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*'Looking for the minimum effective dose'*  
by Sofia Sita

# Cancerworld

Shaping the future of cancer care

Print run 16,000

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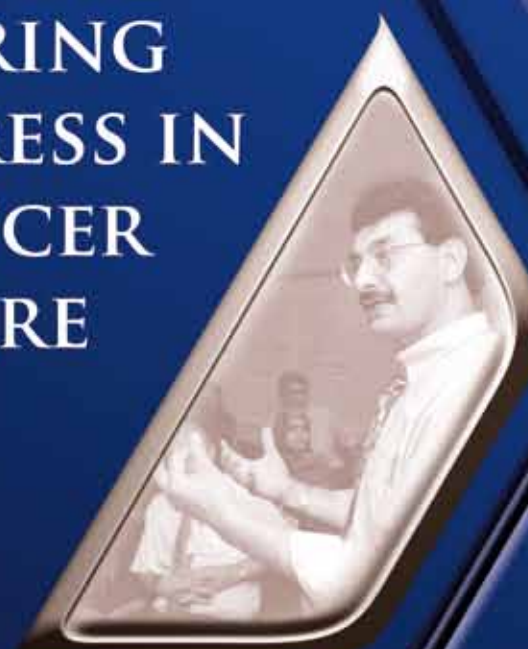
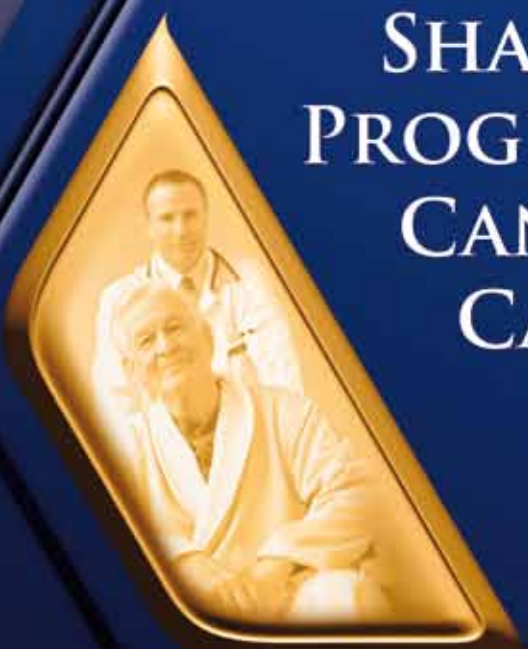
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# The best decisions come from the best run MDTs

Alberto Costa, *Editor*

**H**aving just retired from active clinical practice as a breast surgeon, I can look back at how decision making has evolved over the course of my career, from when a single doctor took the decisions, to the multidisciplinary approach we advocate today.

It was in breast cancer, with the discovery of the importance of hormonal receptors, that we first learned that different tumours respond to different types of treatment, and also that we can often limit the surgical damage by bringing additional treatment modalities into play.

The so-called 'collegial' discussion of cases slowly spread to other solid tumours to become the norm. The initial core group – surgeon, radiation oncologist, and medical oncologist – was later expanded to take on board a pathologist, who was needed to define the precise characteristics of the disease.

Once the principle is accepted that four doctors are likely to reach better recommendations than one, you can become five (by bringing a radiologist on board), then six (a dedicated nurse), seven (a plastic surgeon), eight (a psychologist) – and you have a multidisciplinary team. No single doctor can face the complexity of cancer by themselves anymore.

The case of prostate cancer is illuminating: where the urologist alone is in charge, the rate of prostatectomies is much higher than where a multidisciplinary team decides. Patients managed by a prostate unit are offered the three treatment options – prostatectomy, radiation therapy, active surveillance – in nearly equal parts, according to their individual disease. In most cases patients feel more comfortable

if they know their case has been discussed by several health professionals. It reduces the chance that recommendations are biased by personal factors: Is the doctor a risk taker or risk averse? Optimistic or pessimistic? Keen to recruit patients to a particular trial or try out a new surgical technique? Keen on or hostile to complementary medicine? What are the implications for their bank balance and/or ego?

Science fiction scenarios describe a not-too-distant future where treatment plans will be decided by computers on the basis of patient data and genetic profiles. In the meantime, I believe that the multidisciplinary approach can be expected to improve the quality of cancer care most of the time.

This statement takes for granted, however, that we are talking about multidisciplinary teams that function effectively, where the authority of the team leader derives not just from their knowledge and competence but also their wisdom and human empathy. It means teams that meet regularly to discuss clinical cases that have been prepared with care and made available on time. It means teams that can discuss in a spirit of collaboration, unhindered by egos and by competition between specialties, with each team member taking responsibility for the decisions and nobody zoning out and playing with their iPhone. And it means teams that are committed to making recommendations based not just on the best clinical evidence, but taking full account of their patients' choices and preferences.

If patients could choose their MDT, that's what they would go for.

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# Whatever happened to the minimum effective dose?

Introducing new drugs into clinical use on the basis of the lowest dose that works minimises the impact on patients' quality of life. Higher doses have traditionally been assumed to confer greater impact on the disease, but these assumptions are being challenged by new knowledge about the emergence of resistance. So why are drug developers still failing to explore dosing adequately in early trials, and how can that change, asks **Simon Crompton**.



**F**ive years ago, at a major ASCO event, the head of haematology and oncology products at the US regulator, the FDA, called out the “terrible job” drug developers were doing in exploring dosing. “The emphasis in clinical trials is primarily on efficacy,” said Richard Pazdur, “and drug companies don’t want to do phase II dosing studies to determine whether the maximum tolerated dose is the optimal dose.”

ASCO’s Chief Medical Officer, Richard Schilsky, backed him. “We need to do a better job of balancing the benefits and risks,” he said, “identifying the drug dose at which efficacy is maximised and toxicity minimised.”

With two such major figures telling it like it is, one might have expected this to mark a turning point – a wake-up call that too many oncology drug approvals are on the basis of the high doses trialled, which then simply get absorbed into practice. But it wasn’t. Speaking recently to *Cancer World*, Schilsky sees no movement. “I fully stand by the comments I made and note that not much has changed since they were made,” he says.

The fizz of excitement about designer drugs heralding an end to blunderbuss toxic approaches appears to have fallen flat. The ‘hit it hard, hit it often’ paradigm seems to have become so firmly ingrained into developing cancer drugs for approval that finding the minimum effective dose – above which there is added toxicity but no added benefit – is still an ill-funded, dimly lit corner of the research agenda.

The failure of drug developers to do the work needed to understand how their products can be used to greatest effect is being challenged by major figures in Europe as well

as the US. Writing recently in *Cancer World*, Denis Lacombe, director of the European Organisation for Research and Treatment of Cancer, commented that current models are “heavily driven by commercial interests” using “a chaotic approach” that fails to provide answers to critical questions asked by treating physicians and patients (*Cancer World* 80, October 2017). He called for research to be re-engineered around the needs of the patient.

