

# Targeted Therapeutics

We have entered a golden age for experimental cancer therapy. In realising the full potential of targeted therapy, John Whittaker of Kendle International believes the critical next step will be to match molecularly targeted drugs with molecularly defined patients.



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From the pharmaceutical industry's earliest days, apothecaries, chemists and druggists have made various extracts, tinctures, mixtures, lotions, ointments and pills to treat disease, based upon observed symptoms. The symptomatic approach to describing disease, however, is undergoing something of a revolution in the 21st Century.

There is much evidence that cancers result from the accumulation of multiple biological and genetic events. Studies of the link between lung cancer and the increase of smoking in women, for example, reveal a lag of three decades between an increase in the habit and a marked rise in lung cancer. This time span reflects the accumulation of multiple biological and genetic events – maybe seven or eight interrelated occurrences – over a period of years.

New cancer treatments will result from the application of designer drug strategies to the development of molecularly targeted therapeutics (MTTs) that eventually can be shown to be involved in

the key steps of carcinogenesis: precise therapeutics that act as specific cancer cell signals to halt growth of cancer cells. Sequencing of the human genome linked to high-throughput technology for data analysis has yielded thousands of new molecular targets, against which researchers can test potential new anticancer agents. This has helped accelerate exponentially the rate at which we can develop rationalised drugs against molecular targets in close proximity to patients. Already many targeted therapies are being directed against specific cellular mechanisms involved in cancer, including aberrations in signal transduction, cell cycle regulation, evasion of apoptosis and tumour angiogenesis.

Let us consider some of the implications for those of us involved in developing and evaluating new therapeutics for cancer.

## GENETIC DESCRIPTION OF DISEASE AND PHARMACOGENOMICS

Historically, diseases have been categorised by organ pathology even though the

resultant disease categorisations are often genetically heterogeneous. More recently, pan-genomic assays of gene expression, protein levels and post-translational modifications of proteins have allowed us to move toward a genetic or metabolic pathway-based taxonomy of disease. The resultant regrouping of patients according to shared genetic lesions is anticipated to provide much more precise identification of patients likely to benefit from treatment with a given therapy.

Signalling pathways, essential for embryonic growth, but abnormally activated in cancer, seem to programme cancer cells to develop an abnormal tendency to behave like primitive, undifferentiated cells. The ‘hedgehog’ signalling pathway, for example, is important in many cancers, and is regulated at the cell surface by the opposing actions of the patched and smoothened molecules, together forming a receptor complex for hedgehog signalling. Identification and inactivation of targets of hedgehog signalling, such as the human patched gene, are likely to provide routes to treatment for an otherwise apparently diverse group of patients, including those with familial and sporadic forms of basal cell carcinoma, medulloblastoma (brain tumour) and Gorlin’s syndrome (basocellular neviomatosis) – a dominantly inherited syndrome that confers a high predisposition to cancer, mainly of the skin.

The new rationalised drugs for cancer, with their relatively low levels of toxicity, such as Herceptin® (trastuzumab) for breast cancer, Erbitux® (cetuximab) and Avastin® (bevacizumab) for colorectal cancer, Campath (alemtuzumab) for chronic lymphocytic leukaemia (CLL), Ritux® (rituximab), Bexxar® (tositumoma) and Zevalin® (yttrium-90-ibritumomab tiuxetan) for non-Hodgkin’s lymphoma (NHL) and Velcade® (bortezomib) for multiple myeloma, contrast dramatically with conventional cytotoxic chemotherapy. Conventional cytotoxic chemotherapy kills all dividing cells (good and bad) leading to the inherent side effects of cancer sufferers: nausea, hair loss and skin afflictions.

Cancers with kinase mutations respond to kinase inhibitors, but we also know that mutations in other pathways can mitigate this response. This makes the identification of patients likely to respond to kinase inhibitors increasingly complicated. Critically important to success in this effort, and to exploring mechanisms for kinase dependency, is identification of

pathway-specific molecular biomarkers that can be incorporated into accurate diagnostic assays suitable for use in the clinic (for example, serum markers or imaging probes). In clinical trials, collection of tissue and serum samples from individual patients for microarray analyses will allow us to confirm whether they have a pattern of gene expression known to be a predictor of response.

