Reshaping the landscape of cancer drug discovery and development

The landscape of cancer drug discovery and development is shifting – adjusting and reshaping itself in response to the huge rush of scientific knowledge which has come to the fore over the past few decades. In collaboration with a number of other stakeholders, pharmaceutical companies have successfully tapped into this explosive mine of biology and genetics knowledge. At GlaxoSmithKline (GSK) Oncology we challenge ourselves by seeking new ways to effectively utilise these findings and further GSK's research and development (R&D) efforts. Embracing the new era in targeted oncology medicine will require us to change many things about the way we traditionally approach drug development – evolving our basic discovery paradigms and embracing translational medicine. Our efforts will undoubtedly be intense and costly, but the potential benefits to oncologists and patients are potentially life-changing and warranted.

By Dr Paolo Paoletti

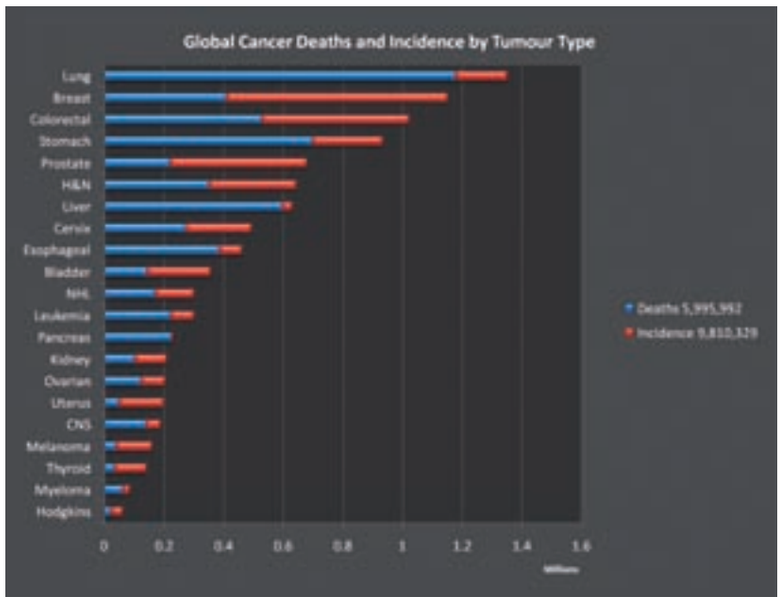
Cancer is a deadly global adversary. Every year, more than 10 million people are diagnosed with cancer and more than 7 million die from the disease, accounting for 13% of all deaths worldwide[1,2].

The most common cancers are breast, colorectal, lung and prostate which, together with gastric and liver cancer, account for more than 50% of global incidence and mortality[3]. Haematological cancers are also a substantial clinical problem. Regional treatment differences abound and, with less aggressive treatment, may contribute to a higher mortality in developing countries for carcinomas such as cervical and gastric[2,3].

By 2020, an estimated 16 million new cases of cancer will occur every year[1]. Key drivers of the disease stem from the combination of today's ageing population with an absence of any cures, plus the level of success the medical community has had in transforming certain cancers into chronic conditions[3]. From a business perspective, cancer will be the largest therapy area by 2010, rising above neurology in terms of volume as the population gets older and lives longer. In many ways oncology is mirroring the cholesterol market 25 years ago, when the industry experienced an explosion of technology and new treatments.

The term 'cancer' covers many different diseases and although needs vary across tumour types, early detection and diagnosis is crucial to survival. **Figure 1** highlights the work still to be done in bringing this early detection and intervention forward.

Early diagnosis in breast cancer by mammography has been associated with improved survival. In



colon cancer, progress has been achieved with the extended use of colonoscopy. In lung cancer, the use of adjuvant treatment is increasing as is early diagnosis and prevention work with imaging spiral computed tomography (CT)[5]. However, malignancies such as pancreatic cancer lie at the other end of the spectrum. Median survival remains very low because the majority of pancreatic cases are diagnosed in stage IV.

