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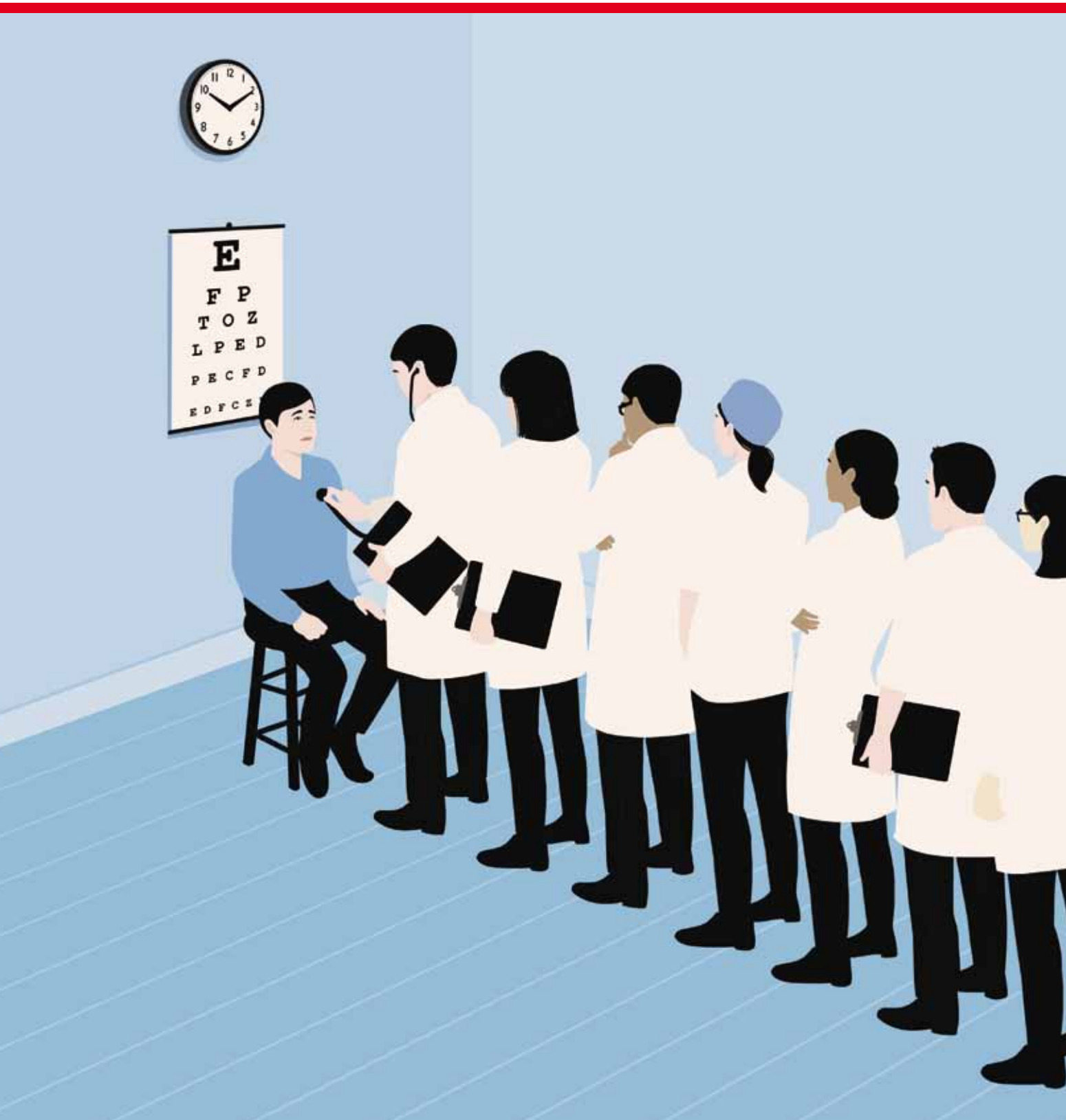

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European School of Oncology

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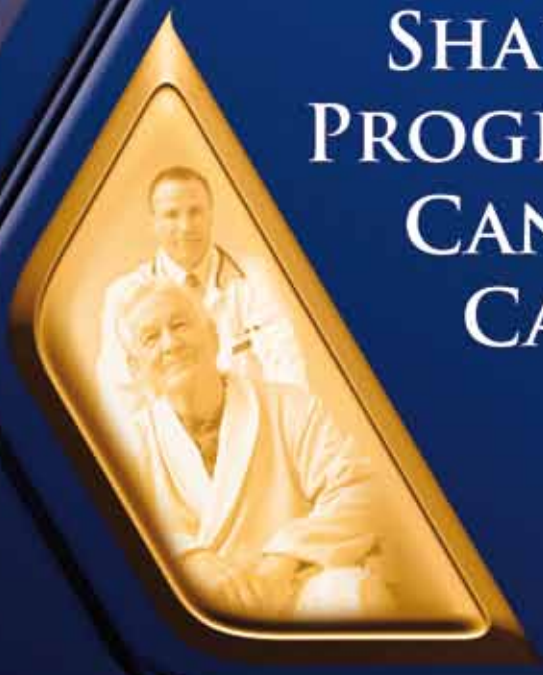
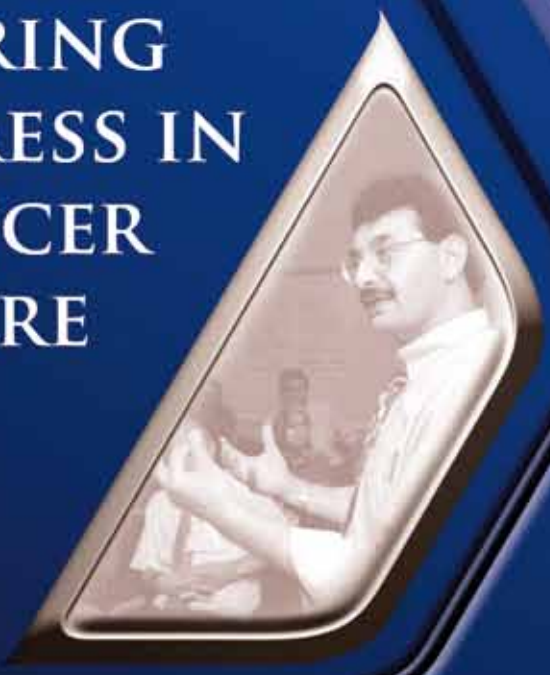
Sharing Progress in Cancer Care





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The more you treat, the more you cure? Challenging the dogma

Alberto Costa, Editor

I was lucky enough to be in the right place at the right time to witness one of the great turning points in our approach to cancer. In March 1973, a medical student at Milan University, I was assigned to the Istituto Tumori for my practical training. A medical oncologist called Gianni Bonadonna was just starting to give a chemotherapy regimen called CMF to breast cancer patients as an 'adjuvant' treatment after surgery. A surgeon, Umberto Veronesi, had just randomised his first patients to a clinical trial that would become known as the Milan I study, and would demonstrate that it is possible to achieve the same survival rates as mastectomy by removing only the part of the breast containing the tumour (quadrantectomy) and then irradiating the remaining mammary glands.

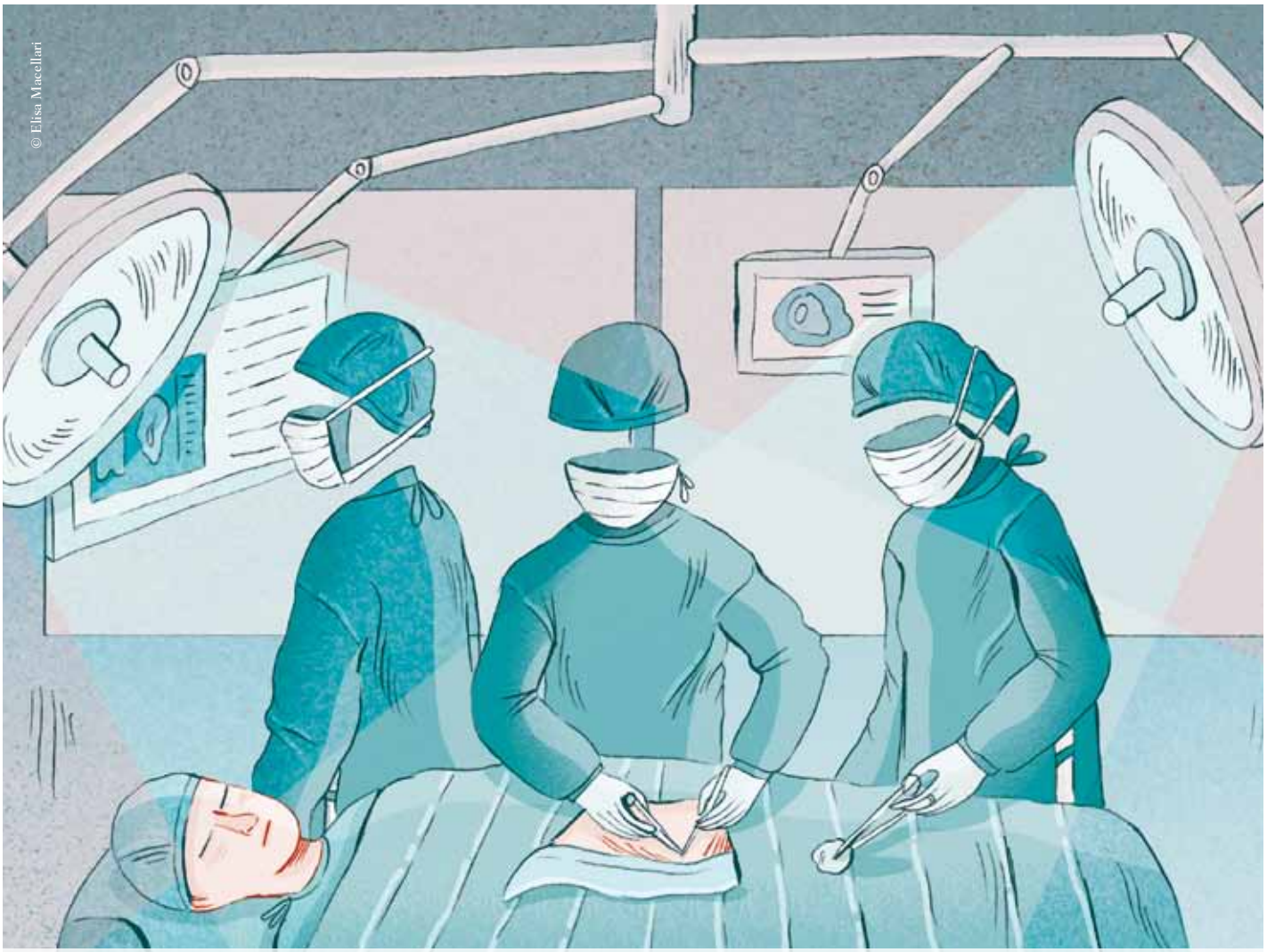
I joined Veronesi, and remained with him for another 30 years. I felt that something important was happening in that nine-storey building, in that least Italian of Italian cities.

A dogma was dying. It was becoming clear that there was no direct relationship between the amount of tissue removed and the curability of the cancer that had developed. I still saw some patients treated with an 'enlarged mastectomy', a procedure that removes both pectoral muscles, and all axillary lymph nodes – the internal mammary and the supraclavicular ones. Did these women live any longer? We now know that they did not – but their bodies were devastated.

The introduction of conservative breast surgery had an impact not only on cosmetic results, but more importantly on survival *per se*: it gave women a real incentive to seek an early diagnosis, and early cancers have in general a better prognosis.

Breast surgeons should be acknowledged for having had the courage to revise their own dogmas, and for continuing to do so, with the introduction of the sentinel node procedure (saving millions of healthy lymph nodes), the nipple sparing mastectomy and now active surveillance in DCIS. Urologists have done the same with prostate cancer, orthopaedic surgeons with bone sarcomas, general surgeons with rectal cancer, and so on, by interacting with other disciplines and combining treatments.

We need now to kill another dogma: the more you treat the more you cure. Overtreatment is everywhere, fueled by anxiety (what if they sue me?), by anecdoctal bias (I remember a case…), by the pressure of the administrators (we need to cover so many costs...), by the need to feel safe (the benefit is minimal, but just to be certain…). Will new generations have the same guts as our predecessors?



The invisible cure

Should we be talking more about cancer surgery?

The best chance of being cured of cancer is through surgery by expert surgeons with a deep knowledge of oncology. Why then are the public, patients and policy makers so focused on drugs, and does it matter? **Anna Wagstaff** investigates.

Mass media have an insatiable appetite for stories about cancer. No mystery in that. As readers, viewers and listeners, we never tire of the topic. We fear it. Many of us have been personally touched by it. We all want a cure.

What is somewhat more surprising is how rare it is for surgery to get a mention, given that top-quality surgery remains by far the single most important key to a cure.

The extent to which cancer surgery seems to be airbrushed out of media coverage is really quite striking.

A widely cited analysis of cancer research stories published between 1998 and 2006 on the BBC website – chosen by the researchers as "an ideal surrogate… for overall media impact" – found that stories about cancer drugs dominated, accounting for around 20% of all coverage (*Br J Can* 2008, 99:569–76)

Stories about research on any other modality of treatment were so few and far between that they didn't even get a mention in the report – the other major research topics, in order of frequency, were stories on lifestyle, genetics, food and drink, and work-related risk factors.

Riccardo Audisio, a consultant surgical oncologist at the University of Liverpool, and president of ESSO, the European Society of Surgical Oncologists, is deeply frustrated by the lack of attention his discipline gets within the public discourse around cancer. "Given that the vast majority of patients who are cured, are cured by surgery, and only around 5% or 6% by medical oncology, the media focus on cancer drugs is totally disproportionate," he says.

This matters, says Audisio. Not because surgeons are somehow entitled to have their contribution publicly recognised, but because the media influence public attitudes and policy agendas. Distorted media coverage feeds through to distorted priorities in individual and collective efforts to cure cancer.

Patients who go to extreme lengths to access a drug that may be of marginal value, he says, may die because they took the quality of their surgery for granted. Policy makers miss opportunities to improve outcomes because they don't take basic steps to protect patients from surgeons who are not up to the task. Funders pour resources into discovery of new medical treatments while efforts to push the boundaries of what surgery can achieve are held back by lack of basic financial support.

Why the obsession with drugs?

The media's obsession with stories about drugs tends to be attributed to the influence of the pharmaceutical industry, which has an interest in getting prominent and positive coverage of its products, and puts huge resources into press and PR.

The rhythm of clinical trials provides multiple opportunities for press releases at each new phase, and the regulatory stamp of approval turns a new drug into a news story regardless of the magnitude of true benefit. Press offices know how to package information in a way that best 'sells' the story, and they facilitate expert comments from researchers and patients, to make things as easy as possible for overstretched health journalists.

While all of that is undoubtedly true, a fascinating article published in the journal of the European Molecular Biology Organization (*EMBO reports*, 2010, 11:572–577), suggests that there is something more fundamental behind our insatiable appetite for stories about drugs. It brought together a growing body of evidence to show that we are all hard-wired, through evolution, to seek medication when we are not feeling well, and that we share this trait with much of the animal world.

Significantly, it linked this trait to the placebo effect – the real biological effect (hence the evolutionary benefit) that has been demonstrated to arise simply from our seemingly irrational belief in the efficacy of an ingested medicine.

"This 'human tropism' towards medicines is skewing the way society allocates its health resources"

The paper carried a message to policy makers. This "human tropism" towards medicines, which played an evolutionary role in our survival, is now fuelling an irrational overvaluation of medicines, which is skewing the way society allocates its health resources. It called for public policies to "take into account the human factor" to ensure that decisions about allocating resources don't "undervalue the contribution towards health and disease management of prevention and non-medicinal modalities, such as surgery."

The dominant narrative

As president of the medical oncology society, ESMO, Fortunato Ciardiello represents a discipline on the winning side of this reported evolutionary bias. He is keen to stress that the optimism over some of the most recent therapies – particularly immunotherapies – is not

all hype. "Some of these drugs are very important in changing the perspective of some tumours, although we still have to define the best way to use most of these drugs."

He agrees, however, that when it comes to understanding cancer and how to tackle it, there is a worrying gap between reality and perceptions among the public, politicians and mass media – and not just about the contributions of different treatment modalities.

"Some of these drugs are very important in changing the perspective of some tumours"

"What we are missing is a public awareness that treating cancer is very complex and requires a high level of expertise among different professionals, working in good health organisations and networks, from the GP – who is often the first person to see the cancer – to different levels of diagnostic centres or hospitals, up to the so-called comprehensive cancer centres, from where eventually the patient is referred back to the family doctor."

If any contribution to tackling cancer is being undervalued, argues Ciardiello, it is at the level of prevention and early diagnosis. "We should recognise why we have this epidemic of cancer. Most of it is changes in lifestyle, obesity, smoking… we need to do things to change these. Also screening, secondary prevention, defining when it is still possible to cure a patient who is not yet symptomatic. Are effective screening programmes really being done in all the tumours for which it is possible?"

When it comes to recognising the contribution surgery makes to cancer care in general, Ciardiello agrees that "tumour surgery is really a key factor for cure, and even long-term survival," and says the need for patients to be treated by expert surgeons must be one consideration in deciding where cancer treatment should be delivered.

The specific role for surgery in the management of different cancer indications is something that can only be decided on the basis of evidence, he says, which is where professional societies have a crucial role to play. "The only thing we know in oncology is through sound well-powered clinical trials that can answer specific questions. We in ESMO have been working on clinical practice guidelines for 20 years to help physicians make decisions in specific clinical situations. Whatever you may hope or imagine may be effective, this is not evidence based and could be a great waste of resources and harmful for the patient."

The view from cancer surgery

The perspective outlined by Ciardiello is very much the dominant narrative in the cancer community, but seen from the standpoint of cancer surgery, things look rather different.

No-one argues with the imperative of evidence-based medicine, says Audisio, but the evidence generated is determined by what you look for. While billions in commercial and public/charitable money are invested in trying to demonstrate often minor benefits from new drugs, other treatment modalities scrabble to find funding to do research.

Based on our knowledge of what works, he says, that is not an efficient allocation of resources.

"We are discussing science and evidence here. Not science fiction. From the time I started in surgery 40 years ago, I've been told that basic science is about to get rid of the need for cancer surgery. It's never happened. I'm very happy to promote drug research, I enjoy staying abreast of the evolving science, but believe it or not, if you get a cancer now, it's surgery. So we need to put more money into making the surgery better."

Audisio says he and his co-principal investigator are currently funding from their own pockets an international study on a new technique that seeks to mitigate the cosmetic impact of mastectomies.

The study is gathering evidence on the risks and benefits of a procedure that allows people to retain their own nipples, rather than having nipples tattooed on following breast reconstruction. The direct impact will be to improve survivors' quality of life, but Audisio believes it will also save lives – people with a familial history of BRCA-related cancers may be more likely to get tested and opt for a preventive mastectomy if the option comes with a lower cosmetic penalty.

"From the time I started, I've been told that basic science is about to get rid of the need for cancer surgery"

He finds it frustrating when patients enrolled in this study proudly tell him how they've been raising funds "for

cancer research", seemingly oblivious to the fact that the novel technique they have opted for *is* cancer research – and it is receiving no research funding. "People just assume the whole battle of cancer is finding new drugs."

Audisio points out that the big advances in cure over recent decades have come from surgery, including a 20% increase in survival rates in rectal cancer and a 'breakthrough' – to coin a phrase – in patients with colorectal cancer that has metastasised to the liver, which used to be terminal, but can now be treated curatively in around one-third of patients.

The hidden toll of bad surgery

This lack of recognition for the contribution of cancer surgery does not only affect research. The real victims are the tens of thousands of patients across Europe who suffer from substandard cancer surgery because of what Audisio sees as the criminal negligence of governments and health systems.

Radiotherapists must learn about cancer. Medical oncologists clearly learn about cancer. But surgeons – the ones who are relied upon to deliver the curative treatment in most cases – do not have to know anything about cancer to be allowed to operate on a cancer patient. Audisio finds this quite astonishing, and believes that the public and patients would be equally shocked if they were aware of this.

If surgery was recognised as the primary treatment for cancer, he says, it would lead to much better education for surgeons. "My problem is not with the other cancer disciplines, it is with surgeons, because they are allowed to do everything. We don't have a system that can protect the community from the general surgeon."

Call yourself a cancer surgeon?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No surgeon should operate on a cancer patient without a solid knowledge about cancer, the pathology and management associated with the particular cancer they are operating, and a broad understanding of holistic care of cancer patients. This is the philosophy behind the **Global Curriculum in Surgical Oncology**, which was developed by the European and US societies of surgical oncology, and published in June in the *European Journal of Surgical Oncology* (vol 42, pp 754–66).

The paper defines a 'surgical oncologist' as "an oncologist who also posesses the expertise to perform operative procedures and interventions". The curriculum is presented as a "foundational scaffolding" for training surgical oncologists worldwide, and is intended to provide a "flexible and modular scaffolding" that individual countries and regions can adapt for their own purposes.

Topics include a knowledge and understanding of the principles of general oncology, including:

- Cancer biology, research, epidemiology and screening
- Chemotherapy, radiation therapy, biologic and immunotherapy, and surveillance
- Chronic pain management and palliative care
- Multidisciplinary care
- Medical imaging and diagnostic pathology

Required core competencies include:

- Holistic care
- Interprofessional team working
- Communication skills
- Experiential learning

The latter should include "a critical assessment of [the surgical oncologist's] own outcomes relative to nationally established benchmarks and implementation of... measures to address areas of deficiency."

For further details see: C Are et al (2016) Global curriculum in surgical oncology. *Eur J Surg Oncol* 42:754–66

SSO Society of Surgical Oncology

esso The European Society of Surgical Oncology

But surely there are specialist units – for example in breast cancer – with a requirement to treat a minimum number of patients? True, says Audisio, but there is something critical missing.

"Surgeons do not have to know anything about cancer to be allowed to operate on a cancer patient"

"There is no philosophy or formal training. You have breast units, but there is no such thing as a breast cancer surgeon. They have created the oncoplastic breast surgeon [in the UK], where young lads are brought into plastic theatre and can do some reshaping. They can print a visiting card that says "oncoplastic surgeon", they can do implants, but they most often show limited oncological understanding."

"This is about more than being specialised in one site," says Audisio. "It's the idea of understanding that you can avoid surgery in this condition, or you need to be very aggressive with that condition, because, yes, we have a medical treatment, but it will never be as effective as good quality surgery.

"I think it is absolutely important to understand genetics, angiogenesis, chemoprevention, screening, follow up, detection, imaging, pathology, medical oncology and so on. Then you need to specialise in one cancer site or another. You need a multidisciplinary background, because of the cross-pollination."

ESSO recently teamed up with the US Society of Surgical Oncology to develop a 'global curriculum', geared towards providing surgeons with just such a multidisciplinary background. Published in June, it offers "flexible and modular scaffolding that can be tailored by individual countries or regions to train surgical oncologists in a way that is appropriate for practice in their local environment," (see box p 7).

Audisio believes that the single most important thing governments could do to improve outcomes would be to forbid surgeons to operate on cancer patients until they have mastered the key basics about cancer and its management. Improving recognition among the public, patients and policy makers of the key importance of high-quality surgery will be key, he believes, to convincing governments to take action.

Getting political visibility in the Ukraine

Andrii Zhygulin is head of the only breast unit in the Ukraine that fully complies with the criteria and standards laid down by the European Society of Breast Cancer Specialists (EUSOMA). This is a country with one of the worst cancer survival rates in Europe, where the chances of surviving a diagnosis of cancer are roughly half those of someone living in Sweden.

Like Audisio, Zhygulin believes that poor quality surgery, along with late diagnosis, is largely responsible for that survival gap. He is on a mission to spread knowledge and expertise throughout the country, and would welcome more recognition and support for what he is trying to achieve.

Investing in the quality of cancer surgery is a no-brainer, according to Zhygulin. "Good surgery doesn't need as much investment as drugs. In many cancers, better oncological surgery could save more lives without great cost, just through education and by the State ensuring that guidelines are being followed."

Zhygulin's breast unit is part of the LISOD Israeli Cancer Care Hospital – located just south of the capital city Kiev. Working with a small group of like-minded specialists, and with the support and backing of the management and the Israeli medical oncologists at the LISOD hospital, Zhygulin is doing what he can to address the quality agenda in his particular specialism, running courses on breast surgery and organising the country's first breast cancer conference.

But this is a large country, with a dysfunctional public health system, he says. The doctors on the front line have low pay and low status: "They just want to do their job as quickly as possible and then go to another hospital to work some more to make enough money."

Many of the top medical professors, meanwhile, speak no English, rely on Russian- and Ukrainian-language literature, and feel threatened by new procedures that they were not themselves trained in.

Zhygulin says the quality campaign that he and his colleagues have started has now spread to other cancer fields, and that discussions at the recent XIII Congress of Ukrainian Oncologists were remarkable for the frank recognition of just how bad things are, and doctors are starting to make real efforts to improve the situation.

He is aware, however, that turning things around will require serious political will and public investment. "For me it is very simple. Only good surgery can improve the outcomes. Who can do good surgery? Good surgeons. To be a good surgeon you need good training and education and good technologies. Who can give it to the surgeons? Only the system of healthcare and medical education. Who can do that? Only the government."

Visibility for precision treatments

Bill Heald at the Pelican Cancer Foundation, which he founded to support research and education into 'precision cancer treatments'

Not much in cancer medicine comes closer to a magic bullet than total mesorectal excision (TME) for rectal cancer.