## “Very few trials, sadly, are asking major strategic questions beyond drug approval”

Patient groups too are voicing concerns. Hans Scheurer, President of Myeloma Patients Europe, says that too few phase II studies examine the lowest effective dose. “The approach is a bad one, especially when you look at patients with an incurable disease like multiple myeloma, because having a good quality of life for the remaining months and years is so important for many people.”

The consequences of high toxicity doses can be far-reaching on patients’ quality of life, particularly when the disease is incurable and many lines of treatment are tried as resistance continually develops. But severe side effects can lead to another life-threatening problem: non-adherence. A survey by the CML Advocates Network, which connects 118 chronic myeloid leukaemia patient organisations across Europe, found that only one third of

patients are highly adherent. One of the most significant factors behind non-adherence was side effects: 41% of patients with well-controlled side effects were highly adherent, while those having considerable difficulty with side effects were only 25% adherent.

## Evidence on dosing

The tantalising irony is that there is a developing body of evidence – gained more from academia than commercial trials – that less aggressive, low dose or intermittent dose approaches hold exciting potential, particularly for controlling cancers that cannot be cured.

At a time when awareness of cancer overtreatment is burgeoning, and watchful approaches to prevent unnecessary surgery in prostate, breast and other cancers are gaining ground, traditional ‘cure at any cost’ drug development paradigms are also beginning to be questioned.

For example, a recent article in the journal *Leukemia* said that current dosing of the drug pomalidomide for myeloma was based on very little comparative data, and there was a significant scientific rationale for using it on alternate days rather than daily. “Very few trials, sadly, are asking major strategic questions beyond drug approval,” said lead author Thilo J Zander, head of Lymphoma and Myeloma Services at the Lucerne Cancer Centre in Switzerland. “Pomalidomide might be one good example of how substantial amounts of money may be saved, probably without affecting patient outcome, by using a different dose or schedule than in the registration trial.”

Similarly, studies have indicated



the effectiveness of lower doses of pembrolizumab for non-small cell lung cancer, and shorter treatment with trastuzumab for HER2+ breast cancer. The problem, as Zander points out, is that once a drug has been approved at a particular dose and schedule, then it becomes very hard to conduct trials exploring lower doses and durations. And even if such studies follow after initial approval, the timescales involved can make them redundant as science moves on.

A UK government-funded trial comparing six months of adjuvant trastuzumab against a year for HER2+ positive breast cancer, shows the risks of de-escalation studies being overtaken by events. The Persephone trial started recruiting in 2007, but – being an adjuvant trial – it took more than ten years to complete.

The results, presented at ASCO in 2018, showed that six months is as effective as a year, and is associated with lower cardiac risk. By that time, however, Roche, the developers of trastuzumab, had already got EMA and FDA approval for a new combination treatment involving the addition of pertuzumab to trastuzumab, with the latter being given for one year.

If the new combination treatment is adopted as the standard of care (currently the UK's NICE is recommending against this), then efforts to show that trastuzumab is as effective using half the duration specified in the approved combination protocol would have to start all over again.

Among patient advocacy groups and many clinicians, the fear is that there are few incentives to investigate the potential of lower dosing, drug holidays or stopping treatment – particularly for drug companies. Lower doses means reduced rev-

### **“There’s no commercial interest in measuring the impact of low dosing... This is quite bad news for us”**

enue, so why fund the trials? That leaves researchers having to cover the increasingly onerous cost of drugs. The issue is getting high on the patient advocate agenda, says Jan Geissler, co-founder of the CML Advocates Network.

“There’s probably no commercial interest in measuring the impact of low dosing on disease and quality of life. There’s little academic funding, it’s hard to recruit patients and little probability of academics and clinicians getting into high tier publications on the subject. Where’s the incentive to run this? This is quite bad news for us.”

### **Pioneering blood cancers**

Despite the disincentives and difficulties, less aggressive approaches to treating cancer as a chronic disease are being pioneered in some blood cancers. Chronic myeloid leukaemia is the classic example of a disease where modern drugs (notably TKIs) have led to a dramatic improvement of survival since their introduction in the early 21st century. There is no evidence as yet to show that CML can ever be cured by these drugs, but most people living with CML can now

expect a near normal lifespan if they adhere to treatment, and those with the lowest levels of residual disease have a chance of discontinuing treatment, with 50% remaining free from relapse over the long term.

There are now good data showing the effectiveness of lower dosages of TKIs. Andreas Hochhaus, head of the Haematology and Medical Oncology Department at the University Medical Centre Jena in Germany, and one of CML’s leading drug researchers, is emphatic that the data has to be there to confirm the right drug level and schedule to control disease. Simply reducing or stopping treatment without supporting research runs the risk of encouraging resistance. “All the discussion on lower doses for better tolerability is very dangerous as long as you don’t have data for it,” he says.

The data on dosing in CML has been hard-won. Hochhaus observes that four of the five inhibitors available – nilotinib, dasatinib, bosutinib and ponatinib – were originally approved at too high doses, and severe side effects in trial subjects resulted in new studies at lower doses. The FDA suspended sales of ponatinib in 2013, a year after original approval, because of an increased number of blood clots in patients taking the drug, and gave

### **“All the discussion on lower doses for better tolerability is very dangerous as long as you don’t have data for it”**



the drug new approval at lower doses in 2016.

For Hochhaus, discontinuation of treatment is as important to investigate as lower dosing. “In CML, I’m now quite happy at the doses currently in clinical use. I think it’s better to discontinue treatment.”

Recent trials demonstrating that some CML patients who have achieved a stable deep molecular response on TKIs can safely stop taking the drug have given rise to the concept of treatment free remission (TFR). Around one third of patients successfully discontinue treatment, with the option of returning to treatment if relapse occurs.

Similar strategies have been found to work in follicular lymphoma. And where blood cancers lead, others can follow, says Hochhaus. “It’s about not aiming to eradicate the disease, but silencing the disease,” he says.

“We’re also seeing TFR in ongoing palliative treatment of inoperable colorectal cancer where there is a very good response to chemotherapy. You can’t continue it for ever, but studies have shown that you can quite successfully stop and restart as needed.

“There are more and more diseases in haematology and oncology where a good response to stopping and restarting is possible, and the applications are quite broad. It’s clear we can learn from CML.”

## Re-thinking resistance

The need to pay more attention to quality of life issues, as people live longer with cancer, is a compelling incentive to increase efforts to better define the minimum effective dose and duration. But this is



about more than maximising quality of life. One of the main lessons learnt from 20 years of personalised cancer medicine is that resistance kills, and dose and duration are now taking centre stage in new strategies aimed at slowing the emergence of resistant clones, particularly in solid tumours.

Advances in our understanding of resistance, backed by early clinical evidence, suggest that stopping and starting treatment, in a calibrated response to treatment-affected changes in the tumour, can encourage competition between cells and prevent or delay resistant clones from gaining free-rein.

