ONCOLOGY DRUG DEVELOPMENT – ACTIVATING THE 5R FACTORS

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Over 1.8 million people were diagnosed with lung cancer in 2012, making it the most common form of cancer worldwide. It is the leading cause of cancer deaths in men, the second in women and 1.59 million people die annually from the disease *(1)*.

Although there have been significant advances in imaging to detect the presence of tumours and testing procedures to determine pathology *(2, 3)*, lung cancer continues to carry a significant mortality and over 60% of patients die within a year of diagnosis *(4)*.

New therapeutic approaches

Since the 1990s, the success rates for drug development have fallen significantly across all therapeutic areas, including oncology. However, there is clear evidence of innovative new medicines making it successfully through the pharmaceutical industry pipelines. An increasing proportion of novel cancer medicines are targeted to patient populations where cancer growth is driven by a pathway specifically inhibited by the drug. Another exciting emerging trend is the understanding of the mechanisms or "checkpoints" controlling the development of an immunosuppressive environment within tumours. Novel medicines are being developed which can affect these "checkpoints" and induce prolonged responses based on reactivation of immune-driven tumour cell killing *(5, 6)*. However, these same opportunities also present challenges which require adaptation of the "traditional" drug development route starting from phase I. Success is indeed possible, and it requires good understanding of the driving biology, the right preclinical models, understanding of the limitations of these models, and close collaboration between drug developers, diagnostic developers, academic investigators and regulatory bodies.

Defining the success factors

At AstraZeneca, we undertook a comprehensive review of our drug projects from 2005–2010. The analysis allowed us to establish a framework based on the five most important technical determinants of project success and pipeline quality, which we describe as the five "R"s: the right target, the right patient, the right tissue, the right safety and the right commercial potential (Figure 1). A sixth factor – the right culture – is also crucial in encouraging effective decision-making based on these technical determinants.

This framework is now being used by AstraZeneca's R&D teams, although it is too early to evaluate the full impact of the 5R approach on oncology drug development. However, there are some interesting differences in the development paths of gefitinib, the first personalised drug for non-small cell lung cancer (NSCLC) and AZD9291, an oral, potent, selective, irreversible inhibitor of both epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) sensitising and resistance mutations in development for the treatment of advanced NSCLC. By examining each approach in more detail, we can see the improved application of emerging knowledge and early signs of the impact of the 5R framework.

Before 5R

Gefitinib entered phase I clinical trials in 1998 *(7, 8)* where evidence of major tumour regression was seen in a small proportion of NSCLC patients. Two doses were selected for investigation in phase II and phase III trials in an unselected patient population in NSCLC. The phase II trial demonstrated an encouraging response rate of 18–19% *(9)*. However, the phase III trials adding gefitinib on to standard of care chemotherapy subsequently failed to show an improvement in overall survival or substantive improvement in progression free survival (PFS) in the unselected patient population *(10, 11)*.

In 2004, it was discovered that "super-responders" to gefitinib had a mutation in the EGFR ATP binding pocket which was shown to be a tumour "driver" *(12, 13)*. When patients are selected based on the presence of a sensitizing mutation in EGFR, the response rates to gefitinib are approximately 70% with median PFS of 9 to 12 months *(14)*. The IPASS trial demonstrated a statistically significant improvement in PFS in the sub-group with EGFR mutations

Figure 1: **The 5R framework based on the five most important technical determinants in project success**

(hazard ratio 0.48, P<0.001) but was associated with a significantly shorter PFS among patients with wild-type EGFR *(15)*.

Gefitinib was initially approved in Japan in 2002, the first EGFR-tyrosine kinase (TK) inhibitor to be approved for use in lung cancer. It was also approved by the US FDA in 2003 as an accelerated approval based on durable responses in third line patients with NSCLC, but when the phase III trials failed to show a survival benefit in combination with chemotherapy or as monotherapy, the FDA modified the label for gefitinib in 2005 to limit the indication to cancer patients known to respond to gefitinib treatment.

In 2009, the European Commission granted gefitinib marketing authorization for the treatment of adults with locally advanced or metastatic NSCLC with activating mutations of EGFR-TK across all lines of therapy – the first drug for lung cancer to be associated with a companion diagnostic test *(16)*.

