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Precision medicine in oncology drug development: a pharma perspective

Simon J. Hollingsworth

AstraZeneca, Innovative Medicines & Early Development – Oncology, Unit 310 – Darwin Building, Cambridge Science Park, Milton Road, Cambridge CB4 0FZ, UK

A rapid expansion in precision medicine founded on the potential for durable clinical benefit through matching a drug to a predictive marker used to select patients has driven the development of targeted drugs with accompanied companion diagnostics for patient selection. Oncology has been at the forefront, with the improvements in patient survival notable. Increasing numbers of molecular subgroups require an equally increasing number (and new generation) of highly selective agents targeting inevitably lower incidence molecular segments, posing significant challenges for drug development. Innovative trial designs (umbrella or basket studies) are emerging as patient-centric approaches and public–private partnerships, cross-industry, government and non-profit sector collaborations are enabling implementation. Success will require continued innovation, new paradigms in oncology drug development and market approval and continued collaboration.

The landscape

The landscape in oncology drug development, particularly early clinical development, is evolving rapidly with recent years seeing the notable expansion of precision medicine (variously termed stratified medicine, personalised healthcare, etc.), the central premise of which is to offer greater potential for durable clinical benefit by matching a drug (and its mechanism-of-action) to a predictive marker used to select patients. The understanding of tumours in unprecedented molecular detail, the 'hallmarks of cancer' [1–6], coupled with modern drug development enabling specific targeting of the implicated pathway or mechanism (hallmark) and development of diagnostic technologies to identify patients (by markers) have collectively enabled notable improvements in survival rates for some cancers [7–14]. The more we have learnt about the molecular mechanisms that drive these tumours, and have thus been able to develop drugs targeted to these mechanisms, the greater the benefit seen in patient survival. Lung cancer, particularly exemplified by non-small-cell lung cancer (NSCLC) [7,8], has seen great development (and success), enabled by the increasing understanding of its molecular subclassification [2,3]. For example, the elucidation of the relationship between epidermal growth factor receptor (EGFR) mutation and response to EGFR tyrosine kinase (EGFR-TK) inhibition [15,16] underpinned the development and subsequent approval of IRESSA® (gefitinib; AstraZeneca) for treatment of adults with locally advanced or metastatic NSCLC with activating mutations of EGFR-TK – following the completion of the Phase III studies IPASS (NCT00322452) [17,18] and INTEREST (NCT00076388) [19,20]. Similarly, and more recently, the identification of anaplastic lymphoma kinase (ALK) fusion oncogene as a molecular driver in some adenocarcinomas [21–23] underpinned the development of the ALK tyrosine kinase inhibitor XALKORI® (crizotinib; Pfizer) [24] and its approval for treatment of patients with late-stage, locally advanced or metastatic NSCLC expressing the abnormal ALK gene – the approval including a companion diagnostic test for the ALK gene (i.e. the Vysis ALK Break Apart FISH Probe Kit) [25]. These are only selected examples in lung cancer but they have particularly marked the developing oncology landscape and its continued evolution towards an increasing number of patient–tumour groups identified by (increasingly complex) diagnostics to enable coupling to molecularly targeted drugs. For up-to-date approvals see the FDA [26–28] and the European Medicines Agency (EMA) [29].

The drivers for precision medicine are clear, and widely and robustly discussed, for examples see [30,31]. For patients (and physicians) advantages include durable clinical benefit, reduced

E-mail address: simon.hollingsworth@astrazeneca.com.

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exposure to noneffective drugs and potential to exploit current scientific and technological advances. For the pharmaceutical industry, the potential to tackle core challenges in discovering and developing better and more efficacious medicines, reducing attrition in drug development and reducing development costs are particularly beneficial.

Precision medicine in oncology drug development

For oncology drug development the increasing number of molecular subgroups requires a portfolio approach with an equally increasing number of agents targeting inevitably lower incidence segments. Not only is there a need for a new generation of highly selective molecularly targeted agents, the drivers for precision medicine, but there is also a need to understand the mechanisms that enable their development once discovered. The intent here is not to review modern oncology drug discovery, rather the development of a candidate drug once ready for clinical trials. The increasing number of highly selective, molecularly targeted agents generates significant challenges for the more established drug development process. For example, current patient screening approaches are suboptimal and are not effective for patients, physicians or industry. Low frequency events are difficult to find, diagnostics sample quality and/or quantity compromise multiple analyses, there is poor patient and/or physician experience with cycles of repeat diagnostics, and current regulatory requirements for randomised trials and to validate companion diagnostics are challenging. Fig. 1 illustrates some of the reality of conventional screening approaches if used in an early clinical development study. The figures are a stark and surprising reality. To run a study testing a new candidate drug in a patient subpopulation selected by a molecular marker with a 2% incidence one would need to screen 78 patients for every one patient recruited to the study, with a standard 20 patient Phase I expansion in this patient subpopulation requiring screening of at least 1560 patients in total. Equally staggering is the cost – if using a relatively simple diagnostic (costing ~US$1000 per assay) the screening costs alone to find these 20 patients would be in the order of US$1.8 million. Significantly, the patient experience is extremely poor with cycles of disappointment being first considered for a trial only then to fail screening (not having the marker for recruitment), requiring repeat biopsies (if possible) to enable analysis of the next marker, and with limited drug options. From a clinical trial operational viewpoint, this is complex and unwieldy. This type of approach is clearly not sustainable.

