European School of Oncology
Learning to care

Cancerworld

www.eso.net

n° 77 March / April 2017

Share your story with us, and it may be featured on The Next Lung Cancer A.C.T. website.*

"I've joined **The Next Lung Cancer A.C.T.** in hopes of encouraging others to be mindful of the risk factors and symptoms of lung cancer and the importance of taking action now."

Jack Huston, Lung Cancer Advocate

Lights, Camera, ACTion!

Have you or a loved one already taken ACTion to prevent, diagnose, or talk to your doctor about the risks of lung cancer?

tell us

Visit **TheNextLungCancerACT.eu** to share your story today!

*Eligibility restrictions may apply. Go to **TheNextLungCancerACT.eu** for details.

Bristol-Myers Squibb

THE NEXT LUNG CANCER A.C.T. Aware Check Talk

Scan to access our website

Cancerworld

Shaping the future of cancer care

Print run 16,000

Contents

Published by
European School of Oncology

Direttore responsabile
Alberto Costa

Registrazione Tribunale di Roma
Decreto n. 436 del 8.11.2004

All enquiries to: ESO Editorial Office,
Via Turati 29, 20121 Milan, Italy
magazine@eso.net +39 02 8546 4522

Correspondence should be sent to
The Editor at editor@eso.net

Recommended by:

OECI
Organisation of European Cancer Institutes
European Economic Interest Grouping

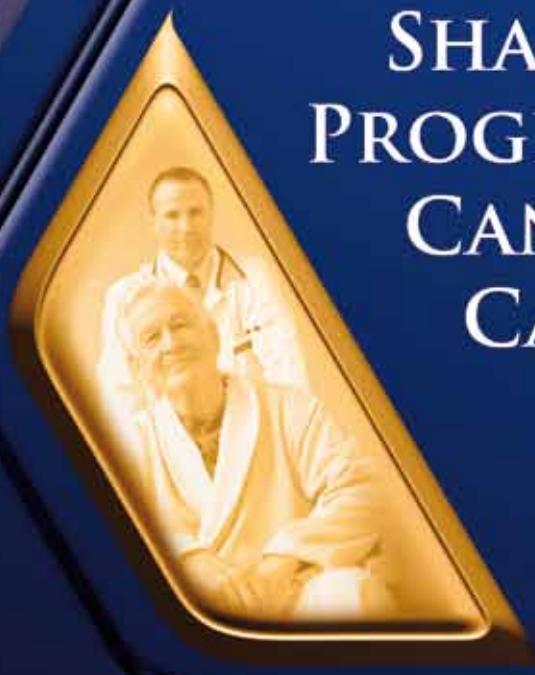
Would you like to receive a regular free copy of *Cancer World*? To receive a printed copy, please complete our online form http://bit.ly/CW-print. If you prefer to read it online, please sign up to receive weekly email alerts of new articles at http://bit.ly/CW-online. The full version can also be viewed online at www.cancerworld.net.

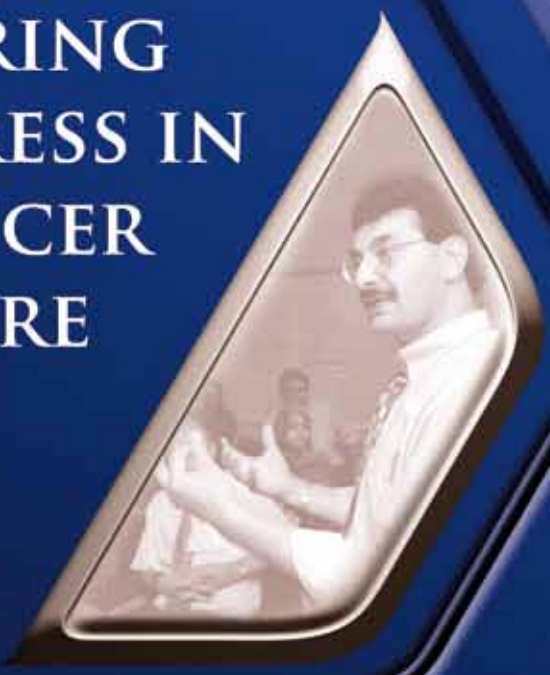
Cancer World is published five times a year by the European School of Oncology. It is distributed at major conferences, and mailed to subscribers and European opinion leaders.

European School of Oncology

Learning to care

Sharing Progress in Cancer Care





PLATINUM SPONSOR:

Bristol-Myers Squibb

Sharing Progress in Cancer Care (SPCC) is a pioneering partnership between ESO and some of the world's leading pharmaceutical companies. Unrestricted grants from SPCC partners support a spectrum of innovative projects implemented by ESO such as *CancerWorld* magazine and the Masterclass in Clinical Oncology. The SPCC partners confirmed as of February 2017 are acknowledged on this page.

GOLD SPONSORS:

HELSINN · Lilly · MERCK · Pfizer Oncology · Roche

SILVER SPONSORS:

Boehringer Ingelheim · Celgene · Genomic Health · NOVARTIS · SANDOZ a Novartis company

Improving outcomes the St Gallen way

Hans-Jörg Senn, Guest Editor

This issue comes out as breast cancer specialists from around the world gather in Vienna for the 15th biannual St Gallen International Breast Cancer Conference, to discuss what we've learnt over the past two years about optimal treatment of early breast cancer, and to agree consensus guidelines based on the latest results of sound, practice-influencing clinical trials.

While the venue has moved from St Gallen in Switzerland to Vienna's spacious Austria Centre, the format remains the same. Questions of clinical uncertainty will be debated at a four-hour public consensus-session held on the last morning, with the aim of reaching a consensus among a panel of 50 of the most influential leaders in the field.

Published evidence has shown that periodic consensus summaries like this one greatly help to standardise optimal therapy at an international level.

The global influence of this conference is rooted in the quality and credibility of the evidence that is discussed and debated – evidence that is derived largely from pivotal, multi-institutional trials run by the world's most influential breast cancer study groups, rather than through exclusively company-sponsored, purely drug-related trials.

This favourable research context is in turn a legacy of longstanding close cooperation between experienced leaders of outstanding trial groups from various continents, all aiming at a common goal – longer relapse-free survival for patients with primary breast cancer, or even definitive cure.

As more therapies and more complex treatment strategies become available for a wider array of common cancers, adopting this successful model of consensus conference might seem an obvious idea, to delay tumour relapse and prolong tumour-free survival for other groups of patients.

That, however, may be easier said than done, given the extent of competition not only between companies, but also between trial groups at a national and international level.

I feel it is important not to close this short editorial without remembering Professor Umberto Veronesi, a great (surgical) oncologist from Milan, Italy, who recently passed away. A global pioneer of this multimodal – surgical and medical – approach to primary therapy of breast cancer, his insights and vision transformed the care of this group of patients internationally.

While missing him sadly in person, and as a compassionate, frequent speaker at our conference, we will actively remember this outstanding leader in our new series of 'Umberto Veronesi Memorial Lectures', which will enrich the scientific programmes of all future St Gallen International Breast Cancer Conferences.

Hans-Jörg Senn is Senior Executive Advisor of the Foundation St Gallen International Oncology Conferences (SONK)

Tackling brain tumours

Meet the doctors set on taming this toughest of cancers

Brain tumours are tough to treat for so many reasons. Progress depends almost entirely on the steadfast commitment of doctors working within international networks. **Peter McIntyre** talked to some of them, to hear about their hopes, their frustrations, and what keeps them going.

It's now 12 years since an editorial in the *New England Journal of Medicine* hailed "a new beginning" for chemotherapy in brain tumours, on the back of the trial that established temozolomide following radiotherapy as a new standard of care for glioblastoma multiforme – one of the most aggressive of all cancers (*NEJM,* 2005; 352:1036–38).

The optimism seemed justified at the time. Not only did this new cytotoxic increase median survival from 12 to 15 months – more than doubling the two-year survival rate from 11% to 27% – but an accompanying study even identified a biomarker – MGMT methylation – that predicts which patients will do much better than the median and which will do worse.

Yet it was a modest beginning, as the researchers well understood. By the time the five-year follow up report was published, confirming the initial findings, 93% of the patients on that trial had died (*Lancet Oncol* 2009, 10:459–466).

And while that new beginning has been followed by important advances in understanding brain cancers, progress finding new treatments has been frustratingly slow Twelve years on, the standard of care is still radiotherapy plus temozolomide.

Over the past decade a number of promising drugs – monoclonal antibodies and immunotherapies – have failed on clinical trials, either because they cannot cross the blood brain barrier, or because brain tumour cells are so diverse in their genetic and metabolic compositions.

It can be dispiriting work, and yet the networks of specialists that were key to establishing the benefits of temozolomide remain as strong and determined as ever, driven by the continuing urgent need to find solutions for their patients.

Fruits of collaboration

Brain tumours are among the most deadly and difficult cancers to treat. While many people live with a low-grade glioma for 10 or 20 years, the majority of aggressive cancers return after surgery, and life expectancy can be measured in months.

As Kathy Oliver, co-founder and chair of the International Brain Tumour Alliance, explains, brain tumours touch all aspects of a patient's life. "Whether it is your cognitive abilities or your physical abilities, every single part of who you are can be affected by a brain tumour, and your quality of life and that of the whole family can suffer enormously."

As well as being hard to treat, brain tumours are also rare, which make them commercially unattractive. Progress continues to rely almost entirely on the unstinting efforts of specialists pooling their efforts in collaborative projects.

The clinical trial that established temozolomide as a standard of care was led from the University of Lausanne, Switzerland, by a young oncologist named Roger Stupp, who, on arriving fresh from qualifying as a haematologist/oncologist in the US, had found himself assigned to "what other people didn't want to do". It was sponsored by the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada Clinical Trials Group (NCIC), and it involved 85 institutes in Europe and Canada, recruiting 573 patients across 15 countries.

What really strikes home from this and subsequent research is the sheer number of centres collaborating across countries, and the length of time. Dozens of researchers have devoted whole careers to painstaking work and testing, enrolling thousands of patients from dozens of countries to make progress. The origins of a number of trials that are still running today date back before the start of this millennium. Such a long-term collaborative process can only be handled by organisations with international status and a core of clinical excellence.

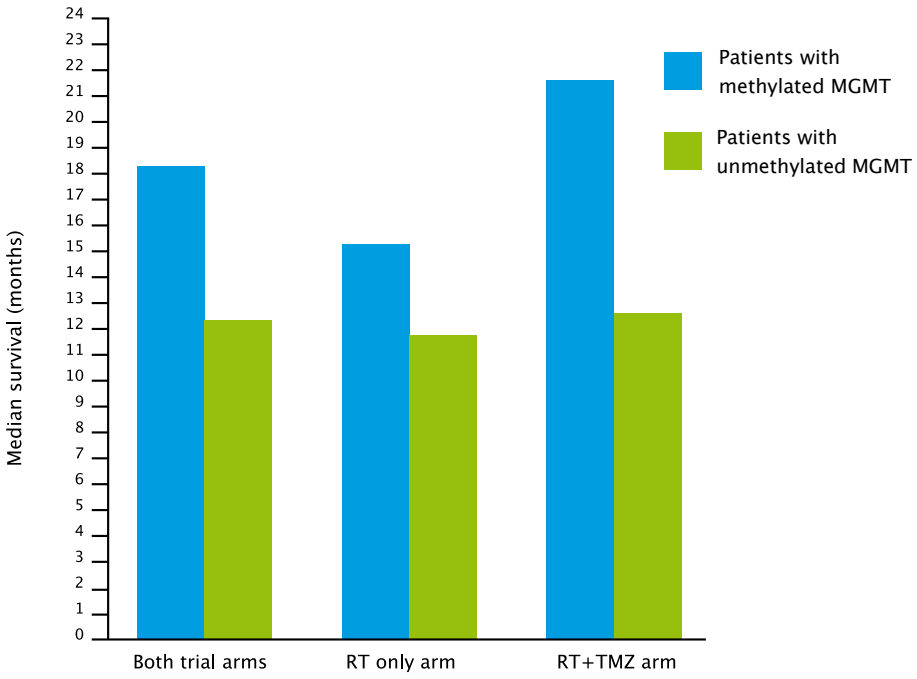
"Whether it's your cognitive or physical abilities, every single part of who you are can be affected by a brain tumour"

The EORTC and its brain tumour and radiotherapy groups drive research ideas and plan collaboration across Europe. In Canada it is the Canadian Cancer Trials Group and the Canadian Brain Tumour Consortium. In the US many centres are affiliated to the NCI-funded NRG Oncology (formerly Radiation Therapy Oncology Group) or Alliance for Clinical Trials in Oncology, while the Trans-Tasman Radiation Oncology Group (TROG) has more than 1,000 members in Australia and New Zealand.

EORTC Director General Denis Lacombe says that linking independent-minded researchers in academic networks with a central organising body can make a real difference to patient care.

"If you look at the plenary session of ASCO, the vast majority of big studies that make a difference are academic studies. Neuro-oncology is an area where few of the drugs that have been tried have made headway. There is a need to work together to exchange ideas and do projects, because we are still in the learning phase of this disease. It is a group effort; a very good example of a large network identifying unmet need

MGMT methylation: the first brain tumour biomarker



A 2005 study analysing data from the phase III trial of temozolomide in glioblastoma, found that patients whose tumour biopsies tested positive for methylated MGMT had a better prognosis regardless of treatment arm, but this survival benefit was markedly greater among patients treated with temozolomide (TMZ) after radiation, than in patients treated with radiation alone (RT) (*NEJM* 2005, 352:997–1003). Other biomarkers such as 1p/19q co-deletion in anaplastic gliomas have since been identified, but progress understanding and treating brain tumours remains painfully slow

and having this continuity over time."

Michael Weller, head of neurology at University Hospital Zurich and chair of the EORTC Brain Tumour Group, says that three headline presentations at ASCO 2016 will help establish new treatment protocols and improve survival and quality of life.

Temozolomide in older patients

The Canadian Cancer Trials Group, together with EORTC and TROG, trialled temozolomide in combination with radiotherapy in 562 patients with glioblastoma, with an average age of 73 – the first time this had been tried in a full phase III trial conducted in older patients.

They showed that adding temozolomide to a shorter course of radiation therapy improved survival without damaging quality of life. Two-year survival rose from 2.8% without temozolomide to 10.4% with combination treatment.

The benefit was greater for the 165 patients who had MGMT methylation.

Temozolomide in anaplastic glioma

A second presentation at ASCO 2016 focused on patients with anaplastic glioma. Some patients live many years with these tumours, but they are almost always fatal in the end.

Earlier trials had shown the benefit of chemotherapy following radiotherapy – either a combination of PCV (procarbazine, lomustine, and vincristine) or temozolomide. PCV benefits were primarily in patients with 1p/19q co-deletion, a genetic marker that seems to indicate greater sensitivity to chemotherapy.

The CATNON trial was established by EORTC to examine options for combining radiotherapy and temozolomide in anaplastic glioma patients who do not have 1p/19q co-deletion.

Because this is a relatively rare cancer and the primary endpoint is overall survival, this is another large and long trial, with 751 patients recruited from 132 centres in 12 countries in North America, Europe and Australia. The first patient was recruited in December 2007 and the trial will continue until 2020, with final results due in 2022.

Unexpected and welcome preliminary results led to the 2016 ASCO presentation. Study coordinator Martin van den Bent reported that patients treated with maintenance temozolomide following radiotherapy showed a significant increase in five-year survival, from 44% (without temozolomide) to 56% with it.

The CATNON presentation became one of the ten most read reports at ASCO, and the ASCO expert in brain cancers, Brian Alexander, welcomed the results and the long road to reach them. "For decades, anaplastic glioma has proven not only hard to treat, but also hard to study, because it is so rare, making this finding even more important."

Like other leading members of the EORTC network, Martin van den

Bent has been working to improve treatments for patients with brain tumours since the late 1990s. He says that collaboration between North American, Australian and European groups has been essential to a series of trials that has gradually established that chemotherapy plays a role in the management of nearly all diffuse gliomas.

"We understood that there was no way that any of the individual groups could successfully conclude the CATNON trial. A company will shift its focus; we are stuck in the marshes and have to answer these real questions that we have on the optimal management of patients. They are not driven by financial and economic considerations."

"A company will shift its focus; we have to answer these real questions on the best management of patients"

However, van den Bent praises the commitment that the pharmaceutical company Schering Plough (now part of MSD) made to the trial, even though directors knew that its patent on temozolomide would expire before the CATNON trial concluded. "The clinical vision of the people at Schering Plough and their willingness to go beyond the classical business model has to be noted."

Bevacizumab in glioblastoma

The third report at ASCO was disappointing. The monoclonal antibody bevacizumab showed promise in a phase II trial in patients whose glioblastoma showed progression. However, an EORTC phase III trial, led by Wolfgang Wick, past chair of the EORTC Brain Tumor Group, found that, while combining bevacizumab with chemotherapy improved progression-free survival, there was no overall survival advantage.

In it for the long term

Such disappointments are the backdrop to the search for progress. The integrin inhibitor cilengitide seemed a highly promising agent that could disrupt communication between glioblastoma cells and the brain microenvironment, until an international phase III trial, led by Roger Stupp, reported in 2014 that it brought no extra benefit added to chemotherapy. The trial had the backing of EORTC, the Canadian Brain Tumour Consortium, and the CENTRIC study team, and it included more than 500 patients with glioblastoma from 146 study sites in 25 countries.

Stupp, who is President of the EORTC, says that even disappointing trials should not be thought of as failures, since they help to prevent patients being exposed to potentially toxic expensive treatment with limited benefit, while the outcome data and tissue samples have the potential to improve understanding of the disease and develop other therapeutic targets.

"When you conduct a scientific experiment, the result can be 'yes' or 'no'. If I get a clear result that something is not working, I don't have the outcome I want, but the experiment worked. From the science point of view, failure means not recruiting or conducting the trial successfully. Patients treated outside the trial – that is what I call failure. Inside the trial, I always learn something for the next generation while giving the best available treatments to my patients."

"Patients treated outside the trial – that is what I call failure. Inside the trial I always learn something"

Brigitta Baumert was principal investigator on another large EORTC trial comparing temozolomide with radiotherapy in 477 patients with a high-risk low-grade glioma.

These are generally the slowest growing gliomas in adults – some people live with them for 10 or 20 years – but risk factors for more aggressive growth include age, tumour size and position, and the presence of neurological symptoms or epileptic seizures.

Baumert points out that the idea for this study was born in 1999 and it was the first study in brain tumours to mandate central molecular tumour characterisation before the inclusion of patients. "From having the idea, to getting the approval, and getting the core group set up took about four years. It took more years to get ethical approval from all national and international committees. Only after that can you run the trial."

Patients started treatment between 2005 and 2012, and because of the long median-survival times, the primary endpoint was progression-free survival. with correlative analyses of progression-free survival by molecular

markers as one of the secondary endpoints. In all, 78 participating centres from 19 countries were required to achieve the necessary patient numbers. Close collaboration with translational scientists like Monika Hegi, who is spearheading this effort within EORTC, is a key characteristic of academic research of this sort, which is ultimately designed to tailor treatment to a patient's individual risk profile.

After four years of follow up, there was no difference in progression-free survival between the two treatment strategies. A further 5–10 years are needed to assess overall survival and cognitive effects of the two treatments and to identify any genetic groupings. Baumert believed it was essential to publish the results. However, it is harder to publish negative than positive results, and it was two years before the trial report appeared in *Lancet Oncology*.

Since her research began in Maastricht all those years ago, Baumert has moved jobs twice. But in this model of research, clinicians stay with their project even when they move. Indeed Roger Stupp is himself shortly leaving Switzerland to take up a new post in Chicago, at the Northwestern University's Brain Tumor Institute. "For such international cooperation you need a very long breath," says Baumert.

The value of independent research

Denis Lacombe, Director General of the EORTC, highlights the importance of research that is free from commercial interests. "Since we started these trials 15 years ago, this has led to the greatest therapeutic improvement for grade 4 glioma patients and we have learned a lot about the biology. The disease is still very aggressive, but we are moving from a completely deadly disease to one where therapeutic progress is being made.

"The biological material from these patients is not going to sit in a commercial silo just because a trial is negative"

"We have collected biological material from these patients, and this is not going to sit in a commercial silo just because a trial is negative. The material will be exploited to see what we can do more. The material collected from neuro-oncology patients is very precious. You have very small pieces and its use is discussed among a panel of experts. They are very cautious about the use of the material and the right question to ask next."

Members of the EORTC Brain Tumour Group and Radiation Oncology Group met with other specialist EORTC groups for two days in early March 2017 in Brussels, to focus on immunotherapy, translational research and real-life effectiveness. Michael Weller sees this as an opportunity for cross-fertilisation. If a vaccine is effective for patients with one cancer, might it also be effective in other cancers with similar molecular markers? It would transform the prospects for treatment of glioblastoma if they could find a vaccine that could make a survival difference for 20–30% of the patient population.

However, Weller believes that academic groups need more financial support to continue to drive innovation. "EORTC landmark contributions have been ground shaking, because they change standards of care. But there is no way that academic institutions can face these challenges in terms of economic burden to do such trials in future. This is what I see as the major threat to how we can continue our successful work and attract companies to invest in it.

"The willingness of industry to invest in big trials is diminishing, especially if we pursue our strategy of identifying molecular subgroups. We are trying to dissect the diseases by their molecular markers, and this automatically makes them less prevalent in the population and a little less rewarding for a company to invest in. If we pursue our academic goal of individualising treatment, it is more difficult to find commercial partners."

Working with the industry and patient advocates

Kathy Oliver, of the International Brain Tumour Alliance, believes that greater collaboration between research groups and industry, as well as greater involvement of patients and their advocates, will be essential for future progress. "There are fantastic people working in academic centres, but I think to really strike a home run, everyone is going to have to develop new models of working together across different stakeholder groups. Particularly for small patient populations as in brain tumours, it has to be everyone working together, including academia, industry and patients – the total deal.

"Part of the problem with a brain

tumour is that it is such a difficult, tough disease to crack. You have to get the therapy across the blood brain barrier and that is a major hurdle. The incredibly challenging nature of treating a brain tumour may be one of the reasons why we are seeing very long clinical trials. Of course, patients are desperate to see research speeded up."

Kathy Oliver, who lost her own son, Colin, to brain cancer, is a patient representative on the EORTC's SISAQOL initiative to set international standards for analysing patient reported outcomes and quality of life data. She sees this as a very welcome step towards a level playing field. "I am welcome to have an equal voice to anyone else on that committee, which involves people from the FDA [US regulators], the MHRA/EMA [UK and European regulators], high-level clinicians, industry and leading researchers."

It is important for clinical trial designers and researchers to listen more carefully to what patients want out of clinical trials and out of therapies, she says.

"Trials will recruit faster if patients are involved in helping to design them"

"Word of a good clinical trial spreads like wildfire through the patient community. If patients think that a trial is good and important and useful, then they will tell other patients. So I think that is one practical way of speeding up trials. In my opinion, trials will recruit faster if patients are involved in helping to design them."

On the front line

© Nicolò Assirelli

Advocacy networks of patients and families also play an essential role driving progress in brain tumours, helping to raise money for research and advise on and recruit to clinical trials, and stoking the sense of urgency and the need to aim high. Featured above are an artist's impressions of some of the many patients and advocates featured in Brain Tumour, the magazine of the International Brain Tumour Alliance (http://theibta.org/our-publications/)

Other approaches

Of course EORTC and their partners on other continents are not the only game in the global town. The GBM Agile trial (see page 61) – principally an Australian/US initiative, now also involving China, is putting together a trial infrastructure that can test a variety of treatments against the standard of care for glioblastoma, across different molecular subgroups of patients. EORTC has itself established a screening infrastructure, SPECTAbrain, to channel patients with brain tumours into relevant biomarker-driven trials, with samples being held in their biobank. The aim is also to speed up the investigation for biomarkers and develop high-quality testing standards for those markers.

