

# The changing world of cancer drug development: the regulatory bodies' perspective

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**Background:** Although not a singular disease entity, advanced cancer continues to be a largely intractable disease and a high unmet medical need situation. Discovery of novel therapeutic modalities, including new drugs targeting cancer, is undoubtedly of major public health interest.

**Methods:** In this article, we discuss current trends in oncology drug development as these are ultimately reflected in regulatory drug approvals.

**Results and conclusions:** These include the shift to targeted therapies which hold the promise of personalized medicine, but also financial pressures, the call for adaptive licensing which places more emphasis on early access and post-authorization studies (patient registries, prospective interventional and observational studies) and real-life effectiveness studies, as well as the emergence of biosimilars in the oncology treatment armamentarium.

**Keywords:** Personalized medicine; molecular targeted therapy; biomarker; biosimilar pharmaceutical; drug approval

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## Introduction

There were 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis) in 2012 worldwide (1). The high mortality rate of cancer serves as a reminder of the need for more effective therapies. At the same time, cancer treatment becomes increasingly individualized and cancer as a whole is turning more and more into a collection of increasingly rarer tumors, their distinction no longer based on exclusively histological criteria. This phenomenon challenges traditional approaches of oncology drug development, especially in a financial environment that calls for prudent utilization of resources both at the level of research and development as well as the level of healthcare and clinical practice.

## From cytotoxics to targeted therapies: how far are we from truly personalized medicine?

The early development of cytotoxic drugs against cancer

was based on the understanding of cancer as a disease of exaggerated and uncontrolled cell proliferation. Cytotoxics target essential cellular functions and they are quite indiscriminate in exterminating both cancer cells and non cancer ones that display high normal proliferation rates. Their clinical utility is limited by their toxicity. The generic mechanism of action for cytotoxics made the prediction of which tumor types might respond to them very difficult, if not impossible, and necessitated a 'trial and error' approach against many different types of tumors.

The most prominent change in oncology drug development in the last 20 years has been the shift from classic cytotoxics to drugs that affect signaling pathways implicated in cancer, which belong to the so called 'targeted therapies'. A progress in the understanding of the biology of cancer revealed cell signaling pathways involving receptor- and non-receptor-tyrosine as well as intracellular serine-threonine kinases that are being hijacked in cancer in order to drive the uncontrolled proliferation, but also cell survival, metastasis, immune tolerance and other hallmarks of cancer. This progress promised to identify drug targets that are

more specific to cancer cells allowing the development of drugs with improved therapeutic index by targeted action. Currently, the majority of targeted therapies approved for the treatment of cancer are either small molecule inhibitors or monoclonal antibodies that inhibit a handful of kinases involved in cell signaling. Monoclonal antibodies have even allowed the revival of cytotoxics that never reached clinical practice in the form of antibody-drug conjugates, such as the recently approved brentuximab vedotin and trastuzumab emtansine; these conjugates employ very effective cytotoxics with toxicities preventing systemic use covalently bound to monoclonal antibodies that deliver them specifically to desirable targets and prevent their systemic toxicity. On the other hand, as our understanding of the biology of cancer goes beyond signal transduction, 'targeted therapies' in development are evolving and target different receptors, enzymes, co-factors and generally molecules purported or shown to belong to intricate cell and tissue biology networks.

Earlier kinase inhibitors, such as sunitinib and sorafenib, but also more recently approved ones, such as regorafenib, were quite unspecific, targeting multiple kinases. This resulted in not only more undesirable toxicities, but also in higher uncertainty of candidate cancers in which the inhibitor could be effective. Oncology drug development is used to such uncertainty, tackled in early phase II studies as a means to decide on attractive targets to take forward to confirmatory trials. With more selective targeted agents, development can be guided by an understanding of the underlying biology, such as the incidence of alterations in the known drug targets in different cancers, so that it can become more efficient and the target population can be more readily identified. However, contrary to the case of early cytotoxics for which tumor response has been an accepted early indicator of activity, the drug is not always causing the tumor to shrink but sometimes to be stabilized instead, so that one has to rely on randomized studies using time-to-event endpoints, such as survival and progression-free survival, which complicates the early exploratory development.

So far, these approaches have delivered some success but also a lot of failures, with high attrition rates during development reported by the pharmaceutical industry (2,3). The small size of observed benefits and substantial toxicities have often made it difficult to recommend approval in cases of promising activity, e.g., gefitinib in an unselected non-small-cell lung cancer population or cetuximab in non-small-cell lung cancer.

Yet outstanding activity from a new drug in early development in high unmet need situations with no therapeutic alternatives might obviate the need for the large confirmatory trials. For example, crizotinib was approved for use in ALK(+) non-small cell lung cancer based on the results of two early single-arm studies with response rate as primary endpoint showing responses in the area of 50-60%. One might foresee that in a not too distant future a better understanding of the underlying biology and pharmacodynamic effect will be such that early activity will be sufficient for approval in a number of high unmet need situations, the quintessential example being last-line of therapy for aggressive tumors of high biological heterogeneity.

