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Learning to care

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## Education & knowledge through people & facts

Jaap Verweij

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# When the trial you need is just over the border

Kathy Redmond ■ EDITOR

The bureaucratic obstacles that often prevent European cancer patients from joining clinical trials in other Member States came under the spotlight recently in the case of a young woman with melanoma. Belgian-based Patricia Garcia-Prieto has stage IV melanoma which is positive for the BRAF V600 mutation. When her disease started to advance she decided her best chance of living longer, with a better quality of life, lay in joining a phase III trial with PLX 4032 that is running in France. Her oncologist agreed that this would be her best option, and the French investigators deemed her eligible for the trial.

The trial does not require hospitalisation and the only costs that her Belgian insurers would have to cover would be some follow-up tests (such as PET scans and MRIs). All she needed from her insurers was an E-112 form – the EU administrative mechanism that gives citizens access to pre-authorised care in another Member State. The insurers refused the request, however, stating that it was the patient's own personal motivation to join the trial – not a need to secure healthcare abroad. Patricia Garcia-Prieto launched a campaign to get that E-112 form, using as many contacts as possible to get the decision overturned. Her story was covered in the respected French-language newspaper *Le Soir* (http://tiny.cc/patriciastory).

As a result of concerted pressure, the insurance company gave her an E-112 form valid for three months. She started the trial on 31 March, knowing that she has only a 50% chance of receiving the trial drug PLX 4032, but happy that she has done everything in her power to give herself the best chance of living longer – a key consideration for any mother of two young children.

With European citizens becoming ever more mobile, issues surrounding their rights in relation to cross-border healthcare need urgent attention. At the end of last year there were strong hopes an agreement could be reached that would have paved the way for an EU Directive that would allow patients like Patricia to join trials in other Member States.

Unfortunately, that agreement is being held up by concerns covering a broad spectrum of issues, none of which should be impossible to resolve. These include protecting the principle of subsidiarity, definitional confusion about what constitutes hospital care, worries about clinical oversight and liability, issues surrounding patient confidentiality and lack of agreement about what can be reimbursed.

Efforts continue to clarify these outstanding concerns, and the few Member States that are stalling the process are under pressure to sign up to revised proposals. The European cancer community can contribute to the current debate by highlighting the problems patients and clinicians face in getting access to cross-border healthcare, and suggesting workable solutions that would be quick and easy to implement.

# Jaap Verweij:

## an intelligent approach to drugs

Marc Beishon

As head of medical oncology and an early-phase trials expert at one of Europe's most dynamic cancer centres, Jaap Verweij has a lot to say about how drug developers are using the wealth of biological information they now have access to. But with therapies increasingly aiming to control rather than cure, he says, an intelligent approach to drugs must also be about tolerability and affordability.

Medical oncologists see themselves at the forefront of research and treatment not because of any superiority, but because of the very nature of cancer. As first-line treatment has improved greatly, the shift to cancer mortality being mainly due to metastatic disease has thrown the spotlight on systemic treatments that reach the whole body, and only drugs can do that.

But with this remit comes great responsibility, as Jaap Verweij, head of medical oncology at the Erasmus University Medical Centre in Rotterdam, is the first to point out. Not only are medical oncologists duty bound to know thoroughly the already-huge arsenal of cancer drugs in the pharmacy from a clinical standpoint, but increasingly they also need to think about the cost of their treatment decisions.

"And those involved in clinical research have a particular responsibility about whether we are investigating the right functionality, and using the right trial designs, regulations and so on. Further, medical oncologists must not confine themselves to knowledge of cancer drugs – interactions with other medicines and with complementary substances such as herbal remedies can also be crucial to clinical practice.

"My view is that the level of knowledge you now need to be a medical oncologist and administer systemic therapies is enormous, given that the therapeutic window can be so narrow before we go over the edge, and that side-effects can be so difficult to manage."

Verweij, who has headed the medical oncology translational pharmacology unit at Erasmus for more than 20 years, speaks from long experience in early-phase clinical trials and a deep interest in the pharmacology of drugs. "I'm not formally a pharmacologist, but all my research is pharmacology driven," he says. "You must have this expertise to bring new drugs to the clinic, using pharmacokinetics and pharmacodynamics to understand both what a drug is doing to the body, and what the body is doing with the drug."

While only some oncologists are involved in this sharp end of trials, Verweij is concerned that far too many are not even receiving the level of training in pharmacology that he feels is necessary for day-to-day work in the clinic, for instance in dealing with adverse drug interactions as well as the therapeutic window.

FRANK VAN BEEK/CAPITAL PHOTOS

"I'm also worried that we are not training enough oncologists in how do to research at any stage of drug development, and in particular it is becoming much harder to attract people into an academic career."

While the Erasmus has an international reputation for cancer research, Verweij has also spent a lot of time helping to raise awareness of best practice and develop world-class tools. Notably he was one of the founders of the RECIST (Response Evaluation Criteria In Solid Tumours) 'language', which sets out common ground for oncologists to describe how tumours change, or not, in trials. He is also a specialist in sarcomas, the complex and difficult-to-treat rare cancers that include GIST (gastrointestinal stromal tumours), and so is an expert now in the use of Glivec (imatinib), which continues to be a key model in what to do – and what not to do – in chasing the functionality of targeted therapy. (The new treatment paradigms now emerging for GIST are explored in this issue's e-grandround article, p15.)

But early drug investigation in all its aspects is Verweij's key topic, and one on which he has spoken and written extensively, in trenchant editorial comments on drug development as well as highly technical examinations of the challenges for trial design. The pharmaceutical industry and regulators have been in his firing line, as indeed have some oncologists, notably for the use of Glivec as an adjuvant therapy in GIST. "My clinical practice is based on hard scientific evidence, but some doctors seem to base their practice more on beliefs," he says.

Unlike many doctors, Verweij's career choice was not based on some early deep conviction – he had 'no clue' what to study after finishing high school. It was his father who forced him to tour university introductory days, and of all things, it was a model of an elephant's heart he saw when touring one medical faculty that decided him. He studied at Utrecht. "Then after the usual phases of wondering what to specialise in, I settled on internal medicine, as it offered the broadest and most holistic approach."

Training in Eindhoven, he worked on the oncology ward. "I became very frustrated by the attitude that, 'It's cancer, there's nothing we can do.' I thought that was terrible – even if there was no treatment, we could at least help patients. My mentors there, Wim Breed and Harry Hillen, were of the same opinion and were very important in shaping my future.

"I sat with a woman who had non-Hodgkin's lymphoma – she knew we couldn't treat her but I lent her my ear during a night shift. I could see her mentally gaining strength while I listened. After my internal medicine training, I wanted to be a medical oncologist."

Verweij wrote to Bob Pinedo at the Free University Medical Centre in Amsterdam and gained a fellowship there. Pinedo was the first professor of medical oncology in the Netherlands, and a great pioneer and lateral thinker, says Verweij. "He's the one who trained me and many others in research, and taught me the relevance of the multidisciplinary – and lateral – approaches to treatment. Whenever we said, 'This is the best treatment option,' he'd say, 'What's another possibility?'"

After that experience, there was little possibility of Verweij returning to a general hospital as an ordinary medical oncologist, and he duly secured a post at the Erasmus where he could carry out cutting-edge research as well as do clinical work. "I set up an early

## A LANGUAGE FOR RESPONSE

Verweij and colleagues at the EORTC (European Organisation for Research and Treatment of Cancer), the NCI (National Cancer Institute in the US) and in Canada developed RECIST in 2001 as a way for researchers to describe what they were seeing, particularly in phase II studies.

Essentially, RECIST is a way to make the life of researchers easier by applying validated criteria from a large and growing database of adult solid tumours, to assess objectively shrinkage and progression, which are both used as endpoints in trials.

The database started with 3000 patients from industry and EORTC trials with validated data, so it had been shown to be reliable, and now it's up to about 10,000. "Of course if we could also build a database with PET scans we could probably come up with something much more precise, but we do not have validated data yet for this."

Just as previous WHO response criteria were subject to modification, and in any case were not validated, the much more robust RECIST has also been revised – Verweij and colleagues issued RECIST 1.1 in 2008, with changes such as reducing the number of lesions to be assessed (see www.eortc.be/recist), while others have worked to address some anomalies. An important one is the response of GIST to Glivec (imatinib), where tumours can appear to progress when in fact they are responding to treatment (see also e-grandround p 15). As another researcher has titled a paper: 'We should desist using RECIST at least in GIST'. More generally, Verweij believes that shrinkage is not a particularly useful way to measure response. "Experts may not be so great at assessing tumour shrinkage, but they are really good at assessing the timepoint where a tumour grows. If we used only that endpoint we could make our life even more simple."

FRANK VAN BEEK/CAPITAL PHOTOS

clinical trials unit and a pharmacology lab. We did phase I trials for chemotherapy drugs, starting in 1986, and also for supportive drugs such as anti-emetics – ondansetron started here and became a standard of care for patients on chemotherapy, among others.

"We also did the first phase '0' trials, before anyone had heard the term – that's where you just test the pharmacology of drugs in a small number of people, and not treatment benefit. We had two oral 5FU 'prodrugs' to test on their pharmacological basis on patients who were at an end-of-life state and who had volunteered for altruistic reasons. We picked one that went on to become capecitabine (Xeloda) – an important drug for colorectal, breast and gastric cancer."

He adds that many other successful drugs have also been among those trialled at the Erasmus, such as Docetaxel (taxotere) and Campto (irinotecan), and indeed Glivec, which in Europe was trialled by his group along with teams in Leuven (Belgium), and London. "But even though we've always tried to keep a critical eye on what we were doing and what everyone else is doing, I must say that during my career I've made all the methodology mistakes you can do in trials."

He points to crucial shifts in understanding, such as learning that drugs could be ineffective for metastatic disease but work well for adjuvant therapy, such as 5FU. "So we learnt that metastatic disease is very different from the situation after surgery. And we've found from molecular biology that drugs can approach the cancer cell in completely different ways."

Verweij worked his way up to become professor of experimental chemotherapy – one of the very few in Europe with this title. "Most of those who do similar work are clinical pharmacologists and based mostly in the laboratory. I was unusual in being clinically based." Now, after stepping up to head medical oncology, his successor has the title of professor of experimental systemic therapy: "That reflects the fact that we don't just give chemotherapy anymore."

Verweij and colleagues had been tracking the emergence of the targeted era since the 1990s. "We became aware that targeting signal transduction was completely different from targeting DNA and was going to be important for cancer. But it's also important for what it means for clinical practice as we also now have a completely different view of what is tolerable for patients, as inhibition of a molecular target requires long-term therapy and not the intermittent treatment we were used to with chemotherapy."

As he adds, with chemotherapy, patients may have vomiting and nausea for a day but can feel well for 20 days until the next treatment. "But suffering from mild nausea daily for 21 days with a targeted drug is awful." He also makes a point that may not be appreciated by many – that the way cancer is turning into a long-term, chronic condition as a result of newer therapies is because the drugs are by their very nature mostly not completely eradicating cancer cells, and we have largely left the idea of a cancer cure

"Chasing 'innocent bystanders' from laboratory to the clinic has been a major weakness of drug discovery"

behind after the successes of a number of chemotherapy drugs. "If we can cure cancer we should of course, and there may be some cures with new agents to come, but turning cancer into a chronic disease is also a great achievement."

For oncologists, he says, healthcare is now much more of a business than before. "Money is a much more important issue when you have to make choices about whether to give very expensive drugs that may only have a very limited benefit. And I do see drugs prescribed now where I wonder whether it is the right thing to do, given the cost. It means we sometimes have to think more like businesspeople than doctors."

But he is not a great fan of the UK's NICE (National Institute of Health and Clinical Excellence) for holding up recommendations for some drugs. "I believe it is almost unethical to do so, but we do owe it thanks for driving down drug costs – the price of Tarceva (erlotinib), for example, has come down by 70%."

That said, under the Netherlands' health system at present only 13% of his department's budget goes on drugs. "By far our biggest cost is personnel. But if we do spend a lot more on drugs, we would have to fire people. That hasn't happened and it won't while I'm in charge, but the risk is there."

Risk is also the key word in Verweij's thinking about how to accelerate the introduction of new drugs and cut the huge waste in the many phase III trials that prove ineffective. Simply observing that an agent inhibits expression of some receptor or enzyme of a cancer cell does not mean it will stop the tumour from growing, and chasing 'innocent bystanders' all the way from laboratory to the clinic has been a major weakness of drug discovery, he says.

"Clearly, if we understand the functionality of a target, our success rate with drugs will be higher. Glivec is the key example, although we did make mistakes with it. We are seeing other fascinating developments now, such as the 'hedgehog' inhibitor for basal cell carcinoma of the skin, and an ALK inhibitor where we are seeing fascinating activity in lung cancer. PARP inhibitors for breast cancer also look very promising.

"But the problem is that if you wait for survival it takes far too long to know whether the drug is truly effective, so we could look at using biomarkers – but which ones are predictive? We still have to wait until later trial phases or until the patient dies from disease to know, and that's the Catch-22 we're in right now. We've spent a huge amount on biomarkers but only received minimal benefit for drug development." (For more on this see Cutting Edge, p 24.)

The aim, he adds, must be for new drugs to be much more effective than many are now. "Two weeks' extra survival – that's a not a drug in my terms. Two years' extra survival certainly is."

In recent talks, Verweij has suggested that certain thresholds of tumour shrinkage in a phase I study could pave the way for more speedy drug registration. "If say we see 60% of patients with tumour shrinkage in a phase I study, there is little doubt that drug will get registered, and with 20%–60% it likely will as well, but once we drop below 20% it becomes much less certain. I don't have the answer about what level of activity you need in a phase I trial to be sure a drug will become a standard of care, but we certainly could raise the current bar."

Preclinical animal models are clearly inadequate at present, he says. "We can hardly use them now as predictors of behaviour in human tumours." Much greater use of pharmacology could supply more answers, he believes, starting at the phase 0 stage and

"We've spent a huge amount on biomarkers but only received minimal benefit for drug development"

FRANK VAN BEEK/CAPITAL PHOTOS

working forward to establish whether drugs are actually reaching the targeted cancer cells and what doses are most effective, even in individual patients.

"For example, in the Glivec studies we showed how the body coped with the drug – the side-effects and exposure to the tumour and normal tissues – and we also learnt that patients with a certain mutation [KIT mutation] were less sensitive to the drug, and so might benefit from a higher dose. We had never seen before that specific target characteristics were important for selecting the dose of a drug."

As he notes, the old concept of just ramping up chemotherapy to barely tolerable levels must be replaced with far smarter approaches for identifying optimal, not maximum, doses for targeted therapies and indeed several approaches are being investigated. PET scanning with a labelled drug is one, but has the problem that the ability to label drugs for radiation emission is still at an early stage.

"One other technique we are researching is microdialysis, where we measure the exposure of the drug in tumour tissue – mostly skin metastases – instead of blood plasma and extrapolate from that. It's probably going to remain extremely difficult though to measure directly the level of a drug in a deeply located tumour, as for most solid tumours. But we are rapidly gaining knowledge and will have the ability to work with specific drug levels to individualise treatment of our patients in the future."

Verweij is especially critical of the role of pharmaceutical companies and regulators in early-stage trials. "Money and time are obviously critical for companies, so they often go to doctors who can offer the patients but not necessarily the detailed knowledge of what they are doing." Almost all phase I studies are done by industry, he adds, and there is a tendency to spread trials around several sites to try and speed them up, which can result not only in the involvement of less experienced investigators and possible increased patient risk, as safety information is not communicated, but can also lead to a longer accrual time – the opposite of what was intended. He notes also that quite often clinicians are offered trials on a take-it-or-leave-it basis with no opportunity to be involved in the trial design and so become 'performers rather than investigators'.

"Academic research needs to be funded much more for applications such as interactions between drugs"

"Regulation is also driving up costs. I used to be able to manage 120 patients with one data manager, but now I need six and a monitor, and then there is an auditor above them and possibly another above that, and they all need salaries. Protocols used to take me a few hours to write. Now they can take months." A rare exception, he notes, to the current industry-driven agenda is the studies led by Cancer Research UK, one of the largest research charities in the field. He considers the present contribution of the European Union to cancer as 'peanuts'.

While drug companies have become more interested in rarer cancers following the success of Glivec, says Verweij, academic research needs to be funded much more for applications such as interactions between drug combinations and with other treatments such as radiotherapy. "The companies tend to back off as this is too complex and the registration paths too difficult," he says. From experience with chemotherapy, where in most cases more than one drug works better, more investigations of combinations with the new agents could be very beneficial, but the complexity of investigation can be very high. "A lot of what has been done has been more or less alchemy. Just putting drug A with drug B without detailed pharmacological investigation is not science."

The strict labeling of drugs for certain treatments also severely restricts researchers he adds, as insurance companies won't pay for other uses. "In the past we were able to use a drug such as doxorubicin in any cancer we found it worked in. Now I can only give Glivec to patients with CML [chronic myeloid leukaemia] or GIST and with the KIT mutation and not for any other patients, based on scientific evidence."

As he notes, the group of companies that market Erbitux (cetuximab) did take the risk with investigating it in conjunction with radiation for head and neck cancer. "But there are only very few other industry-funded studies on other agents known to be synergistic with radiation such as Avastin [bevacizumab] – they are mostly academic studies but they are slow and short of finance."

With later trial phases, RECIST has added much-needed rigour to determining how drugs are working, he says. But there are still big problems with the way researchers are advancing knowledge and halting unproductive paths. "We need to be much better at writing up studies with negative results so we don't make the same mistakes," says Verweij. "This is not about bad drugs but bad research and bad writing. There isn't a single trial I've done that hasn't taught me something."

One example is learning that shrinkage is not as important as progression in driving treatment decisions. Another is giving Glivec for the KIT expression without mutations, which has not proved fruitful, he says, noting that this has not stopped other investigators trying Glivec on other tumours expressing non-mutated KIT, such as prostate and non-small-cell lung cancer, with no success.

"Expression is not the same as functionality," he comments, adding, "We've done a very good trial on EGFR-expressing synovial carcinoma with an EGFR inhibitor and have not seen any positive effect, but again we have learnt we should not chase something that isn't functional. The trouble is researchers aren't always good messengers."

He has also noted that Herceptin (trastuzumab) is widely continued beyond progession, simply changing the cytotoxic drug added to it, without any randomised evidence that this works. "Unfortunately, one trial that did randomise continued Herceptin with a chemotherapy drug was stopped prematurely. It is now unlikely we will ever learn whether such an approach truly enhances outcomes and whether it is cost effective." And again, he's spoken out about the application of Herceptin to cancers other than breast, where there is no evidence of HER2/neu being a functional target.