SPECTAbrain is open for business, thanks in part to initial support from Celldex, but it will need more buy-in from pharmaceutical companies. "We like SPECTAbrain, but it needs to be financed," says Weller. "We need to generate more revenue and actionable targets to keep it alive."

There is also a non-drug treatment

that is making waves. The FDA has approved for adjuvant use a device that is worn by patients and delivers low-intensity, intermediate-frequency, alternating electric fields directly on the scalp through electrodes. This Optune device may sound as daft as crystal treatment, but benefits have been shown by a large randomised clinical trial led by Roger Stupp, which demonstrated longer progression-free survival and overall survival.

Roger Stupp says the Tumor Treating Fields (Optune) results provide a lesson in following the data rather than preconceived notions. "It is a nice example of how something which to many of us looks like voodoo medicine has shown it improves survival in a similar magnitude to temozolomide ten years earlier."

He contrasts this with the results from some of the newer drugs at the cutting edge of knowledge. "We have been jumping up and down about immunotherapy for 25 years and so far [in brain tumours], nothing works."

The future

Stupp says there is no short cut to finding better treatments – it requires patience and systematic work. "If you ask me to predict what will succeed, then I am going to be very inaccurate because we don't really know. Let's be honest. When we had successes it was not really predicted.

"The advances came when we really sat down and did things systematically and one after the other and put the resources together rather than everybody on his own."

His biggest frustration is that nothing has yet replaced temozolomide. However, standards of care for people with brain tumours have continued to improve. "If you look at what really has happened since temozolomide became available, there is more awareness. Before, patients got radiation and steroids and were sent to hospice care. Now we have a better delivery of care for patients with brain tumours, independent of chemotherapy."

He expects that molecular signatures will eventually identify patients most likely to benefit from new treatments, even though many molecular markers, such as EGFR amplification and IDH, contribute little to daily decision making in the choice of therapeutic agent so far. "It is disappointing we have only 10–15% of patients alive at five years, but it is particularly disappointing we have not been able to identify which 15%. A kind of 'one fits all' approach is probably one reason we are not that successful.

"If 60–70% of patients in a clinical trial just produce noise, you may miss the true signal that tells you that an agent and an avenue may be active. There may be good avenues, good ideas and good treatments that we have discarded because we have not been able to recognise the activity."

"The advances came when we did things systematically, one after the other, and put the resources together"

In recent years, dozens of clinical trials on glioblastoma treatments that have shown preclinical promise have shown minimal quality of life or overall survival benefit. Many were stopped early. Rindopepimut is one immunotherapy agent that looked highly promising in uncontrolled phase II trials in patients with newly diagnosed EGFR-positive glioblastoma. An industry-sponsored international phase III study, with substantial contributions from EORTC researchers led by Weller, was discontinued in March 2016 when it became clear that the vaccine did not improve survival beyond standard care.

But as activated EGFR is found in more than 40% of all glioblastomas, no one is giving up looking. EORTC and the global pharmaceutical company AbbVie are awaiting results from a recently completed trial with ABT 414, an antibody-drug conjugate that binds to an EGFR epitope. This trial, involving 240 patients in 22 countries, is another example of collaboration between the EORTC and a commercial company.

One critical point will be to ensure that innovative agents do indeed reach their targets. "Some of the EGFR agents that have been tested do not cross the blood brain barrier. These are agents that, by their chemical properties, are not the right agents to study in brain tumours," says Stupp.

Some glioblastoma patients treated in the late 1990s are still alive 20 years later, and one promising line of research is to identify patients who defy the odds. The Brain Tumor Funders Collaborative (BTFC) of north America has put $2 million into an EORTC-led study to understand the reasons for such long-term survival. This research, headed by Michael Weller, will study more than 300 patients who have survived glioblastoma for more than five years, and will involve analysing tumour biopsies banked by the EORTC and other academic groups over many years.

Martin van den Bent believes there

is still some room for improvement in combinations of existing treatments. "We have established that chemotherapy works and the basic questions for diffuse glioma in chemotherapy have been answered.

"Some say in 10 years immunotherapy may have replaced chemotherapy, but this is no excuse not to continue"

"What we have not really answered is the question on the optimal timing of chemotherapy treatment in low-grade glioma. It will be a difficult project and it will take 10 to 20 years to complete, but this is about whether we can postpone safely treatment in patients and avoid side effects or can we improve outcomes. Quality of life will be an important question."

Some may say that in ten years immunotherapy will have replaced chemotherapy, but van den Bent says this is no excuse not to continue. "Over the past decade, when we were making these efforts, people said we will have new drugs. We are now ten years down the line, the drug is not on the horizon and we are glad we made the effort.

"Of course I would love to see the breakthrough drug. However, the indications are that diffuse gliomas show too much variance and that one drug is likely to affect only a limited proportion of patients."

Weller on the other hand is much more optimistic about immunotherapy. "I am sure that what we can do with radiation and chemotherapy is done. I am very optimistic we are going to see some progress in immunotherapy, and probably also some novel concepts stopping the invasion of tumour cells. It is about understanding how we can make tumour cells identifiable by the immune system, and understanding what is different biochemically and metabolically and then going selectively after the tumour. That is all part of individualising cancer therapy."

Who will pay?

If the road ahead looks long and uncertain, how will research be funded?

The EORTC Cancer Research Fund is supported by some national cancer leagues, social responsibility programmes and charitable donations. Many trials are partly funded by foundations; support that is vital since answers to many of these questions have no direct commercial benefit and will not be supported by industry.

Stupp is convinced that cooperation with pharmaceutical companies, and conduct of carefully designed clinical and translational research by an independent organisation like EORTC, is the most efficient way to benefit patients.

Academia contributes in kind substantially to clinical research, with hundreds of hours of clinician and research associate input, without financial benefit, even if one of the trials is spectacularly successful.

While EORTC can bid for grants from the EU Horizon 2020 funding, there is no direct funding from the EU. Denis Lacombe says: "In an ideal world, the EU would recognise the EORTC as the clinical research infrastructure at a European level and give some core support. I think it is a dream that will never happen. We have some European money based on a competitive approach, but absolutely no core European money. Absolutely not."

Nobody likes to fund the growing infrastructure requirements of clinical research. Stupp says that the benefits of expertise, quality assurance, innovation and dedication are seriously undervalued, as they spread beyond research to patients in routine clinical care. "If we are not careful, we are going to suffocate the system," he warns.

So what makes a clinician stay with a line of research for decades knowing that disappointment is as likely as success? Roger Stupp says that oncologists need be able to tolerate some frustration because the disease is so difficult.

"Our patients do not want to give up, and I get energy from my patients"

"Our patients do not want to give up, and I get energy from my patients. As a researcher you need curiosity and openness and rigour in order to test something in a scientific way."

EORTC has a 53-year record of working for improvements in patient care, and Lacombe says that this will continue. "We have a commitment to patients. If we think that a research question is important for patients, we make it happen. We say to our scientists and our doctors, EORTC is the place to go because we have the capacity to do this kind of international trial. If you have a good idea and it is a good project, we will find a way."

Palazzo dei Congressi, Lugano (Switzerland)
June 14-17, 2017

14-ICML

14th International Conference on Malignant Lymphoma

IMPORTANT DEADLINES:

February 28, 2017 – EARLY REGISTRATION
March 01-June 07, 2017 – LATE REGISTRATION
or up to 3000 attendees
March 15, 2017 – ABSTRACT SUBMISSION

FOR ANY INFORMATION, PLEASE CONTACT:

Cristiana Brentan
ICML Secretariat
IOSI, Ospedale San Giovanni, CH-6500 Bellinzona
e-mail: cristiana.brentan@lymphcon.ch

14-ICML is supported by ESO – European School of Oncology

The 14-ICML program will be once again part of the Certificate of Competence in Lymphoma, a 14 months ECTS program developed by the European School of Oncology (ESO) and academically recognized by the Ulm University. The aim of the Certificate of Competence is to provide a curriculum of studies to advance knowledge and science in the management of lymphoma patients.

www.lymphcon.ch

Efficacy in three indications

Metastatic pancreatic cancer
in combination with gemcitabine for first-line treatment of adult patients

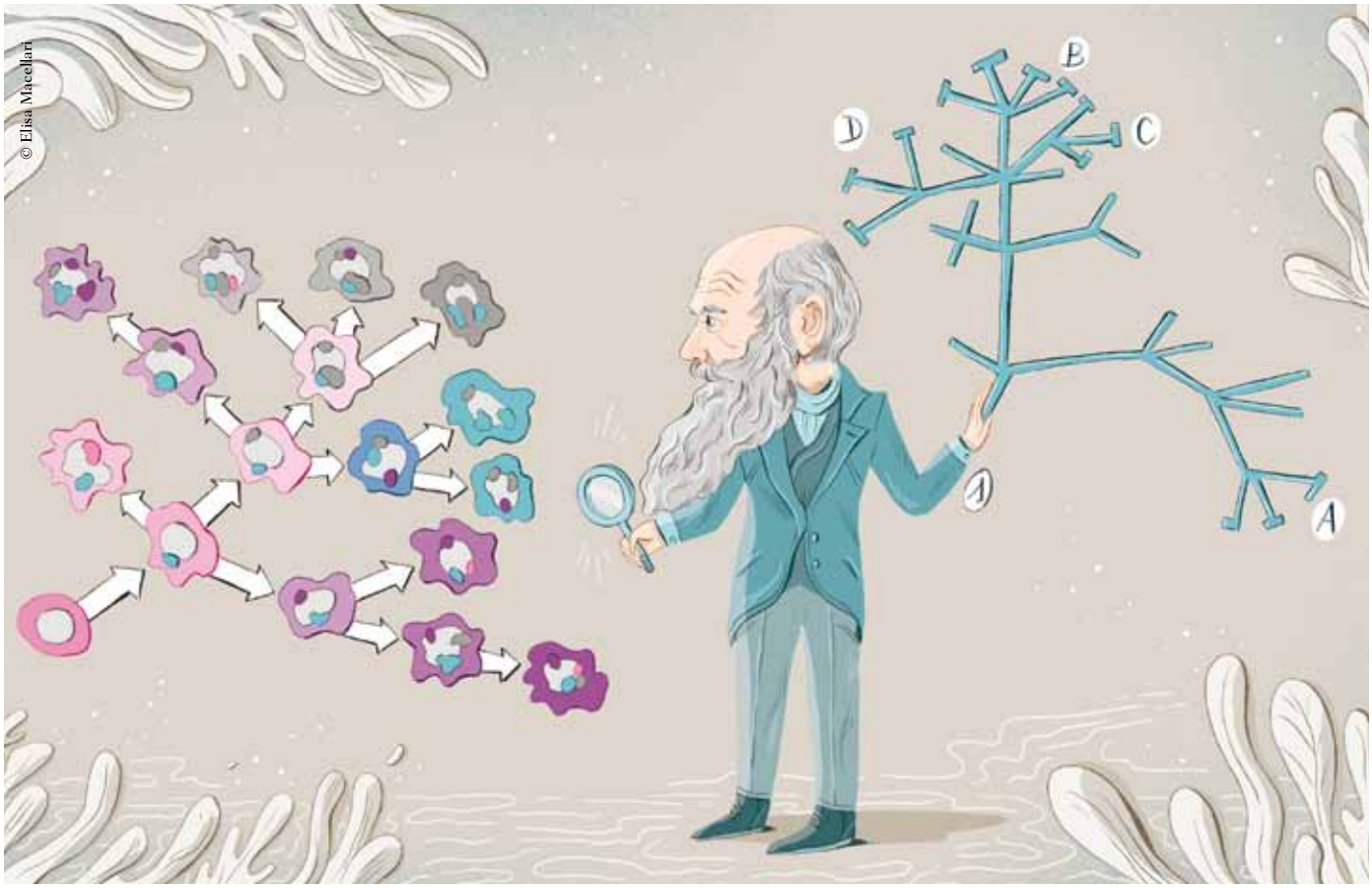
Metastatic breast cancer
as monotherapy when first-line treatment fails and anthracycline containing therapy is not indicated

Non-small cell lung cancer
in combination with carboplatin for first-line treatment when surgery and/or radiotherapy are not indicated

Abraxane®
nanoparticle albumin bound paclitaxel

Prescribing Information: Abraxane® 5 mg/ml powder for suspension for infusion.
Refer to the Summary of Product Characteristics (SmPC) before prescribing.
Name of medicine: Abraxane 5 mg/ml powder for suspension for infusion **Active ingredients:** paclitaxel formulated as albumin bound nanoparticles. **List of excipients:** Human albumin solution (containing sodium, sodium caprylate and N-acetyl DL tryptophanate). **Available dosage form:** Powder for suspension for infusion. The reconstituted suspension has a pH of 6-7.5 and an osmolality of 300-360 mOsm/kg. The powder is white to yellow. **Authorised indication(s):** Abraxane monotherapy is indicated for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated. Abraxane in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas. Abraxane in combination with carboplatin is indicated for the first line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy. **Dosage regimens and routes of administration:** Breast Cancer - The recommended dose of Abraxane is 260 mg/m² administered intravenously over 30 minutes every 3 weeks. Pancreatic adenocarcinoma - The recommended dose of Abraxane in combination with gemcitabine is 125 mg/m² administered intravenously over 30 minutes on Days 1, 8 and 15 of each 28-day cycle. Non-small cell lung cancer: The recommended dose of Abraxane is 100 mg/m² administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of each 21-day cycle. The recommended dose of carboplatin is AUC = 6 mg•min/ml, on Day 1 only of each 21-day cycle, beginning immediately after the end of Abraxane administration. Refer to the full prescribing information for dose adjustments during treatment in case of haematologic (neutropenia and/or thrombocytopenia) and other adverse reactions. Administer reconstituted Abraxane suspension intravenously using an infusion set incorporating a 15 µm filter. Following administration, it is recommended that the intravenous line be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure administration of the complete dose. **Reference to special groups of patients:** Patients with hepatic impairment: For patients with mild hepatic impairment (total bilirubin > 1 to ≤ 1.5 x ULN and aspartate aminotransferase [AST] ≤ 10 x ULN), no dose adjustments are required, regardless of indication. Treat with same doses as patients with normal hepatic function. For metastatic breast cancer patients and non-small cell lung cancer patients with moderate to severe hepatic impairment (total bilirubin > 1.5 to ≤ 5 x ULN and AST ≤ 10 x ULN), a 20% reduction in dose is recommended. The reduced dose may be escalated to the dose for patients with normal hepatic function if the patient is tolerating the treatment for at least two cycles. For patients with metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment, there are insufficient data to permit dosage recommendations. For patients with total bilirubin > 5 x ULN or AST > 10 x ULN, there are insufficient data to permit dosage recommendations regardless of indication. Patients with renal impairment: Adjustment of the starting Abraxane dose is not required for patients with mild to moderate renal impairment (estimated creatinine clearance ≥30 to <90 ml/min). There are insufficient data available to recommend dose modifications of Abraxane in patients with severe renal impairment or end stage renal disease (estimated creatinine clearance <30 ml/min) Older people: No additional dosage reductions, other than those for all patients, are recommended for patients 65 years and older. Paediatric population: The safety and efficacy of Abraxane in children and adolescents aged 0-17 years has not been established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Lactation. Patients who have baseline neutrophil counts < 1500 cells/mm³. **Warnings:** Abraxane should not be substituted for or with other paclitaxel formulations. It is an albumin-bound nanoparticle formulation of paclitaxel, which may have substantially different pharmacological properties compared to other formulations of paclitaxel. Rare occurrences of severe hypersensitivity reactions, including very rare events of anaphylactic reactions with fatal outcome, have been reported. If a hypersensitivity reaction occurs, the medicinal product should be discontinued immediately, symptomatic treatment should be initiated, and the patient should not be rechallenged with paclitaxel. Bone marrow suppression (primarily neutropenia) occurs frequently with Abraxane. Neutropenia is dose dependent and a dose limiting toxicity. Frequent monitoring of blood cell counts should be performed during Abraxane therapy. Patients should not be retreated with subsequent cycles of Abraxane until neutrophils recover to >1500 cells/mm³ and platelets recover to >100,000 cells/mm³. Sensory neuropathy occurs frequently with Abraxane, although development of severe symptoms is less common. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose reduction. If Grade 3 sensory neuropathy develops, treatment should be withheld until resolution to Grade 1 or 2 followed by a dose reduction for all subsequent courses of Abraxane is recommended. For combination use of Abraxane and gemcitabine, if Grade 3 or higher peripheral neuropathy develops, withhold Abraxane; continue treatment with gemcitabine at the same dose. Resume Abraxane at reduced dose when peripheral neuropathy improves to Grade 0 or 1. For combination use of Abraxane and carboplatin, if Grade 3 or higher peripheral neuropathy develops, treatment should be withheld until improvement to Grade 0 or 1 followed by a dose reduction for all subsequent courses of Abraxane and carboplatin. Sepsis was reported at a rate of 5% in patients with or without neutropenia who received Abraxane in combination with gemcitabine. Complications due to the underlying pancreatic cancer, especially biliary obstruction or presence of biliary stent, were identified as significant contributing factors. If a patient becomes febrile (regardless of neutrophil count), initiate treatment with broad spectrum antibiotics. For febrile neutropenia, withhold Abraxane and gemcitabine until fever resolves and ANC > 1500 cells/mm³, then resume treatment at reduced dose levels. Closely monitor all patients for signs and symptoms of pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with Abraxane and gemcitabine and promptly initiate appropriate treatment and supportive measures. Because the toxicity of paclitaxel can be increased with hepatic impairment, administration of Abraxane in patients with hepatic impairment should be performed with caution. Patients with hepatic impairment may be at increased risk of toxicity, particularly from myelosuppression, and such patients should be closely monitored for development of profound myelosuppression. Abraxane is not recommended in patients that have total bilirubin > 5 x ULN or AST > 10 x ULN. In addition, Abraxane is not recommended in patients with metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN and AST <10 x ULN). Rare reports of congestive heart failure and left ventricular dysfunction have been observed among individuals receiving Abraxane. Most of the individuals were previously exposed to cardiotoxic medicinal products such as anthracyclines, or had underlying cardiac history. Thus patients receiving Abraxane should be vigilantly monitored by physicians for the occurrence of cardiac events. The effectiveness and safety of Abraxane in patients with central nervous system (CNS) metastases has not been established. CNS metastases are generally not well controlled by systemic chemotherapy. If patients experience nausea, vomiting and diarrhoea following the administration of Abraxane, they may be treated with commonly used anti-emetics and constipating agents. Carefully assess patients with pancreatic adenocarcinoma aged 75 years and older for their ability to tolerate Abraxane in combination with gemcitabine. Give special consideration to performance status, co-morbidities and increased risk of infections. When reconstituted, Abraxane contains 0.183 mmol sodium, which is 4.2 mg of sodium. To be taken into consideration by patients on a controlled sodium diet. **Clinically significant interactions:** Abraxane is indicated for as monotherapy for breast cancer in combination with gemcitabine for pancreatic adenocarcinoma, or in combination with carboplatin for non-small cell lung cancer. Abraxane should not be used in combination with other anticancer agents. Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cioplidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures. **Reported side effects:** The most common clinically significant adverse reactions associated with the use of Abraxane have been neutropenia, peripheral neuropathy, arthralgia/myalgia and gastrointestinal disorders. Prescribers should consult the summary of product characteristics in relation to other side-effects. **Storage conditions:** Keep the vial in the outer carton in order to protect from light. Neither freezing nor refrigeration adversely affects the stability of the product. This medicinal product does not require any special temperature storage conditions. **Price: Classification:** Medicinal product subject to medical prescription. **Marketing Authorisation Numbers:** EU/1/07/426/001, EU/1/07/426/002. **Marketing Authorisation Holder:** Celgene Europe Limited, 1 Longwalk Road, Stockley Park, Uxbridge, UB11 1DB, United Kingdom. **Date of last revision:** 11/2010. **Internal ID of the printed material: INT-ABR170002**
Date of preparation: February 2017

Celgene



Using Darwin's notebook to outsmart resistance

Clonal evolution and the 'survival of the nastiest' remain the chief obstacles to curing cancer. But what if we could find a way to use the principles of evolution to beat evolving cancers cells at their own game? **Simon Crompton** explores cutting edge efforts to do just that.

As notebook scrawls go, this one was earth-shaking. In 1837, 12 years before his book *On the Origin of Species* was published, Charles Darwin sketched a spidery tree depicting how evolution might work, and wrote the words "I think" above it. This was the beginning of what became known as Darwin's tree of life – and it forms the basis for our understanding of species evolution to this day.

What Darwin might not have predicted in 1837 was that, here in the 21st century, his tree of life would also be forming the basis of a new understanding of the way cancers advance. Today, a group of innovative scientists are using Darwinian

principles to not only understand the daunting genetic complexity of advancing and metastasised tumours, but also to devise innovative approaches to controlling them.

The new wave of interest in Darwinian principles has been spearheaded by Charles Swanton, Chair in Personalised Cancer Medicine at University College London's Cancer Institute, and leader of the research group at the Francis Crick Institute examining genetic diversity in cancer.

His research has indicated not only that single biopsy samples are likely to severely underestimate the genetic variety of cells within tumours, but also that this heterogeneity will nearly always lead to the failure of therapies that target specific types of cell.

His first paper demonstrating the extent of heterogeneity, published in the *New England Journal of Medicine* in 2012, has been cited more than 3,000 times in the past four years, and prompted an unprecedented number of publications focusing on the evolutionary processes that cause such a diverse 'fauna' of cancer cells within a single tumour.

On the one hand, this new understanding of the branched evolutionary progress of advanced cancers provides a bleak analysis of why so many treatments ultimately fail. But on the other, it gives researchers and clinicians a new and firm grounding on which to constructively face their continual frustrations about treatment resistance, setting a new agenda for investigating new and potentially effective treatment options. Researchers have now embarked on work finding ways to harness evolutionary forces to control competing cells, or to cut off advanced cancers at their evolutionary trunk.

"I'm massively optimistic about the prospects, but we're engaged in a battle of wits with evolution," says Swanton, a practising oncologist at University College London Hospital, as well as one of the UK's leading cancer researchers. In November 2016 he won the Biochemical Society's GlaxoSmithKline Award in recognition of research leading to new advances in medical science.

"This heterogeneity will nearly always lead to the failure of therapies that target specific types of cell"

Cancer Research UK is supporting the work of Swanton and his team, and has invested £14 million into an ambitious national collaboration between six clinical centres and four science centres, to track and understand the evolutionary genetic changes in non-small-cell lung cancer over time in 850 patients (the TRACERx study).

But it isn't just Cancer Research UK that is convinced of the importance of understanding cancer evolution. The Institute of Cancer Research has just established a new Centre for Evolution and Cancer, led by Mel Greaves. "We have the objective of applying evolutionary principles to forge what we think is a paradigm shift in how we think about and understand cancer," says Greaves, who specialises in examining the genetic influences and biological pathways that lead to childhood leukaemia. "The implications for cancer treatment are extraordinary."

