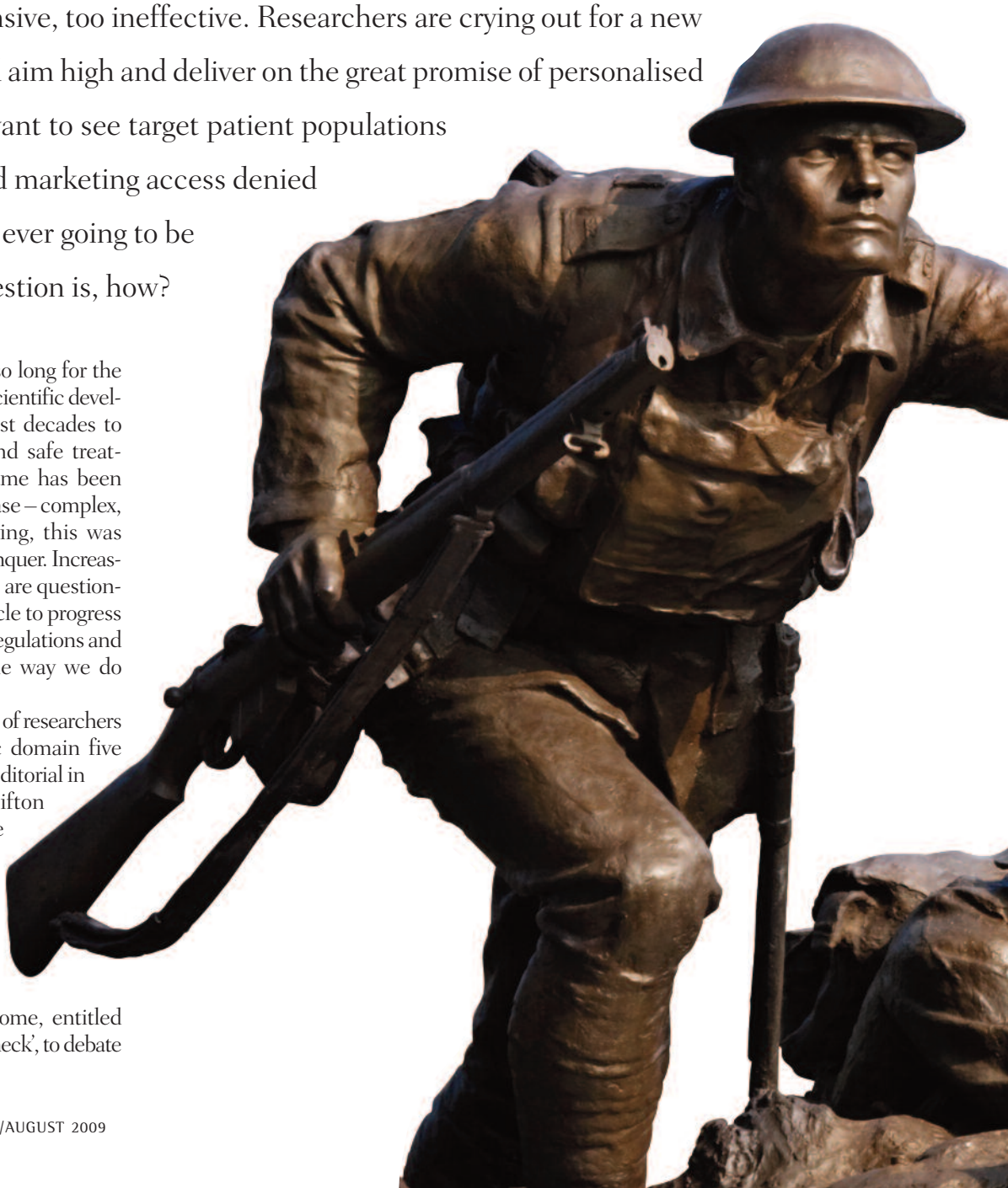
Beyond trench warfare

American and European researchers in search of a winning strategy

➜ Marc Beishon

Too slow, too expensive, too ineffective. Researchers are crying out for a new battle plan that will aim high and deliver on the great promise of personalised therapies. We all want to see target patient populations identified early, and marketing access denied to drugs that aren't ever going to be much use. The question is, how?



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Why is it taking so long for the extraordinary scientific developments of past decades to translate into effective and safe treatments? Traditionally, blame has been laid at the door of the disease – complex, mutating and metastasising, this was never going to be easy to conquer. Increasingly, however, researchers are questioning whether the real obstacle to progress may lie in the paradigms, regulations and incentives that govern the way we do cancer research.