CHAPTER 1: Cornerstone increments in cancer care

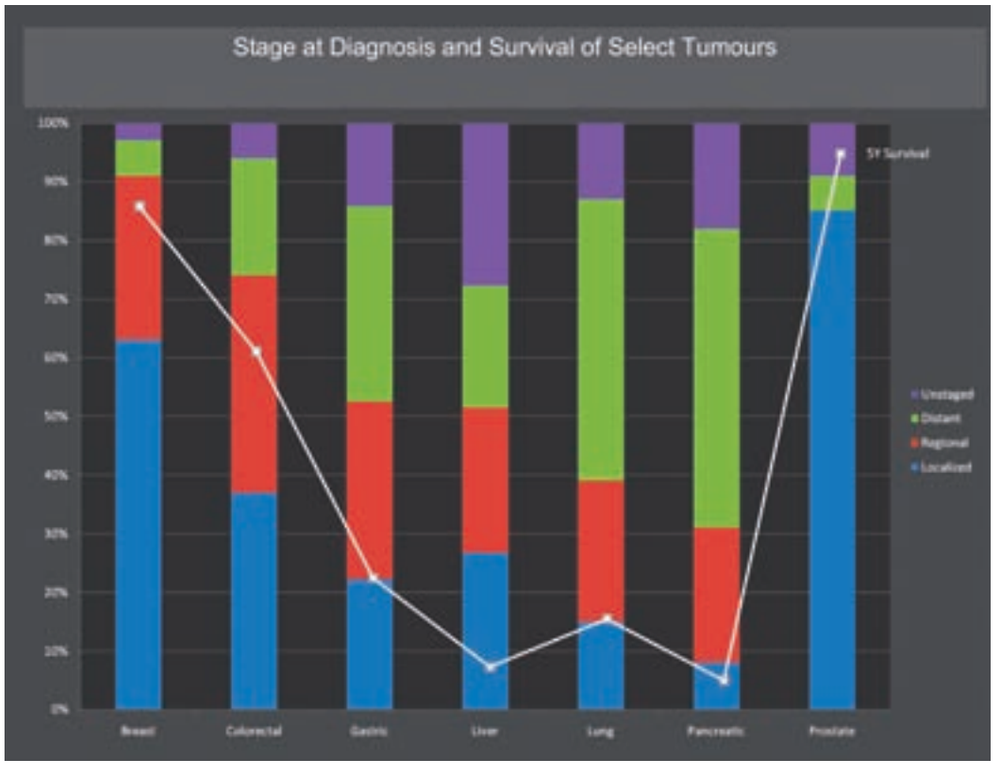
Over the past four decades, oncology medicine has taken huge strides forward and nowhere is this more clearly illustrated than in breast cancer.

The cytotoxics

Cytotoxic chemotherapy has developed and advanced steadily over the past 40 years. In particular, combination cytotoxic therapy has been refined in different tumour types. We have also learned how to use cytotoxics optimally by managing associated side-effects through intensive supportive care. While most of these agents were developed empirically, the targets and mechanism of action (MOA) of these agents is now well described.

In testament to this developmental progress, cytotoxic therapy has evolved to become an important cornerstone of modern-day cancer treatment and the standard-of-care for many tumour types. However, the price cancer patients pay for employing these aggressive cytotoxic treatment regimens is high – sometimes too high with

Figure 1



toxic deaths. While there is no doubt that cytotoxics are effective in killing tumours, the significant and cumulative toxicity burden of chemotherapy has accelerated our drive towards targeted treatments that for the most part spare healthy cells from bystander damage.

Despite this undisputed progress in combination chemotherapy, clinicians have reached an efficacy plateau in many diseases. For example, in a recent pivotal study involving more than 1,200 lung cancer patients, none of the four different cytotoxic combination regimes which were compared offered any significant survival benefit over the others (**Figure 2**)[6]. Oncologists have begun to question whether another combination regimen substantially enhances clinical outcomes, and this study suggests that, indeed, we are likely to make the next advances by taking a different direction entirely. Similar situations are also emerging in other tumours.