Regulatory authorities, such as the US Food and Drug Administration (FDA), encourage voluntary submission of pharmacogenomic data supporting applications for marketing approvals. Such data is likely to become an important and integral part of clinical trials and a requirement for regulatory submissions in the near future. Already, it is believed that pharmacogenomic information is being collected in four out of five new trials of anti-cancer agents. The hugely increased use of microarrays as diagnostic kits for selection of sub-groups of patients into more focused, often smaller, clinical trials is anticipated, along with the serial use of such kits on a routine basis in the clinic for administration of appropriate personalised treatment to individual patients.

It is still an unfortunate fact that as many as half of all drugs do not work for the people for whom they are prescribed. One size does not fit all where therapeutics are concerned.

#### **SUCCESS WITH TARGETED AGENTS**

MTTs, such as Herceptin® (trastuzumab) and Glivec® (imatinib), are designed to activate or deactivate exquisitely complex molecular interactions in the body. Human epidermal growth factor (HEGF) is a protein that occurs naturally in the body. When it attaches itself to the Her2 protein on the surface of breast cancer cells, cell division is promoted. Herceptin blocks this process by attaching itself to the Her2 protein so that HEGF cannot reach the breast cancer cells, thereby stopping the cells from dividing and growing. The compound also stimulates the body’s own immune cells to target and destroy cancer cells. All patients with breast cancer should undergo Her2 testing at diagnosis to determine their suitability for treatment with Herceptin. The significant clinical utility of MTTs for well-defined subpopulations of patients with breast cancer has been demonstrated in various recent trials. In recent NSABP (B-31) and NCCTG (N-9831) clinical trials comparing Herceptin® (trastuzumab)/Taxol® (paclitaxel) versus single agent Taxol®

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(paclitaxel) following on from doxorubicin/cyclophosphamide therapy, the Herceptin® combination regimen significantly increased progression-free survival. More good news came from results of a recent ECOG trial (2100) that demonstrated that Avastin® (bevacizumab), given as first-line therapy, increased progression-free survival for patients with locally recurrent or metastatic breast cancer.

The 2005 meeting of the American Society of Clinical Oncology (ASCO) saw the presentation of results of the HERA clinical trial described by eminent oncologists as ‘astonishing beyond belief,’ ‘the most stunning results in a clinical trial’ and a ‘revolution in the treatment of cancer.’ Results relating to the international HERA study, conducted in 39 countries and involving 5,000 women, showed that Herceptin® had achieved a 46 per cent reduction in the risk of recurrence of early-stage aggressive breast cancer. Other recent trials have shown similar results in women with an advanced stage of the disease. These results are achieved against a backdrop in which breast cancer remains the third most common cause of cancer death, with nearly 10 per cent of women likely to be diagnosed with the condition during their lifetime and around 13,000 victims each year. The HERA result suggests that if every breast cancer patient could be tested for Her2, and all positive patients treated with Herceptin (after surgery and with other chemotherapy), then the lives of 2,800 women could be saved each year. There is hope that Herceptin may have a role in saving the lives of patients with cancers of the lung, prostate, stomach and ovary, as well as leukaemia.

### THE RANDOMISED DISCONTINUATION TRIAL DESIGN

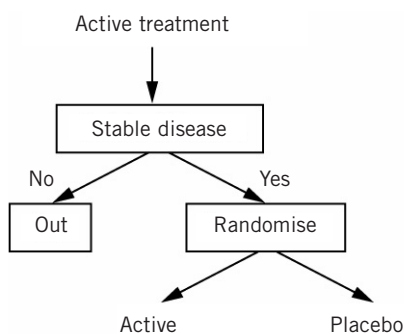
If we accept that one type of drug is not ideal for all patients then our concept of the ideal clinical trial must change accordingly. It is no longer a radical idea to believe that many previous Phase II designs for evaluating anticancer agents are wrong and outdated, and that we need a new approach to clinical trial methodology in oncology. To an increasing extent, in breast cancer studies such as the one mentioned above, we are finding that it is the biology of the tumour, as opposed to nodal status, age or hormone status, which determines outcome or benefits of therapy.