The TME technique, pioneered in the late 1980s by Bill Heald, at a hospital in Basingstoke in the UK, led to a more than five-fold reduction in local failure and a doubling of survival rates.

Yet 10 years after these results were first recorded, some patients in the UK were still being treated with outdated techniques.

Heald is painfully aware that if a drug had come along that conferred even a fraction of that survival benefit, it would have been hailed by a media fanfare, and eligible patients would all have had rapid access.

He is philosophical about the lack of public recognition of the importance of cancer surgery. "We may seem to be a bit invisible, but one knows that it is much easier to get press and TV attention for drugs, which don't really make a huge difference," he says.

"I've heard it calculated that if you organise a meeting talking about medical oncology, you would raise 10 times as much sponsorship as you would for a meeting of similar calibre about surgery. You are invisible if you don't have any money behind you."

The TME technique was based on an understanding that rectal cancers tend to stay within the embryological gut unit, and that excising that unit completely and in one go was therefore key to the cure.

The concept of the total excision of the "innermost dissectible layer" – referred to by Heald as the "Holy plane" – is now being transferred to improving outcomes from colorectal cancer surgery, and also to cancer of the stomach. Even the new techniques for curative treatment of liver metastases draw on the same principle, says Heald. "Various lobules of the liver are also discrete from each other, so if you get into the right plane you do a better job in curing secondaries."

Heald believes that advances in precision treatments – surgery, highly targeted radiotherapy, interventional radiology and other "mechanically precise" techniques – remain the best hope of making progress against cancer. He has done his own bit towards raising both their visibility and funding, by setting up the Pelican Cancer Foundation, which remains one of the only foundations in the world focused exclusively on improving cancer outcomes through "precision treatments".

The question is how that political will can be generated, given that in the Ukraine – as elsewhere – when it comes to cancer, public and policy attention is so heavily focused on the drug agenda?

Turning things around will require serious political will and public investment

There are no easy answers, says Zhygulin, who describes public attitudes that reflect the EMBO paper suggestion that we are hard-wired to favour drugs. "People think surgery is just normal, and is done every time and everywhere and is boring. And some people are afraid to talk about it.

"When we are talking about new drugs, in contrast, it is something special, like hot news. In the Ukraine, we say 'people are doctors,' – they think they can understand everything in medicine. So if they hear about a new drug, this is much closer to the mind of the population."

And, of course, people hear about new drugs all the time, because of the effort that goes in to promoting them. "No one does that for surgery."

Getting guidelines visibility in Germany

Pompiliu Piso is head of general and visceral surgery at the Barmherzige Brüder teaching hospital of the University of Regensburg, in Germany – a country where many 'all-rounder' surgeons are still commonplace in most hospitals.

He highlights the efforts by the German Cancer Society to improve the quality of cancer care through a system of certification of specialist centres based on their performance and results.

A crucial element has been introducing greater transparency about surgical quality. "Nowadays, surgeons and their partners can at any time get information, for instance, about their rate of R0 resections, morbidity and mortality. This also enables benchmarking across centres, and shows the nationwide quality of care, such as rate of good TMEs for rectal cancer."

Piso is now working with ESSO to promote the idea that surgeons who operate on cancer patients must specialise in particular sites and must have an educational grounding in cancer.

He agrees with Audisio that the importance of the quality of surgery is under-recognised in cancer. He also strongly agrees on the need for surgeons to understand the basics of the cancer, and the potential contributions of all treatment modalities, to be able to participate fully in multidisciplinary team meetings. "This is the only way to define a tailored strategy for each patient," he says.

But he also agrees with ESMO's Ciardiello on the importance of working according to evidence-based guidelines, and says that surgeons need to increase their contribution within guideline committees, as this will also increase their visibility.

"Guidelines will reflect the importance of surgery if there are surgeons involved who can point out why surgery plays an important role for a certain therapeutic aspect," says Piso. Their input can be particularly influential, he says, where the issue under discussion is controversial. "This, of course, assumes that surgeons are aware of important data in medical oncology, gastroenterology, pathology etc., including results of most recent published trials."

While the final drafts of guidelines are written by consensus, the process of developing them, in Germany, is mainly coordinated by medical oncologists or gastroenterologists, he says.

Piso believes it would make more sense for surgeons to be the coordinators, "at least for solid gastrointestinal tumours that are mainly cured by surgery."

It's up to surgeons themselves, to make this happen, he argues. "Surgeons have to take the initiative to try to be more present at interdisciplinary meetings and conferences. We need to stress how important the quality of surgery is, and to show that surgeons are willing to improve the quality of surgery.

"We have to get more involved in these major decisions. Being in the operating room is important, but being in the meetings and committees, and showing the work we do and our results to the medical – and not only medical – community, is also important."

"Surgeons have to take the initiative to be more present at interdisciplinary meetings and conferences"

Ensuring all cancer surgeons get specific training in surgical oncology could be an important step towards this goal. This will help ensure that surgical oncologists not only fully grasp the importance of a multidisciplinary approach, but have the detailed knowledge they need to play a key role in discussions on developing guidelines and applying them to individual patients.

Too affordable: how can we overcome the drug repurposing paradox?

Looking for anticancer activity among off-patent drugs that are already approved to treat other conditions might seem a sensible way to speed up access to affordable new therapy options. **Linda Geddes** asks how such a strategy can work in practice, when the drugs are so cheap but the cost of approval is so high.

When Pan Pantziarka's teenage son, George, failed to respond to standard treatment for osteosarcoma, Pan did what many scientifically literate friends or relatives would do in this situation: he started searching Pubmed and reaching out to clinicians in the hope of finding an alternative.

The suggestions they came up with – things like the anti-diabetic drug, pioglitazone, and the non-steroidal anti-inflammatory drug, celecoxib – were widely used for other indications, had shown some anti-cancer activity, and even produced some promising phase I or II trial results. Yet for one reason or another they had been abandoned as oncology drugs.

It's impossible to know if they would have changed George's fate; he never got to try them because his oncologist was resistant to the idea. But even after his death in April 2011, the idea of repurposing drugs stuck with Pan. Today he works for the Belgium-based Anticancer Fund (anticancerfund.org), co-ordinating the Repurposing Drugs in Oncology (ReDO) Project, which seeks to identify existing drugs that could be turned into cancer treatments – either as additions to existing oncology drug regimens, or in combination with multiple repurposed drugs.

It's an approach that's starting to garner interest from others, besides desperate cancer patients. The cost of new cancer drugs is exploding. In 2013, $91 billion was spent on oncology drugs worldwide – almost double the GDP of Bulgaria. In 2014, no cancer drug was approved that cost less than $100,000 for a course of treatment, and in 2015 eight drugs cost more than $120,000. "If the current trajectory continues, then by 2030, we could see the first $100,000 per month treatment," says Paul Cornes, a Bristol-based oncologist and part of the steering group for the European School of Oncology's Working Party on Access to Innovation in Cancer Treatment. "The cost of cancer drugs has been rising five times faster than any other medicine. We've realised the power of targeted precision drugs, and they are expensive to make. But at some point this will bankrupt health systems."

Repurposing the large arsenal of approved, non-cancer drugs might therefore seem like an attractive solution. Many of the drugs identified by the ReDO project, and other repurposing initiatives, are cheap and already have a large body of safety data. Assuming that they are effective, this should hasten the approval process and provide patients with more new options, sooner. But are they? This question is proving perplexingly difficult to answer – precisely because they're so cheap and widely available.

Cancer drugs cost crisis

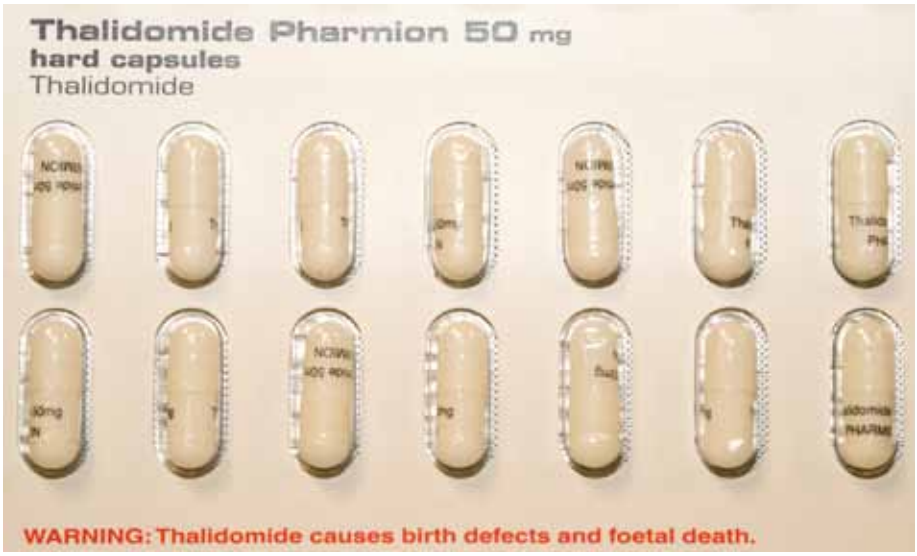
The current crisis in cancer drug costs has been building for some time. Aging populations mean more cancer, and in today's world, patients demand access to the latest and very best treatments. But developing these drugs is expensive: the current cost of bringing a new cancer drug to market is estimated at $2–4.5 billion, including all the failures along the way. "We now believe that 90% of the cost of developing medicines isn't the high-tech lab work, it is the clinical trials," says Cornes. "But one reason why we're having to run very large trials is because we're looking to statistically prove small differences."

The sad truth is that, in spite of all this investment, the improvement in survival yielded by targeted therapies is modest. "Some of the newer drugs are extremely expensive, but don't bring very much," says Mario Dicato, an oncologist at the Centre Hospitalier de Luxembourg, and co-chair of the ESMO World Congress on Gastrointestinal Cancer. He cites pancreatic cancer as one example. The addition of erlotinib to gemcitabine treatment around a decade ago increased costs by approximately $16,000 per patient, yet boosted median survival by just ten days. "Everybody uses this drug – including me – but in the end it's just ten days, and in those patients where it doesn't work you get the side effects," Dicato says. "It's a poor trade."

"Many of the drugs identified by the ReDO project are cheap and already have a large body of safety data"

That's not to say oncologists should give up on targeted therapies. It is likely these will eventually be made to work better, and the costs will come down, but that is going to take time and investment. "In the meantime, we need to learn how to use these drugs to make big differences and not little ones," says Cornes.

Part of the problem stems from our incomplete understanding of cancer biology. It's becoming increasingly apparent that there are far more cancer-initiating and driving DNA mutations than we anticipated – a complexity that's also reflected in the tumour microenvironment, says Francesco Bertolini, director of the Laboratory of Haematology–Oncology, at the European Institute of Oncology in Milan. This makes combinatorial approaches essential – at least in



A repurposing success story. Thalidomide, the drug responsible for thousands of birth malformations in the late 1950s, re-emerged 40 years later as a significant new treatment for people with refractory multiple myeloma

advanced tumours – and yet, "the cost of new drugs would no longer be sustainable if we use only on-patent drugs in combinatorial therapies," he says.

Possibly though, we've missed a trick, says Cornes: "The question is, in our rush to commercialise targeted therapies, have we overlooked opportunities to improve cancer outcomes that would be much more cost effective?"

Repurposed drugs could be one such opportunity. "My opinion is that we could actually get more if we stopped putting all our efforts into the new, and spent more time tinkering with what we already have," says Gauthier Bouche, medical director of the Anticancer Fund.

Tinkering with what we have

One of the earliest examples of a successfully repurposed drug is thalidomide. Originally developed as a sedative in the 1950s, it was later used to treat morning sickness in pregnancy – until babies started being born with severe deformities. Its resurrection came in the late-1990s, when clinicians at the University of Arkansas set up a trial of thalidomide in 84 multiple myeloma patients who had failed to respond to therapy, and were therefore expected to die within months. Twelve months later, 48 of them were still alive, a quarter of them event-free (*NEJM* 1999, 341:1565–71). Even so, thalidomide is an unpleasant drug, and treatment with it carries a high risk of neuropathy, so researchers started to develop less toxic analogues. One of them was lenalidomide, which today generates around $4 billion in worldwide sales per year.

Possibly there are other effective cancer medicines sitting undiscovered on pharmacists' shelves. So far, the ReDO project has compiled a list of more than 70 non-cancer drugs for which there is some pre-clinical and clinical evidence of anti-cancer action, and published detailed reviews on the six most promising through the open-access journal *ecancer*. They are: the anti-helmintic drug, mebendazole; the antacid, cimetidine; the angina drug, nitroglycerin; the broad-spectrum antifungal agent, itraconazole; the antibiotic, clarithromycin; and the NSAID, diclofenac. As well as identifying these drugs, ReDO is working with clinicians in different countries to design and fund more advanced clinical trials. Trials are already underway of nitroglycerin in non-small-cell lung cancer, perioperative ketorolac in high-risk breast cancer, and fluvastatin-celecoxib in optic nerve gliomas.

Elsewhere, large clinical trials are investigating the potential of aspirin, the beta-blocker, propranolol, and the antidiabetic drug, metformin, in a range of common cancers, including breast, colorectal, and prostate cancer – as well as less common ones, such as angiosarcoma (see, for instance, Drug repurposing in oncology, *Cancer World* May–July 2016).

"The painkiller, diclofenac, does multiple jobs that are of interest to cancer, in one tablet"

Admittedly, few of these drugs are being proposed as an alternative to targeted therapies. "We don't expect to find a magic bullet, so we are primarily looking at combinations – either with chemotherapy and standard therapies, but also combinations of repurposed drugs," Pantziarka says. Many of these older drugs hit multiple targets, and because of this, clinicians often regard them as dirty drugs – and yet this could be their strongest suit. Take the painkiller, diclofenac: "It is a great anti-angiogenic drug, it modulates the

immune system and it has some effect on sensitising the body to chemotherapy and radiotherapy," says Pantziarka. "It does multiple jobs that are of interest to cancer, and it does it in one tablet."

Patient-centric not patent-centric

It's a more patient-centric approach than the one being taken by many pharmaceutical companies, which identify a molecular target and then tailor their research to the approval of the drug they've developed to block it. This in itself may boost the chances of success, says Bertolini: "The drug-centric approach selects the patients according to the needs of an approval process, the patient-centric approach combines drugs independently from the presence of a patent pending."

In some cases, the idea is simply to see whether giving one of these drugs post-surgery could reduce the risk of recurrence. Add-Aspirin, a randomised clinical trial taking place in the UK and India, is currently recruiting 11,000 participants to help find out whether regular aspirin use after treatment for an early stage breast, colorectal, gastro-oesophageal or pancreatic cancer can delay or prevent cancers coming back.

However, some non-cancer drugs are being investigated precisely because they have the potential to hit specific targets, such as the STAT3 pathway, which often becomes activated in lung cancer patients taking an EGFR inhibitor like gefitinib (Iressa). "We know that when you are targeting one molecular pathway, the cells almost immediately activate parallel signalling pathways and develop mechanisms of resistance," says Niki Karachaliou, Director of the Medical Oncology Department (Rosell Oncology Institute) at the University Hospital Sagrat Cor in Barcelona. "We are trying to understand what other pathways are being activated, what we need to target, and we're then screening for compounds that have been reported to hit that target." One STAT3 blocker they've identified is the anti-helmintic drug, niclosamide. Another is the diabetes drug, metformin.

"For a pharmaceutical company, it may be more appealing to search for a new drug from the beginning; however, patients want faster solutions," Karachaliou says. "If the drugs are already used for other indications, we know the side effects, we know the doses; there are fewer uncertainties."

All the same, it's unlikely that AstraZeneca, which owns the patent on Iressa, would fund larger trials of metformin or niclosamide – even if they made Iressa work more effectively (its patent is due to expire next year). Instead they're more likely to focus on their own next-generation antisense oligonucleotide inhibitor of STAT3, which is already in the pipeline.

This is a key problem facing those involved in drug repurposing. "A drug company that invests money in supporting a clinical trial is not guaranteed to recoup that money if the trial is successful, because some other manufacturer could come in and sell the same drug at a lower price," says Pantziarka. Not only do those researchers who choose to go it alone have to secure funding to run a clinical trial, they will often have to buy the drugs and package them up themselves. Then, if the trial is successful, they will need to find a way of funding the application for a new license. The costs of licensing a drug in Europe are between €83,700 and €278,800 – plus an annual cost of €100,000 to maintain market authorisation.

Who will pay for market access?

"The question is who actually could and should pay for the work that would be required to get a license and market a drug for oncology," says Nigel Blackburn, Cancer Research UK's director of drug development, who is currently involved in phase I trials of a repurposed anti-inflammatory drug. "Pharmaceutical companies have to turn a profit at the end of the day, and if there is no prospect of them getting a return on that investment they won't touch it. Meanwhile, there is no movement that I know of in any government or regulatory body to do anything about this: it just doesn't seem to be on their radar."

Possibly charities like Cancer Research UK could step into the breach; it is the biggest supporter-led cancer charity in the world, and spent around £435 million last year on research. But

"One option would be initiatives involving governments, health insurers or foundations"

the extremely high costs involved in running clinical trials make this unlikely, Blackburn says: "A phase II trial will typically cost £20–30 million [€23–35 mn], and a phase III trial, £50–70 million [€58–81 mn]. We could do it, but we would have to stop an awful lot of the other things that we do."

Another possibility, suggested by Bertolini at the EIO, would be public–private initiatives involving governments, health insurers or foundations. Using this model, governments or health insurers could potentially recoup their

Getting new options into the clinic

Cancer patients who no longer respond to recommended treatments need affordable new options now.

Many existing drugs that are off-patent, and whose side effects are already known, are likely to offer benefit to certain cancer patients, based on their mechanism of action or observational data or even multiple clinical trials.

Thalidomide (in multiple myeloma) and docetaxel (in advanced prostate cancer) are examples of off-patent drugs that have shown benefit well beyond what most novel drugs offer, and at a fraction of the price.

However, the low price of off-patent drugs, and lack of exclusivity, means that getting them approved for new indications is commercially unviable.

Exploiting the potential of repurposing off-patent drugs for use in cancer may require new incentives and a greater acceptance of uncertainty within the context of shared decision making.

investment by lowering the overall cost of cancer treatment if the repurposed drug was shown to be effective in advanced disease or in preventing cancer recurrence. For foundations that focus on rare cancers, repurposing existing drugs may be the cheapest way to provide their patients with new treatments.

Who will champion their use?

In some cases, though, these drugs have been through extensive trials, show clear benefits – and yet they're still not being used, because there is no-one to champion them. Take cimetidine, a patent-expired anti-ulcer drug. Five randomised trials have shown that adjuvant cimetidine – either around the time of surgery for colorectal cancer, or in the period afterwards – reduces the risk of death from recurrence, and a Cochrane meta-analysis also confirms this. But having scrutinised European, American and Japanese guidelines for the treatment of colorectal cancer, Cornes says he can find no mention of this data. "Cimetidine is a drug whose side effects are known, it is inexpensive, and you can buy it over the counter in the pharmacy," he says. "It fundamentally raises a question about what level of proof we want to accept in our next generation of guidelines for colorectal cancer."

There's also the question of what clinicians should tell their patients. Not every doctor is happy to prescribe drugs off-label – they may come under pressure not to from their peers or managers, or find themselves in trouble if something goes wrong. But in the absence of funding to run large randomised clinical trials or apply for new licenses, drugs repurposers and oncologists find themselves in a Catch-22 situation.

Some maintain that further data are necessary before drugs can be recommended to cancer patients – even ones as widely used as aspirin. Others, like Cornes, believe an honest conversation is the best approach: "We know that our patients are desperate for help, and that perhaps a third to a half of Europe's cancer patients take unproven therapies alongside the therapy we give them," he says. "Why don't we give them the opportunity to take proven but unlicensed therapies, and discuss our uncertainties with them about the exact dose and schedule – things that a licence would force you to have?"

Most of all, however, Cornes believes the time has come for a debate about what constitutes good value in oncology. Is it pouring billions of dollars into producing targeted therapies that society then can't afford to prescribe? Or is there value in revisiting the arsenal of drugs we've already got and finding smarter ways of using them? This principle doesn't only apply to bathroom cabinet stalwarts, like painkillers, and to diabetes drugs, but to older cancer drugs as well. The STAMPEDE trial revealed that adding cheap, patent-expired docetaxel to standard hormone therapy for prostate cancer added, on average, ten months to men's lives, compared to standard treatment alone. And in the case of those whose cancer had metastasised, adding docetaxel increased survival by an average 22 months (*Lancet* 2016, 387:1163–77).

Although tinkering may be less financially rewarding from a commercial perspective than engineering new drugs, both are necessary, and even complementary, says Bouche, from the Anticancer Fund. "When you look at the history of medicine, tinkering is found at the early stages of multiple major therapeutic advances such as surgery, psychological interventions, hygiene, vaccines – but also drug development," he says. Tinkering could also be part of the next big advance in cancer treatment – if we let it. But it needs to be incentivised.

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Who truly represents the patient perspective?

As researchers, regulatory bodies and health systems give patients more of a voice in consultation and decision making, advocacy groups are questioning what it really means to represent the patient view. **Simon Crompton** reports.

Nothing about us without us. So goes the mantra of patient organisations around the world, asserting their right to have a say in health decision-making.

Five words that make patient involvement sound so simple. But a growing body of patient and cancer organisations are asserting that it's anything but simple: the whole idea of 'patient representation' is flawed and needs a re-think, they say.

Conventional models of patient representation bring risks. For some committees, companies and organisations, having a patient on the panel simply means they can tick the patient involvement box and move on. At least that's the view of Deb Maskens, founder of Kidney Cancer Canada and Vice Chair of the International Kidney Cancer Coalition (IKCC).

"It's far too easy for health technology assessment organisations or pharmaceutical companies to say that they have a patient on their committee and therefore they have had patient input," she says.

Equally, long-standing patient representatives can lose their independent perspective as they become embedded into formal committees and organisational norms. "Some even see it as a conflict to be in touch with the patient advocacy group – that if they consult patient organisations or advocates they've somehow gone over to the other side and will introduce bias. The esteemed people on the committee become their tribe and closest affiliation."

And then there's the question of how 'representative' patient 'representatives' can actually be. Several European patient organisations have become concerned about

the number of committees where one or two firmly established patients are there to represent all cancer patients – even in discussions that relate to a type or stage of cancer entirely different from their own. That situation, says Maskens, is "absolutely ludicrous".

Bettina Ryll, founder of the Melanoma Patient Network Europe, Chair of ESMO's patient advocacy working group and a patient representative on many committees, agrees. As long as patients on committees are expected to represent the views of hundreds of people whose experiences may be entirely different from their own, they are in a very vulnerable and ineffective position.

"It's very very difficult to be representative. I'm fed up with being challenged about this wherever I go. People say: 'Yes, but how representative are you anyway?' and this is a very easy way to take out the patient perspective if it's not convenient. It's an especially pressing issue because not everyone in health systems is happy with patient voices becoming more integrated into health decision-making. Undermining difficult patient views happens very frequently, and in the end, just the 'yes-sayers' are left over. That's not sufficient."

Those who represent patient interests in complex technical discussions are also vulnerable to criticism. Discussions on the relative risks and benefits of specific drugs, for example, may require some expert knowledge from the patient representative. But people with that degree of understanding are then accused of no longer being representative of most patients. "It's a double bind," says Ryll. "You can't win."

Evidence-based advocacy

But there may be a way forward. A growing number of patient advocacy groups are adopting the idea of 'evidence-based advocacy' to replace conventional ideas of 'representation'. It involves letting go of any expectation that one patient should be able to represent everyone. Instead, patients on groups or committees gather, filter and convey information about the patient perspective on a particular issue from a variety of sources. They become a conduit for evidence from the relevant patient community, not a narrator of personal experience or opinion.

"I don't in any way want to take away from the value of people conveying their personal narratives," says Maskens. "But patient representatives now need to be equipped with a new skill set.

"For some, having a patient on the panel simply means they can tick the patient involvement box"

"Those on established committees should have to have an ear to the ground of what is happening in that disease space. There are thousands of people online in some form, and so before a review decision comes up, patient representatives can take a deeper dive into that patient community – listening to them, asking open-ended questions.

"If a committee includes a patient who cannot demonstrate how they regularly engage with a broader community, then I think we should be calling that representation into question. In the worst cases that representation is bringing in commentary that is subjective and not in any way evidence-based. It's come out of the blue sky."

According to Ryll, there are plenty of opportunities for gathering information from specific groups of patients, including conducting online surveys through software such as Survey Monkey, gathering opinion at conferences, and conducting Facebook polls.

"Because of social media, it's never been easier to gather information," she says. "It's not that hard to produce data."

A recent pilot study from the European Medicines Agency showed the potential of this kind of evidence gathering. The EMA worked with the Melanoma Patient Network Europe and Myeloma Patients Europe to investigate how studies into patient preferences might inform the regulatory review of medicines. Could a uniformity of view about the relative risks and benefits of drugs be found in patient subgroups that could usefully inform market authorisation decisions?

A survey of 139 patients with advanced (stage IV) cancers, along with carers, advocates, regulators and health professionals, suggested it might. It found that patients were significantly more accepting of the potential risks of a treatment than their carers – and that patient advocates were more risk averse than either (see panel overleaf). Ryll says that this kind of study indicates that the views of advocates are not necessarily those of patients with advanced cancer, and provides vital information on what a specific group of patients really think. The EMA and Myeloma UK are now working on a follow-up study to find out more about the degree of risk patients are prepared to accept in treatments.