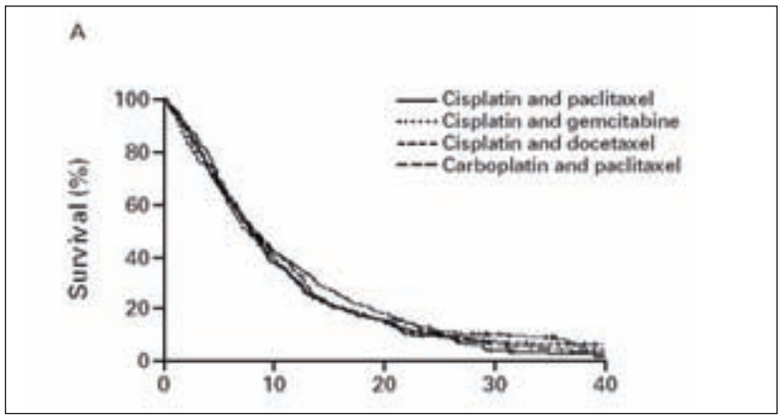


Figure 2

CHAPTER 2: The thinking behind today's cancer therapy

Cancer is characterised by 'autonomous' cell growth, proliferation, invasion, colonisation, neoangiogenesis formation and reduced cell death associated with genome instability. While working hard to optimise cytotoxic regimens, our knowledge of the biology and genetics of cancer has also grown exponentially. Six key factors have been identified as the hallmarks of malignant growth in the majority of solid tumours and the key drivers behind cancer development (**Figure 3**)[7].

The complex signal transduction processes in cancer cells present tantalising targets. Three of the major pathways that play a central role in promoting cancer development are[8]:

1. Phosphatidyl inositol-3 kinase (PI3K)/AKT
2. Mitogen-activated protein kinase (MAPK)/Ras signalling cascades
3. Protein kinase C (PKC) family

Figure 4 highlights some of the nodes of pathway deregulation which have piqued interest at GSK and other companies as molecular targets in oncology.

Biological breakthroughs bringing targeted therapy advances

The explosion in cancer knowledge has helped fuel the development of targeted therapies for cancer, adding advanced ammunition to the oncologist's therapeutic armoury. Once a specific genetic mutation has been identified, a specific drug can be devised to hit this target. A perfect example of this is imatinib (Gleevec®/Glivec®). The central role of the BCR-ABL fusion kinase in driving malignant transformation and excessive cell proliferation in Chronic Myelogenous Leukaemia (CML), along with the poor response of this disease to conventional therapy, provided the impetus for a targeted inhibitor development programme which culminated ultimately in the creation of imatinib. The cytogenic hallmark of CML is the Philadelphia chromosome (Ph), which produces a BCR-ABL fusion gene[9]. The product of this BCR-ABL fusion