As our understanding of system biology and pharmacogenomics advances, biological methods can be used to a much greater extent to select different therapeutics for different people. It is time now for drug developers to concentrate to a much greater extent on trying to identify the optimal regimens for individual patients, rather than planning large trials in which all patients get the same kind of treatment.

The randomised discontinuation design is an example of an approach that enables different treatment regimens to be targeted at the subset of patients most likely to benefit from them. There are advantages and disadvantages of such an approach compared to what has been the standard one-size-fits-all approach that has been adopted generally thus far. One of the major disadvantages is that relatively small numbers of patients receive a given treatment compared to a large starting population. One of the distinct advantages of this approach, however, is that a given therapy can be evaluated in a small but considerably enriched population. Any therapeutic benefit is likely to be amplified proportionately to the degree of such enrichment – assuming that the enrichment is appropriate for the agent and molecular target.

Sorafenib (BAY 43-9006), a novel signal transduction inhibitor that prevents tumour cell proliferation and angiogenesis through blockade of the Raf/MEK/ERK pathway (at the level of Raf kinase and the receptor tyrosine kinases VEGFR-2 and PDGFR- $\alpha$ ), was recently evaluated in a Phase II multicentre, randomised discontinuation trial. This study allowed enrolment of patients with a wide variety of solid tumours. After an initial treatment course of 12 weeks, patients were sorted according to their initial response. Those with tumour shrinkage of at least 25 per cent continued on the drug. Those with stable disease (tumour shrinkage or growth less than 25 per cent) were randomised to receive either the active drug or a placebo. In this trial, with an agent originally conceived for treating colorectal cancer, it soon became apparent that many patients with kidney cancer were responding. Interim results presented at the 2004 ASCO Annual Meeting demonstrated a significant and lasting benefit for a subset of patients with advanced renal cell cancer. Of the 37 (out of 106) patients who had at least 25 per cent tumour shrinkage in the first 12 weeks, 88 per cent were progression-free after 24 weeks. For this group, the median time to progression was nearly one year (48 weeks). Sorafenib appeared to cause tumour regression in a subset of patients, to maintain those regressions and to do so with limited toxicity – even though most of the patients had advanced disease that had not responded to at least one and sometimes several previous systemic treatments. This is against a backdrop in which only 10 to 15 per cent of patients with metastatic kidney cancer respond to standard immunotherapy, which can be very toxic. In this study, about 15 per cent of patients had a comparable ‘partial response,’ but nearly two-thirds of the patients had stable disease when measured at 12 weeks, and for many of them this persisted

Figure 1: Randomised Continuation Design



for months. These results were sufficiently encouraging to justify commencement of a Phase III trial to test the agent in 800 kidney cancer patients.

The randomised discontinuation trial design allows testing of a new drug for effects in many tumour types, and then subsequent concentration on patients most likely to benefit. It provides broad information about a drug's activity including assessment of disease stabilisation. The value of this flexibility is evident from the high response rate in kidney cancer obtained with an agent designed originally for colorectal cancer. The trial design may well have rescued a promising drug from obscurity. Sorafenib might have been abandoned had its effects in renal cell cancer not emerged, as it showed little efficacy in 138 patients with colon cancer. Sorafenib also appears to be active in sarcoma and thyroid cancer.

### ENDPOINTS FOR REGULATORY AUTHORITIES

Drug developers and regulatory authorities need to work together to gain acceptance of new trial designs for registration of novel MTTs. The oncology Drugs Evaluation Office of the FDA recently issued two new guidelines for discussion: the 'Experimental IND' and 'Critical Path Approach.' Both of these initiatives are evidence of an openness and willingness by regulators to help establish a new paradigm for early stage evaluation of MTTs, which often have low levels of organ toxicity, such that they can be assessed according to pharmacodynamic endpoints rather than in terms of dose-limiting toxicities. In later studies, such agents are difficult to assess in terms of tumour response (not being cytoreductive in effect, so requiring novel specific biomarkers for determination of their efficacy in terms of clinical benefit). Few biomarkers are expected to be accepted by regulators in the near future as truly validated surrogate endpoints of clinical benefit. Currently, validated surrogate endpoints are rare indeed.