Bringing the 5Rs to life

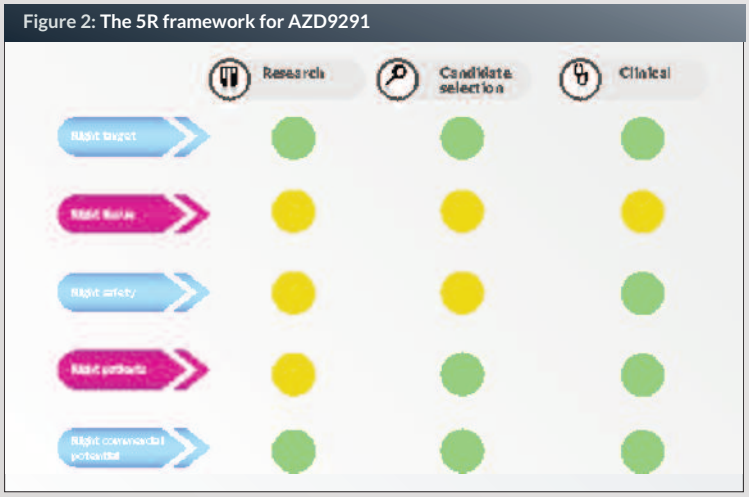
- **Right target:** Fast forward now to March 2013, when an AstraZeneca candidate drug AZD9291 entered clinical trials. This drug was designed to overcome a common resistance mechanism, the so-called "gatekeeper" mutation T790M *(17, 18)*. We knew how the target would affect disease and what we could do to ensure that our confidence improves as we move from research into clinical development.
- **Right safety:** The development of this drug was also driven by further understanding of the challenges with first generation EGFR TKIs, due to their similar potency versus the wild type EGFR compared with the mutated form which can lead to diarrhoea and rash as dose-limiting toxicities. The selection of AZD9291 was based on a large margin of potency for the double mutant EGFR versus the wild type EGFR *(19)*. The rationale was that improved efficacy would be seen if increased target inhibition could be achieved at doses well below those that would inhibit wild type EGFR and produce rash and diarrhea.
- **Right patient:** This detailed understanding of the mechanism underlying disease progression alongside the substantial years of experience gained in kinase chemistry underpinned the ability of the discovery scientists at AstraZeneca to select AZD9291 as a candidate drug for the treatment of patients with NSCLC and a sensitising mutation in EGFR who have developed resistance to EGFR inhibitors *(20, 21)*. In contrast to gefitinib's development, the relevant patient population most likely to respond to this therapy was identified well before starting phase I development and those patients were enrolled into the first clinical trials. We had a clear understanding of the potential to increase therapeutic benefit and reduce risk in these patients. In fact, durable clinical responses to AZD9291 were seen in the first cohort of patients treated.

Data presented at the World Conference on Lung Cancer in Sydney in October 2013 demonstrated unconfirmed and confirmed responses in 9 of 18 patients with T790M mutations *(22)*. Accrual to the phase I trial has been very rapid, with sites open in European Union countries, the United States and in Asia. The rapid generation of data demonstrating a high and durable response rate has led to Breakthrough Therapy designation by the US FDA, and rapid entry into pivotal phase II/III trials. Although it is too early to see tangible benefits to the AstraZeneca pipeline, since the implementation of the 5R framework we have seen directional improvements in the quality and success rates of our current cohort of programmes.

Open innovation leads to the "Right commercial"

The increased identification of patient subgroups in diseases such as NSCLC, presents challenges to recruit patients into early phase clinical trials particularly if those subgroups represent less than 10% of the NSCLC population. Screening large numbers of patients takes considerable time and money and does not serve patients, investigators or pharmaceutical sponsors well. An emerging alternative is "basket" studies, which include one or more screening tests for multiple genetic aberrations and directs patient enrolment to a clinical trial

Figure 2: The 5R framework for AZD9291



arm based on the specific aberration in their tumour. One such trial by Cancer Research UK is run in collaboration with AstraZeneca and Pfizer, who will provide access to up to 14 different drugs – 12 from AstraZeneca and 2 from Pfizer.

We recently announced collaborations with Qiagen to develop a diagnostic both in Europe and a companion diagnostic in the United States. Gefitinib is the first EGFR TKI in Europe with a label allowing the use of circulating tumour DNA (ctDNA) obtained from a blood sample, to be used for the assessment of EGFR mutation status in those patients where a tumour sample is not an option. Roche is collaborating with us to develop a companion diagnostic for AZD9291. Successful drug discovery requires novel mechanisms of collaboration across academia and industry – a more open approach to innovation and an approach which shares both the risks and the rewards.

In summary, the explosion of information about the genetic aberrations underlying cancer has led to several changes in the paradigm of how we develop drugs for this disease. The nature of clinical trials designed to address this new understanding is already changing and will change further. Far from there being a decline in innovation in pharmaceutical development, I see that we are in one of the most exciting times in cancer drug development with innovation in every aspect of how we discover and develop new therapies. I have no doubt that it is only by working together across academia and industry and sharing our scientific expertise that we stand the best chance of reaching our bold ambition of one day eliminating cancer as a cause of death. •

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