Recent studies by Robert Gatenby and his team from the Cancer Biology and Evolution Program at the Moffitt Cancer Center, in Florida, challenge current treatment protocols in metastatic prostate cancer, where normally the same drug is given at the maximum possible dose

over and over again until progression. The Moffitt work opens up the possibility of another option.

In a pilot clinical trial reported last year, the Moffitt researchers treated 11 patients with metastatic castrate-resistant prostate cancer with abiraterone until their

**“There are more and more diseases in haematology and oncology where a good response to stopping and restarting is possible. We can learn from CML”**

PSA level dropped to half the pre-treatment level. At that point, they stopped treatment until PSA reached pre-treatment levels, and then treated again. The tumours grew but remained treatable because treatment-sensitive cells could keep competing with treatment-resistant cells.

The trial found that time to progression was increased compared to standard treatment, and this was achieved with a lower cumulative dose. Some patients received treatment less than once a year. The Moffitt researchers now plan further clinical trials of this 'adaptive therapy' approach for melanoma, ovarian, thyroid, breast and lung cancer as well as prostate cancer.

### Hitting tumours as hard as possible for as long as possible with the maximum tolerated dose becomes the norm to achieve these endpoints

Charles Swanton, Leader of the Cancer Evolution and Genome Instability Laboratory at the Francis Crick Institute in London and Cancer Research UK's Chief Clinician, says that such work makes a "very compelling case" that traditional ways of researching new drug treatments need a major re-think.

"The mainstay approach is generally that you hit your maximum tolerated dose in phase I, and you

move into phase II with that, and then you explore response, so that hasn't changed for decades," he says. "But if we accept that resistance to targeted therapies is inevitable in over 90% of patients, if not more, one has to work out how to prevent that resistant sub-clone from evolving."

A problem with current models of regulatory approvals, he says, is that they are based on clinical trials revolving around reporting minimum progression free survival, response rates and occasionally overall survival outcomes. Hitting tumours as hard as possible for as long as possible with the maximum tolerated dose becomes the norm to achieve these endpoints.

"The difficulty with this model is that inevitably you select out resistant sub-clones that can't be treated as effectively or at all, and then you've lost the battle."

In other words, approvals have not kept up with scientific progress, and there's little appetite for commercial trials using innovative approaches using low doses and breaks in treatment.

It is not a problem of lack of financial incentive for drug companies, according to Swanton. The main reason is a lack of validated approaches to measure the relative proportion of different clones in a tumour – measurements that are crucial for benchmarking drug doses and cycles of administration.

"I think drug companies and researchers are reluctant to go this way because understanding what the doses might be, or the schedules that you might apply to patients in a clinical trial, is currently very hard to establish. This is partly due to the lack of reliable markers of evolving resistant sub-clones."

There are, however, indications that some drug companies are responding to the new evidence about the possibilities of stopping and restarting. Andreas Hochhaus was involved in research leading to the 2017 approval of Novartis' TKI Tasigna (nilotinib) as the first and only CML therapy to include information about attempting treatment discontinuation on its prescribing information. The FDA approval was based on safety and efficacy analysis of two open label trials evaluating the potential to maintain major molecular response after stopping Tasigna therapy among patients with Philadelphia chromosome-positive CML. The trials demonstrated that almost half of the patients who discontinued Tasigna remained in treatment free remission approximately two years after stopping treatment.

"It has long been our ambition at Novartis to make it possible for some people with CML to discontinue therapy," said Bruno Strigini, Novartis Oncology's CEO.

Hans Scheurer says there are signs of growing openness to this approach from some companies working in the field of myeloma. Myeloma Patients Europe, as part of an umbrella of haematology patient organisations, invited nine pharmaceutical companies to a recent community advisory board meeting – 'Hem-CAB' (see Patient Voice, p 53) – and found that some were more stuck in their own agenda of development than others. The more established companies were, the more likely they were to listen and to take patient perspectives into account when designing a clinical trial.

"The design should be focused on the benefit to the patient right from the start, not after the Euro-



## **“The design should be focused on the benefit to the patient from the start, not after the EMA sends it back saying it’s based on too high a dose”**

pean Medicines Agency sends it back saying it’s based on too high a dose,” he says. “Some companies are better at this than others.” At future advisory board meetings, he wants drug companies to address directly engaging with patients’ organisations on dosing.

### **In the absence of data**

Given the general lack of strong data, what are the implications for clinicians who, after discussions with patients, want to take a ‘gentler’ course of treatment, with the emphasis on avoiding unpleasant drug side effects? There are few hard and fast guidelines.

According to Scheurer, haematologists have very different takes on balancing quality and length of life when it comes to incurable but treatable conditions such as myeloma. Some haematologists tend to focus on hitting the disease as hard as possible, based on findings that the disease could stay away longer. But Scheurer says there needs to be awareness that this is a statistical approach, and not suitable for every patient.

“There’s a balance you need to keep advocating, because these kind of approaches tend to look at treatment isolated from the rest of life,” he says. “The reality is that there are a lot of new treatments being introduced, and they are often used one after another as one starts not to work.

“We know that the fitter you are when you start treatment, the better the treatments work. So there’s a case that, although hitting the disease hard at the start may make it stay away longer, it may also make you more frail, and successive treatments may be less effective. So I believe very strongly that there should always be consideration given to how hitting it hard affects the fitness of the patient.”

Scheurer himself, who has had the disease for 13 years, knows about this balancing act. As he contemplates next steps now his cancer is growing again, he’s expecting to have conversations with his doctor that will embrace his daily routines, family life and aspirations – and the effects the drugs will have on him. But not all physicians feel able to personalise care, he says.

“The treatments improve and guidelines change so fast in myeloma at the moment, and most doctors and haematologists become a bit insecure and stick to the guidelines or latest journal articles. The picture of the individual patient fades.”

Jacob Hygen, Vice Chairman of the Norwegian Blood Cancer patient advocacy group, has had multiple myeloma for 19 years, and after initial high-dose therapy his treatment has generally avoided high doses of new drugs, or drugs in combination. This is partly because there weren’t so many options avail-

able when he started drug treatment in 2010, and he and his doctor stayed with the same approach because it seemed to work.

“There is debate in Norway among haematologists about how aggressive you should be in treatment,” he says. “On doses and the use of multiple drugs, the reality is that knowledge of myeloma is still behind other blood cancers, so it is a trial and error approach: they just have to see what works for the individual patient.”

His doctor is Anders Waage, from the Department of Haematology at the Norwegian University of Science and Technology, and one of Norway’s leading multiple myeloma experts. He says the ‘less is more’ debate partly reflects how complicated it can be to find dosages and approaches that suit individual needs. Some patients will need high doses, others will prioritise fewer side effects, and finding effective ways to discriminate is important.

But generally in cancer there is a bias towards overtreatment, says Waage. “Certainly in multiple myeloma, there’s a very marked tendency to start at high doses and continue to relapse, and I’m not sure that’s the right thing to do for all patients.” If there are signs

## **“Most doctors become a bit insecure and stick to the guidelines... The picture of the individual patient fades”**

of the disease coming back after treatment, there's a real tendency to treat again early if the patient is not on maintenance treatment," he says.