One way of increasing the magnitude of effect from targeted drugs is through the use of predictive biomarkers which select patients most likely to respond. Such biomarkers have been most successfully used in cases where single driving factors are partially or primarily responsible for the survival and growth of the tumor, such as HER2/neu overexpression in breast cancer and the bcr-abl proto-oncogene in Philadelphia chromosome positive leukemias, respectively. Identification of such biomarkers during early development is encouraged by regulatory guidance, but it is often limited by inadequate understanding and complexity of tumor biology and by non-specificity of the drug.

More selective kinase inhibitors, such as vemurafenib, dabrafenib and crizotinib, were approved for use recently in biomarker defined populations. Unsurprisingly, these were quickly found to suffer from another well-known problem in cancer therapy: that of resistance development limiting the time that such inhibitors can remain effective. The resistance is due to the genetic instability of tumors which allows them to develop heterogeneity in the form of clones harboring mechanisms bypassing the treatment applied. Under the selective pressure of the treatment such clones prevail and the disease as a whole adapts and becomes refractory to the treatment. Mechanisms for resistance to selective kinase inhibitors are being elucidated and appear to include development of secondary mutations in the drug target, overexpression of the target, up-regulation of other upstream, downstream or parallel factors in the drug target pathway and activation of alternative pathways that compensate for the inhibition of the drug target pathway (4,5). On the other hand, in Philadelphia chromosome positive leukemias where the bcr-abl proto-oncogene rearrangement and constitutive abl activation is the driver genetic abnormality of the disease, secondary mutations

in bcr-abl are the main mechanism of resistance (50% of cases) to the less selective inhibitors of bcr-abl (imatinib, dasatinib, nilotinib) (6).

Possible solutions to the resistance issue already in development include the combination of two inhibitors targeting the same pathway, e.g., combination of dabrafenib that inhibits B-RAF with trametinib that inhibits MEK, which are two consecutive kinases in the MAP kinase signal transduction pathway. This has led to accelerated approval of an extension of the therapeutic indication for trametinib in combination with dabrafenib in the USA for patients with unresectable or metastatic melanoma that harbour a *BRAF V600E* or *V600K* mutation based on results from a small randomized, open-label phase II trial with response rate as the primary endpoint. Phase III trials with the combination are ongoing.

In the future, one hopes that by controlling the nature and timing of drug combinations targeting different pathways and mechanisms depending on the specific biology of each individual tumor, one may be able to outsmart cancer. This approach considers that each individual patient and tumor is unique and dynamic, constantly evolving in the course of the disease. Different mechanisms drive tumor progression in the course of the disease and by identifying the driving mechanisms one may use, alone or in combination as appropriate, relevant agents at the relevant point of the disease course. Importantly, the mechanisms and drug combinations are personalized for each patient and treatment modalities are not decided based on histology alone but on an understanding of the evolving molecular biology of the tumor in the course of the disease. However at this point of time, this approach is still a theoretical possibility and there are already at least three identified obstacles preventing it from being realized.

The biological obstacle stems from tumor heterogeneity and the need for repeated if not constant diagnostic interrogation of the patient and the tumor in order that the underlying biology is understood for therapeutic decisions to be made. As a result, one has to repeat the biopsy at will in order to have the tumor under constant surveillance and modify the treatment to adapt to the constantly evolving disease. The solution could come from circulating tumor cells or cell-free tumor DNA derived from easily accessible material, i.e., peripheral blood. However, the use of diagnostic methods in clinical decision-making requires validation, which is currently lacking for these specific ones.

The second obstacle lies in the need to co-develop compounds often belonging to competitor companies and

in non-conventional trials in which the treatment of each patient in the trial is individualized (7). Pharmaceutical companies have quickly come to realize the need for collaboration, but testing a multitude of drug candidates in a flexible trial design creates difficulties in achieving enough power for statistical comparisons necessary for regulatory approval. On the other hand, commercial confidentiality issues could be overcome through the use of non-industry third parties as sponsors of the trials which the owners of the drug candidates could trust to test. One could also employ the necessary adaptive trial designs in order that successful drugs or drug combinations are identified. One could hope that drugs or rather combinations with outstanding activity are identified which do not require large randomized trials to show substantial and convincing benefit. In addition, one could achieve the buy-in of academic centers and learned societies to create a network capable of recruiting patients without therapeutic alternatives and delivering the statistical power necessary to test promising drugs or drug combinations. However, what stands in the way of truly personalized treatment is such a level of understanding of tumor (and patient) biology that the need for statistical comparisons to overcome uncertainty becomes almost unnecessary; this is the third and most difficult obstacle to overcome.