Figure 3

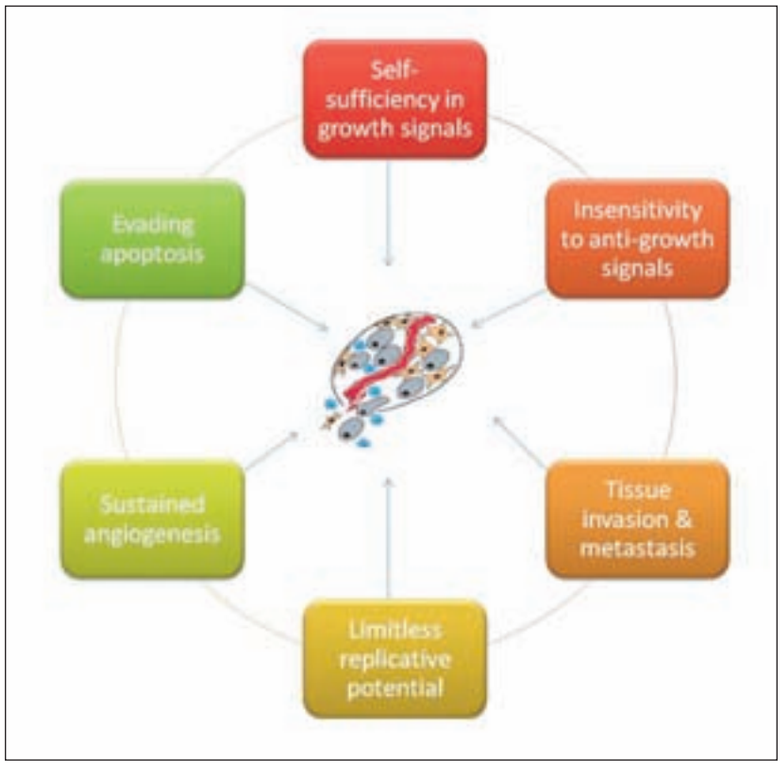
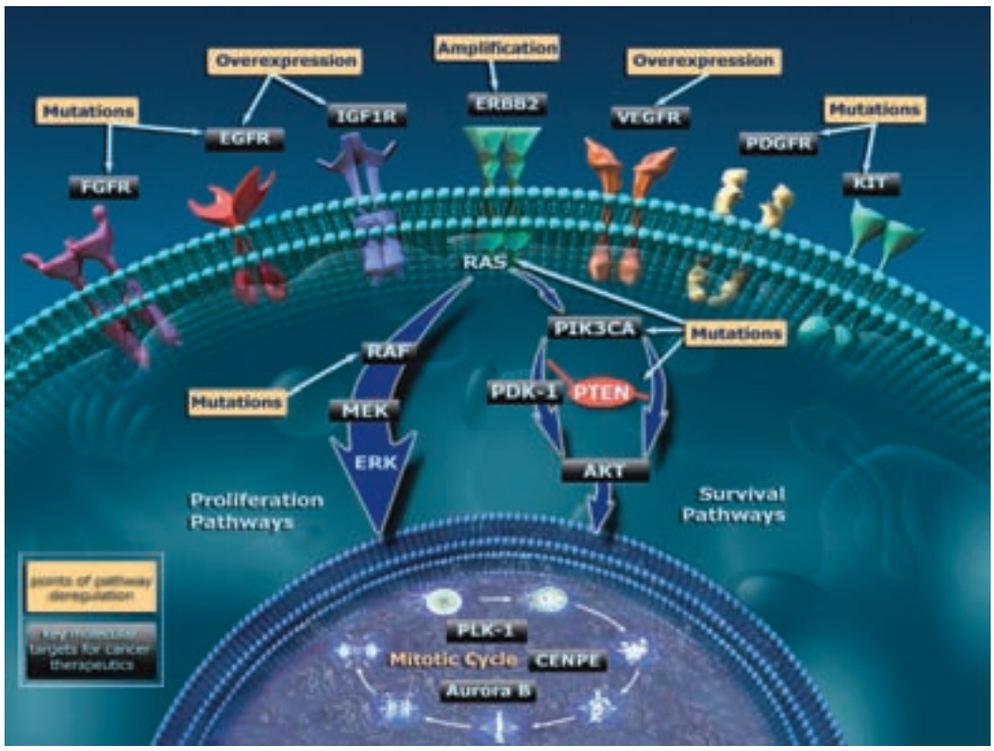


Figure 4



gene, occurring in 95% of CML cases, is a deregulated protein tyrosine kinase[9]. Imatinib, which targets ABL, was developed with this knowledge in mind, pursuing a targeted development pathway which resulted in a new drug with potent and reasonable specific activity against BCR-ABL[10]. In testament to the success of this targeted approach, the advent of imatinib has brought with it an historical change in the epidemiology of the disease itself. Global mortality from CML has been reduced by introduction of this novel tyrosine kinase inhibitor[11].

Biological breakthroughs have also taken place in the targeted therapy of breast cancer, where understanding the role of the ErbB2 oncogene has ultimately led to the advent of trastuzumab (Herceptin®) – a targeted monoclonal antibody against the ErbB2 protein. The work of Slamon and colleagues was crucial in the discovery of the gene and relating its overexpression to a poor prognosis[12]. The ErbB2 story began to gather momentum in the late 1980s when the link between the oncogene and certain breast cancers was eventually confirmed[12]. ErbB2 encodes a cell-surface receptor tyrosine kinase, which – when phosphorylated – relays signals triggering cell division[12]. 1-2 million ErbB2 receptors reside on the cells of women with ErbB2 positive breast cancer, versus the normal number of 20,000-100,000[12]. However, it was the origin of these extra receptors that was to prove the key to refining the trastuzumab approach.

With ErbB2 there is a clinically critical distinction between over-expression and gene amplification. In original work on the ErbB2 antibody trastuzumab, growth inhibition was only seen in cells with gene amplification[12]. This paradigm was eventually verified with the development of fluorescence *in situ* hybridisation (FISH) technology, a test which conclusively confirmed that only amplified tumours responded to trastuzumab[12]. As ErbB2 knowledge was still evolving, difficulties arose in Phase III studies, as screening for ErbB2 positive participants did not distinguish between overexpression and gene amplification, which led to the inclusion of patients (without the gene amplification subtype) in whom the drug would not be expected to work[12].

