Oncology 2020: a drug development and approval paradigm

A dramatic increase in our knowledge of the molecular underpinnings of cancer is finally translating into the discovery and development of important new treatment approaches and drugs. Yet cancer remains and will continue to be, for the foreseeable future, one of the highest unmet medical needs. Regulatory authorities, especially in the Western world, have begun to show an admirable flexibility in considering new and creative ways of assessing the suitability of novel cancer drugs for marketing approval. This has led to a significant increase in the speed of approval of new drugs over the past 3–4 years; yet more is needed to adapt to the changing realities of oncology.

limitations of the current paradigm of drug approval

Current regulatory framework for approval of new drugs evolved in the middle of the 20th century, largely as a result of high-profile safety issues, e.g. congenital malformations induced by thalidomide. Inevitably, and appropriately, this led to a safety-first mindset for the assessment of new drugs. The traditional drug development paradigm has relied on a relatively standardized battery (especially for safety) of preclinical tests followed by clearly defined and generally understood sequential clinical development steps with increase in the size of the trials and duration of treatment associated with discrete regulatory milestones, leading to approval (Figure 1). Once approved, a series of well-defined, discrete additional clinical trials are carried out to expand the label indication. In recent years, as molecularly targeted therapies have begun to come into clinical use, a corresponding pathway for companion diagnostics has been pursued.

The limitations of such a paradigm for enabling expeditious approval of promising drugs for life-threatening diseases are obvious. Over the last 25 years, many attempts have been made to tweak the process, especially to meet the needs of oncology. Examples of these include, among others, use of end points other than overall survival (e.g. disease-free survival, progression-free survival) for approval. In addition, conditional approval (EU) and accelerated approval (US) mechanisms were introduced.

Industry has routinely sought to get accelerated approval based on some level of response rate (historically ~20%; in recent years higher) in patients with a defined histological tumor type who have failed standard therapy for their disease. A sample size of 100–150 patients has often been accepted. A similar strategy to obtain conditional approval in the EU has been successful as well, albeit much less frequently. This is typically followed by multyear confirmatory trials to convert to full approval based on more traditional end points. This strategy significantly reduced the time to first approval for a number of important drugs in the 1990s and 2000s. However, over the years, this paradigm has increasingly become an exercise in intellectual creativity to define a patient population as narrowly as necessary to gain regulatory acceptance of ‘failed standard therapy’ and aim to somehow cross the minimum hurdle required to gain approval. Obtaining such an approval is a major feather in the cap of those involved and typically is followed by industry attempts to get the drug as widely used as possible even before confirmatory trials have been completed. This has come under justifiable criticism.

The challenge for oncology drug development today is quite different and much more substantial and requires a much more ‘science-focused’ approach.

evolution of personalized medicine in oncology

Consider the following three scenarios:

Scenario I: drug A—a small molecule; known target (an oncogenic tyrosine kinase); 30/33 patients treated above a threshold dose respond in phase I, including several complete responses; median duration of response not reached at 6 months; no unusual toxicity other than known mechanism-related mild–moderate reversible side effects.

Scenario II: drug B—a multitargeted drug; response rate—20% among 100 relapse/refractory patients in a defined histologic tumor type; median duration of response 4 months; overall safety database ~300 patients.

Scenario III: drug C—an injectable antiproliferative drug; conventional clinical development leading to a randomized phase III trial; OS benefit of 2–3 months in a randomized phase III study against the standard of care (best supportive care or active comparator).

In the experience of most industry physicians and academics involved in drug development, drug C by and large would have very little difficulty in getting full approval (e.g. nab-paclitaxel for pancreatic cancer, regorafenib for colorectal cancer), whereas drug B could get accelerated approval under many circumstances. In contrast, drug A would not get approved under most circumstances with the dataset described above even though it is obvious from these data that it is far more interesting and promising than the other two drugs. It would take substantially more clinical experience before patients could get widespread access to this drug. I suspect that, given a choice, most practicing oncologists would choose drug A over drug B or C if they themselves had a diagnosis of cancer.
In case the reader is wondering, drug A in the example above is imatinib for chronic myelogenous leukemia at the end of the first phase I trial! Increasingly, and fortunately, such instances are becoming more common, for example, drugs such as AZD9291 for T790 mutant NSCLC. Of course, these are simple examples that are easy to conceptualize and could easily be put into the category of a ‘no-brainer’. The emerging landscape of targeted oncology therapeutics is considerably more complex because the biomarker–response relationships are not as straightforward. At a conceptual level, we can posit that each patient’s cancer is a unique disease and, in fact, often consists of more than one molecular disease subtype, each of which can evolve further during the natural history of the tumor as well as during adaptation to anti-cancer treatment. Of course, such an extreme view would paralyze the development of new drugs. A more pragmatic way to deal with this view of tumors is that each tumor at a given point in time consists of a finite number of genetic, epigenetic and phenotypic alterations which drive its behavior in the context of tumor–stromal interactions. Targeting a subset of these through one or more targeted drugs can control the disease for a meaningful period at the end of which other drug/s may be needed to further control the disease. We have an increasing number of novel drugs and treatment modalities to target these changes. The challenge is to devise efficient, practical and economically feasible ways of testing and proving their utility. A natural corollary of such a view of the tumor biology is that each cancer type is an extremely rare disease. In fact, so rare that one may need several months or years to enroll even the 100–150 patients typically required for accelerated approval even though the exceptional efficacy and safety of the drug may be obvious after treating 10–15 patients.