Another concern for Verweij is bringing drugs for supportive care into clinical practice. "This is about regulation and measurable endpoints for drug trials. While it's easy to understand evaluations for breast cancer – say, patients live longer or the disease stops

growing for longer – how do we measure a condition such as fatigue? I talk to a lot of pharmaceutical companies and they are coming up with interesting supportive drugs, but they are struggling to bring them to market because of the lack of endpoints and regulation to guide them. So instead they focus on the underlying, major malignant diseases."

Along with the dangers of drug interactions (see box) it all reinforces Verweij's already strongly held view that medical oncologists need to be well trained in pharmacology, and if they do not have access to this training in a cancer department when they start out in the specialism, it should be offered elsewhere. But few cancer centres have the kind of cancer pharmacology expertise of the Erasmus – he mentions the Netherlands Cancer Institute, the Royal Marsden in London, and centres in Newcastle, UK, and Chicago and Pittsburgh in the US, as of similar standing.

"I want also to see more oncologists trained to be researchers, not just in the science but how to manage regulations. We have so many studies that need to be done, but a survey in the US shows that the number of academic researchers is going down there – salaries of course are just not as high as in private practice or industry. But hopefully not too many of us will be motivated by money alone."

Verweij says he tries to keep out of what he calls 'onco-politics'. He is pleased that the major cancer societies have came together in ECCO (European CanCer Organisation), but laments the lack of funding for the EORTC. "Its budget has only been about 14 million euros a year and the NCI has much more – but even so we have had three times as many patients in trials. We have been pretty creative and efficient." In the Netherlands he chairs the scientific advisory council of the Dutch Cancer Society.

Bob Pinedo, and also sarcoma 'godfather' Allan van Oosterom (a former EORTC president), are his key mentors and are no doubt supportive of a current controversy where Verweij has made a big stand, on the approval of Glivec as an adjuvant therapy in GIST. "We should not be comparing early with delayed treatment, as we'd be giving Glivec on relapse anyway. We should be looking at overall survival – that's the aim of any adjuvant treatment, not prolonging time to recurrence, which is all this trial has yet shown. Based on the published absence of improved survival at four years it can be estimated that the cost per life year gained may run into many millions of euros and is simply unaffordable."

Verweij flies small planes as a hobby – sometimes to meetings when the weather's good – and has three children, one of whom is studying to be a molecular biologist, which he considers is altogether more clever than being a clinician. His wife, Monique, runs a primary healthcare organisation in Eindhoven.

In the nine years he has until retirement he says he'll be happy with a few more drugs like Glivec – he's not expecting major breakthroughs – and progress in trial design. "I'd like to see more Europe-wide studies to show the world we've survived the European Clinical Trials Directive," he adds. "I'd like also for us to show more altruism outside our drive to make our own names, and work together more closely. It will take a lot of motivation but it can be done."

### BEWARE OF INTERACTIONS

The large number of patients who also take herbal products that are not regulated as drugs is seen by Verweij as an alarming trend. "In the Netherlands 40% of patients are taking other pills without telling us. Research we've done shows that some interactions with cancer drugs can be dangerous." The commonly taken St John's Wort, for example, can decrease the activity of drugs, while other substances can increase the toxicity to lethal levels.

Prescription medicines can have similar effects – a recent study in the *BMJ* has found, for example, that women with breast cancer who take the antidepressant paroxetine at the same time as tamoxifen are at an increased risk of death owing to a suppression of the cancer drug. This type of interaction can be overlooked by doctors who have had little or no training in drug treatment.

"Most doctors, however, are not routinely asking about the complementary products people are taking, and we have published several papers that show what effects they can have," says Verweij. Patients, he adds, are accessing a huge amount of information on the Internet – much of it wrong – and tend to regard herbal products as natural and harmless.

"We should be looking at survival – that's the aim of any adjuvant treatment, not prolonging time to recurrence"

# The treatment of gastrointestinal stromal tumours (GIST)

A better understanding of the different mutations that drive GIST is leading to new paradigms of tailored treatment that break many of the traditional norms of chemotherapy, particularly with respect to management of progression.

Gastrointestinal stromal tumours (GIST) are rare tumours, with an incidence of 10 new cases per million population per year, giving 4000–5000 new cases in the European Union each year. GIST was thought to be extremely rare, but the discovery of the specific molecular alteration that was driving these tumours in the late 1990s revealed it was slightly less rare than had been thought. This work showed that a mutation in the KIT gene drives the tumour. The molecular characterisation of GIST is at the centre of this review.

GIST can be detected in all organs of the digestive tract: the stomach, the small bowel, the rectum, the oesophagus and, in some rare cases, the mesentery. Mutation can occur in different parts of the KIT gene, and this can affect where the tumour develops. KIT exon 9 mutations occur most often in the small bowel lesions. Mutations in the PDGF receptor-alpha (PDGFRα) gene occur most often in gastric lesions. This interesting parallel between the molecular anatomy of this tumour and the location of GIST needs to be kept in mind, because it will drive the treatment of patients in the future.

**European School of Oncology**
**e-grandround**

The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading European experts in the field. One of these will be selected for publication in each issue of *Cancer World*.

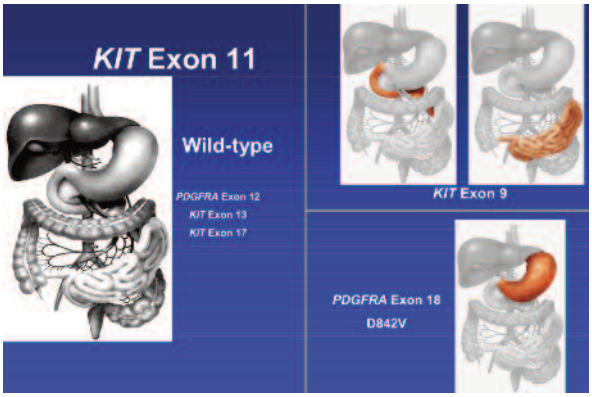
In this issue, Jean-Yves Blay, of the Centre Léon Bérard, Lyon, France, who is director of the Conticanet network of excellence and president of the EORTC, provides an update on the latest evidence for the treatment of GIST. Daniel Helbling, of the Onkozentrum Zurich, Switzerland, poses questions that explore the issues further. The presentation is summarised by Susan Mayor.

**The recorded version of this and other e-grandrounds is available at www.e-eso.net/home.do**

The majority of GIST lesions have mutations in KIT, with most occurring in the juxtamembrane region of the kinase (just inside the cell membrane). These mutations have functional consequences, including a constitutional activation of the kinase, which can be blocked by tyrosine kinase inhibitors (TKIs).

More recently, it was discovered that another gene – PDGFRα – can be mutated in this tumour. This occurs less frequently than KIT mutations – approximately 5% in the metastatic setting but probably 20% in localised tumours. The two mutations are mutually exclusive, with a GIST tumour having only one mutation to start with. However, additional mutations occur in the case of resistance.

**MUTATIONS VARY BY SITE**




**Understanding which gene mutation drives the GIST in a given patient will determine treatment choice in the future**

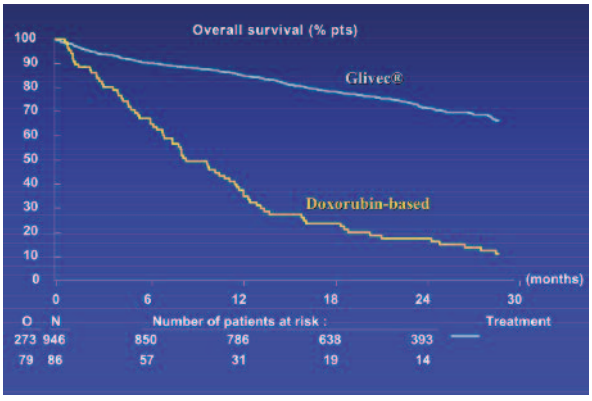
*Source:* C Corless, Presentation at the GOLS meeting 2008

## The impact of imatinib on survival

The introduction of imatinib (Glivec) for the treatment of metastatic GIST substantially increased overall survival, showing the most dramatic impact of a novel treatment on the outcome of patients with solid tumours in the last 20 years. Imatinib significantly improved survival compared to the previous treatment, doxorubicin. The large increase in overall survival led to the approval of imatinib for GIST without the usual requirement for a randomised controlled trial.

Results from the Conticanet network's series of GIST patients show the overall median survival in GIST patients treated with imatinib is around five years, while the median progression-free survival is approximately 24 months. This is of interest because it is the longest series we have to date on the treatment of GIST, and includes patients from before the imatinib era. It shows that imatinib is able to improve not only progression-free survival but also overall survival even beyond the time of progression. This is very important for the treatment strategy for GIST.

**IMATINIB GREATLY IMPROVED SURVIVAL IN GIST**




**Results from the Conticanet series of GIST patients demonstrated the huge survival benefit conferred by the new therapy**

*Source:* Adapted from J Verweij et al. *The Lancet* 2004, 364:1127–1134

**Question:** *The curve is not flat at the end, so does this mean that there is no cure in GIST with Glivec?*

**Answer:** *We do not have a final answer to this question. We do not know whether there will be a plateau at the end. We know that some patients have not progressed after 10 years of treatment, so that is reassuring, but this proportion of patients is relatively small, at less than 25%. However, this takes into consideration different GISTs with different mutations, and survival is probably different between mutations.*

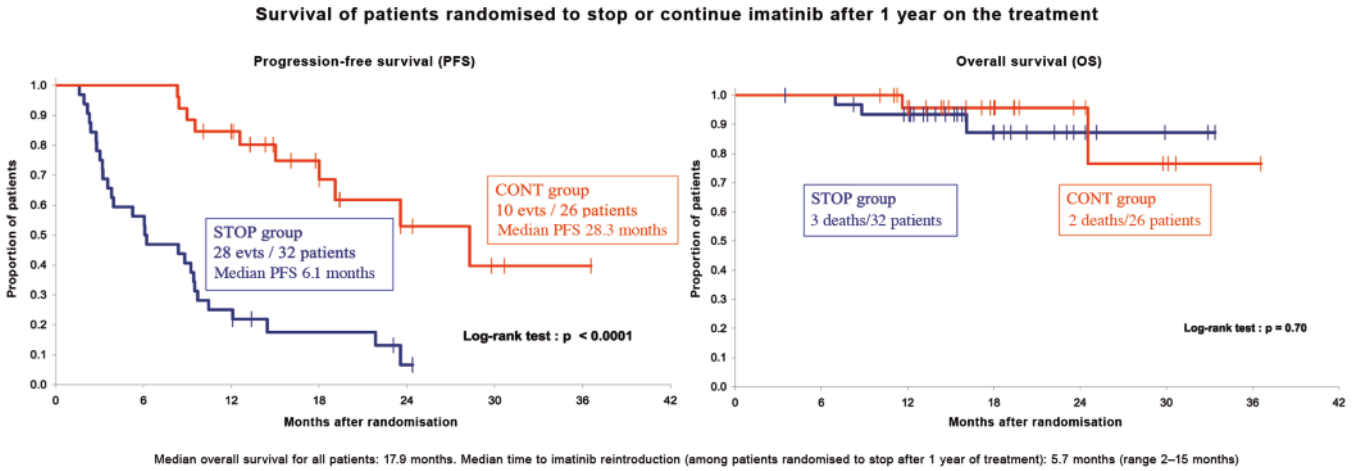
The development of a new treatment that is extremely effective in improving outcomes for these patients has led to a number of evolving paradigms.

## Evolving paradigm 1

### Double the imatinib dose for a patient progressing on the standard dose

The best treatment for a patient with metastatic GIST who is progressing on 400 mg/day of imatinib is probably to double the dose. This is, to my knowledge, the only example in oncology of a treatment where the dose is increased in the case of progression. This approach was tested in the EORTC 62005–S0033 trial, which compared 400 mg/day with 800 mg/day in advanced GIST, with patients on the lower dose being given the opportunity to cross over to 800 mg/day on signs of tumour progression.

## ONE YEAR IS NOT ENOUGH




**The BFR14 trial showed much shorter progression-free survival in patients randomised to stop imatinib therapy after one year**

*Source:* Based on JY Blay, A Le Cesne et al. *JCO* 2007, 25:1107–1113

The results showed that about one-third of patients achieve tumour control simply by doubling the dose of imatinib. Approximately 20% of the patients will not progress in the years following a dose escalation. Why is that?

Investigation of the pharmacokinetics of the drug measured the trough level of imatinib after one month of treatment and showed that patients in the lower quartile of exposure had a lower response rate and a higher risk of progression than those in the upper three quartiles (GD Demetri et al. 2008, ASCO Gastrointestinal Cancers Symposium, abstract 3). This suggested that exposure to the agent is correlated to the outcome. This has previously been observed in the treatment of chronic myeloid leukaemia, which is the other disease targeted by imatinib. There was a trend to higher rates of clinical benefit with higher imatinib exposure (67% in the first quartile vs 84% in the fourth quartile), with greater clinical benefit for patients with the KIT exon 11 mutation, which is particularly sensitive to imatinib (100% for the fourth quartile, *P*=0.009).

Question: *This is the only situation where a dose increase is recommended in oncology. Is that because the tolerance of the drug is good?*

Answer: *Tolerance to dose escalation of imatinib is good compared to usual cytotoxic agents, but it is not always very easy. Even though you have fewer side-effects by escalating the dose rather than starting with 800 mg/day, some patients have difficulty maintaining the 800 mg/day dose.*

Question: *How long do patients benefit from the dose increase?*

Answer: *The median progression-free survival after dose escalation is probably in the range of 3–4 months, and only 20% of the patients have not progressed at one year. However, we still have some patients on an escalated dose who are doing well after several years. This is very rare compared to other treatments. Some patients have shown sustained tumour control on 800 mg/day for more than two years after progression on 400 mg/day. This shows that exposure of the tumour to the agent is critical in understanding why these patients are responding.*

## EVOLVING PARADIGM 2

### Never stop systemic treatment in the advanced phase

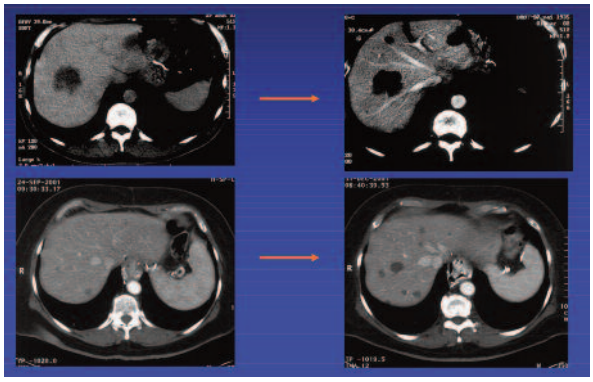
How long should we continue to treat with imatinib? This is an important question, and one that patients often ask after three to four years of treatment. To address this question, the French Sarcoma Group BFR14 trial randomised GIST patients to imatinib that was either stopped after one year and then restarted on progression or treatment was continued until progression. Results showed the median progression-free survival for patients stopping treatment at one year was six months, which was very significantly inferior to that in patients continuing treatment. The good news is that all patients, apart from one who died

from an unrelated side-effect, responded to restarting imatinib. This showed that treatment for one year does not kill all tumour cells, because all patients who stopped imatinib relapsed, although this occurred after three years in one patient.

The same trial went on to randomise patients to stop or continue at three years, with the same result. The median progression-free survival is six months, which was significantly inferior to the continuation arm. Again, all patients responded to restarting imatinib, which is reassuring.

What is more worrying is that the median progression-free survival is exactly the same in groups stopping after one year as after three years, showing that during the first three years the treatment is simply delaying progression. It is stopping the proliferation of cells, and not killing the last cancer cell. Therefore, we should probably treat with imatinib for more than three years. We are just completing a five-year randomised trial, with results being presented this year.

**FALSE PROGRESSION ON CT SCAN**



The new hypodense lesions visible on the right-hand scans do not represent tumour progression, but are caused by the treatment

*Source:* Courtesy of JY Blay, Centre Léon Bérard, Lyon

## Evolving paradigm 3

### Response does not equal reduction in tumour volume

The idea that response cannot be equated with a reduction in tumour volume is a very important change in the way we are used to seeing responses to cancer treatment. We are used to thinking that to have a response we need the patient's tumour to shrink, and that the tumour increases in volume when progression occurs. This is probably not true for the treatment of GIST with imatinib, and is probably not true for other targeted agents in other cancers. Response does not necessarily mean reduction in tumour volume, and progression does not necessarily mean a volume increase.

False progression can be seen in GIST patients treated with imatinib. The figure above shows CT scans for a patient treated in the early days of imatinib. After three months, there appears to be new lesions. However, these are hypointense lesions caused by the treatment, typical of a false progression. Conversely, you can also have a false response. Even though the patient has a response according to RECIST criteria, the disease is continuing to progress. We should be aware of this, as we should probably be ready to change our practice in years to come.

We should assume that a CT scan is the gold standard. It is also important to listen to the patient. If a patient has a partial response but is feeling unwell, we have to suspect that a partial or limited progression may possibly be occurring. On the other hand, if despite an increase in tumour volume on a scan they say they are feeling well and have no more pain, this could be a false progression. In such a case, it is important to weigh up the level of suspicion.

Question: *If you have a patient who is doing clinically better but you see on the CT scan that the lesion is increasing, do you continue with the same treatment or are you suspicious?*
Answer: *It depends on the level of the suspicion. One of the aspects that is very important to take into account is the density of the tumour measured in Hounsfield units. Most of the responding lesions have decreasing Hounsfield units. An index based on the so-called 'Choi criteria' enables you to distinguish responding from non-responding tumours. This needs to be reproduced, but it is quite convincing, and it is quite well accepted that hypointense lesions are responding lesions.*

*Concerning treatment, yes, we could continue. If I had doubts, I would probably explore with a PET scan. If I have no doubts, I would simply see the patient again within six weeks with a new CT scan and clinical evaluation, instead of the usual three-month follow-up.*
Question: *So you do not do PET scans straightaway, you reserve them for investigating areas of uncertainty?*
Answer: *Correct. There is another indication for PET scan in the ESMO guideline, which is when you start new adjuvant treatment in large tumours before resection, and you want to make sure the tumour is responding rapidly and is not a primary resistant tumour, which is rare – only 5%.*

## Evolving paradigm 4

### Understanding the molecular biology of tumour resistance is important for routine treatment of the patient

The molecular biology of resistance is a very important issue. There are different subtypes of mutation, with different

sites of mutation of KIT: exon 9 and exon 11. A meta-analysis of the two large trials mentioned – the US S0033 and the EORTC 62005 trials (1640 patients) – showed significantly different progression-free survival treating exon 9 patients with 400 mg/day (see below, *blue line*), compared to 800 mg/day (*green line*). This does not occur in exon 11 patients (*red and yellow lines*). Information on which mutation a patient has is important because we need to double the imatinib dose in a patient with an exon 9 mutation. This strategy is recommended by the ESMO and the NCCN guidelines in the US.