In contrast to Herceptin®, gefitinib (Iressa®), a small molecule epidermal growth factor receptor (EGFR) inhibitor was developed without a targeted methodology which led to negative clinical trials because the population of highly responsive patients was a small subset of the total[13]. In 2004, Haber and Meyerson showed that lung cancers activating mutations in EGFR mutation had a very

high likelihood of responding to gefitinib[14,15]. Overexpression of EGFR is observed in 40%-80% of cases of non-small cell lung cancer (NSCLC) but has not been conclusively linked to response to gefitinib therapy, and EGFR gene amplification is uncommon[16]. Exploiting ethnic differences in lung cancer, gefitinib is now an established treatment for pre-treated advanced NSCLC in Asia Pacific regions, where EGFR mutations are present in approximately 30% of NSCLC patients (as opposed to approximately 5% in North America and Western Europe)[13].

The gefitinib story paints a potent picture of the problems posed by our increased understanding of cancer biology and genetics. The issue was not just targeting by over-expression of EGFR, but with the additional complication that patients had to have over-expression plus a specific genetic mutation. Only in the presence of this mutation was the drug revealed to be active.

Meeting unmet needs

The development of targeted agents to date marks a massive step forward in cancer medicine, but it is not the complete solution. Despite the tremendous impact which trastuzumab has had in the early stages of breast cancer, 50% to 60% of patients will not respond to treatment despite being HER-2 positive[17]. To overcome these challenges we need to understand the mechanisms of *de novo* and acquired resistance to targeted agents, which is still yet to be determined.

In the meantime, GSK has developed lapatinib (Tykerb®/Tyverb®); an oral, small molecule dual tyrosine kinase inhibitor shown to be effective in combination with capecitabine in treating metastatic breast cancer in patients who progress on prior therapy including an anthracycline, a taxane and trastuzumab[4]. Here is the first example of a targeted agent which exploits a different molecular mechanism to remain active where another therapy targeted at the same molecule has stopped being effective. Lapatinib blocks both ErbB1 and ErbB2 receptor-mediated pathways via inhibition of the intra-cellular domain of each receptor[4]. Lapatinib offers oncologists an alternative targeted treatment in refractory patients after trastuzumab has failed.

Breast cancer is a very complicated and heterogeneous disease. While trastuzumab effectively blocks the disease at most anatomic sites, it cannot penetrate the blood brain barrier (BBB) and, in the original registration trial, 10% of patients receiving trastuzumab had CNS metastasis as site of first relapse[18,19]. Additional research now suggests that as many as 30% of women with ErbB2 positive cancer develop brain metastases[20,21]. GSK is currently investigating the role Tykerb may play in the prevention and treatment of metastatic cancer in the brain in women with ErbB2 positive breast cancer[4].

Optimising discovery paradigms

What wisdom can we extract from the early targeted therapy experiences with trastuzumab and gefitinib to apply to cancer drug discovery paradigms moving forward? First and foremost, it is clear that targeted drugs must be developed in a targeted way. Even then, the multifactorial nature of the disease may mute the effectiveness of blocking just one pathway, and limit the effectiveness of single agent approaches. The future of anticancer therapy therefore may lie along two potential routes:

- Multiple targeted agent combinations given together in an attempt to block different pathways simultaneously.
- Sequential use of targeted agents with inhibitory activity against different signal transduction pathways, according to the natural evolution of the disease.
- Combinations of targeted agents and lower dose (thus less toxic) standard cytotoxics.

These approaches should be exploited within the context of selecting patients based on the specific molecular/genetic alteration against which the drug was developed or other target-specific predictive markers. The rationale for multitargeted therapy is compelling, homing in on the mechanisms at work within cancer cells as well as their interplay with each other and the surrounding tissues. Targeted agents may also boost the efficacy of conventional cytotoxics. Anti-angiogenic agents, for example, act to normalise tumour vasculature, improving bloodstream delivery of cytotoxic drugs[8].