**a proposed framework for novel oncology drug development**

Several years ago, I proposed a model paradigm to deal with this emerging problem. This was first presented publically at the ECCO Meeting in 2007 in a symposium entitled ‘European Oncology 2020’ [1] and subsequently at the Annual AACR meeting in 2008 in a symposium entitled ‘Targeted Therapy for Personalized Cancer Care: Matching the Economics to Evolving Science’ [2], as well as in other public and private forums with regulators.

The central philosophy behind this concept is that we need to move drug development from a series of linear, landmark events to a flexible and iterative process (Figure 2). In this new paradigm, a flexible approach is proposed for drug approval based on the drug and the intended use population. Specifically for novel targeted drugs, ‘Limited Approval’ is proposed based on limited initial clinical investigation. I purposely refrain from using phrases such as conditional approval, accelerated approval, expanded access and approval under exceptional circumstances, which already have well-defined connotations that are hard to change along with their regulatory/legal implications.

The key criteria to consider a drug for limited approval would be based on
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is not the end of investigation of the drug in that tumor type; and diagnostics.

(i) Known target with a well-defined mechanism of drug action
(ii) Ability to define a target patient population based on the known mechanism of drug action
(iii) High efficacy in the intended use population; Note: There is no specified minimum number of patients to be treated; the higher the efficacy (e.g. proportion of patients responding and the depth and durability of the response), the fewer are the number of patients needed. It is expected that the efficacy threshold will generally be higher and the patient number lower than those typically required for accelerated/conditional approval
(iv) No unusual or unexpected non-mechanism-related toxicity in the clinic
(v) Preferably supported by additional biomarker evidence, e.g. PK/PD correlations

In such an approval scenario, it is understood that initial approval is not the end of investigation of the drug in that tumor type; rather, it is just the end of the beginning. The drug would be used for carefully defined and limited groups of patients. Much greater emphasis would be placed on collecting data in the post-marketing setting to ensure that the real-life performance of the drug mimics that seen in the limited clinical exploration before drug approval. Technological innovations in electronic medical records and data mining approaches can facilitate more efficient collection and analysis of post-marketing data. Continued additional translational work, in addition to the usual response and survival data, is essential. This would include rational combinations as well as further biomarker exploration to define the most rational use of the drug. It is understood that data will evolve rapidly in the post-marketing setting; thus, a flexible approach to modification of the label is required on the part of both the sponsor and the regulators. However, this will occur in a series of iterative changes in short time frames (could be as short as every 6–12 months in the first few years) rather than discrete, large dosiers for supplemental New Drug Application, supplemental Marketing Authorization Application at intervals of years. In such a framework, the approved label of a drug would be a ‘living’ document! A formal full approval may still take several years, but in the meantime, the drug would be used more intelligently and for greater benefit. It is noteworthy that in such a model, a similar data-driven flexibility for use of biomarkers for patient selection is envisaged as it is not always possible to a priori have companion diagnostic tests available.

How can we be confident that such an approach is even feasible and will not lead to a repeat of the catastrophic mistakes of the mid-20th century? Key tenets underpinning this proposal are as follows: (i) we have a much better understanding of the targets; (ii) we have better and more targeted drugs against these targets; (iii) we have better understanding of signaling and resistance pathways leading to mechanistic biomarkers that provide greater confidence in the clinical efficacy data from limited number of patients (iv) improved preclinical testing and the targeted nature of the drugs reduce the likelihood of non-mechanism-related toxicity, and (v) limiting the scope of label to carefully defined patient populations based on biomarkers will limit the potential for negative surprises. All of these tenets have been borne out by clinical experience with a variety of targeted drugs that have been approved in the last 3–4 years. Many of these new-generation drugs, e.g. small molecules such as crizotinib and vemurafenib, and biological such as Kadcyla (ado-trastuzumab emtansine), showed compelling efficacy and safety in phase I studies. Extended phase II or III experience has not changed the profile of these drugs in any meaningful way. Of course, this does not completely eliminate the risk of negative surprises. However, this can be minimized through an active and transparent collaboration between the various stakeholders and close post-marketing activities.