According to Francesco Pignatti, Head of Oncology at the EMA, this work is part of a general movement from patients, regulators, industry and academia to find the best ways of eliciting the values of specific groups of patients – with different cancers, at different stages – and using this knowledge to inform treatment decision-making and regulatory and payment decisions.

"It's an important part of our work to get quantitative data," he says, "to elicit whether there is a heterogeneity of views and to get a comprehensive understanding of how the different groups – elderly versus young, for example – think."

The changing role of advocacy

There are many other examples of patient organisations taking on the role of 'evidence gatherers', rather than 'representatives', to best make the case for treatment improvements.

Who can speak for patients?

The level of risk that patients who are dying of cancer are prepared to take in the hope of some benefit may be underestimated even by the people closest to them. This was one of the findings of a pilot study conducted by the European Medicines Agency.

A group of regulators, healthcare professionals, patients, carers and advocates were asked about what percentage increase in the probability of toxicity they would be prepared to accept for every 1% increase in the probability of surviving 12 months (*Clin Pharmacol Ther* 99:548–554).

Responses showed that regulators and healthcare professionals were more risk averse than the group of patients, carers and advocates. More surprising were differences within the melanoma subgroup, which consisted of stage IV patients, stage IV carers and advocates. Patients said they would accept more risk than carers, and much more risk than advocates. Indeed advocates were more risk averse than the regulators.

While the results of this subgroup analysis need to be confirmed, they provide ammunition for those who argue that, where priorities and preferences are concerned, every effort must be made to consult widely among the affected patient population, to allow their authentic voice to be heard.

In 2013, for example, the CML Advocates Network – an international network of organisations supporting patients with chronic myelogenous leukaemia, made an impact with its survey into how well patients stuck to their Glivec prescriptions.

The survey received more than 2,150 responses online and almost 400 on paper, and resulted in a highly influential report, documenting the surprising extent to which patients on long-term medication miss doses, even when their illness is potentially life-threatening.

It illustrated how successful advocacy organisations could be in gathering information that doctors and official bodies might have difficulty uncovering, and has paved the way for similar work by other patient bodies.

At a Masterclass in Cancer Patient Advocacy held by the European School of Oncology in June, organisations for patients with kidney cancer, neuroendocrine tumours, pancreatic cancer and lymphoma gave presentations on how they were contributing to discussion and advancing treatment through gathering information.

Charlotte Roffiaen, Regional Director of Lymphoma Coalition Europe, described how the coalition's patient experience survey and database on access to care had helped identify the priorities of patients with different disease subtypes. Its findings are being used in discussions with regulators and pharmaceutical companies about patient unmet needs.

Ali Stunt, Chief Executive of Pancreatic Cancer Action, argued that patient surveys play a vital role in advocacy. They provide richer information about the real impact of disease and treatments than disease statistics, and also move beyond the purely anecdotal. Her organisation's 2015 patient and carer survey collected 400 responses via Survey Monkey, and provided important evidence of inequalities in care.

According to Ryll, regulators and HTA Boards are welcoming this new type of advocacy. If anything, she says, it's a challenge to advocates from patient organisations, because it is demanding and needs resources. She'd like to see public and educational bodies support advocacy organisations in becoming expert at producing qualitative and quantitative data.

"We are sitting on a phenomenal resource that can have a huge impact on what our patients are exposed to, so it's not just an opportunity but also a responsibility. If we are the ones with that type of access to primary data, it's our responsibility to use it and learn on behalf of our patients."

Advocating on broader issues

However, not all patient organisations believe that collecting data about the detail of patient experiences and preferences should be a core concern. Large umbrella organisations such as Europa Donna – the European Breast Cancer Coalition – and the European Cancer Patient Coalition (ECPC) believe that their constitutional frameworks and relationships with members ensure they can represent a wide range of people, and gain input on specialist areas when necessary.

ECPC President Francesco de Lorenzo says there is a danger of patient advocates getting too involved in the minutiae of decision-making in areas which can require some expert knowledge. Their priority has to be campaigning against inequalities in cancer treatment and care.

"We have to make clear what the role of the patient advocate is. I don't think they should become professionals," says De Lorenzo, a colorectal cancer survivor and medical doctor, who has been involved in patient advocacy since 1997. The ECPC has represented patients in initiatives with the professional societies for medical and radiation oncologists, and with European bodies such as the Expert Group on Cancer Control. It also selects cancer patient representatives to take part in the EMA's benefit–risk evaluations.

"I think patient advocates should raise awareness of patients' new needs and defend

the right to equal access to innovative and sustainable medicines, and access to clinical trials. That doesn't mean they should be involved in supervising clinical trials. We need to trust the experts and scientists: they're not against the patient. That's the position of the ECPC."

He says that the organisation gathers a wide range of perspectives on specific cancers and circumstances through its diverse board and close relationships with its 400 member organisations in 44 countries. They provide the direction and the messages for advocacy.

"We know that inequalities are the worst thing affecting patients, so we want to find and fight the worst disparities in treatment. We know that this is the problem that each patient organisation is fighting. We want to ensure meaningful innovative treatments for all who need it. So we are working with members of the European Parliament to bring change."

Susan Knox, Chief Executive Officer of Europa Donna, believes that the organisation's diverse board and membership in 47 countries ensures that it represents and can draw on a wide range of cancer experiences. Constitutionally, Europa Donna is set up to meet the needs of its member organisations. All members agree on Europa Donna's campaigning priorities, which are reviewed twice a year at General Assembly meetings.

"We've been operating for 22 years, and I can honestly say that nobody has ever raised their hand and said, 'We're not sure you're representing us,' she says.

But is there a danger that some patient representatives get too engrained in systems and lose their independent perspective? Knox acknowledges the risk, but says that the fast turnover of its board members ensures against this.

"It's true that there are more and more requests from professional organisations for us to participate in their activities: Europa Donna is now being asked to serve on trial committees, be part of the international breast groups, understand very complicated trial protocols, get involved in all kinds of consent forms. To be a patient representative in some of these areas requires an expertise that isn't always easy to find."

New skills sets. 'Evidence-based activism' was among the topics discussed by delegates from 17 European/international organisations at the ESO Masterclass on Cancer Patient Advocacy, in June

So Europa Donna provides training, particularly in the research field, so that they can do their job effectively. "This means that patient representatives can do an effective job, and not just rubber stamp what is handed to them by organisations and scientific investigators."

More than one approach

So where next for patient advocates? Keeping independent, having expert knowledge, being informed by data, being alert to grass roots opinion, pushing for equity of service: it's a ridiculously tall order to keep everyone happy.

Organisations such as the EMA are excited about the potential of evidence-based advocacy. But they are not expecting it to provide all the answers.

"My view is that patient involvement is best achieved through a collection of approaches," says Pignatti. "We don't expect patients to be taking over the role of the regulators, but the decision will be much more informed by this variety of approaches, sometimes expert opinion, sometimes a more population-based study on patient preferences and so on."

EMA's patient relations coordinator, Nathalie Bere, agrees. "Sometimes a single conversation with a single patient will highlight something really important to follow up," she says. "It's not that there's one best way to engage with patients. It depends on what the level of activity is, and what information you want at that particular time. You need a toolkit of approaches you can choose from."

As for Ryll, she just believes that things can be, and should be, so much better.

> **"If we are the ones with access to this type of primary data, it's our responsibility to use it"**

"I'm not a missionary for evidence-based advocacy," she says. "I'm just trying to make a difference in melanoma. But for us, having an evidence base to your advocacy takes away the criticisms of how representative you are. It brings you closer to your population. It guards against bias. And, in a way, it's liberating, because you're free to explore and measure. It's not about being right. It's about understanding what the problem is."

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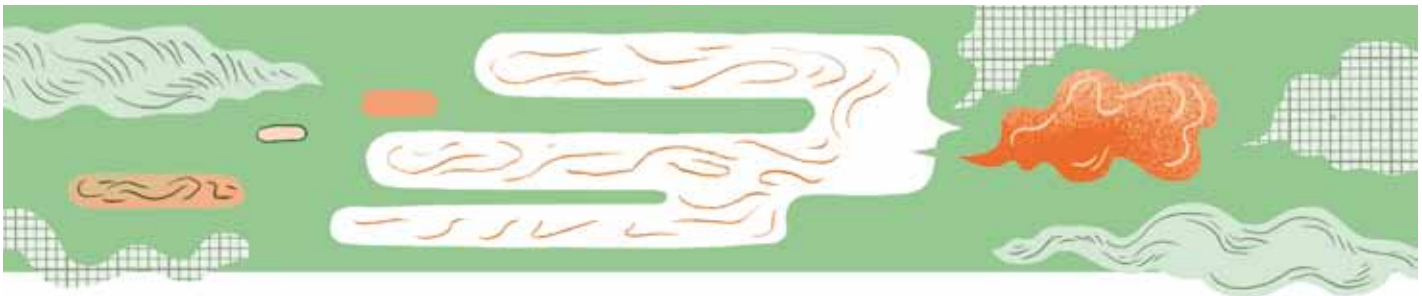

Joseph Gligorov: *oncologiste sans frontières*

Based in a large Paris hospital, breast cancer specialist Joseph Gligorov feels privileged to be able to offer his patients a very high standard of care. He talks to **Anna Rouillard** about his efforts to help those working in more challenging settings do the same.

Joseph Gligorov is not alone in having been drawn to practice oncology by the unique quality of the patient–doctor relationship and the highly collaborative nature of the work.

Few others, however, can match his career-long commitment to improving and extending both. From his involvement in national and international guidelines conferences, to his role promoting cooperation among oncologists in the Mediterranean area, and his local initiatives training patients to use their own experience and insight to support other patients, Gligorov is a doctor who is constantly looking for ways to communicate and collaborate to improve the quality of cancer care.

It was on embarking upon an internship in medical oncology at Rouen, followed by his senior position in oncology at Tenon hospital, and Pierre & Marie Curie University in Paris, that Gligorov discovered the special demands of interacting with patients. "Cancer is a disease where patients need to discuss a lot of things," he says. "The disease itself is clearly the central focus, but because of the stress and anxiety it provokes, and the uncertainty about the future, patients often open up to their doctors and share a lot. So not only do you have to know a lot about medicine, there is also a psychological aspect."

The psychological aspect of care is something Gligorov believes is an integral part of quality cancer care, and he dedicates time each week to training the next generation of medical oncologists to communicate effectively with their patients.

"The interaction we have with patients is a kind of coaching. It is not just about offering information on the disease, it is about effective engagement that positively influences the patient's acceptance of their treatment and their compliance with it. Training covers how to deliver what can sometimes be difficult information, such as the patient's prognosis or certain side effects or safety issues of treatment."

He adds, though, that doctors can only go so far in educating and supporting patients. "Of course I do my best, but at the end of the day, if I have not experienced a particular treatment myself, I can only explain what other patients have shared with me. I cannot know first-hand what it feels like to wake up and have lost my hair, or for my children to look at me in a certain way because I look different". For this reason, he is rolling out a programme at the Tenon hospital in which cancer survivors are trained to coach current patients.

Learning from AIDS advocates

This is the first programme of its kind in oncology, but it was inspired by successful initiatives in another disease. "At the beginning of the AIDS epidemic, HIV was considered the new cancer, with people using the same terrible words that were associated with cancer: no treatment, suffering, death." But at that moment, Gligorov says, HIV patients organised themselves and worked together to raise awareness about the disease and about the importance of involving patients in fighting it. As a result, they became involved in the process of drug development, treatment strategies, and clinical trials.

"We want to draw on this experience for oncology," Gligorov enthuses. "Part of the reason that recruitment to clinical trials in cancer is so low, at around 10–20%, is that patients are often afraid. But if they can speak directly to somebody who has been through a clinical trial, who can reassure them and give them a positive picture, we may be able to improve these numbers."

Through the programme, which will be rolled out in 2016/17 at Pierre & Marie Curie University, cancer survivors will receive training from nurses, doctors and patients, as well as psychologists, to equip them to lend support to people currently undergoing treatment. "What the patient needs in this kind of disease is to be able to look to the future and envisage a life after treatment," says Gligorov. "We believe that this programme, which puts them in direct contact with people who have gone through what they are experiencing and have come out the other side, will help them to be able to project a positive future for themselves."

This work is becoming increasingly important, he says, as more and more cancers are being cured. "We need to prepare patients to acknowledge that these will be difficult months or years, but that going through the treatment will be worth it, as they will be able to close the door on cancer, put their experiences behind them and go back to their daily activities."

Spreading progress through guidelines

While new treatments have played a role in improving survival rates, Gligorov believes that improved organisation of care has also been key, and that working according to multidisciplinary guidelines is the cornerstone of well organised care. Guidelines are particularly valuable for physicians who are working within structures that do not have access to the full range of expertise and

specialties found in larger centres, he says. "In some countries and hospitals, cancer patients may be treated by general oncologists, or by physicians who are not even specialised in oncology. For me, guidelines are of highest importance for these people, and it means providing them with clear information about what we know, what is the state of the art, what is possible and what is potentially risky."

Collaboration between disciplines is one of the things that first attracted Gligorov to a career in oncology. "The feeling that you are working in a team and all going in the same direction was very important for me," he remembers. Twenty years ago, however, while the various care providers did work very closely, with a lot of interaction and discussion, the whole effort was not formalised in guidelines in the way it is today. As he explains, the organisation of cancer care has inevitably had to evolve rapidly in response to the availability of novel treatments and advances in understanding of the disease.

Gligorov has played an important role in developing some of these guidelines, at an international level as well as specifically for use in France. He has been on the panel of the St Gallen Breast Cancer Conference – which develops consensus guidelines for the care of people with early breast cancer – as well as the International Consensus Conference for Advanced Breast Cancer (ABC) – the first initiative to develop guidelines for treatment of advanced disease, which has now met three times. "Both St Gallen and ABC are very interesting, because they promote the sharing of knowledge and expertise, with experts coming from different parts of Europe and the world. We see that people view situations from different perspectives depending on their cultural or political backgrounds, and obviously these factors contribute to the recommendations that come out at the end of the process."

"Having this confrontation between what we as doctors think and what the patients think helps balance the recommendations"

Of particular interest in the ABC Conference is the role patients play in the process. "Having this confrontation between what we as doctors think and what the patients think, having a photograph of both sides of the picture, is incredibly useful, because it helps balance the recommendations. We sometimes find ourselves being more modest, or strict, in our recommendations, having been able to hear the patients' experiences and viewpoints."

Gligorov's personal history in breast cancer is closely associated with the introduction of clinical guidelines for breast cancer geared specifically to the French system. The guidelines conference, held annually in the beautiful medieval town of Saint Paul de Vence, near Nice, emerged out of one of the very first educational courses in breast oncology, founded more than 30 years ago by two of Gligorov's close friends, breast oncologists Moise Namer (Nice) and Marc Spielmann (Paris).

After 11 years of the course, which had been part of the original teaching programme of the newly founded European School of Oncology, Gligorov and Namer decided to develop national guidelines for early and advanced breast cancer, which became known as the Saint Paul de Vence guidelines. "Breast cancer experts from France and other French-speaking countries are brought together every year and asked to answer specific questions identified by the scientific committee, and every two years consensus guidelines are produced."

Gligorov sees this work as a central part of his investment in breast cancer education. "Moise [Namer] is one of the top breast cancer specialists in France, and probably in Europe. When you talk to him, you have the feeling you have a large chapter of breast cancer history in front of you. As far as Saint Paul de Vence is concerned, I am merely trying to continue what he built."

A universal oncologist

Born in France to Yugoslav parents, Gligorov regularly visits colleagues and family members in Macedonia and neighbouring countries. These ties have given him direct insight into the challenges these countries face in medicine in general and in oncology in particular. Beyond that, they have no doubt helped foster a huge appetite for learning about, and interacting with, people from different cultures. Gligorov says he considers himself very fortunate to have had access to books, to be able to learn, and to travel. He is fluent in French, English, Macedonian, Serbian, Croatian, Italian, Russian and Bulgarian.

So when he started exploring ways to help countries with less developed health systems to improve the quality of their cancer care, he looked for solutions that could benefit the region as a whole. This was the idea behind AROME, the Association of Radiotherapy and Oncology of the Mediterranean Area, launched in 2006 with the aim of promoting knowledge and development of oncology around the Mediterranean basin, covering countries in southern Europe, the Balkans, the Levant and north Africa. "These countries share a lot of common history and values," says Gligorov, "and the idea was to create a network to share experiences and promote exchange of information on education, care, epidemiology and access to innovation."

Improving outcomes around the Mediterranean basin. Gligorov cofounded the Association of Radiotherapy and Oncology of the Mediterranean Area, AROME – whose board is pictured above – to facilitate networking and education between countries in the region.

"In the most developed countries discussions in oncology often revolve around the approach towards certain important drugs," Gligorov explains. "But there are a lot of countries where the prime concerns are rooted in the basic organisation of care, such as ensuring that screening programmes are in place or that there are quality surgeons and radiotherapy machines."

There is a high level of frustration in these countries, he adds, "because they are receiving information from the internet on trial results and new drugs, but they simply cannot afford them." This frustration is compounded by the much higher proportion of cancers diagnosed at a late stage. "The less developed the country, the more advanced disease there is, and the more drugs you need. In developed countries, it is common to have mostly diagnoses of early breast cancer, which may be cured with surgery and radiotherapy alone, and potentially some endocrine treatment. But this is pretty rare in the Mediterranean area, where population-based education programmes on prevention and early detection are generally absent."

AROME was founded by Gligorov together with two good radiotherapist friends, Yazid Belkacemi (Paris) and David Azria (Montpellier), with the support of Abraham Kuten, a radiotherapist from Israel. With members based across 21 countries on the Mediterranean rim, the association organises educational seminars, as well as exchange programmes between hospitals in the member countries.

It has also started to provide guidance on access to cancer care innovations in emerging countries, with a first meeting on this subject held in Montenegro last year. "Following this meeting we are putting together a paper that sets out guidance on the key areas that we believe need to be addressed to improve cancer care in each country. There are recommendations on prevention, screening, organisation of the multidisciplinary team, quality-assured centres, as well as criteria for identifying the most efficacious drugs."

While this may sound like it overlaps with the work already undertaken by the World Health Organisation, with its Essential Drugs for Cancer Chemotherapy list, and by the European Society for Medical Oncology, with its recently devised Magnitude of Clinical Benefit Scale, Gligorov argues that tailored guidance is needed for the AROME countries. "The paradox is that the rich countries are trying to tell the poorest countries what they need and what they do not need. But the epidemiology of the poorest countries is such that they have specific needs when it comes to cancer drugs, which are different from our needs."

He argues too that the learning process is by no means all in one direction, in particular when it comes to understanding the values and priorities of patients. "In the large cities of western Europe, we have sometimes quite significant populations of immigrants from the Mediterranean countries. Learning about their perceptions of disease, and of cancer, is highly beneficial and helps us tailor treatments to specific cultural settings here in France."

It's a comment that neatly sums up Gligorov's whole approach to quality cancer care. Whether it's about doing your best for the patient in front of you, or getting the best results from cancer services as a whole, there are no universal answers – it requires making the effort to understand each specific situation, and communicating and collaborating to find specific solutions.

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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. Verpoort K, Mihler 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: PS-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 MU/0.5 ml and 48 MU/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 0.1 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 mobilized 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.

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Strengthening health systems is not our business

A narrow focus on cancer prevention, detection and care can only succeed as part of wider efforts to strengthen public health systems.The cancer community needs to start playing its part in that effort.

Richard Sullivan – Director of the Institute of Cancer Policy, and Conflict and Health Programme, at Kings Health Partners Comprehensive Cancer Centre, London

Health systems strengthening (HSS) has become the new focus for global health. The strategy is enshrined in the Sustainable Development Goals and calls for universal health coverage, but it dates back to the 1978 Alma Ata Declaration of Health for All.

Since 2005, resources and attention have shifted from disease-specific approaches to strengthening health systems. HSS is described by the World Health Organization as a single framework with six 'building blocks': service delivery; health workforce; information; medical products, vaccines and technologies; financing; and leadership and governance (stewardship).

These sorts of 'building blocks' for health are much loved by academics and policymakers. There are as many variations on HSS as there are stars in the sky, from diagonal approaches to complex investment models. Whilst a great deal of the HSS discourse is, frankly, 'ploughing the sea', there is a serious issue. This is the conceptual framework around which funding for global health now fits – be it research, official donor assistance or structural funding from bodies like the IMF. So the question is, how does cancer fit into this 'new' paradigm?

Firstly it's worth pointing out that cancer control (prevention, early presentation, affordable high-quality control, cure and palliation) can only be built on strong existing health systems. I've made this point before (*Cancer World* Jan–Feb 2016): health systems that are not properly funded and structured *de facto* will never be able to deliver affordable, equitable cancer control.

> "Cancer control can only be built on strong existing health systems"

The cancer fraternity tends to get somewhat wrapped up in its own world, but we also need to advocate for better public health for all. It's clear that, as a global community, cancer has not been universally good about building resilience into nascent and emerging cancer control systems, to help them weather political

unrest, economic turmoil and man-made disasters such as the conflicts in Libya and Syria (*Lancet* 2016, 388:207–10).

Serious investment as a public good by wealthy countries and research funders can and does pay dividends in building the health and cancer workforces of tomorrow (*Lancet* 2013, 381:2118–33). We need to do much more of this, and not treat it as exceptional.

Real improvements in cancer outcomes are composite endpoints of systems – social systems, which determine when and how patients present, and health systems, which are only as good as their weakest component. It's easy to see why approaches to cancer control have predominantly been technocentric and specific to particular modalities (medical oncology, surgery etc). That's the way the money flows.

If public and industry funding were rational and followed patient outcomes, then they'd only ever fund through multidisciplinary structures. Looking from the outside, it defies rationality to advocate for access to cancer medicines in countries unable to deliver the most basic system for cancer surgery.

"It's time for the cancer community to stop being parochial, and focus on building pathways of care"

When disease-specific funders such as the GAVI vaccine alliance are investing in HSS, it's time for the cancer community to stop being parochial, and focus on building cancer systems and pathways of care. So how do we go about this?

First we have to recognise that there is a *real-politik* to cancer systems, and that is their breathtaking complexity. Moreover the concept of health systems strengthening for global cancer remains vague, and there is a weak evidence base for informing policies and programmes for strengthening health systems generally (*Health Policy Planning* 2013, 28:41–50). But both these hurdles are surmountable.

Funding could and should be directed at cancer systems research, and we need to recognise that health services research is not a poor cousin, but the lifeblood for evidenced-based cancer control plans. The disciplinary approaches also need to breach the orthodox boundaries to embrace political economy, social science and all manner of disciplines capable of shedding light into the darkest recesses of cancer systems.

Women in the Iringa region of Tanzania attending a mass screening day for HIV and cervical and breast cancer, November 2015. The organisers, Pink Ribbon, Red Ribbon, make a point of acknowledging that the initiative, which screened 1,500 women over two days, and treated or referred on women who tested positive, relied on having a functioning local health system already in place *(see http://tinyurl.com/Screening-Tanzania).*

We also need to recognise that the discourse we have in high income countries about HSS and cancer are of limited relevance to many countries that have fragmentary, low-capacity and discontinuous health services. Radically different thinking and approaches are needed here to get cancer into the mainstream of HSS. John Kingdom, one of the doyen's of public policy, argued that issues get onto policy agendas when three independent streams – problems, policies and politics – flow together (*Agendas, Alternatives, and Public Policies* 1984; Little, Brown).

Defining cancer as a systems problem would go a long way to neutralising onco-tribalism, and make cancer a more cohesive global force in health systems. So too would embracing policies relevant to social determinants, as well as the structures and organisation of cancer care. The slavish adherence to cancer as a technical problem puts it at odds with a lot of the conceptual underpinnings of HSS. And finally, the politics of cancer needs to move away from the non-communicable diseases 'box' and into the areas that really matter to HSS, such as development and the equality agenda.

BCC 2017

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Managing adult soft tissue sarcomas and gastrointestinal stromal tumours

Sarcomas and gastrointestinal stromal tumours include a wide variety of biologically diverse cancers, many of them very rare. **Paolo Casali**, a leading expert, presents an update of the latest evidence on the best way to manage them.

This is an edited version of a presentation by Paolo Casali, from the National Cancer Institute, Milan, Italy, that was first transmitted to the 2nd ESO–ESMO Latin-American Masterclass in Clinical Oncology for the European School of Oncology. It is edited by Susan Mayor.

Sarcomas and gastro-intestinal stromal tumours (GISTs) are rare cancers. The incidence of soft tissue sarcomas in adults is 4.5 per 100,000 population per year, and for GIST it is 1.5 per 100,000 population per year. Osteosarcoma has an incidence of 0.3, Ewing's sarcoma 0.2, and rhabdomyosarcoma (RMS) 0.1 per 100,000 per year.

The very low incidence of these rare cancers contrasts with an incidence rate of 300 per 100,000 per year for benign tumours. This poses a challenge for clinicians and inevitably results in delays in diagnosis. This is true for a range of soft tissue lesions, such as uterine leiomyosarcomas, whose benign counterpart – uterine leiomyomas (fibroids) – is one of the most common conditions in women.