The difference in progression free survival does not translate into overall survival, although the number of patients in each group was quite limited. However, 800 mg/day is the standard dose for exon 9 patients, and this means that we need information on the patient's mutation when treating in the metastatic setting. This is not easy because information on the type of mutation is available in less than 50% of patients, and testing for mutation type is not available everywhere. Testing requires complex technology and good reproducibility, but this is the way to go forward, certainly for exon 9.

**Question:** *Do we need to test only for exon 9, or for the other mutations as well?*
**Answer:** *We certainly have to test for exon 9. We suspect that different mutations in PDGFRα or exon 11 may also be associated with different prognoses and we are expecting data on this at ASCO this year. If this is the case, then we should have a more exhaustive evaluation of the nature of the mutation than just a single evaluation of exon 9.*

## What strategy should be adopted at progression?

There are several things we should do if a patient progresses.

### Check adherence with therapy

The first thing to check is whether a progression is related to non-adherence to imatinib. A study on the number of packs of imatinib bought by patients in the US showed that this was only 75% of the amount prescribed, which indicates that the adherence is, at best, three-quarters. This is not very high, and we know that the exposure to imatinib correlates to the outcome. It is not simple to take a pill every day for the rest of your life. We need to try to improve patient adherence, and we have to listen to the experience from other fields, such as HIV, where adherence to long-term treatment has been studied extensively.

### Check exposure

The pharmacokinetic levels of imatinib are important, as mentioned previously.

### Consider surgery

Surgical treatment is very interesting, but still experimental. A small study by CP Raut and co-workers found that patients operated on while they had limited progression showed a longer time to secondary progression than those who had surgery at general progression, and those operated on with stable disease showed even better outcomes (*JCO* 2006, 24:2325–2331) This is of interest, but it is not yet proven to be superior to treatment with sunitinib.

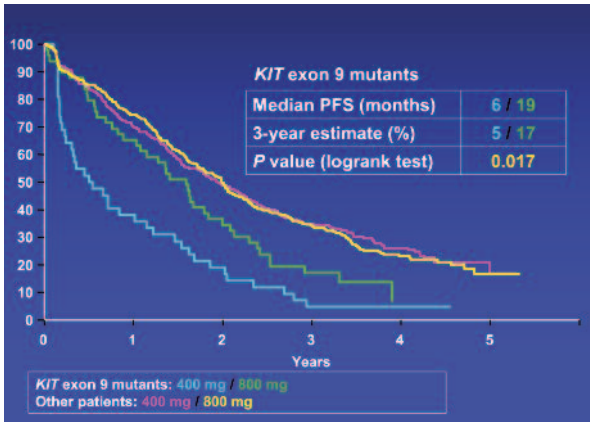
We have started a trial randomising patients with metastatic GIST responding to imatinib either to imatinib plus resection of their lesion at the time of best response (within one year) or to continue with imatinib, with surgery delayed until the time of progression. This is an extremely important study, but very difficult.

### Switch to another TKI

Sunitinib has a broader spectrum of activity in terms of kinase inhibition than imatinib, so we expected that it could have an additional effect. This additional effect was demonstrated in a trial comparing sunitinib with placebo in imatinib-resistant patients, showing an improvement in progression-free survival. Both blinded and open phases showed improved time to progression with sunitinib (P Casali et al. ASCO 2006, abstract 9513; IR Judson et al ESMO 2006, abstract 506). Some would argue that placebo was not the appropriate control arm, but the trial is very important because it demonstrates the activity of sunitinib.

Progression-free survival with sunitinib differs in patients with exon 9

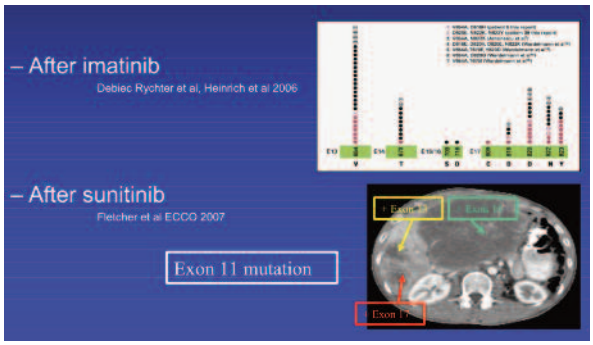
**THE MUTATION DICTATES THE RESPONSE**




**Doubling the dose for imatinib-resistant tumours is effective, but only for tumours with the exon 9 mutation**

*Source:* Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). Presented at ASCO 2007

**MOLECULAR HETEROGENEITY AT PROGRESSION**




**Though GIST starts with only one mutation, multiple mutations can develop within a single tumour after treatment with imatinib and/or sunitinib, which we must learn how best to manage**

*Source:* CT scan: courtesy of JY Blay, Centre Léon Bérard, Lyon

mutations compared to other mutations. In relapse, patients with exon 9 and wild type seem to have a better outcome, so this is the opposite to what is seen with imatinib. The finding does not mean that sunitinib is inactive on exon 11, but rather that we have possibly selected a resistant clone with additional mutations.

At the time of progression, we have observed the emergence of resistant clones which are associated with additional mutations of the kinase. This mutation codes for a protein that is resistant to imatinib and/or to sunitinib. These additional mutations are located on exon 13, 14, 17 and 18 of the same kinase. There is a high level of heterogeneity in these tumours – with mutation of exon 13 and 14 in one region, and mutation of 17 in another place. This is a level of complexity that has not been addressed previously and which we do not yet know how to handle, but it needs to be characterised because outcomes differ according to the nature of the secondary mutation.

Unfortunately, a lot of patients progress on sunitinib, so what is the next step? There are several other TKIs, in addition to other strategies. Nilotinib (Tasigna) is a TKI that blocks the BCR-ABL. It has been tested in a phase I/II trial in patients with resistant GIST. The outcome of patients treated with a combination of imatinib and nilotinib, or with nilotinib as a single agent for intolerant patients, was not bad in terms of tumour control, as evaluated by complete response (CR) + partial response (PR) + stable disease rate. Progression-free survival was comparable with that of patients treated with second-line sunitinib.

Is nilotinib really useful? This is being explored in a pragmatic trial to be presented at ASCO 2010, comparing nilotinib versus 'doctor's choice': either best supportive care alone, imatinib or sunitinib. This was a very interesting trial, but it was complex because maintaining TKI pressure using a kinase inhibitor that has been failing in the past cannot be described simply in the protocol – it is the investigator's judgement. Results during 2010 will show whether nilotinib is an active agent.

**Question:** *Do some patients respond after imatinib and sunitinib to being given imatinib again?*

**Answer:** *Yes, this happens in third, fourth, fifth and sixth line. When we say response, we do not always mean tumour shrinkage, but it may be prolonged tumour control and clinical benefit for the patient and no progression according to RECIST.*

A fourth agent, sorafenib (Nexavar), was tested in a phase II and compassionate use programme for patients who had failed on imatinib and sunitinib. It showed a similar control rate of approximately two-thirds of the patients, with a median progression-free survival of four to five months. This kinase inhibitor has a profile similar to sunitinib, but has some activity in the third- or fourth-line setting in imatinib- and sunitinib-resistant GIST (HS Nimeiri et al., ASCO Gastrointestinal Cancers Symposium 2008, abstract 7). Unfortunately, there will be no prospective trial addressing this question from the pharmaceutical company, but we may be in a position to try to explore this in the academic setting.

The fifth drug being explored is the heat shock protein 90 (HSB90) inhibitor IPI 504. A phase I study showed some level of tumour control in a substantial proportion of patients with GIST. On the basis of this, the HSB90 inhibitor was tested in a phase III trial, but unfortunately this was stopped because of toxicity in the treatment arm. This is definitely a strategy that needs to be further explored.

Another pathway that is critical for the development of resistance is mTOR inhibition. A trial is exploring the combination of imatinib, sunitinib and sorafenib with RAD 001 – everolimus – which shows long-term tumour control in some patients. About 20% of patients greatly benefit from the treatment at six months. These data were presented at ASCO 2008, but have not yet been published. The combination is not standard yet, but should be further explored.

The figure opposite shows one of my patients with a huge liver metastasis who progressed after treatment with 800 mg/day imatinib. He was included in the RAD 001 trial and is still alive more than three years after resection. This patient would not have been operated on without this treatment.

## Evolving paradigm 5

### Continuing TKI therapy in case of progression under TKI

How to respond to progression of a tumour being treated with a TKI is still a changing paradigm. There is no other situation where we would maintain a treatment demonstrated to be inactive. However, in this case, the rationale for doing just this is that survival after progression on imatinib is much longer than expected from previous experience with GIST (median overall survival: 58 months versus 26 months). The second issue is focal resistance, where the majority of cell clones remain sensitive, so it is not logical to stop a treatment that is still active in a large proportion of clones. Maintenance of KIT blockade is probably very logical, based on these two observations.

What about treatment in the adjuvant setting? This question was addressed in the phase II trial ACOSOG Z9000. Imatinib treatment after surgery showed overall survival of 99% at one year and 97% at three years. The ACOSOG phase III Z9001 trial demonstrated that exposure to one year of treatment with adjuvant imatinib substantially reduced the risk of progression during and after this time period. The magnitude of risk reduction is in the range of two-thirds in all populations of patients.

Even though patients have delayed relapse, the majority will relapse after the end of the treatment. There is a high degree of suspicion that one year of treatment may not be enough. This needs to be further explored, but the basic message is that we do not yet know for how long we should treat. The Scandinavian trial, SSG/AIO, randomised patients to one year versus three years of treatment in the adjuvant setting, while an EORTC trial (62024) is studying two years of treatment. Results will be available in 2011.

The questions on adjuvant treatment that remain include:

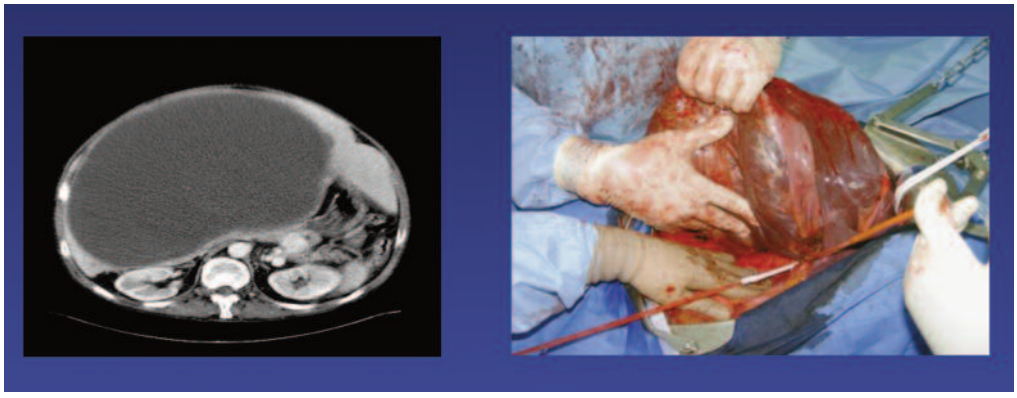
- Whom should we treat?
- What risk level?
- What duration?
- What mutational type?
- What is the impact on secondary resistance?
- What will be the impact on overall survival?

## Conclusions

Surgery and adjuvant imatinib can be considered standard treatment in localised GIST, but a lot of questions remain about adjuvant treatment. First-line imatinib is the only standard, at a 400 mg/day dose for non-exon 9, and at 800 mg/day for exon 9 patients. We should continue treatment until progression or intolerance, because patients will experience a recurrence if treatment is stopped. Molecular biology is becoming increasingly important for prognostic and treatment selection.

The evaluation of response to imatinib is not simple, and can be determined using the RECIST criteria, WHO criteria, and Choi criteria. However, we know there are false progressions and false responses and that we should integrate not only reduction in volume but also density and prolonged stabilisation as useful criteria. Surgery is not of proven benefit in the metastatic phase; it needs to be explored, and I encourage everybody to participate in the EORTC Intergroup study testing surgery in the randomised setting. The final question is whether we should maintain treatment in patients where everything has failed. The expert opinion from ESMO and the NCCN is that we should maintain treatment at least to control sensitive clones.

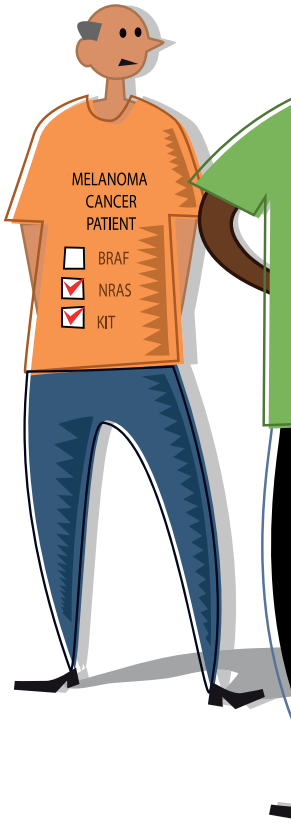
**THE ROLE OF mTOR INHIBITION**



**This imatinib-resistant GIST patient had a huge liver metastasis resected after treatment with the mTOR inhibitor everolimus**

*Source:* Courtesy of Pierre Meeus, Centre Léon Bérard, Lyon

# Who's who in the world of personalised cancer treatments?




Anna Wagstaff

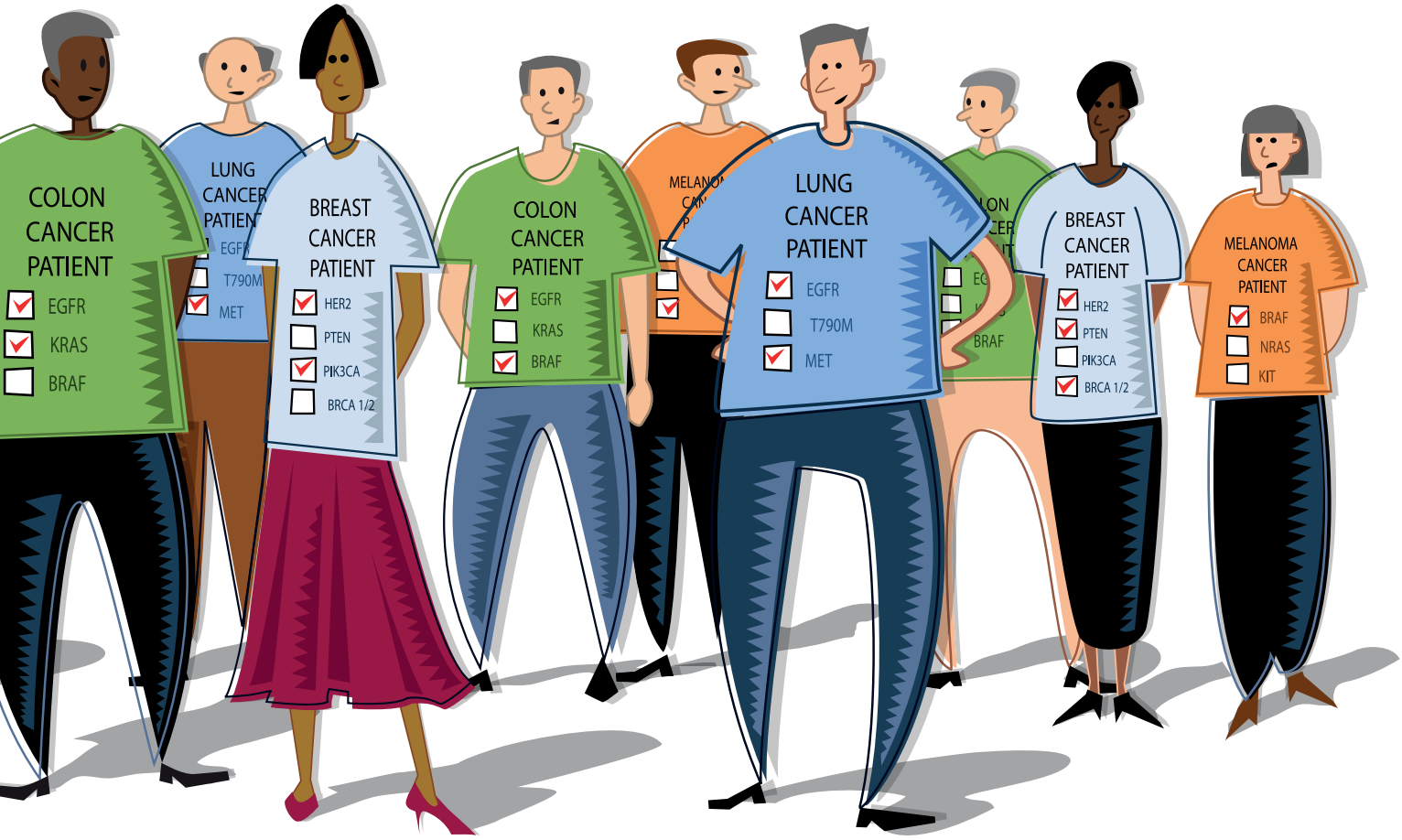
The number of gene mutations implicated in cancer is growing at a steady pace – one cancer centre is now screening for 124 of them. The number of drugs being developed to target specific mutations is also rising steadily. But finding which targeted therapies work best for which sets of mutations is proving an elusive goal.

It's been many years since biologists first offered the tantalising prospect of a future in which every cancer patient could be prescribed a tailor-made treatment aimed at the unique molecular 'signature' of their particular disease. In the intervening years, an ever-growing list of overexpressions, amplifications, translocations and deletions has become part of the academic oncologist's vocabulary with its own bewildering dictionary of acronyms – KRAS, BRAF, VEGFR, EGFR, HER2, ALK, c-KIT, exon 9, mTOR, MEK, PDGFR, BRCA – to name but a few. In routine clinical practice, however, only a tiny minority of patients are actually tested for these 'biomarkers' and treated accordingly.

So what's the hold up? This question has increasingly been exercising Patrick Johnston, head of the Centre for Cancer Research and Cell Biology at Queens' University, Belfast. A specialist in '-omics' diagnostics (genomic, proteomic, metabolomic…), he says we now have targets a-plenty to aim at and a wealth of new drugs – some in the clinic, many more in the pipeline – to aim at them. But despite hugely powerful technologies that can do whole-genome sequencing or identify the expression of thousands of genes in a matter of 24 hours, we still do not know which signatures (or sets of biomarkers) predict response or resistance to which drugs. This work is simply not being done, says Johnston, or at least not well enough.

"In my own disease, colorectal cancer, there are something like 60–70 new drugs currently in various phases of development. There are small molecules, antibodies, peptide-related things and even some novel antisense type molecules. All these are in the mix now. The challenge to the drug companies today is no longer of finding novel targets," says Johnston, "it is finding where those drugs are likely to produce most benefit."

But this is not proving easy. Herceptin (trastuzumab) was approved on the basis of an immunohistochemical assay that was meant to identify patients who stood to benefit, but turned out to be less than satisfactory. "The histochemical assays did not correlate well with the genomic assays for gene expression that we were doing," says Johnston. "We went forward and marketed the test even though it had never been properly quality assured within the literature or beyond." Though it has now largely been replaced by the FISH (fluorescent




*in situ* hybridisation test), this too has never been validated in a randomised controlled trial and is widely believed to miss some patients who would benefit from Herceptin.