"And the clear tendency in myeloma is that all patients should be on maintenance treatment, which is wrong."

Why is this happening? "I think there's the intuitive thought that if it works well for one dose it might work twice as well if you double the dose," he says. "And of course, there's a lot of pressure from the drug companies. They want to sell more drugs. I think that's a very simple explanation."

He admits that charting a gentler approach with patients, often with the emphasis on quality of life, is not always easy. With studies hard to fund and organise, and in the absence of clear guidelines, physicians like himself effectively go out on a limb if they don't take the 'standard' approach – taking an overview of evidence, drawing on personal experience. In patients whose disease is taking a more indolent, benign course, rather than continuing maintenance treatment he will consider lowering doses or pausing treatment and waiting for relapse – which might take several years.

It doesn't put him in a difficult position, he says – maintenance treatment was not considered standard until recently. "But I think many people are now considering doing as I do, particularly in Europe as opposed to the United States," he says. "We can never let the treatment be worse than the disease."

What doctors like Waage would like to see is a greater balance in drug research: always acknowledg-

ing that, for some patients, high or continuous doses will be the right option, but that for many others an approach that maximises quality of life is required – even if it reduces length of life. The problem is that, currently, the evidence base to validate these approaches is badly lacking. The balance is tilted to toxicity.

### Ways forward

What needs to happen for drug developers to heed the call of Pazdur and others to do a better job of exploring dosing and duration?

A good first step would be to follow the advice of the EORTC's Denis Lacombe, to "re-engineer" the drug development process around finding solutions for patients rather than approval for new products – a problem hardwired into the whole regulatory system.

**"I think there's the intuitive thought that if it works well for one dose it might work twice as well if you double the dose"**

Closer consultation and involvement of patients in setting the research would inevitably bring the issue of toxicity and minimum effective dosing to the fore. The Hem-CAB meeting convened in June 2018 by Myeloma Patients

Europe, where advocacy groups from a spectrum of haematology diseases were able to discuss their needs and concerns with nine companies active in that field, could make a big difference here.

Other mechanisms that have been floated include a proposal to oblige companies to commit to giving adequate attention to dosing issues as a 'quid pro quo' for getting patients to sign informed consent to participating in first-in-human trials. As Lisa Hutchinson, founding Chief Editor of *Nature Reviews Clinical Oncology*, wrote recently in *Cancer World*, this would not only minimise the risk for patients in trials, but it would also encourage a greater sense of trust in the trial process generally (issue 82, May 2018).

"If sponsors had to sign a commitment to perform optimisation work, it may give patients on the trial the best chance of benefit, and maximise the improvements for future patients by ensuring that when new drugs reach the market, we would have a good idea about optimum dosing and cost-effectiveness," she wrote.

Growing scientific knowledge about the way cancers develop is likely to add to pressure for change: trials and approvals that ignore the emerging evidence about the heterogeneity of tumours, the evolutionary causes of resistance and related dosing issues will be increasingly open to criticism.

Charles Swanton points to a future of approvals based on new types of trials that address emerging resistance in tumours, and pinpoint individualised dosing approaches rather than perpetuating the full frontal attack formula. Finding technologies to benchmark





doses and schedules according to cancer activity will be key.

"I think there is some promise here," he says. "I think one of the ways of dealing with this might be through sensitive measuring of circulating free DNA from mutant clones in the blood." Swanton's team has already published research in *Nature* showing the feasibility of profiling circulating tumour DNA for non-small-cell lung cancer, and there's also evidence that it will work for other metastatic cancers, including breast cancer.

"One attractive model to begin addressing the drug resistance problem is a bespoke sequencing approach where we know what the mutations are in the tumour – we

know the trunk and branch mutations from analysis after surgery – and then we can use sensitive targeted sequencing approaches to see the evolution of one or two branches, which is the hallmark of metastatic recurrence, from blood tests. This means we can begin to see the evolution of therapy-resistant sub-clones before we see disease progress on a CT scan – so-called minimal residual disease.

"Through sensitive resistance sub-clone monitoring in blood, we may be able to think about ways in due course of toggling drug dosing on and off, proportionate to the evolution of resistant markers that come up in blood. I think if the biomarkers improve, these studies

will become more feasible."

There are understandable fears among some clinicians and researchers that publicity about the prospect of treatment free remission in some cancers with reduced, intermittent or discontinued treatment has its dangers. Improvised do-it-yourself approaches to dosing do not work. Dosing and treatment interval issues are complex and we need data. But that is the point. We need to know more, and those involved in drug development, as well as academia, need to be playing their full part in building understanding.

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# The CAR T cell revolution: what does it offer, and can we afford it?

In August 2018 the first therapies aimed at re-engineering patients own T cells to attack cancer entered the European market. **Rachel Brazil** looks at how they work, what they achieve, and what the logistical and cost barriers will mean for patients hoping to get access.

In 2012, Emily Whitehead, a six-year-old from Pennsylvania, USA, with chemotherapy resistant acute lymphoblastic leukaemia (ALL) was given an experimental treatment – an infusion of her own

T cells, which had been genetically engineered to attack cancer cells. She was not the first patient to be treated with chimeric antigen receptor (CAR) T cells, but the publicity surrounding her complete remission

hit the headlines in countries across the world: Could this new form of immunotherapy represent a leap into a new era for cancer treatment?

Subsequent clinical trials provided stunning results for several

B-cell malignancies, where two or more lines of therapy had failed, particularly in children and young adults (see box opposite). In late 2017 and early 2018 the US regulator, the FDA, approved the first two CAR T-cell therapies – Gilead's axicabtagene ciloleucel (Yescarta), for adult patients with relapsed or refractory large B-cell lymphoma, and Novartis's tisagenlecleucel (Kymriah), for patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse. The European Medicines Agency (EMA) followed suit in August 2018, also approving Kymriah for use in adults with relapsed or refractory diffuse large B-cell lymphoma, on the basis of results that had become available subsequent to the FDA approval. As a result, the first two CAR T-cell therapies can now be marketed across Europe.

However, as big pharma has moved into the development of CAR T cells, pricing concerns have arisen. Within days of the EMA approval, England's National Institute for Clinical Excellence (NICE), recommended that Yescarta – priced in the US at \$373,000 – should not be used in the National Health Service, on the grounds of cost-effectiveness. Add to this the drug's potentially serious side effects, plus the difficulties in manufacturing the cells, and it's clear that many hurdles have yet to be jumped before this new cell therapy can become widely available.

### How it works

Haematologist Michael Schmitt is running several CAR T cell clinical trials at Heidelberg University Hos-

pital, in Germany. He explains that a number of different approaches to CAR T-cell therapy are being explored, which are all designed to take advantage of the human immune system's ability to kill.