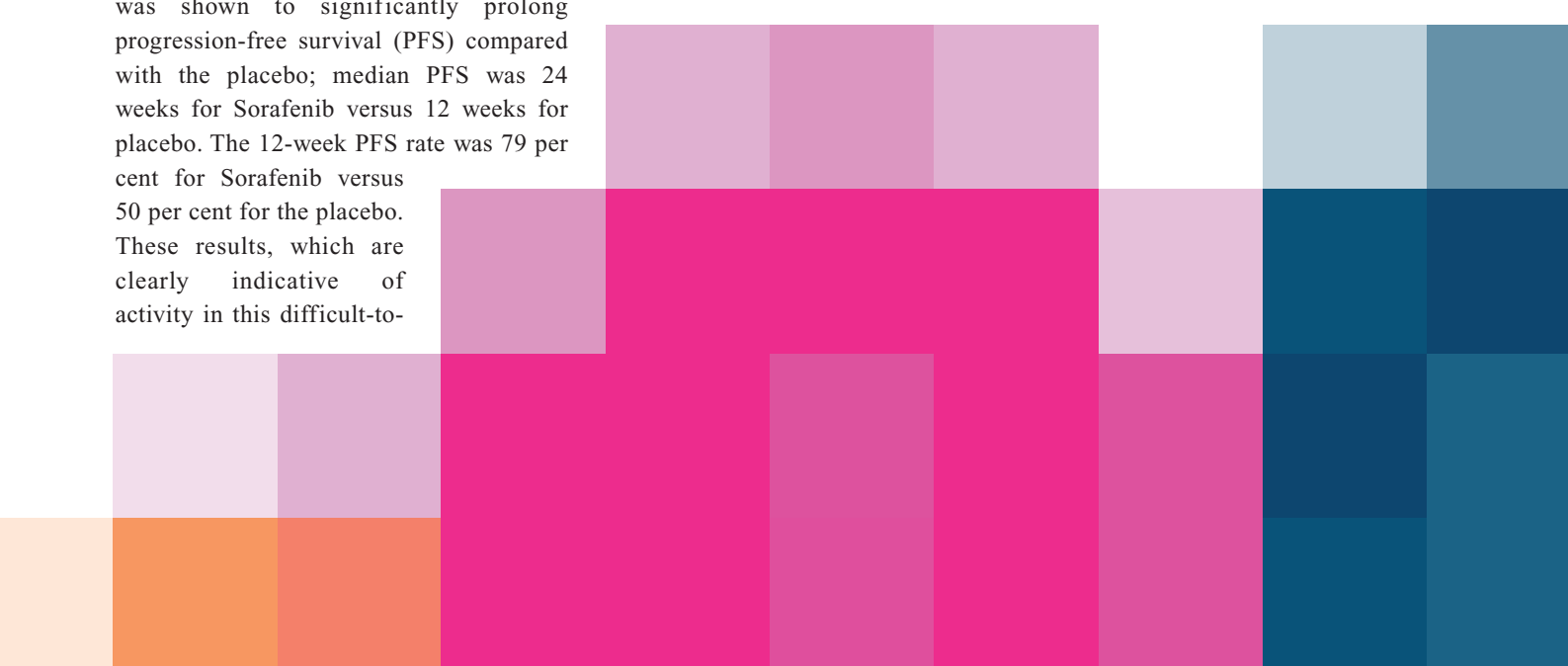
Results of the Phase III study of Sorafenib (mentioned above) were presented at the 2005 ASCO Annual Meeting. In this double-blind trial studying patients with previously treated confirmed advanced clear-cell RCC, Sorafenib was shown to significantly prolong progression-free survival (PFS) compared with the placebo; median PFS was 24 weeks for Sorafenib versus 12 weeks for placebo. The 12-week PFS rate was 79 per cent for Sorafenib versus 50 per cent for the placebo. These results, which are clearly indicative of activity in this difficult-to-