The theory of cancer evolution

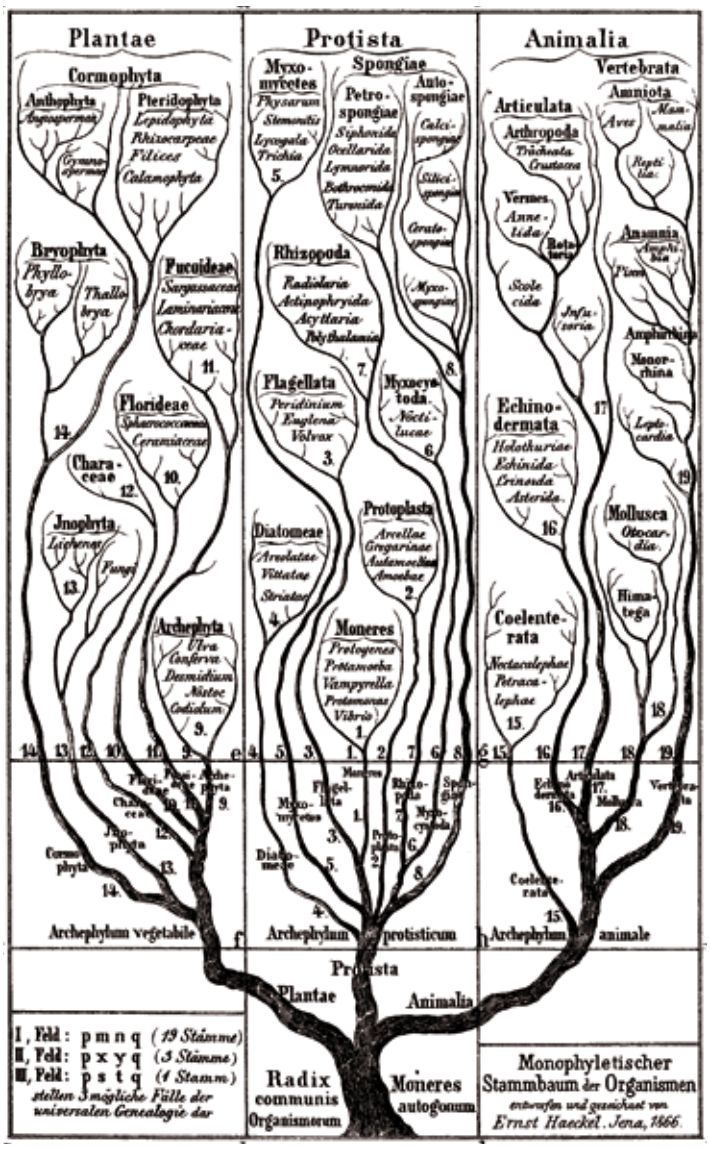
Researchers have long known that mutations accumulate as cancers develop. But traditional ways of explaining this process never made sense to Charles Swanton. When he was a medical student 20 years ago, he was taught that cancers evolve in a linear manner.

The theory went that a normal cell acquires a mutation – say to the APC gene – that allows that cell to proliferate, dominate other cells and form a tumour. Then one of the cells in the tumour mass also develops a mutation in the p53 gene, and that in turn becomes dominant. Then one of those cells loses chromosome 18, and those cells take over. The process continues, and the tumour grows into a roughly homogenous mass, each cell having the same gene mutations. If that theory were true, wherever you took your biopsy in the tumour, the results of genetic sequencing would be more or less the same.

But when Swanton became a clinician, he couldn't square this theory with what he saw happening in patients. Why were they becoming resistant to drugs that were targeting the same mutations found in biopsies? He could only think that there must be greater genetic diversity in the tumour than accounted for by linear evolution – that there must nearly always be some cells in the tumour resistant to treatment which would survive and take over.

So his team asked what happened if you performed genetic sequencing on ten biopsies from different parts of a tumour, rather than the customary single biopsy.

"We wanted to know how accurate a picture one biopsy gave you of the tumour genome," says Swanton. "And the answer is, depending on the type of



Targeting the truncal mutation. If cancer cells evolve along Darwinian lines, as illustrated in this 1866 diagram by Ernst Haeckel, then it would make sense to target mutations that happened at the earliest possible point, as they are the ones all the evolved cells will have in common. Swanton is exploring ways to do this by making truncal tumour neo-antigens visible to the body's immune system

tumour you're looking at, not very." The results were published in his influential 2012 paper in the *New England Journal of Medicine*, which revealed that in multiple kidney cancer biopsies from the same person, no two samples were the same. For each person studied, Swanton's team found more than 100 mutations in each tumour sample sequenced, but only one third of them occurred in all samples.

"What's happening is there's not linear evolution at all – you very rarely see that. What you see instead is branched evolutionary trajectories of tumours, as Darwin would have predicted, creating tremendous diversity from one region of the tumour to another and between primary and metastatic sites.

"So yes, it all comes back to a common ancestor, a single cell back in the history of the tumour, but what's happened over perhaps ten years is constantly branching evolution has created huge amounts of diversity and robustness, and that's allowed one or more cells to be resistant to therapy over time."

That means Darwin's tree of life can be applied almost exactly to cancers. As Darwin wrote: "The affinities of all the beings of the same class have sometimes been represented by a great tree... As buds give rise by growth to fresh buds, and these, if vigorous, branch out and overtop on all sides many a feebler branch, so by generation I believe it has been with the great Tree of Life, which fills with its dead and broken branches the crust of the earth, and covers the surface with its ever branching and beautiful ramifications."

Ironically, it is the ever branching and beautiful ramifications of the evolving tree that causes advancing cancer to become untreatable and lethal.

The implications

On the face of it, the implications are depressing. If each tumour has the variety and individuality of a snowflake, are all therapies doomed to fail eventually?

The obvious way of meeting the challenge of resistance is to use combination therapies – targeting two or more mutations at once to try and control disease for much longer periods. There is some evidence that this works in some patients. A modelling exercise led by Bert Vogelstein from Johns Hopkins Kimmel Cancer Center, a pioneer of research into the genetic changes that drive cancer, predicted that dual targeted therapy could result in long-term disease control for most pancreatic, colorectal, and melanoma cancer patients with metastatic disease.

But Swanton believes that turning to combination therapies is impractical for two reasons. First, because every

tumour has a unique combination of driving genetic events, finding the right combination of available therapies – and designing the trials to demonstrate effectiveness – would be unfeasibly complicated. Second, all targeted therapies have associated toxicity, and combinations will always be limited by what a patient's healthy tissue will be able to stand. So Darwinian understanding of tumours provides little prospect of advanced cancer being cured by drugs targeting single mutations.

But it does present hope elsewhere – and a new perspective on how to tackle the infuriating complexity and resilience of cancer.

According to Mel Greaves, Director of the Centre for Cancer and Evolution at the Institute of Cancer Research, there are several areas where evolutionary understanding of cancers offers enormous potential.

"First, the more we understand cancer evolutionary biology, the more we understand how important it is to intervene early: once cancer evolution is up and running there's a point of no return. Second, it has implications for personalised treatment and targeted medicine: we need to ask whether a target molecule is in every cancer cell or a side branch of an evolutionary clone. Ideally we should be targeting mutations in the trunk of the tree.

"The third point is whether we can envisage a Darwinian by-pass – directing our approach not directly at cancer cells but towards their micro-environmental habitats and changing their habitat and dependencies. Anti-angiogenesis is a prime example of this tactic.

"A further alternative is to seek to control cancer rather than eradicate it, confronting drug resistance in some cells by allowing competitor cells to survive and consume resources that would otherwise benefit resistant clones."

New approaches: targeting the evolutionary trunk

Given the diversity of cells within a tumour, the overwhelming challenge is to get a treatment that affects all the cancer cells – not just those that have sprung from an evolutionary branch. Targeting the mutations where it all started and which are present in every cell – the trunk of the evolutionary tree – is the obvious way to fell the entire structure.

But this is not as easy as it sounds. Although we know that there are some key driver gene mutations for many cancers, and that some mutations – for example p53 and KRAS – are found in a large proportion of tumours, they have proved very hard to target with small molecules.

"But even if we do find ways of targeting these molecules, I still fear that resistance is inevitable," says Swanton. "I think we're going to have much more success exploiting the immune system – the very system which has evolved over four billion years to target the kind of ever-changing diversity that tumours display."

The reason for Swanton's optimism about immunotherapy largely lies in the findings of another groundbreaking study carried out by his team at University College London, and published in *Science* last year. It discovered that all cancer cells have distinctive 'flags' on their surface, deriving from multiple trunk mutations. These can help direct the body's immune system to attack all cancer cells, not just the branch clones.

Immunotherapies help the patient's disease-fighting T-cells hunt and destroy cancer cells. But despite their immense potential, trials show they work only in a proportion of patients, and they sometimes also damage healthy tissue, causing severe side effects.

The challenge seems to be precision: how do you help the immune system identify and then lock onto the best targets – the cells that are all cancer cells, and that make up most of the tumour? T-cells find their target by locking onto distinctive proteins on the surface of cells (antigens) – so one solution would be to help them find a protein that is on the surface of all cancer cells, a protein that has been passed down the generations of cancer cells from the very first mutated cell at the bottom of the evolutionary trunk.

"Truncal tumour neo-antigens could allow scientists to target and destroy tumours without harming healthy tissues"

Analysing data from over 200 patients with two types of lung cancer, Swanton and his team discovered that in every cancer patient there are unique 'flag' proteins present on the surface of every cancer cell, and only on cancer cells, which can be used to alert the immune system to attack (*Science* 2016, 351:1463–69). They are called truncal tumour neo-antigens and they could allow scientists to target and destroy tumours without harming healthy tissue.

Their continuing research is examining why the 'flags' are being hidden or protected from the immune system, and how to harness the immune cells that do recognise the targets.

A new treatment route looks possible: identifying truncal tumour neo-antigens from biopsies, then finding and harvesting T-cells within the tumour which recognise these, replicating them

in the lab and then injecting them into the patient. "This takes personalised medicine to its absolute limit, where each patient would have a unique, bespoke treatment," says Swanton.

Such advances might be a way off, and will inevitably be expensive – at least in the short-term. But Darwinian understanding of cancer opens up other avenues too.

New approaches: adaptive therapy

What if researchers took a completely new approach to controlling advanced cancers – not fighting against the branching evolution that drives the cancer, but working with it for the benefit of the patient?

This is exactly the approach that researchers in Florida are taking, in work examining whether low doses of chemotherapy might keep cancer at bay more effectively than trying to destroy the tumour completely with high doses.

The work, led by Robert Gatenby from the H. Lee Moffitt Cancer Center, centres on the evolutionary principle of survival of the fittest. If high dose chemotherapy kills off all the cancer cells that respond to chemotherapy, only those that are resistant to chemotherapy will remain. And, freed of the competition from non-resistant cells, they become fit and free to grow and roam – bringing back the cancer with a vengeance.

Gatenby's team studied this dynamic in mice being treated with Taxol for two different types of breast cancer. When given standard doses, their tumours initially shrank, but grew back as soon as the treatment stopped. But when the researchers gave an initial high dose followed by progressively lower doses as the tumour responded, the mice lived much longer. Between 60 and 80% of the mice could be weaned off the drug completely over an extended period without suffering relapses.

The research, published in *Science Translational Medicine* in February 2016, indicates that keeping resistant and non-resistant cells in a delicate balance of competition might be the best way to hold both back – not curing the cancer, but controlling it for long periods. The technique is called adaptive therapy.

"The evolutionary principles that govern adaptive therapy may be applicable to a wide range of breast cancer treatments including hormonal manipulation and immunotherapy, although they will need to undergo further testing in those settings," says Robert Gatenby, who is leader of the Cancer Biology and Evolution Programme at Moffitt.

> **"We doctors need to learn from environmental ecology and cancer evolutionary biologists"**

Based on these promising preclinical results, the Moffitt researchers have begun the first clinical trial assessing an adaptive treatment strategy for relapsed prostate cancer patients. It will examine whether the conventional approach of giving the hormone therapy abiraterone at the maximum tolerated dose extends progression-free survival more or less than an adaptive approach. This has particular relevance to African-American men, who tend to develop resistance to hormone therapy more rapidly than other ethnic groups.

The Moffitt scientists aim to use the molecular and clinical data from the trial to develop computer models that might guide adaptive therapy in the future.

New ways of thinking are required

If adaptive therapy based on Darwinian understanding of cancers holds much promise, it will also demand a significant rethink of the way cancer treatments are researched. The expectations of doctors and patients, and the very structure of clinical trials, will have to change, according to Charles Swanton.

The problem is that response rate is currently the key marker of a drug's efficacy. But with adaptive therapy, the aim is not a spectacular response but keeping the tumour stable. "That's not going to sit comfortably with clinicians and patients," says Swanton.

"Traditionally, we want to shrink the tumour as much as possible until you can hardly see it on the scan. Naturally one thinks the less of a tumour is there the better, but maybe that's not the case. Maybe we need to utilise the drug-sensitive tumour clones to out-compete the drug resistant tumour clones that we have no way of treating."

If researchers and ultimately clinicians are genuinely going to tap in to the insights that Darwinian theory brings to confronting cancer, they are going to have to learn to think more creatively and more strategically.

"We doctors need to fight evolution," says Swanton. "We need to think about how we can manage evolution in a very clever way, and most importantly how we can learn from environmental ecology and cancer evolutionary biologists like Robert Gatenby." The battle of wits with evolution is likely to be a long one, but at least the enemy now stands clear in view.

EVENTS DIRECTORY
2017 - 2018

ECCO - the European CanCer Organisation manages multidisciplinary meetings of excellence on behalf of its Members:

EVENTS	SAVE THE DATE
MCCR WORKSHOP	**17 – 23 June 2017** *Zeist, Netherlands* MCCRWorkshop ECCO-AACR-EORTC-ESMO Workshop on Methods in Clinical Cancer Research
2nd Special Conference EACR AACR SIC	**24 – 27 June 2017** *Florence, Italy* EAS2017 2nd EACR-AACR-SIC Special Conference onThe Challenges of Optimising Immuno and Targeted Therapies
EBCC 11 European Breast Cancer Conference	**21 – 23 March 2018** *Barcelona, Spain* EBCC11 11th European Breast Cancer Conference
EACR 25	**30 June - 3 July 2018** *Amsterdam, Netherlands* EACR25 25th Biennial Congress of the European Association for Cancer Research

To discover more about ECCO: www.ecco-org.eu

IEO education
European Institute of Oncology

UMBERTO VERONESI
MILAN
BREAST CANCER CONFERENCE

Innovation in Science and Care

22-23 June, 2017

Chair: Paolo Veronesi - Aron Goldhirsch

Topics

High Risk of developing breast cancer
In situ disease
Global approach to breast surgery
Breast Surgery live theater
Radiation therapy
New targets and new drugs
Adjuvant and neoadjuvant systemic therapies

Spotlight

Liquid biopsy: clinical implications

Scientific Committee

B. Bonanni, M. Colleoni, G. Curigliano,
V. Galimberti, M. Intra, R. Orecchia,
V. Sacchini, G. Viale

Conference Venue

Auditorium "Gruppo 24 Ore"
Milan, Italy

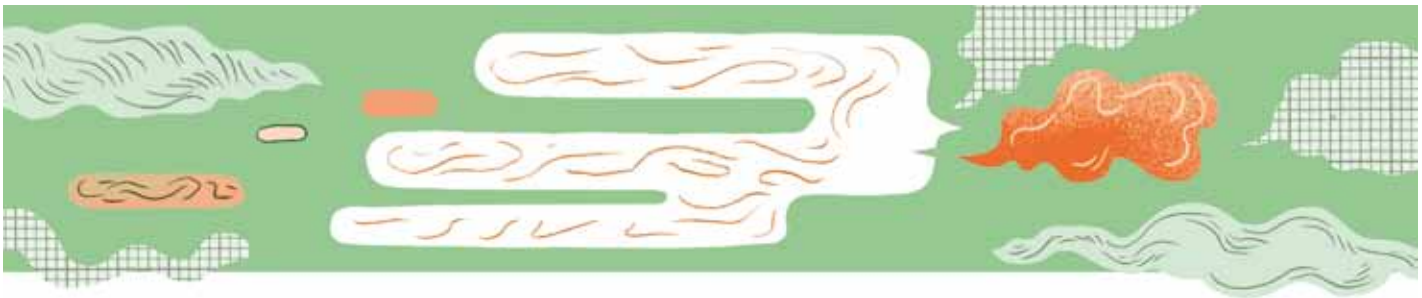
mbcc@ieo.it
www.breastmilan.com

THE ONLY THING MORE RELENTLESS THAN CANCER IS THE PEOPLE WHO FIGHT IT.

Because no two cancer patients are alike, Lilly Oncology is committed to developing a broad portfolio of therapies, including those tailored to unique patients, and meaningful support solutions that accelerate the pace and progress of cancer care.

We're determined to continue making life better for those affected by cancer. Learn more about all we do at LillyOncology.com.

Lilly | ONCOLOGY



Elżbieta Senkus: Facing down the fear

How is it possible to help patients decide on the best treatment option for them, when they are scared, and when there is such uncertainty? Elżbieta Senkus, a specialist in breast and prostate cancers, talks to **Anna Rouillard** about her own approach and the urgent need to learn more about how the recommended treatments should best be used.

Good cancer care is about balancing the twin goals of preserving quantity and quality of life in line with the priorities and preferences of each patient. Great cancer care adds something extra, helping patients regain the confidence and drive to go out there and live their lives, whatever their prognosis. That is how four young Polish women treated by oncologist Elżbieta Senkus see things, anyway.

With Elżbieta's help, they have just set up a foundation for young women with breast cancer, choosing as its logo a high-heeled shoe with a pink ribbon saying "breast cancer doesn't limit you". And at a recent meeting, says Elżbieta Senkus, "they thanked me for helping start their organisation, and for always being positive and wearing the highest heels around!"

Qualified in both medical and radiation oncology, Senkus is based at the Medical University of Gdansk on Poland's Baltic coast, where she specialises in breast and prostate cancers. It's a career path she decided on at a very young age, and doggedly pursued in the face of opposition from both parents: "When I was growing up, medicine was not considered a wise career choice for women in Poland," she says.

It has certainly worked out well for Senkus, who has combined her career with bringing up two sons, now aged 19 and 22, and pursuing her love of travel and beautiful things – she has on occasion designed her own jewellery, and says interior design would have been her alternative career option.

As it is, she spends most of her time helping people with cancer get the most satisfaction and fulfilment out of their own lives, choosing to specialise in two cancers – breast and prostate – that offer her the opportunity to do what she does best.

"Both are hormone-driven diseases, are common, affect largely the ageing population, and progress over years rather than months. Being amenable for endocrine therapy, patients can tolerate treatment over long periods."

The lack of urgency, she explains, means she finds it a luxury to treat these patients – there is time to interact meaningfully to help them make the best treatment decisions for each person's disease and lifestyle.

"Just this morning a lady in her seventies came in with early

breast cancer, explaining she had decided on a mastectomy. Such radical treatment was simply not necessary in this case, and I explained that she would have just as good an outcome with breast conserving therapy," said Senkus.

Part of the problem, she believes, is that patients are referred by surgeons who recommend that they do major surgery, "and because the patients are scared, they agree in order to be cured." Once they've had the full range of options available presented to them, she adds, they often take a different path, and are relieved to have been informed about alternative solutions. "Talking to patients is absolutely crucial," says Senkus. "It does take time, but I always try to have this time for patients."

Indeed her patients are even invited to attend the discussion at the multidisciplinary team meeting, which Senkus sees as vital. "We see the patient in the MDT meeting at the beginning of their journey. This often makes the meetings very long, but it is so important to see the patient and not just the papers. You need to observe how she or he is behaving, and how fit they are. The first impression is very important."

Talking about advanced disease

Having a conversation about the pros and cons of more gentle treatment options can be particularly difficult with patients whose cancers are no longer curable, says Senkus. "Patients know that metastatic breast cancer is a very serious disease, and they tend to presume that it needs to be treated aggressively. Aggressive treatment means 'strong' chemotherapy, and that means toxicity. But when we suggest an alternative option, one that is just as effective but offers a higher quality of life with fewer side effects, they are often unconvinced, and even question our competence as doctors!"

She cites as an example a patient who she had no doubt was an obvious candidate for treatment with endocrine therapy, which she accordingly recommended to the patient. But the patient wasn't convinced, and sought a second opinion from another oncologist. The second oncologist offered chemotherapy, and Senkus's patient agreed, "believing that a more aggressive treatment would be more effective."

"Patients sometimes actually complain that I am not

offering a strong and presumably effective enough treatment," says Senkus, "And there begin the very long talks and explanations."

The concept of minimally disruptive medicine is at the core of Senkus's philosophy for treating patients with advanced breast cancer. It seeks to minimise the burden of illness on the sufferer as well as the burden of treatment, which can become overwhelming for patients, and can affect their level of adherence.

The concept of minimally disruptive medicine is at the core of Senkus's philosophy for treating patients with advanced breast cancer

"Quality and quantity of life are the main priorities in metastatic disease", she says, adding that many oncologists overtreat with chemotherapy, partly due to the pressure that patients put on them to do so. "We have major challenges trying to persuade physicians, particularly community oncologists, to give less chemotherapy. I feel this is a bigger problem in my part of Europe than in western Europe."

Preserving quality of life, she says, is about retaining as much normality as possible. "My goal in treating patients with metastatic disease is to enable them to lead relatively normal lives, and to do the same things they had done a year earlier. If they work, I tell them to continue working. Working means belonging to the normal, healthy population. Being on sick leave means moving to the ill population."

In advanced disease, she adds, patients' enjoyment of life, and their fulfilling of wishes, is more important than strict adherence to treatment. "If one of my patients wants to go away to visit her grandchild in another country, or go on a cruise, or take time out to fulfil a life-long aspiration, I encourage them to go, and to continue their treatment when they come back. I reassure them that nothing bad is going to happen to them."

A 'two-in-one' oncologist

Senkus has an unusually broad perspective on cancer therapy, specialising as she does in both medical and radiation oncology. This is not a formal model but rather a tradition that is common at Gdansk Medical University, which offers medical graduates a unique opportunity to obtain full specialisation in both disciplines. Senkus is a product of this system and a strong proponent of the importance of multidisciplinary training for oncologists.

"Radiation oncology is very often a great mystery for medical oncologists, and this lack of understanding can lead to prejudices and even fear of it. On the other hand, radiation oncologists are technicians who are well versed in physics, but do not necessarily understand the biology of cancer very well. In Gdansk we had five to six years of radiation oncology specialisation, usually followed by a break of a few years, and then, as a practising radiation oncologist, a further five years of training in medical oncology. Having full competence in both medical oncology and radiation oncology, I really feel I can offer comprehensive care to my patients."

There is also a practical advantage to being treated by a 'two in one' oncologist. "Precious time is saved, as I do not have to refer patients to other specialists for opinions or therapy. In a palliative setting, for example, if I have a patient with bone pain, I simply give him or her a shot of radiation the same day or the day after. The logistics of treatment are far simpler."

Nowadays a lot of chemo-radiation is given simultaneously, for which knowledge of both modalities is very important, adds Senkus. "In rectal cancer, for example, where chemo-radiation is a typical indication, one person gives radiation therapy and another gives chemotherapy, but what happens when the patient has a complication that is a common complication of the area? Who is going to treat it? And who is to blame for it?"

Separating radiation and medical treatments is artificial, she argues. "The only way to treat a disease as complex as cancer is to combine knowledge on all the available treatments, and to specialise in organs, rather than in treatment modalities."

"Five minutes" for triple negative breast cancer

Senkus has always sought to go beyond merely "combining knowledge" – as her research record shows, she is always looking for ways to develop new knowledge about the best treatment options for each of her patients.