Then there is Erbitux (cetuximab), another important targeted drug, which was designed to block the expression of epidermal growth factor receptors (EGFRs), and was originally approved for use in all metastatic colorectal cancers and in head and neck cancers that showed positive for EGFR overexpression. Only after the drug was brought to market did it come to light that a substantial proportion of the target group of patients (estimated at more than 25% of colorectal cancer patients) receive no benefit from the drug, due to a mutation in KRAS – a gene that plays a role earlier in the signal pathway.

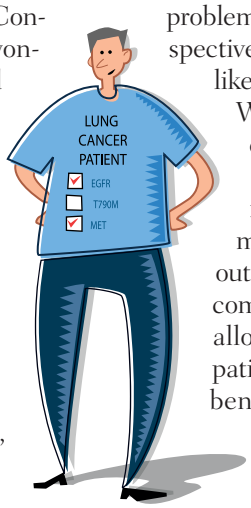
This indicates a methodological failure, says Johnston, in the development of both Erbitux and Vectibix (panitumumab) – a similar EGFR inhibitor, also approved in colorectal cancer. "It is only serendipity that has suggested that actually KRAS is a discriminator." The importance of KRAS could have been identified much earlier, he argues, if a systematic approach had been taken early in the trials of both drugs to measure the various components of the signalling pathway – MEK, KRAS, BRAF, EGFR – in parallel with studying the main target. "This is where the intellectual and the

"The intellectual, preclinical and clinical strategies need to be thought of together, rather than in isolation"

ILLUSTRATION: FRED VAN DEELEN, WWW.ORGANISARTCO.UK

preclinical and clinical strategies need to be thought of together, rather than in isolation. Sometimes, even so, a drug candidate will come forward without really having due reference to what has been discovered preclinically."

"We are trying our best," is the response from the industry. Confounding the sceptics who wondered why big pharma would dedicate resources to identify biomarkers that would narrow down the market for their therapies, drugs companies really do seem to have spent the last few years restructuring themselves around the new paradigm of developing the right drug for the right patient. Most now have teams bringing together biologists, preclinical, translational and clinical specialists, with good technical platforms and biostatistical backup, who try to identify what distinguishes responders from non-responders and develop and validate tests that can be used in the clinic to identify which patients will benefit from the drug.




## A COMPETITIVE EDGE

They are motivated in part by increasing demands from the regulators that, in order to get approval of new therapies, sponsors will need to demonstrate which patients respond, and come up with a test to reliably identify them. As important, however, is the recognition that, with so many agents chasing so many targets, market share is now all about who can identify most quickly and accurately the marker that predicts which patients will really benefit.

As Wolfgang Wein, head of Global Oncology at Merck Serono (Merck KGaA) points out, "You have a competitive advantage if you are ahead of the game. If you are a follower, and a biomarker pops up while your study is already underway, then you have the problem that you have to do a retrospective analysis, which is not much liked by the regulators." As far as Wein is concerned, the discovery that patients with a mutant KRAS gene do not respond to Erbitux – a drug marketed by Merck Serono outside the US – is entirely to the company's benefit. "The KRAS allows us to identify those patients who are most likely to benefit from treatment with Erbitux. This can be shown whether you are looking at time to progression, overall survival, response rate or however you want to measure it," he says. "It strengthened the profile of the drug compared to the competition."

Yet, as he points out, drug companies are limited by the current state of knowledge of the disease. "Biomarker development somehow emerges from academia. It is an expression of where academia stands at a certain point in time. You may start your trial using one biomarker, but it might turn out during the trial to be not a very precise one, or better biomarkers come up in the meantime. I see the problem as one of validation: to know when it is really confirmed as a good biomarker. There are examples where a biomarker has been proposed, there are several publications, and then it turned out that they could not be confirmed in a randomised study."

What critics often don't appreciate, he adds, is that when it comes to exploring how your drug works in real cancer patients, you can rarely conduct the studies most likely to answer your questions. Most targeted therapies are developed and approved in combination with other, usually cytotoxic, therapies, because the regulators would not accept that a patient could be denied the current standard of care. Yet the combination of therapies may muddy the signals of who is responding to the targeted therapy and who is not.

It is also in the very nature of cancer, he adds, that you often need to hit several targets at once. Four drugs, hitting four targets, could give you a very clear signal of response in patients with tumours relying on that particular signalling network, while any one of those drugs tested alone might produce no such signal. Again the regulators, for understandable reasons, have resisted giving approval to more than one experimental drug at a time – though Wein says they are increasingly open for discussion on such 'novel–novel' approaches.

"We are therefore limited in what we can really do by what can be funded and what is acceptable in terms of efficacy and toxicity," says Wein. "Even with the best intentions, you can just try to gain ground within these limits." Just how difficult this can be was most recently demonstrated by attempts to find a marker of response to Erbitux among patients with non-small-cell lung cancer – which, as Wein points out, is really an umbrella term for a collection of cancers with different histologies. "We did an enormous amount of work, but we didn't find a solution," says Wein. Last

"You may start your trial using one biomarker, but it might turn out during the trial to be not very precise"

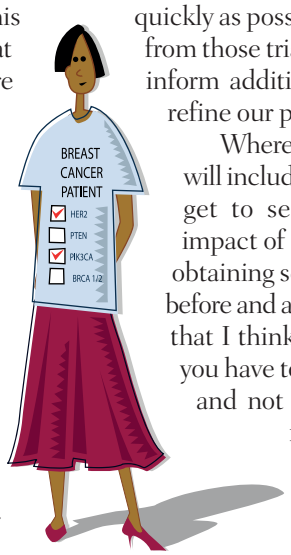
"We are all working with an incomplete understanding of the disease, and the art is to identify the right questions"

year EMEA turned down an application for Erbitux to be extended for use in non-small-cell lung cancer on the grounds that the added benefit did not outweigh the additional toxicity in an undifferentiated patient population.

## That's science for you

David Reese, Executive Director of Medical Sciences at Amgen, which developed the EGFR inhibitor Vectibix, doesn't necessarily agree with Johnston's assertion that the development of the drug was flawed and that KRAS was later identified as a biomarker of response by 'serendipity'. Reese speaks from a certain experience, having both worked with Dennis Slamon's team at the UCLA (University of California, Los Angeles) when Herceptin was being developed, and later helped on the team that unravelled the KRAS story.

KRAS, he says, was among the first human oncogenes to be identified. Although we have known for 30 years that activating mutations in this gene could drive tumour cells, at the time of the early trials there was very little literature delineating the role that KRAS plays in the signalling network that fed into the target Vectibix aimed to block, says Reese. In addition, preclinical models were a little misleading, "because there are cell lines with the KRAS mutation that appear to respond to Vectibix, or other anti-EGFR therapies *in vitro*, whereas in the clinic we have not really seen that."




Later on, when a number of studies "primarily single-arm, single-institution retrospective studies" began to flesh out the components of EGFR signalling pathways and flag up mutant KRAS genes as possible predictors of resistance to drugs such as Vectibix, Amgen went back to the tumour samples it had collected during the phase III trial to do its own retrospective analysis. "We were able to obtain KRAS status on 92% of patients in that study. The analysis showed a very strong correlation between the presence of KRAS mutations and resistance."

It may not be the ideal way to identify your biomarker of response, says Reese, but that's science for you. We are all working with an incomplete understanding of the disease, and the challenge and the art is to identify the right questions to ask.

"It is an iterative process," he adds. "Observations are made in the lab. It is incumbent upon us to try to sort those out in our early-phase clinical trials as quickly as possible. Often observations from those trials will then feed back to inform additional work in the lab to refine our preclinical models."

Where feasible, says Reese, this will include looking beyond the target to see the wider biological impact of the drug, for example by obtaining serial tumour biopsies for before and after exposure. "One thing that I think is now apparent is that you have to view these as pathways and not even pathways but signalling networks. Understanding the effect on the network is critical in terms of understanding what sort of effect your drug may be having."

Where he does agree with Johnston is that the technologies for gathering the necessary biological readouts from samples are no longer a limiting factor. But the issue then becomes what you do with those readouts. "It can also mislead you if inappropriately used, because of the massive amount of data that pour out. It is more critical than ever to ask very careful questions with an extremely well-defined hypothesis."

Getting the question right is, however, only the half of it. To find the answers they must convince clinicians and patients to take part in what can often be a logistically complex, time consuming and sometimes unpleasant process – for instance where repeat biopsies or PET scanning may be required.

It may be significant that, when asked to name some 'model trials' currently underway, Johnston found the question hard to answer – and the two at the top of his list – one being run by ECOG and the other by the EORTC – were both having difficulty accruing patients. "The fact that I can't point to very well-defined trials that are set up in this way shows the problem," he says.

## Some questions can't be answered

As Anne-Marie Martin, Director for Clinical Biomarkers and Clinical Development, Oncology R&D, at GlaxoSmithKline, explains, "Something that can be done with a very controlled set of experiments in a lab or with animals does not necessarily translate into the clinical setting. So it is important not

"It is important to balance what we are able to do in our preclinical research with what is clinically feasible"

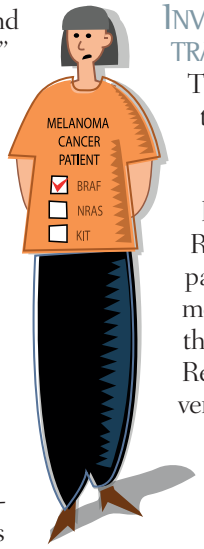
only to ask the right questions, but also to balance what we are able to do in our preclinical research with what is clinically feasible."

Identifying patient groups where there is a strong unmet medical need remains important for clinical development, says Martin, but it is also important to choose a disease indication where you believe a high proportion of patients are likely to respond. "For instance, in our early development portfolio, we are developing a BRAF inhibitor. We know there are mutations in the BRAF gene and those mutations are commonly found particularly in malignant melanoma."

However, BRAF mutations are also known to be present in some colorectal cancers and papillary thyroid cancers, and Martin says their team could explore the effect of their inhibitor in these cancers as well, but it makes sense to start with malignant melanoma, where approximately 50% of patients' tumours have this mutation.

Critical to the whole process, she says, is enabling the preclinical scientists, the clinicians and the translational scientists to work effectively together. "My team straddles the bridge between basic research and the clinical groups. Working closely with the project teams, my team understands the issues from a basic science point of view which leads to the questions that we may want to ask in the clinic."

She accepts, however, that this sort of research requires cooperation at the clinical level with a wider team in addition to the treating oncologist. "In order for us to be entirely successful in translational research, we will need to rely on pathologists, interventional radiologists and maybe even surgeons to access the right samples to perform translational research. We have found that it's better to do that little bit of extra legwork upfront, and by reaching out to these individuals, explaining the purpose of the research and how important it is, usually we are successful in obtaining the right samples and hopefully on our way to answering the key questions."




## Investing in translational research

The importance of high-quality tissue sampling is one of the things Astra Zeneca is now focusing on in a major collaboration with Cancer Research UK to accelerate the pace of biomarker development. The initiative is centred at the Paterson Institute of Cancer Research at Manchester University, and coordinated through the NCRI (National Cancer Research Institutes). From Astra Zeneca's point of view, it represents a strategic attempt to address the single biggest challenge to realising the dream of getting the right drug to the right cancer patient: boosting translational research efforts to understand the basic mechanisms of the disease.

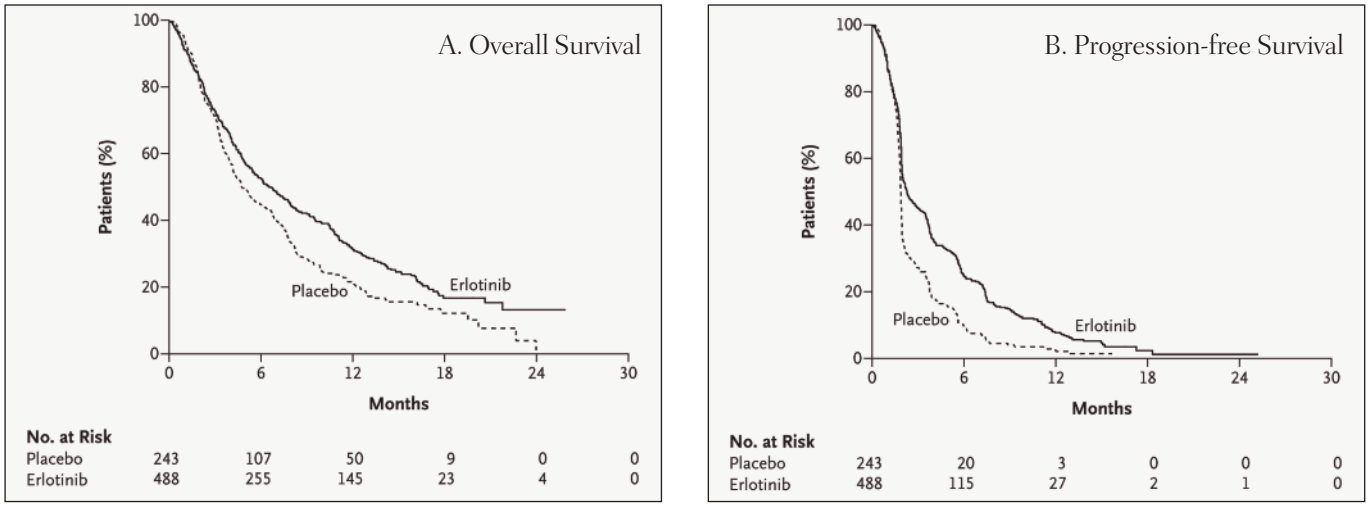
This is how Astra Zeneca's Head of Early Clinical Oncology Development, Andrew Hughes, describes the problem. "Take the target Akt. You can look in many different types of cancer and see that Akt is upregulated, but as to which cancers are addicted to that upregulation of Akt versus those that are not, i.e. which cancers are most likely to respond, it's an open question, despite the fact that we have now very potent and selective inhibitors of Akt."

The result, he adds, is that we have an increasing number of targeted drugs coming through development without understanding how best to use them.

"We are looking very much to science external to Astra Zeneca to help us understand the basic biology of human cancer," says Hughes. "Once we understand which part of the molecular lesion in a cell the cancer is addicted to, then of course pharma is well suited to applying its high-throughput screening, its molecular chemistry, its pharmacokinetics, its optimisation and drug manufacture to go capitalising upon that innovation. But pharma I don't think has the same spectrum of resources as academia has to unlock the basic understanding of cancer question."

The trouble is, says Hughes, that academia faces the same challenges obtaining human cancer tissue as industry. "There has been an awful lot of investment in yeast, non-mammalian systems, cell lines because they are easy to acquire. But to ask researchers to research on human disease material requires them to step out of their labs and into clinics and hospitals to partner with a research-minded physician, and appropriately consent patients to use their tissue to try and understand human diseases." The funding is more expensive and the multidisciplinary infrastructure becomes more of a challenge. "In the

## IT'S ALL ABOUT THE TAIL




**The tail ends of these curves show that a small minority of patients with non-small-cell lung cancer derive very significant benefit from the EGFR inhibitor Tarceva (erlotinib). Progress towards personalised cancer treatments is all about learning how to determine in advance which patients are likely to benefit and which will not**

*Source:* FA Shepherd et al. (2005) Erlotinib in previously treated non-small-cell lung cancer. *NEJM* 353:123–132, reprinted with permission

region of translational research there has been less than we would have liked to have seen."

Finding ways to reorientate cancer research away from the headline-hitting basic science towards more expensive, logistically demanding translational studies is a challenge that has preoccupied many in the cancer research community over recent years. In collaborating with CRUK's biomarker programme, Astra Zeneca is now looking to give the company the answers it needs to inform some of its own clinical trials while at the same time boosting the general capacity of the academic sector to undertake this sort of research. Amongst other things, the funding goes towards running a joint, co-funded PhD course in translational research, and raising the quantity and quality of tissue available for research by placing technicians with the appropriate skills in cancer hospitals.

### LOOKING FOR THE BIG RESPONSES

Efforts to improve the research community's access to quality-controlled biological specimens is something every pharmaceutical company would applaud. But Bill Sellers, Global Head of Oncology for Novartis, wants to go one step further. He would like those quality-controlled specimens to have been pre-screened for biomarkers known to be of interest.

Sellers is looking for the big responses he believes are waiting to be found, and argues that, if and when you find them, all the issues about identifying who is responding, finding biomarkers and developing a test for that biomarker become highly manageable. He cites, as an example, the extension of Glivec [imatinib] to treat KIT-mutant GIST patients.

"The mutation in KIT was actually discovered by a group in Japan. A second group then showed that cell lines with those mutations were highly responsive. Patients with GIST were identified by detection of cKIT by immunohistochemistry for anti-CD117(cKTIT) and then treated with Glivec. At that time it had not been shown that this specific test for CD117 identified all KIT-mutant patients nor all patients who responded to Glivec. However, the immunohistochemistry test itself showed good technical performance, and the FDA (US regulators) did not demand validation of that test as a precondition of extending the indication of Glivec to KIT-mutant GIST patients. It asked, instead, for a post-marketing commitment from Novartis to 'assure the availability of a validated test for detection of CD117 tumour expression by immunohistochemistry.'"

Far from being a special case, says Sellers, that is the future we can look forward to. He mentions an ALK inhibitor for lung cancer patients with a rearranged

ALK gene, and various BRAF inhibitors for melanoma patients with BRAF mutations as examples of therapies in the pipeline that are showing promising results in their target patient population.

