Imaging Biomarkers in Oncology Drug Development

Introduction
Biomarkers are defined as measurements or characteristics that are evaluated as indicators of normal biological or pathogenic processes, or responses to therapeutic interventions. Biomarkers have become increasingly important to physicians, medical product developers (both drugs and devices), and regulatory agencies, impacting treatment decisions as well as drug approvals in their ability to define both efficacy (therapeutic benefit) and safety (the likelihood and extent of undesirable off-target responses). This article focuses on imaging biomarkers as employed in efficacy assessments in oncology drug development.

Background
Cancer remains one of the world’s leading public health concerns. Approximately 12.7 million cancer cases and 7.6 million cancer deaths are estimated to have occurred in 2008; of these, 56% of the cases and 64% of the deaths occurred in the economically developing world.1 For females, breast is the leading cancer site and accounts for 23% of the total cancer cases and 14% of the cancer deaths. For males, lung is the leading cancer site, comprising 17% of the total new cancer cases and 23% of the total cancer deaths. While greater international education and prevention campaigns are clearly desirable, the development, availability, and use of new pharmacotherapies are critical.

Kelloff and Sigman2 discussed the use of biomarkers in the context of drug development, citing those that are expressed as a consequence of cancer development and progression. Two categories of such biomarkers, those that are most relevant for identifying patients who are likely to respond to a given therapy and those that are most effective for measuring patient response to therapy, are of particular interest. The authors also discussed “innovative designs of clinical trials and methodologies that are used to validate and qualify biomarkers for use in specific contexts.”

Imaging Biomarkers
Imaging biomarkers play a key role in evaluating the efficacy of new candidate drugs and/or innovative therapeutic regimens (and can cost between 10% -15% of the total budget of clinical trials). However, their employment during clinical trials requires several issues to be addressed satisfactorily. First, image interpretation must be standardised to the greatest degree possible, meaning that reduced inter- and intra-reader variability is essential to minimise bias. Second, the volume of data generated by state-of-the-art imaging modalities requires computing facilities capable of storing, managing, and analysing the data: streamlining data management workflow, therefore, is a practical necessity. Web-based cloud computing technology that is made available at all participating sites facilitates state-of-the-art image interpretation directly at investigator sites in an automated and standardised process, thereby reducing inter-reader variability.

Traditionally, in many cases where data from many investigator sites need to be interpreted, assessed, and analysed, employment of a central (core) laboratory has been considered the ‘gold standard.’ However, the time taken to respond by central labs and discrepancies with investigator site assessments leading to bias (e.g., wrong decisions on including, treating, or excluding subjects/censoring bias) have been critical issues. In the future, this may change in this field as individual sites and readers increase in expertise and standardisation. This would allow sponsors to access imaging biomarker data in near real time. This would therefore enable sponsors conducting Phase II trials to make go/no-go decisions more quickly, while implementing adaptive designs to collect data more efficiently and consistently employing the same imaging biomarker for Phase III trials.

Tumour Characteristics of Interest
While evaluation of tumour characteristics via single-dimensional measurement criteria such as the Response Evaluation Criteria in Solid Tumors (RECIST) criteria,3-5 and bi-dimensional measurements (e.g., using WHO Evaluation Criteria in Solid Tumors (RECIST) criteria,6-8 newer characteristics of interest include quantitative lesion parameters such as volume9-11 and density.12 As new drugs are developed, the effects of alternative mechanisms of action (e.g., drugs that are antiangiogenic vs. cytotoxic) need to be assessed. Some effects may not be observed by size measurements alone, requiring instead assessments of changes in other characteristics such as density, pattern, and perfusion.

Use of Automation
In the analysis of many types of data collected in clinical trials, the putative advantages of computer-aided and standardised systems include speed and reliability. Here, automated detections of lesions, organ and lesion segmentation, and assisted extraction of the parameters mentioned earlier (volume, density, and others) are of great interest. However, such systems must not only be reliable in consistently providing the same reading and interpretation of data, they must be reliable and correct. Demonstrating such characteristics is at the moment a hot topic for the medical imaging community. Several initiatives are currently promoting such systems and paradigms, and gathering academic, regulatory, and industry contributions to confirm their performances and perform validation. Attention is focusing not only on drug development activities but also on routine clinical practice.13-14
Partnerships and Alliances in Contemporary Drug Development

Partnerships and alliances between different stakeholders in integrated pharmaceutical medicine are becoming more common, given the increasing demands and pressures of bringing new drugs to market. These include partnerships and alliances between biopharmaceutical companies and companies manufacturing companion diagnostics, and between biopharmaceutical companies and contract research organisations (CROs).

The need to incorporate companion diagnostics into development efforts is a growing demand, and one that requires companies to plan ahead to ensure that relevant companion diagnostics are brought to the marketplace along with the respective drugs and their (new) indications.

An informative example is provided by crizotinib, which was approved by the US Food and Drug Administration (FDA) to treat patients with late-stage (locally advanced or metastatic), non-small cell lung cancers expressing an abnormal variant anaplastic lymphoma kinase (ALK) gene. It required approval along with a companion diagnostic test that determines if a patient’s tumour expresses this abnormal gene, and is therefore a suitable candidate for crizotinib therapy.

With regard to imaging biomarkers, a three-way partnership or alliance between a biopharmaceutical sponsor, a CRO, and an imaging company can prove fruitful. As Smith et al. noted, “Involvement of a CRO or central laboratory as a facilitator between biopharmaceutical and diagnostic companies can have many benefits as these organizations have an intimate understanding of the drug development process and have significant practical experience with developing and deploying biomarker tests in a real-world setting.”

An alliance between the authors’ companies provides an instructive case study. Thanks to its experience in enabling novel imaging biomarkers, and to its system being adopted by radiology departments around the world for not only clinical trials but also routine clinical practice, MEDIAN leverages its approved software medical device, differentiated clinical trial imaging services offering, and biomarker development capabilities that are essential to such collaborative initiatives. Quintiles, in turn, leverages its comprehensive understanding of the biopharmaceutical industry in general and its expertise and experience in conducting multi-site and multi-regional clinical trials.

Biomarker Technologies and Challenges

While there is considerable diversity in biomarker research and development, each faces the same set of challenges: qualification, clinical validation, and hence the requirement of analysis platforms for biomarker evaluation. Various approaches may be used for these purposes. Some insight is provided by ICH Guideline E16 which focuses on genomic biomarkers. The guideline comments as follows: “Qualification is a conclusion that, within the stated context of use, the results of assessment with a biomarker can be relied upon to adequately reflect a biological process, response or event, and support use of the biomarker during drug or biotechnology product development, ranging from discovery through post-approval.” The extent of the difficulties of validation led Smith et al. to comment, “The challenges of incorporating biomarkers into clinical development programs...are nearly as great as the enormous potential that such technology affords.” It will be of considerable interest to all stakeholders in pharmaceutical medicine, and also clinical practice, to see how imaging biomarkers, and biomarkers in general, continue to evolve.

Additional references are provided to guide further reading.

References