The growing frustration of researchers spilt over into the public domain five years ago, with a 14-page editorial in *Fortune* magazine by Clifton Leaf, entitled 'Why we are losing the war against cancer'. In 2007 international figures from research, industry and regulators gathered at a media forum organised by the European School of Oncology in Rome, entitled 'Cancer: time for a reality check', to debate

whether the problem lies in dysfunctional structures and practices, and if so, what to do about it (see *Cancer World* January–February 2008).

This January, David Stewart and Razelle Kurzrock, both medical oncologists at one of the world's top institutions, MD Anderson in the US, joined the debate. In a paper in the *Journal of Clinical Oncology*, 'Cancer: the road to Amiens', the pair discuss the factors that are keeping drug trials in the 'trenches' and what could break the war of attrition, leading to a battle that makes much more progress (Amiens refers to a famous battle that achieved just that in World War I). The key points are that the efficacy bar for trials is set too low, and the safety bar too high, and progress over two or more decades now has been at a snail's pace since genuine breakthroughs were made in diseases such as leukaemia and testicular cancer.

"Setting the efficacy bar low was to ensure that we were not throwing out good drugs by setting it too high – that was reasonable 25 years ago, but it has not worked," says Stewart. "Looking back, it was childhood leukaemias that were held up as a model, where one small advance was made after another, but the difference is that researchers then were not looking to prolong life by a few months but to increase the cure rate. So we have not followed that paradigm at all."

As long as much research is directed at one tumour category rather than the many different types it actually is, in breast, lung, colon and so on, the large randomised studies simply will go on failing to find much benefit even though a small subset may gain greatly. "And so we toss the drug out because it was not effective in 95% of a patient population, or those that do get a *P*-value of 0.05 and change survival by just a few weeks get high-profile presentations at the annual ASCO (American Society of Clinical Oncology) conference and an expensive and often toxic drug then becomes the standard of care. Everyone gains except the patient – the researchers get their *P*-value for the drug, the drug company gets to sell it and the cancer centre gets to charge for it."

Discarding a drug like this or accepting low efficacy are both unacceptable, says Stewart, but of course raising the efficacy bar may prove to be very difficult. Increasing personalised approaches are, of course, the answer, and he is pleased that ASCO made 'personalising cancer care' the theme of its main conference this year, and that there are encouraging examples of agents that target relatively small subsets of patients with certain tumours. He mentions that, in his field, there are EGFR (epidermal growth factor receptor) inhibitors that are active agents in non-small cell lung cancers (NSCLC) with uncommon EGFR mutations, and if patients are properly selected, a high proportion may benefit. Many oncologists are also calling for much better molecular profiling of tumours, to combine this information with the usual histopathology, and Stewart now feels that the many millions of dollars spent on large randomised phase III trials would be much better used in concerted attempts to develop such profiling and move towards smarter, smaller phase II and III trials.

"The experience with NSCLC, and with trastuzumab [Herceptin] in breast cancer and imatinib [Glivec] in chronic myeloid leukaemia and GIST, tells us smarter approaches are possible if we keep on looking," he says. "The problem with thinking it is too hard is it becomes a self-fulfilling prophecy, and you won't find it." By trying to identify subpopulations much earlier, or by specifically looking at subgroups in larger controlled trials, he feels we have a much better chance of investigating cases where high activity occurs. "You also have a better chance of finding out why a drug did not work if it is a complete bust."

Aiming high

The practical difficulties of pursuing the smarter route, however, are many. Tumour sample acquisition and molecular profiling are very costly, but investing much more at this point, say Stewart and Kurzrock, means that we can "find the right study for the patient rather than the right patient for a study". Further, phase II trials should target highly resistant tumours, rather than what is termed 'lightly pretreated patients', where successful trials often actually do no better than older drugs and the phase III trials then fail. We also need, they say, to find out why some tumours grow back after a substantial shrinkage, and the way we measure response needs redefining. We should not be happy either with converting cancer to a chronic disease – cell killing and eventual eradication should be the aim as, like tuberculosis, cancer builds up resistance

over time. Progression-free survival is, however, a better measure than overall survival in metastatic disease (because of confounding factors such as comorbidities), but at least a six-month absolute increase should be aimed for.

Then there is the high bar of safety, with animal studies being poor predictors of toxicity (and also antitumour activity), and an 'obsession' with not allowing deviations from protocols. Stewart notes that if trial regulations stipulate a very low toxic death rate and if rules overall also delay advances by five years (which is typical in his view), the number of life years saved in a large study could be very small compared with those that might have been gained by speeding things up.

He also says chemotherapy and targeted agents are mainly all we have to work with at present, although other drug therapies and approaches are promising, such as gene therapy (he mentions a study that is delivering missing tumour suppression genes into cells). "But I tell my medical oncology residents that immunotherapy has been about to cure cancer for 40 years, but they may be able to get on the cover of *Time* magazine with a study with little data that doesn't prove to work."