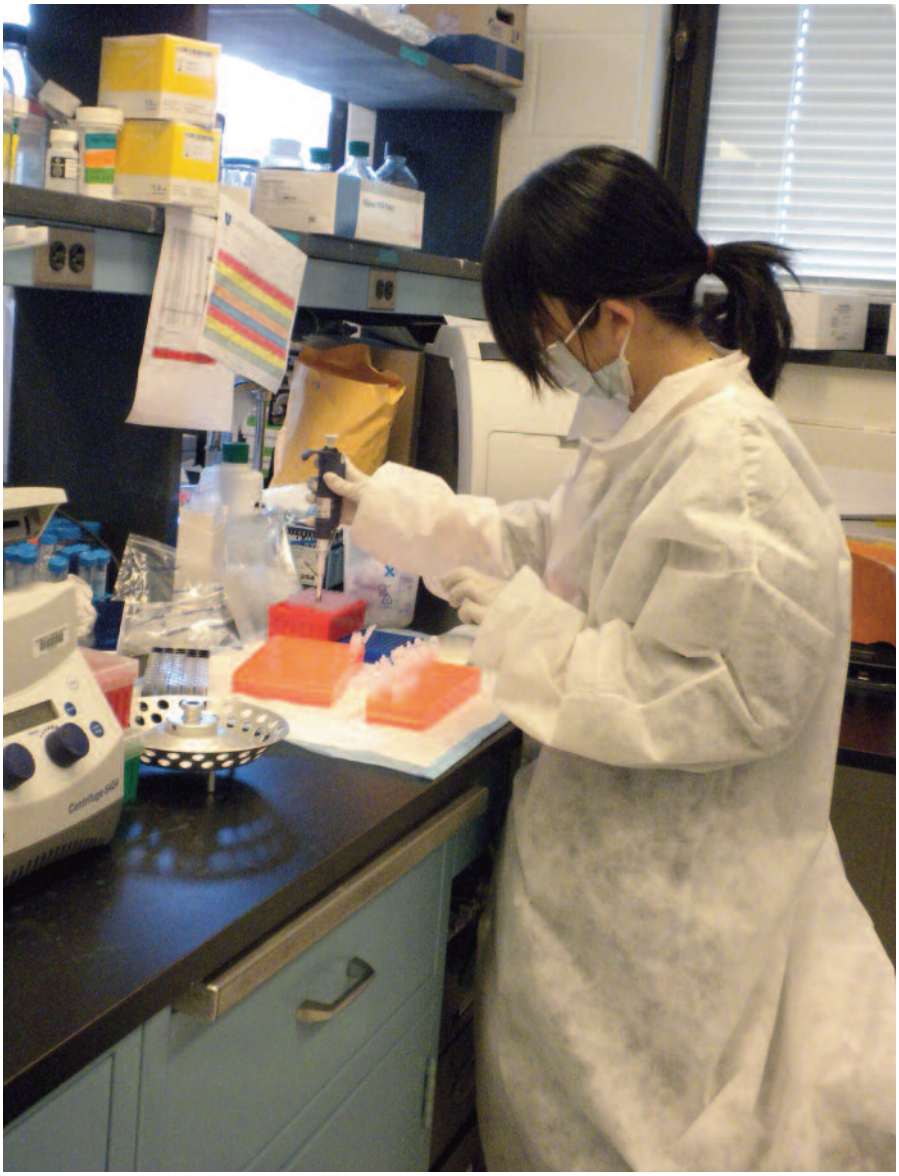
"In the case of melanoma we are doing a trial of our drug Tasigna [nilotinib] in KIT-mutant melanoma only, because given the emerging phase II data, where essentially five out of the first seven patients treated with Tasigna have responded, there would be no way to do the trial in KIT-null patients at this point."

What is holding back progress towards personalised therapies, says Sellers, is the time and effort it takes to recruit the particular patients you need to the trials you want to carry out.

"Imagine you are doing a trial in a population of lung or breast cancer, or melanoma, where only 10% of patients have the mutation that you want. You start the trial and no one out there has been screened for that mutation. Then every patient who enters the trial, you have to consent for the trial, do the test and then tell them you are not eligible nine out of ten times."

Tracking down the patient's tumour sample can itself be a tricky business. "Sometimes that tumour was isolated at a different hospital, and not at the hospital where they are now being treated. You have to find the tumour. You have to make DNA from the tumour; have it sequenced, so it takes time. And then they might not have the right mutation for your trial."

Not surprising, then, that clinicians and patients are not always enthusiastic. How much better, suggests Sellers, if this genetic profiling for alterations considered to be important for cancer genetics was



KATIE MARQUEDANT/MGH CANCER CENTER

**Towards truly tailored treatments. In this translational research laboratory at the Massachusetts General Hospital Cancer Center, specimens from lung and colorectal cancer patients are routinely tested for 124 biomarkers. Prospectively profiling patients in this way should greatly facilitate translational research to discover which combinations of biomarkers are significant for which treatments in which cancers**

"Pharma doesn't have the same spectrum of resources as academia to unlock the basic understanding of cancer"

"You have to consent every patient, do the test and then tell them you are not eligible nine out of ten times"

done on a routine and regular basis, rather than only when they are about to become eligible for a clinical trial.

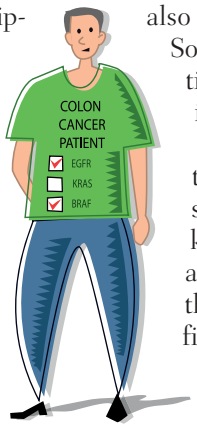
One way this could be done is through a lead-in epidemiology trial to profile patients, so that ahead of time researchers already know how many patients there are at which centres who are bearing this mutation. Better still, says Sellers, is the practice that has recently been adopted at Massachusetts General Hospital and other cancer centres, where many cancer patients are now being offered the option of profiling for sets of mutations and being consented. "When some company has an interesting drug for one of those mutations, they will know if they are eligible."

## A SIGN OF THINGS TO COME

The initiative at Massachusetts General Hospital (MGH) could signal an interesting restructuring of cancer research efforts, tying the patient care side into the translational research side on a scale that has never previously been done. More than that, it would seem to represent the first rays of the long-awaited dawn of the new era in which cancer therapies are routinely personalised in everyday clinical practice.

The hospital is not generating a genetic fingerprint for every cancer patient – at least not yet. But as part of its routine clinical practice, it is now testing some patients for the steadily increasing number of markers that have been identified in the literature as playing a role in driving certain cancers, and it is using this information to direct the patients towards the therapies that are most likely to benefit them. Darrell Borger, Co-Director of the MGH Translational Research Laboratory, points out that there's nothing to stop your average cancer hospital from doing likewise – indeed a number of hospitals across the US are now taking part in a lung cancer project using the assays developed at MGH.

"We've developed assays and software methods that are easily portable that we can transfer across different institutions. It makes that equipment readily available – plug and play – to do this kind of clinical genotyping." The beauty of it, says Borger, is that it is becoming a routine test for some clinicians. "There is nothing additional that the patients need to provide. They fill out a consent form so they understand that their tumour will be tested and they agree to that testing. Then after the diagnosis is made, our pathology department sends the very same sample that they evaluated themselves to our laboratories, and we take a little bit more of that sample to extract the genetic information that we test for. So we use all the material that is currently provided at all institutions to the pathology departments. We don't need anything extra."




All the information relating to the assays developed at the MGH Cancer Center will soon be available in the literature, he adds, and other institutions are welcome to use or improve on them. He hopes that companies could develop some assays as kits that would be commercially available at a price affordable even for small institutions.

Currently all lung and colorectal cancer patients at MGH can have their tumours tested for 124 important cancer gene mutations, chosen according to which are most common over all cancers as a whole. "In lung cancers we know what the important genes are to look for, and of course we look for those," says Borger, "but by having this broad fingerprint, we are finding that there is a small number of patients who also have uncommon mutations." Some of these 'uncommon' mutations could well be very common in other types of cancer, he explains. "And this is the question we will be addressing fairly soon: Can you take what you know in a particular cancer with a particular mutation and apply that in another cancer where you find that same mutation?"

Many other institutions are now also "very very close" to bringing personalised cancer therapies to their patients, according to Borger, in both the US and across Europe. Interestingly, soon to take up his post as Chief of the Division of Hematology/Oncology and Associate Director of the MGH Cancer Center is José Baselga, immediate past president of ESMO (European Society for Medical Oncology). Borger expects the presence of Europe's chief champion of translational research will strengthen collaboration across the Atlantic. "What we are interested in is providing a model that many people can benefit from, incorporate and even improve on. A big collaborative effort, and we all have our contribution to make."

# Blazing a trail in a new type of research

➜ Simon Crompton

When confronted with the novel gene technology of the early '70s, molecular biologist **Axel Ullrich** posed the question: what use can this be to medicine? In doing so, he opened the door on the era of translational research and a personal career which went on to encompass lead roles in the development of two of the first intelligently designed cancer drugs.

He's the man behind the first monoclonal antibody drug Herceptin (trastuzumab), and the innovative kidney cancer treatment Sutent (sunitinib). He has come as close as anyone to finding a 'magic bullet' for cancer, but Axel Ullrich still feels a sense of failure. At the age of 66, with four years to go until compulsory retirement, there's a deadline for making the really big breakthrough, the one that will change cancer treatment forever. The clock is ticking, and the prospect that he won't be able to achieve it makes him sad.

"I feel this responsibility…" he says, "Having to retire now, I feel a little bit of a defeat, even though there is no one else who has brought two cancer drugs to the market from bench to bedside. I hope there will be one or two more. But with cancer, it's only a partial victory."

It's a battle that started as an intellectually intriguing skirmish, and has grown into an increasingly personal war over the years. For all his dissatisfaction, Ullrich stands as one of the living giants in cancer research, for 25 years a leader in translating discoveries in molecular cloning into usable therapies. Last year he was awarded the prestigious Dr Paul Janssen Award for Biomedical Research, cited as "one of few basic scientists whose work not only has influenced academic research, but also has helped millions of patients suffering from major chronic diseases." He is among the top 10 most cited biologists in the world.

How does it feel to have such an influence on people's lives? Ullrich deflects the question. "Well, there are many stories to be told…" he says, and continues with the tale he has begun about the problems he had making drug companies understand the concept of monoclonal antibodies as a targeted cancer therapy. It's not modesty that makes him change the subject. Ullrich sticks to an agenda for what he wants to talk about.

## The Ullrich agenda

The reason that Ullrich still thinks a magic bullet for cancer might be achievable (and many would disagree with him) is that he has already pioneered a different direction of cancer treatment from anyone else in the face of reluctance and disbelief. He did

AXEL GRIESCH/MAX PLANCK INSTITUTE OF BIOCHEMISTRY

it, by his own admission, through a dogged refusal to go in directions people told him to. He doesn't like being told where to go if he believes another way is better – whether that be in academia, within the pharma industry or in an interview.

Ullrich knows that very few people operate like this. He directs my attention to a picture on his office wall of some of the 100 research students at the Institute under his supervision over the past 20 years. "There are a few of them," he says, "just very few who spot what the most important thing is, and go for it straight away."

The difference between those few, he explains, and the remainder, is partly that they refuse to be "book-keeper scientists who just add one stone to another." Some simply have a creativity of approach that inevitably puts them at odds with others.

"The essence of creativity is to see connections where other people don't see them. You can only make breakthroughs if you don't go the most logical common track."

He provides an example of his counterintuitive creativity in his current research at the Max Planck Institute. Examining gene structures in a cancer tumour, one of his students stumbled on an abnormal variant in a gene. Was it relevant to why the tumour formed? Research revealed that the aberration was not restricted to the cancer. It was what is known as a single nucleotide polymorphism (SNP) – a type of variant that also occurs in non-cancerous genes, and which is responsible for the variety and individuality of humans. The SNP that the student had found, it transpired, was one of the more common of around 10 million in the human genome.

A dead-end then. Most colleagues believed so. But Ullrich thought it looked interesting, so continued with experiments. They revealed that though the SNP didn't cause cancer, it did appear to make breast cancer more aggressive. Reports of his research, published in 2002, were met with scepticism: the influence of such SNPs was hard to prove, and was likely to be marginal, he was told.

So Ullrich devised a new experiment to prove the

"Very few people spot what the most important thing is, and go for it straight away"

critics wrong, breeding mice with his newly discovered SNP with others with a gene variant known to make mice more susceptible to cancer. The way cancers developed, progressed and metastasised in the mice clearly indicated that the new SNP influenced how aggressive tumours were. The results were published in *Cancer Research* in January.

"Even my students said, 'Why are you continuing to look at this?' Now we are translating the results back into humans, and are making even more exciting discoveries, because the people we can identify as having a bad prognosis through this SNP may respond much better to some types of treatment than those who do not have the allele."

AXEL GRIESCH/MAX PLANCK INSTITUTE OF BIOCHEMISTRY

So what was it that made him go on? "I had this feeling that there's something important, and that made me fascinated by the beauty of this experiment – of changing one single nucleotide in a mouse and seeing what the effect was on a major disease."

It has been the same story through his career. Ullrich says he's never had a rational approach to his work – he has been led by his 'inner compass', his instinctive sense that some leads need to be followed because they are interesting or important.

He was born in Lauban, Silesia, in 1943. His parents had fled from the Northern Czech Republic – formerly known as the Sudetenland – and lost everything in the process, so they set up a grocery store to make a living. He was good at biology and chemistry at school, but no one told him he could become a scientist. All he really knew was that he didn't want to be a teacher – which is interesting for a man who has spent much of his professional life supervising students. "I hated teachers. I'd seen how they could set out to destroy the life of a young child."

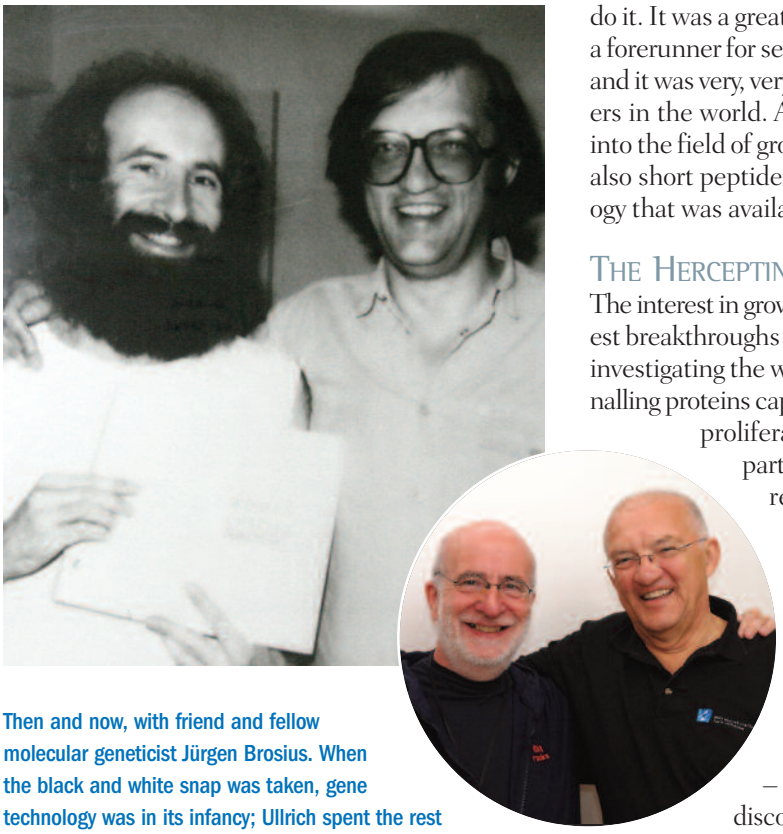
With his parents giving him total freedom on career choice, he decided to study biochemistry at the University of Tübingen, and then went on to earn a PhD in molecular genetics at Heidelberg in 1975. Realising that if he was to stay in science, he would have to learn its international language, English, he decided his next step should be to go to the US – preferably somewhere where the quality of life was good. California for example. So he applied for a fellowship, and a postdoctoral tenure in biochemistry at the University of California, San Francisco. He got them.

## A first for gene technology

It was a time when the first reports about the potential of gene technology were beginning to circulate. He decided to see whether he could do anything 'medically relevant' with the new technology. In the mid '70s, DNA sequencing was still not possible, but Ullrich thought insulin looked a promising

He decided to see whether he could do anything 'medically relevant' with the new technology

# "We made an antibody that blocked the function of this oncogene. So this was a first, first, first…"



Then and now, with friend and fellow molecular geneticist Jürgen Brosius. When the black and white snap was taken, gene technology was in its infancy; Ullrich spent the rest of his career putting it to work to treat disease

area for investigation – it was a small polypeptide with probably a small, manageable gene.

It was a long fight to convince colleagues that this was a good route for research, but by 1977 he had come up with the molecular cloning process that could produce synthetic insulin. The breakthrough occurred just before his fellowship was due to expire, and allowed him to stay on in America to work with the pioneer biotechnology company, Genentech, to develop human insulin, or Humulin – the first treatment developed through gene-based technology.

"I told the founder of the company, Bob Swanson, that I wanted to explore my own ideas. I was probably a pain in the neck for him, but he let me do it. It was a great time for Genentech, which was a forerunner for semi-academic industrial research, and it was very, very exciting. We were the best cloners in the world. And so I got through insulin and into the field of growth factors – because they were also short peptides, and accessible to the technology that was available at the time."

## The Herceptin story

The interest in growth factors was to lead to his greatest breakthroughs in cancer therapy. Ullrich started investigating the way in which growth factors – signalling proteins capable of stimulating cell growth or proliferation – function. He looked in particular at how they interact with receptors – molecules that take their messages into cells. He and colleagues from the UK and Israel cloned receptors, and found a new type of receptor for a growth factor called epidermal growth factor (EGF). They called it HER2.

There was, he says, excitement – but not at the implications of the discovery for countering a disease. "It was the technical challenge," he says.

Its major implications became clearer when they found its peptide sequences were related to an oncogene. In 1987, Ullrich, working in collaboration with Dennis Slamon and others, discovered that the gene for HER2 was overamplified or overexpressed in at least 25% of invasive breast cancers. "The end of the story was Herceptin – the first targeted drug against the product of a gene that was abnormally amplified in about a quarter of all mammary carcinomas. We made an antibody that blocked the function of this oncogene. So this was a first, first, first…"

But Ullrich also felt disappointment, especially when initial trials showed that just 15% of HER2-positive patients responded to Herceptin alone (later trials showed it helped many more in

combination with other drugs). "As a biologist, it had to be all or nothing. I had much higher expectations, whereas for oncologists who work with these patients every day, it was a huge breakthrough."

Then there were disputes with Genentech, which, he says, was initially reluctant to develop and produce an antibody as a therapy. In the end, clinical development didn't begin until 1992 and Herceptin was only approved in 1998. "The story of my life includes many discoveries that were made too early and not understood." Partly as a result of his frustrations with the company, Ullrich took up an offer to become director of the Department of Molecular Biology at the Max Planck Institute of Biochemistry in 1988.

On a personal level, it wasn't an easy time. He had left a house and a wife in California. Each month he spent three weeks in Munich, one week in California. "That lasted about five years and ended in a divorce."

But on a research level, things were moving on. Ullrich, who throughout his career has straddled the academic and commercial spheres, convinced the Max Planck Institute that the best way to translate basic scientific discoveries into treatments was to link an academic lab to a company. They allowed him to start a company to develop the products of research – it was based in the US and called Sugen.

## The Sutent story

It was here that Sutent was developed – the first multikinase inhibitor drug, now a standard for treating renal cell carcinoma and gastrointestinal stromal tumours. It came into being after a new receptor cloned by a research student at Max Planck was found to be critical to the formation of blood vessels (angiogenesis). Angiogenesis is a key process in tumour development, and Ullrich and his colleagues believed they could develop an angiogenesis inhibitor. Initial trials of a Sugen-developed drug based on the discovery were disappointing – they revealed that it also inhibited other receptors.