The overall objective of anticancer therapy is to cure (whenever possible) or transform cancer into a chronic disease and this is what GSK is striving to achieve. Partial success has been achieved in the cure of breast cancer and also in transforming it into a chronic disease with therapies at hand. However, despite these achievements we still have a long way to go – the bleak figure of 5% survival for pancreatic cancer serves as a stark reminder of work still to be done[4].

The challenges of targeted therapy development

The volume of knowledge which has been amassed on cancer biology and genetics is now enormous. Unearthing these new targets and

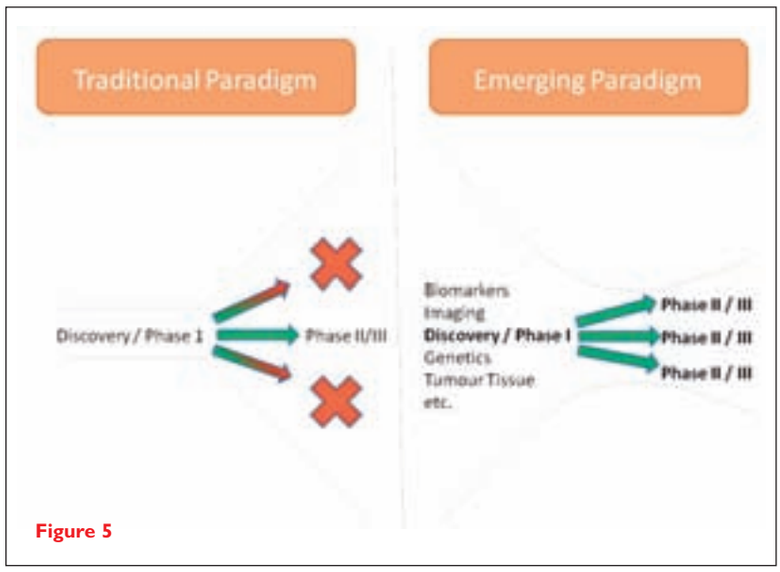


Figure 5

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pathways has fuelled an explosion in cancer R&D with more than 600 anticancer agents currently in clinical development. Where we still fall short is translating our new wisdom into medicine that can really make an impact on cancer care. There are two reasons for this knowledge gap. Firstly, from a biological perspective, the validity of this plethora of new targets is still unknown. Secondly, we have to ask ourselves if we are developing these new drugs in the 'right' way or if we still falling victim to traditional R&D paradigms of old.

A striking example of the perils of applying traditional R&D benchmarks to new targeted therapies can be seen with lapatinib. This agent showed a low response rate in early clinical trials where patients were not selected for ErbB2 amplification and was once viewed as a developmental disappointment. In addition, the old 'cytotoxic paradigm' was applied: lapatinb was given in 3rd/4th line heavily pre-treated patients. Only when studies were shifted to selected patient populations and in earlier stages of the disease, were more promising responses observed.

In some cases, the drug developer is a victim of the traditional approach. For example, if a cytotoxic is the standard of care then for patients it is very difficult to abandon this belief. Patients question the risk of a new, experimental drug when they are content in the knowledge that the standard treatment is already helping to shrink their tumour.

In addition, while tumour volume reduction is clear evidence of the biological activity of the drug, and also well accepted by regulators and clinicians, the new generation of targeted agents may affect important pathways by delaying the progression, causing 'stable disease', which is not 'visually' detected. New imaging technology such as PET may be relevant to early identification of the activity of a drug, but they are not yet validated and accepted.

Another important aspect of targeted drug development is that *in vitro* biology studies, which are important in decisions to progress the development of a drug, are not performed in heavily pre-treated cultured cancer cells. In this setting, critical biological determinants of response may differ between cultured cells and patient tumours. This observation highlights the importance of testing drugs in minimally pre-treated patients, the complete opposite of what we have done for the past 30-40 years.

Translational medicine

Today we are living in a transitional phase of cancer treatment. Drug development and clinical science is moving away from the old era of chemotherapy towards new targeted therapies and combination treatments. Rather than attacking cancer 'shot gun' style with a barrage of cytotoxic therapies we are becoming ever more refined and elegant in our approach.

As part of this metamorphosis, application of translational research by pharmaceutical companies is a critical part of the R&D process.