Although constantly progressing, an understanding of cancer biology is far from complete. The ability to develop new compounds or generate biological data predictive of the clinical situation relies on good quality basic research data (8,9), although the complexity and constantly evolving biology of the tumor may be to blame for the frequent non-reproducibility of research results. Systemic biology approaches of the -omic type still generate largely incomprehensible, mostly due to their volume, analytical data, few pieces of which are currently actionable/drug-gable. Finally, animal models of cancer are similarly unable to predict the clinical situation (10). Science and research are vital if we want to make progress, but they are also costly investments. This brings the discussion to another important aspect which affects current oncology drug development in multiple ways.

### **Financial pressures on oncology drug development**

Cancer drug development is costly and drug developers have traditionally relied on high drug prices to both make up for the cost and finance further development, while high

income societies have historically been ready to accept the high cost of new oncology drugs. However, this situation is changing. Healthcare systems are under pressure and health technology assessment (HTA) bodies, set up to make decisions on drug pricing and reimbursement, need to ensure value for money.

A regulatory decision towards approval requires that the drug is shown to be safe and effective or that the benefits from its use outweigh the risks associated with it, i.e., it is a decision made on the basis of a positive benefit-risk balance. In many cases, a positive benefit-risk balance could be established even with small demonstrated benefits in the absence of major toxicity and alternative options. However, in case of limited benefits, the cost-effectiveness may not be evident and the drug becomes practically inaccessible to patients.

Notwithstanding the above, proposals have been made towards increased flexibility in the drug approval and HTA, and proposals have been put forward for learning healthcare systems (11) that accept higher uncertainty at the time of regulatory drug approval to be minimized in the initial phases of actual marketing by intense collection of post-marketing data, e.g., in the form of clinical trials, prospective interventional or observational studies, patient registries and real-life effectiveness studies. Such proposals require the buy-in of not only HTA bodies but also of drug regulatory authorities and the two would need to work together towards agreeing an acceptable post-initial approval development plan that should satisfy both regulatory and HTA requirements (12).

### **Biosimilar monoclonal antibodies in oncology drug development**

One could not describe the changes in oncology drug development in the current economic climate without reference to the emergence of biosimilar monoclonal antibodies. This is because some of the targeted therapies in oncology approved in the last 15 years are monoclonal antibodies and related molecules. Some of these have already lost the market protection foreseen by the European Union (EU) pharmaceutical legislation and they are soon also coming off-patent thus lending themselves to biosimilar development.

EU legislation foreseeing similar biologic(al)s (biosimilars) has been in place since the early—to mid-2000s and US—and other region legislation has developed more recently. The first biosimilar monoclonal antibodies of infliximab

were approved in 2013 in the EU and shortly before in Korea.

Biosimilar legislation intends to provide alternatives to innovative biologicals that have the same efficacy and safety profile and contain ‘the same’ active substance as the reference medicine. Ultimately, the intention of the biosimilar legislation is to create therapeutic alternatives that are as close as possible to the reference product and to the best of our ability to ascertain, so that the resulting market competition can reduce the cost of therapy and ease the pressure on healthcare systems.

The demonstration of biosimilarity depends on the success of an extensive comparison between the reference biological and the intended biosimilar conducted in such a way as to detect differences between them, if any. Towards this end, pharmaceutical/analytical development of the biosimilar has to reassure not only of the acceptable pharmaceutical quality but also of the similarity in all aspects between biosimilar and reference product. The (bio)similarity is further confirmed in non-clinical and clinical studies which have to be designed in a way that maximizes the possibility of detecting differences between biosimilar and reference product, if there are any. With this in mind, the clinical comparison has to occur in a population and disease setting sensitive to show such differences. The comparison has to make use of primary endpoints sensitive to detect differences while secondary efficacy and safety endpoints are expected to point in the same direction. Ultimately, the totality of the evidence from analytical and biological assays as well as non-clinical and clinical studies has to support the claim for biosimilarity.

Acceptability of biosimilars by physicians and patients is growing slowly (13,14). While the market uptake of biosimilars is evolving, innovator drug developers have produced second generation compounds with more favorable safety and efficacy profiles (e.g., the recent approval of a trastuzumab-emtancine antibody-drug conjugate, and the new anti-CD20 monoclonal antibody obinutuzumab).

### **Future prospects**

Despite the financial pressures, in the short term things are still looking up in oncology drug development with numerous compounds in development targeting different biological mechanisms and pathways and with an increasing number of those reaching the stage of marketing authorization application. In the longer run, to what extent or how soon the development might shift from large,

randomized trials testing a single hypothesis to small studies confirming biological hypotheses of predicted clinical relevance remains to be seen. The key to this shift lies with the ability to make good predictions of clinical relevance out of biological knowledge and ultimately requires an all-encompassing understanding of biology, co-operative research, and bridging the gap between regulators and payers.

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