But again, Ullrich turned defeat into triumph. "So we rationalised," he says. "We said, okay, maybe this is good. Maybe other oncogenes are also inhibited by the drug, and therefore this drug will be effective against cancer in many ways. This is what happened." Sutent, it turned out, was what Ullrich calls a "broadband antibiotic against cancer" – a new type of multi-targeted drug. Research continues into possible new applications.

Ullrich, who in 2001 set up his third biotech company, U3 Pharma, continues to work on developing similar multikinase inhibitors, which are effective against a broad range of cancers. His work continually demonstrates the importance of translational research, yet it worries him how slowly the translation from bench into clinical practice generally occurs – the result, he says, of simple lack of nerve.

"When I look at how much money and time pharma companies say it takes to develop a new drug, I think this is not necessary. All this could be done in half the time quite easily." How? "By hiring better people and giving them responsibility. You need people who are passionate, who don't just see it as a job, and you need to give them the power to take risks."

It's an opinion clearly born of the frictions that have arisen as his confident approach has been viewed as too risky. But he's not a risk-taker in his personal life. He lives with his partner, a medical doctor, and they enjoy the relatively sedate occupations of travelling and cooking. Most of his kicks, he confesses, come from his work, and there are no children to distract him.

It isn't surprising, then, that retirement holds no allure. Ullrich wants to be in the thick of it, pushing forward translational research and encouraging interaction between academics and medical scientists, so that access to biopsies and patient data is easy, and basic science can be put into practice as quickly as possible. It's here, he believes, that the future of cancer research should lie. Stem cell therapies, he emphasises, are unlikely to lead to novel cancer therapies. Focusing on immunology, he believes, on harnessing the body's own ability to fight disease, provides the best chance of defeating cancer.

"You need people who don't just see it as a job, and you need to give them the power to take risks"

Speaking at an ESO meeting at the World Conference of Science Journalists. One of most frequently cited biologists in the world, Ullrich argued that increasing pressures on academic scientists to get coverage in the wider media can lead to them exaggerating the significance of their findings, which may undermine their credibility

JASON HARRIS

# "Only the immune system is so clever that it can track down a cancer cell wherever it is in the body"

## The magic immune system

Ullrich believes that immunology holds out the tantalising prospect that, somewhere out there, a magic bullet for cancer still awaits discovery. Even though cancer is hundreds of diseases, they all have a single common denominator. "The biggest problem is the instability of the genome. It's not important whether you have stem cells or not, but it's important that the cancer cells that have stem cell characteristics have an unstable genome. This is the biggest problem. But you will never defeat cancer without the immune system. It is your ally. Only the immune system is so clever that it can track down a cancer cell wherever it is in the body."

It's the end of the interview and Ullrich, candid but pragmatic throughout, is just beginning to reveal some of the passion that he advocates so strongly in researchers. In a career where he was led to investigate cancer by instinct and curiosity rather than by a sense of mission, in latter years his work seems to have accumulated meaning. He has seen more and more people die of cancer – his father and friends, one of them young, and just a few days ago.

"I only began to appreciate the incredible complexity of cancer after the clinical phase I Herceptin results. I've felt it as an incredible challenge – you know, to take up the War on Cancer that Richard Nixon declared in 1971. I have to say, it has become really, a sort of a calling. I sometimes feel a little depressed that I have to go without having made a really strong impact. But it's a realisation that cancer is just an incredible, formidable enemy."

# Trials and tribulations in primary CNS lymphoma

Stephen Ansell and Vincent Rajkumar

A minority of patients with primary central nervous system lymphoma achieve a complete response to therapy and most patients have a poor prognosis. A recent randomised phase II trial demonstrated that the addition of high-dose cytarabine to high-dose methotrexate increases the complete response rate and improves patient outcome.

Primary central nervous system lymphoma (PCNSL) is an uncommon extranodal B-cell non-Hodgkin lymphoma confined to the central nervous system (CNS) that represents approximately 1% of all non-Hodgkin lymphomas. Although this disease has been observed in patients with immune deficiency, the incidence in immunocompetent patients has increased, particularly among elderly patients.[1]

Due to the rarity of PCNSL, randomised studies have been very difficult to conduct. Patients with this disease have not benefitted from the progress made in systemic B-cell lymphoma, in that standard treatment approaches such as cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) chemotherapy have not been effective in PCNSL because of poor drug penetration into the CNS.[2] The use of therapies that are considered effective – high-dose methotrexate, autologous stem-cell transplantation and whole-brain radiation therapy (WBRT) – has proved challenging because many patients are elderly and more susceptible to the toxic effects associated with these treatments.

The initial treatment for patients with PCNSL was to use WBRT. While PCNSL tumours are very radiosensitive, local disease relapses are frequent and there are virtually no long-term survivors.[3] Based on its ability to penetrate the CNS, methotrexate was subsequently used in clinical trials, and high doses with folinic acid rescue were found to improve patient outcome.[4] While there is no consensus as to the exact dose that should be used, it is generally accepted that 'high-dose' methotrexate regimens utilise between 1 g/m$^2$ to 8 g/m$^2$ administered every two to three weeks. Other agents, including cytarabine, procarbazine, temozolomide and rituximab, have since been added to high-dose methotrexate and have produced higher response rates and potentially improved progression-free survival.[5] However, a higher instance of

nature REVIEWS CLINICAL ONCOLOGY

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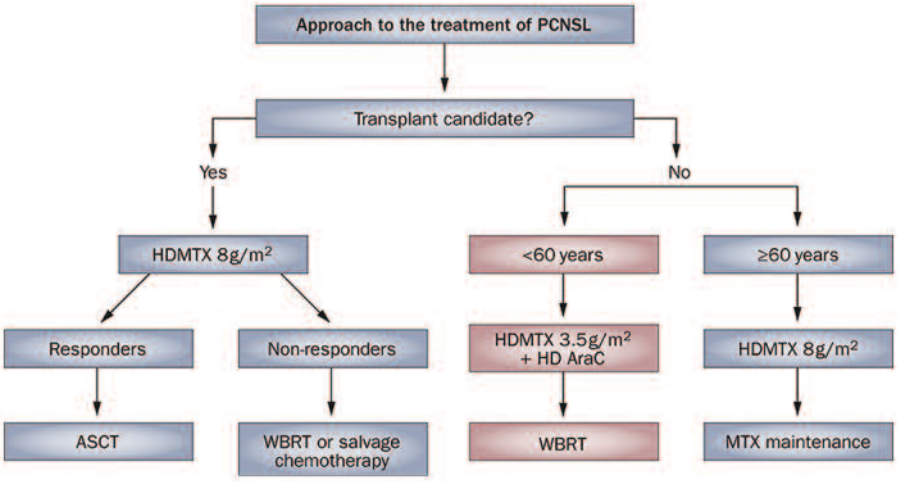
toxic effects have been seen in studies testing chemotherapy combinations, resulting in higher rates of treatment-related mortality compared with high-dose methotrexate alone.

In most of these studies, chemotherapy formed part of a combined modality approach and WBRT was given as consolidation after induction therapy. A high incidence of neurotoxicity was seen, particularly in patients older than 60 years who received combined modality treatment.[6] Recent studies have attempted to limit neurotoxicity, either by omitting radiation therapy[7] and in some studies consolidating the response to initial therapy using autologous stem-cell transplantation,[8] or by use of lower doses of radiation therapy.[9] In studies in which autologous stem-cell transplantation was added and radiation therapy omitted, it was evident that patients who benefitted most were those who had a complete response to initial induction therapy. Similarly, lowering the dose of WBRT to diminish potential long-term neurotoxicity might only be feasible in patients who have a complete response to treatment. Therefore, to utilise these approaches we need to identify treatment regimens that result in high complete response rates.

High-dose methotrexate has become a standard approach for many groups treating patients with PCNSL, and doses of up to 8 g/m$^2$ are given every two weeks. A recent study by Ferreri et al.[10] suggests that the addition of high-dose cytarabine to high-dose methotrexate results in a superior complete response rate and overall response rate when compared with methotrexate alone. In this randomised phase II trial, 79 patients were randomly assigned to receive methotrexate 3.5 g/m$^2$ alone or in combination with cytarabine 2 g/m$^2$ twice daily on two days for four cycles as primary therapy for CNS lymphoma. The primary endpoint of the study was complete response rate. In total, 46% of patients receiving both high-dose methotrexate and high-dose cytarabine had a complete response to treatment compared with 18% of patients receiving high-dose methotrexate alone. The overall response rate and subsequent outcomes of patients were improved with the addition of high-dose cytarabine to high-dose methotrexate. Although significant haematological toxic effects were seen, this was managed with growth factor administration and adverse effects were felt to be acceptable. These findings suggest that intensification of induction therapy as demonstrated by this study might improve long-term patient results.

Although the findings are persuasive, certain caveats need to be kept in mind when interpreting these results. First, as in most CNS tumours, radiographic assessment of response is not always easy, and has limitations as a surrogate for clinical benefit. This is further exacerbated in non-blinded studies. Second, although studies of combination chemotherapy and combined modality therapy in this disease have used varying doses of 'high-dose' methotrexate, the trials that use high-dose methotrexate as a single agent have employed a dose of 8 mg/m$^2$ every two weeks. This dose results in a high response rate, is well tolerated, and can be administered repeatedly until progression in most patients. The study by Ferreri et al.[10]

**TREATMENT OF NEWLY DIAGNOSED PCNSL PATIENTS**




Transplant-eligible patients receive high-dose chemotherapy followed by an autologous stem-cell transplant, in patients who respond to treatment. Elderly patients are treated with a chemotherapy-only approach to avoid neurological toxicity associated with WBRT. Younger patients who are not eligible for an autologous stem-cell transplant could be treated with high-dose chemotherapy followed by WBRT (as per the data from the clinical trial of Ferreri et al.[10] (*highlighted in the figure*).

ASCT – autologous stem-cell transplantation; HD AraC – high-dose cytarabine; HDMTX – high-dose methotrexate; MTX – methotrexate; PCNSL – primary central nervous system lymphoma; WBRT – whole-brain radiation therapy

used a lower dose of methotrexate, 3.5 g/m$^2$ delivered every three weeks, which might account for a lower response rate than has been reported in other studies. Third, the vast majority of patients (77%) received WBRT as consolidation after the initial induction chemotherapy. Many groups favour consolidation with autologous stem-cell transplantation rather than administering WBRT, because of the increased neurotoxicity seen with WBRT. Finally, dose reductions were necessary in 44% of patients treated with the combination approach (compared with 3% of patients treated with methotrexate alone), suggesting that it might be easier to intensify therapy by increasing the dose of methotrexate than by adding a second drug, such as high-dose cytarabine.

The data presented by Ferreri et al.[10] could be particularly relevant in patients or practices where high-dose therapy with autologous stem-cell transplantation is not employed. For many groups, the initial decision might be to define which patients are eligible for transplantation. In eligible patients, high-dose methotrexate at a dose of 8 g/m$^2$ could be considered with autologous stem-cell transplantation performed in patients who respond to this therapy.

Nonresponders are commonly managed with salvage chemotherapy including temozolomide, rituximab and other treatment approaches, or alternatively receive WBRT (see algorithm). In patients where an autologous transplant is not considered or at centres which do not employ this approach, the data presented by Ferreri et al. could be of value. In view of the fact that patients aged over 60 years receiving WBRT might have significant neurotoxicity, these patients could be managed with chemotherapy alone and could receive methotrexate with or without other chemotherapy agents. Alternatively, younger patients might benefit from the results presented by Ferreri et al.[10] and these patients could be treated with high-dose methotrexate in combination with high-dose cytarabine and then receive consolidation treatment with WBRT.

Primary CNS lymphoma remains a challenging disease and further trials are needed to provide information to further optimise the care of patients with this devastating illness. The use of drugs that penetrate the blood–brain barrier at increased doses seems to be the best approach. Patients responding to this therapy might further benefit from consolidation approaches, including autologous stem-cell transplantation or lower dose WBRT.

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## Practice point

The use of high-dose cytarabine in combination with high-dose methotrexate followed by whole-brain radiation therapy could be effective in younger patients with primary central nervous system lymphoma for whom autologous stem-cell transplantation is not planned.

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# Androgen deprivation therapy for prostate cancer: true love or heartbreak?

Jason Efstathiou, William Shipley, Anthony Zietman and Matthew Smith

The addition of hormonal therapy to radiation therapy improves survival in men with unfavourable risk prostate cancer. Yet, men with prostate cancer have higher rates of non-cancer death than the general population and most will die from causes other than their index malignancy. Comorbid cardiovascular disease is strongly associated with cause of death and this raises the possibility that prostate cancer or its treatment increases cardiovascular disease risk and possibly mortality.

The relationship between androgen deprivation therapy (ADT) and cardiovascular disease is not a new story, although interest has renewed in recent years. Diethylstilbestrol, a non-steroidal oestrogen, was historically used in treating metastatic prostate cancer but was abandoned because of excess cardiovascular and thromboembolic risk. More recently, prospective studies have demonstrated that gonadotropin-releasing-hormone agonists adversely affect some traditional cardiac risk factors, including lipid profiles, insulin sensitivity and obesity. In a large population-based study, Keating et al.[1] reported that these agonists are associated with increased risk of incident diabetes mellitus and cardiovascular disease.

The results of the novel observations by Keating et al.[1] spawned a host of *post-hoc* analyses of randomised trials and observational population-based studies to evaluate the relationship between ADT and cardiac morbidity and mortality.[2–6] To date, the evidence from these studies suggests that ADT modestly increases risk of cardiovascular disease but does not necessarily increase cardiovascular mortality. The absence of an apparent increase in cardiovascular mortality does not, however, exclude the possibility of ADT increasing non-cancer mortality. Previous reports suggested higher non-cancer mortality in men treated with long-term versus short-term adjuvant hormonal therapy for advanced disease[3] and decreased overall survival in those receiving neoadjuvant hormonal therapy before prostate brachytherapy for early-stage disease.[7]

Within this framework, Nanda et al.[8] attempted to evaluate the relationship between short-term ADT and all-cause mortality in men treated with brachytherapy for early-stage prostate cancer. This single-institution, retrospective experience included 5077 men with localised or locally advanced prostate cancer treated

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with or without a median of four months of neoadjuvant ADT followed by brachytherapy. ADT was linked to greater all-cause mortality ($P$=0.04) after a median follow-up of 5.1 years in a small subgroup ($n$=256) of men with coronary artery disease- (CAD-) induced congestive heart failure or prior myocardial infarction, but not among the majority of men without those conditions.

We commend the authors on their attempt to define a subgroup of patients in whom ADT is possibly dangerous, and agree that hormonal therapy is not suitable for everyone. Yet, caution must be exercised in the interpretation of the results of this study. First, because prostate cancer is an indolent disease, it is unclear why men with clinically significant cardiovascular disease were treated with brachytherapy rather than managed by active surveillance. Second, there is no established survival benefit for ADT in combination with brachytherapy and it is unclear why so many men received ADT in this setting. Third, there are concerns raised over ascertainment biases in that the main conclusion associating ADT with greater all-cause mortality in men with CAD-induced congestive heart failure or prior myocardial infarction is based on a small subset representing only 5% of the entire study population, and a difference of only seven events.

The choice of all-cause mortality as an endpoint is particularly surprising because the men who received ADT had more adverse features than patients who did not receive it, including older age, and more-aggressive cancers. Unfortunately, the authors did not report cancer-specific or non-cancer mortality, so it remains unclear whether the link to greater all-cause mortality was related to prostate cancer, its treatment, or the selection of patients at greater risk for death.

Notably, an analysis of a large, multicentre, prospective randomised controlled trial with long follow-up found that, even within subgroups of men with high-risk of cardiac death (that is, age 70 years or older, prevalent cardiovascular disease or diabetes) there was no apparent increase in cardiovascular mortality in those treated with adjuvant ADT for locally advanced prostate cancer.[2] Similarly, analyses of another large randomised trial[4] have also reported no excess cardiovascular mortality in men receiving short-term ADT in combination with radiation therapy versus radiation alone.

Herein lies the true lesson of the Nanda study. ADT as an adjunct to radiation was adopted in the 1990s for advanced disease on good evidence. In fact, it is firmly established that hormonal therapy decreases cancer-specific and, in some cases, all-cause mortality for men with locally advanced or high-grade localised prostate cancer. Regrettably, this evidence of improved survival has, in part, led to the increase in the use of hormonal therapy across the entire spectrum of disease even among men with lower-risk prostate cancer and older men with significant competing causes of mortality.[9] This over-exuberant expansion in the indications for hormonal therapy might reflect both the optimism and good intentions of treating physicians; however, the issue of financial reimbursement could be involved as well.[10]

The results of the Radiation Therapy Oncology Group (RTOG) 94-08 study (presented as a late-breaking abstract at ASTRO annual meeting 2009) are of paramount importance to informing proper patterns of practice. This landmark trial demonstrated that short-term ADT before and during radiation therapy modestly improved overall survival ($P$=0.03) in patients with early-stage localised prostate cancer and notably did not increase the risk of intercurrent death. The actuarial 10-year death rate from intercurrent disease (excluding deaths from prostate cancer) was 35% in the ADT plus radiation therapy arm and 37% in the radiation alone arm ($P$=0.49). The results of the risk group analysis revealed that the intermediate-risk subgroup experienced the greatest benefit from short-term ADT, although it is debatable whether this remains valid in the era of dose-escalated radiation therapy (which is being addressed in an ongoing RTOG trial). Results of this risk group analysis, however, demonstrate that there is no role for hormone therapy in low-risk disease. Secondary analyses from this important randomised trial will help shed further light on the unintended adverse effects of hormonal therapy in early-stage disease, including those with significant cardiac comorbidity.

We strongly recommend limiting use of adjunctive ADT to settings with an established survival benefit. These evidence-based indications include men receiving external-beam radiation therapy for intermediate and high-risk disease. The absence of an established survival benefit should be sufficient reason to avoid ADT in other settings, including men receiving brachytherapy and/or external-beam radiation therapy for low-risk disease. The increased understanding of potential adverse effects of ADT serves to reinforce careful selection of appropriate candidates for treatment.

Clinicians should not necessarily withhold ADT from men who might benefit from it in terms of cancer-specific survival despite a history of cardiac comorbidity after careful consideration of the risks and benefits. Good general medical care dictates that patients with underlying cardiac disease receive secondary preventive measures, including lipid-lowering, antihypertensive, glucose lowering, and antiplatelet therapy as appropriate. There is no evidence to recommend additional cardiac testing or coronary intervention in patients with cardiovascular disease before initiation of ADT. In lieu of a randomised controlled trial directly

addressing the question of the effect of ADT on cardiac health, we believe future trials of ADT as well as novel forms of hormone therapy should prospectively assess cardiovascular risk factors and stratify patients according to their comorbidities.

The questions raised by the relationship between ADT and cardiac health in prostate cancer patients are complicated. The initial excitement surrounding hormonal therapy could now be over, as the relationship finds a new balance based on evidence.