At GSK, extensive preclinical work precedes the first human dose, where the focus is on collecting tissue samples in order to enhance *in vivo* understanding. Key questions such as: is the mechanism of action (MOA) of the drug reflected in a biopsy of the tumour or circulating cancer cells? What molecules are being effectively inhibited by the drug? Whatever the perceived MOA of the drug, the aim is to see this demonstrated *in vivo*. Once this hurdle has been overcome, it then becomes important to establish whether the target MOA is actually translating into clinical efficacy.

Translational medicine is a crucial element to achieving development success with the new generation of targeted anticancer agents. The clinical revolution, where we can translate our biological knowledge into clinical benefit, is yet to happen.

Bench to bedside and back to the bench

With translational medicine, each cycle of research is a refinement of knowledge. The bench to bedside to bench approach enables us to optimise our

research – transforming it into the best patient care and the development of better technology for the future. The key to understanding the biology of the tumour is using cycles of learning.

Front-loading the discovery paradigm is something which GSK has advanced (**Figure 5**). More discovery efforts upfront bear fruit in focused and successful development further down the pathway. Key tools are pharmacodynamic and predictive biomarkers, use of bioimaging and genetic characterisation and analysis of human tumour samples from clinical trials. Phase III development is then focused and non-empiric.

1 Initially, treatment options for breast cancer were limited to a radical mastectomy. However, this extensive surgery was not associated with improved survival and patients carried the psychological and physical scars of invasive surgery.

2 Thirty years ago saw the implementation of more conservative surgery (lumpectomy) and the pioneering work on adjuvant therapy from Dr Gianni Bonadonna and others. Introduction of hormonal therapy for breast cancer has also had a significant impact over the past 15 years.

3 Further advances were made with the use of increasing effective cytotoxic agents (anthracycline and taxanes). Metastatic treatment also improved with the use of more active chemotherapeutic agents and combinations, giving further boosts to survival rates.

4 The discovery of ErbB2 (Her2/neu) as a prognostic factor in breast cancer and the development of trastuzumab (Herceptin®), a novel antibody targeting this critical growth factor receptor, opened the new era of targeted agents in patients with the overexpression of ErbB2. Expanding the use of trastuzumab in the adjuvant setting has now resulted in another substantial increase to survival.

5 In the past year, lapatinib (Tykerb®) a small molecule kinase inhibitor, in combination with capecitabine, showed efficacy in ErbB2 positive breast cancer patients who progressed after anthracyclines, taxanes and trastuzumab.

These advances in technology bring us up to date and, collectively, have contributed to a very significant increase in the overall survival of women with breast cancer across the Western world.

CHAPTER 3: Changing outcomes and endpoints

Having applied the knowledge gleaned from translational medicine to the development pathway, how do we then assess the clinical efficacy of these new anticancer agents? The traditional way of measuring anticancer efficacy, through response rate and tumour shrinkage, is a relic of the cytotoxic age – attributable to the ability of those potent agents to reduce tumour volume. In contrast, many of the new generation targeted drugs may stabilise the disease; the tumour does not grow any further but becomes effectively 'frozen'.

Efficacy must therefore be assessed in a different way. Important valid efficacy parameters in the targeted domain are focused on progression – specifically, progression-free survival and time to progressive disease. This requires randomised Phase II trials as a proof-of-concept and not Phase II single-agent studies. In testament to the importance of embracing new efficacy endpoints, erlotinib (Tarceva®), another EGFR inhibitor, was approved after Phase III studies showed a response rate of just 9%-10%[22,23]. However, survival was significantly increased – in fact, almost doubling[22,23]. Measures must reflect the fact that targeted agents result in stable disease still underpinning their anticancer efficacy and translating into prolonged survival.

Regulatory challenges

In this transition period – moving towards new efficacy measures but still intrinsically linked to the old cytotoxic benchmarks – key regulatory challenges emerge. Historically, the regulatory perspective has been fixed firmly on overall survival as a clinical endpoint. This was considered valid, because cytotoxics are very toxic, hence an impact on survival was and is still expected. With the new generation of targeted drugs, the benefit/risk ratio may be dramatically shifted, therefore TPD or PFS should be considered as a valid end-point. Indeed, the recent approvals of Sutent and Nexavar by the FDA, and CHMP and Tykerb by the FDA demonstrate that there is movement towards accepting these end-points. However, in other instances, even with an effect on progression-free survival, an overall survival benefit may be required to convince regulators of activity. So what is the solution?