Senkus has a theory that each cancer has its 'five minutes'. "Renal cell cancer had its five minutes in 2005, prostate in 2010." Most of the five minutes for breast cancer, she says, have been for HER2 positive tumours. This type of breast cancer has seen huge progress, she says, with trastuzumab, lapatinib, then pertuzumab and the antibody-drug conjugate T-DM1. "But now there's not much of interest happening in

HER2 positive disease."

The spotlight is now on luminal disease, she feels, where combination with targeted treatments is becoming a new standard. "CDK4D inhibitors are a huge step forward – a number of trials show prolongation of progression-free survival with the first line of treatment in the range of ten months, and they also have a very good toxicity profile," she says.

"What we really need," she stresses, "is five minutes for triple negative breast cancer". Triple negative breast cancer, the least common subset of breast cancer, is not a single disease but several separate diseases, each characterised by lack of receptors, not by any positive factor, and probably having a different biology. "Each of them also probably requires different treatments and for the time being the progress is limited to very narrow subgroups."

Senkus argues that more research is needed into the use of current treatments, and not only novel treatments. "As with any single drug or treatment modality, there are always unanswered questions," she says. "One of the directions in which systemic treatment is moving now is metronomic chemotherapy, where patients receive smaller doses at more regular intervals. We have data that some chemotherapies are more active, and better tolerated, when they are split into smaller doses. You can probably also give higher cumulative doses this way. But we are missing data on this approach for many diseases and many treatments."

"Breast cancer doesn't limit you". *Main image:* Elżbieta Senkus, pictured here in a fancy hat in a Vienna restaurant, enjoys life and encourages her patients to do the same. *Inset:* The logo chosen by a group of her younger breast cancer patients for their newly established foundation Fundacja Omea Life (*www.facebook.com/FundacjaOmeaLife/?pnref=lhc)*

Even when a treatment exists, it is not necessarily evidence-based. She cites the example of docetaxel in prostate cancer, where a major trial has demonstrated that a bi-weekly dose of 50 mg/m^2 is better tolerated, and also possibly slightly more active, than 75 mg/m^2 every three weeks. "However, there are currently no data on its use in a hormone-sensitive setting. Thus we face a dilemma: being tempted to use this regimen, but at the same time being aware of how much is at stake if the approach proves not to be equally effective in this setting.

"In breast cancer we also lack data on replacing docetaxel, a rather unpleasant chemotherapy, by weekly paclitaxel, which is much better tolerated, but for which there are no data for many clinical situations. The problem is that this kind of trial will not attract industry funding."

Questions about treatment de-escalation also need urgent answers, says Senkus. "We tend to add new treatments on top of previous ones, and I am sure we are overtreating many patients." However, giving less treatment may be risky in an adjuvant setting, she adds, since you may be compromising long-term survival and cure. "Some research is being undertaken,

"We tend to add new treatments on top of previous ones, and I am sure we are overtreating many patients"

but we need more trials that will demonstrate that we can avoid giving chemotherapy to patients where it can safely be spared or simply will not be effective. Predictive biomarkers are badly needed, she says. "In spite of billions of dollars being spent on research into new predictive factors, there have been no real new ones in breast cancer since oestrogen receptors 30 years ago and HER2 20 years ago. People are really trying. It's a kind of holy grail of oncology."

"In spite of billions of dollars of research, there have been no new predictive factors since oestrogen receptors 30 years ago and HER2 20 years ago"

The issues are slightly different in metastatic disease, she adds, "where we are talking equally about outcome and quality of life and trade-offs." Patient advocates have a particularly important role in helping define best practice in this setting, she says, and she points to the ABC (Advanced Breast Cancer) conferences as a great example of involving patient advocates as equal partners in drawing up consensus guidelines on treatment and care. Senkus has been involved with the ABC initiative from its earliest days, and will be co-chairing ABC4, which will take place in Lisbon in early November this year.

Closing the gap

At home in Poland, patient advocacy is in transition from an old-fashioned model to a more modern one. "Since breast cancer is a common disease, we do have patient advocates, and they are quite active, but not as active as in some other countries. I think the modern approach to patient advocacy is going to happen now and over the next few years."

The four patients who set up the breast cancer foundation for young women are all aged between 30 and 35, and more traditional styles of advocacy were clearly not for them, says Senkus. "These are young, active, positive and energetic women. They have very positive messages for patients, and one of them told me that she went to church to thank God for her cancer, as the experience has changed her, and her life, for the better."

"I hope the cancer will not be too high a price for this change of life," she adds, "but for the time being I think her life has now indeed become more valuable, for her and for others."

Like much of central and eastern Europe, Poland's cancer services are still going through a period of transition in an effort to raise the quality of care and close the outcomes gaps with western countries.

The most recent EUROCARE study, looking at people diagnosed between 2000 and 2007, showed that the survival time for women diagnosed with breast cancer in Poland was around 10% lower than the European average. "So unfortunately it's not doing very well," says Senkus, "but hopefully it's getting better." There's a lot of talk about breast units, and things are changing in that direction, she says, though few have yet been fully established and they still lack any legal or regulatory framework.

The country still has no cancer plan, she adds, or at least there is one, "a great document", but it has never been approved by the government. Two years ago the government did introduce a cancer 'package', "but it's a completely separate document… and actually it's created probably much more noise than real effect."

On the plus side, it has speeded up the diagnostic pathway, so new patients get their CTs done quickly. However, adds Senkus, nothing has been done for patients already on treatment, who may even wait longer for diagnostic tests, because patients coming through the new pathways get the "good places" on the waiting lists.

"The introduction of multidisciplinary teams is a plus, but the quality criteria needed to make them work properly are not yet there"

Another plus is the introduction of multidisciplinary teams, but the quality criteria needed to make them work properly are not yet there. "There is no volume requirement, which I think is a big disadvantage," says Senkus, "because it can be that there is a surgeon, a medical oncologist and a radiation oncologist who basically have no experience with certain diseases, and they do an MDT meeting, and may only see five colorectal cancer cases a year, for example."

"So there are some steps forward, but it's not exactly in the right direction. Fortunately, improvements are planned, following monitoring of the system and identification of weak points over the past two years."

INFORMING LIFE DECISIONS

- The only multigene assay that helps to identify risk of distant recurrence[1,2] and the likely benefit of chemotherapy[3,4]
- Intended for newly diagnosed patients with early-stage, ER-positive, HER2-negative invasive breast cancer that is node negative or with 1-3 positive nodes[1,2]

Visit us at **www.oncotypeDX.com**

oncotype DX®
Breast Recurrence Score

References

1. Paik S et al. *N Engl J Med* 2004; 351: 2817-2826; 2. Dowsett M et al. *J Clin Oncol* 2010; 28: 1829-1834; 3. Paik S et al. *J Clin Oncol* 2006; 24: 3726-3734; 4. Albain KS et al. *Lancet Oncol* 2010;11: 55-65.

GHI10448_0217_EN_INT

Making cancer care smarter.™

oncotype IQ® Genomic Intelligence Platform

Genomic Health® LIFE. CHANGING.

Improving pharmacovigilance through direct patient reporting

With increasing numbers of cancer drugs being approved on shorter trials that involve fewer patients, getting accurate reports of adverse events and side effects after approval is increasingly important. **Maria Delaney** reports on efforts to encourage us all to be alert for – and report – possible side effects from the medications we take.

Have you ever suffered a side effect while taking medication? Ranging from mild to severe, the majority of us have experienced some type of side effect. If so, what did you do about it? Hope that it would pass, shrug it off, notify your doctor, stop your medication...

Side effects are a common reality for patients on cancer therapies and they can often be very severe. Despite this, new studies show that they are under-reported by physicians in clinical trials, by as much as 74% for some toxicities.

And it isn't only physicians who under-report. Gilliosa Spurrier-Bernard, melanoma advocate from Melanome-france, says that getting patients to report side effects during a clinical trial is quite hard, as they are terrified they will lose their place on the trial. She says this "is bad for pharmacovigilance after the trial, when the drugs go out into normal practice."

As more innovative targeted therapies move from trials to the general market, continued reporting of side effects is something that some members of the oncology community are striving to improve. One way they are doing this is by putting power in the hands of patients: side effects can now be directly reported to pharmacovigilance centres in each country across the EU.

But is this direct reporting actually happening, what are the benefits, and how can it be improved?

Progress in pharmacovigilance

Pharmacovigilance has developed substantially since the initial WHO pilot Program for International Drug Monitoring was set up in the early 1960s, following the thalidomide disaster, according to Rebecca Chandler, from the Uppsala Monitoring Centre – the WHO Collaborating Centre for International Drug Monitoring, based in Sweden. "We thought it was very important to set up a network of countries so that [events] that might be occurring on a rather small level in individual countries might be seen better from a global perspective."

The initial 10 pilot countries has now expanded to 125 participants, with over 14 million adverse event reports collected. These reports are entered into the Monitoring Centre's VigiBase database. As Chandler explains, there is much overlap with the data gathered by the US regulatory body, the FDA, with their reports making up approximately 50% of the entire database. This is due in part to a large number of reports collected by drug companies with headquarters in the US.

"In the United States, people often report to the drug company first, but Europe is different, with patients in individual countries reporting directly to the national pharmacovigilance centres," says Chandler, though she adds that, in Europe, the option to report to either the company or national pharmacovigilance centres is there for both patients and physicians. The Uppsala Monitoring Centre does not collect reports directly from patients, but it would like to see more patient reporting done at a local level.

Direct reporting by patients to local pharmacovigilance authorities was first introduced by Denmark and the Netherlands in 2003. Today it should be possible for patients in all EU countries, as EU Pharmacovigilance legislation passed in 2012 requires all national centres in Europe to have a system that can receive reports directly from patients, says Chandler. In spite of this new requirement, it is still difficult for patients to report side effects in some countries due, for instance, to forms not being set up for online completion, or being simply too complex.

Outside the EU, there are many countries that have no option for patients to directly report side effects. A recent study found that patients were not allowed to report in 34 countries, or 24% of the National Competent Authorities surveyed.

Patient vs doctor reporting

Patient reporting without the influence of a healthcare professional is important, as "we know doctors underestimate certain side effects and overestimate others in terms of importance or relevance to a patient," says patient advocate Spurrier-Bernard. "Doctors will categorically dismiss fatigue because they don't really know what to do with it, whereas for the patient it's very important."

Even when side effects are reported, there are differences in how doctors and patients report them. A 2014 study found that patients' reports are more focused on the subjective impact of the adverse event, whereas reports from health professionals include a lot of clinical information, but less on the experience of the patient.

"Doctors will dismiss fatigue, because they don't know what to do with it, whereas for the patient it's very important"

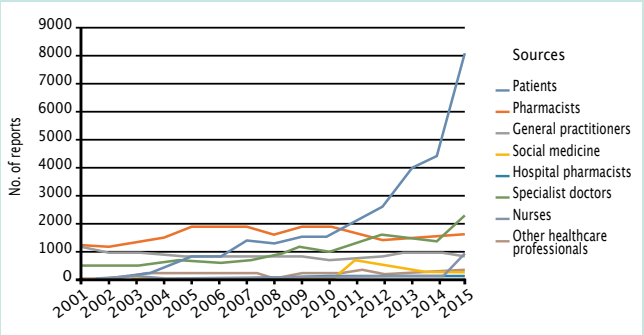
Francesco Perrone, director of the clinical trials unit at the National Cancer Institute of Naples, has studied the difference between doctor and patient reporting in a clinical trial setting, and has found that under-reporting of toxicities in anticancer treatments by physicians ranged from 40.7% to 74.4%. He thinks the reasons for this include not having the time to talk to patients about side effects, patients being afraid to lose treatment, and not noticing side effects such as hair loss in male patients.

This leads to a problem for drugs now on the market, as there is a lack of clear knowledge of the side effects of a new drug or treatment strategy. Perrone feels "there is a high probability that the patient will be misinformed" in clinical practice, as all the side effects will not be mentioned in studies of the drug.

Spurrier-Bernard says this happens a lot from her experience in the melanoma patient group. Doctors tell patients that certain side effects are 'nothing to do with this drug', but "we know that these drugs are new and the doctors themselves don't know all the side effects."

Chandler agrees, and says that this is often due to the nature of precision

Patient reporting in the Netherlands



The Netherlands Pharmacovigilance Centre, Lareb, began accepting patient reports in 2003. Fourteen years on, patients are now filing more reports than all other sources put together, with direct reporting having quadrupled over four years (see figure above). Florence van Hunsel, head of signal detection at Lareb, told *Cancer World* why they initiated patient reporting, and how it has developed.

An initial pilot was completed in 2003. The patient reports submitted during the pilot were analysed, and were found to be very useful. "After the pilot," says van Hunsel, "we had a culture change in our organisation, as we wanted to be more patient oriented."

More than 170 patient reports were submitted in the first year, but Lareb wanted to increase that number. They started to advertise the reporting site, and publish their experience. They promoted adverse event reporting in patient magazines, and on patient organisation websites.

"One of the most important things is working with patient organisations," says van Hunsel.

Most recently Lareb produced a series of radio commercials as part of an EU-wide drive to increase patient reporting. The centre also takes part in TV programmes on pharmacovigilance topics. Their efforts led to an impressive increase in patient reports, with more than 8,000 being collected in 2015.

Online forms were always the preferred option for Lareb, says van Hunsel, because it enables them to receive information in a more structured manner, and is more manageable. They recently developed a reporting app, which has been online for a number of months. The hope is that this will further increase reporting levels – 135 reports have already been submitted via the app by patients and healthcare professionals.

As well as direct reporting, Lareb are exploring other ways to improve pharmacovigilance. They are part of the Web-Recognizing Adverse Drug Reactions (WEB-RADR) consortium, which is a large group looking at innovative ways to get pharmacovigilance information. This includes exploring the possibility of data mining of social media, such as Facebook and Twitter, for adverse events, and researching frameworks that need to be in place for this.

Though patient reports are now an important part of pharmacovigilance, van Hunsel stresses that they also need information from healthcare professionals. "I don't think we would do a great job without them. The mix is ideal."

medicine dividing patients into specific genetic mutations for new treatments for rare diseases, and other sub-populations when it comes to cancer. "Drugs are getting licensed based on a relatively small number of patients, so it is incredibly important that pharmacovigilance systems are ready."

Changing systems

One area that has improved greatly in the past two years is that data on reports of adverse events and side effects held on the Uppsala reporting database is now publicly accessible through a portal, VigiAccess. "It's been shown that the best way to encourage people to report is to give something back," explains Chandler, who adds that there is also a move in many organisations – including the FDA and its European counterpart the EMA – to be more transparent.

It took several years to finalise VigiAccess, and it gives the public very basic access to this global database. The first release of VigiAccess has a structure which is recognisable to those who are familiar with the practice of pharmacovigilance," says Chandler, who adds "hopefully in the future it could be adapted to make it easier for patients to use directly."

A certain amount of medical knowledge is also required when searching the database. A familiarity with the system used to code adverse events or side effects is also a plus.

Patient groups are already using VigiAccess to help patients with their side effects. Spurrier-Bernard helps people with melanoma search for side effects they are experiencing so that they are better equipped for their next

doctor's visit. "It's extremely useful, as you can go back to your doctor and tell them to think again about side effects they dismissed, and deal with them. It gives patients extra confidence."

Reporting apps

New tools are also being rolled out to the public in some countries to help patients report side effects. Apps are being developed on a pilot basis in the UK, the Netherlands and Croatia.

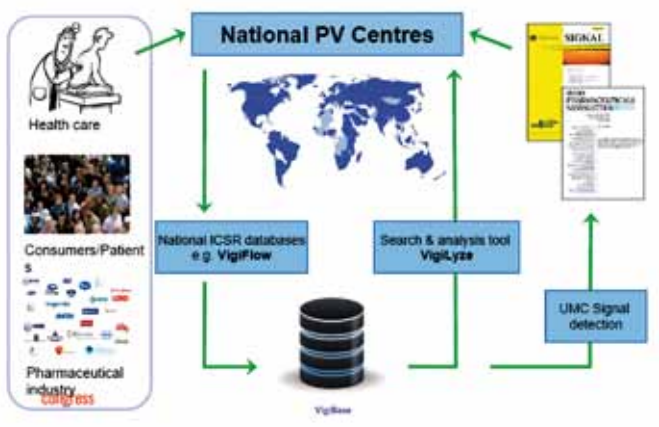
One example is the Yellow Card in the UK, which was a paper-based form and is now available as an app developed by the Medicines and Healthcare Product Regulatory Agency. Its main advantage, according to Chandler, is that "it eliminates the need to track down a paper form."

Though patients have been able to report in some countries for a number of years, requiring them to find and return paper forms or navigate multiple links online has acted as a significant deterrent, she argues. The development of apps, she says, shows "a lot of progress is being attempted to make it as easy as possible for patients."

In a similar way to VigiAccess, these apps also offer patients access to data on adverse events and side effects. Spurrier-Bernard was asked for some input about the type of feedback patients would like to receive during the development of the Yellow Card app. "It was really quite cool, as they asked: 'Would you like data on all the drugs related to melanoma or just your drug?' It gave people flexibility in what type of feedback they wanted."

She feels that this feedback is really important, as patients want to know that, if they take the trouble to fill out a report, then something will happen with the data. "Why would people do it if they thought it wasn't going anywhere?"

Side effects reports: flow of information



Individual case safety reports (ICSRs) are submitted to national pharmacovigilance (PV centres), which feed them into VigiBase, the WHO international database at the Uppsala Monitoring Centre (UMC) in Sweden. The data can be searched and analysed using the Uppsala centre's VigiLyze software, to make it easy for national centres to pull out and analyse relevant data. The Uppsala centre conducts its own analysis, looking for patterns and signals, and reports its findings back to national centres. Since 2015, members of the public have been able to search for side effect reports by drug via the VigiAccess portal.

Getting the message out

Improving public awareness about the importance of reporting side effects, and how that can be done without going through a doctor or pharmaceutical company, remains a big challenge. One way the Uppsala Monitoring Centre has tried to address this issue is through their 'Take & Tell' campaign, which aims to "make pharmacovigilance – monitoring, assessing and understanding adverse effects, or other drug-related problems – into an easily understood, household name… and change the way people view the process of taking medicines and to facilitate dialogue between the health care provider and patient."

The campaign consisted of posters and other advertising material, such as the 'Take & Tell' song, which can still be watched on YouTube, including a reggae version and a version in Chinese.

Some of the countries that participate in their pharmacovigilance programme have limited resources, says Chandler, so the campaign was designed to aid those countries in particular. "It encourages patients to report and is also a general message to everyone to increase awareness that drugs can have adverse events and you can do something about it."

Adapting reporting tools

Apps and adverts may improve patient understanding of side effect reporting and make it easier to report them, but tools are also needed to ensure the correct data is recorded on these systems.

Oncologist Perrone feels that more research is needed into the tools used in side effect reporting by physicians and patients. He helped develop the Italian version of PRO-CTCAE, a patient-

What does the public get out of it?

People who report side effects contribute to a system designed to improve patient safety, which benefits everybody.

And since 2015, members of the public have also been given direct access to the WHO Uppsala Monitoring Centre database, via VigiAccess, where they can search for adverse event reports on any medication. This can be important in helping make sense of their own experiences and also give them confidence to press the point if their doctor is reluctant to give a fair hearing to their side effects complaints.

Some national pharmacovigilance agencies take on a public information role, publishing the results of their analyses of the side-effect data they receive and providing an information service to respond to specific questions. The Dutch Lareb pharmacovigilance centre, for instance, claims in its 2015 report to have contributed to 10 television and radio broadcasts and 40 articles in the lay press, and responded to almost 2000 queries.

The impact of side effect and adverse event reporting would be all the greater if information gathered on side effects and adverse events was used in a concerted way to improve our ability to manage them.

reported outcome measure developed to evaluate symptomatic toxicity in patients on cancer clinical trials. He suggests that, while it is clear that these sorts of instruments need to be used in clinical trials, maybe they should also be used in clinical practice.

There is a caveat though, as Perrone feels that more research is needed into their use outside of a clinical trial setting. "There is some evidence that patients staying in touch with the clinical team with this kind of instrument may reduce the impact of side effects, and increase quality of life. It may also reduce dependence on the emergency room," he says.

From reporting to managing – the HIV example

Side effects can be fatal – more often they blight lives. Photosensitivity induced by the B-RAF inhibitor vemurafenib, for instance, turns patients into 'vempires', keeping them inside when the sun is out. Poorly controlled diarrhoea keeps people from straying far from a toilet. Sensitive nerve endings can affect mobility and fiddly tasks. Unsightly rashes can also deter people from leaving home. Disturbed sleep patterns can make it hard to function. All of these and more can impact on adherence to potentially life-saving or life-extending drugs. While improving reporting is a good start, Chandler argues that more needs to be done to help patients manage them.

"One area that is currently not being fully addressed in the drug regulatory process, in my opinion, is providing advice to patients and their physicians on how to manage adverse events," she says. Having met with many patient groups around Europe, cancer patient groups in particular, she feels that as a next step, they need to figure out how to deal with adverse events, so they can advise patients.

Chandler talks about how shocked she was to hear people say that they won't take their drug that is saving their life, "if they can't sleep at night, or have a very itchy rash". Rather than leaving management of side effects with the oncologist or patient, she would like to see regulators having a greater role in providing advice or encouraging research on management of adverse events.

Using her previous role as an infectious disease physician as an example, Chandler says, "the HIV story is remarkable, and they have a lot of adverse events that people have learned to manage." As people with HIV lived longer and the disease became more treatable, management of side effects became more important. Drugs to treat it can lead to bad rashes, fever, and liver failure, but research into adverse events with HIV medicines uncovered that certain genetic predispositions were found to make people more susceptible. Now patients can be tested to minimise their risk of adverse events.

While improving reporting is a good start, Chandler argues that more needs to be done to help patients manage side effects

Many cancers have now reached a similar stage, with prognoses being improved on a regular basis by new innovations. Many people with stage 4 melanoma are now living long enough for side effects to have a real impact, according to Spurrier-Bernard. "Unfortunately, up until three years ago patients with this diagnosis only lived from three to six months, so they had no time to develop a decent reporting system." New therapies changed that and direct reporting is now vital. "There's no messing around anymore!"

Highlights from the ECCO2017 European Cancer Congress

The ECCO2017 European Cancer Congress, held at the end of January, attracted a multidisciplinary audience of oncologists of every specialty: scientists, nurses, primary care professionals, as well as patient advocates, government officials, policymakers and representatives from the ECCO Member Societies.

The Scientific Programme consisted of over 200 hours of sessions, more than 400 speakers and 762 abstracts submitted, out of which 625 were accepted. Significant studies were released during ECCO2017 congress, including:

- **Breath test could be used to detect deadly cancers.** A simple breath test, which has recorded 85% accuracy in trials, could make diagnosing stomach and oesophageal cancer easier. "A breath test could be used as a non-invasive, first-line test to reduce the number of unnecessary endoscopies. In the longer term this could also mean earlier diagnosis and treatment, and better survival."
- **Reconsidering mastectomies for some types of breast cancer.** Breast conserving therapy (BCT – breast conserving surgery combined with radiation therapy) is superior to mastectomy in certain types of breast cancer patients. "These results do not mean that mastectomy is a bad choice. For patients for whom radiotherapy is not suitable or feasible due to social circumstances, for whom the risk of late side effects of radiotherapy is high, or who have the prospect of a poor aesthetic outcome following BCT, a mastectomy may still be the preferable treatment option. The study showed that BCT is at least as good as mastectomy and that some patients might benefit more than others from BCT in the future."
- **Diabetes or its rapid deterioration can be an early warning sign for pancreatic cancer.** "Doctors and their diabetic patients should be aware that the onset of diabetes or rapidly deteriorating diabetes could be the first sign of hidden pancreatic cancer, and steps should be taken to investigate."