### **“Inside the donor organism an Armada is built, acting against cancer cells”**

T cells are a type of white blood cell that can be armed to recognise and destroy cancer cells via the antigens they display on their surfaces. This can be done by harvesting a patient's own T cells from their blood, isolating the cells, and then introducing the chimeric antigen into them, which is done by inserting a gene using a viral vector – as if ‘infecting’ the cell with the antigen receptor gene.

This gene then adds the chimeric antigen receptor – a small synthetic protein – to the surface of the T cell, from which location it will be able to recognise a specific marker (known as an antigen) on a cell's surface. Many different antigens exist on cells, but to date most CARs have been designed to recognise a marker called CD19, which is found on the surface of all B cells (the white blood cells responsible for producing antibodies), including the malignant B cells that cause certain leukaemias and lymphomas.

The modified T cells are then cultured and returned to the patient in a single infusion. This is usually preceded by a course of chemotherapy, designed to deplete the patient's own immune cells, which helps

the CAR T cells to multiply in the patient's body. The CAR T cells then fuse to cancer cells with the CD19 marker, which initiates several signalling pathways, leading to elimination of the targeted cancer cell as well as triggering the ‘expansion’ (multiplication) of the CAR T cells.

“Inside the donor organism an Armada is built, acting against cancer cells,” says Schmitt. “You see tumours shrinking, you see billions of leukaemia cells going into apoptosis [cell death].”

### Side effects

There's a catch, however, as CAR T cells can induce serious off-target effects. The intracellular signalling that damages the cancer cells also triggers the release of cytokines – cell-signalling molecules that form a normal part of the immune response system. When present in excess, these cytokines can trigger a huge inflammatory response, known as cytokine release syndrome (CRS). The response is also referred to as a ‘cytokine storm’.

Pere Barba, a haematologist at the Vall d'Hebron Institute of Oncology in Barcelona, describes the impact on the patient. “This is a syndrome that occurs quite early, a few days after infusion, and consists of fever, hypotension, problems breathing, and tachycardia.” Doctors currently use corticosteroids or the rheumatoid arthritis drug tocilizumab to dampen down cytokine release, he says, but stresses that, “Although it's manageable with medication, in some cases it can be life-threatening.”

There are other side effects, adds Barba, who is currently involved in the first pan-European clinical trial with CAR T-cell therapy for patients

## CAR T-cell therapies – the evidence

### Childhood ALL

The first CAR T-cell therapy to reach the market was Novartis's Kymriah (tisagenlecleucel). It was approved by the FDA in August 2017 for treating childhood B-cell precursor acute lymphoblastic leukaemia (ALL) that is refractory or in a second relapse, based on the early results of ELIANA, a global phase II trial (American Society of Hematology annual meeting 2016, abstracts #221 and #2801). Complete remission was achieved at three months in 41 out of 50 patients (82%). A 2018 update of 75 patients who had completed three or more months of follow-up showed an overall remission rate of 81%. Remissions were durable, with 80% of those who had achieved remission remaining free from relapse at six months.

Patients did however suffer serious side effects, including cytokine release syndrome, pyrexia, decreased appetite, febrile neutropenia and headache. The most serious side effect was cytokine release syndrome, which occurred in 77% of patients, resulting in admission to intensive care for 35 of them. Neurological events occurred in 40% of patients within eight weeks of infusion; it was grade 3 in 13% of patients, with no instances of grade 4. Kymriah received marketing approval from the EMA in August 2018.

### Adult lymphoma

Two CAR T-cell therapies have been approved for use in treating certain adult lymphomas – Novartis's Kymriah and Gilead's Yescarta (axicabtagene ciloleucel).

**Kymriah** gained approval for use in adults with relapsed or refractory diffuse large B-cell lymphoma, on the basis of the JULIET trial, which showed an overall response rate of 52% among 93 evaluable patients,

with a complete response in 40% and partial response in 12% (European Hematology Association annual meeting 2018, abstract #S799). Among those reaching complete response, 83% remained in complete response at 12 months. Patients had a 65% chance of being relapse-free one year after onset of response. Cytokine release syndrome grade 3/4 was recorded in 22% of patients, and grade 3/4 neurologic adverse events in 12%. Grade 3/4 cytopenia lasting more than 28 days, grade 3/4 infections, and grade 3/4 febrile neutropenia occurred in 32%, 20% and 15% of patients, respectively. Approval for this indication was given by the FDA in May 2018, and by the EMA in August 2018.

Approval of Gilead's **Yescarta** for patients with diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma who had refractory disease was based on the pivotal phase II ZUMA-1 trial (*NEJM* 2017, 377:2531-44). Among the 111 patients who were enrolled, axicabtagene ciloleucel was successfully manufactured for 110 (99%) and administered to 101 (91%). The objective response rate was 82%, and the complete response rate was 54%. With a median follow-up of 15.4 months, 42% of the patients continued to have a response, with 40% continuing to have a complete response. The overall rate of survival at 18 months was 52%. The most common adverse events of grade 3 or higher during treatment were neutropenia (in 78% of the patients), anaemia (in 43%), and thrombocytopenia (in 38%). Grade 3 or higher cytokine release syndrome and neurologic events occurred in 13% and 28% of the patients, respectively.

Yescarta was approved by the FDA in October 2017, and by the EMA in August 2018.

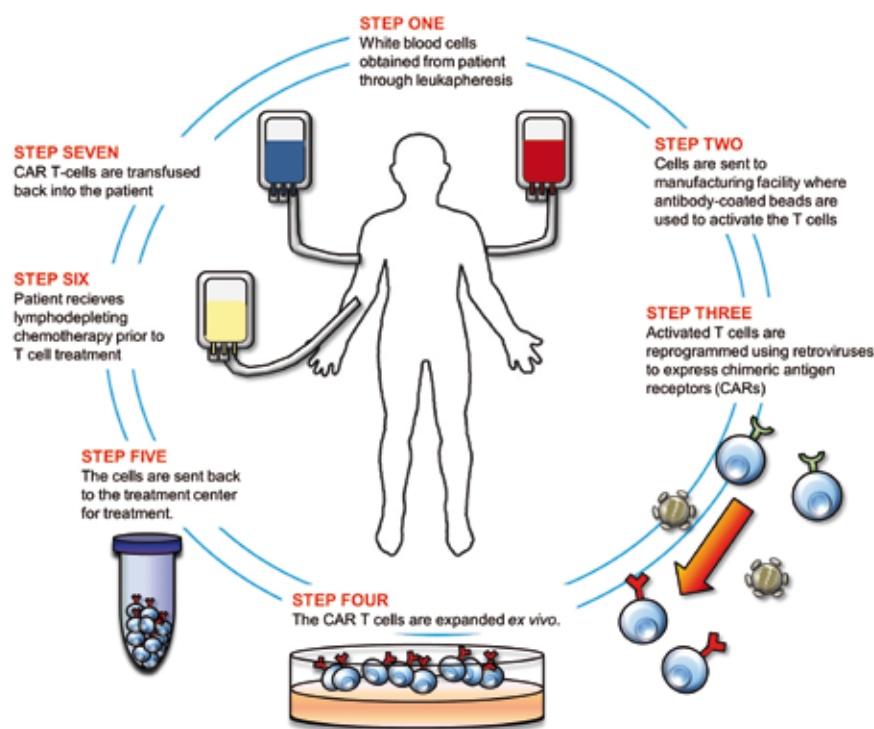
with aggressive B-cell non-Hodgkin lymphoma. "It's not very well understood, but patients can have a large variety of neurological symptoms including seizures, speaking problems, confusion, and dizziness, and this tends to come seven to ten days after CAR T infusion." He also mentions longer term risks of infection, as patients will have been immunosuppressed.