For the pharmaceutical industry, there is an important trade-off in such a drug approval paradigm. The industry stands to gain substantially both in terms of the time and money required to obtain approval of a drug. However, in return for this, industry would have to make a genuine commitment to limit off-label promotion. It is quite likely that these targeted drugs may have efficacy beyond the initial use population. For example, vemurafenib may be effective in B-raf mutant colorectal cancer or lung cancer but only in combination with other synergistic drugs (synthetic lethality) and, unlike in melanoma, not as a mono-therapy. Similarly, crizotinib may be effective against ALK or ROS mutant solid tumors other than lung cancer but be ineffective against certain ALK mutations in NSCLC. This argues for a more scientific approach to label expansion/refinement rather than ‘brain-dead’ off-label marketing. The rarity of these mutations has required many years to even perform a preliminary investigation of these questions. Therefore, a flexible and iterative approach to label expansion appears to be a reasonable trade-off to accelerate such studies in the future. Such an approach can accelerate getting truly effective drugs quicker to the market while slowing down the development of me-too drugs. This will also change the behavior of the industry and lead to greater research focus on transformative drugs.

Implicit in such a paradigm is that we cannot take a one-size-fits-all approach to modern drug development. For some of the novel treatments, e.g. immuno-oncology drugs and drugs targeting tumor–stromal interactions, preclinical models are often poor predictors of efficacy and toxicity in the clinic. Similarly, for certain new modalities, e.g. CAR-T cells, where there is substantial

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**Figure 2.** Oncology 2020—integrated, continuous development of drugs and diagnostics.
uncertainty about the determinants of safety and efficacy, significant clinical experience would be required before initial approval.

It is clear that intelligent flexibility rather than rigid dogmas are essential for such a paradigm to be successful. Therefore, a close and transparent collaboration between the various stakeholders is necessary to avoid chaos. Especially relevant is the role of academic leaders and professional societies such as ESMO and ASCO. They can provide an important bridge between the regulators and industry given the considerably greater requirement for rigorous ongoing scientific scrutiny and clinical practice guidelines in such a flexible context. Although not the focus of this article, such an approach fits in very well with the emerging pay-for-performance paradigms in oncology being adopted by payers.

impact of other recent developments

Two recent developments in the United States have already started a movement in the directions envisaged in this article. The passage of Advanced Breakthrough Medicines for Patients Act is already accelerating the development of transformational drugs through more continuous dialogue between the sponsors and the FDA. The House of Representatives recently passed the 21st Century Cures Act that, among other things, is designed to create a framework for patient-focused drug development, improve tools to evaluate and advance precision medicine, and expand FDA flexibility. It encourages the FDA to consider various means, including biomarkers, to accelerate the approval of new drugs. These are important steps in the right direction. However, their eventual impact will depend on how they are implemented. In fact, resistance is already emerging even to the 21st Century Cures Act with high-profile concerns being expressed about the potential for adverse impact on patient safety [3]. In the EU, most of the debate about oncology drugs continues to center on cost. It is important for all the stakeholders in the EU to come together and enable rational acceleration of novel therapies and access to these therapies for the most appropriate patients.

In conclusion, an exciting new era of rational cancer treatments is upon us. The same knowledge expansion that is driving the search for new cancer cures is also leading to a segmentation of the oncology market that makes traditional paradigms of drug discovery, development and marketing non-sustainable. A flexible approach that is based on the evolving scientific and clinical data is essential if we are to fully realize the promise of this new age of oncology.

disclosure

KD serves on the Board of Directors and/or Scientific/Clinical Advisory Boards of a number of companies and nonprofit organizations. Present Board of Director appointments include Exosome Diagnostics (Chairman), Median Technologies (France), Advanced Accelerator Applications (France) and Autolus (UK). Previously, he served on the BoD of Algeta (acquired by Bayer), YM Biosciences (acquired by Gilead), Micromet (acquired by Amgen) and Biovex (acquired by Amgen), and Epitherapeutics (acquired by Gilead), among others.

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