ECCO's ground-breaking work on quality cancer care resulted in two new papers just published in *Critical Reviews in Oncology/Hematology* and evaluated at the congress:

- **ECCO Essential Requirements for Quality Cancer Care: Colorectal Cancer**
- **ECCO Essential Requirements for Quality Cancer Care: Soft Tissue Sarcoma in Adults and Bone Sarcoma**

The ECCO2017 policy sessions brought government officials, EU as well as national policymakers, together with oncology experts and patient advocates, to discuss how to strengthen multidisciplinary practice to ensure optimal patient outcomes, as well as the challenges in cross-border cancer care. Expert patients contributed to several scientific sessions of ECCO2017, including the organ-based sessions on critical reviews of trials and implications in practice.

The new Primary Care track discussed integrated models of cancer management with the views of patient advocates on how to bring the wide range of primary care professions, including general practitioners, closer together with oncology specialists, to pave the patient's pathway. The Patient Advocacy track highlighted topical issues for patients and survivors, including side effects reporting, translating research into patient value and coping for caregivers.

We are proud that the ECCO2017 European Cancer Congress proved itself as the only truly multidisciplinary oncology congress in Europe, and hope for your active participation in the future.

Professor Peter Naredi – President of ECCO (2016/2017) and Professor of Surgery and Chairman of the Department of Surgery at the Sahlgrenska Academy, University of Gothenburg.

MADRID 2017 ESMO congress

esmocongress.org

ESMO 2017

Integrating science into oncology for a better patient outcome

MADRID SPAIN
8-12 SEPTEMBER 2017

CALL FOR ABSTRACTS

IMPORTANT DEADLINES

10 May 2017	Abstract submission
7 June 2017	Early registration
19 July 2017	Late-breaking abstracts
9 August 2017	Late registration

Organiser

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Partner

EACR
European Association for Cancer Research

Developing new drugs for children and adolescents with cancer

Stimulating development of more and better paediatric cancer drugs will be key to making progress, particularly in some of the hardest-to-treat childhood cancers. **Gilles Vassal,** past-President of the European Society for Paediatric Oncology, outlines emerging strategies to make this happen.

This grandround was first presented by Gilles Vassal, Director of Clinical Research at the Gustave Roussy Cancer Campus, Villejuif, France, as a live webcast for the European School of Oncology in collaboration with the European Society for Paediatric Oncology SIOPE. It is edited by Susan Mayor. The webcast of this and other e-sessions can be accessed at e-eso.net.

Cancer is a rare disease in children and young people in Europe, but around 6,000 die each year from the disease. It is the leading cause of death due to disease in children and young people over the age of one year, and is therefore an important public health issue.

Thirty-five thousand young people are newly diagnosed with cancer each year in Europe, of whom 15,000 are children under 15 and 20,000 are young people aged 15–24 years. Eighty percent of them are disease-free at five years across all cancers, with modern treatments and care by a multidisciplinary team.

This means there are currently 300,000 EU citizens who are childhood cancer survivors; about two-thirds of them have long-term side-effects, which are severe in around half.

Paediatric malignancies are different from adult cancers. The most frequent cancers in children are leukaemias, followed by central nervous system tumours and lymphomas. More than 60 different cancers occur from newborns to teenagers and beyond, but this number is much greater when considering the different molecular types of each cancer.

For example, there are four different subtypes of medulloblastoma, defined by their molecular biology, which have different prognoses and survival rates and require different treatments. This means that every cancer in a young person is either rare or extremely rare, which impacts on clinical research and the way in which new drugs are

Fighting for better treatments. Barriers to drug development in paediatric populations means that younger patients are failing to benefit from the new types of targeted drugs and immunotherapies that have been fuelling progress in adult cancers

developed for patients in this age group.

There are wide variations in survival rates for childhood cancer across Europe, underlining the importance of addressing inequality. Five-year survival is 10–20% lower in some countries than in others, with children in many eastern European countries doing particularly badly compared to others (*Lancet Oncol* 2014, 15:23–34).

Little progress has been made in hard-to-treat cancers in children over the last 10 years. Medulloblastoma, high-risk sarcoma and high-risk leukaemia, for instance, have shown no improvement in survival, and urgently require new drugs to improve outcomes.

This is why the European Society for Paediatric Oncology (SIOPE) has developed a strategic plan to improve the management of cancers in children and young people over the next 10 years (www.siope.eu/SIOPE_StrategicPlan2015/), with three key goals: to increase cure rates in patients with poor-prognosis malignancies, to improve quality of life in survivors, and to tackle inequalities.

The SIOPE strategic plan has seven objectives:

- Develop innovative therapies for high-risk malignancies.
- Develop and use precision medicine in routine clinical practice, including making use of molecular information from patients' tumours to drive treatment.
- Improve knowledge of tumour biology to inform treatment and to develop new drugs based on science.
- Provide equal access across Europe for essential medicines and for innovative therapies.
- Address cancers in teenagers and young adults, taking account of their special needs and working with a multidisciplinary team to provide the best quality of care for this age group.
- Improve quality of survivorship.
- Increase understanding of the causes of paediatric cancers, which is necessary to develop new treatments.

Question: Is there currently an issue regarding access to essential medicines in Europe compared to the rest of the world? Are there any countries in Europe that do not have access to essential cancer medicines for children?

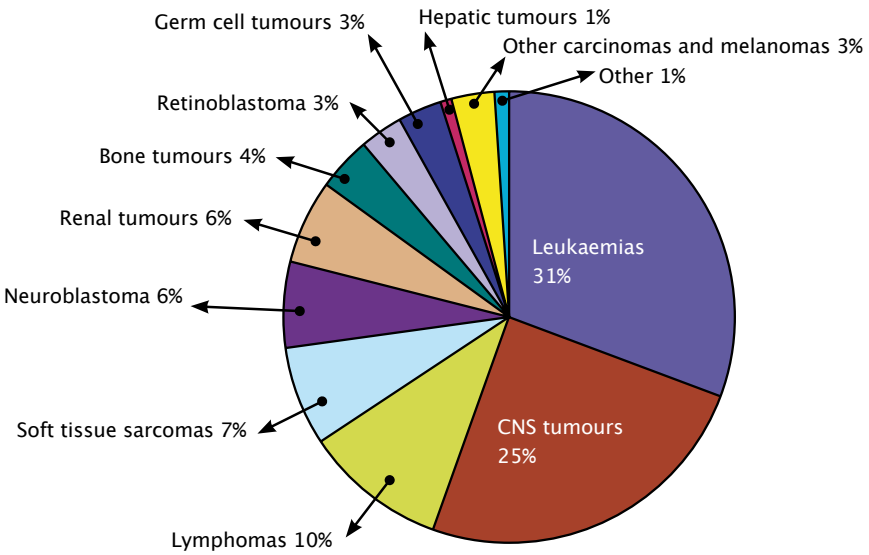
Answer: There shortages of older medicines, now produced as generics, in several countries in Europe and other areas. Shortages of these drugs jeopardise the treatment of children with cancer.

Question: With such a high cure rate for many paediatric tumours, is there still room for clinical research in some of these highly curable diseases, such as first-line leukaemias? Or should we focus research on hard-to-treat, relapsed or refractory tumours?

Answer: We definitely need to focus on cancers that are hard to treat at the moment. But treating patients within a prospective protocol is important because it provides the best quality of care and generates knowledge of these diseases, so integration of care and research adds value in paediatric oncology.

Question: What's the proportion of children compared to adults with

Paediatric cancers are different from adult cancers



More than 60 different malignancies can be found in young people, from newborns to teenagers and beyond – even more when molecular subgroups are taken into account. All childhood cancers are therefore rare or extremely rare

CNS – central nervous system

cancer that are treated at academic sites, and the proportion treated in private practice in clinical trials?

Answer: Most children (around 95%) and young people with cancer in Europe, are treated in public and university hospitals or cancer centres by paediatric oncologists. We have integrated clinical trials with routine care in paediatric oncology for many years, which means that more than 40% of children are included in clinical trials and more than 80% are treated and prospectively monitored based on standard of care protocols shared by all institutions. This is also a very good context in which to develop new drugs for children with cancer.

Question: What is the role of networking inside and outside Europe, considering that paediatric tumours are so rare? How does collaboration in research on childhood cancers compare with that in adult oncology where there are many more patients and greater opportunities for clinical trials.

Answer: Networking is absolutely crucial in paediatric oncology and has been essential to the significant progress that has been made over recent years. The only way forward to improve care and research is to run trials through co-operative groups at a European or global level rather than at a national level.

Drug development: strategy and organisation

There has been a real explosion in new oncology drugs approved for adults over the last few years, with 70 new drugs approved between 2011 and 2015. While most patients are still not cured of their cancer, and chemotherapy and radiotherapy remain the main modes of therapy, there has been real progress with new drugs based on increased understanding of cancer biology. For example, immunotherapy is completely changing the landscape, with activity across different cancers and offering effective treatment in patients with advanced disease.

PD-1 and PD-L1 blockade is relevant and effective in a wide range of different cancers (see figure opposite, *top*). An important question is whether these drugs are also effective in paediatric patients, bearing in mind that these cancers are biologically different from adult tumours, with a much lower rate of mutations (*Science* 2013, 339:1546).

These biological differences mean that some of the targets for cancer drugs in adults do not exist in children. However, we do have several examples of targets in adult cancers that are also relevant in children, with some shared alterations that can drive drug development. For example B-RAF, which is the target in B-RAF-mutated melanoma, is also mutated in some rare paediatric gliomas. The figure opposite (*bottom*) shows scans from a patient aged 2.5 years with a peduncular anaplastic BRAFV600 mutated ganglioma, demonstrating a major reduction of the tumour at 19 months after starting treatment with the B-RAF inhibitor vemurafenib.

There are three situations regarding the development of new anticancer drugs for children:

Diseases that are the same in adults and children. Examples include acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), osteosarcoma, and Ewing's sarcoma. Drug development should

occur across all age groups at the same time for these cancers.

Diseases are different but share common targets. The ALK mutation present in some adult lung cancers, for instance, is also present in some paediatric anaplastic large cell lymphoma (ALCL), neuroblastoma and inflammatory myofibroblastic tumours (IMT). The B-RAF mutation present in some adult melanomas is also present in some paediatric ganglioma and histocytosis.

Specific paediatric targets. These include the disialoganglioside GD2 in neuroblastoma, which is an exquisitely specific target that is now being investigated with an agent designed to target it.

Understanding cancer biology is essential for developing new drugs, and molecular information will increasingly be used for guiding treatment choice. Europe is ready to run a biology-driven new drug development strategy with well-organised networks.

The Innovative Therapies for Children with Cancer European Consortium (www.itcc-consortium.org) has been set up to carry out phase I and early phase II trials for drug registration. It is a consortium of 52 institutions in 13 countries across Europe and Israel, working in collaboration with other networks in specific cancers.

These networks include the IBFM Study Group in lymphoma and the SIOPE Brain Tumour Group. In addition, there is co-operation with groups in the US and globally, providing the scale to develop drugs for rare cancers.

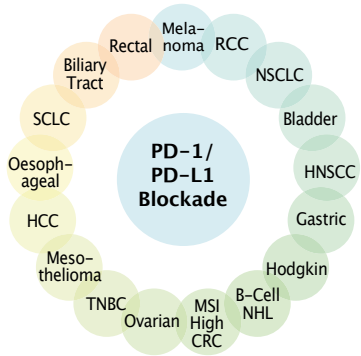
The strategy (see figure overleaf) is firstly to perform a tumour molecular profiling for each individual patient at relapse. Then clinical and biological data are collected in a large European database to generate new knowledge, targets and pathways.

Molecular profiling information in paediatric tumours is now being collected and matched to drug targets in four major studies in Europe as part of the ITCC Precision Cancer Medicine programme: INFORM (Germany); MAPPYACTS (France, Spain, Denmark and Italy), iTHER (Netherlands) and S-PED (UK). The number of phase I and phase II trials being conducted by the ITCC is increasing, and includes the MATRIX trial, providing rapid access to atezolizumab and cobimetinib, and the ESMART trial, which was launched in August 2016 with seven treatment arms based on five drugs provided by several companies for children with molecular alterations in relapsed cancers.

Question: How would you compare the collaboration between academic consortia and industry in paediatric oncology with that in adult cancers?

Answer: It's new for industry to work with paediatric oncologists and for paediatric oncologists to work with industry. This is a real opportunity to work out how best to collaborate together, along with parents and regulatory bodies, to develop new drugs in a way that may be different to the process in adult cancers. Co-operation is essential to do our best for the development of

Adult cancers that respond to PD-1/PD-L1 blockers

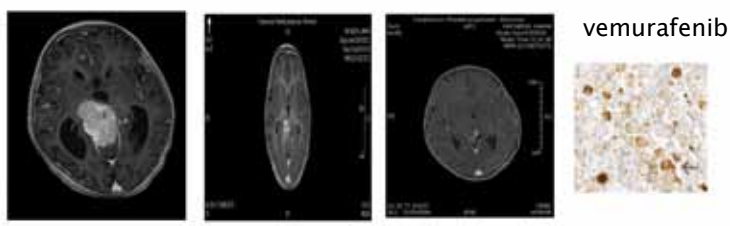


PD-1 and PD-L1 antibodies work in a wide range of adult tumours. Might they work in some paediatric cancers?

***RCC** – renal cell carcinoma, – **NSCLC** non-small-cell lung cancer, **HNSCC** – head & neck squamous cell cancer, **NHL** – non-Hodgkin lymphoma, **MSI** – microsatellite instability, **CRC**– colorectal cancer, **TNBC** – triple negative breast cancer, **HCC** – hepatocellular carcinoma, **SCLC** – small-cell lung cancer*

BRAFV600 inhibition in paediatric gliomas

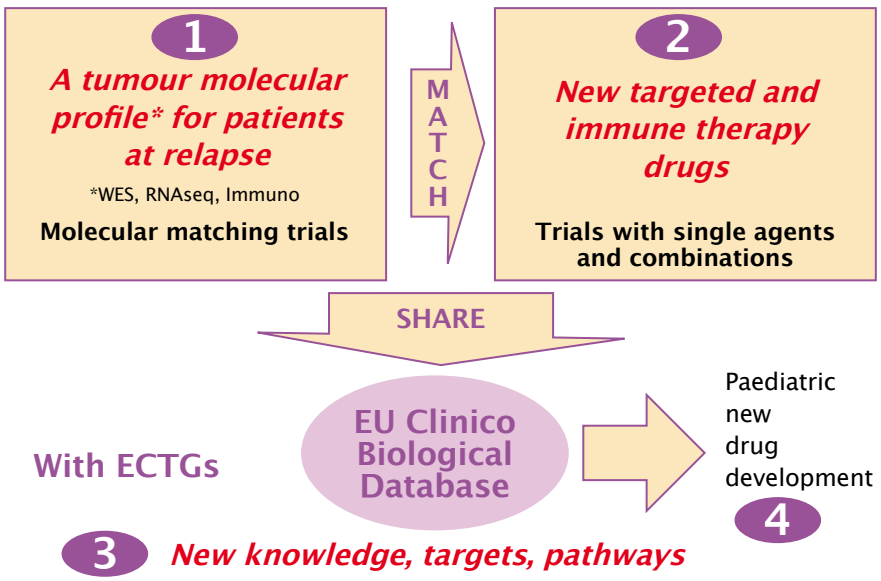
A 2.5-year-old girl with peduncular anaplastic *BRAFV600*-mutated ganglioma



Targets in adult cancers can also be relevant in children, as in the case of the B-RAF inhibitor vemurafenib, which was approved to treat B-RAF-mutated melanoma, but has also shown efficacy in children with BRAFV600-mutated gliomas

Source: F Bautista et al (2014) *Paediatric Blood Cancer* 61:1101-03, John Wiley and Sons

The innovative therapies and precision cancer medicine programme



WES – whole exome sequencing, ECTGs – European clinical trial groups

innovative treatments in childhood cancers, where patient populations are often small.

Question: The number of actionable targets is relatively limited in childhood cancers. How do you envisage giving access to innovative drugs where there is no molecular target yet identified, so these children can benefit?

Answer: Only 15–20% of children have alterations in tumours that are targets for drugs that we can identify at the moment. However, we have set up studies to provide access to treatments for children, whether their tumour has a drug target or not. This is because molecular alterations with targeted drugs, such as B-RAF or ALK, are very rare, so we are generating molecular information in all patients considered appropriate for treatment with innovative compounds.

Question: Development of single agents is necessary to study pharmacokinetics, efficacy and safety, especially in children. However, cancer requires multimodal treatment – radiation, surgery and combination chemotherapy. Combinations have been studied less in children than in adults. How can the development of combinations be accelerated?

Answer: We definitely need to accelerate the development of combination treatments. In the ESMART trial, six of the seven treatment arms are combinations including new drugs. We are moving to new types of trial, for example with the first cycle being single-agent therapy and the second cycle being combination therapy including new drugs. We need to carry out more trials with combination therapies and, in addition, move rapidly from trials in relapsed disease to first-line treatment trials. For example, we are currently running a trial in children with diffuse intrinsic pontine gliomas, introducing new drugs with radiotherapy at diagnosis.

Improving the regulatory environment

The current regulatory landscape for paediatric medicines was set out in EU regulations published in 2007 (http://ec.europa.eu/health/human-use/paediatric-medicines/index_en.htm). At that time, developments in new drugs for childhood cancers were based on drugs that were already available, with little input from pharmaceutical companies. Current approaches to develop innovative treatments require effective collaboration, working together more effectively to develop new drugs in paediatric oncology.

The 2007 regulations aimed to ensure high-quality research into the development of medicines for children and to ensure, over time, that the majority of medicines used by children are specifically authorised for such use. However, 50% of the drugs we currently use to treat children with cancer are used off-label. The regulations approved drugs for children at the time of submission for marketing authorisation in adults, based on the obligatory requirement for a paediatric investigation plan, which can be waived or deferred in certain cases. If completed, this allows for a six-month extension of market exclusivity, whatever the results.

This was a 'stick and carrot' system that clearly worked, illustrated by the increasing number of drugs available to the ITCC through paediatric investigation plans. A single drug (imatinib), when it was set up in 2003, increased to 12 drugs in 2013. However, only two new targeted drugs have been authorised for use in cancer in children over the last 10 years.

There are three key issues that need to improve in the regulatory environment. The first of these concerns unjustified class waivers, such as for crizotinib, which in Europe secured a waiver of the requirement to develop a paediatric investigation plan because the disease it treats (ALK-positive non-small-cell lung cancer) does not occur in children – even though a phase I trial in children showed responses in relapsed anaplastic large-cell lymphoma, inflammatory myofibroblastic tumours and neuroblastoma.

The European regulation ignored the fact that the drug could be active in malignancies other than lung cancer, including paediatric cancers.

The second regulatory issue that needs revisiting is where paediatric investigation plans prove unfeasible. The vemurafenib paediatric investigation plan, EMA/193393/2011, for example, was unable to recruit.

Thirdly, delays in starting paediatric drug developments also need to be addressed.

To improve the regulation of drugs in children, a working group has made a number of suggestions (*EJC* 2016, 62:1–8):

- Paediatric development should be based on a drug's mechanism of action instead of the adult indication.
- Drugs should be prioritised for evaluation in children according to the mechanism of action, needs and feasibility.
- Decisions should be made through a multi-stakeholder forum, using stronger biological and preclinical data.
- New incentives and rewards should be offered for developing new drugs for paediatric use, and measures introduced to reduce the time before starting paediatric drug development.

Conclusion

In summary, we need to improve the regulations for developing new drugs to treat children with cancer. In addition, we need a change in mind set, moving innovation in paediatric medicines from an issue of regulatory compliance to one of research and development, working collaboratively and facilitating referral of children to centres conducting relevant clinical trials. In addition, we need to invest in the development of new oncology drugs specifically for children.

OECI
Organisation of European Cancer Institutes

ecancermedicalscience

ESO Recommended

TJ Tumori Journal

Oncology Days

OECI 39

BRNO 2017
GENERAL ASSEMBLY, SCIENTIFIC CONFERENCES AND RELATED EVENTS

Brno, Czech Republic - June 21st-23rd
Hotel International

OECI Oncology Days 2017 Programme

Wednesday June 21st - All day

- **Pathology Day**
  N-1 trial consortium: collaboration among oncologists, pathologists, bioinformatics and ethics experts

Thursday June 22nd - All day

- **Scientific Conference**
  Rising cancer prevalence as emerging challenge for oncologists

Friday June 23rd - Morning

- **OECI General Assembly 2017**

10th ANNIVERSARY Oncology Days

For more information
www.oeci.eu/Brno2017.aspx

A TOUGH NUT TO CRACK

A man's prostate may be as small as a walnut,

but that doesn't mean it should be ignored

It is estimated that one in seven men will face some form of prostate cancer over their lifetime.

The majority of these prostate cancers are low risk, evolving slowly and rarely needing treatment or become life threatening. However, medium and high-risk cancers require immediate attention as soon as they are discovered. Early treatment is essential before they progress into metastasis, which can have fatal consequences. These early forms of cancer can often be symptomless, so it is essential to be vigilant. All men from the age of 45 should ask their doctor about a PSA blood test. The result can provide indication of their prostate's health and whether further testing is needed.

www.europa-uomo.org/awareness

EUROPA UOMO

Europa Uomo, the European Prostate Cancer Coalition is the umbrella organization for prostate cancer patients with members in 24 countries.

The role of Internet resources in clinical oncology: promises and challenges

Bradford Hesse and colleagues explore insights gained from over a decade of data gathered by the US National Cancer Institute to monitor changes in the communication environment regarding cancer-related information.

This is an abridged version of Bradford Hesse, Alexandra Greenberg and Lila Finney-Rutten (2016) The role of Internet resources in clinical oncology: promises and challenges. ***Nat Rev Clin Oncol*** *13:767–776, doi:10.1038/nrclinonc.2016.78. It was edited by Janet Fricker and is published with permission* © *Macmillan Publishers Ltd*

nature REVIEWS CLINICAL ONCOLOGY

Around the turn of the 21st century, anecdotal evidence suggested cancer patients were walking into doctors' offices armed with printouts downloaded from the World Wide Web. For clinicians, questions remained around whether patients benefited from accessing online resources or whether the unregulated nature of the Internet left them exposed to information of dubious origins.

In 1998, these questions were posed at the US National Cancer Institute (NCI) Conference on Risk Communication, and subsequently discussed in the 1999 *Journal of the National Cancer Institute* monograph (pp 124–133). The NCI set aside resources to stay 'ahead of the curve' by understanding how changes in the communication environment might be leveraged to improve oncology outcomes.

In 2001, the NCI launched the Health Information National Trends Survey (HINTS), a general population survey fielded to a representative sample of US adults aged 18 years and older to monitor changes in the communication environment regarding cancer information and to assess implications for oncology prevention and treatment (*J Health Commun* 2004, 9:443–460). Currently, seven iterations of HINTS exist: HINTS 1

(2003), HINTS 2 (2005), HINTS 3 (2007), HINTS 4 Cycle 1 (2011), HINTS 4 Cycle 2 (2012), HINTS 4 Cycle 3 (2013), and HINTS 4 Cycle 4 (2014).

When the first survey was developed in 2001, Internet communications were accessed through World Wide Web sites or email systems. Since then, subsequent versions of HINTS have expanded to include smartphones, social media applications, gaming systems, tablet computers, and a host of other mobile devices. Throughout the different surveys, HINTS has preserved the wording: "Have you ever gone online to access the Internet or World Wide Web, or to send and receive email?"