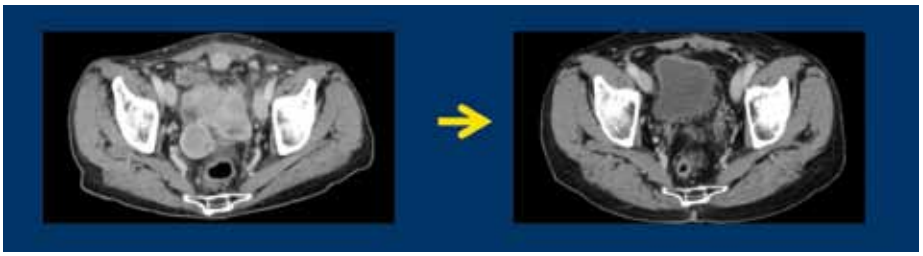
Treating localised tumours

Surgery is the standard approach for treating localised adult soft tissue sarcomas. Radiation therapy is used quite frequently, although possibly less frequently in current practice. However, when soft tissue sarcomas are high grade, deeply located and require surgery that is not compartmental surgery, then radiation therapy is indicated in principle. Use of adjuvant doxorubicin plus ifosfamide is not standard treatment, although it can be used on an individualised basis.

Treating advanced disease

Surgery is standard treatment for isolated metastatic disease to the lung. Standard chemotherapy is doxorubicin, although doxorubicin plus ifosfamide is widely used, depending on a patient's presentation. Histology-

Dedifferentiated liposarcoma



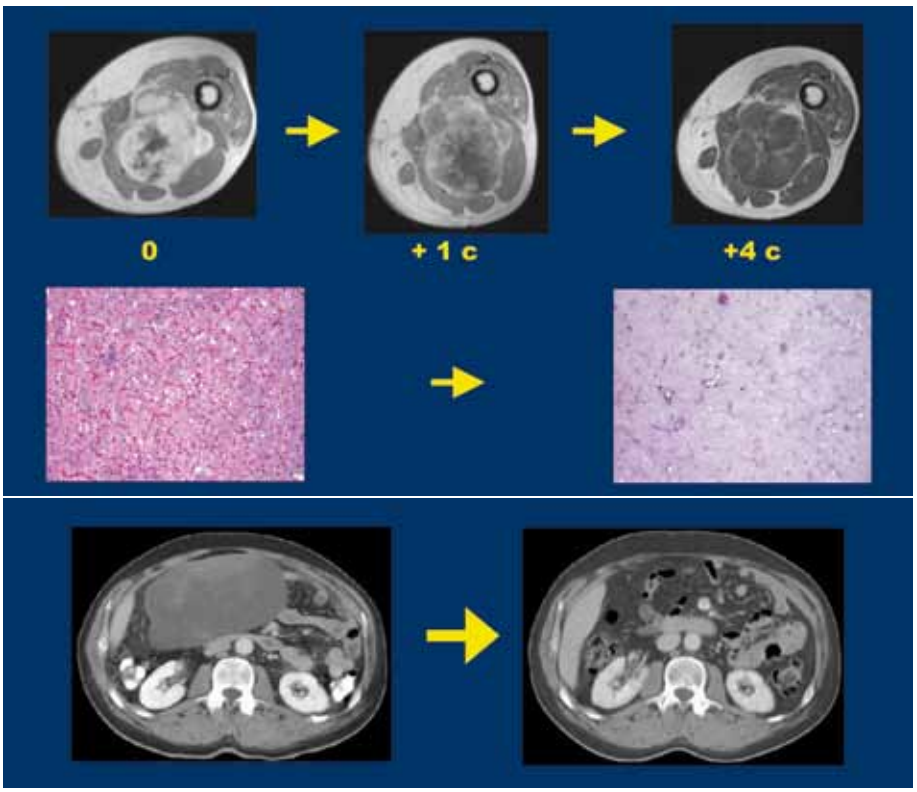
Continuous-infusion high-dose ifosfamide has been shown to be active in dedifferentiated liposarcoma

driven chemotherapy may be a choice as second- or later line therapy.

Surgery for lung metastases may be the used when lesions are isolated in the lungs. The indication for surgery is higher in patients where the previous disease-free interval was long and the number of lesions reasonably low. These are the best prognostic factors. However, there are a variety of clinical presentations, so it is always questionable as to whether to resort to surgery or not.

We are inclined to use chemotherapy in addition to surgery in cases where prognostic factors are favourable. There is no evidence behind this, but it seems logical. The question as to whether or not to add chemotherapy to surgery has not yet been settled by clinical studies. We generally give chemotherapy before surgery in these cases, to help ascertain if the patient is responsive to chemotherapy in order to tailor the overall strategy.

Myxoid liposarcomas



Trabectedin is approved for treating soft tissue sarcomas and has been shown to induce a strong pathological response in myxoid liposarcomas (*upper*) and in some cases also tumour shrinkage (*lower*)

The choice of chemotherapy in advanced disease

Doxorubicin plus ifosfamide. A randomised trial carried out by the EORTC Soft Tissue and Bone Sarcoma Group compared the standard treatment of doxorubicin (75mg/m^2) alone with doxorubicin (75mg/m^2) plus ifosfamide (7.5g/m^2). The results showed a difference in progression-free survival in favour of the combination; however, the difference in overall survival was not statistically significant (*Lancet Oncol* 2014, 15:415). This means that single-agent doxorubicin could still be regarded as the standard treatment. Depending on the clinical presentation, the combination of doxorubicin plus ifosfamide may be used, particularly if it is believed that a tumour response could be useful.

This randomised trial put together all histologies, but the question is how far we need to take account of the complexity of the histology of soft tissue sarcomas. This is a particular challenge for managing the disease and also for clinical trials. The more you put the different histologies together, the less likely you are to see differences that may apply only to some histologies and not others.

Ifosfamide. In terms of the main drugs used in soft tissue sarcomas, ifosfamide is not active in leiomyosarcomas according to retrospective evidence (*JCO* 2007, 25:3144–50). As a result, many institutions do not use ifosfamide in leiomyosarcomas. In contrast, ifosfamide

is very active in synovial sarcoma. It is also active given as a continuous high-dose infusion over 14 days in dedifferentiated liposarcoma (see figure opposite, *top*). Two retrospective series suggest efficacy of high-dose continuous infusion in dedifferentiated liposarcomas (*Sarcoma* 2013, doi.org/10.1155/2013/868973; *Clin Sarcoma Res* 2014, 4:16).

Trabectedin. Trabectedin is another drug that is now approved in the US and Europe for soft tissue sarcomas. This agent is active in dedifferentiated liposarcoma, but probably primarily in those with less aggressive behaviour. It is especially active in myxoid liposarcomas, more so than in dedifferentiated liposarcoma, with tumour shrinkage in some cases and very convincing pathological response – despite lack of tumour shrinkage – in other cases (see figure opposite, *bottom*). This may be because trabectedin has a targeted mechanism of action in myxoid liposarcoma, in which the drug displaces the fusion transcript specific to this type of tumour from target genes and promotes a type of differentiation (*Mol Cancer Therap* 2009, 8:449).

Trabectedin is active in metastatic liposarcoma and leiomyosarcoma, after failure of conventional chemotherapy (*JCO* 2015, doi: 10.1200/JCO.2015.62.4734). This includes uterine leiomyosarcomas (*Gynecol Oncol* 2011; 123: 553–56).

Eribulin. More recently there has been some evidence to show eribulin may be active in liposarcoma, providing an increase of seven months in overall survival compared to dacarbazine (*Lancet* 2016, 387:1629–37)). However, it is not clear why there is less improvement in progression-free survival. This drug has now been approved by the US regulators, the FDA, and has received a positive opinion from the Committee for Human Medicinal Products of the European regulators, the EMA.

Dacarbazine. Dacarbazine is active in leiomyosarcoma, but much less so in liposarcoma.

Gemcitabine. Gemcitabine is active in leiomyosarcomas although not in any other soft tissue sarcomas, with the exception of angiosarcoma. One study has shown improved progression-free survival with gemcitabine plus docetaxel compared to gemcitabine alone (*JCO* 2007, 25: 2755–63), but other studies did not confirm this. An option, which we follow at our institution, is to use gemcitabine alone in leiomyosarcomas. This is much better tolerated.

Pazopanib. The antiangiogenic drug pazopanib has demonstrated improved progression-free survival in a phase III study of all soft tissue sarcomas, with the exception of liposarcomas, which were not included (*Lancet* 2012, 378:1879). Some histologies, including uterine leiomyosarcomas and synovial sarcomas, are more responsive. However, the rebound effect that can occur with antiangiogenic agents may limit the use of pazopanib.

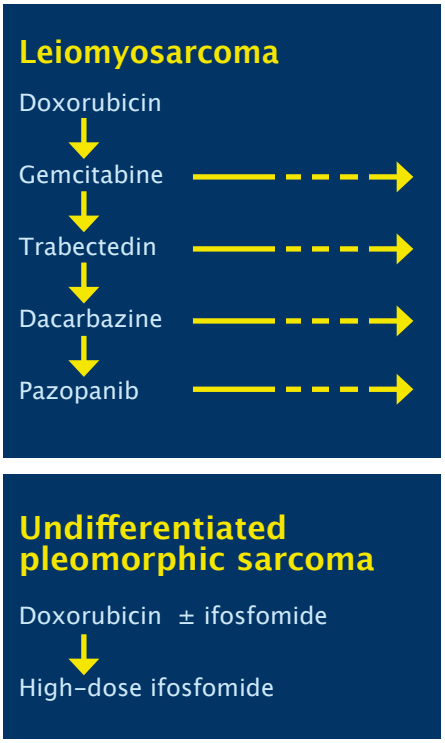
In summary, in some histologies of soft tissue sarcomas, such as leiomyosarcoma, it is possible to use several chemotherapy drugs. Some of these drugs can be used for a relatively long time. Other histologies, such as undifferentiated pleomorphic sarcoma, have far fewer options for medical therapy.

Rarer histologies

Certain rarer histologies may respond to specific drugs:

Angiosarcoma responds to taxanes, which have no effect on other soft tissue sarcomas, at least as single agents. Angiosarcoma also responds to gemcitabine.

Low-grade endometrial stromal sarcomas respond to hormonal therapy with progestins or aromatase inhibitors, but not to tamoxifen, because it is an agonist. The evidence is only anecdotal, but this type of sarcoma is very rare. This type of sarcoma has a non-random chromosomal change. High-grade endometrial stromal sarcoma has a different chromosomal change. Undifferentiated endometrial sarcoma, another type, is very aggressive and not responsive to hormonal therapy.



Some sarcomas have many more treatment options than others

Desmoid tumours may be responsive to hormonal therapy, but their natural history is very erratic, sometimes progressing and sometimes spontaneously regressing. We are using less and less surgery in desmoid tumours and have published a consensus-based algorithm of drug options (*Ann Oncol* 2014, 25:578–83). Different histologies respond to different drugs. For example, dermatofibrosarcoma has a chromosomal translocation, with an overproduction of PDGF-beta, and responds to imatinib.

This underlines the importance

Histology-driven chemotherapy

Leiomyosarcoma: gemcitabine, trabectedin, DTIC (& temozolamide) …
Liposarcoma, dedifferentiated: ci-hd ifosfomide, trabectedin …
Liposarcoma, myxoid: trabectedin …
Angiosarcoma/intimal sarcoma: taxanes, gemcitabine …
Synovial sarcoma: hd ifosfomide, trabectedin …
Solitary fibrous tumour: DTIC (& temozolamide) …
MPNST: ci-hd ifosfomide, VP16 + …
Pleomorphic rhabdomyosarcoma: gemcitabine …
Epithelioid sarcoma: gemcitabine …

DTIC dacarbazine, ci – continuous infusion, hd – high-dose, MPNST – malignant peripheral nerve sheath tumours

Histology-driven targeted therapy

Dermatofibrosarcoma: imatinib
Leiomyosarcoma: pazopanib …
Synovial sarcoma: pazopanib …
MPNST: pazopanib …
Desmoids: hormones, sorafenib, imatinib …
Alveolar soft part sarcoma: pazopanib, sunitinib, cediranib …
Solitary fibrous tumour: sunitinib, pazopanib, …
Extraskeletal myxoid chondrosarcoma: pazopanib, sunitinib …
Inflammatory myofibroblastic tumour: crizotinib …
Lymphangioleiomyomatosis and PEComas: m-TOR inhibitors
Epithelioidsarcoma: pazopanib …
Clear cell sarcoma: pazopanib …
Hemangioendothelioma: m-TOR inhibitors, interferon
Angiosarcoma: pazopanib, sorafenib …
Pigmented villonodular synovitis: imatinib …

MPNST – malignant peripheral nerve sheath tumours

of histology in treating soft tissue sarcomas, with different histologies responding to different chemotherapies and targeted drugs (see tables above). The range of different histologies makes it difficult to carry out randomised controlled trials in soft tissue sarcomas. Results from the trials that are carried out need to be interpreted cautiously, because putting different soft tissue sarcomas together makes it difficult to make sense of the findings.

Adjuvant chemotherapy

A systematic meta-analysis suggested a 10% advantage with adjuvant chemotherapy in high-risk, localised, resectable soft-tissue sarcomas (*Cancer* 2008, 113:573). However, the studies included showed divergent results, with some being negative and others positive.

A study in our centre compared three cycles of epidoxorubicin, followed by surgery with or without radiotherapy, with the same regimen followed by a further two cycles of epidoxorubicin in patients with high-grade spindle-cell sarcoma. Results were the same, so we currently propose three cycles of chemotherapy to patients at high risk, quite often before surgery. This is because surgery in patients with high-risk sarcomas can be quite challenging and may potentially involve reconstructive surgery, so it may be better to give chemoradiotherapy before surgery and not after (see figure opposite, *top*).

We developed an app (Sarculator, see www.sarculator.com) to assess prognosis in patients with soft tissue sarcoma, based on our series, which may be helpful to make treatment decisions on chemotherapy.

Gastrointestinal stromal tumours (GIST)

Treatment of GIST is quite simple, with standard treatment being surgery. Imatinib is used as adjuvant treatment in high-risk GIST. For advanced disease, imatinib, sunitinib and regorafenib are the three molecularly targeted agents available as first-, second- and third-line treatment. Surgery for metastasis is not standard, but can be used in some cases, even though we do not have convincing evidence for this in addition to medical therapy.

This treatment approach is based on the molecular biology of GIST, with molecular analysis being essential to make decisions on medical therapy (see

figure below). Not all GIST responds to imatinib. Exon 11-mutated KIT, which is the most common mutation (60%), responds, but GISTs with the exon 9 mutation may require 800 mg or 400 mg doses of imatinib. The exon 18 D842V mutation is completely insensitive to imatinib. The 10% of GIST cases that are wild type have a completely different natural history and do not respond, in practice, to imatinib, although they may respond to sunitinib or regorafenib. These are divided into two main groups: succinate dehydrogenase- (SDH-) negative and SDH-positive.

In unresectable or metastatic GIST expressing KIT, imatinib gives a median progression-free survival of two years and a median overall survival of five years (*JCO* 2008, 26:626–32). Some patients show much longer progression-free survival; however, we do not know who they are, whether they are just the tail of the curve, or whether there are specific reasons why they survive for so long. There are speculations that some kind of immune response may play a role in these patients, with imatinib potentiating antitumour T cell responses through the inhibition of IDO (*Nature Med* 2011, 17:1094).

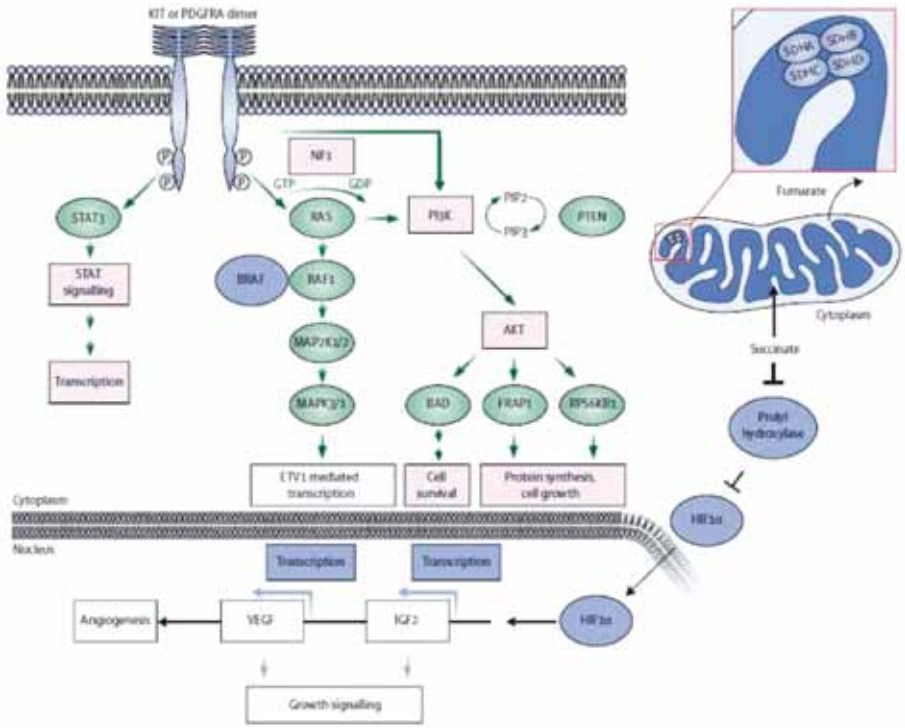
Sunitinib demonstrates prolonged progression-free survival and overall survival in patients with advanced GIST after failure of imatinib (*Lancet* 2006, 368:1329), and regorafenib is also active as third-line therapy, with a benefit of some months compared to placebo (*Lancet* 2013, 381:295).

Medical therapy with these agents should be continued long term, otherwise patients lose response. It may be assumed there is not complete pathologic response to imatinib. Radiologically, the response pattern shows typical hypodensity, although there may not be tumour shrinkage.

The case for neoadjuvant treatment

Chemotherapy is sometimes used before surgery in patients with high-risk sarcomas, as they can be quite challenging and may potentially involve reconstructive surgery

Molecular biology of GIST



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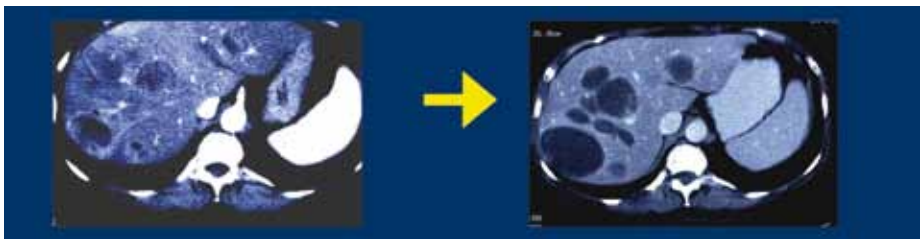
Secondary resistance is the limiting factor, with the main mechanism being molecular heterogeneity. Biopsies show different secondary mutations, in a similar way to other tumour types. Although available drugs show activity against different secondary mutations, this is not helpful in predicting response, because of the heterogeneity.

Focal progression can occur in GIST,

Radiological response of GIST to imatinib



so surgery may be an option in patients who progress on imatinib, essentially to prolong survival, as it will not cure metastatic GIST.

Surgery of widely progressing disease is not effective, but surgery for focal progression may provide some benefit. Restarting imatinib can prolong progression-free survival in cases where there are no other drug options to use after failure of imatinib and sunitinib (*Lancet Oncol* 2013, 14:1175).

Adjuvant imatinib is effective after resection of localised GIST (*Lancet* 2009, 374:1097). Longer duration treatment improves survival, with one year better than no adjuvant imatinib, two years better than one, and three years better than two. However, the cure rate is not increased. The benefit of longer-term imatinib is currently unclear, but results from the PERSIST study, which investigated five years of treatment, are awaited.

The decision to use adjuvant imatinib should be made jointly with the patient, depending on their risk and the molecular biology of their GIST. The risk assessment should be based on the tumour size, mitotic rate and tumour site (see Table 3). An additional factor to take into account is whether tumour rupture has occurred, because this is a very adverse prognostic factor.

Risk stratification in GIST

	Size (cm)	Mitotic rate M/50HPF	Gastric	Jejunal/ ileal	Duodenal	Rectal
1	≤2	≤5	0 none	0 none	0 none	0 none
2	>2≤5	≤5	1.9% very low	4.3% low	8.3% low	8.5% low
3a	>5≤10	≤5	3.6% low	24% moderate	3a	>5<10
3b	>10	≤5	12% moderate	52% high	34% high	57% high
4	≤2	>5	0	50%	54% high	4
5	>2≤5	>5	16% moderate	73% high	50% high	52% high
6a	>5≤10	>5	55% high	85% high	6a	>5<10
6b	>10	>5	86% high	90% high	86% high	71% high

Source: M Miettinen (2006) *Semin Diagn Pathol* 23:70

Revising the guidelines

We are currently updating the European Society for Medical Oncology's Clinical Practice Guidelines for the diagnosis, treatment and follow-up of GIST and soft tissue sarcomas, which will incorporate the research reviewed in this grandround.

Forthcoming educational events

Update on rare adult solid cancers, 25–27 November 2016, Milan

This is the first of an annual event organised by the European School of Oncology (ESO), in association with the European Society for Medical Oncology (ESMO) and Rare Cancers Europe.

Postgraduate Master's degree in rare cancers

ESO is planning to provide an individualised educational pathway for young oncologists to develop their careers in rare adult solid cancers in collaboration with the Università Degli Studi di Milano and the Fondazione IRCCS Istituto Nazionale dei Tumori. For more information contact: raretumours@eso.net

This information is intended for healthcare professionals in the European Union

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*fatal cases have been reported

Classification for supply: Medicinal product subject to restricted medical prescription. **Marketing Authorisation Holder:** Bayer Pharma AG, D-13342 Berlin, Germany. **Date of the underlying Prescribing Information:** December 2014. Bayer Pharma AG, 13342 Berlin, Germany.
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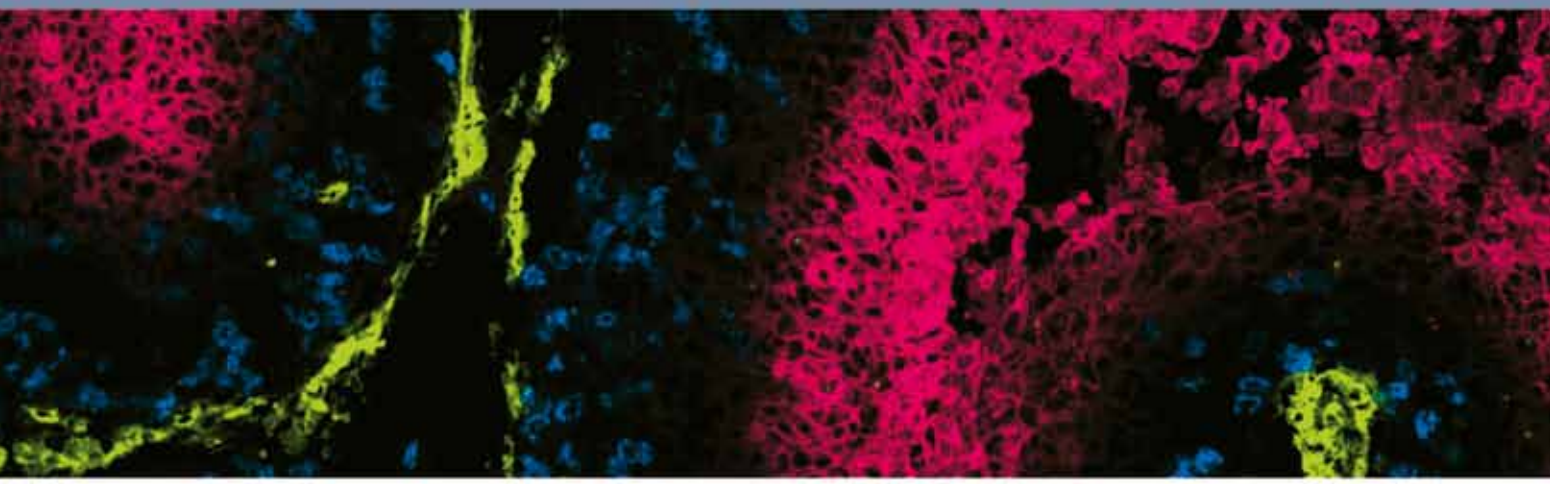


DON'T MISS OUR RECENTLY PUBLISHED CONTENT

Clinical development of new drug–radiotherapy combinations
Ricky A. Sharma, Ruth Plummer, Julie K. Stock, Tessa A. Greenhalgh, Ozlem Ataman, Stephen Kelly et al. and on behalf of the *NCRI CTRad Academia-Pharma Joint Working Group*
doi:10.1038/nrclinonc.2016.79

Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease
Giampaolo Bianchini, Justin M. Balko, Ingrid A. Mayer, Melinda E. Sanders and *Luca Gianni*
doi:10.1038/nrclinonc.2016.66

Balancing efficacy of and host immune responses to cancer therapy: the yin and yang effects
Yuval Shaked
doi:10.1038/nrclinonc.2016.57

Population-based screening for cancer: hope and hype
Yiwey Shieh, Martin Eklund, George F. Sawaya, William C. Black, Barnett S. Kramer and *Laura J. Esserman*
doi:10.1038/nrclinonc.2016.50

Treating cancer with selective CDK4/6 inhibitors
Ben O'Leary, Richard S. Finn and *Nicholas C. Turner*
doi:10.1038/nrclinonc.2016.26

Essential requirements for quality cancer care

Peter Naredi – President of the ECCO Board of Directors (2016/2017) and Professor of Surgery and Chairman of the Department of Surgery at the Sahlgrenska Academy, University of Gothenburg, since 2013

In the previous issue of *Cancer World* I discussed the need for defining multidisciplinary organisational criteria on how to deliver optimal cancer care to each patient and for quality performance indicators that can help measure the efficacy of existing clinical guidelines.