Overall, Stewart feels strongly that complex regulatory structures and a culture of inertia among clinicians to embrace change are the chief culprits. "The biggest barriers I see are fear of government agencies that they will be blamed if regulations are changed and something goes wrong; the reluctance of investigators to change the outcome goals; and there are some major disincentives to change. A major problem in the US is the number of different agencies that come up with regulations, and even though each one appears to be reasonable the net effect of combining them is substantial. One grain of rice will not plug the drain in your sink, but you do not need to put too many together before you have enough of them to markedly slow drainage.

"And I feel that US actions have an adverse ripple effect around the globe. The problem is magnified by the fact that most drug companies try to target the US market, and if the US National Cancer Institute funds an international study, our rules tend to be applied and this further internationalises some of the regulatory issues that arise from US agencies."

European alliance

Stewart says he expected some hostile reaction to the paper, but has largely received positive responses, especially from Europe, and adds that well-known medical oncologists support similar reform – José Baselga, president of ESMO (European Society for Medical Oncology) for one. Jaap Verweij, head of the department of medical oncology at the Erasmus University Medical Centre, in Rotterdam, and a phase I trials expert, is another – on the crucial issue of increasing efficacy, he fully agrees with Stewart on the need to move away from the 'crazy' situation of aiming for small survival gains in large patient populations.

But he worries that there is too much optimism about the possibilities for personalisation. "If you want to focus on a selected population, that is the best way to go, but how do you know beforehand if it is the right one? They [Stewart and Kurzrock] give the example of imatinib, which I was involved with, but we did not know what to look for when we started some eight years ago. It was not until after phase III studies we found out how to select our patients. The dilemma is you can only find out the predictor once you have done phase III development – then you have the information you wish you'd had at the beginning."

Stewart and Kurzrock, he adds, correctly point out the need for preclinical models that better predict human response, and give examples of treatments based on molecular changes, but these have been found only after looking at thousands of patients. "I fully agree with the concept, but it will take a while before we get there and we need to be realistic," says Verweij, who also notes that researchers need to be certain about selection of patients in early phases for drug mechanisms – as the wrong assumptions could lead to other activity being missed later on.

He gives an example where such a wrong assumption could have led researchers down the wrong path, in a paper entitled 'No risk no fun: challenges for the oncology phase I clinical time-performance', a topic he also addressed in the Michel Clavel lecture given at last year's EORTC-NCI-AACR symposium on Molecular Targets and Cancer Therapeutics ('No risk no fun' being a saying of the late cancer medical oncologist Michel Clavel, meaning 'Take your chances and don't be too defensive').

In Verweij's view, "Regulations and overprotection are the real mud – we should never compromise on safety, but we can be overconcerned." Like many in Europe, he worries that the European clinical trials directive has brought trials 'almost to a standstill' in several countries and estimates that restrictions are lengthening drug research by four to five times.

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THE SLOW GAINS OF TRENCH WARFARE

Drug	Mechanism	Disease	Random Assignment	No. of Patients	Survival (months) Median	Change	*P*
Gemcitabine	Cytotoxic	Pancreatic cancer	Gemcitabine vs fluorouracil	126	5.65 vs 4.41	6 weeks	0.0025
Bevacizumab	Anti-VEGF antibody	Colorectal cancer	Bevacizumab + FOLFOX4 vs FOLFOX4	829	13.0 vs 10.8	2.2	<0.05
Erlotinib	EGFR inhibitor	Pancreatic cancer	Erlotinib + gemcitabine vs gemcitabine + placebo	569	6.24 vs 5.91	11 days	0.038
Bevacizumab	Anti-VEGF antibody	Non-small-cell lung cancer	Bevacizumab/carboplatin/paclitaxel vs carboplatin/paclitaxel	878	12.3 vs 10.3	2	0.013
Sorafenib	VEGFR and Raf kinase inhibitor	Renal cancer	Sorafenib + supportive care vs placebo + supportive care	902	4 vs 2	2	<0.001
Temozolomide	Cytotoxic	Glioblastoma multiforme	Temozolomide + radiation therapy vs radiotherapy alone	573	14.6 vs 12.1	2.5	<0.01
Docetaxel	Cytotoxic	Prostate cancer	Docetaxel + prednisone vs mitoxantrone + prednisone	1,005	18.9 vs 16.5	2.4	0.0094
Topotecan	Cytotoxic	Cervical cancer	Topotecan + cisplatin vs cisplatin	293	9.4 vs 6.5	2.9	<0.05
Cetuximab	Anti-EGFR antibody	Colorectal cancer	Cetuximab + supportive care vs supportive care	572	6.1 vs 4.6	1.5	<0.05

These randomised clinical trial results show that few of the most commonly used anti-cancer drugs approved in recent years have been able to improve survival by even three months, while some give as little as 11 extra days

VEGF = vascular endothelial growth factor, EGFR = epidermal growth factor receptor, FOLFOX4 = fluorouracil/leucovorin/oxaliplatin, VEGFR = vascular endothelial growth factor receptor
Source: D Stewart, R Kurzrock (2009) *JCO* 27:328–333

A JOINED-UP STRATEGY

His prescription is for investigators and regulators to talk to each other much more and discuss how to adjust, for example, dose escalations in early-stage trials and more flexible protocol designs, and other avenues he discusses in his paper. "Phase I work is also dominated by the pharmaceutical industry, but they need academic interventions to do the work – ultimately we have the same aim in wanting to find the best agents and make optimal use of each other's expertise."