General Internet access

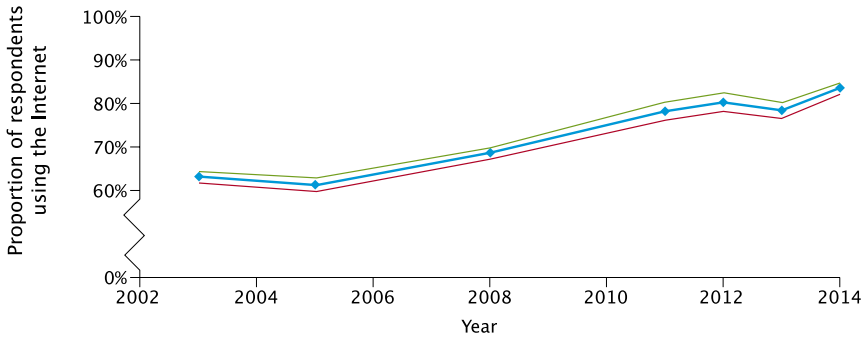
Between 2003 and 2014, HINTS surveys show the percentage of adults with Internet access rose from 63% to 83% (see figure). Analysis by sociodemographic characteristics reveals that education levels and age have a strong influence on Internet use, with sex, race and ethnicity playing lesser roles. Such trends reveal digital divides between individuals most likely to use Internet-based health communication and those most likely to forgo it.

Efficiencies can be gained from offering younger populations the ability to make appointments online, download medical records, receive electronic reminders when screening tests are due, and communicate electronically with healthcare teams.

Internet-averse populations have to be engaged proactively by telephone, text message, or through an assigned oncology nurse navigator.

The role of family members in supporting patients needs recognition.

Trend in Internet usage over time in the USA



Proportion of respondents to the National Cancer Institute Health Information National Trends (HINTS) survey answering 'yes' to the question: 'Have you ever gone online to access the Internet or World Wide Web, or to send and receive email?', 2002–2014 (with 95% confidence intervals). *Data available at http://hints.cancer.gov*

According to HINTS, in 2013 two-thirds of the online population reported looking for cancer or other medical information on behalf of someone else. Given the importance of social support, policy makers should consider ways of providing 'safe proxy access' to online oncology resources for designated family members or care givers.

Sources of cancer information used by the public

In 2003, HINTS showed that 49% of all respondents preferred to first consult their doctors for cancer information, while 34% preferred to use the Internet as their initial source of information. By 2013, the percentage of all respondents preferring to approach their doctor first increased to 56%, while the number indicating they would probably go online first fell to 26%.

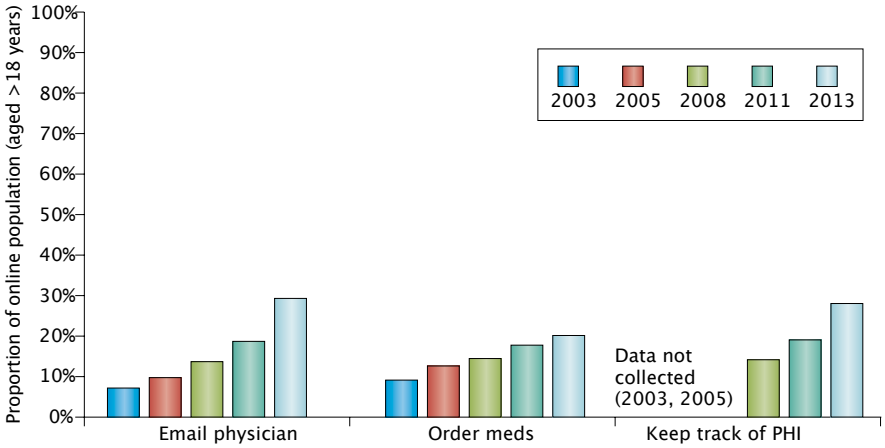
In 2003, among those who had actively searched for information on cancer, approximately 48% indicated they had used the Internet first, and only 7% had gone to their providers. By 2008, 55% reported searching the Internet first, and 23% relied on their doctor as the first port of call.

In spite of more people going online for cancer information before consulting healthcare providers, patients' indications of trust in their providers improved with time. Patients increasingly need help to interpret what they find online. Technical information posted on academic sites generally requires a college education, and can be filled with jargon, leaving many people with more questions than answers.

Use of health information repositories among cancer survivors

Cancer survivors are of particular concern to oncologists since they must choose between multitudes of care options after treatment has been completed. HINTS reveals that over the period 2003–2013, 69% of people with a personal cancer history reported proactively seeking information on cancer from any source, compared with 51% with a family history but no personal history, and 30% with no

Online consumer behaviour with regard to healthcare



Responses to successive Health Information National Trends (HINTS) surveys show that use of the Internet for healthcare purposes has increased steadily over time in the US population; however, the most recent data suggested that less than 30% of the population used the Internet to contact doctors or access personal health information (PHI), and less than 20% had ordered medications online. *Data available at http://hints.cancer.gov*

personal or family history.

The proportion of cancer survivors actively seeking information increased over time, rising from 66.8% in 2003 to 80.8% in 2013. Individuals seeking information were significantly more likely to be middle-aged (35–49 or 50–64 years old), better educated (college level), and earning more than US $75,000 per year. Survivors reporting going first to the Internet for information tended to be younger (aged 18–34).

In the 2011 HINTS survey, 4.7% of the sample (around 7.5 million people in the US) used the Internet to access online support groups for people with similar medical issues.

An electronic survey of new subscribers to the Association of Cancer Online Resources (ACOR) electronic mailing lists in 2005 showed that 62% of respondents used mailing lists to learn how to deal with their disease, 42% used online communities for social support, and 37% used mailing lists to help others. Over the past decade, online support options have increased, with cancer patients contributing to online video channels, blogs, discussion groups and other online social platforms.

Internet-based connection of patients with healthcare systems

While the transition to digital services in healthcare has been slower than in other industries, a public evolution has nevertheless occurred. In 2009, Congress passed the Health Information Technology for Economic and Clinical Health (HITECH) Act, outlining incentives for 'meaningful use' of health information technologies to improve healthcare. The act required institutions to demonstrate that 5% of patients had downloaded or viewed personal medical information and used emails to communicate with care teams. HINTS data showed that, between 2003 and 2013, email communications with doctors rose from 7% to 30%.

The proportion of patients accessing personal health information (PHI) through provider-sponsored patient portals increased from less than 15% of online adults in 2008 to almost 28% by 2013. The proportion of patients ordering medications online grew more slowly, with only around 20% of respondents with Internet access in 2013 indicating that they had purchased medications electronically.

A Department of Veterans' Affairs report concluded with "moderate strength" that secure messaging technologies improve healthcare requiring attentive self-management (e.g. diabetic glucose control) and patient satisfaction. The authors were unable, however, to conclude with certainty that patient-portal functionality leads to better health outcomes.

Kaiser Permanente in Hawaii found virtual consultations cut costs by reducing office visits (*Health Aff* 2009, 28:323–33). Patients generally report that increased communication options help them to better manage work and family lives (*Prostate Cancer Prostatic Dis* 2005, 8:189–93).

On the negative side, many doctors have not re-adjusted workflows to compensate for new channels of communication, and they find responding to emails occupies a considerable amount of their limited office hours.

Has the way patients access the Internet changed?

HINTS surveys tracked the way Internet access has changed from traditional dial-up access to cable broadband access, and finally access through mobile devices. HINTS is only just beginning to report on mobile apps.

A new generation of wearable devices

Take home message from the authors

Bradford Hesse and Alexandra Greenberg (*left and centre*) are affiliated with the Health Communication and Informatics Research Branch of the Behavioral Research Program, National Cancer Institute, Bethesda, Maryland, USA. Lila Finney Rutten (*right*) is at the Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, Minnesota USA



"Data collection has revealed a nuanced profile of how the public utilises online information about cancer. Although patients' ratings of trust in their own physicians have remained high, the majority of patients and their families admit going to the Internet first for cancer information. The implication is that Internet-based resources are gradually becoming part of the fabric in which patients and their providers live and communicate. But these changes are not entirely predictable. When the NCI launched HINTS in 2001, social media and smart phones did not exist. Now we are tracking a rapid diffusion of mobile devices accelerating our ability to deliver care at a 'point of need' rather than a 'point of care'. Such changes allow oncologists to innovate the ways in which they conduct their practice, with further changes expected as patients' access to personal medical information improves.

Implications for clinical practice

Clinicians need to embrace the fact that many patients make sense of their conditions by reaching out to other patients through social media, using online news sources and engaging in patient portals. Such activities can enhance shared decision making. Many clinicians have been experimenting with providing patients with 'information prescriptions', directing them towards credible, trustworthy sites online. It should be recognised that not all patients can utilise these resources equally, and that older and less educated populations still require traditional communication. Due to the rapid evolution of computational processing power and spread of interconnectivity, medicine is becoming more predictive, pre-emptive, personalised and participative than ever before. To take full advantage of these opportunities, the oncology community needs to be innovative.

Further studies

We echo the US President's Cancer Panel which, on 15 November 2016, declared 'The time is now' to take advantage of the growing role of technology in society to connect cancer patients to the knowledge, information, and people to ensure more effective delivery of care. The Panel prioritised three research areas:

- Electronic connectivity to achieve more effective teamwork in healthcare. Here 'distributed cognition' allows machine learning to complement human learning in delivering timely information to cancer patients.
- Identification of strategies to enhance individual patient engagement. Healthcare-engaged patients are less expensive to treat and have better outcomes than their disengaged counterparts.
- The creation of environments where data can be collected from patients passively or through patient reported outcomes to contribute to scientific studies."

and sensors is being introduced to extend remote monitoring capabilities of Internet technologies to the home and workplace, and even allow use during travel.

In one study of patients with head and neck cancer, researchers used home-based sensors and wearable devices to monitor for dehydration during radiation therapy by capturing data on weight, blood pressure, pulse and patient-reported outcomes (*J Natl Cancer Inst Monogr* 2013, pp 162–168).

ASCO's 2015 review of mobile apps relevant to oncology documented 389 apps spanning the oncology continuum from primary prevention (smoking cessation, nutrition, and sun protection), screening (with breast and cervical cancer screening most used), diagnosis (36 apps for patients, 35 for physicians, 1 for both) to treatment (33 apps for patients, 28 for providers). The researchers concluded that efficacy data is currently lacking.

Anticipated trends: 2015–2025

We predict the following trends:

- Advances in telemedicine, eHealth, mHealth (health applications

delivered through mobile devices), medical informatics and wearable sensors will enable patients to feel fully connected to healthcare teams.

- Increased access to Internet resources from mobile phones means that people no longer need to be 'anchored' to desktop computers to send or receive messages, make appointments or get answers to questions. 'Just in time' interventions can provide prompts to change unhealthy behaviours (for example quitting smoking), and mobile reporting can be used for adverse events in home environments. Notably, patients with advanced-stage lung cancer, who were receiving palliative care, had a two-month survival benefit when adverse systems and complications were reported via mobiles to clinicians (*J Am Med Inform Assoc* 2008, 15: 679–86).
- Wearable devices can help oncologists monitor physical activity and nutritional habits, with potential for portable saliva readers to assess biochemical responses to treatment. The FDA will take responsibility for regulating medical devices where impaired function would lead to physical danger.
- Mobile Internet devices with passive and active data-collection can help patients contribute data to research projects on symptoms, treatment, lifestyles and adverse effects.
- The Internet can offer social support for complex emotions that are experienced throughout the cancer journey.

Conclusions

Lessons from observations of the unfettered Internet are that simple exposure to health information is insufficient to support improved oncology care. Well intentioned websites presenting information in a way that is too technical for the average patient can result in confusion. But if successful, Internet efforts can lead to a new era in clinical oncology, where evidence-based information is presented to every member of the care team as well as patients and their families, precisely when needed, in order to allow full multidisciplinary participation.

FOR PATIENTS REQUIRING G-CSF THERAPY

The #1 prescribed daily G-CSF in Europe and the first FDA-approved Biosimilar[1,2]

- More than 6 years of real-world clinical experience in neutropenia management and mobilisation of peripheral blood progenitor cells[3–8]
- Proven efficacy and safety profile[3–8], more than 9.4 Million patient-days exposure[2]
- A high quality G-CSF[9], manufactured by Sandoz, the pioneering leader in biosimilars[4,10,11]

ZARZIO® filgrastim

TRUSTED EXPERIENCE

1. Aapro MS, et al.; Eur J Cancer. 2011; 47: 8–32. **2.** Sandoz data on file, US Brand name: Zarxio® (filgrastim-sndz). **3.** Zarzio® Summary of Product Characteristics. **4.** Gascón P, et al.; Support Care Cancer 2013; 21(10): 2925-2932. **5.** Vercpoort K, Mohler TM. Ther Adv Med Oncol 2012; 4(6): 289-293. **6.** Salesi N, Di Cocco B, et al.; Future Oncol 2012; 8(5): 625-630. **7.** Bonig H, et al.; Transfusion 2015; 55: 430–439. **8.** Gascón P, et al.; Cancer Res 2015; 75: P5-15-19. **9.** www.sandoz.com, accessed 26 May 2015. **10.** Sorgel F, et al.; Biodrugs 2010; 24(6): 347-357. **11.** Gascon P, et al.; Ann Oncol 2010; 21(7): 1419-1429.

ABBREVIATED Prescribing Information. Zarzio® (Filgrastim). Zarzio® (Filgrastim) Abbreviated Prescribing Information. Please refer to the Summary of Product Characteristics before prescribing Zarzio®. Zarzio® is a recombinant human Granulocyte-Colony Stimulating Factor (G-CSF). **Presentations:** 30 MIU/0.5 ml and 48 MIU/0.5 ml solution for injection or infusion in pre-filled syringe. **Indications:** Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia. Mobilisation of peripheral blood progenitor cells (PBPC). In children and adults with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of ≤0.5 x 10^9/l, and a history of severe or recurrent infections. Treatment of persistent neutropenia (ANC ≤ 1.0 x 10^9/l) in patients with advanced HIV infection. Please refer to the Summary of Product Characteristics for full prescribing indications. **Administration:** Zarzio® should only be given in collaboration with appropriate and experienced specialist centres with the necessary facilities. If required, Zarzio® may be diluted in glucose 50 mg/ml (5%) solution; see Summary of Product Characteristics for details. *Established cytotoxic chemotherapy:* Subcutaneous injection or intravenous infusion (over 30 mins). *Patients treated with myeloablative therapy followed by bone marrow transplantation:* Intravenous short-term infusion (over 30 mins) or a subcutaneous or intravenous continuous infusion over 24 hours. *Mobilization of PBPC:* Single day subcutaneous injection (5-7 consecutive days) or subcutaneous continuous infusion over 24 hours. *Severe chronic neutropenia (SCN)/HIV infection:* Subcutaneous injection. **Dosage:** For the approved indications the typical dosage range is from 0.3 MU/kg/day to 1.2 MU/kg/day. For the detailed instructions on dosage, please refer to the Summary of Product Characteristics. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions:** Special warnings: Zarzio® should not be used to increase the dose of cytotoxic chemotherapy beyond established posology regimens. Zarzio® should not be administered to patients with severe congenital neutropenia who develop leukaemia or have evidence of leukaemic evolution. Established cytotoxic chemotherapy: *Malignant cell growth:* Zarzio® is not indicated for use in patients with myelodysplastic syndrome or chronic myelogenous leukaemia. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia. Caution should be taken in patients with secondary acute myelogenous leukaemia (AML). Safety and efficacy of filgrastim administration in *de novo* AML patients (55 years with good cytogenetics (t(8;21), t(15;17), and inv(16)) have not been established. *Leucocytosis:* White blood cell counts should be performed at regular intervals during therapy. If leukocyte counts exceed 50 x 10^9/l after the expected nadir, Zarzio® should be discontinued immediately. For PBPC mobilisation, Zarzio® should be discontinued or reduced if the leukocyte counts rise to >70 x 10^9/l. *Risks associated with increased doses of chemotherapy:* Intensified doses of chemotherapeutic agents may lead to increased toxicities including cardiac, pulmonary, neurologic, and dermatologic effects (please refer to the Summary of Product Characteristics of the specific chemotherapy agents used). Regular monitoring of platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia. *Other special precautions:* In patients with reduced precursors, neutrophil response may be diminished (see Summary of Product Characteristics for details). There have been reports of Graft versus Host Disease (GvHD) and fatalities in patients receiving G-CSF after allogeneic bone marrow transplantation (refer to Summary of Product Characteristics). Mobilisation of PBPC: *Prior exposure to cytotoxic agents:* After extensive myelosuppressive therapy, Zarzio® may not show sufficient mobilisation of PBPC to achieve the recommended minimum yield or acceleration of platelet recovery (see Summary of Product Characteristics for details). *Assessment of progenitor cell yields:* Results of flow cytometric analysis of $CD34^+$ cell numbers vary depending on the precise methodology used, therefore, recommendations of numbers based on studies in other laboratories need to be interpreted with caution (see Summary of Product Characteristics for details). *Normal donors prior to allogeneic PBPC transplantation:* Only to be considered in normal donors for the purpose of allogeneic stem cell transplantation. Thrombocytopenia has been reported very commonly in patients receiving filgrastim. Platelet counts should therefore be monitored closely. Transient thrombocytopenia following G-CSF administration and leukapheresis has been observed (see Summary of Product Characteristics for further details). Zarzio® should be discontinued or the dose reduced if the leukocyte counts rise to >70 x 10^9/l. Donors who receive G-CSFs for PBPC mobilisation should be monitored until haematological indices return to normal (see Summary of Product Characteristics for details). Transient cytogenetic modifications have been observed in normal donors following G-CSF use. Spleen size should be carefully monitored. A diagnosis of splenic rupture should be considered in donors and/or patients reporting left upper abdominal pain or shoulder tip pain. *Recipients of allogeneic PBPCs mobilised with Zarzio®:* Immunological interactions between the allogeneic PBPC graft and recipient may be associated with an increased risk of acute and chronic GvHD when compared with bone marrow transplantation. *SCN: Blood cell counts:* Thrombocytopenia has been reported commonly in patients receiving filgrastim. Platelet counts should be monitored closely, especially during the first few weeks of therapy. Consideration should be given to intermittent cessation or decreasing the dose in patients who develop thrombocytopenia. Other blood cell changes occur, including anaemia and transient increases in myeloid progenitors, which require close monitoring of cell counts. *Transformation to leukemia or myelodysplastic syndrome:* Special care should be taken in the diagnosis of SCNs to distinguish them from other haematopoietic disorders. Complete blood cell counts with differential and platelet counts, and an evaluation of bone marrow morphology and karyotype should be performed prior to treatment. It is recommended to perform morphologic and cytogenetic bone marrow examinations in patients at regular intervals (approx. every 12 months - see Summary of Product Characteristics for details). *Other special precautions:* Causes of transient neutropenia, such as viral infections should be excluded. Splenic enlargement is a direct effect of G-CSF and spleen size should be monitored regularly. Regular urine analyses should be performed to monitor haematuria/proteinuria. The safety and efficacy in neonates and patients with autoimmune neutropenia have not been established. HIV infection: *Blood cell counts:* ANC should be monitored closely, especially during the first few weeks of Zarzio® therapy (see Summary of Product Characteristics for details). *Risk associated with increased doses of myelosuppressive medicinal products:* Regular monitoring of blood counts is recommended (see Summary of Product Characteristics for details). *Infections and malignancies causing myelosuppression:* The effects of G-CSF on neutropenia due to bone marrow infiltrating infection or malignancy have not been well established (see Summary of Product Characteristics for details). Other special precautions: Pulmonary adverse reactions such as interstitial pneumonia have been reported following G-CSF treatment, and patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk. Monitoring of bone density may be indicated in patients with underlying osteoporotic bone diseases who undergo continuous therapy with Zarzio® for more than 6 months. Physicians should exercise caution when considering the use of Zarzio® in patients with sickle cell disease and carefully evaluate the potential risks and benefits of treatment (see Summary of Product Characteristics for details). Capillary leak syndrome has been reported after G-CSF administration and patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions. Excipients: Zarzio® contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not use Zarzio®. In order to improve the traceability of G-CSFs, the trade name of the administered product should be clearly recorded in the patient file. **Interactions:** Use is not recommended in the period from 24 hours before to 24 hours after myelosuppressive cytotoxic chemotherapy. Preliminary evidence from a small number of patients treated concomitantly with G-CSF and 5-fluorouracil indicates that the severity of neutropenia may be exacerbated. Possible interactions with other haematopoietic growth factors and cytokines have not yet been investigated in clinical studies. Lithium is likely to potentiate the effect of G-CSF. **Pregnancy and lactation:** There are no or limited data in pregnant women available. There are literature reports where the transplacental passage has been demonstrated. Animal studies show no evidence of teratogenicity. Zarzio® should be used in pregnancy only if the expected benefit outweighs the potential risk to the foetus. Use whilst breast-feeding is not recommended. **Effects on ability to drive and use machines:** Zarzio® has no or negligible influence on the ability to drive or use machines. **Undesirable effects:** In cancer patients, the most frequent undesirable effects were musculoskeletal pain which was mild or moderate in 10%, and severe in 3% of patients. GvHD has also been reported. In PBPC mobilization in normal donors the most commonly reported undesirable effect was musculoskeletal pain. Leucocytosis was observed in donors and thrombocytopenia following G-CSF and leukapheresis was also observed in donors. Splenomegaly and splenic rupture were also reported. Some cases of splenic rupture were fatal. In SCN patients the most frequent undesirable effects attributable to G-CSF were bone pain, general musculoskeletal pain and splenomegaly. Myelodysplastic syndromes (MDS) or leukaemia have developed in patients with congenital neutropenia treated with G-CSF (see Summary of Product Characteristics for details). Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported uncommonly (≥ 1/1000 to < 1/100) in cancer patients undergoing chemotherapy and healthy donors undergoing peripheral blood progenitor cell mobilisation following administration of G-CSFs (see Summary of Product Characteristics for details). In clinical studies in patients with HIV, the only undesirable effects that were consistently considered to be related to G-CSF administration were musculoskeletal pain, bone pain and myalgia. **List of excipients:** Glutamic acid, sorbitol (E420), polysorbate 80, water for injections. **Shelf life:** 36 months. **Special precautions for storage:** Store in a refrigerator (2°C-8°C). Keep the pre-filled syringe in the outer carton in order to protect from light. Within its shelf-life and for the purpose of ambulatory use, the patient may remove the product from the refrigerator and store it at room temperature (not above 25°C) for one single period of up to 72 hours. At the end of this period, the product should not be put back in the refrigerator and should be disposed of. **Nature and contents of container:** Pre-filled syringe (type I glass) with injection needle (stainless steel), with or without a needle safety guard, containing 0.5 ml solution. The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex; see Summary of Product Characteristics for details). Pack sizes of 1, 3, 5 or 10 pre-filled syringes. Not all pack sizes may be marketed. **Legal category:** Medicinal product subject to restricted medical prescription. **MA numbers:** EU/1/08/495/001, EU/1/08/495/002, EU/1/08/495/003, EU/1/08/495/004, EU/1/08/495/005, EU/1/08/495/006, EU/1/08/495/007, EU/1/08/495/008, EU/1/08/495/009, EU/1/08/495/010, EU/1/08/495/011, EU/1/08/495/012, EU/1/08/495/013, EU/1/08/495/014, EU/1/08/495/015, EU/1/08/495/016. Availability of pack sizes may vary between individual EU member states. **MA holder:** Sandoz GmbH, Biochemiestr. 10, A-6250 Kundl, Austria. Further information is available from: Sandoz International GmbH, Industriestr. 25, 83607 Holzkirchen, Germany. Additional information may be obtained also from your local Sandoz office. **Last revision of text:** December 2014

SANDOZ
a Novartis company

Farewell to chemotherapy?