Toxic side effects, principally connected to cytokine release syndrome, have led to the deaths of between three and four out of every hundred patients in trials so far. One precaution could be to design 'kill switches' into the CAR T cells so their effects can be controlled. This is an approach being developed by Cellectis, a French biotech spin-out from the Institut Pasteur, which is now devel-

oping its own CAR T-cell therapies in collaboration with the pharmaceutical company Servier. "We have been adding two genes: one to be able to recognise the cancer cell and one additional gene to be able to eliminate the [CAR T] cells if needed," says Laurent Poirot, head of early discovery at Cellectis. The second, 'kill switch', gene produces a receptor embedded into the CAR molecule on



## How it's done



A patient's T cells are harvested through leukapheresis, followed by T cell activation on antibody-coated beads (which act as artificial dendritic cells). The activated T cells are transduced with a construct encoding the chimeric antigen receptor (CAR). These reprogrammed CAR T cells are culture expanded and subjected to quality control testing prior to cryopreservation for transport of cells to the treatment facility. Prior to CAR T cell infusion, the patient receives chemotherapy to deplete native lymphocytes that can decrease efficacy of the infused cells

**Source:** Debbie King (2017). FDA Approves First CAR T-Cell Therapy - The evolution of CAR T-Cell Therapy. (CAR T Cell Therapy Workflow) Retrieved from <https://cellculturedish.com/fda-approves-first-car-t-cell-therapy-the-evolution-of-car-t-cell-therapy/>

the surface of the T cells. If a patient suffers dangerous levels of toxic side effects, a monoclonal antibody drug, rituximab, can be injected. It will bind to the 'kill switch' receptor and trigger cell signalling that leads the patient's own immune system to kill the CAR T cells.

Houston-based Bellicum Pharmaceuticals have also developed a 'kill switch', which uses the small-molecule drug rimiducid to set it off.

The CAR T cells are engineered with two proteins that combine in the presence of rimiducid, and this activates an enzyme that precipitates cell death.

## CAR T in Europe - the roll out

The task of rolling out CAR T-cell therapy across Europe poses a number of logistical issues, as Zack

Pemberton-Whiteley, who chairs the Acute Leukemia Advocates Network, explains. "It isn't a tablet where you can just start handing it over," he says, "there is lots of commissioning that needs to be in place, so it's an unusual situation." One hurdle is the manufacturing of the CAR T cells, which need a facility with GMP (Good Manufacturing Practice) certification as well as a licence to handle genetically modified organisms (GMOs).

Currently Novartis and Gilead are manufacturing their CAR T-cell products in the US, shipping patients' cells in and out of centralised facilities. Novartis is also collaborating with the Leipzig-based Fraunhofer Institute to manufacture CAR T cells for European clinical trials. The companies intend to continue these arrangements initially, but both have announced plans to build their own European facilities. In July 2018, Novartis announced a partnership with French manufacturer Cell for Cure, based in Les Ulis, near Paris, which is set to open in 2019; Gilead are developing a site in the Netherlands.

Currently CAR T-cell therapy takes a minimum of 18 days from removal of a patient's cells to infusing the modified and expanded cells back into the patient. Most producers are now freezing the modified cells to allow the infusion to be delayed, if that should be required on the grounds of the patient's health or any other reason.

The complex logistics involved have opened up a specialist niche in the health technology market that is spawning companies such as TrakCel, which helps with collation, tracking and documentation involved in cell and gene therapy. Founded in Cardiff, Wales, in 2012, it is now expanding into the US market.

“There is a real challenge just around ensuring the chain of identity for each individual [patient’s cells] and being able to maintain from a regulatory perspective all the correct documentation and records that are required,” says Matthew Lakelin, TrakCel’s Chief Scientific Officer. The task is not just ensuring the right cells are given to a patient, but making sure the right facilities and personnel are available to administer the therapy and deal with the side effects. “It becomes a little bit of a headache as you add more and more patients and more and more clinical sites,” he says.

As a consequence, argues Lakelin, treatment in Europe is likely to be restricted to a small number of clinical centres to which patients will need to travel. “It’s almost going to be similar to how kidney dialysis started, in very specialist units with trained physicians. They then moved dialysis into smaller hospitals and eventually into cottage [local] hospitals. So I think you will see a spread of these products over the next ten years, and they will become more commonplace.”

CAR T cell manufacturers are also dealing with a fairly complicated regulatory landscape in Europe, which is overseen by the EMA Committee for Advanced Therapies. The modified CAR T cells themselves are considered as Gene Therapy Medicinal Products but, as Lakelin explains, the starting material – i.e. the patient’s own cells – are governed by transplant and blood product legislation, “so there is no [single] existing pathway through from a regulatory perspective.” On top of this, the final CAR T cells are classed as genetically modified organisms (GMOs), which are regulated differently by each European country.

## “It’s not just about giving the right cells to a patient, but having the right facilities and personnel available to administer the therapy and deal with the side effects”

It’s complicated admits Martina Schübler-Lenz, who is deputy head of the Advanced Therapy Medicinal Products section at the Paul Ehrlich Institute, in Langen, Germany, and chairs the EMA’s Committee for Advanced Therapies. But the EMA has a framework for dealing with advanced therapies, she says, and “new regulations are currently not needed.”

### Putting a price on CAR T cells

With two CAR T-cell therapies now approved, the focus is moving to pricing, and the fear that high costs will limit patient access. Even though European prices are likely to be less than those in the US, price will still be a huge issue. Reimbursement is negotiated by individual European countries, and the picture so far looks mixed. In Germany, Novartis has set a list price of €320,000 (\$371,000), which will be subject to the usual negotiations and cost-benefit assessments with insurers. In the UK, NICE made a speedy agree-

ment with Novartis to green-light Kymriah at £282,000 (\$361,000), for children and adults with refractory or relapsed B-cell ALL – less than the \$475,000 price listed in the US. Yescarta did not fare so well, although Gilead will get a chance to present further data on clinical and cost-effectiveness.

In a report published in June 2018 – *CAR-T Cell Therapies: How much for survival?* – the Access to Medicines Task Force of the Association of European Cancer Leagues (ECL) argue that, even if they are effective, the high price would be unsustainable in Europe. “It will be a challenge (if not impossible) for European payers to ensure access to the CAR-T-cell therapies for all patients under the current functioning of healthcare systems,” they conclude ([bit.ly/ECL\\_CAR-T\\_cost](http://bit.ly/ECL_CAR-T_cost)).