Since June, ECCO has taken significant steps forward with its project on essential requirements for quality cancer care (ERQCC), starting with two tumour types: colorectal cancer and bone and soft tissue sarcomas.

In April 2016, ECCO member societies appointed their high-level experts to participate in the ERQCC multidisciplinary working groups on colorectal cancer and bone and soft tissue sarcomas. These groups gather together medical oncologists, radiologists, surgeons, patient advocates, representatives of oncology institutes, nurses, pharmacists and psychologists. The first meetings of the working groups – consensus days – took place in Brussels at the end of May 2016, where agreement was reached on a draft list of ERQCC for each tumour type.

The draft is now with the member societies for their contributions, and later this year the working groups will meet again to finalise the two ERQCC manuscripts. The manuscripts will be submitted for publication in the *European Journal of Cancer* before the end of 2016.

The ERQCC project aims to:

- Improve outcomes for cancer patients in Europe through the adoption and implementation of essential requirements for quality cancer care in Europe;
- Complement existing clinical guidelines and improve their efficacy;
- Shape the policy environment at European and national levels to improve quality of cancer care across Europe and decrease inequalities in cancer outcomes.

ECCO strongly believes that the essential requirements for quality cancer care will be influential in improving cancer care in Europe, and will work very well alongside current clinical guidelines. We will take every opportunity to engage with relevant stakeholders, including EU institutions and member states, to promote the results of the ERQCC project.

The success of ERQCC will depend on the level of awareness and the influence of ERQCC on national policies and practice. Policy efforts by national organisations will therefore be a determining factor.

The ERQCC results will be presented during the ECCO2017 European Cancer Congress in Amsterdam on 27–30 January 2017. Join us and participate in a lively discussion!

"Independently from screening or treatment, over next decades, death from melanoma is likely to become an increasingly rare event"

Philippe Autier, Alice Koechlin and Mathieu Boniol (2015) The forthcoming inexorable decline of cutaneous melanoma mortality in light-skinned populations. *EJC* 51:869–878

Mortality data show that a precipitous rise in deaths from cutaneous melanoma in countries of northern Europe, Australia and north America, which started in the 1950s, may now be stabilising.

Yet a paper published last year confidently predicts that, rather than flattening out, the decades-long upward trend is now set to go sharply into reverse, revealing the deaths from fatal melanoma to have been the results of a "temporary epidemic".

How did the researchers arrive at this conclusion? **Anna Rouillard** talked to lead author, Philippe Autier, to find out.

Philippe Autier is Vice President of the Population Research Unit at the International Prevention Research Institute in Lyon, France

Anna Rouillard: *Your finding that fatal melanoma in light-skinned populations is in "inexorable decline" was highly unexpected. What prompted you to look into this topic?*

Philippe Autier: Before embarking on this study, we observed two trends: firstly that in some countries, such as the United States and Australia, there were signs that melanoma mortality was stabilising, and that this stabilisation was a result of a mix of continued increasing mortality in older subjects and the start of a decline in mortality in younger subjects. The second observation was that there have been changes in behaviour to sun exposure, especially amongst children. And while we knew that behavioural changes could impact melanoma in the population, the precise nature of this impact was unknown. This is how the project started.

AR: *How did you set about your research?*

PA: We decided that we had to clarify what was going on, and to find the answers we chose to undertake a large-scale study that would give an overview of melanoma mortality trends in light-skinned populations worldwide. We didn't know what we were going to find, but the results were striking and showed a common pattern in all countries. Melanoma mortality among older people (especially men over the age of 70) was still considerable, whereas amongst the under 50s it had been decreasing as of the late 1980s. This decrease has actually been quite dramatic in some populations, notably in Australia, the United States and the Nordic countries.

AR: *Can you be certain about your claim?*

PA: This pattern can be clearly seen in graphs that show how mortality rates change according to when the patient was born – their birth cohort (see figure overleaf) – instead of the more common time-trend graphs that show when they died, where the dramatic drop in deaths among people born in later time periods is hidden by a rise in deaths among people from earlier birth cohorts.

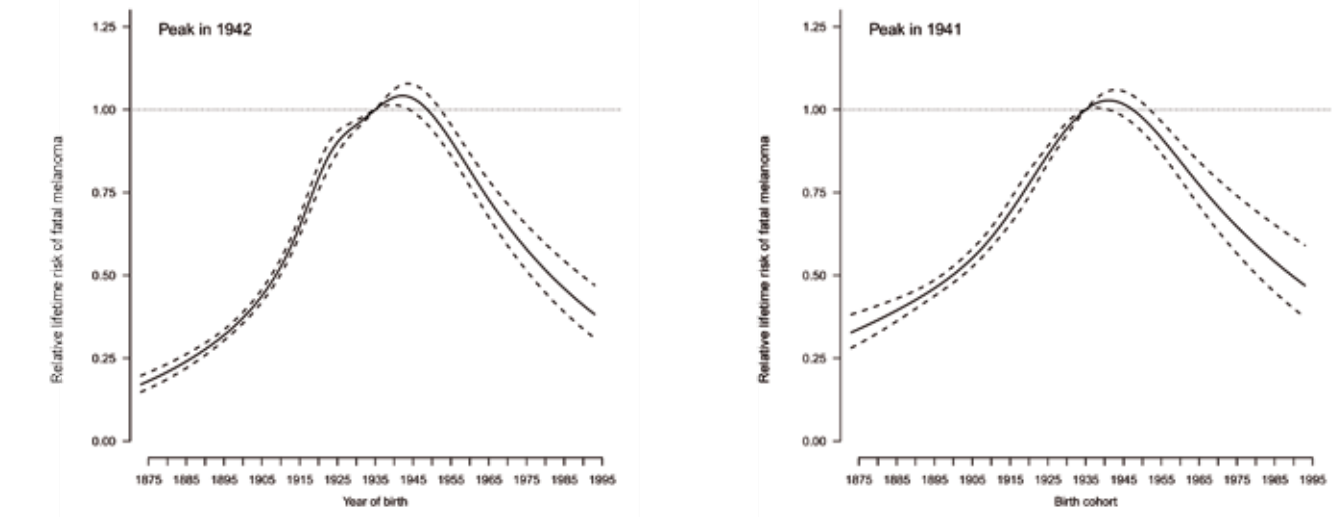
Looked at this way, death rates from melanoma form bell-shaped curves, which are typical of 'birth cohort' effects. The tips of all these curves are around 1935–1950. This means that people who were born in that period were at the highest risk of dying from melanoma, while the risk was very low at the beginning of the twentieth century and dropped dramatically again after the 1960s. What surprised us was that this pattern occurred in all light-skinned populations. This indicates that there was a window of exposure affecting men and women who were born between World War I and the 1960s, during which time these individuals accumulated some risk of dying from melanoma in adult life.

When we uncovered the patterns, it was a matter of looking at the literature to determine what could be the common denominator in terms of exposure that was causing them. We then unraveled an incredible history of the medical use of ultraviolet radiation in young children, ostensibly to promote their health (see overleaf), starting around World War I.

This practice slowly disappeared in the fifties and sixties, after the link between exposure to ultraviolet radiation and skin cancer was made. This is reflected in the dramatic decline in mortality rates among people born around this time.

AR: *Medical use of ultraviolet radiation is no longer practised, but haven't new generations of light-skinned people been exposed to new risks – more holidays in hot countries and greater use of sunbeds?*

PA: I'm talking about deadly melanoma – most melanomas are not deadly. Our conclusions are that you need to be a light-skinned child (less than 10 years



These bell-shaped curves show that the 'epidemic'of fatal melanoma in Northern Europe reached its peak among children born in the 1940s, and has been falling steeply for subsequent birth cohorts – a correlation that is masked in the more common time-trend graphs
Source: P Autier et al. (2015) The forthcoming inexorable decline of cutaneous melanoma mortality in light-skinned populations. *EJC* 51:869-878

old) and exposed to very intense ultraviolet radiation, particularly UVB, to develop deadly melanoma in later life. Age is important, because, during childhood, our immune system is immature, and if light-skinned people are exposed to intense ultraviolet sources, this will initiate a number of melanocytes, which will contain lesions that are compatible with extremely aggressive melanoma in later life. The reason it then takes so long for deadly melanoma to develop has to do with our immune system. The immune system protects us against cancer, and as we age, our immune system weakens, making the growth and development of abnormal cells more likely.

So the good news is the radical change in exposure of light-skinned children to intense ultraviolet radiation sources. While such exposure was regarded as 'healthy', and recommended by most doctors in the first half of the 20th century, this public health belief faded away in the 1960's, and was replaced by recommendations for protecting children against ultraviolet radiation.

Everything that has been done in terms of sun protection, in particular for children, has been very successful in some settings, for example in Australia and the Nordic countries.

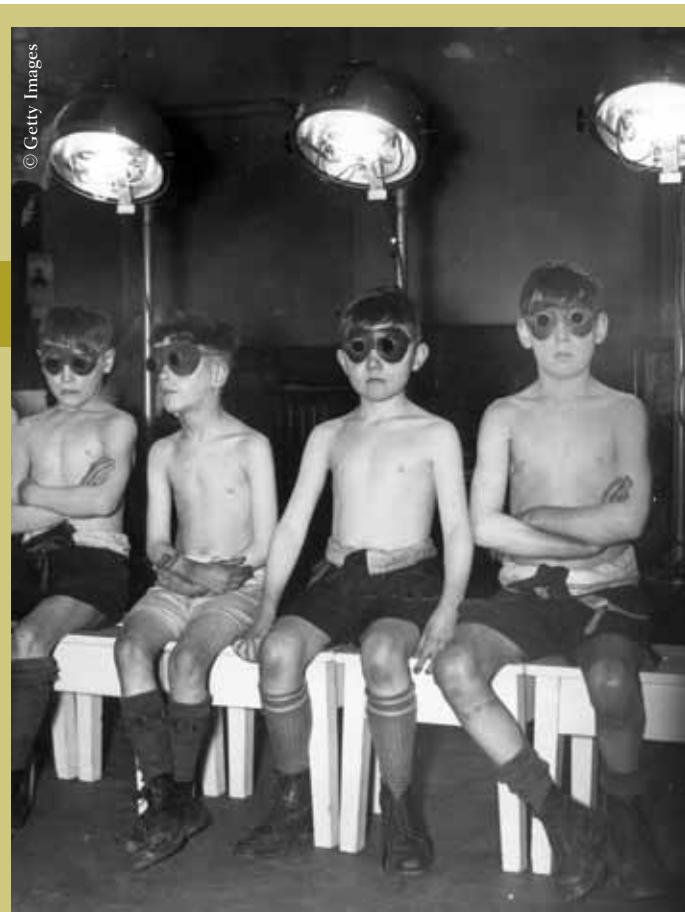
However the message about protecting small children from exposure to intense sunshine is less well understood in many countries, especially in Southern and Central Europe, where there is clearly more work to be done. This should be given high priority in public health strategies. Our study shows the enormous potential of preventative approaches to wipe out deadly melanoma.

***AR**: So the message is that exposure to intense UV in childhood is where the fatal danger lies. What about exposure in adulthood?*

PA: In contrast to exposure trends among light-skinned children, the ultraviolet exposure of adolescents and adults has continued to increase, especially thanks to the sunbed craze and the ease of travel to sunny areas. Also, ultraviolet irradiation of moles affects their appearance, which often prompts their removal, especially after the summer holidays. Therefore, the number of people diagnosed with a melanoma is still increasing. However, because it is the exposure of adults that is still on the rise, and not that of children, most of the increase in melanoma consists of tumours that would never progress into deadly disease.

The use of sunbeds could be a worry. Sunbeds contain mainly UVA radiation, but also some UVB. The problem is that the intensity of sunbeds is enormous – ten times the intensity of the Mediterranean summer sun. The sunbed fashion started in the nineties, and it is their use amongst young people that causes concern. If people started using sunbeds before they'd reached 15 or 16 years old, we may see a dramatic effect on melanoma mortality later on.

The history of a medicine-inflicted epidemic



Children undergoing 'sunray treatment' at Manchester's Open Air School for Delicate Children, 1939

By the late nineteenth century, theories about the effects of sunshine on health had begun to abound. One physician, Theobald Palm, having noticed the absence of rickets in Japan compared to the high prevalence of the disease in Britain, suggested a link between rates of sunshine and rates of rickets.

Danish physician Niels Ryberg Finsen then started investigating the effects of exposure to sunshine on his own health, believing that his anaemia and fatigue could be due to lack of sunshine. In 1893 he started experimenting with sunlight therapy and discovered that lupus vulgaris, a skin lesion caused by tuberculosis, could be treated through exposure to a specially designed powerful ultraviolet lamp – a breakthrough that won him the Nobel Prize in 1903.

Discussions about the preventative and curative effects of sunlight gathered momentum in the early twentieth century, with Leonard Hill from the National Institute for Medical Research stating that: "sunshine, whether natural or as produced artificially by electric arc lamps, had a most profound effect on health. Rickets in children could be cured by it…" (reported in *The Times*, 1925).

By this time, vitamin D, the 'sunshine vitamin', had been discovered and linked to health benefits. All of these findings led to recommendations for the medical use of ultraviolet radiation, including for the prevention and treatment of a large number of common diseases.

The interest in the health benefits of ultraviolet radiation was so huge that engineers started to produce ultraviolet lamps specifically for medical use, and a whole industry grew up around actinotherapy. 'Sunray treatment' was prescribed for a vast array of conditions from acne to anaemia to sore throats, and thousands of children and adults were exposed to ultraviolet radiation until the practice ended in the sixties, due to important advances such as antibiotics, vaccines, improved hygiene practices and healthier environments.

Various studies had pointed to a link between exposure to ultraviolet radiation and skin cancer as far back as the 1920s and 1930s, but sunray treatment had become so popular that these concerns were largely ignored. It was later proven that the UVB and UVC rays that were found in the sunlamps of this period were highly carcinogenic. Many of the patients were children when they received repeated sunlamp sessions, and today, as Autier's study proves, we are bearing the health repercussions of exposure of a whole generation of children to a deadly medical practice.

LET'S THINK

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New drugs for childhood cancers: could biotechs end the drought?

The chances of surviving a childhood cancer have changed very little over the past two decades. **Sophie Fessl** talked to parents, doctors, regulators and researchers about what has to be done to address this disastrous impasse.

"It feels odd to say this, but Elliot is one of the lucky ones." The comment comes from Nicole Scobie, and refers to her son, who was only four years old when he was diagnosed with a stage IV Wilm's tumour. His left kidney was engulfed by a huge cancerous mass and his lungs were full of metastases. The heart-stopping diagnosis was just the start of a rollercoaster of emotions, hospital stays and exhaustion. But this is a story with hope: Elliot responded well to chemotherapy. He went into remission after 10 months of treatment, and has remained so for the past four years.

"At least for his cancer, there is a treatment that works," says Nicole. Not all the children she and her son befriended during their long stay at the Lausanne University Hospital's children's cancer ward can consider themselves as 'lucky'. Elliot became close friends with Zoe, a little girl battling an aggressive neuroblastoma. But while Elliot's prospects looked good, for Zoe, the odds were stacked against her. In the end, there was nothing her medical team could do: Zoe died in her mother's arms aged four.

The difference between Elliot and Zoe? Elliot had a type of cancer that has been successfully treated for decades, being one of the first childhood cancers – alongside acute lymphoblastic leukaemia – to benefit from the chemotherapies pioneered by Sydney Farber back in the 1950s. His is part of the celebrated success story that saw cancer survival rates among children increase from 10% to 80% over 50 years.

Zoe, by contrast, had a type of childhood cancer that remains fatal in the majority of cases. Her story is shared by 6,000 children and young people under 24 who are still dying of cancer each year in Europe. For parents like Nicole Scobie, who've seen their child's life in the balance, that is a heartbreaking statistic. But there's a worse one – the mortality rate from childhood cancers has barely changed over the past 16 years.

Last year, Scobie was one of a large group of parents and advocacy organisations that got together to found Unite-2Cure (unite2cure.org), an advocacy organisation that aims to kickstart progress again. It looks particularly to work

The lucky ones. Elliot Scobie, with his mother Nicole, who is campaigning for regulatory changes to incentivise the development of new drugs for paediatric cancers

with key players in the drug development ecosystem to improve the efficiency of developing new therapies for childhood cancers. A key focus will be the EU Paediatric Medicines Regulation, which came into force in January 2007 to try to address the obstacles to developing new drugs for children, and which is up for revision in 2017.

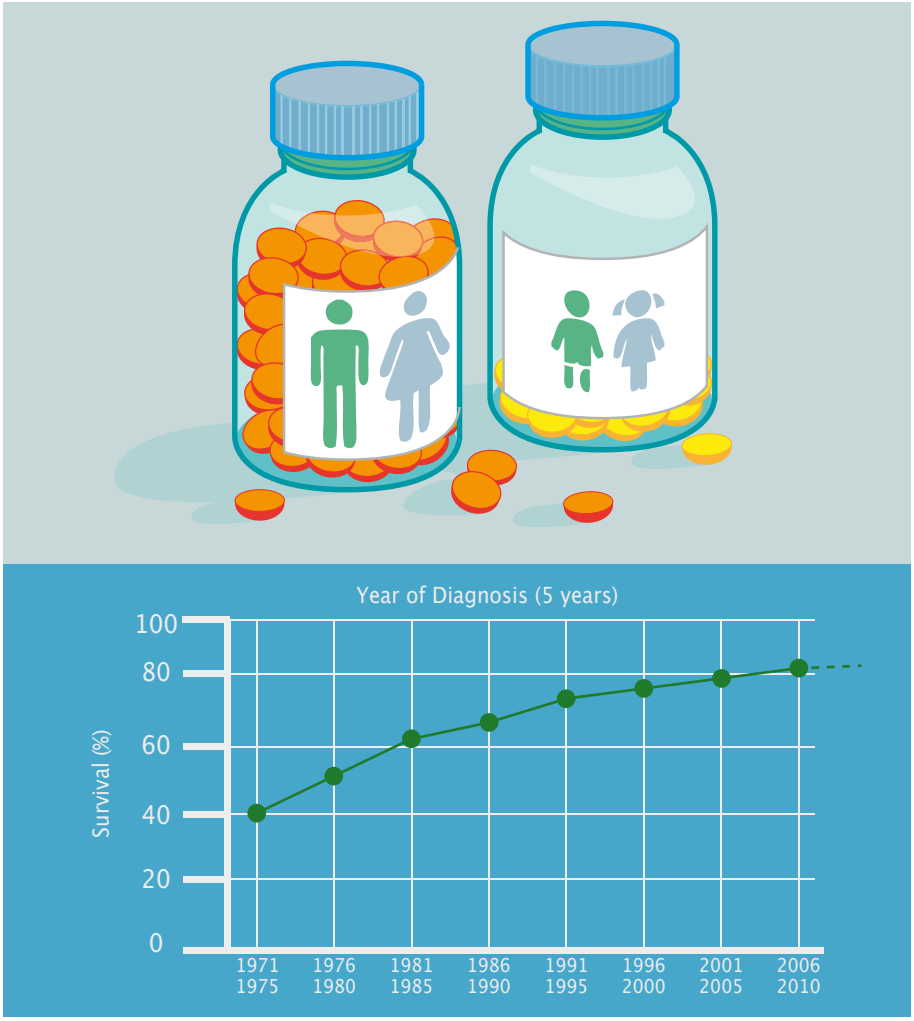
The Paediatric Medicines Regulation

The 2007 Paediatric Medicines Regulation sought to boost the development of drugs for use in children through a combination of obligations and rewards. Companies are required to discuss the potential for use in children of every drug they develop, and where appropriate to agree a Paediatric Investigation Plan (PIP) with the European regulators, the EMA. The results of studies carried out according to the PIP have to be included as part of any application for marketing authorisation for the new drug, unless the studies with children are not yet completed or were not required at all. In return for carrying out these studies, companies get an extension on their patent protection.

Under the regulation, 48 new anti-cancer drugs for adults have come on the market – and six for children. Gilles Vassal, president of the European Society of Paediatric Oncology (SIOPE), welcomed this as important progress, but argues that much more needs to be done, and much faster.

"The mortality rate from childhood cancers has barely changed over the past 16 years"

"The paediatric regulation has definitely changed the landscape for drug development. The situation now differs positively from that before 2007. We have more access to new drugs and clinical trials. However, the



Only six new drugs have been approved for childhood cancers compared with 48 for adult cancers since the Paediatric Medicines Regulation came into force in 2007; progress in survival rates has almost stalled over the same period
Source: Survival figures come from www.cancerresearchuk.org and are for the UK

regulation does not address the needs of children with cancer adequately. Major breakthroughs have been achieved in cancer care for adults, and these have not translated into breakthroughs for children.

"Cancer is still the number one cause of death by disease beyond one year of age. Less than 10% of children with life-threatening forms of cancer have access to new compounds. To increase survival, we need changes to accelerate the development of, and access to, new drugs," he says.

Nicole Scobie shares his sense of urgency. "We parents just want our children to live. We are willing to do anything to get there. But the problem is that there is still not enough research, not enough drugs and not enough options. At Unite2Cure, we are calling for very specific changes to the paediatric regulation to harness the major advances made in adult cancer treatments for children." As of August 2016, more than 2,700 supporters have signed Unite2Cure's petition.

Academics are also uniting to call for improvements in treatment. Three years ago, the Cancer Drug Development Forum (CDDF), whose mission is "to facilitate interactions between all stakeholders to improve the efficiency of cancer drug development," set up a CDDF-Paediatric Platform to promote discussion in preparation for the 2017 revision of the paediatric regulation. This was done in partnership with a variety of groups including the European Consortium for Innovative Therapies for Children with Cancer (ITCC), the European Network for Cancer Research in Children and Adolescents (ENCCA), the European Society of Paediatric Oncology (SIOPE), regulators and industry, as well as advocacy groups such as the Unite2Cure movement.

Ending the class waivers loophole

Unite2Cure and the CDDF are both calling for a much greater focus on biology in strategies for developing drugs for childhood cancer. This is partly to close a 'loophole' in the current regulations that allows companies to seek exemptions from testing and developing adult drugs in children on the grounds that the drug is intended for use in treating a disease that only occurs in adults – such as prostate cancer – even if there is a biological rationale to believe it could be of value to some childhood conditions. "Indication-based approval makes sense, for example, for drugs treating Alzheimer's, as we don't want to subject children to unnecessary trials," Nicole Scobie points out, "but in cancer, the name of the cancer doesn't matter. It is the biology that counts."

The ALK gene is a case in point. This gene is implicated in a small minority of non-small-cell lung cancers, characterised by a MET-ALK dislocation. It is also implicated in

several childhood cancers, such as some lymphomas (characterised by an NPM-ALK dislocation), some neuroblastomas (which have a mutation within the ALK gene itself) and a subtype of soft tissue sarcomas.

In 2012, an ALK-MET inhibitor, crizotinib, was approved for the treatment of ALK-positive lung cancer. However, as lung cancer does not occur in children, the developers had applied for, and received, a class waiver to exempt them from having to test the drug for use in children. This waiver was given by the EMA in 2010, a year after the company had been mandated to carry out paediatric development studies of crizotinib in the US, the results of which have since shown responses in children with lymphoma and sarcoma.

"This situation is paradoxical," says Scobie, "considering that 90% of the drugs used for treating children with cancer in the past 40 years were originally developed to treat adults, often for a different cancer condition." Unite2Cure is now demanding that the provision for class waivers be revoked as part of the revisions to the Paediatric Medicines Regulation.

They may be pushing at an open door, at least as far as the regulators are concerned. The EMA themselves do not appear to be happy with current progress in developing paediatric cancer drugs. "We share patients' perspective that not enough has happened in terms of completed trials and approved drugs," says Ralf Herold, Senior Scientific Officer at the EMA. "I fully understand that they are impatient. The clear progress for adult patients with cancer is not reaching children. A drug's mechanism of action has been considered in all our discussions with companies since 2008. When we at the EMA see where and how a drug could be used in children, we flag it up to the companies developing the medicines. In fact, mechanism of action is also relevant for other areas of paediatric drug development. However, the EMA can only encourage, not force, companies to develop drugs for children based on their mechanism of action."

Jeffrey Skolnik, Vice President Clinical Research at Tetralogic Pharmaceuticals and member of the CDDF, sees two reasons why pharmaceutical companies may feel reluctant to develop paediatric drug programmes. "Paediatric diseases are thankfully rather uncommon, and very few children develop cancer. It is therefore hard to invest in a paediatric drug programme: return on investment is low, but costs may not be lower. Pharma is a for-profit industry, and we need to provide financial return for our stakeholders. Secondly, children have historically been perceived as especially vulnerable. Companies are therefore very hesitant to dose children with experimental drugs."

He recognises, however, that something has to change. "For cancer, this approach is not working."

Prioritising the most promising

While closing the class waiver loophole may be seen as a priority by clinicians, researchers and advocates, ironically perhaps they also fear the reverse problem: too many companies chasing too few patients for their paediatric trials. Childhood cancers are rare, many of them very rare, which means that there aren't a lot of patients to go round.

"With almost a thousand new drugs being developed in adults with cancer, we cannot study all of them in children," says Vassal, who argues that prioritisation is key. "We need to find a way to choose the best drugs among the pipeline of all companies, taking into account their mechanism of action and the feasibility of trials," he says.

This view is shared by at least some in the industry. Tetralogic's Skolnik argues that "Drug prioritisation as a way to decide which company should move a programme forward – and which shouldn't – could result in better use of resources, especially if we take a mechanism of action approach for cases where a minimum of preclinical data or adult data are available. If we optimise, prioritise and divvy out responsibilities, we can focus on the most likely successes rather than testing every single option."