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## Practice point

Androgen deprivation therapy is associated with many adverse effects, including cardiovascular disease. Its use as an adjunct to local therapy, such as radiation, in the treatment of prostate cancer should be limited to settings with proven survival benefit.

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# NEWSROUND

Selected reports edited by Janet Fricker

## Cetuximab rash is a good sign in head and neck cancer

➜ Lancet Oncology

For patients with locoregionally advanced squamous-cell carcinoma of the head and neck (SCCHN), the latest five-year overall survival data confirm that radiotherapy plus cetuximab is better than radiotherapy alone. Furthermore, the US investigators found that cetuximab-treated patients with a prominent cetuximab-induced rash (grade 2 or above) had more than 2.5 times longer overall survival than patients exhibiting no rash or mild rash.

In 1998, James Bonner and colleagues from the University of Alabama (Birmingham, Alabama) designed a randomised trial investigating the value of adding cetuximab to radiotherapy in 424 patients with locally advanced SCCHN. Results at three years showed that survival was 55% among those randomised to cetuximab and radiation compared to 45% for those randomised to radiotherapy alone. Of particular interest to the investigators were several studies across multiple cancers (including colorectal, non-small-cell lung cancer and pancreatic cancer) suggesting a correlation between overall survival and presence of a cetuximab-induced acne-like rash.

In the current paper, Bonner and colleagues report the five-year survival data and investigate the relationship between cetuximab-induced rash and survival. Patients with locally advanced SCCHN of the oropharynx, hypopharynx or larynx with measurable disease were randomly allocated in a 1:1 ratio to receive either comprehensive head and neck radiotherapy alone for six to seven weeks ($n$=211) or radiotherapy plus weekly doses of cetuximab (400 mg/m$^2$ initial dose, followed by seven weekly doses at 250 mg/m$^2$, $n$=213).

Results show that median overall survival at five years was 36.4% in the radiotherapy-alone group versus 45.6% in the cetuximab/radiotherapy arm (HR 0.73, 95% CI 0.56–0.95; $P$=0.018). The median overall survival in the radiotherapy-alone group was 29.3 months (95% CI 20.6–41.4) compared with 49.0 months (32.8–69.5) in the cetuximab group.

As expected, patients randomised to cetuximab experienced a greater number of grade 3 and 4 infusion reactions than those who received radiotherapy alone. Of the patients who received cetuximab, those with a prominent cetuximab-induced acneiform rash (grade 2–4) had a 68.8-month median overall survival compared with 25.6 months (HR 0.49, 95% CI 0.34-0.72, $P$=0.002) in those who developed mild or no rash (grade 0–1). The small number of patients in the radiotherapy-alone group who developed acneiform rashes showed no survival difference compared with patients not exhibiting rash.

"These updated survival results provide further support for considering the combination of cetuximab and radiotherapy as a standard option in the treatment of locally advanced SCCHN," write the authors, adding that their previous report provided the impetus for the inclusion of cetuximab and radiotherapy as a treatment option for locally advanced SCCHN in the 2007 National Comprehensive Cancer Network (NCCN) guidelines.

It is possible, add the authors, that the acneiform rash is a biomarker of an immunological response conducive to optimal outcomes. "In the future, the presence or absence of a cetuximab-induced rash [might be used] to identify patients who benefit from more prolonged treatment with cetuximab or treatment with other agents," write the authors, adding that further work will be necessary to determine the mechanistic significance of the acneiform rash.

In an accompanying editorial, Kevin Harrington, from the Institute of Cancer Research (London, England), writes, "The relatively rapid onset of skin reactions (>75% exhibited the rash within two weeks) seems to offer the prospect of making decisions to continue or stop cetuximab after the first few weeks of treatment."

He adds that the National Cancer Institute Common Toxicity Criteria were used to define the boundary between mild rash (grade 1) and prominent rash (grade 2). "This discrimination rests on the absence (grade 1) or

presence (grade 2) of symptoms, rather than an objective measure of the rash. Therefore, the reliability of this measure must be confirmed in future studies."

He comments too on the implications of recent studies showing important survival differences between SCCHNs that were associated with the human papillomavirus (HPV) and those that were not. While the importance of ensuring balance in human papillomavirus (HPV) status between the treatment groups could not have been anticipated when the study was conceived, writes Harrington, the better prognosis of patients with HPV-positive locally advanced SCCHN means that HPV status must be included as a stratification factor in future studies.

■ A Bonner, P M Harari, J Giralt et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol* January 2010, 11:21–28

■ KJ Harrington. Rash conclusions from a phase 3 study of cetuximab [editorial]. *ibid* pp 2–3

## Abbreviated radiotherapy effective for breast cancer

➜ New England Journal of Medicine

An intense three-week course of radiation therapy was found to be just as effective as the standard five-week regimen for women with early-stage breast cancer, report Canadian researchers.

In women with breast cancer who undergo breast-conserving surgery, whole-breast irradiation reduces the risk of local recurrence and can prevent the need for mastectomy. Radiobiologic models have suggested that a larger daily dose of radiation (hypofraction), given over a shorter time (accelerated therapy) might prove just as effective as standard treatment, consisting of 50.0 Gy of radiation given in 25 fractions over a period of five weeks in daily fractions. Such an abbreviated regimen would offer the advantage of being both more convenient for patients and less resource intensive than standard schedules.

In 2002 Tim Whelan, from the Michael G DeGroote School of Medicine at McMaster University, Hamilton, Ontario, reported the five-year results of a randomised clinical trial comparing abbreviated radiation with the standard approach. At the time, local recurrence rates were the same (3%) for both groups, and cosmetic outcomes (reflecting the radiation-related morbidity) were also similar. "Nevertheless, because radiation-related microvascular damage increases over time, there was concern that late toxic effects of radiation associated with the hypofractionated regimen could develop," write the authors, who in the current study report their findings at a median follow-up of 12 years.

Between 1993 and 1996 the investigators recruited women with invasive breast cancer who had undergone breast-conserving surgery with negative axillary lymph nodes who were randomised to either standard whole-breast irradiation (50 Gy given in 25 fractions over a period of 35 days, $n$=612) or accelerated hypofractionated irradiation (42.5 Gy given in 16 fractions over a period of 22 days, $n$=622).

Results at 10 years showed that the risk for local recurrence was 6.7% among the standard-treatment group and 6.2% among women in the hypofractionated-treatment group (absolute difference, 0.5 percentage points; 95% CI –2.5 to 3.5).

There were 126 deaths in the standard-treatment group and 122 in the hypofractionated-treatment group ($P$=0.79).

At 10 years, 71.3% of the women in the standard-treatment group and 69.8% in the hypofractionated-treatment group had good or excellent cosmetic outcomes (absolute difference, 1.5 percentage points; 95% CI –6.9 to 9.8).

Although there was a worsening of the cosmetic outcome over time, say the authors, which coincided with the increase in toxic effects of irradiation of the skin and subcutaneous tissue, there was no increase in toxic effects in women who received accelerated hypofractionated radiation therapy as compared to those who received standard therapy.

"Our long-term results provide support for the use of accelerated, hypofractionated, whole-breast irradiation in selected women with node-negative breast cancer after breast conserving surgery," write the authors, adding that such an approach was both more convenient and less costly than standard treatment. "Its availability as a treatment option may lead to an increase in the number of women who receive breast irradiation after breast conserving surgery."

Potential limitations, write the authors, were that the trial was restricted to women who had node-negative, invasive breast cancer. For this reason the results are not applicable to patients for whom nodal irradiation is planned. Furthermore, women with large breasts were not included, and few women received adjuvant chemotherapy – a treatment that may place them at increased risk for adverse cosmetic outcome with standard radiotherapy. "So it is unclear whether hypofractionation would lead to an outcome that would be any worse than that with standard treatment," write the authors.

■ T Whelan, J P Pignol, M Levine et al. Long-term results of hypofractionated radiation therapy for breast cancer. *NEJM* 11 February 2010, 362:513–520

## Adding MRI to breast cancer assessment does not cut reoperations

➜ The Lancet

The addition of MRI scans to conventional triple assessment techniques for the diagnosis of breast cancer has no effect on the reoperation rate, reports the UK COMICE trial.

The COmparative effectiveness of Magnetic resonance Imaging in breast CancEr (COMICE) trial was the first randomised trial to assess whether contrast-enhanced MRI in women with primary breast cancer scheduled

for wide local excisions decreased their need for reoperations. The COMICE trial was inspired by observational studies showing greater accuracy for MRI than for X-ray mammography or ultrasound (*JCO* 17:110–119). It is known that around 20% of women return to surgery for 'reoperation' because their tumour has not been completely removed. The COMICE investigators hoped that by better delineating the extent of the tumours the 'reoperation' rate would be minimised.

Lindsay Turnball and colleagues, from the Centre for Magnetic Resonance Investigations at Hull Royal Infirmary (Hull, England), recruited 1623 women aged 18 years or older with biopsy-proven breast cancer from 45 centres in the UK. In addition to receiving triple assessment (defined as clinical examination, imaging of the breast by X-ray mammography and/or ultrasound, and pathological assessment of the lump by fine-needle aspiration cytology or core biopsy) women were randomised to receive MRI (*n*=816) or no further imaging (*n*=807). The primary endpoint of the study was the proportion of patients undergoing a repeat operation or further mastectomy within six months of randomisation, or a pathologically avoidable mastectomy at initial operation.

Results show that 19% of women (*n*=153) needed reoperation in the group that received MRI in addition to conventional triple assessment, compared with 19% (*n*=156) in the group that did not receive MRI (OR 0.96, 95%CI 0.75–1.24; *P*=0.77).

The researchers also found no differences in health-related quality of life between the groups 12 months after initial surgery, and no significant difference in costs ($8877.36 per MRI patient vs $8402.10 per non-MRI patient; *P*=0.075).

"However, in terms of total costs, results suggested a difference between the two trial groups, with the MRI group costing more than the non-MRI group, although the difference was not statistically significant," write the authors. "In view of the similar clinical and health related quality-of-life outcomes of patients in both groups, we conclude that the addition of MRI to the conventional triple assessment might result in extra use of resources at the initial surgery period, with few or no benefits to saving resources or health outcomes, and the additional burden on patients to attend extra hospital visits."

In an accompanying commentary, Elizabeth Morris, from Sloan-Kettering Cancer Center and Weill Cornell Medical College (New York), said that the COMICE study does not fully answer the question of whether preoperative breast MRI adds benefit, because recurrence and overall survival were not examined. "It is too early to completely dispense with preoperative breast MRI. Importantly, COMICE has shown that preoperative breast MRI might not be for all women and that routine breast MRI in the evaluation of early breast cancer, as managed by those participating in this study, does not decrease reoperation rates."

■ L Turnbull, S Brown, I Harvey et al. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. *The Lancet* 13 February 2010, 375:563–571

■ E Morris. Should we dispense with preoperative breast MRI? *ibid* pp 528–530

## Combination chemotherapy no advantage in kidney cancer

➜ The Lancet

Combined treatment with interferon-α2a, interleukin-2, and fluorouracil did not improve overall or progression-free survival compared with single therapy using interferon-α2a alone, found a joint MRC (British Medical Research Council) and EORTC (European Organisation for Research and Treatment of Cancer) study. However, the investigators, led by Martin Gore from the Royal Marsden NHS Trust (London, England), concluded the combined regimen may still have a role to play because it produced remissions of clinically relevant length in some patients.

In metastatic renal cell carcinoma the immunotherapy regimen associated with the highest response rates has been the combination of interferon-α2a, interleukin-2 and fluorouracil, with response rates as high as 39% being reported by Atzpodien and colleagues (*Br J Cancer* 85:1130–1136). Not all groups, however, have been able to reproduce such high response rates. The MRC and EORTC therefore decided to mount a large-scale randomised trial comparing interferon-α2a alone, the then standard of care in Europe, with combined interferon-α2a, interleukin-2 and fluorouracil.

Between April 2001 and August 2006, the RE04/30012 trial, undertaken in 50 centres across the UK, the Netherlands, Slovakia, Germany, Belgium and Denmark, randomly allocated 1066 patients with metastatic renal cancer to treatment with interferon-α2a alone (*n*=502) or treatment with interferon-α2a plus interleukin-2 plus fluorouracil (*n*=504). Treatment was not masked.

Results show that the median overall survival was 18.8 months for patients receiving interferon-α2a versus 18.8 months for combination therapy (HR 1.05, 95%CI 0.90–1.21; *P*=0.55). The absolute difference in overall survival was 0.3% at one year and 2.7% at three years, favouring single-agent interferon-α2a.

The best overall response, however, was significantly higher in patients receiving combined therapy, at 23%, compared with 16% for patients receiving interferon-α2a alone (*P*=0.0045), though this was not nearly as high as that reported by Atzpodien and colleagues.

Not surprisingly, grade 3/4 toxicity was more common among patients receiving the combined therapy (53% vs 36%, *P*<0.0001).

On the basis of these findings, the authors conclude that, "Although combination therapy does not improve overall or progression-free survival compared with interferon-α2a alone, immunotherapy might still have a role because it can produce remissions that are of clinically relevant length in some patients. Identification of patients who will benefit from immunotherapy is crucial."

They note that dose modifications and breaks occurred with both regimens, but that

breaks were more frequent for patients receiving combined therapy than for those receiving interferon-α2a, with three-quarters of patients given interferon-α2a alone receiving 80% or more of their expected dose.

The high degree of dose reduction with combined therapy might provide an explanation for the absence of benefit with this regimen, write the authors. "However, we believe that this finding is representative of the feasibility of this treatment, and no difference existed between the treatments according to size or experience of the treating centre."

The study, they add, might be criticised for limiting the cycles of combination immunotherapy to two, although this decision was taken after wide consultation with major cancer centres where cytokine therapies were used.

In an accompanying editorial, Bernard Escudier from the Gustave Roussy (Villejuif, France) congratulated the MRC RE04/EORTC GU 30012 investigators on undertaking the largest ever trial in mRCC. "They have clearly answered the initial question: the triple regimen was definitively not superior to interferon-α2a and was more toxic. Thus, although the response rate is higher than with interferon, chemoimmunotherapy should no longer be used in mRCC."

The study, he added, emphasises that interferon remains an acceptable option in patients with good-risk features, and that the safety of interferon appears to be better when used by doctors who have wide experience of the drug compared with those who do not. For example, grade 3–4 fatigue occurred in 18% of patients in RE04/30012 study, run in UK and EORTC centres, compared with 30% of patients in the CALGB study in the US.

■ ME Gore, CL Griffin, B Hancock. Interferon alpha-2a versus combination therapy with interferon alpha-2a, interleukin-2, and fluorouracil in patients with untreated metastatic renal cell carcinoma (MRC RE04/EORTC GU 30012): an open-label randomised trial. *The Lancet* 20 February 2010, 375:641–648

■ B Escudier. Chemo-immunotherapy in RCC: the end of a story [editorial]. *ibid* pp 613–614

## Molecular profiling predicts Hodgkin's lymphoma outcomes

➜ New England Journal of Medicine

Increased numbers of tumour-associated macrophages are strongly associated with shortened survival for Hodgkin's lymphoma patients, a Canadian study has reported. These latest findings offer a new biomarker for risk stratification, allowing clinicians to predict which patients can be cured with standard treatments and which are more likely to relapse.

Currently most patients receive at least four cycles of polychemotherapy and, if indicated, radiotherapy. Autologous haematopoietic stem-cell transplantation can rescue about 50% of patients in whom primary therapy has failed. Despite advances in treatments for Hodgkin's lymphoma, around 20% of patients still die from progressive disease. None of the prognostic-factor scoring systems currently available are able to identify those patients in whom treatment is likely to fail.

Randy Gascoyne and colleagues, from the British Columbia Cancer Agency (Vancouver, Canada), set out to build "a robust discriminative model" predictive of treatment failure, that might be used to identify a small set of genes that could be used to separate patients into the different outcome groups. The study was undertaken in two stages.

The first stage of the study involved analysing 130 frozen samples obtained from patients with classic Hodgkin's lymphoma during diagnostic lymph-node biopsy for gene expression profiling to determine which cellular signatures correlated with treatment outcome. Primary treatment was defined as a failure if the lymphoma had progressed at any time after the initiation of treatment, while treatment success was defined as the absence of progression or relapse. The second stage involved validating the findings in an independent cohort of patients with immunohistochemical analysis.

Results of the first stage of the study showed that gene-expression profiling identified a gene signature of tumour-associated macrophages that was significantly associated with primary treatment failure ($P$=0.02).

Of the potential markers identified in the first part, the researchers further analysed CD68+ macrophages, CD20+ B cells, and matrix metalloproteinase-11 (MMP11) by immunohistochemical staining of samples from an independent cohort of 166 patients. CD68, they discovered, "stood out because of its significant correlation" with survival. On a scale of 1 to 3, a score of 3 (representing the highest concentration of CD68+ macrophages) was associated with lower 10-year disease-specific progression-free survival of 59.6%, compared to 88.6% for a score of 1 ($P$=0.003), as well as an increased likelihood of relapse after stem-cell transplantation ($P$=0.008).

In patients with limited-stage disease, a CD68 score of 1 was associated with 100% 10-year disease-specific survival ($P$=0.04).

"Our study showed the value of enumerating CD68+ macrophages in diagnostic lymph-node samples for prediction of the outcome after primary treatment and secondary treatment (in particular, autologous stem-cell transplantation)," write the authors. "The absence of an increased number of CD68+ cells in patients with limited-stage disease defines a subgroup of patients for whom the rate of long-term disease-specific survival is 100% with the use of available treatments."

In an accompanying editorial, Vincent DeVita and José Costa, from the Yale School of Medicine (New Haven, Connecticut), wrote that the technology should enable "the selection of patients with a particularly poor prognosis (regardless of stage) for aggressive treatment, which can bring more logic to the treatment of this curable cancer." Most patients, they add, could be spared a combination of therapies or radiotherapy with attendant long-term toxic effects.

■ C Steidl, T Lee, S Shah. Tumor-associated macrophages and survival in classic Hodgkin's lymphoma. *NEJM* 11 March 2010, 362:875–885

■ V DeVita, J Costa. Towards a personalised treatment of Hodgkin's disease [editorial]. *ibid* pp 942–943

# Should you respect a dying wish?

Anna Wagstaff

Some terminally ill cancer patients, seeing only suffering and indignity ahead, want to die at a time and in a manner of their own choosing. But how does legal backing for assisted dying impact on efforts to strengthen palliative care? And is helping patients to die compatible with the duty of doctors, nurses and carers to save life and protect the vulnerable?

For George and Hannah, the decision to end their lives at a time and in a manner of their choosing was not difficult. Both were dying from cancer. After 50 happy years of married life, they saw their lives spiralling downhill out of control.

