-1 reveals that this phase 1 study led directly into the phase 2 expansion trial used to support approval. For axicabtagene ciloleucel, investigator INDs provided the work that allowed cytokine release syndrome to become manageable. In addition, the company performed a thorough assessment of the competitive landscape to identify a study population with a high potential for success. Ultimately, the population studied was adult patients with relapsed/refractory large B-cell lymphoma after 2 or more lines of systemic therapy. These planning and

[8] Novartis. Novartis receives first ever FDA approval for a CAR-T cell therapy, Kymriah™ (CTL019), for children and young adults with B-cell ALL that is refractory or has relapsed at least twice. https://www.novartis.com/news/media-releases/novartis-receives-first-ever-fda-approval-car-t-cell-therapy-kymriahtm-ctl019. Published August 30, 2017. Accessed November 16, 2017.

time-saving processes efficiently moved the product to approval in October 2017 based on 101 subjects treated and a 72 percent objective response rate.[9]

Venetoclax was approved in April 2016 for the treatment of patients with CLL who have a 17p deletion and who have been treated with at least 1 prior therapy. Approval was based on a subset cohort of 31 subjects with 17p deletion among the 106 total patients enrolled. Within this subset, there was a 71 percent overall response rate, again underscoring that approval is possible with a single-arm study where safety is managed and efficacy is demonstrated in a small population.[10] Notably, venetoclax has since received multiple Breakthrough Therapy Designations for additional indications in CLL and AML.

Lessons Learned

In the age of immunotherapy and other novel therapies, oncology clinical trials are becoming more complicated and complex than ever. What we have learned from the examples of tisagenlecleucel, axicabtagene ciloleucel, and venetoclax, combined with our extensive clinical trial experience, is that rapid development and accelerated approval can be accomplished in a short time frame. To do this, you need effective and safe/manageable experimental products; a well-thought-out development plan that considers populations, biomarkers, and design; and, most important, oncology expert execution at the ground level for the end points of the study.

Staying Ahead of the Curve

Today, biotech and pharmaceutical organisations are leveraging genomic insights and enhanced computing power to develop precision oncology medicines. These companies are bringing together excellent scientific minds, data, and experience to put forth specific, targeted, and exciting new products that can significantly improve the lives of patients with cancer.

Just as patients with cancer require multidisciplinary teams to coordinate and deliver their care, oncology therapeutic development requires cross-functional collaboration of experts in biomarkers, modern clinical trial design, and study execution to carve out a rapid and efficient path to market. Innovative science has brought great opportunity to the cancer treatment world, but it has also created the need for complex protocols. Precision for Medicine, Oncology and Rare Disease was deliberately and strategically designed to implement innovative science through expert operations. By bringing translational and clinical teams together under one roof, we have assembled an experienced group of professionals who work together to ensure that good, novel science is expertly executed.

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[9] Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374:311-322.

[10] US Food and Drug Administration. FDA approves a new drug for chronic lymphocytic leukemia in patients with a specific chromosomal abnormality. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm495253.htm. Published April 11, 2016. Accessed November 16, 2017.

At Precision for Medicine, Oncology and Rare Disease, our mission is to accelerate the development of oncology therapeutics from molecule to market. Our approach is holistic. We understand not only what is needed from a biomarker or sample collection standpoint, but also what is feasible and how to best communicate with stakeholders and support sites with the logistics of clinical trial execution. Oncology experience matters, and we put our experience to work for you with the goal of accelerating the development of medicines that will transform the lives of patients.

Why We Go to ESMO

In today's rapidly evolving therapeutic landscape, attending meetings such as ESMO matters more than ever. ESMO creates opportunities for us to talk and collaborate with pioneers who are on the forefront of drug development in hematologic malignancies. These enable us to continue to advance effective therapeutic development approaches that help bring precision medicines to market with previously inconceivable speed and efficiency.

We look forward to discussing these new approaches with any company interested in efficient drug development that moves innovative science through market approval. We welcome the opportunity to help you bring the best care to patients with cancer—sooner. Come visit us at Booth 162 or email us at info-ord@precisionformedicine.com to arrange a time that works best for you.

About Precision for Medicine, Oncology and Rare Disease

Precision for Medicine, Oncology and Rare Disease is exclusively devoted to oncology innovation. As the first precision medicine research organisation specifically dedicated to oncology research, Precision for Medicine, Oncology and Rare Disease integrates novel biomarker approaches with excellence in oncology clinical trial design and execution. From preclinical assay development and patient stratification to "first patient in" and all the way through registration, we take a holistic approach to drug development. Precision for Medicine, Oncology and Rare Disease takes novel science and optimises the research to support it, reducing risk and optimising the value of new cancer treatments.

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