> **"The clear progress for adult patients with cancer is not reaching children"**

The EMA's Ralf Herold sees the issue in a rather different light. "Actually, prioritisation is not yet needed. So far, we don't have enough drugs developed for children or studied as it is. We would rather like to see more relevant drugs studied, and work on an approach to get more medicines into trials for children. But we haven't lost hope yet – maybe prioritisation will become an issue [with the revision of the regulation] after 2016."

Uncoupling development for children and adults

As much as the Paediatric Medicines Regulation may have changed the landscape for drug development for children, the elephant in the room remains: what can be done to promote development of drugs exclusively to treat children with cancer?

The PIP process treats drug devel-

Kickstarting progress. The advocacy group Unite2Cure, pictured at the CDDF-ITCC SIOPE 4th Annual Paediatric Oncology Conference, January 2016, where their call for changes to the EU Paediatric Medicines Regulation got an enthusiastic reception

opment for children as an extension of adult drug development. It does not encourage testing of specific drugs for childhood-only indications. Indeed pharmaceutical companies may choose to abandon PIPs even if positive responses are seen in children, in cases where the adult trial is unsuccessful, as happened with IGFR-1 inhibitors.

Rather than relying entirely on 'big pharma', there could be a case for looking to small biotech companies to play a key role in developing new paediatric oncology drugs – companies such as the Vienna-based start-up Apeiron Biologics. Their lead project is an antibody, dinutuximab beta (APN311), which has already been submitted for marketing authorisation in the EU for the treatment of neuroblastoma – the cancer that killed four-year-old Zoe.

Dinutuximab beta offers an interesting model for how cooperation between academia and companies might bring new drugs to children with cancer. Originally, APN311 was studied exclusively by academic researchers, for the European market, with funding by European charities. Apeiron Biologics then picked up the development and took it further to submission for marketing authorisation.

CEO Hans Loibner, believes this project sets a precedent: "Initially, we were interested in APN311 because it was a cancer immunotherapy already in clinical trials rather than because it was a medicine for paediatric cancer. But our work has shown us that it makes sense to develop medicines for children with cancer. This project is worthwhile ethically – we help seriously ill children – and the project for us is commercially reasonable." The company, which has several drugs already in their pipeline, is committed to developing more drugs for treating childhood cancers, he says.

Loibner believes small biotechs may be particularly well suited to developing drugs for small patient populations. "We develop drugs smarter, more streamlined than big companies," he says. "Usually, this line of development is not interesting for pharma because investment is high and the market small. A reasonable sales prediction for our neuroblastoma treatment is in the range of €100 million turnover worldwide. This may not be enough for a big pharma company, in which drug development is much less flexible. But the support received for developing orphan medicines, together with the prices that can be achieved, make it an attractive model for small companies. I believe that in the future, orphan drug development will be a domain for small and mid-size companies."

New incentives

As Loibner points out, the attraction and viability of developing drugs for childhood cancers depends in large part

on the incentives offered to compensate for the small market size. Tetralogic's Skolnik is developing ideas on how this should be done, as part of a CDDF working group.

The discussion, he says, centres around risk-sharing models, which provide earlier, up-front awards for developing paediatric programmes. "These could be based on stratified PIPs that segment the drug development process. If, for example, a phase I study with efficacy test is performed to satisfy the first part of a PIP, the company could receive some investment as reward, such as a few months of patent extension."

Creating new incentives to encourage the development of specific paediatric oncology drugs is one of the aims of Unite2Cure and the CDDF Paediatric Oncology Platform. One idea comes from the US, where the Creating Hope Act of 2011 encouraged the development of three new paediatric oncology drugs through new market incentives.

The Creating Hope Act provides a 'priority review voucher' to companies that develop drugs specifically for serious and rare diseases, including paediatric cancers. This voucher can be used to secure expedited approval of any drug, not just for rare indications. As the priority review voucher can be sold to another company, using a system somewhat analogous to the carbon emissions trading scheme, market value is created even for smaller companies with very limited drug pipelines.

The voucher given for Unituxin under the US Creating Hope Act shows how much value they carry: originally received by United Therapeutics for its neuroblastoma treatment, in 2015 the company sold the voucher to AbbVie for $350 million.

Can paediatric review vouchers work in the European market? All stakeholders agree that new incentives need to be suited to the European reality. The EMA's Herold argues that additional tools may be needed for stimulating the necessary research: "Paediatric review vouchers can be applied if the paediatric development of a drug is successful. However, studies showing that promising drugs eventually turn out not to be efficacious, or are not safe enough, are also important research." The ideal incentives, he says, would be related to the quality of research carried out.

Skolnik sees new models of cooperation and a multi-stakeholder approach as key to incentivising paediatric drug development: "Currently, the burden in drug development falls on the pharma industry in terms of time, resources and money. New incentives could share this burden with different stakeholders, including academics and people passionate about raising money, to de-risk paediatric development.

"A multi-stakeholder approach is starting to happen, but it is not crystalising into results"

For example, companies could put in the research and provide the compound, while foundations may invest money, so that the for-profit organisation performs a study it otherwise would not do."

One thing everything seems agreed on is that urgent changes are needed to the way the EU regulates the development of paediatric medicines. Jordi Llinares Garcia, who heads up the EMA's Product Development Scientific Support department, puts it this way. "Much has been achieved since the regulation came into force. There has been a significant change in the focus of companies on paediatric development as an additional line of research. But we are not there yet – much remains to be done for children with cancer. A multi-stakeholder approach to drug development for childhood cancer is starting to happen, but it is not crystalising into results. We need to take another step: to deliver and actually improve outcomes."

Nicole Scobie, and the advocacy movement she works with, are determined to see that step taken, and soon. "I don't want to watch any more mums lose their child. I don't want to hear any more dads talk about their daughter in the past tense. I can't. I won't."

Cancer World journalists' grant scheme

This article originated in a proposal submitted by the author for consideration for a Cancer World journalists' grant, a scheme set up to encourage journalists working in print, broadcast or online mass media to tackle more complex, multi-source, analytical articles that explore systemic issues that have an impact on patients. Further information about the grant can be found at *http://cancerworld.net/media/cancerworld-journalist-grant/*

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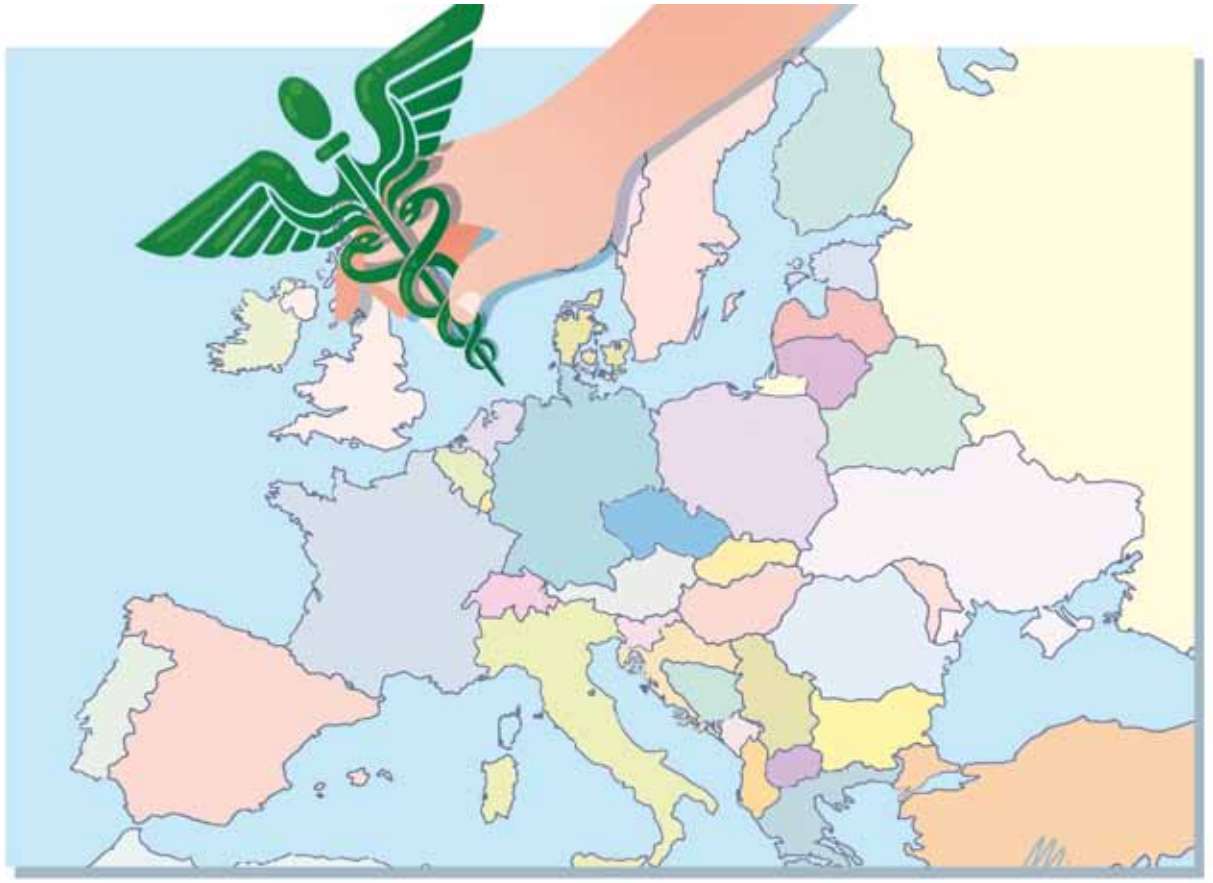

Is Europe ready for centralised ethical approval?

Starting next year, trial sponsors can negotiate ethical approval in a member state of their choice, and have the same terms applied across all EU countries. **Daniela Ovadia** looks at the implications of the new regulation.

Conducting research on human beings is ethically challenging. It requires respect for patients, their priorities and expectations, and it requires trust on the part of the patient.

Because of the toxicity associated with most cancer drugs, oncology trials tend to involve patients instead of healthy subjects, even at the earliest stages of the tests. Usually this will be patients who are in the late stages of the disease, who have the most to gain and the least to lose, as an experimental treatment may be their last hope.

When such experimental treatments have shown strong early evidence of meaningful benefit to patients in great need, with an early side-effects profile that appears to be within the bounds of acceptability, ruling on whether there is an ethical basis for trialing the drug may be easy enough.

The more usual case, however, is far more finely balanced.

The benefit–risk equation is typically less favourable, and with health services and health insurances beginning to take a harder line on reimbursing costly new drugs of only incremental value, there are ethical questions about the value of running a trial for a drug that may well not be widely accessible even if it reaches the market.

Judging which drug trials are ethically worth pursuing, and which are not requires expertise. But it also requires value judgements. This makes it essential for all stakeholders to have an input – from doctors to patients, but also hospitals and health service representatives and drug manufacturers. It also raises questions about the extent to which value judgements made by one community or country can be translated to other settings, where different cultural values or objective contexts may apply.

Currently, responsibility for giving ethical approval for clinical trials is in the hands of individual member states, according to their own criteria and procedures, which may be national, regional or even operate at a hospital level. This is all set to change, however, when the new Clinical Trials Regulation comes into force, in January 2017.

Under the new system, ethical approval will be centralised, so that sponsors of trials set to run in more than one European country – which account for more than a quarter of all clinical trials in the EU and enrol almost 70% of all trial subjects – only have to obtain ethical approval in one member state.

The move has been welcomed by some, because it will relieve the financial and time burden associated with getting ethics approval on a country by country basis, and should address some of the worst variations in levels of expertise between ethics committees in different countries. Others, however, are concerned that the new regulation could narrow the range of stakeholders involved in ethics evaluations and open the way for trial sponsors to seek ethical approval from member states most likely to comply with their wishes.

A matter for expert evaluation

Elmar Doppelfeld, Board member and former President of EUREC, the European Network of Research Ethics Committees, believes it's high time the ethical evaluation of new trials was given the attention it deserves, and says the complexity of assessing the ethicality of proposed new trials is often underestimated. "Ethics assessment of a drug trial is not only an administrative task nor it is limited to the evaluation of the process leading to informed consent. It also involves evaluation of the scientific validity of a trial, of its goals and design," he explains.

While considerable effort has been put into improving the assessment of the scientific validity and integrity of clinical trials in recent decades, says Doppelfeld, there is still "a discordance in the degree of attention clinicians devote to dealing with the scientific dimension and the ethical dimension of clinical research."

Most oncologists who are involved in trials and have to deal with research ethics committees (RECs) feel that they lack sufficient expertise in the field, he says, adding that it is common for them to conduct a very superficial assessment of the ethical issues raised by their trial, applying local norms and requirements in a formulaic way.

Mark Bernstein, a neurosurgeon at the University of Toronto, Canada, who authored a seminal review on ethics assessment in oncology published in 2006 (*Curr Oncol* 2006, 13:55–60), agrees that a superficial grasp of ethical issues is not enough. "Although most clinical investigators are virtuous and well-meaning doctors, it is easy to unknowingly and unwittingly transgress ethical boundaries, just as it is easy for a clinical oncologist, without proper training in clinical trial design, to use improper methodology," he says.

Under the new rules, clinical trial applications will be submitted through a centralised electronic portal

"Some ethical dimensions are obvious because of common sense, common practice, or common law – for example, the requirements to submit the design of the clinical trial to the relevant institutional research ethics board and to obtain informed consent from research participants.

"Other dimensions are subtle and nuanced – such as the non-financial conflicts of interest experienced by clinical investigators during the course of clinical research, and even the interpretation of the results in terms of clinical meaning".

The new EU regulation

Under the Clinical Trials Regulation, clinical trial applications will be submitted through a centralised electronic portal. Applications will then be evaluated by the national research ethics committee of the country where the request originated. The national REC will be free to ask

other national RECs for information and opinions, but it alone will be responsible for the final decision.

The assessment of a proposed trial will focus on three main areas: compliance, patient safety and scientific value of the trial itself.

Francesco Perrone, Director of the clinical trials department at the National Cancer Institute in Naples, Italy, and former consultant to the Italian Drugs Agency (AIFA), believes the requirement to assess the scientific value of the trial is an important step forward.

This aspect of the evaluation is already carried out by research ethics committees in some countries, he says, "but in others it is not, so this will be a major improvement for many European countries."

The aim of this aspect of the evaluation, he explains, is to weigh up the ethical value of the clinical goals the researchers want to achieve. "The goals of the drug company can be very different from the goals of the clinician and even from the goals of the patients," he says.

"In the absence of a common health system, the perception of what is valuable for a patient can be hugely variable"

The design of clinical trials involving new targeted cancer therapies can also raise ethical challenges, he argues. "For instance, there are issues of accessibility and affordability of the new treatments to the health service and to patients. Even the choice of the criteria to define a successful trial can be problematic."

With the new rules, the assessment by the reporting state will be valid across the European Union. Individual member states will be able to prevent the clinical study from taking place on their territory, but they will not be able to modify it in any way, to adapt it to local needs or structures.

As the main goal of the new regulation is to harmonise the rules for ethical assessment of drug trials, this could be considered a necessary step, but it raises some concerns.

For instance, while the new EU regulation spells out procedures for the assessment, rules governing the composition of ethics committees will still be based on national laws. In some countries this means patients, lay persons, legal experts and religious representatives would all participate in the ethical evaluation; in others only doctors and experts will get a say.

One procedure, diverse values

The new Clinical Trials Regulation is a good example of what is going on in the EU in the field of ethics. While the Commission is putting a lot of effort and money towards pushing for common procedures and ethical criteria, ethicists highlight the fact that values still differ greatly from country to country , which is reflected in the feelings of doctors and patients. "In the absence of a common health system, the perception of what is valuable for a patient can be hugely variable," says Örjan Brinkman, President of the European Consumer Organisation (BEUC).

BEUC was one of the first civic bodies to scrutinise the new directive, says Brinkman, who describes the original proposal as 'deregulation' rather than a new regulation. "The aim of the proposal was to deregulate research conducted on human subjects: all reference to ethics committees was expunged, and certain measures would have left member states incapable of protecting participants in clinical trials conducted on their territory."

The first version of the proposal, he says, put "impossibly short deadlines" for evaluating applications for authorisation to conduct trials, and stipulated that the conclusions of one reporting member state were to be binding on all member states.

It was only thanks to the mobilisation of many organisations representing civil society that several measures to protect trial participants were introduced, including the right for countries to refuse to allow a trial to run in their territory if their national ethics committee issues a negative opinion. A more reasonable timeframe for assessing applications was also introduced: 45 days in total, with the possibility of prolonging this deadline for certain categories of drugs.

Things to look out for

Despite these amendments, major issues remain, which will need to be addressed in the coming months, and will require close attention from patient advocacy groups and civic organisations.

Neither the members of the European Parliament nor EU health ministers seized the opportunity offered by the adoption of this new regulation to insist that new drugs must be tested against standard treatments.

The new regulation also contains what some feel amounts to a potential loophole, in that it considers certain clinical trials in which a drug is used outside its authorised

Transparency: in principle and in practice

The new Clinical Trials Regulation was supposed to bring more transparency and facilitate access to the raw data of all clinical trials, commercial or academic. This is something the academic community has long been calling for, to maximise opportunities for learning, to allow independent scrutiny of all trial results, and to enable clinicians to select the most appropriate population to be treated with new compounds, especially when budget limitations don't support their widespread use.

The final version accepts the principle of public access to "all information submitted in the clinical trials application and during the assessment procedure," but with the exclusion of data where "confidentiality of the information can be justified on the basis of the protection of commercially confidential information or the protection of personal data."

This is considerably more permissive on access to personal data than had been envisaged in the first draft.

The changes were made in response to feedback from a public consultation together with concerted pressure exerted by a number of research, professional and patient organisations, which called for a sensible balance between protecting the patient and freeing up vital data to progress research and personalised medicine.

The final wording acknowledges that "the processing of special categories of personal data may be necessary for reasons of public interest in the areas of public health without consent of the data subject," and it rules out the use of such data for other purposes, by third parties, "such as employers, insurance and banking companies".

The regulation also accepts the right of companies to restrict public access to trial data to protect their commercial interests. This could effectively thwart progress towards greater transparency, as sponsors will be able to cite commercial protection as a reason to keep the raw data secret.

indications (off-label use) as 'low-intervention' trials, which are subject to less stringent regulation.

This provision may be welcomed by the rare cancers communities, as it should make it easier to trial in rare cancer patients drugs that have already been approved for more common cancers. But the converse is also true. Drug companies will have an interest in applying for marketing approval in settings where it is easiest to get approval – where small patient populations can be used to justify small trials and lack of existing therapeutic options set a low efficacy bar. They may then be able to promote off-label use of the same drug, applying for additional indications based on 'low-intervention' trials.

In effect this makes it easier to pursue a strategy that has already become established for targeted cancer drugs, which are typically initially tested on a narrow group of patients, with very specific and restricted genetic mutations, then extended to a larger number of cancer types and so to a larger population.

In a joint position paper published last year in the *Annals of Oncology* (vol 26, pp 829–32), the European Society for Medical Oncology (ESMO) and European Organisation for Cancer Research and Treatment (EORTC) argued that the new Clinical Trials Regulation represents "one of the most important changes in the field of clinical trials in the last decade." They welcomed the opportunity it offered "to facilitate clinical cancer research in Europe and reduce some of the burdens that have proven so costly in the past."

However they also raised concerns, about whether clinicians are equipped to use the centralised electronic portal, in terms of understanding all the ethical issues that need to be flagged up, and having access to the administrative back-up needed to compile and input all the data.

They also flagged up key issues around which they hope to stimulate an inclusive debate, particularly within national oncology societies, in the hope of reaching "a consensus for a common position on clinical trials throughout Europe".

Key among these issues is the need to safeguard the patient voice within the ethical approval procedure, which the authors argue requires agreement on a "comprehensive definition" of patient involvement. "Cancer patients clearly have a high degree of interest in participating in the design and decision making of clinical trials," write the authors. "They should be given the opportunity to become involved with a subject that will frame how research on their disease needs to be conducted, and how the data gained from studying their data and tissue is to be used."

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Therapeutic options in recurrent glioblastoma – an update

Standards of care are not yet defined for patients with recurrent glioblastoma. In this critical review, **Katharina Seystahl** and colleagues summarise the available literature for patients with recurrent (progressive) glioblastoma treated with repeat surgery, re-irradiation, chemotherapy or immunotherapy approaches.

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Glioblastoma is a devastating disease with a median overall survival (OS) of 8.1 months for the period 2000–2003 and 9.7 months for 2005–2008 in population-based studies in the US (*J Neurooncol* 2012, 107:359–64).

The current standard of care in newly diagnosed glioblastoma was established based on the trial of the European Organisation for Research and Treatment of Cancer (EORTC)/ National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG), showing prolonged median OS of 14.6 months by addition of temozolomide (TMZ) during and after radiotherapy compared to radiotherapy alone (12.1 months) (*N Engl J Med* 2005, 352:987–96). Promoter methylation of the O6-methylguanine-DNA methyltransferase (*MGMT*) gene is a predictive biomarker for benefit of TMZ in newly diagnosed glioblastoma (*N Engl J Med* 2005, 352:997–1003). Currently, no standard of care is established for recurrent or progressive glioblastoma (*Lancet Oncol* 2014, 15:e395–403). Identification of effective therapies has been complicated by lack of appropriate control arms, selection bias, small sample sizes and disease heterogeneity.

Diagnosis of progression and response

The RANO (Response Assessment in Neuro-Oncology) criteria are considered to be the most accepted approach for diagnosis of progression and response in recurrent glioblastoma (*J Clin Oncol* 2010, 28:1963–72). In suspected pseudoprogression, repeat MRI imaging in shortened time intervals is recommended, while usually maintaining treatment.

Surgery at recurrence

The role of repeat surgery in progressive or recurrent glioblastoma remains controversial, underlining the need for prospective randomised trials. While some, mainly retrospective, studies suggest survival benefits for repeat surgery (*J Neurooncol* 2014, 117:147–52; *World Neurosurg* 2015, 84:301–7), others do not (*Neuro Oncol* 2014, 16:719–27; *Eur J Cancer* 2012, 48:1176–84). A *post-hoc* analysis of the prospective DIRECTOR trial in a subgroup of 59 evaluable patients stratifying for extent of resection showed superior survival only in those patients having received complete resection of gadolinium-enhancing tumours (*Neuro Oncol* 2016, 18:549–56).

Beyond an expected therapeutic efficacy, acquiring tumour tissue at repeat surgery could distinguish between recurrent disease and radiation necrosis, and help biomarker-based decision making.

Repeat radiotherapy

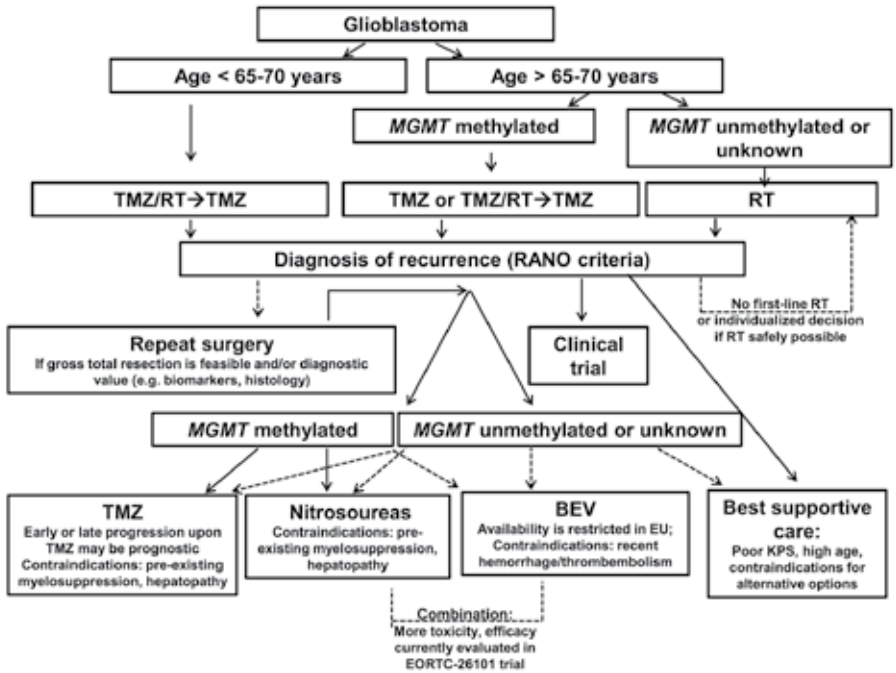
Evidence for re-irradiation is limited, highlighting the need for more randomised controlled trials. Concerns around repeat radiotherapy include radiation necrosis and neurocognitive impairment as well as limited efficacy.

Chemotherapy for recurrent glioblastoma

Nitrosoureas

Nitrosoureas, such as carmustine (BCNU), lomustine (CCNU), nimustine (ACNU), and fotemustine, are DNA alkylating agents and have been extensively used in glioma treatment. The use of nitrosoureas increased for recurrent disease when TMZ became standard of care in newly diagnosed glioblastoma.