Šarunas Narbutas, president of POLA (Lithuanian Cancer Patient Coalition), who has campaigned for the introduction of modern, effective leukaemia treatment in Lithuania, agrees. “I am pretty confident that there won’t be any hospitals in Lithuania which will be receiving CAR T therapy patients,” he says.

He hopes, however, that companies may agree to patient access and compassionate use schemes, particularly as many of those eligible will be children. “[In Lithuania], I am aware that there are currently over 60 [access] agreements in place with industry regarding products,” says Narbutas. He adds though that, given the extensive infrastructure required for CAR T-cell therapy, this will not be simple and may require a close working relationship with a clinical centre in another part of Europe.

Schmitt, who is running a number of CAR T clinical trials, argues that

### The pricing controversy

The Access to Medicines Task Force of the Association of European Cancer Leagues (ECL) has suggested the debate on CAR T cell pricing represents the current debate on drug pricing models and a push towards 'value-based' drug pricing ([bit.ly/ECL\\_CAR-T\\_cost](http://bit.ly/ECL_CAR-T_cost)). A value- or outcome-based pricing model suggests that, rather than relating price to development costs, a drug's price should relate to the benefit it provides. For example, it has been reported that in the US Novartis had briefly suggested (and quickly dropped) a plan to only charge for Kymriah where patients responded in the first month.

The value-based model has many supporters, but "the problem with this is that [the idea] has become hijacked to justify the price [pharma] want to charge," says Anna Prokupkova, Policy & Project Officer at the ECL, and a co-author of the Task Force report '*CAR-T cell therapies: How much for survival?*' There still needs to be some basic agreement on what constitutes a fair price, even for a medicine that may save children's lives, she argues. Pharma argue that high prices represent the high research and development costs for novel technologies such as CAR T-cell therapy. Novartis have said they spent more than \$1 billion since 2012 on bringing Kymriah to market ([bit.ly/Forbes-CAR-T\\_cost](http://bit.ly/Forbes-CAR-T_cost)). 'We do think that we should award innovation, but there has to be some sort of a scale where you can actually measure this,' says Prokupkova.

And as she points out, in the case of CAR T-cell therapies, that innovation was funded in part by public research money – which has been estimated at around \$200 million in the US alone. This should be taken into account, she argues, so tax payers do not end up paying twice. But Joseph Jimenez, Novartis's CEO, has said their spending "dwarfs anything the government has invested through NIH grants."

In a blogpost published by the health policy journal *Health Affairs*, David Mitchell, co-founder of the US advocacy group Patients for Affordable Drugs, estimated that "Novartis could cover both its historic margins and continuing research and development spending at a retail price [for Kymriah] of \$160,000," rather than the \$475,000 current US price tag for Kymriah ([bit.ly/Mitchell\\_CAR-T\\_cost](http://bit.ly/Mitchell_CAR-T_cost)).

Obviously there are many arguments to be made over the exact costs; for instance, Mitchell uses a value of \$40,000 for the cost of manufacturing CAR T cells per patient, while Novartis have said the true figure is much larger, although they have been unwilling to provide details ([bit.ly/Forbes\\_CAR-T\\_cost](http://bit.ly/Forbes_CAR-T_cost)).

Yet even at \$160,000, Kymriah will still be unaffordable in some parts of Europe. "In (many eastern European) countries, they don't even have the basic immunotherapies, so their access to CAR T can be absolutely forgotten for now," says Prokupkova.

price will be crucial in determining whether the new therapy will be used in more than a small subset of refractory patients. "What needs to be proven is that, in the long run, CAR T-cell therapy is really superior over allogeneic transplantation, which is almost a give-away compared to the price of CAR T-cell therapy – only 20% of the costs," he says.

But making these types of decision is very hard without long-term data. "We say this is a potentially curative therapy, but actually we don't have any patients who have been on it beyond 15 years," says Pemberton-Whiteley. In February 2018 the EMA held a workshop on how to col-

lect such long-term real-world data ([bit.ly/EMA\\_CAR-T\\_workshop](http://bit.ly/EMA_CAR-T_workshop)), and the Agency is committed to supporting existing registries and establishing a centralised process for obtaining data.

### Where next for CAR T-cell therapies?

The extraordinary results with blood cancers has spurred interest in CAR T-cell therapies for solid cancers. "If you go to breast cancer, colorectal cancer, or prostate cancers – the big killer diseases – there was much hope, but this has not been

proven in animal models so far," says Schmitt. In the blood, cancer cells can be flooded with CAR T cells, he explains, but many solid tumours have few blood vessels at their centres and T cells are therefore unable to reach their targets. Tumours also create their own barriers: "You have something like a fence – a cluster of cells around tumours that are like an armour suit and defend the tumour against T cell attacks."

There are examples of success, however. Researchers at Baylor College of Medicine in Houston produced CAR T cells that respond to antigens on glioblastoma (brain cancer) cells. The first trials have



established safety as well as promising efficacy (*JAMA Oncol* 2017, 3:1094–101). The French biotech, Cellectis has also been trying to tackle the problem; they have generated CAR T cells that are active only in the sort of hypoxic environment that is characteristic of solid tumours.

## Allogeneic CAR T cell therapy uses donor cells, avoiding the high costs, and the delays, involved in genetically engineering each patient's cells separately

Cellectis are also pioneers in the field of allogeneic, or universal – ‘off-the-shelf’ – CAR T cells. This therapy uses donor cells, avoiding the high costs, and the delays, involved in harvesting and genetically engineering each patient's cells separately. The challenge here is how to overcome the problem of graft-versus-host disease – a serious complication that can occur with cell transplants. “Anytime you inject a foreign body into a person it can be rejected, but also the foreign cell can attack,” explains Stéphane Depil, executive vice president of research and development at Cellectis. The patient suffers skin rashes, intestinal inflammation and liver problems, and these can be fatal, he says.

### Origins of CAR T-cell therapy

The origins of CAR T-cell therapy can be traced back to observations made in the 1980s that infusing relapsed leukaemia or lymphoma patients with donor T cells (or T lymphocytes) alongside stem cell transplants could be beneficial. In 1989, Zelig Eshhar at the Weizmann Institute of Science came up with the idea of engineering a T cell that could target and kill cells (*Proc Natl Acad Sci USA* 86:10024–28). Over the next 20 years, researchers developed the approach, including Carl June at the University of Pennsylvania who treated the first patient with so-called CAR T cells in 2010 (*Cancer Res* 2010, 70:9053–61).

By 2012 the pharmaceutical industry had jumped on board, with Novartis partnering with the University of Pennsylvania to develop and commercialise CAR T-cell therapies. The potential for the treatment fuelled multi-billion-dollar acquisitions – Gilead acquired the small, Santa Monica-based, biotech KITE for \$11.9bn in 2017, and in 2018 Seattle-based Juno therapeutics was acquired by the US biotech Celgene for \$9bn. Other companies joining the field are Pfizer, who have licenced technology from Cellectis, GSK working with Philadelphia-based Adaptimmune, and Johnson & Johnson, partnering with China's Legend Biotech.