Hannah (names have been changed for reasons of privacy) had pulled through a week she was not expected to survive. Blockages caused by advanced GIST (gastrointestinal stromal tumour) had triggered colonitis and peritonitis. Dosed with large amounts of diamorphine, she was troubled by nightmarish hallucinations – though fully conscious, she had been unable to move or tell anyone what she was going through.

Her husband, suffering late-stage colon cancer that had spread to the liver, had been through a similar acute crisis and bad experiences with his pain medication.

They were unable to get about or to eat or drink properly and they knew that their pain and discomfort would only get worse. In addition, Hannah could not stray far from a bathroom and was effectively housebound.

Despite expert and dedicated care from doctors and nurses, both faced the prospect of progressively losing control over their bodies while remaining mentally active and alert. "Having seen what their end would be like, they very quickly made their decision," said daughter Diana.

If deciding what they wanted was easy, achieving their aim was not. Their oncologist, GP and palliative care workers at the hospice were all deeply sympathetic and helpful. But this was the UK, where there was no lawful way they could intervene to help end a life. Like others before them, disabled and unwell as they were, George and Hannah found a way to make the trip to Switzerland, together with their children, where they ended their own lives on their own terms at a Dignitas clinic.

Initially very hostile to the idea, Diana changed her mind as she saw what a tremendous relief her parents felt at taking back control. "Seeing somebody frightened of the way they are dying is a horrible thing," she says, "Not having any control over your body or how you are looked after; knowing then that all you have to do is have a drink and go to sleep. The peace that they reached – certainly in my parents' case – was extraordinary. I think it is absolutely inhuman that we should be left to the last weeks of harrowing deterioration, pain, not being able to eat, drink, walk…"

Why should anyone be able to tell someone in this position that they can't just slip away, she asks?

Diana is careful to be very specific about the question she poses. This is not about doctors or anyone else deciding that a person is suffering too much or their life is no longer worth living. Nor is it about a right to die that applies to everyone at any time regardless of their circumstances. It is about the right of people who are dying and who are suffering to be able to get assistance in ending their lives with dignity, without having to travel abroad and be reviewed by doctors they have never met. "You are not choosing to die – fate has determined that. You are choosing the method of your death and that is the fundamental thing," she says.

## Public sympathy

The stories of George and Hannah are far from unique. All over Europe public sympathy is growing for people who find themselves in this unenviable situation. Pressure is building for legal changes that would allow people who are suffering with a terminal illness to die in the manner they wish – as is already possible in a handful of countries including the Netherlands, Belgium and Switzerland.

Opposition to such legislative change comes from various quarters. There are those who, often for religious reasons, believe that taking a life – even your own life – under any circumstances is morally wrong and must always be a crime. But there are also those whose opposition takes a more pragmatic form. If laws are changed to help people in genuine need, like Hannah and George, the argument goes, a line would be crossed. We'd be on a slippery slope, ending a life would become socially acceptable, and vulnerable people would be at risk.


The extreme example often cited is the Nazi programme of killing 'life unworthy of life' – people deemed useless to society because they were old and infirm, disabled or had learning difficulties. This is the spectre raised by Baroness Campbell, who has muscular dystrophy and spearheaded opposition in the House of Lords to a British bill on assisted dying, which would have granted immunity from prosecution to people helping friends or relatives make the trip to Switzerland to die. She described listening to doctors discussing whether or not she was worth resuscitating when she was hospitalised with an acute chest infection. "'You wouldn't


COURTESY OF CORRIERE DELLA SERA, THE GUARDIAN, LIBERATION, TROUW AND DIE WELT

want to be resuscitated,' they said, causing me to even doubt myself. Why were they saying this? What did they know that I didn't? It could have been a death sentence, one that I was too ill to resist."

Given that the proposed legislation was about terminally ill people who expressed a consistent and independent wish to end their own lives, the argument may say more about the emotive and often muddled nature of public and political debate on this issue than about the real dangers inherent in legalising assisted dying. Yet evidence from the Netherlands does seem to indicate that changing the law to relieve the suffering of people like Hannah and George may result in the law gradually being applied to a wider group of people than originally intended. In the Netherlands, since 2002 doctors have lawfully been able to end a patient's life at his or her request – they use the term 'euthanasia'.

## A question of control

Lars Johan Materstvedt is a professor of philosophy who specialises in this area. Based in Trondheim University, Norway, where he conducts research on medical ethics, he was lead author of the position paper drawn up by an Ethics Task Force of the European Association for Palliative Care (EACP) in 2003. He says that while the Dutch euthanasia regulation was drawn up to address situations where medicine was unable to deal with 'medical' problems, today it is increasingly being used to deal with issues of 'personal control'. "In those situations of extreme physical symptoms – pain, dyspnoea and so on – they are using more and more palliative care and palliative (terminal) sedation. The main reasons people want assisted suicide or euthanasia is not pain, shortness of breath or vomiting. It is more and more a psychological and psychosocial thing."

The legislation specifies that doctors can only consider agreeing to a request by a patient to end their life by drugs where there is 'unbearable' suffering with 'no prospect of improvement', and where doctor and patient agree that there is no 'reasonable' (palliative) alternative in light of the patient's situation. Wanting to die on one's own terms rather than slowly collapsing into incontinence and dependence, losing the will or motivation to fight on, are not strictly medical needs. Yet these sorts of issues prompt an increasing proportion of requests to die, says Materstvedt. "Research has shown that in many cases, doctors think there are good alternatives, but the patient says 'no, this is intolerable, I don't want

"In many cases, doctors think there are good alternatives, but the patient says 'no, this is intolerable'"

further treatment, I want an injection instead.' Doctors cannot force the patient to undergo treatment, so this puts them in a very difficult position. Sometimes they give in."

Today, there is debate in the Netherlands over whether being 'tired of life' should be sufficient reason to have the right to assisted dying. This seems unlikely to happen any time soon, and would presumably require a shift away from the current Dutch system, in which doctors are the sole arbiters, to something more akin to the Swiss model, where much of the process of assisted dying is in the hands of civic society, in the form of lay volunteers working in 'Right to Die' societies like Dignitas.

## TERMS OF DEBATE

The term '**euthanasia**' comes from the Greek words *eu-* "good" + *thanatos* "death". Its first recorded use in English was in 1869, signifying "legally sanctioned mercy killing".

Misuse of the term to provide cover either for a state policy of killing people deemed of no value to society or for paternalistic doctors taking it upon themselves to decide which patients should be 'put out of their misery' and which 'had lives worth living', led to the adoption of the term '**voluntary euthanasia**' to refer to situations where the patient has made his or her own request to die. Many now reject this term, arguing that all euthanasia is voluntary by definition – helping a patient to die without their explicit request is '**murder**'.

In the Netherlands, Belgium and Luxembourg, legal sanction for helping patients to die rests only with doctors and is reserved for patients who have requested help to die, who are mentally and psychologically competent to make that request (this does not necessarily exclude people suffering mental illness), who are suffering unbearably and for whom there is no prospect of improvement in their situation. These countries use the term '**euthanasia**'.

In Switzerland, 'euthanasia' – as in a doctor administering a lethal drug – is illegal. However, clause 115 in the penal code states that assisting someone to commit suicide is punishable 'if done for selfish motives', which effectively makes it lawful for any citizen to help someone end their life so long as they can show it was done for altruistic reasons and that they do not administer the drug themselves. The law was originally conceived as a way to enable 'honour suicide' in the days when bankers who reduced their clients to destitution might choose to 'fall on their swords'. Today this is the law that allows Right to Die societies like Dignitas to help people die through '**assisted suicide**'. Only a doctor, however, can prescribe the drug (usually natrium pentobarbital) and there are strict rules of professional ethics – similar to those that apply in the Netherlands – that govern the circumstances under which this can be done.

Though understandable given its historical context, the term 'assisted suicide' is considered by many as inappropriate and demeaning when applied to people who are terminally ill. Debates about both 'euthanasia' and 'assisted suicide' now often use the term '**assisted dying**'.

As a palliative care specialist who practised for 25 years in the Netherlands, Ben Zylicz (now based in the UK) is uncomfortable with the Dutch legislation. He resents the way many patients now feel they can visit a doctor and demand their 'right' to die. "My view is that everybody has his own autonomy, within this he may wish to die. Autonomy of the patient also means autonomy of the doctor and of society. My view is that they should look together for somewhere halfway between. The patient may ask, but not demand, that the doctor kill him. The doctor may never say, 'Sorry, I'm not at home' because you are asking for this. They should look for a compromise. A kind of compromise is palliative care."

He worries that the attitude that sees assisted dying as a right is leading to doctors agreeing to perform euthanasia as a 'first resort', without making sufficient efforts to persuade the patient to try alternative options.

"Most patients who are requesting assisted dying are not aware of what palliative care can do. Many hundreds of patients I came across who wanted to die earlier were first of all very afraid they would have terrible pain. It was not actual pain, but fear of complications of very bad, poor dying. Many of them had experience of their parents or grandparents dying like this. They just wanted to avoid this. These are the patients who, when they seek our help, we can help in nearly 100% of cases. That's our daily bread."

Zylicz classifies patients asking for euthanasia into five categories – A to E – based on a study of 200 patients he did around 15 years ago.

BEN STANSALL/AFP/GETTY IMAGES

**"A huge step towards a more compassionate law". Last July, multiple sclerosis sufferer Debbie Purdy won a landmark ruling that effectively gives the green light for her husband to accompany her to Switzerland to die. Though assisting a suicide remains a crime in England and Wales, punishable by up to 14 years in prison, the legal authorities have now been forced to spell out the circumstances under which those accompanying people like Debbie to clinics abroad will – or won't – face prosecution**

A stands for Afraid. Patients who need reassurance about what palliative care can do for them.

B stands for Burn out. Very often in the past these patients were very effectively treated for their disease, and their disease is halted or absent, says Zylicz, but they are so damaged that they cannot live. "They are exhausted by their lives. For these patients it is very difficult to help them, and the only thing is to prevent these cases from happening." His message to oncologists is, "Be very careful of heroic operations, of overtreatment of the disease, because sometimes we can create this kind of exhausted patients who are very difficult to treat."

C stands for Control freak. "People who are not medically ill, but they think that they can just come to a doctor and the doctor will just take out a syringe and kill them. They want to be in control. And think everybody around has a duty to support them in this," says Zylicz. "This is a very difficult group for us, and palliative care is not a very good approach for them."

D stands for Depression. Research has consistently found a significant link between depression and requests for euthanasia, and is a factor in about one-third of all euthanasia requests that are turned down by Dutch doctors. "With these patients, recognition and treatment of depression can change enormously their wish to live."

E stands for Extreme. These are patients who do not respond to treatment or cannot tolerate the side-effects – only 3%–4% of patients requesting euthanasia fall into this category, says Zylicz. "These patients are really not to be helped by medical means. You may sometimes look for the last resort of terminal sedation, providing they are terminally ill and dying."

There seems to be a fair consensus on the general outlines of this classification among professionals involved in this area, though many show a bit more understanding for the wishes of the 'control freaks' – presumably the people Materstvedt talks about, who for 'psychosocial' reasons don't want to lose control of their bodies and become dependent.

## The role of palliative carers

Like many palliative care specialists, Zylicz defines his job as helping people live the best lives they can, and sees euthanasia as incompatible with this aim. He talks about the need to go the extra mile to win patients' trust, to give them the confidence that there will always be someone there for them, even at 6.00 am on New Year's Day. He talks too about fears among many of the elderly people he cares for at the Dove House hospice in Hull, England, that the doctors will take it upon themselves to end their lives prematurely, under cover of administering pain-relieving medication. And he feels very strongly that palliative care specialists should not be expected to end lives – "If we had a duty to comply with patients' requests for euthanasia, I think that would be the end

"Most patients who are requesting assisted dying are not aware of what palliative care can do"

of palliative care" – and nor should they take on the task voluntarily – "I cannot do euthanasia for one patient and give morphine to relieve the pain of another patient. I need a clear description of my job, for both our sakes, but particularly for the patient."

That said, he concedes that in the case of the Netherlands, the quality of palliative care accessible to the average patients has jumped from a very low level 15 years ago to a standard comparable to what is available today in the UK, where the palliative care and hospice movement started 50 years ago. Part of that, says Zylicz, is thanks to pressure on the Dutch Minister of Health, who was criticised, at the time the euthanasia bill was being debated, for failing to invest in the country's palliative care services. Equally important, though, was the impetus the new law gave for doctors to train up in palliative care techniques. "Many GPs and consultants realised that if they do not have the knowledge to deal with these problems they would maybe feel they had to comply with these requests when they did not want to. This process is still continuing; there is an enormous interest in Holland in palliative care among GPs."

Eight years on, Zylicz believes that the way euthanasia requests are handled in the Netherlands is now improving. "This was a problem in the Netherlands for a long time that doctors were doing this without exploring alternatives. That's dangerous. I think this process is now reversing in the Netherlands. Doctors have more choices and patients have more choices."

A good result, surely. Yet questions remain over whether greater choice will always be the outcome of introducing rights to assisted dying. As Materstvedt comments, "If we look 10, 20, 30 years ahead, there is this tsunami of old people who are going to need palliative care, and the costs are going to be enormous. Do you have the money for all that treatment as people live longer and get diseases like cancer? There is an economic issue."

The danger that legalisation of assisted dying could be seen as a cheaper alternative to developing palliative care services is a major concern, particularly for palliative care organisations, which are still fighting to become part of mainstream medical practice in much of Europe.

But some believe these fears are misplaced – including Georg Bosshard, a GP and medical ethicist who was involved in the medico-legal investigation of early assisted suicide cases in Switzerland, and has been following the issue closely ever since. "There is no evidence that, once you have open legislation on assisted suicide, palliative care will have less support than before. I think the truth is the opposite. If you look at places like the Netherlands, Belgium, Oregon, you see that discussion on assisted suicide has always forced discussion on palliative care. I cannot see an opposition of these two worlds. The goals are different."

This is a view strongly shared by Franco Cavalli, medical oncologist and director of the Southern Switzerland Institute of Oncology (IOSI) in Lugano, who is currently trying to make it easier to help the small minority of hospitalised cancer patients who want assistance in dying.

## Patient choice

With very few exceptions, hospitals and nursing homes in Switzerland do not permit assisted dying to be carried out on the premises, and most people, of course, want to end their lives at home. However, there are occasions when for various reasons this is not feasible. While IOSI has long provided palliative care as an integrated part of individual care plans, Cavalli believes that being able to offer assistance in dying gives patients an added option and is part and parcel of patient choice. While he sympathises with the battle palliative care specialists are still having to establish themselves in many parts of Switzerland, and agrees that lack of access to palliative care is still a significant problem, blaming this on the legal availability of assisted dying, he says, is simply incorrect. As he points out, countries with the strongest opposition to assisted dying are often also the most restrictive when it comes to giving patients in acute pain access to opioid medication – still a major issue in parts of Europe.

"To be able to help someone at the end to die increases the autonomy of the patient, and if you try to do this you also will try to give them the best palliative care you can offer. And patients in general are very much in favour of more palliative care. So you cannot say that at the end you can decide more about your death but not about which type of palliative care you are going to get. I am personally convinced that, even if we were to become more liberal in assisted suicide and euthanasia, that would not impact negatively on palliative care. It would even impact posi-

"Every country must find a way that fits its culture and institutions"

tively in the sense that it is recognising the autonomy of the patient and that the patient can decide."

There is, however, a caveat here. "Switzerland is Switzerland, the Netherlands is the Netherlands and the UK is the UK," as Bosshard puts it. "Every country must find a way that fits its culture and institutions, and there is no gold standard on how to approach this issue." The Netherlands and Switzerland are two of the most liberal states in Europe, with populations that get involved in civic issues. The right to euthanasia or assisted dying only came about after decades of debate and public pressure, and was part and parcel of a concerted move away from a traditional culture of healthcare based on paternalism to one that put patients much more in the driving seat.

It's a moot point whether the same could be said about Belgium and Luxembourg, both of which introduced euthanasia provisions very similar to the Dutch system shortly after it was introduced in the Netherlands, prompting criticism from some quarters that there had been insufficient public debate within their own countries.

Certainly lively discussions have been underway for many years in countries like Scotland, where an assisted dying bill is currently being debated in Parliament, France, where a similar bill is being sponsored by the Socialist Party, and England, which has reached an uncomfortable compromise on the rights of friends and family accompanying someone to Switzerland to die. Even in Germany, where awareness of past crimes has made any talk of assisted dying complete taboo within the medical establishment, public debate is growing, and there are calls to open up debate on this issue within the German general medical council.

The real concerns are, perhaps, about countries where palliative care services are rudimentary and the concept of patient autonomy is not well developed. "People tend to ask what would happen if euthanasia were allowed in Italy or Greece or Spain," says Cavalli, "but that is a theoretical question, as there is no immediate prospect of these countries becoming very liberal as regards euthanasia because of ideological reasons."

The same does not apply to many of the former eastern bloc states, where healthcare retains much of the paternalistic culture of former communist days, adds Cavalli. "I'm afraid that, in the current situation of financial crisis and very poor healthcare systems, if you do not really specify in the law that assisted suicide and euthanasia is possible only with the absolute consent of the patient and you have measures to enforce that, you might even have some kind of 'social euthanasia', because doctors in geriatric homes will say these are people of no value any longer and are just a burden to society."

This does not mean, says Cavalli, that debate on the issue should be avoided or suppressed. "I think public debate can only improve the situation. Because you cannot talk about autonomy of the patient for the last hour of their life and not talk about the rest of their life. If you start to recognise the autonomy of the patient and the right of the patient to decide, not the doctor or the state or the Pope, in the end your whole approach to the patient will change."

## Views from the frontline

Primary care physicians in the Netherlands have mixed feelings about their role performing euthanasia according to a study by Harm van Marwijk and colleagues published in the journal *Palliative Care* (2007, 21:609). No study has yet been done to investigate views on assisted dying among oncology professionals.

- "I can say 'no' now, with my acquired palliative knowledge, without leaving patients in the cold. I want to be skilled in palliative care and also able to perform euthanasia well. I want to feel good about this."
- "I now say clearly to everyone: I don't perform euthanasia any more. To my surprise a number of people say: 'Doctor, you are so right, I understand completely.' Then I thought to myself: how deep do these requests really go? I found that disconcerting to notice."
- "I wish they would no longer ask me, but I'm scared to say so. Perhaps I will have the courage to say so in a few years time. I feel very close to people, but I also feel angry: 'what do you think you can ask of me?"
- "I found it [performing euthanasia] very hard and lonely the first time, but I felt I'd done a good thing."
- "What has struck me most is the commitment of the family [to the patient's circumstances], they all sympathized. I found that unique, and stood there with tears in my eyes."
- "I need to care deeply for someone to be able to perform euthanasia. I have only performed euthanasia for people for whom I cared and whom I knew well."
- "We were crazy to do it, looking back. Who am I to do this? Euthanasia was put on my plate. It's a rotten job… I wish they would no longer ask me, but I'm scared to say so."