The scientific community and the regulators must work together to redefine the paradigm, agreeing on those crucial elements which will show whether or not the drug works. First and foremost, does the drug block the metabolism of the tumour and prevent progression? To fully answer this question, we

must redefine the methods used to characterise drug activity and tumour progression using validated methodologies (eg real time blind assessment of responses and progression by an independent panel of experts). In addition to changing response criteria, genetic characteristics of the responding tumours must also be born strongly in mind by regulators. For example, high response rates in genetically selected tumours may not require large Phase III trials to validate activity in prospectively selected patients.

Cost

In the future, oncologists will find themselves in possession of a host of targeted agents. These next-generation cancer medicines may be used to treat specific patients (taking us a step closer to the concept of personalised medicine), given sequentially over time or employed in targeted combination regimens to block different pathways in parallel. But what are the cost implications of multitargeted therapy – looking at a future picture where several targeted agents used in combination may prove powerful enough to extend life by 20 or more years?

There is no simple solution. As a society we need to approach the cost considerations of targeted therapy together. Partnership is the key principle here. Pharmaceutical companies cannot resolve the cost dilemma alone but must rely on collaboration with governments, charities, doctors, patients and payers.

Opening a window of opportunity in targeted trials

Part of the problem in past clinical trials is that new agents were combined with toxic chemotherapeutic drugs – clouding our ability to see the benefits of targeted therapy. In addition, traditional trials were carried out in late-stage cancer patients after multiple lines of treatment when it is the most difficult to show efficacy. If we persist in developing our new targeted drugs like cytotoxics then the true value of these agents will remain hidden and unexploited.

Fortunately, a trend towards earlier studies is already emerging in the oncology arena. Neoadjuvant trials have been designed which open a small window of opportunity for targeted therapy before surgery. This approach has a two-fold advantage: imaging reveals if the drug has been effective in early disease, while tissue biopsy during surgery confirms if the MOA is as expected and defines the effect of the disease on the tumour.

The interesting paradigm emerging with this new thinking is the realisation that, in the past, cancer drugs have been developed backwards – not in the sequence in which the disease progresses. By treating patients in the early stage of disease with better chances of survival, we are looking for new and innovative ways to target and intervene earlier and smarter in cancer treatment. What we are doing now is opening a window of opportunity to better targeted drug development. Putting drug development and disease in step will not only improve the success of drug development, it may ultimately revolutionise cancer care for our patients.

Looking to the future

While looking for the cancer treatments of the future, drug developers must equally apply themselves to changing paradigms in oncology R&D – fixing what is wrong with current models and moulding their efforts, first and foremost, to the new targeted framework of therapy.

Identification of specific genetic changes or profiles associated with response or resistance to targeted agents will be a key element of translational medicine going forward. In addition, GSK and others are engaged in work to identify the genetic drivers of toxicity.

Looking even further ahead, cancer stem cells constitute a promising prospect for the future. This minority cell population exhibits extensive self-renewal capabilities and apoptosis resistance, with the ability to recapitulate tumour pathophysiology in immunocomprised animal models[24]. Stem cells also contain ATP-binding cassette transporters which remove drugs from the cell and thus render chemotherapy ineffective[24]. The concept of cancer stem cells has profound implications – both for our understanding of tumour biology and for the development of new treatments targeting these crucial cancer cells. Thus current therapeutic strategies must consider targeting cancer stems cells and their microenvironmental niche.

In addition to cancer stem cell targeting, the future may also bring the development of agents which allow us to intervene directly at the DNA level, preventing expression of oncogenes or enhancing expression of apoptotic genes.

Conclusion

Independent of market size, we are devoting research resources to truly unmet medical needs in oncology. I personally believe that each of these tumours share some common genetic drivers. In the future we may be able to treat tumours

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independently from their histology, by identification of specific genetic and biological elements. I foresee this understanding of tumour genetics, linked to key components at the biological and molecular level, as the key factor which will accelerate our success in developing cancer therapies of the future. DDW

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