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.

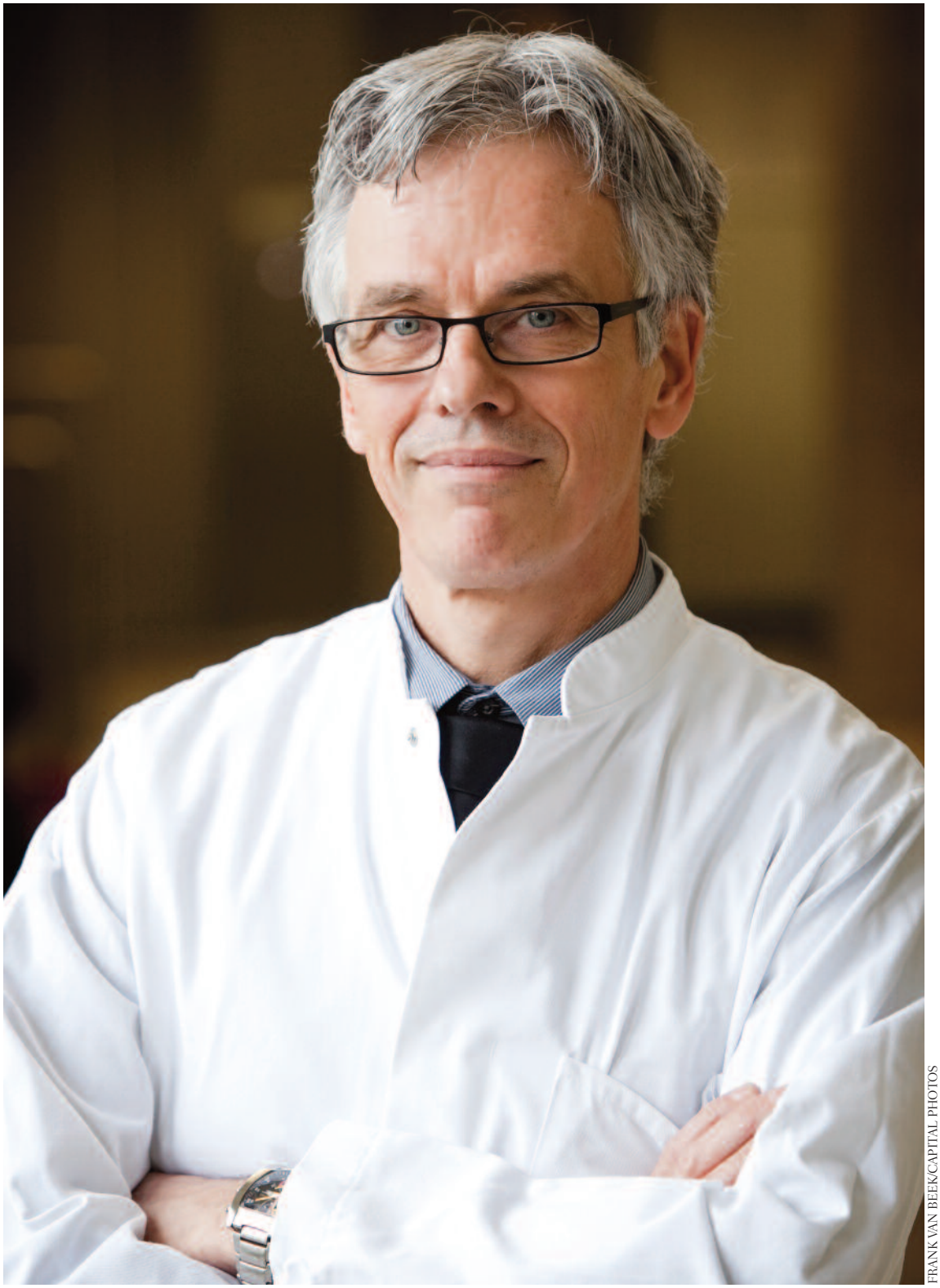
But with this remit comes great responsibility, as Jaap Verweij, head of medical oncology at the Erasmus University Medical Centre in Rotterdam, is the first to point out. Not only are medical oncologists duty bound to know thoroughly the already-huge arsenal of cancer drugs in the pharmacy from a clinical 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.