With all the good news about precision medicine, it can be difficult to explain why many patients are still being treated with expensive and toxic drugs that do not benefit them. **Pia Heinemann**, science editor for the German newspaper *Die Welt*, won the 2016 Cancer World Best Reporter prize for an article, republished below, that helped readers make sense of the complex reality.

Chemotherapy. That's the word Jana Hermann doesn't want to hear under any circumstances. She has breast cancer; she received the diagnosis four weeks ago. She underwent surgery to remove one of her breasts and five lymph nodes. The tissue was sent off to pathology; the 53-year-old was discharged from hospital with pain that was not as bad as she had feared.

Two weeks later, the tumour tissue and the lymph nodes have been examined, the multidisciplinary team has met, and Jana Hermann is sitting in her doctor's office. She looks at him. He is studying his computer screen, running over her medical records – and he says: "chemotherapy".

Marion Kiechle encounters this situation 200 times a year – but from the other side of the desk. She is medical director of the Women's Hospital of the Technical University of Munich, and she knows how hard it is for doctors to give bad news to their patients. "Chemotherapy puts an enormous strain on patients," says Kiechle, "and most of them are very fearful." She recommends chemotherapy only if it is absolutely necessary – as a last resort in fighting the cancer.

Cytotoxic drugs are designed to destroy rapidly

"Breast cancer patients can now be tested to determine whether or not chemotherapy is necessary"

proliferating cancer cells – but they are very non-specific and also attack other rapidly multiplying cells. Because of this, patients lose their hair, suffer from nausea, and sometimes their blood count falls. Patients cannot hide the fact that they are having chemotherapy: everyone can see that they have cancer. But most patients want to hide their illness. Jana Hermann is not using her real name. She does not want people who know her to find out that she has cancer. "Chemotherapy," says Kiechle, "can easily become a stigma." That is why she talks to her patients about a test that can determine whether chemotherapy is a sensible option for them. Such a test could save many patients from undergoing the harsh treatment.

Every year almost 500,000 people in Germany are diagnosed with cancer. Half of them get away with surgery alone. But of those for whom surgery is not sufficient, many can only hope that their lives will be prolonged if they take the hard chemotherapy route. 'Chemo' is the treatment of choice if the cancer is at an advanced stage, if it has spread, or if it is aggressive. But although the cytotoxic drugs that are used have improved significantly in recent years and the side effects have been reduced, many patients still find the treatment worse than the cancer itself.

Scientists have therefore been trying for decades to reduce the side effects of chemotherapy and find entirely new ways of treating tumours. They are also trying to develop tests that indicate whether a cancer patient really needs chemotherapy – or whether a different type of treatment would be preferable.

Breast cancer patients like Jana Hermann can now be tested to determine whether or not chemotherapy is necessary. In Germany alone, about 15,000 breast cancer patients a year could in future be spared chemotherapy. In other areas of oncology, too, diagnosticians are attempting to test the molecular characteristics of different tumours to design tailored treatments for each patient.

Developing the right tests and treatments will be a major challenge for the coming decades. If the researchers fail, the costs to the healthcare system will be enormous.

Sort it out! Heinemann's article, published in *Welt am Sonntag*, highlighted the growing importance of genomic testing to avoid over-treatment, and flagged up flaws in the way access to tests is being rolled out in Germany

And patients will have to endure unnecessarily harsh treatments.

"In our society, the female breast is incredibly important – it is a key part of our culture," says Werner Schlake. He is a reticent man, who prefers to talk about the subject face-to-face rather than on the phone. Schlake – who has white hair, a white beard and glasses – is a pathologist in the city of Gelsenkirchen. He is one of around 1,800 pathologists in Germany, and president of the German pathologists' association, the BVDP. Right now he is furious, because the test that could spare thousands of women chemotherapy is not being offered as standard in Germany.

"Two hundred and fifty years ago, pathologists made their diagnosis with the naked eye," says Schlake. Then microscopy came along. "We pathologists start off by getting a tissue sample, a piece taken from the tumour.

It looks like a worm, two or three centimetres long." This sample is first examined macroscopically by the experts at the pathology institute. Then it is cut into wafer-thin slices, treated with various dyes, and examined under the microscope. The pathologist is looking for specific cell structures. In the pathology lab, each patient's cancer is classified.

"But now," says Schlake, tapping the table top, "now we can even examine the molecular level." In recent years tests have become available that indicate which genes are active in the cancer tissue. Experts call these tests "gene expression tests," and the ones that have been licensed now include MammaPrint, Oncotype, Endopredict and Prosigna.

With breast cancer in particular, says Schlake, the correct diagnosis is vital: a lot hinges on it. "The pathologist makes the diagnosis. Cancer or not, aggressive or not." Only with the correct diagnosis can the doctors select the right therapy – they must decide whether the patient needs radiotherapy or chemotherapy, or whether standard hormone treatment would be sufficient.

The gene expression tests provide the basis for this decision – or rather, this is what they must do in future. At present many breast cancer patients do not get these tests. That is why Schlake is so angry – because there have been great advances in pathology, but patients are not benefiting as they should.

"There have been great advances in pathology, but patients are not benefiting as they should"

Germany's joint federal committee of health insurance providers approved the gene expression tests on August 10th 2016 – but only for 'outpatient specialty medical care' (Ambulante Spezialfachärztliche Versorgung, or ASV). All patients who want to have the test in ASV can have the cost met through their compulsory health insurance scheme. "That's great," says Werner Schlake – he pauses, leans back, leans forward again – "but it is also a scandal," – because ASV requires certain structures. Established cooperation partners, such as a pathologist and a clinic, must work together and set up a unit to ensure that patients can be cared for outside the hospital system. But these ASV units that would enable every patient to access the tests don't yet exist.

The gynaecologist Marion Kiechle says that, even in hospitals, the test could in fact be used for all patients. "But we can't charge health insurers for them." The tests, which cost roughly €44 million a year, but would cut the cost of unnecessary chemotherapy by €145 million, have to be cross-financed. The hospital therefore re-allocates unspent money earmarked for other treatments and uses it for the tests.

"The tests cost roughly €44 million a year, but would cut the costs of unnecessary chemotherapy by €145 million"

It is not only pathologists like Schlake who are infuriated by this. The introduction of the gene expression tests that could spare patients unnecessary suffering, while also cutting the cost to the healthcare system, reveals a fundamental flaw in Germany's health insurance legislation.

The lawmakers' aim is to facilitate patients' transition from hospital to outpatient care. At the same time, the intention is to relieve the financial burden on hospitals – which at present are unable to pay for the tests via their charging system. But because the system has not yet been established, patients can get the tests only at breast centres or specialist hospitals like the one Marion Kiechle manages in Munich.

And yet so many patients could benefit: Schlake picks up a piece of paper on which a map of Germany is printed in red. The number '74,500' is printed on it in bold type. That is the number of new cases of breast cancer in Germany each year. One-third of those diagnosed cannot avoid having chemotherapy, because it is absolutely necessary, Schlake says. Another third definitely do not need chemotherapy. "But until now we have been uncertain about the final third." The number '22,000' is accompanied by a prominent red question mark. These 22,000 patients are usually recommended by their doctors to have chemotherapy. Over-treatment is unpleasant, but not normally fatal.

However, researchers and physicians now know that two-thirds of these 22,000 patients do not in fact need chemotherapy. Even without it they will not develop metastases. "And it is these 14,500 patients that we can

now identify", says Schlake. Tissue that until a few years ago was hard to classify can be classified precisely with gene expression tests.

"Tissue that until a few years ago was hard to classify can be classified precisely with gene expression tests"

Carsten Bokemeyer is another person who believes in the new world of testing. An oncologist, he is director of Medical Clinic no. II at Hamburg University Hospital in Eppendorf, and chairman of the German Society of Haematology and Medical Oncology. "For the 'right' patients, the new molecular tests enormously enhance the effectiveness of cancer treatment," he says.

X-rays of lung cancer patients regularly prove to him what is possible. The cancer cells that show up as light in colour on the X-ray before treatment start to vanish within a few days of therapy. "They just seem to dissolve," says Bokemeyer.

The new anti-cancer drugs can be divided into several groups. The first group consists of 'small molecules'. These are so tiny that they can penetrate the cell surface and dock onto certain structures. This interrupts signal transmission in the cancer cell: the cell can no longer divide and tumour growth is halted.

Another group involves tyrosine kinase inhibitors, which have been called a "Lazarus drug" – a treatment that can raise the dead – because of their effect on lung cancer patients who have a specific genetic mutation. They can have a similarly miraculous impact on other types of cancer. Imatinib (Glivec) is one example: for patients with chronic myeloid leukaemia, this is a wonder drug. Before its invention, very few drugs were available to these patients, and many died. The substance can block the modified blood stem cells so effectively that the disease can now be virtually cured.

In passive immunotherapy, another new treatment method, antibodies are produced that can recognise structures on the surface of cancer cells. They then block these structures and, through various mechanisms, cause the cells to die or prevent them multiplying further. These "designer antibodies" are now being used to treat breast cancer as well as colon cancer, lymphoma and other malignancies. "For example, in a typical case of lung cancer caused by smoking, the cancer cells display a lot of changes in their genetic makeup," explains Bokemeyer. "These tumours behave particularly aggressively. Here the molecularly targeted drugs rarely work, but patients can benefit from active immunotherapy involving what are known as checkpoint inhibitors."

Carl June of the University of Pennsylvania has helped active immunotherapy achieve a breakthrough. The doctor has spent more than 20 years working on ways of activating the patient's immune system so that it targets cancer cells in the patient's body. Normally cancer cells disguise themselves and tell the immune system that they are perfectly normal body cells, thereby protecting themselves from attack. But in pioneering studies, the American doctor was able to show that it is possible to take immune cells from the patient's blood and modify them genetically in the lab so that when they are returned to the blood they are able to recognise cancer cells and destroy them.

"In cancer cells displaying a lot of genetic changes, targeted drugs rarely work, but patients can benefit from immunotherapy"

Among the patients he treated was Emily Whitehead, a young girl who was diagnosed with acute lymphatic leukaemia (ALL) on May 28th 2010, a few days after her fifth birthday. She had chemotherapy for 26 months. The doctors gave her an 85–90% chance of a cure if the chemotherapy was effective. But eighteen months later the cancer was back. Emily's chance of recovery dropped to 30%. She received a second course of chemotherapy and was about to undergo a bone marrow transplant when, two weeks before the planned transplant, she suffered another relapse. A third course of chemotherapy failed. Eventually it was suggested to Emily's parents that Dr June might be

able to help their daughter, and so the child took part in a highly experimental study. In April 2012 she received genetically modified immune cells. A few months later it was clear that the active immunotherapy was working. The cancer cells were no longer able to hide from Emily's immune system and they were destroyed. Emily left hospital in June 2012. She is now eleven years old – and still well.

"We are learning that some substances work very well for certain cancer patients but not for others with the same kind of tumour"

"We are learning that some substances work very well for certain cancer patients but not for others with the same kind of tumour," says Carsten Bokemeyer, the oncologist from Hamburg. Active immunotherapy is highly successful for lung and kidney cancer, malignant melanoma and certain types of lymphoma. It is also likely to be approved for bladder, gastric and breast cancer. "But each of the new treatments has advantages and disadvantages. For example, passive immunotherapy is effective for colon and lymphatic cancer, but it requires two to four months to take effect," says Bokemeyer. For other types of cancer, tests must be performed before treatment starts, to identify which drugs can even be considered.

At present the new treatments that can supplement or replace chemotherapy are being applied only sporadically. "In Germany, between 10,000 and 15,000 people per year could benefit from modern antibody immunotherapy," says Bokemeyer. That is 15,000 people who doctors have until now often been unable to help.

One of the reasons why more patients are not benefiting from the new therapies is that they are very expensive. Of the €5 billion that are spent on treating compulsorily insured patients each year, more than €1.5 billion is already accounted for by the modern drugs – even though they make up considerably less than a quarter of prescriptions.

Another reason is that the new drugs have not yet been sufficiently tested, and are only approved for special applications.

The new targeted drugs can also have serious side effects such as nausea, vomiting, and blood disorders. Doctors are therefore only allowed to prescribe them if the patients have been tested to check that the treatment will be effective.

Choosing the right therapy for each patient will be an enormous challenge in the coming years. "If we choose wisely, we will be able to significantly increase the survival of many cancer patients and avoid subjecting others to unnecessary treatment," says Bokemeyer. "Otherwise, in using the new substances we will simply be burdening patients with side effects – and imposing costs on the healthcare system."

But it is not only funding that presents problems for modern oncology. Every week, the results of new studies are published, reporting further advances in oncology – basic research is making enormous progress. But nobody yet knows whether this progress will have a lasting effect on patients. There are not enough data. We do not yet have the long-term studies that would show whether a new treatment really prolongs patients' lives.

"If we choose therapies wisely, we will be able to significantly increase the survival of many cancer patients and avoid subjecting others to unnecessary treatment"

There are lots of highly specific drugs, but patients cannot be tested to see whether the drugs are an option for them. The international consulting company IMS Health estimates that, by 2020, tests will only be available for a third of the new drugs that are coming on the market.

The era of precision medicine, in which exactly the right drug can be found for each patient, is only just beginning.

Jana Hermann's tissue samples were analysed in a gene expression test. She didn't discover that until she asked. Her doctor hadn't wanted to raise false hopes. Because for Jana Hermann, there is no alternative to chemotherapy.

This article was first published in *Welt am Sonntag* on 18 September 2016, and is reprinted with permission.

1ST EUROPEAN CANCER NURSING DAY - MAY 18TH 2017

Recognising the Importance of Cancer Nursing

RECOGNISING EUROPEAN CANCER NURSING

RECaN

EUROPEAN ONCOLOGY NURSING SOCIETY

The theme of the inaugural European Cancer Nursing Day will be Advocacy, based on the EONS strategic **CARE** plan

For further information please visit:
www.europeancancernursingday.eu or www.cancernurse.eu

CELEBRATE WITH US; YOU ARE ALL INVITED!!

A breakthrough business model for drug development

Anna Wagstaff looks at changes in the business, regulatory and science arenas that could open the way to delivering better cancer treatments, faster and cheaper.

- **Of 91 new therapies approved for solid tumours between 2002 and 2016, the median reported gain in overall survival was 2.2 months.**
- **Cancer drugs costs are rising five times faster than any other class of medicine.**
- **Eight cancer drugs approved in 2015 have an annual cost of more than $100,000 per patient.**
- ***Forbes* analysis of average profit margins by sector consistently shows health technology topping the league table.**

The statistics cited above don't tell the whole story about the value of these drugs to patients, the costs of developing them, the issues around capturing overall survival data, or the risk and attrition rate involved in drug development.

They do, nonetheless, give grounds for questioning whether the current big pharma business model is the most efficient way to develop drugs in the era of personalised medicines.

Four leading figures in academic drug development addressed this question in an article in *Cell* published on February 9, which was widely covered in the mass media, including an editorial in the UK newspaper, *The Times*.

Under the title, 'How much longer will we put up with $100,000 cancer drugs?', the authors, from top centres in the US, the UK and the Netherlands, called for "the formation of new relationships between academic drug discovery centers and commercial partners, which can accelerate the development of truly transformative drugs at sustainable prices."

Speaking to *Cancer World*, lead author Paul Workman argues that efforts to speed the translation of new discoveries into products that help patients live longer and better have hit the buffers, because the pharmaceutical industry business model avoids the higher risk, more innovative research.

This will continue, he believes, so long as key payers agree to continue paying high prices for low-risk drugs offering incremental benefits.

"You've got the fundamental problem that the big pharma companies have an addiction to the big four- to five-billion-dollar drugs like Lipitor, and they just have to price what they have to replace them and keep the business going," says Workman, who is Chief Executive of the Institute of Cancer Research (ICR) in London.

Current efforts to encourage greater innovation cannot succeed, he believes, because they fail to address the issue of price and sustainability. The emphasis, he argues, is on promoting public–private partnerships aimed at enabling the academic sector to generate more innovative high-risk ideas, and then also do much of the work to 'derisk' them, "so that when industry finally does come in, they don't have to take so much risk, they have a good idea about the patient population, they know the biomarker, they know that maybe a prototype drug is already available and showing promise."

The flaw in the strategy, he argues, is that even when the lion's share of the drug development has already been done for them, "the project can often seem to end up with a conventional, large phase III trial model, and payback to the pharmaceutical companies based on the maximum the market will bear."

He would like to see a dramatic shake up to ensure new drugs can make it to market at a price that is more sustainable and better reflects the extent of public/philanthropic investment in their discovery and development. And he would like to see more drug development done in an academic setting, which he says is more open to taking risks in search of high pay-offs, and better at conducting "small, smart trials", cutting costs and development time.

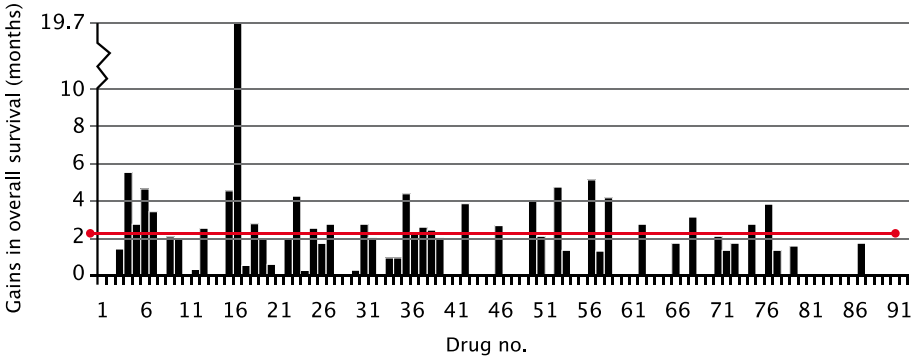
Workman has spent 20 years at the ICR building the largest drug development unit within an academic setting anywhere in the world. Since 2005, the ICR has discovered 20 innovative preclinical drug candidates, and taken nine new drugs into clinical trials – among them abiraterone, approved for advanced prostate cancer.

"A mixed economy would probably evolve. It would be a massive change, and a massive change is required"

However, he emphasises that this is not as simplistic as academia versus commercial enterprise. Indeed, Workman says experience at the ICR backs up criticisms from the industry that much 'landmark' academic cancer research published in top journals and from reputable labs cannot be reproduced or is not robust across different models.

Workman was himself scientific founder of two successful biotech companies, one of them acquired by Roche, and he sees the biotech sector as an important source of innovation. He has also spent time working in big pharma, including four years heading AstraZeneca's Cancer Research

Are drug developers aiming too low?



The median reported gain in overall survival of new therapies approved by the FDA between 2002 and 2016 for solid tumours was 2.2 months. The graph shows overall survival gains from 91 consecutive drug approvals, starting with imatinib in GIST (no.1, Feb 2002). Where a bar does not appear, it is because overall survival was not a pre-specified endpoint for this indication.

Source: Courtesy Tito Fojo, Columbia University Medical Center, New York. An earlier version of this graph, alongside data for each drug, was published in T Fojo et al. (2014) *JAMA Otolaryngol Head Neck Surg* 140:1225–36

Bioscience Section. He has huge regard for the quality of the science and the skills within the industry, but is now convinced that their best efforts will not deliver for cancer patients, because the business strategy is inefficient and leads to high levels of duplication.

"Most companies have moved all, or large parts, of their portfolios, almost like a pendulum, away from small-molecule, molecular targeted agents," says Workman. "Everybody is doing PD-1 and PD-L1 [antibodies that block immune checkpoints]. Everyone wants those in their own portfolios so they can bundle them with other agents of their own, and so they end up with combinations that will be their own... That is massive duplication, adding to costs and also opportunity cost on the innovation that would have been done if everybody just said: 'We only need, say, three or four of those, and meanwhile let's get on and innovate with other targets'."

That opportunity cost, he adds, includes failing to explore the therapeutic potential for targeting the full range of cancer genes that have been identified. "We still only have 5% of the cancer genome covered, so that means 95% dark matter that is yet to be explored. We have to get a heck of a lot more innovative drugs through, with new mechanisms of action, so we can combine them. Otherwise the cancer cells will just find ways to get around them. For these combinations to be created, we have to get those very novel drugs approved."

Workman believes it is time to trial disruptive approaches for bringing new cancer drugs to market. When appropriately resourced, in expert centres, he argues, academic scientists can discover drugs and work with clinical colleagues to run clinical trials. However, they cannot, and should not, get into the business of marketing their own drugs. He suggests that new forms of biotech or even generics companies, which are already present in the drug manufacturing business, but can operate at far lower profit margins than big pharma, could offer a possible solution.

Under this model, he explains, a drug discovered in an academic setting would be developed with a combination of research grants and charity and philanthropy, or even some venture capital, and at some point would get licensed to one of these new forms of company, which will then be responsible for taking the drug through to approval. "They may need to recruit in skilful people who are very good at more innovative work, and getting regulatory approval," says Workman, but he argues that it is "addressable".

Crucially, price caps would be written into the terms of the licence, to keep prices sustainable.

Workman speculates that, with this model, more traditional pharma companies would have to adapt to compete, some would need to downsize considerably and decrease their duplicational marketing costs. "Some would probably go out of business, and some would find creative solutions that would be competitive, and reduce costs to more sustainable levels. A mixed economy would probably evolve. It's a real possibility. It would be a massive change, and a massive change is required."

Where is the steam?

Frustration at the slow speed at which new knowledge and understanding about cancer is translating into effective treatments in the clinic is a theme that has been addressed by many commentators in recent years.

Siddhartha Mukherjee, author of T*he Emperor of all Maladies*, is one of them. Interviewed in *Cancer World* (Sept–Oct 2012), he referred to the widely used metaphor that science inevitably produces a boil that lets itself out as

steam through technology. "But if you are living in the world of cancer, there is a lot of boil, especially from the basic science world, but there is little steam which would make the engine move. ... So we have all this knowledge, and the public is asking, and we are all asking: where are the medicines that come out of this knowledge?"

Lack of innovation from the pharmaceutical industry and biotechs was one of the problems he identified. "I'm waiting for good exemplars of this change in which the drug emerges from research performed primarily by biotech or pharma companies. I've yet to see that. The reality typically still remains investigator-initiated trials or protocols."

Signs are emerging, however, that the head of steam is beginning to find a way out in the form of new business models more heavily geared towards innovation.

Boston-based PureTech Health is a good example of one such new model. Its focus is on addressing intractable problems across life sciences by scanning the horizon to identify "breakthrough" science at an early stage, and steering it through its preclinical and clinical development, in partnership with the principal investigator and a team of drug development experts.

Last year, Siddhartha Mukherjee became one of those principal investigators, when PureTech Health launched a new company, VOR, around a core technology licensed in from Mukherjee's lab at Columbia University, where he is working on developing CAR T-cell therapies in a novel way that could extend their application to tackling some of the hardest to treat cancers.

Established in 2005, PureTech Health has a number of products at human proof-of-concept stage, two of which are in pivotal trials to gain market approval. The company has a star-studded top team, including a Nobel Prize winner and many scientists with impressive track records within biotech, pharma and academia. It was floated on the main market of the London Stock Exchange in the summer of 2015.