We need innovative trial designs better suited to development of targeted molecules and that, in turn, require innovation and change in those aligned areas integral to the implementation and success of such trials – new generation multiplex diagnostics coupled with diagnostic standards and methods standardisation, regulators willing to engage with new types of (different) datasets and improved patient access to diagnostics and candidate drugs. Addressing many of these points has seen the emergence of umbrella (within tumour types, selected by different markers for single or multiple candidate drugs) and basket (across tumour types, often selected by single marker or for a single candidate drug) studies in early clinical development. Whereby, rather than using serial, single diagnostics to align patients to different trials, a single multiplex diagnostic is used to assign patients to different candidate drugs (or trial arms) within the same trial. Designs vary but the principle remains: 'select the trial for the patient, not the patient for the trial'. Such studies offer greater options for patients, with candidate drugs aligned closely to their tumour characteristics and significant efficiencies made possible in screening and patient flow. In theory, this should reduce timelines and costs of clinical development and provide a more patient-centric and sustainable way forwards for drug development.

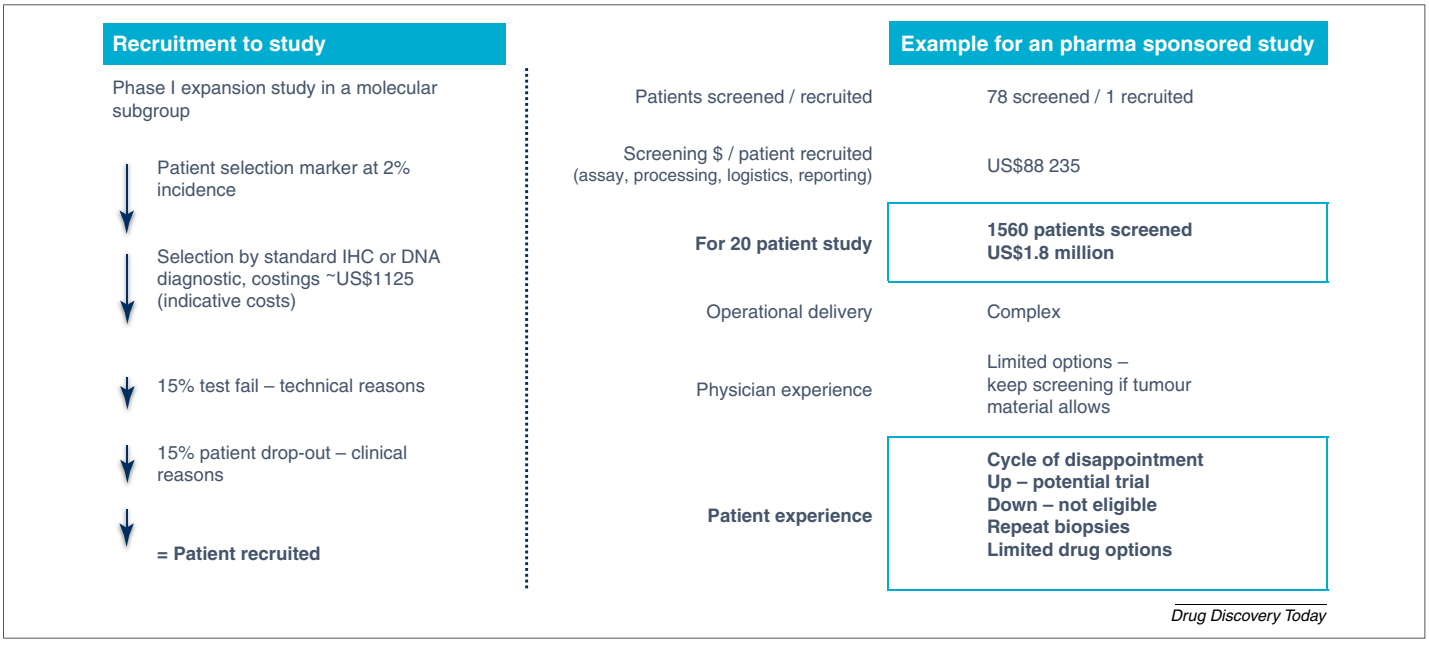

FIGURE 1

The reality of conventional screening approaches in an early clinical development study. For a Phase I expansion in a group of patients selected based on a molecular marker with 2% incidence, using a standard diagnostic approach (e.g. IHC or DNA test, with indicative cost), and indicative rates of screening failure and patient drop-out.