Verweij expresses exasperation that where certain molecular mutations are clearly known, as with targets for Glivec, "still people started chasing the non-mutated characteristics – that does not make any sense". He is also critical of the European Medicines Agency (EMEA) for recently approving Glivec for adjuvant treatment in GIST, despite no evidence of improved survival (although of course the drug is 'fantastic' for metastatic disease). "We can calculate then that we could spend more than €10 million for each quality life year gained through this adjuvant treatment," he says. "The US Federal Drug Administration [FDA] is also setting bad examples with approvals like this. If I look at the budget of my department, about a quarter goes on drugs and many are making minimum contributions to survival, but the healthcare system demands them because they are approved for use."

Regulators and industry certainly come under much fire from academic

oncologists such as Verweij. Another seemingly extraordinary example he cites is a trend for drug companies to try and sign up many sites for trials – "We have just had a simple phase II protocol sent to us where they are trying to accrue 38 patients – across 30 sites. I can't see how they will get results like that and it will also slow them down tremendously, given all the extra regulations involved every time you add a site." It is common, he adds, for such protocols to be sent out on a 'take it or leave it' basis – and he feels strongly that there is big gap between the 'paper pushers' and doctors who actually deal every day with real patients.

But regulators are certainly well aware of the issues. In the US, there are programmes such as the FDA's Critical Path Initiative, an effort to modernise the scientific process through which a 'potential human drug, biological product, or medical device is transformed from a discovery or proof of concept into a medical product'. Further, in 2007 the FDA set up the Clinical Trials Transformation Initiative in partnership with Duke University, and ASCO and the FDA have convened a group of experts to discuss alternative trial designs.

A strategic balance

In Europe, experts from EMEA published a detailed opinion paper last October, entitled 'Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma'. This is a very detailed look at the issues facing approvals for all types of drug, and the authors point out that the various and increasing pressures on regulators may all be worthy but ultimately irreconcilable.

The many issues discussed include the pitfalls of early approval, as exemplified by gefitinib (Iressa) in NSCLC where, after accelerated approval by the FDA, licensing was restricted when later studies showed no survival benefit (but Stewart notes that Iressa is one of the drugs that showed real benefit to a subgroup). An example where a faster track approval has met with more success is with EMEA's 'conditional' approval of sunitinib (Sutent) for renal cancer, which showed high activity in selected patient groups, and which gained full authorisation fairly quickly after more data on progression-free survival was provided. Metastatic renal and also thyroid disease are among Verweij's own list where new, more effective, targeted inhibitors are becoming available.

In turn, the trade-offs of early market access strategies are examined – the use of biomarkers and surrogate endpoints for efficacy; results from interim analyses; and a reduced-size safety database. The mechanism of conditional and staggered (for different indications) approvals for drugs are explored, as are establishing a risk management system over the full lifecycle of drugs, and the 'young science' of pharmacoepidemiology – bringing in data from healthcare providers after the drug is approved.

And the authors are optimistic about the impact of personalised approaches and the earlier demonstration of a positive risk/benefit profile by way of smaller or shorter trials. Overall, they speculate that a gap that exists now in the regulatory hurdles between drugs for life-threatening and non-life-threatening conditions will widen in favour of the former.

Undoubtedly, there are huge institutional as well as scientific challenges in the war against cancer. But picking the battles that can be won much more quickly and efficiently – and getting everyone on the same side – is surely one promising way to proceed.

Tactical discussion documents

Key background documents to this article include:

- Cancer: the road to Amiens, by David Stewart and Razelle Kurzrock (*JCO* 27:328–333)
- No risk no fun: challenges for the oncology phase I clinical time-performance, by Jaap Verweij (*Eur J Cancer* 44:2600–2607)
- Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma, by Francesco Pignatti et al (*Nature Reviews Drug Discovery* 7:818–826

For more general background, see also:

- Why we're losing the war on cancer (and how to win it), by Clifton Leaf (*Fortune* magazine, 22 March 2004)
- Our responsibility, our choices: ESO invites the media to a reality check on cancer, by Anna Wagstaff (*Cancer World* magazine January–February 2008)

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