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"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."

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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

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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

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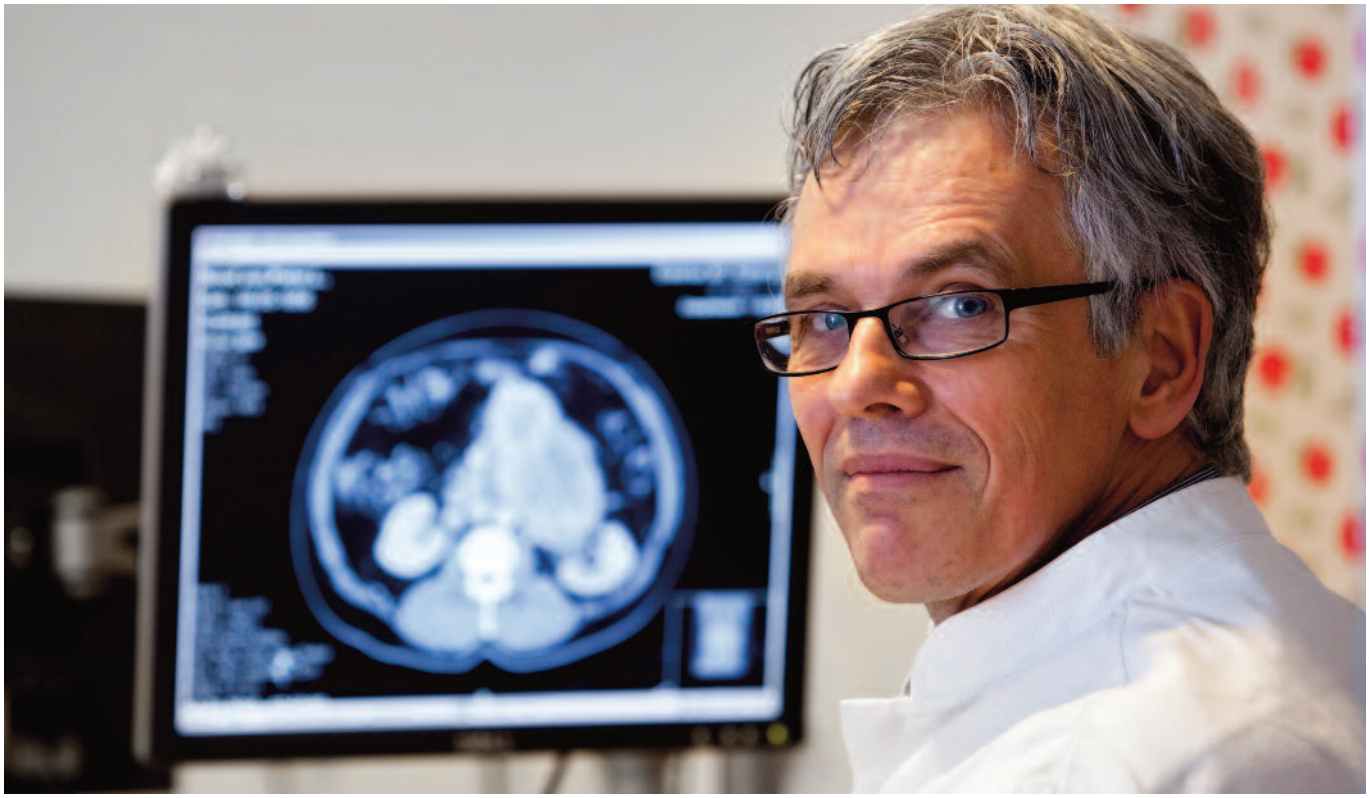

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working forward to establish whether drugs are actually reaching the targeted cancer cells and what doses are most effective, even in individual patients.

"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.

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