Approach for individualised treatment decisions in patients with glioblastoma



Continuous arrows indicate evidence-based current clinical practice. Dashed arrows represent possibilities of individual decision-making which has still to be confirmed. CCNU – lomustine, KPS – Karnofsky performance scale, RT– radiotherapy, TMZ – temozolomide, TMZ/RT → TMZ – radiotherapy with concomitant and maintenance TMZ

Five single-arm phase II trials and six randomised phase II or III trials comprising one arm with nitrosourea monotherapy were reviewed. Comparison of the data is complicated by inclusion of TMZ-naïve or TMZ-pretreated patients in some trials. Progression-free survival at 6 months (PFS-6) ranged between 17.5% and 61.5%, and median OS between 6.0 and 11.1 months for monotherapy of nitrosourea agents. Notably, in the randomised studies, lomustine as monotherapy, commonly intended to be a 'control' agent, showed comparable results with the investigational agents enzastaurin (*J Clin Oncol* 2010, 28:1168–74), cediranib (*J Clin Oncol* 2013, 31:3212–8), galunisertib (*J Clin Oncol* 2015, 33:suppl, abstr 2014) or bevacizumab (*Lancet Oncol* 2014, 15:943–53), pointing towards relevant single-agent activity of the 'control' agent or lack of efficacy of the experimental agents.

The combination of lomustine plus bevacizumab showed prolonged median PFS and OS and higher PFS-6 than the single agents in the BELOB phase II trial (*Lancet Oncol* 2014, 15:943–53). The promising efficacy signal of this combination was not confirmed in the EORTC 26101 phase III trial comparing lomustine plus bevacizumab with lomustine alone in patients with recurrent glioblastoma, which did not report a difference in OS (8.6 vs 9.1 months), although prolonged PFS (1.5 vs 4.2 months) was confirmed (*Neuro Oncol* 2015, 17:suppl 5, abstr LB05).

In summary, nitrosoureas remain one standard of care at least for current

clinical trials. It is likely to expect that clinical efficacy will be more prominent in patients with tumours with *MGMT* promoter methylation (*Lancet Oncol* 2014, 15:943–53; *N Engl J Med* 2000, 343:1350–4).

Temozolomide (TMZ)

TMZ was approved for recurrent glioblastoma in 1999 based on two phase II trials, which both used a schedule of TMZ 150–200mg/m^2 for five out of 28 days. In one of these trials, TMZ was superior to procarbazine in patients, 60% of whom were pretreated with nitrosoureas, with a PFS-6 rate of 21% versus 8% and median OS prolonged by 1.5 months (*Br J Cancer* 2000, 83:588–93). The second trial, conducted as a single-arm study, showed a PFS-6 rate of 18% (*Ann Oncol* 2001, 12:259–66). PFS-6 rates of other prospective studies, mainly without previous TMZ treatment, using this schedule ranged from 21% to 24% (*Jpn J Clin Oncol* 2007, 37:897–906; *Ann Oncol* 2001, 12:255–7; *Oncology* 2002, 63:38–41; *Hong Kong Med J* 2005, 11:452–6). Several mainly single-arm trials evaluated alternative TMZ dosing schedules aiming at overcoming TMZ resistance. Yet, it seems very unlikely that there are relevant differences between the various dose-intensified TMZ regimens, and their superiority over standard-dose TMZ, for patients experiencing recurrence after a TMZ-free interval, has not been demonstrated either. The DIRECTOR trial demonstrating no outcome differences for two alternative TMZ dosing schedules established the role of *MGMT* promotor methylation as a prognostic marker for benefit of TMZ in recurrent glioblastoma (*Clin Cancer Res* 2015, 21:2057–64).

Prospective trials evaluating TMZ-based combination regimens, mainly conducted as single-arm studies, have failed to provide convincing efficacy signals beyond single-agent activity.

Bevacizumab

Bevacizumab, an antibody to the vascular endothelial growth factor (VEGF), was approved by the FDA in 2009 for treatment of recurrent glioblastoma based on two phase II trials showing an overall response rate of around one third and PFS-6 rates of 42.6% and 29% (*J Clin Oncol* 2009, 27:4733–40; *J Clin Oncol* 2009, 27:740–45). Approval in Europe was refused due to the lack of a bevacizumab-free control arm. In nine phase II trials with a bevacizumab monotherapy arm, PFS-6 rates ranged from 18% to 42.6%, with a median OS from 6.5 to 9.2 months. The BELOB phase II trial, comprising a bevacizumab-free control arm, showed comparable activity of bevacizumab versus lomustine as single agents, and increased OS of the combination of bevacizumab and lomustine (*Lancet Oncol* 2014, 15:943–53). In contrast, the EORTC 26101 phase III trial showed no difference in OS of the combination bevacizumab plus lomustine versus lomustine alone (*Neuro Oncol* 2015, 17:suppl 5, LB05).

More than a dozen prospective trials combining bevacizumab with other agents failed to show an efficacy signal beyond single-agent activity. Agents tested include irinotecan (*J Clin Oncol* 2009, 27:4733–40), carboplatin (*Neuro Oncol* 2015, 17:1504–13), the histone-deacetylase inhibitor vorinostat (*J Clin Oncol* 2015, 33:suppl, abstr 2012), the multikinase inhibitor dasatinib (*J Clin Oncol* 2015, 33:suppl, abstr 2004), etoposide (*Br J Cancer* 2009, 101:1986–94), the mTOR inhibitor temsirolimus (*Anticancer Res* 2013, 33:1657–60), the EGFR-targeted tyrosine kinase inhibitor erlotinib (*Neuro Oncol* 2010, 12:1300–10), the multikinase inhibitor sorafenib (*Clin Cancer Res* 2013, 19:816–23) or the histone deacetylase inhibitors panobinostat (*Neuro Oncol* 2015, 17:862–7) or vorinostat (*J Clin Oncol* 2015, 33:suppl, abstr 2034).

In conclusion, bevacizumab has clinical activity with prolonged PFS in recurrent glioblastoma, but an effect on OS remains uncertain.

Targeted therapy

There is plethora of clinical trials, mainly single-arm studies, evaluating agents aiming to target receptors or soluble factors involved in angiogenesis, oncogenic pathways or factors involved in tumour cell stemness or tumour invasiveness. Agents tested in a randomised design include cilengitide (*J Clin Oncol* 2008, 26:5610–7; *J Neurooncol* 2012, 106:147–53), erlotinib (*J Clin Oncol* 2009, 27:1268–74), cediranib (*J Clin Oncol* 2013, 31:3212–8; *J Clin Oncol* 2009, 27: 1268–74), enzastaurin (*J Clin Oncol* 2010, 28:1168–74), galunisertib (*J Clin Oncol* 2015, 33:suppl, abstr 2014), vorinostat (*J Clin Oncol* 2015, 33 suppl; abstr 2012) and dasatinib (*J Clin Oncol* 2015, 33:suppl, abstr 2004), with disappointing results.

EGFR-targeting agents such as gefitinib or erlotinib showed poor results in glioblastoma (*J Clin Oncol* 2009, 27:1268–74; *Neuro Oncol* 2015, 17:430–9; *J Neuro Oncol* 2009, 92:99–105; *Neuro Oncol* 2013, 15:490–6). However, efficacy of EGFR-targeted agents might be improved in target-selected patient populations, since a subgroup analysis of afatinib in a phase II study showed longer median PFS for patients with EFGRvIII-positive than negative tumours (*Neuro Oncol* 2015, 17: 430–9).

Immunotherapeutic approaches

Therapeutic principles of immunotherapy include immunomodulatory drugs aiming at activating the immune system against the tumour, treatment with oncolytic viruses, and different vaccination

Take home message from the authors

Katharina Seystahl (*left*) and Michael Weller (*right*) are from the Department of Neurology at the University Hospital Zurich, in Switzerland; Wolfgang Wick (*centre*) is from the Department of Neurology and Neurooncology Program of the National Center of Tumor Diseases, at University Hospital Heidelberg, in Germany.



"There is little evidence for effective treatment options in recurrent glioblastoma due to the paucity of randomised controlled trials and, more importantly, active agents. Most clinical trials are single-arm studies lacking a control arm. Based on the available data, alkylating chemotherapy with temozolomide or nitrosoureas represents the currently most widely accepted option for systemic therapy at tumour recurrence. *O*6-methylguanine DNA methyltransferase (*MGMT*) promoter methylation may serve as a biomarker predicting benefit from chemotherapy with temozolomide or nitrosoureas, not only for newly diagnosed glioblastoma but also at recurrence. Bevacizumab, the antibody to the vascular endothelial growth factor, has clinical activity with prolonged progression-free survival in recurrent glioblastoma, but an effect on overall survival is uncertain. The BELOB phase II trial pointed towards efficacy regarding overall survival of the combination of bevacizumab with nitrosoureas; however, this was not confirmed in the EORTC26101 phase III trial.

Clinical implications

Treatment for patients with recurrent glioblastoma should be somewhat individualised. Age, general condition of the patient, previous therapy and response to the respective treatment should be taken into account as well as molecular markers, especially *MGMT* promoter methylation and quality of life with regard to expected toxicities.

Furthermore, we should aim to treat patients within clinical trials in order to improve the knowledge on effective therapies for the future.

Future studies

Instead of small uncontrolled trials, novel therapeutic concepts should be tested in a randomised fashion already at an early stage of the development of the drug. Identification of predictive biomarkers will help to further develop evidence-based concepts for patients with recurrent glioblastoma."

approaches, either cell-based or antigen-based or both. All approaches theoretically should work best if applied early in the course of the disease to patients with minimal residual disease. This is why the majority of immunotherapeutic studies in glioblastoma today are conducted in the first-line setting and no longer in recurrent glioblastoma.

Immune checkpoint inhibition, interfering with inhibitory T cell signalling via programmed death 1 (PD-1), the PD-1 ligand or cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), offers a promising approach.

Regarding vaccination, encouraging results were reported for rindopepimut, a vaccine consisting of a peptide sequence of EGFRvIII, which was evaluated in combination with bevacizumab versus a control vaccine plus bevacizumab in bevacizumab-naïve patients. The rindopepimut arm had a higher overall response rate (24% vs 17%), prolonged PFS-6 (27% vs 11%) and median OS (12 vs 8.8 months) (*J Clin Oncol* 2015, 33:suppl, abstr 2009).

Other approaches

An alternative treatment concept comprises a portable device, called tumour-treating alternating electric fields (TTFields/NovoTTF), delivering low-intensity, intermediate-frequency electric fields, aiming to physically interfere with cell division. A phase III trial randomising patients to NovoTTF versus best physician's choice of chemotherapy showed comparable results for PFS-6 and median OS in both arms (*Eur J Cancer* 2012, 48:2192-202). Another 'chemotherapy-free' approach, evaluating a ketogenic diet in 20 patients with recurrent glioblastoma, reported disappointing results (*Int J Oncol* 2014, 44:1843–52).

Conclusion

Treatment should be individualised, and take into account factors such as patient age, performance status, *MGMT* promoter methylation, response to previous regimens, and quality of life with regard to toxicities (see figure, p51). Further investigations are needed to improve the prognosis for patients with recurrent glioblastoma.

Advertorial

Helsinn Group

40 Years building quality patient care

In the year of the 40th anniversary of the company, Riccardo Braglia, Helsinn Group Vice Chairman and CEO, offers a few words on Helsinn's long commitment to building quality cancer care and its plans for the future.

What does Helsinn stand for?

Helsinn, the Swiss pharmaceutical Group, is a family-run company delivering leading cancer care products, built on strong values of respect, integrity and quality. At the heart of everything we do is improving the daily lives of people with cancer by bringing high quality therapeutics, treatments, services and medical devices. This year, Helsinn Group is proud to be celebrating its 40th anniversary, a testament to our success in meeting the needs of people with cancer, and we look forward to using our values, expertise and innovation to continue to improve patients' lives.

How important to Helsinn is innovation?

We seek to deliver solutions for unmet needs in cancer. Patients require treatments and care that can improve patients' everyday quality of life, and innovation is key in order to be able to deliver this. We innovate in a number of ways: through our high quality internal research and development engine, through a unique licensing model with partners who share our values, through high quality manufacturing and through our business model. In the last five years, we have reinvested an average of 30 percent of our each year total sales in R&D, demonstrating our commitment to maintaining a high level of investment in bringing the best quality products to market.

In what areas of therapeutic and secondary care is Helsinn currently developing new products?

We recently broadened our focus beyond cancer supportive care products, into the development of oncology therapeutics, with a drug candidate for the treatment of acute myeloid leukemia (AML) and other potential indications. The remainder of our broad pipeline of programs focuses on addressing the key unmet needs in cancer care, and due to our excellent network in this area, we have an unparalleled understanding of patient need. Our current areas of focus include chemotherapy-induced diarrhea, cancer anorexia cachexia and chemotherapy-induced neuropathic pain. We also have some early stage development programmes exploring the role of ghrelin in metabolic diseases.

What has driven your recent move into the area of non-pharmaceutical products for cancer patients through the creation of Helsinn Integrative Care?

The company's long-term vision is to offer people with cancer trusted and high quality solutions wherever there is demand, not only with pharmaceutical products, but also through medical devices, supplements, and medical foods that are clinically validated and under the control of healthcare practitioners. A growing number of people with cancer seek supplements and herbs to help manage the side effects of cancer treatments without professional medical advice. The goal of Helsinn Integrative Care is to provide products that meet this growing market need but are based on robust clinical evidence and are complementary to other therapeutic and secondary care treatments. At Helsinn, we believe that our reputation for trust and quality will play an important role in guiding patients in this expanding new market.

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Building quality cancer care together

Can't we learn any faster?

Patients who have run out of options don't have time to wait for lengthy trials. But they also need treatments that offer proven benefit, and not just hope. **Peter McIntyre** asks whether we can speed up the learning process without sacrificing certainty.

Shortly before Robert Califf was appointed head of the US Food and Drug Administration in February 2016, he told a seminar in Washington that clinical trials were regarded as "too slow, too expensive, not reliable, and not designed to answer the important questions". His priorities include streamlining clinical trials to make better use of real-world data in "a learning healthcare system".

The views of the man who heads the US regulatory body reflect widely expressed opinions in Europe among researchers, patients and industry. Some suggest that the days of the gold standard randomised controlled trial (RCT) are numbered, arguing that they take too long to answer a single question, and condemn too many patients to stay on a treatment arm that is not working for

"You would not buy a mobile phone today based on a review of phones in 2005" *Iain Galloway*

them in order to generate the required statistical significance.

There is also an increasing demand for 'real world data' from high-quality registries to supplement or even replace traditional clinical trials, to demonstrate the effectiveness of promising new treatments in everyday practice, and to define the sub-groups who best benefit from molecular targeted therapies and immunotherapy. There are concerns, however, that abandoning RCTs could open patients up to untested treatments that will turn out to have limited impact on overall survival.

Wrong questions, too slow

The weaknesses of the traditional approach are felt most in rare cancers (collectively 22% of cancers in Europe) and in cancers with limited treatment options and low overall survival. A consensus paper from Rare Cancers Europe in 2014 called for new approaches to collect and analyse evidence, using adaptive trial designs that feed performance data back during the trial, allowing patients to switch treatments. The availability of electronic patient records and patient-reported outcomes, it argued, make it possible to use retrospective cases as surrogate control arms.

Iain Galloway runs the Ocular section of the Melanoma Patient Network Europe, and is strongly campaigning for better trials. Ocular melanoma is a very rare cancer and about half of patients develop liver metastases, with a very poor prognosis. Galloway, who has a full-time job and a family, has himself had a large part of his liver removed, and is now on pembrolizumab. Though currently well, he is looking ahead to next steps should his disease progress, and he feels too little effort is being made to investigate new options for people in his position.

Galloway has written to the NHS England Specialised Services Clinical Reference Group complaining of the treatment options offered in England to the 200 or so people who develop metastatic ocular melanoma every year, saying many are "sent to die on useless treatments such as dacarbazine," which has no long-term clinical benefit.

Some patients are so desperate, he says, that they seek places on skin melanoma trials of BRAF inhibitors, even though mutations in the BRAF gene are very rare in ocular melanoma. "We are subjected to ineffective trials that are not going to benefit us. It is little more than intellectual masturbation," he says.

At the same time, he adds, patients may be missing out on treatments that really could help them because of what he sees as the 'outmoded' way health technology agencies conduct their analyses. He cites, as an example, a chemosaturation approach to treating the sort of diffuse liver metastases typically associated with ocular melanoma. This involves isolating the liver and saturating it with high concentrations of an alkylating agent (melphalan), which is then filtered from the blood before it flows back to the heart.

In May 2014, NICE, the health technology assessment (HTA) agency for England and Wales, found limited evidence of effectiveness, with a significant incidence of serious adverse effects. In July 2016, NHS England concluded that "there is not sufficient evidence" for chemosaturation to be routinely commissioned, on the grounds that that the studies they looked at were small and lacked control groups and none were of high enough quality to draw firm conclusions on safety.

Galloway acknowledges that the filtering of the toxic treatment was inadequate in early trials, but says that adaptations have been made on the basis of early experiences, and that NICE and the NHS are failing to keep up. "You would not buy a mobile phone today based on a review of phones in 2005, and these cancer treatments are changing at about the same speed," he says.

A study of 20 consecutive patients published as a poster presentation at ASCO 2015 (*JCO* 33, 2015, suppl; abstr e20000) recorded no treatment-related mortality, with only one grade 4 event and five grade 3 events. Thirteen patients (65%) showed a partial response in the liver and two patients (10%) showed a complete response. At the time of publication, 55% (n=11) had survived for one year, and 15% (n=3) for more than two years – compared to a one-year survival rate of 15–20% without the treatment. "The research team concluded that chemosaturation can provide significant benefits in a carefully selected group of patients as part of a multidisciplinary approach."

As is often the case with very

> "We can't afford to wait five or 10 years while one medicine wends its way through the lengthy traditional trial process" *Kathy Oliver*

rare cancers, the metastatic ocular melanoma patient community is well networked, and Galloway says the results presented at ASCO reflect the positive experiences of many who were part of that study, which was conducted at the Southampton University Hospital in the UK.

He wrote to the group that reviewed the treatment for the NHS, saying "It is evident that those who benefit from chemosaturation have a very high quality of life and suffer very few of the side effects noted in your research. It appears that your research is woefully and unacceptably outmoded. Adverse effects reporting and treatment morbidities are now very considerably lower than those stated in your statistics."

Kathy Oliver, co-director of the International Brain Tumour Alliance agrees that patients with aggressive cancers need rapid access to effective treatments, and don't have time to wait for a succession of lengthy RCTs.

"The median survival for a patient with glioblastoma [GBM – a highly aggressive brain tumour] – is about 14.6 months, so we urgently need new drugs to be developed quickly. We can't afford to wait five or ten years while one medicine wends its way through the lengthy traditional trial process. "Our patient population is desperate, and one of the ways they can possibly have a chance of surviving a little bit longer is to try innovative approaches."

These approaches are at the heart of the GBM AGILE trial that will start recruiting patients in the USA, Australia, China and Europe in the autumn, under a master protocol agreed with the FDA. Initial drug treatments will be based on genetic markers found in each patient and the trial will be guided by Bayesian statistical approaches.

Treatments will be adapted as centres learn what works and what does not, so similar patients (as determined by subtypes and enrichment biomarkers) will have a higher probability of being assigned to something that might benefit them, and will be less likely to be randomised to agents that perform poorly in their subtype.

Anna Barker, director of the GBM AGILE trial, is a former deputy director of the National Cancer Institute and was one of the founders of The Cancer Genome Atlas project (TCGA).

"The Cancer Genome Atlas has created literally thousands of investigations about the pathways involved in this disease, so we have a pretty good sense of the genes that are perturbed in these pathways and we know certain biomarkers are of potential significance.

"Almost any drug that has not yet been tested in GBM could be a candidate because we don't know what is going to work in this disease." Barker says that they may also retest some drugs that were deemed to have failed in the past. "There are all kinds of reasons why these drugs have failed, and frankly there may be drugs out there already tested in GBM but just not tested very well."

She hopes the evidence generated will enable them to pick strong potential 'winners', good enough to show their value in short, small phase III trials.

It is not only rare cancers where patients believe trials are failing them. Many people with cutaneous melanoma – diagnosed in more than 100,000 people in Europe each year – feel the same way.

Before the arrival of new immunotherapies, the median survival time for patients with stage IV metastatic melanoma was less than a year. Bettina Ryll watched her husband die from the disease at a time when new treatments were just within reach, and founded Melanoma Patient Network Europe to campaign for better treatments.

She says that the design of clinical trials needs to keep pace with molecular and medical advances to ensure rapid learning. Patients in desperate situations

> "We don't learn systematically, and that is for me a terrible waste" *Bettina Ryll*

"I don't think you can defend yourself by saying that the patient wants it. Hope sells just about anything"
Lex Eggermont

need early access to promising drugs, combined with systematic data capture about safety and efficacy.

"We are running trial designs invented 50 years ago to deal with a situation that has fundamentally changed. Our people were dying in six to nine months, so any uncertainty should be compared to that timeframe. Running one RCT – which takes time to plan and prepare and start and see it published – before starting the next one, is a very inefficient way to generate evidence."

Opportunities are still being missed, she says, citing as an example an early access programme for a PD-1 antibody which collected data on safety, but not on efficacy. "We don't learn systematically, and that is for me a terrible waste."

Don't sacrifice reliability

Amidst all the calls for change however, some of Europe's leading cancer specialists are warning that the security and confidence generated by RCTs must not be put at risk.

Lex Eggermont, director general of the Gustave Roussy Institute, Paris, accepts that special measures are required when breakthrough therapies appear for rare cancers, but says that the level of evidence must remain high before introducing expensive new treatments for large groups of patients where there is already treatment available.

"What is not well understood by the public is that RCTs protect you against overtreatment and what I would call 'religion' rather than 'science'.

"It is very risky to drop the mechanism by which we compare our standard therapy to new treatment and go through a rigorous evaluation of whether the benefits are truly what we think they are bringing.

"We have been wrong so often in the past. Randomised controlled trials demonstrated that the benefit was totally marginal and in no way justified the costs and the associated toxicity. If we make conclusions without randomised controlled trials, it would mean that we have not learnt anything from our past experience and declare that our understanding is so much more profound. This is a very dangerous path."

The fact that the new therapies hold so much promise makes RCTs even more important, he says. "We need to keep our heads cool to ensure we are not going to prescribe all sorts of stuff that has marginal activity and actually would block patients from getting access in a couple of years from now."

Eggermont is concerned that there are few reliable biomarkers for testing who benefits from new immunotherapies, and doubts whether governments and insurance systems will pay €160,000 a year for a new treatment unless they are confident it will show results.

He points to the huge off-label demand in the US for checkpoint immune blockers for indications where there is little or no data. "People are selling their houses and sacrificing the college funds of their kids, and if the kids are already independent, they feel forced to sell their house as well, and this is all based upon nothing. I don't think you can defend yourself by saying that the patient wants it. Hope sells just about anything."

Fatima Cardoso, Director of the Breast Unit at the Champalimaud Cancer Clinical Centre in Lisbon, also advises caution. Novel trials help to form treatment hypotheses, she says, but do not provide final evidence. "As far as I am concerned, at the moment, I don't think we can move away from these phase III trials."

She is concerned that pertuzumab (Perjeta) has been approved in Europe as a neoadjuvant treatment for early breast cancer on the basis of pathological complete response in a phase II trial – a finding that does not always translate into best survival or fewer relapses.

Such early approval is acceptable in areas of unmet need, she says, but not where there are already good treatments. "For pancreatic cancer I would be totally OK with providing temporary or conditional approval pending phase III results. For early breast cancer it is quite a stretch to say this is also unmet need."

Cardoso argues that one reason for slow progress in metastatic cancer has been the acceptance of inadequate endpoints such as progression-free survival. Progression-free survival for the metastatic patient does not make a difference to how long you survive, she explains. "Basically it means that you are going to die the same day, but you will die with or without progression of your disease for a few more months.

"One reason for slow progress in metastatic cancer has been the acceptance of inadequate endpoints such as progression-free survival" *Fatima Cardoso*

That is only meaningful if the patient has a lot of unpleasant symptoms from their disease, in which case it is very important that you control the disease. In breast cancer most of the time progression does not lead to significant symptoms.

"I am always fighting for our end point to be survival: only drugs that really increase survival should be given priority."

Real world learning

One solution increasingly talked about is to do a lot more learning outside of trials, within registries, where data are systematically collected on patients treated in a real world setting. This has the advantage of showing how new treatments perform in their intended patient population, as opposed to the selected group who make it into trials.

The European Cancer Drug Development Forum held a workshop in July on the use of real world data to optimise oncology drug development and access. The workshop – attended by regulators, clinicians, HTA/payers, and policy makers – focused on how to generate evidence on efficacy and safety in the real world setting in a way that would also inform reimbursement decisions.

Richard Bergström, Director General of the European Federation of Pharmaceutical Industries and Associations (EFPIA), strongly supports such an approach. He points out that people were sceptical about the difference that drugs like Herceptin would make, even after successful clinical trials. Now many are used in an adjuvant setting, with dramatic results. "You have real population outcome data and you see stark differences. That is very difficult to disagree with. That suggests that we should capture data in real time in real lives. We should not have to wait 10–12 years for some academic to come and do this."

He has a vision of 'super centres' for cancer that are able to offer all promising new treatments and capture data on efficacy and safety in highly computerised registries. Patients can be stratified according to prior disease, age, sex and other variables, and randomised to different new treatments, based on advanced molecular diagnostics. This, says Bergström, would lead to more rapid learning of how best to use new therapies and in which patients, and would speed up access to new treatments.

"We need data capture for every patient going forward in real time, so we get real world evaluation both for effectiveness and for value. You can then do payment by results for one-year, two-year or three-year survival."

Generating this sort of data would require much better sharing of data through well organised registries.

It would also require a change of culture in the prestige and attention given to reports of real world data. Martine Piccart, Head of the Department of Medicine at the Institut Jules Bordet, points out that at international conferences clinical trial reports are usually delivered from the platform, while real world results are not. "If you submit a study of 1,000 patients who have been treated with new drug x after registration in the real world, most of the time you will end up in a poster presentation and that is a pity."