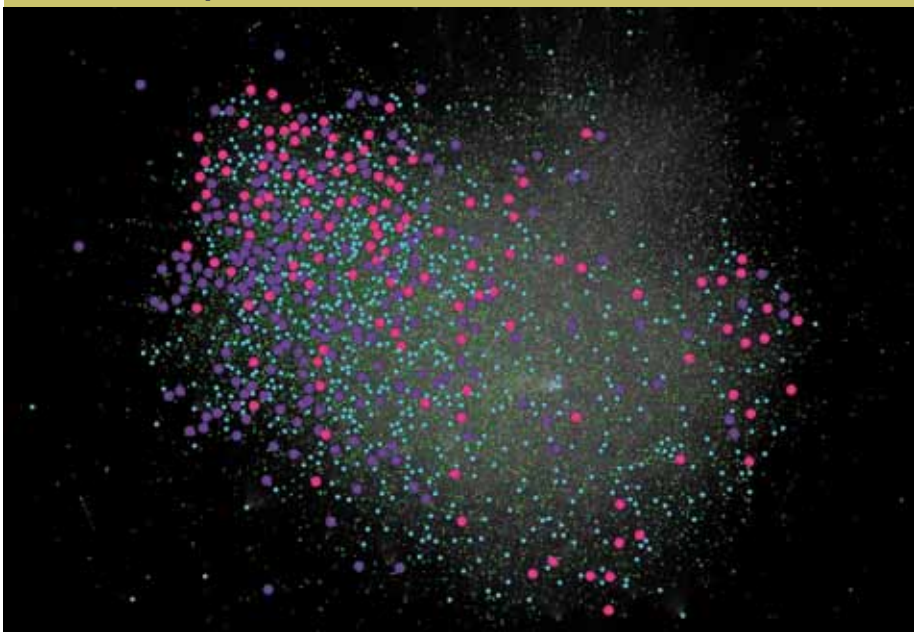
Aleks Filipovic is one of the PureTech Health scientists charged with scanning the horizon for cancer products. She is a practising clinician, who developed monoclonal antibodies against a novel target for invasive breast cancer for her PhD at Imperial College, London, and went on to do a stint at Bristol Myers Squibb as an Associate Medical Director. She clearly enjoys her current job.

"What really distinguishes us from everyone else is the balance between big academic science and practical experimental work. We search for breakthrough academic science which, for example, hasn't even been published yet, and we will develop the project in collaboration with the scientist."

The PureTech Health business model relies on ensuring that the early preclinical development is done with the speed and rigour that allows hard-nosed business decisions to be taken quickly, says Filipovic. "We parallel source many experiments, we have weekly calls with our scientists and we do reviews rigorously, with general preclinical development completed more quickly, bringing us to the point where we can apply for a phase I trial. It cuts the development time greatly and it gives us reassurance, because we understand the science in depth. We ask ourselves the hard questions."

From an industry perspective, one of

Who will explore all the dark matter?



Targeted drugs exist for only 5% of known cancer genes, so the question is who will go after the other 95%, asks Paul Workman from The Institute of Cancer Research, London. In this figure showing the human protein interaction environment, pink spots represent targets of approved cancer drugs, blue spots indicate targets of approved drugs from non-cancer therapeutic areas, and the light and dark green spots indicate targets predicted to be druggable.

Source: C Mitsopoulos, AC Schierz, P Workman, B Al-Lazikani (2015) Distinctive Behaviors of Druggable Proteins in Cellular Networks. *PLoS Comput Biol* 11(12): e1004597. doi:10.1371/journal.pcbi.1004597, republished under a creative commons license. © C Mitsopoulos et al. 2015

the key things about this model is that it aims to build sustainable 'product platforms', rather than one-off bubbles that collapse once a product makes it (or fails to make it) to market. "We like a platform-based approach, so that this particular technology can give us a lead product, but there is a pipeline behind that can be developed as the programme matures."

This template, she says, is already working in some of their more mature platforms.

"What really distinguishes us is the balance between big academic science and practical experimental work"

Third Rock, another Boston based company, established in 2006, professes a similar strategy, claiming to "discover, launch and build great companies based on bold ideas that meet at the intersection of science, strategy, business and medicine." One subsidiary, Igenica Biotherapeutics, is developing novel antibodies and antibody drug conjugates for treating cancer, while another, Constellation Pharmaceuticals, specialises in epigenetics and chromatin biology, and is looking to develop novel cancer therapeutics that target transcriptional pathways and acquired dependencies in tumour cells.

Will these innovation-led companies be the model of the future? "I hope so", says Filipovic, "because this is where science and the clinic meet in the most meaningful way to really address the unmet medical needs."

It's a good model for rapidly taking innovation from academia and getting effective new therapies to market, agrees Workman. What it won't do, he suspects, is make these new therapies any more affordable.

Not-for-profit innovation

One solution to the affordability problem could be offered by the increasing investment in drug development that is being financed through philanthropic foundations and charities.

Much of this is quite fragmented and focused on particular cancer types – often driven by patient advocacy groups. Sarcoma UK, for instance, recently announced it had raised more than £1 million for research, which has financed work on new treatments, for instance, for chordomas and advanced sarcomas.

But there have also been moves to consolidate cancer research funds into sizeable investment companies that can emulate the business model adopted by PureTech Health and Third Rock, but in a not-for-profit setting.

Syncona, for instance, was set up in 2013 by Wellcome, the world's largest medical research charity, with the aim of creating an expert team to establish and operate healthcare companies built around innovative life science technology.

By May 2016, one of its start-ups, Blue Earth Diagnostics, had achieved its first US product licence – for an injected imaging agent which shows the parts of the body where prostate cancer has recurred after treatment.

Syncona's portfolio includes Autolus, focused on developing novel CAR-T cell therapies, and Achilles Therapeutics, focused on therapies developed around the work of Charles Swanton, at the UK's Francis Crick Institute, that target tumour neo-antigens that originated from trunk mutations (see also Cutting Edge p 14).

At the end of last year, the money available to fund these sorts of start-ups took a quantum leap with the announcement that Syncona, together with the sizable investment fund from Cancer Research UK, will be absorbed into BACIT – the Battle Against Cancer Investment Trust – to create a £1bn fund that aims to become a "national champion of life science investing".

Big pharma: an evolving model

So can the big pharma model that thrived in the era of block buster medicines still survive in the more fragmented and complex era of personalised medicine?

Anne White, Vice President, Next Generation Development & Project Management, and Christopher Slapak, Vice President, Oncology Early Phase Clinical Research at Eli Lilly, accept that the personalised medicine paradigm, and the sheer speed at which science is progressing, do pose a challenge. But they argue that the industry has responded by learning to work much more efficiently, through increased collaboration between companies and by partnering with academic bodies.

Lilly, which is one of the top 10 pharma companies for oncology, was given a prominent mention in a 2012 *Drug Discovery Today* review for its involvement in innovative precompetitive public–private partnerships and open innovation (vol 17, pp 1088–102).

White singles out TransCelerate, a non-profit organisation set up in 2012 to help "simplify and accelerate the research and development of innovative new therapies", as a prime example of the new more collaborative approach. Today, she says, Lilly works alongside 17

members of TransCelerate – including almost all the big names in cancer drugs – on a range of initiatives.

She mentions, as an example, efforts to coordinate training of staff at clinical research sites, and to harmonise trial protocol formats. "Right now every pharma has its own protocol templates. Now we are standardising across the industry for our academic partners to read our protocols, and consistently find where the drug information or the dosing is, or the eligibility criteria. That is a really nice example of streamlining to improve efficiency," says White.

An agreement involving some of the TransCelerate members also facilitates sharing of clinical trial material, "If another company wants access to our medicines, if they are part of this Comparator Network we share materials and we expect the same. That has helped advance science quite a huge amount. These exchanges have potential to speed trials and reduce clinical trial costs and complexity, reduce the risk of unblinding and improve patient safety by ensuring that comparators are used as intended."

The company is also embracing big data, as a decade of efforts to force the industry and academia to open up access to all trial data are beginning to pay off. To this end, Lilly has invested in advanced analytics: "If we are designing for instance a new trial, we always looked at all the applicable data we had, but now we are able to do Bayesian statistics on a broader set of data, which potentially helps you better predict, for instance, what size the study needs to be to show the difference that you desire."

Trial designs are also changing in an effort to identify a defined target patient population as quickly as possible, says White. "We used to start a new trial to ask every question: 'Can you combine it with this agent?' 'Is it effective in this tumour type?' Now we often design from the get-go multi-arm studies that can roll

Cure Brain Cancer Foundation

GBM AGILE: a model of efficiency

GBM AGILE is an example of an innovative trial design being used to speed up progress by testing multiple therapies across a range of subgroups – in this case patients with the highly aggressive brain tumour glioblastoma multiforme.

Timothy Cloughesy, Director of the Neuro-Oncology Program at the University of California, Los Angeles, describes this as a 'platform' trial, because it uses a single infrastructure, "to ensure harmonisation with regard to imaging, tissue acquisition, and how the clinical trial data run through," and also a single control arm where patients receive the current standard of care.

Once the platform is established, any number of therapies can be tested in the different patient subgroups, in what is envisaged as a "continual process". Patients are recruited into a control arm, or one of several experimental arms. Data from the different arms are then regularly assessed, so that trial arms that are performing badly can be terminated, new arms can be introduced, and if certain treatments appear to work particularly well for certain patient subtypes, patients with that subtype will be more likely to be randomised to those treatment arms as the trial goes forward.

While the experimental arms come and go, the control arm remains constant and continues to accrue patients, which gives the study precision and statistical confidence.

AGILE will start with three different populations in each trial arm: patients whose disease has recurred following standard treatment, and previously untreated patients, who will be separated into those with and without MGMT methylation. The hope is that, as the trial progresses, more biomarkers will be identified that predict for greater response to particular treatments.

There is almost no limit to the range of therapies that can be trialled using this platform, says Cloughesy: "small molecules and antibodies, agents that affect the micro-environment of the tumour, viruses, vaccines, checkpoint inhibitors, standard chemotherapies, and even different ways of delivering radiation".

What makes the trial uniquely efficient is that the GBM AGILE team unanimously agreed that agents that show strong evidence of efficacy for a given patient group should not have to prove themselves from scratch in a phase III trial – one of the big frustrations mentioned by Paul Workman. The FDA agreed that GBM AGILE could continue as a second stage within the AGILE framework right through to registration, which will save time and money.

http://nbdabiomarkers.org/gbm-agile

directly from part A to part B, without having to go through the difficulty of starting a new trial."

They've also managed to cut the total time to enrol to combined trial phases by around a year, through working closely with advocacy groups and clinicians, says White. Trial protocols are now routinely given a "dry run" by clinicians at the testing sites, using theoretical patients, to help ensure any issues that could deter people from joining or sticking with the trial are identified and ironed out before the trial starts.

"It's all about finding ways to do things faster and better, and it's a process of evolution"

It's all about finding ways to do things faster and better, and it's a process of evolution, she says, a continuous process to "learn, confirm and make adjustments as we go along."

Responding to the charge that pharma are risk averse and swing behind the latest 'big thing', White argues that companies need a mix of high-risk and lower-risk products in the pipeline to be sustainable, but that addressing unmet medical need is an important criterion. "A portion of our portfolio very much says we want to be first. And with that comes more risk. You need a portfolio that has a mix of high-risk and ones that you believe you will improve on what is already out there."

Slapak points out that, while the company does have its own PD-L1 antibody in the pipeline, it has also just delivered the first new therapy for first-line treatment of advanced soft tissue sarcoma for more than 40 years.

Olaratumab, a novel PDGFRα antibody, was approved by the FDA last year on the basis of data from the phase II portion of the pivotal phase 2 trial showing almost 12 months benefit in overall survival, almost doubling the survival using the erstwhile standard of care.

He adds that partnerships with academic institutions, such as the Harvard-affiliated Dana-Farber Cancer Institute, help them stay abreast of the science and "tap into some of the best innovation out there".

In the past, he says, they used to just design a protocol and hand it to an institution and say: "Please find patients". "Collaborations are now also about the best path forward for the molecule, the right patients etc. We propose areas of work and we are open to what they think. We listen to what they say and we solicit proposals from their investigators and we review them."

From the company's point of view, says White, learning to do things faster and better has also been driven by an effort to offset costs. "We face increasing drug regulations and expectations by regulators and by payers and reimbursement groups, she says, adding that rising prices across healthcare also contribute to pushing up the company's drug development costs, as pharmaceutical companies reimburse many of the procedures that patients receive as part of the trial, "so we incur that cost as well." On top of that, of course, comes the higher costs associated with developing biologicals compared with small molecules.

Change is coming

Richard Barker is Director of the UK's Centre for the Advancement of Sustainable Medical Innovation (CASMI), an independent, non-profit body uniting Oxford University and UCL (University College London) with a mission "to create new, sustainable models of the medical innovation process to translate advances in basic research into patient benefit more quickly and effectively."

He comments that many of the new ways of working described by White are broad trends across the pharmaceutical industry. "There is no doubt that both academic efforts and biotech efforts are tremendously important in the pipeline of cancer drugs, and you are beginning to see larger companies reaching beyond the biotechs to make relationships with networks of academics. Across the US a number of different cancer centres are coming together to work with pharma companies to find targets and potential early leads on new drugs."

But he also points to changes in clinical trials and regulatory practices that he believes could make it much easier for smaller companies and philanthropic organisations to bring new drugs to market.

CASMI has played an important role in discussions around proposals for using 'adaptive pathways' to speed up regulatory processes and health technology appraisal for certain categories of drugs, eg where there is demonstrated unmet need and early data suggests a positive risk–benefit profile.

Adaptive pathways could offer an alternative to large and lengthy phase III 'pivotal' trials, which require the sort of money to which only major pharmaceutical companies have access. These pathways would rely instead on a development plan tailored to the drug in question, which would provide enough information on risk versus benefit to enable an early decision on conditional approval for use in a specific patient population, followed by monitoring of the drug's effectiveness and safety in a real-world setting.

This adaptive pathways model was

piloted last year, and the European regulator, the EMA, says it is now committed to "further explor[ing] the adaptive pathways concept as an approach to bringing promising medicines to patients with an unmet need in a timely manner."

Barker also points to the potentially disruptive impact of innovative types of trial, such as basket trials – where a targeted drug is tested across a range of cancers in patients who test positive for the relevant target – and umbrella trials – which test a range of drugs in patients and patient subgroups in a single disease.

He mentions as an example of the latter the I-SPY trials, which started in 2002 and have focused on trying a range of drugs in eight molecular subtypes of patients with stage 2 or 3 breast cancer, and the Lung Matrix trial, looking at different treatments in eight subtypes of patients with non-small-cell lung cancer.

"I think the general feeling in the industry is that this is the direction of the future, where we have enough knowledge of those mutational patterns to combine forces across companies and try to home in on the populations most likely to respond to each drug," says Barker.

Running trials in this way is hugely more efficient than each company running its own trial on every subgroup. That means it's a good deal for companies that might otherwise have run their own separate trial, and by lowering development costs it could also help open the market to smaller commercial and philanthropic organisations (see also GBM Agile box p 61).

And as Barker comments, the landscape of drug development is already opening up. He mentions in particular the involvement of patient organisations, which he says "are increasingly investing in research, and sometimes creating their own molecules."

He suggests that, "if disruption of the current business model is needed, then patient organisations can play a very major role. "If they are funding a trial they can do it with different rules of engagement if they so choose, depending in part on who is coming up with the investment money."

Could this all add up to the "massive change" that Workman at the ICR is so keen to see? On the basis of this evidence, maybe it could.

Item 1: Improving value for money from public investment in academic drug discovery and development, by using new types of partnership agreements to bring them to markt.

Item 2: New interest – both commercial and philanthropic – in investing in and incubating highly innovative science at an early stage.

Item 3: Changes within the pharmaceutical industry towards greater efficiency through more collaboration within the industry and with academia.

Item 4: Changes in the way drugs are being trialled and in the regulatory processes that bring down costs and speed up results.

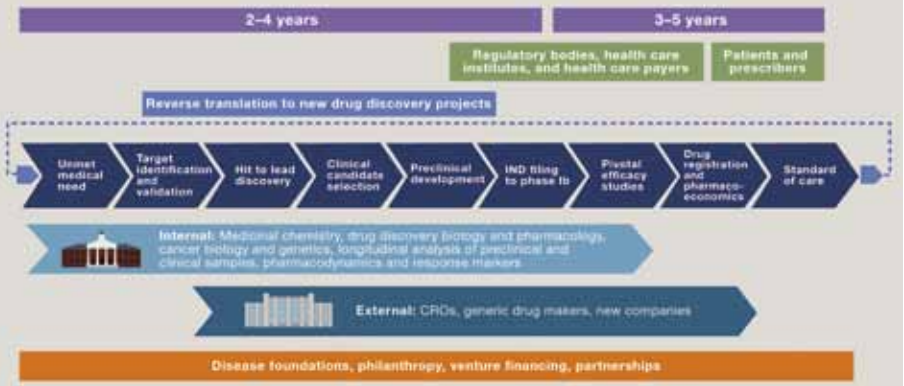
Item 5: Increasing involvement of patient and philanthropic organisations in the drug development arena.

There may also be an item 6.

At his pre-inauguration press conference, US President Donald Trump flagged up his intention to introduce national price negotiations for drugs, for the first time in the country's history. If that happens, it could, for instance, increase the incentive to go for novel drugs that could make a big difference, by reducing the rewards for bringing 'me too' drugs to market.

One way or another, it seems change is on the way.

A new paradigm for not-for-profit drug development



Key academic figures in the UK, US, and The Netherlands have issued a call to redefine relationships between academic drug discovery centres and commercial partners, in order to accelerate the development of "truly transformative drugs at sustainable prices". In an article published in *Cell*, they argued that, through comprehensive integration of expertise within an academic setting, cancer biologists and geneticists, drug discovery scientists and pharmacologists are able to precisely formulate a 'Clinical Candidate Profile' based on tumour subtype(s) and patient population that might best benefit from treatment. Financing can come from a variety of sources, including philanthropic foundations. Not-for-profit entities can retain control right through to commercialisation, by partnering with clinical research organisations (CROs) and generic drug makers or other new forms of company.

Source: P Workman, G F Draetta, J H M Schellens, R Bernards (2017) How Much Longer Will We Put Up With $100,000 Cancer Drugs?' *Cell* 168:579–583, reprinted with permission from Elsevier

ESTRO SCHOOL OF RADIOTHERAPY AND ONCOLOGY

WWW.ESTRO.ORG

2017

ESTRO School

POSTGRADUATE COURSES IN EUROPE

Comprehensive and Practical Brachytherapy
5-8 March 2017 | Budapest, Hungary

Particle Therapy
6-10 March 2017 | Essen, Germany

Lower GI: Technical and Clinical Challenges for Radiation Oncologists
22-24 March 2017 | Rome, Italy

Upper GI: Technical and Clinical Challenges for Radiation Oncologists
25-28 March 2017 | Rome, Italy

Dose Modelling and Verification for External Beam Radiotherapy
2-6 April 2017 | Warsaw, Poland

IMRT and Other Conformal Techniques in Practice
9-13 April 2017 | Madrid, Spain

ESTRO/ESMIT Course on Molecular Imaging and Radiation Oncology
10-13 April 2017 | Bordeaux, France

Cancer Survivorship
21-23 May 2017 | Brussels, Belgium

Multidisciplinary Management of Prostate Cancer
21-25 May 2017 | Porto, Portugal

Physics for Modern Radiotherapy
4-8 June 2017 | Bucharest, Romania

Advanced Skills in Modern Radiotherapy
11-15 June 2017 | Prague, Czech Republic

Evidence Based Radiation Oncology
11-16 June 2017 | Ljubljana, Slovenia

Combined Drug-Radiation Treatment: Biological Basis, Current Applications and Perspectives
15-18 June 2017 | Brussels, Belgium

Target Volume determination - From Imaging to Margins
25-28 June 2017 | Lisbon, Portugal

Brachytherapy for Prostate Cancer
29 June - 1 July 2017 | Brussels, Belgium

Advanced Treatment Planning
3-7 September 2017 | Barcelona, Spain

Clinical Practice and Implementation of Image-Guided Stereotactic Body Radiotherapy
3-7 September 2017 | Budapest, Hungary

Palliative Care and Radiotherapy
7-9 September 2017 | Brussels, Belgium

Multidisciplinary Management of Breast Cancer
10-13 September 2017 | Dublin, Ireland

Research Masterclass in Radiotherapy Physics
10-13 September 2017 | Florence, Italy

Basic Clinical Radiobiology
16-20 September 2017 | Paris, France

Comprehensive Quality Management in Radiotherapy
2-5 October 2017 | Brussels, Belgium

Quantitative Methods in Radiation Oncology: Models, Trials and Clinical Outcomes
8-11 October 2017 | Maastricht, The Netherlands

Best Practice in Radiation Oncology - Train the RTT Trainers
16-18 October 2017 | Vienna, Austria

Multidisciplinary Management of Brain Tumours
22-24 October 2017 | Vienna, Austria

Image-Guided Radiotherapy and Chemotherapy in Gynaecological Cancer: Focus on MRI Based Adaptive Brachytherapy
22-26 October 2017 | Prague, Czech Republic

Image Guided Radiotherapy in Clinical Practice
29 October - 2 November 2017 | Athens, Greece

ESTRO/ESOR Multidisciplinary Approach of Cancer Imaging
2-3 November 2017 | Rome, Italy

Imaging for Physicists
5-9 November 2017 | Malaga, Spain

Paediatric Radiotherapy
30 November - 2 December 2017 | Brussels, Belgium

POSTGRADUATE COURSES OUTSIDE EUROPE

Transition from Conventional 2D to 3D Radiotherapy with a special emphasis on Brachytherapy in Cervical Cancers
8-11 March 2017 | Bengaluru, India

ESTRO-KOSRO GI: Technical and Clinical Challenges for Radiation Oncologists
2-4 June 2017 | Seoul, South Korea

Comprehensive Quality Management in Radiotherapy
5-9 July 2017 | Chengdu, China

Multidisciplinary Management of Head and Neck Oncology
9-13 December 2017 | Singapore, Republic of Singapore

PRE-MEETING COURSES

Five Pre-Meeting Courses at ESTRO 36
5 May 2017 | Vienna, Austria

UNDERGRADUATE COURSES

Medical Science Summer School Oncology for Medical Students (Vienna/Groningen)
10-21 July 2017 | Vienna, Austria

ESO-ESSO-ESTRO Multidisciplinary Course in Oncology for Medical Students
28 August - 8 September 2017 | Antwerp, Belgium

- MULTIMODAL CANCER TREATMENT
- RADIOTHERAPY TREATMENT PLANNING AND DELIVERY
- BIOLOGY
- IMAGING
- RESEARCH
- BEST PRACTICE

35 years ESO European School of Oncology Learning to care

LEUKAEMIA AND LYMPHOMA

10-13 June 2017
Ascona, Switzerland

Chairs:
M.F. Fey, CH - J.O. Armitage, US - E. Zucca, CH
Hosting Chair:
F. Cavalli, CH

REGISTRATIONS WILL BE PROCESSED ON A FIRST-COME/FIRST-SERVED BASIS
FURTHER INFORMATION AVAILABLE AT: **WWW.ESO.NET**

ORGANISING SECRETARIAT: European School of Oncology (ESO) | Piazza Indipendenza 2 | 6500 Bellinzona | Switzerland
Dolores Knupfer | ph +41 91 820 09 52 | dknupfer@eso.net | **www.eso.net**

An intensive and interactive course held in co-operation with and preceding the 14th International Conference on Malignant Lymphoma

INTERNATIONAL CONFERENCE ON MALIGNANT LYMPHOMA Lugano, Switzerland

COURSES AND SEMINARS

Cancerworld

Get your copy in the mail (free)

HOW TO SUBSCRIBE?