treat population, were achieved despite a very low (two per cent) partial response rate, although tumour shrinkage occurred in a high proportion of patients. Whilst there was substantial tumour shrinkage, it was not sufficient in most patients to meet the strict 30 per cent reduction criterion required by the RECIST standards to constitute a partial response. The commonly used RECIST criteria for assessing response serve us well for conventional cytotoxic agents, but may well underestimate the utility of targeted cytostatic agents with limited cytoreductive properties.

It is interesting to note that when Iressa® (gefitinib) received accelerated FDA approval as a monotherapy third-line treatment of patients with locally advanced or metastatic NSCLC, the overall objective response rate (for two test doses combined) was 10.6 per cent (15 of 142 patients) (95 per cent confidence interval 6 per cent-16.8 per cent). The 142 trial patients who were refractory to, or intolerant of, a platinum and docetaxel, comprised the evaluable population for the efficacy analysis. A partial tumour response occurred in 14 per cent (9 out of a possible 66) of patients receiving Iressa® 250 mg/day and in 8 per cent (6 out of a possible 76) of patients receiving gefitinib 500 mg/day. Iressa® was approved under accelerated approval regulations on the basis of a surrogate endpoint response rate. No controlled Iressa® trials conducted to date demonstrate a clinical benefit, such as improvement in disease-related symptoms or greater survival. Iressa® plus chemotherapy has demonstrated no improvements in survival, time to progression, or response rate over chemotherapy alone. Tarceva® (erlotinib) is the only drug in the epidermal growth factor receptor (EGFR) class to demonstrate an increase in survival in a randomised Phase III clinical trial in advanced NSCLC patients, and to receive full regulatory approval in advanced disease.

### PERSONALISED MEDICINE ON ITS WAY?

New molecular targets arising out of the human genome project have helped accelerate the rate at which we can develop rationalised drugs against molecular targets in close proximity to patients. Already many targeted therapies are being directed against specific cellular mechanisms involved in cancer. The



age of molecularly targeted cancer therapeutics has arrived and drug developers need to consider the implications that this is having, and will have, on clinical trial design.

By extrapolating from genetic to sporadic illness, it becomes possible to group together for treatment with a given therapy all those patients with apparently disparate diseases who share the same underlying molecular defect. In clinical trials, proof of concept in one member of this group of illnesses might well be applicable in other members of the genetic group with a different illness.

We know that cancers with kinase mutations respond to kinase inhibitors, but we also know that mutations in other pathways can mitigate this response. This makes identifying patients likely to respond to kinase inhibitors increasingly complicated. Therefore, appropriate diagnostic testing will be important.

Many conventional Phase II trials test the effects of a new drug on patients with a specific disease, such as colon cancer, and limit the goal to determining the percentage of patients who have at least a 30 per cent reduction in tumour size. Using clinical trial approaches, such as the randomised discontinuation trial design, patients can be enrolled with a wide variety of solid tumours. Drug

developers can use rational science to guide the drug development process selecting appropriate patients for a given therapeutic. The design enables enrichment of the patient population from those likely to benefit for a given treatment and has the potential to rescue a promising drug from obscurity.

We need to be careful, though, in using tumour response rate as an endpoint for MTTs. A response rate of 10 per cent, which caused so much controversy with Iressa, may be typical of such agents in unriched general populations of patients, but should not necessarily be an impediment to approval of non-cytoreductive agents.

Ultimately, the best endpoint for clinical studies of anti-cancer agents is enhanced survival, whether in overall terms or as represented by surrogates such as PFS. Personalised medicine in clinical practice is the end goal, but we struggle with the difficulty of proving that genetic markers correlate reliably with clinical outcome (across patient groups and geographies). Personalised medicine is about the patient, and that is what we drug developers and clinical trials specialists need to be about too. ♦

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