Change is coming

The growing influence of cancer patient advocacy means that change will happen one way or another.

Kathy Oliver from the International Brain Tumour Alliance accepts that it is tough for clinicians to move away from the randomised controlled trial as the gold standard for evidence. However, her son Colin died from a brain tumour

"We need data capture for every patient going forward in real time, so we get real world evaluation both for effectiveness and for value" *Richard Bergström*

Testing by pathway

One approach to developing new treatments is to target molecular pathways across several tumour types, rather than focusing on a single histological site. Denis Lacombe and colleagues at the European Organisation for the Research and Treatment of Cancer explored "histology agnostic cancer clinical trials" in a 2014 paper, in which they argued that drug development one cancer site at a time can be "inefficient, time-consuming and expensive" (*Mol Oncol* 2014, 8:1057-63).

Channelling patients to trials on the basis of genetic markers is what lies behind EORTC's SPECTA programme, and it is also the basis for the US-based NCI-MATCH trial.

NCI-MATCH focuses on patients who are not responding to standard therapy

NCI-MATCH focuses on patients who have solid tumours or lymphomas that are not responding to standard therapy. Through DNA sequencing, patients will be evaluated for inclusion on one of 24 treatment arms trialling drugs approved for another cancer indication or under trial. They include inhibitors that target EGFR, HER2, MET, ALK, BRAF, FGFR and other markers.

Overall 5,000 patients will be screened for 4,000 genetic variations across 143 genes. Those who are put onto treatment arms will continue for as long as the tumour shrinks or remains stable. If treatment fails they may be considered for a second arm of the trial. The aim is that at least 25% of patients will have rare cancers. Drugs that produce promising results may be incorporated into larger future studies.

While there is huge interest in this pioneering trial, NCI-MATCH also demonstrates the limitations of this approach. Only 9% of the first 500 patients assessed could be matched to treatment arms, and only 33 patients (about 7%) were actually treated. Following expansion of the trial, researchers expect to match about 20% of patients to treatment arms.

It has also been shown that drugs that are effective on one cancer may not work on another despite a common genetic mutation. For example, BRAF inhibitors put the brakes on melanoma in patients with the BRAF mutation, but have little effect on BRAF-positive colorectal cancer.

Lex Eggermont, President of the Gustave Roussy Cancer Institute in Paris, warns that the promises of genetic targeting are being oversold. A full molecular portrait – RNA and DNA sequencing and comparative genomic hybridisation (CGH) – will probably identify genetic targets in 50-60 of every 100 patients, he says, but he points out that only half of these targets currently have drugs available. For the 30 patients who can enter a suitable treatment arm, a response rate of around 25% can be expected. "You are left with seven or eight responding patients out of the 100 patients for whom you did all this sequencing and created a molecular portrait."

For patients who encounter resistance, a similar attrition rate can be expected in a second round of treatment. "You are going to quickly run out of time because the percentages are not going to go upwards, they are going to go downwards. That is not understood by the public because there is an oversimplification in the promises, as if this is a standard approach, whereas it is one big clinical and translation research project."

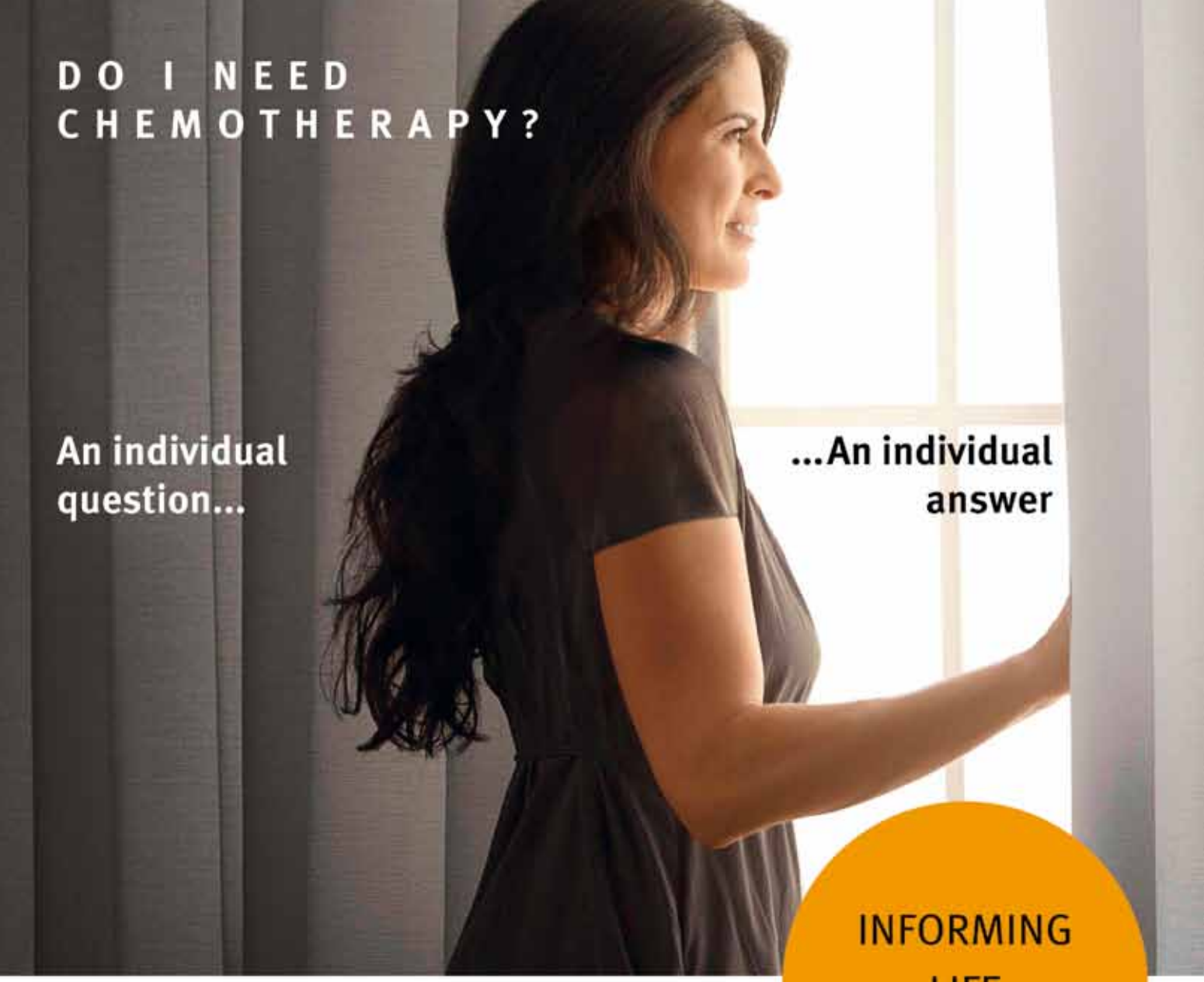
"It is one big clinical and translational research project"

In his paper, Denis Lacombe calls for international efforts to conduct these sorts of trials to be pooled. "Histology agnostic trials may become more common in the future, particularly to investigate the effectiveness of therapeutics on rare cancers, but the model still needs to prove its feasibility. It is quite apparent that this kind of trial needs to be based on a strong biological rationale and should not be used to complement weak preclinical data."

in 2011 at the age of 32 and she says that patients with rare and intractable cancers do not have time to waste. "Progress in brain tumour treatments is far too slow. We need to really get a move on here, challenge the status quo and think outside the box."

Iain Galloway's group is developing criteria for a traffic lights system for ocular cancer, with amber warning lights for melanoma trials that test promising new treatments against something old-fashioned and ineffectual. "We have now some drugs with amazing efficacy and they cannot be trialled against old chemotherapy."

Bettina Ryll warns that better-informed patients will no longer accept being on ineffective treatment arms. "In the past we wrapped it up as good research and sold it to patients as 'heroes' on trials. People are less and less willing to put up with it. They will vote with their feet and empty the trial."



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Harnessing big data to drive up quality of care

Pooling data that tell the unique story of each cancer patient reveals patterns that could help us learn about which treatments work best for which patients in everyday clinical practice – and about which clinics stick most closely to clinical guidelines. **Marc Beishon** reports on a US initiative that hopes to do just that.

Where do you turn when you have a patient with a rare cancer for which there are a number of possible treatment options? What if current guidelines do not say which is best, or there are no guidelines that are relevant to patients like yours – similar age, gender, health status, treatment history? The literature could reveal some relevant cases and guidance, and colleagues can be consulted for opinions. But that could be hit or miss and add little to your own experience. And there is no time to lose.

It's a scenario that CancerLinQ (https://cancerlinq.org), an ambitious project in the US, aims to address by pooling the 'real time' experience of treating millions of cancer patients in a 'big data' computer system. Any oncology practice can log in and search for patients with profiles similar to theirs, and look up how they were treated and what their outcomes were.

The project is billed as a 'rapid learning system' for cancer, with a primary mission to improve the quality of everyday oncology practice across the country. It can also be used to test hypotheses for clinical trials,

generate new clinical guidelines, and bring in results from trials, registry data and patient reported outcomes.

CancerLinQ is one of a series of initiatives by the American Society of Clinical Oncology (ASCO), and, according to ASCO's medical director, Richard Schilsky, the most challenging and potentially transformative. "In recent years we've moved from being mainly reactive to starting projects that we believe will change cancer care," he says. "These include the ASCO Value Framework [which assesses the value of new cancer therapies], our first ever clinical trial – a genomic matching study called TAPUR [Targeted Agent and Profiling Utilization Registry] – and CancerLinQ, which we started in 2012.

"We've taken the view that we can do much more than the usual dissemination of information through journals and meetings, by helping to change practice, and to some extent research, by filling gaps in knowledge that can't be filled by the traditional mechanism of the prospective clinical trial."

As Schilsky adds: "The only way we have learnt anything in oncology is by conducting clinical trials, but we have to recognise that only a small percentage of adult patients participate in them in the US, and there is only a certain number of trials that can be completed with limited resources. Yet every day we continue to treat patients whose information is never available to the wider oncology community, because there is no mechanism to collect, analyse and learn from it."

The goal of CancerLinQ, he says, is to aggregate and analyse data from millions of cancer patients in the US and also potentially from centres abroad, to identify new areas of research, but especially to improve care by feeding back to oncologists information on how well they are serving patients, according to quality guidelines. As Schilsky points out, there is a drive in the US and in other countries to monitor and improve healthcare quality, but existing methods have reached their limits.

Quality control in real time

"For example, for the past decade ASCO has run the Quality Oncology Practice Initiative, QOPI, which has been successful, but it is retrospective, as it is based on manual extraction of data from patient charts done at the practices – it gives a sense to oncologists on what they were doing rather than what they should be doing. CancerLinQ is taking QOPI and converting it into an electronic prospective system with built-in quality measures that can be reported back to doctors nearly in real time." Apart from insights from the 'big data', those quality measures will tell oncologists if they have documented factors such as pain and carried out tests such as for HER2 within certain times, and compare their day-to-day performance with that of their peers.

CancerLinQ is designed to take data from most electronic health or patient record systems that are in use in oncology practices and cancer centres. Although these patient record systems have had a tough gestation in the US, they are now in wide use. Schilsky says about 90% of the several thousand oncology practices in the US have a record system suitable for integration – and apart from some interconnection work, there is no more that needs to be done to upload data to CancerLinQ, as the practice will be collecting it anyway.

The data collected comprises both structured information – such as the pathology and treatment of the cancer, and mandatory reports like standard scales of pain and emotional distress – and also unstructured data, which are mainly the notes that accumulate for each patient. Essentially, it collects the whole patient record.

Initially, the structured data are the easier to analyse, and in this early stage of the project there are several examples that show its potential for what many will no doubt see as the more exciting side of the project, as demonstrated at ACSO's annual meeting in June, which was billed as being about 'collective wisdom'. At this point, says Schilsky, there were about 750,000 patient records in CancerLinQ, but only 130,000 had been 'cleaned up' sufficiently for analysis.

But even using this limited data base, he says, his team has been able to select a cancer that is uncommon and which most oncologists are unlikely to have much experience with – namely male breast cancer – and pull out 350 records. "That's one of the largest series of cases anyone's seen, and we were then able to ask a straightforward question – what treatments were administered to those men? – and we were plotted a histogram of those treatments against patients who received them. If you're an oncologist who hasn't seen a case for ten years or more, you can see what your colleagues are doing now in a couple of mouse clicks." The system is presented to oncologists as a 'dashboard' interface, he says.

And they also looked at another trial that made the news at the conference. "There was data reported on a prospective randomised controlled trial on metastatic colon cancer, and outcomes depending on whether the tumour was on the left or right of the colon," says Schilsky. "So we pulled out all the colon cases in CancerLinQ, looking at the side and treatments given, and found that, regardless of the location, most patients got bevacizumab [Avastin] in addition to chemotherapy, yet the trial indicates that left-side colon cancers did better with cetuximab [Erbitux] and chemotherapy. So now we are in a position to see whether oncologists will shift to cetuximab on the left side. This kind of analysis will inform us about the dissemination of research results into practice."

LinQing up

ASCO also announced that 58 oncology practices have signed up for CancerLinQ. These are mostly smaller, outpatient practices rather than the comprehensive and academic cancer centres – Schilsky says they have fewer patient numbers and

could have more to gain, while the larger centres tend to take a proprietary view of their data and have more bureaucracy to navigate. But all centres should have just as much interest in analysis of current practice, and he is optimistic that most will sign up over time. Currently, there is no charge for signing up to CancerLinQ, with much of the $40 million or so spent so far coming from ASCO's Conquer Cancer Foundation.

One of the practices is Michiana Haematology Oncology, which has six locations in northern Indiana. Robin Zon, a senior partner and a medical oncologist, says it has been difficult to implement an electronic patient record system, but it became much easier once a shared platform among a network of local institutes was set up. As she explains, like many US practices, Michiana has certain expertise – it mainly carries out medical oncology and radiotherapy, so most surgery and pathology data needs to come from other providers. "We are certified for ASCO's QOPI, which means that we cannot treat without a pathology report for each diagnosis, for example," she says.

Like most cancer practices, Zon and colleagues run tumour boards, some 120 a year, and use guidelines, principally from the National Comprehensive Cancer Network (NCCN), but as she says, while primary treatments can be straightforward, recurrent and metastatic cases often have many options and little guidance on what to use. "CancerLinQ will give us additional data points on how past patients have behaved when they have certain parameters that take in real life experience, not just those in trials. If there are two patients with similar pathology, stage, age and gender, they might be different in other ways, such as other medication, co-morbidities and certain blood chemistry, and we may then be able to differentiate them by treatment."

Zon can't emphasise enough that basing treatment decisions on clinical trials from just 3% of the population is like comparing apples with oranges, and applying trial results to an often older group of patients can soon show that the treatments are not appropriate (or indeed can be a "nightmare" as she puts it).

She adds that oncology centres can use different therapies that are seen as equivalent based on their experience and culture, mentioning chemotherapies given to lymphoma patients about to undergo bone marrow transplants. "We use a different regime to the Mayo Clinic, where one of our patients has recently gone for a transplant," she says. "We use 'collective wisdom' at our tumour boards, but this is mostly not based on documentation. Of course we are using precision medicine where we can, but this is for a minority of patients in some cancers. In lung cancer, for example, the new genomic targets are not found in most, so what do we give them? CancerLinQ will help show whether what we are doing is correct or maybe way off – I anticipate using it at our boards to inform our recommendations."

The IT challenge

There are a lot of administrative and technical issues that have had to be solved with CancerLinQ, such as anonymising the data and ensuring data are collected for the same person over time, so that comprehensive comparisons can be made about when, how and where they were treated, and how they fared at least for five years. Given that in the US there is no national patient identifier code, this is a big challenge. Schilsky explains that most standard data about a cancer is likely to be in oncologists' systems, given they can't practise without it, but pulling in data from primary care, and other specialists such as cardiologists who provide care during the cancer journey, is more a vision than reality at present.

He mentions that ASCO is now collaborating with the American Society of Radiation Oncology (ASTRO) to include data from its practices; another collaboration is with the Cancer Informatics for Cancer Centers (CI4CC). "And we also want to build in patient-reported outcomes using a mobile phone app that allows people to link how they are feeling with their patient record. That will greatly enrich the data." Zon, who leads ASCO's pathways task force, says CancerLinQ can be seen as part of the bigger quality picture of clinical cancer pathways, which should aim to manage care from diagnosis to end of life.

A European LinQ?

Is there anything like CancerLinQ in Europe? Probably not at present, as healthcare systems and cancer centres are developing different tools according to various priorities for quality and research. But 'big data' is a common theme. A recent paper, 'Unlocking the treasure trove of information in cancer registries', which focused on improving outcomes in prostate cancer, pointed to the trend for population-based cancer registries to merge with clinically-based registries as an important 'direction of travel' (*Eur Urol* 2016, 69:1013–14).

Healthcare managers may want to receive up-to-date metrics on factors such as population needs, waiting times and quality of care, while oncologists and researchers will in future also be served with the broad amalgamation of data on incidence and survival from databases, increasingly enriched with patient-level information (see also 'Explaining Europe's survival gaps', *Cancer World* May/July 2016).

In Germany, for example, the 'Klinische Datenintelligenz' (KDI, clinical data intelligence) project, funded by the Federal Ministry for Economic Affairs and Energy, is developing systems that can provide a single view of all data collected from a patient, not just cancer – although breast cancer is one of the first applications mentioned in a paper (The Clinical Data Intelligence Project,

Informatik Spektrum 2016, 39:290–300). It is described as "the first German medical data intelligence initiative where clinical data is tried to be turned into smart data for clinical decision support", with sources including the Bavarian Breast Cancer Cases and Controls database.

Peter Fasching, a gynaecologist and cancer specialist at Erlangen University Hospital in Bavaria, who is involved with KDI, comments that the US CancerLinQ is an advance, especially for analysing large amounts of data "to find a population similar to the patient sitting in front of you", given that, increasingly, patients are part of smaller groups as treatment becomes more personalised. He says that the integration of imaging, molecular and biobanking data will be the next step for decision support in personalising treatment, which is what KDI is investigating.

He adds that oncologists don't need to wait for national initiatives – they can start their own databases. "For example, in Germany a group around the country has built one of the largest real-time registries on metastatic breast cancer, called Praegnant [www.praegnant.org] – it is helping us to scrutinise clinical and molecular data to improve patient care right now."

There are many other projects around Europe. Sweden, for example, has developed a real-time reporting system for its national prostate cancer registry, which oncologists can use to compare data among all of Sweden's 21 counties. "Data include waiting times between referral and first consultation, time between biopsy procedure and cancer information, selection of treatment, surgical outcome (positive margins) and many other pertinent aspects of cancer care" (see *BMJ Qual Saf* 2014, 23:349).

There are certainly a lot of claims being made. The Netherlands Comprehensive Cancer Organisation (IKNL) says the country's national registry (NCR) will include a tumour-specific dataset, and more data will also be gathered about the course of the disease, "thus making the NCR a continuous patient follow-up system – unique in the world".

A flexible tool for clinicians. An ASCO delegate checks out the different functions CancerLinQ can offer

Jem Rashbass, of Public Health England's National Disease Registration and Cancer Analysis Service, says the UK is probably the closest to achieving something similar to CancerLinQ – it has the great advantage of integration among all tiers of healthcare, and a much smaller number of oncology centres. In 2013, Public Health England, which had assumed responsibility for all the English cancer registries and the National Cancer Intelligence Network, announced it would develop the world's largest single database of cancer patients.

"We have made great progress since 2013," says Rashbass, "and now pool nearly all cancer-related-data – referral pathway, screening, pathology, molecular diagnostics, imaging, multidisciplinary discussion, radio- and chemotherapy – at a record level on all patients diagnosed with cancer across England, and from the end of the year Wales. This will be around 32 million records, on over 500,000 tumours, this year.

"We are now about to test feedback to clinicians that will provide them with a view of all the information we know about the patient sitting in front of them. It is an interactive infographic of the whole medical record for that patient. In time we expect to use machine learning algorithms to infer possible outcomes for individual patients."

A typical example he gives for how the system in England will work is creating an aggregate view of patients such as older women with breast cancer, to provide details on outcomes, mean time to relapse, and added benefits of adjuvant therapies. A dashboard will also show all the health-related events for a particular patient.

"But there are some datasets that we are working on where I feel we don't have enough information. Our collection of molecular data is limited to about 30 markers at the moment; we need a better assessment of co-morbidity – we are about to link primary care prescription data to do this, and we need to be better at identifying and capturing recurrence and relapse.

"The challenge for all of us is scale and data quality. In comparison with the US potential, our scale in the UK will inevitably be smaller, but we do cover all the 55 million people in England. We are obsessed with data quality, because if personalised medicine is really to deliver, we don't want to spend time tracing spurious data anomalies, so we have around 150 cancer registration staff collating and quality-assuring the data."

This seems to be a well-balanced big data 'arms race' across the Atlantic, which can only be good news for the quality of cancer care.

Fortunato Ciardiello

ESMO President

Fortunato Ciardiello took on the presidency of the European Society for Medical Oncology at a time when the profession is being required to deliver treatments of unprecedented complexity and cost. *Cancer World* Editor, **Alberto Costa**, asked him how he plans to address the challenges this poses for his members and the cancer community as a whole.

Alberto Costa: *What is your vision for ESMO over the coming five years?*

Fortunato Ciardiello: Equipping our members to fight cancer more effectively is ESMO's principal goal. Our '2020 Vision' is to promote integrated cancer care, provide specialised education and advocate for sustainable cancer care. Integrated cancer care involves creating bridges between cancer research, diagnosis and treatment in a concerted effort to improve outcomes for patients. Specialised education is needed now more than ever, as medical oncologists must have in-depth, disease-specific knowledge which enables them to collaborate effectively with other specialists within integrated, multiprofessional teams.

As part of our vision for sustainable cancer care, we will continue to advocate for access to optimal cancer care for all patients worldwide, as cancer is a global issue

that reaches beyond wealthy western countries towards developing countries. This is becoming increasingly important as the costs of diagnosing and treating cancer grow and inequalities in the options available become evident between, and even within, countries.

AC: *ESMO is increasingly active beyond the borders of Europe. Where are ESMO's priority areas of international work?*

FC: ESMO has become a global society, maintaining its European roots. As a testament to our international appeal, we now have more than 13,000 members from more than 130 countries, and 24% of members are from the Asian region.

ESMO is now able to nurture a community of professionals working together to find solutions to complex questions and to drive the pace of change even further in the best interests of patients across the world. ESMO has very strong ties and interaction with national societies and oncology professionals working in Asia.

Last year we held the first ESMO Asia Congress, attended by almost 3,000 participants, who had the chance to share expertise and knowledge on a regional and international scale. The congress was organised in collaboration with our partners in Asia to ensure regional issues were addressed, on top of providing up-to-the-minute information on all types of cancer, with a focus on those most prevalent in the region.

AC: *Surgeons are under increasing pressure to stop 'doing everything', and to specialise by organ site. Should medical oncologists do the same, or does ESMO still support the concept of a 'totipotent' medical oncologist?*

FC: Integrated, disease-specific teams are becoming the gold standard for delivering high-quality care in comprehensive cancer centres. In order to collaborate effectively within multiprofessional teams, keeping pace with the fast evolution of medical oncology, professionals in this field – like in many others – must become specialists, not least because complex molecular tumour analysis plays a fundamental role in choosing the most appropriate treatments for patients. The ESMO 2020 Vision supports this evolution.

Our young oncologist development framework promotes fully integrated education based on early-career disease-oriented specialisation, as well as understanding of the role of immunotherapy in cancer treatment. In addition, we support specialisation with the full series of ESMO Preceptorship courses and with disease-specific meetings such as the European Lung Cancer Conference (ELCC), the ESMO World Congress on Gastrointestinal Cancer, and the ESMO Immuno-oncology Symposium.

We also have to be realistic, though: in real life there are many physicians who must deal with different types of cancer. This is particularly relevant for smaller hospitals in less affluent countries, or where there is no public health system. ESMO provides *ad hoc* educational opportunities for those oncologists to ensure they remain updated and can offer the best possible care to their patients.

AC: *How do you see your interaction with ECCO after what many are calling a 'divorce' from the biannual joint conference?*

FC: To keep their clinical practice up-to-date in a fast-moving field, medical oncologists deserve a dedicated annual congress where the latest advances are presented, discussed and put into clinical perspective by leading experts.

ESMO is, and remains, a founding member of ECCO, the umbrella organisation for oncology societies in Europe. We are committed to supporting ECCO to develop its role and mandate in oncopolicy, to make sure cancer is high on the political agenda in Europe.

Our own achievements in oncology policy demonstrate our commitment: our support for the new Data Protection and the Clinical Trials regulations; ESMO's European and global opioid policy initiatives on barriers to access to opioids for cancer pain; ESMO's European and international surveys on availability and accessibility of anti-cancer medicines; and the ESMO Magnitude of Clinical Benefit Scale, a tool to help clinicians choose the most effective anti-cancer medicines for patients and to aid regulators to identify those drugs with significant clinical benefit so they can be adopted rapidly across Europe.

Fortunato Ciardiello is Full Professor of Medical Oncology, Head of the Laboratory of Experimental Therapeutics, Head of the Division of Medical Oncology, Director of the Department of Clinical and Experimental Medicine and Surgery, and Member of the Academic Senate, at the Seconda Università di Napoli in Naples He has published more than 380 papers in international scientific publications.

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