Despite this, in 2011 Cellectis took a bet on allogeneic approaches and started using gene editing to make donor CAR T cells compatible with anyone. They knew certain cell receptors are responsible for graft-versus-host disease, by allowing T cells to discriminate between self and non-self. “Our strategy was to inactivate specifically those genes in the CAR T cells so that, while we are providing them with a receptor that can redirect them to cancer cells, we are removing the receptor that allows them to recognise non-self cells and attack the patient,” explains Depil.

Their CAR T cell, UCART19, met early success at Great Ormond Street Hospital, London, in 2015, putting two children with ALL into molecular remission, which persisted until conditioning ahead of successful allogeneic stem cell transplantation (*Sci Transl Med* 2017, 9(374): eaaj2013). Cellectis now has two candidates in clinical trials,

and in April entered a partnership with Pfizer to further develop their CAR T-cell therapies. Several other companies are developing similar strategies, including San Francisco-based Allogene Therapeutics, Belgian biotech Celyad and Massachusetts-based Crispr Therapeutics.

As TrakCell's Lakelin points out, whether or not allogeneic CAR T cells turn out to be the next step in cell therapy, right now “industry and clinicians are going to have to get used to the context and cycles of the autologous CAR T cell.” CAR T-cell therapies could be the start a whole new era of cancer treatment. And ironically, in an era where everybody is talking about patient-centred medicine, says advocate Pemberton-Whitely, “CAR T is one of those examples that really brings it home, because the medicine wouldn't exist without the patient!”

To comment on or share this article, go to [bit.ly/CW84\\_CARTCell-Revolution](http://bit.ly/CW84_CARTCell-Revolution)

Does your metastatic breast cancer (MBC) patient have a  
germline *BRCA* (g*BRCA*) mutation?

THERE'S

# POWER

IN

## KNOWING



### THERE'S POWER IN TESTING FOR g*BRCA*

#### 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer

In the ABC setting, results from genetic testing may have therapeutic implications and should therefore be considered as early as possible.

Genes to be tested depend on personal and family history; however, at present, only germline mutations in *BRCA1/2* have proven clinical utility and therapeutic impact.<sup>1</sup>

#### What g*BRCA* mutations account for

~**5-10%**  
of female breast cancers<sup>2,5</sup>

~**4-16%**  
of male breast cancers<sup>6</sup>

~**25%**  
of hereditary breast cancers<sup>2,3</sup>

#### Testing at MBC diagnosis

Testing for a g*BRCA* mutation at MBC diagnosis may help inform treatment planning.<sup>7\*</sup>

\*Relevant for patients who did not receive previous g*BRCA* testing and/or for patients who received only somatic *BRCA* testing.



ABC=advanced breast cancer; *BRCA*=breast cancer susceptibility gene; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; TNBC=triple-negative breast cancer.

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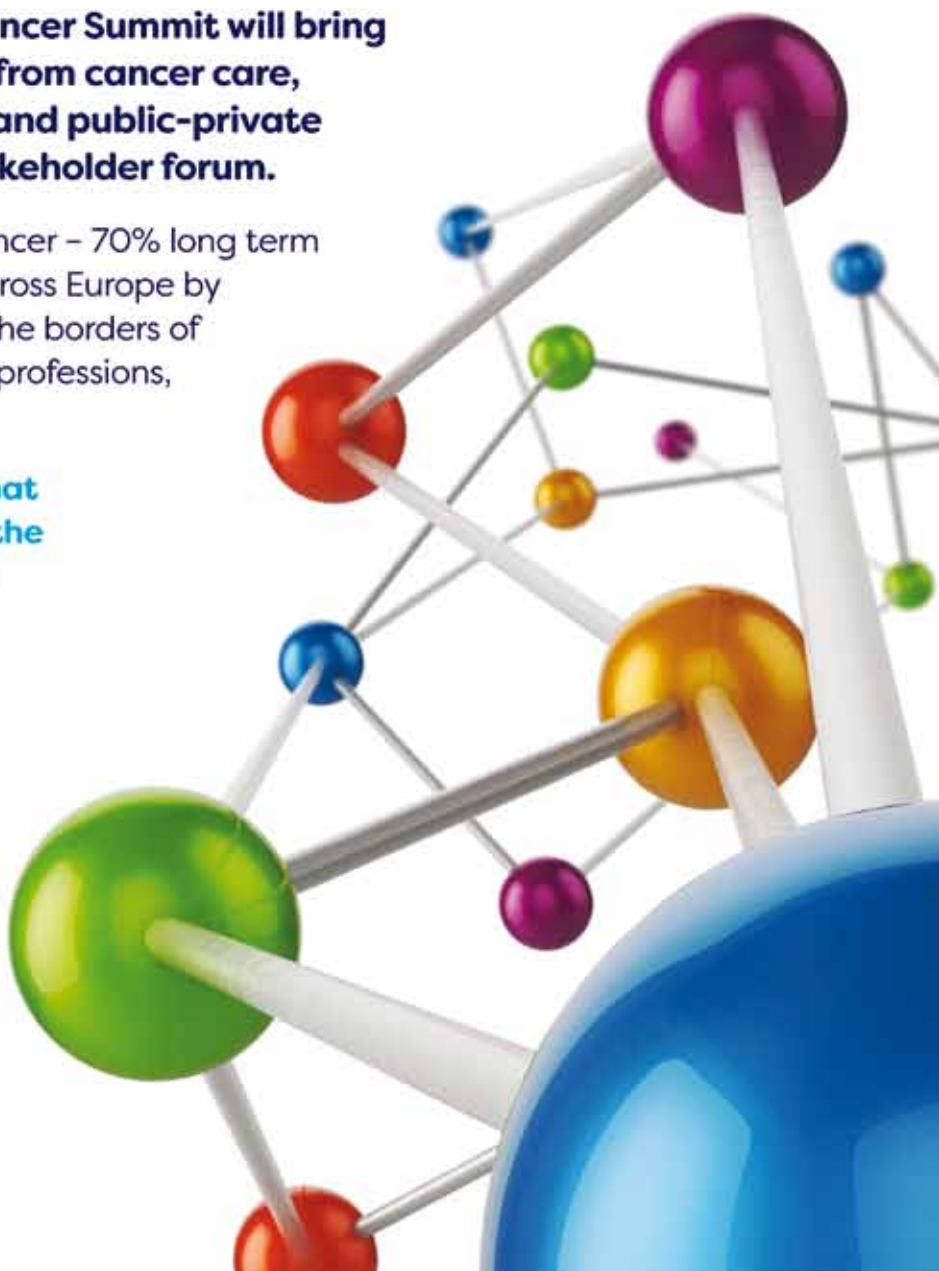
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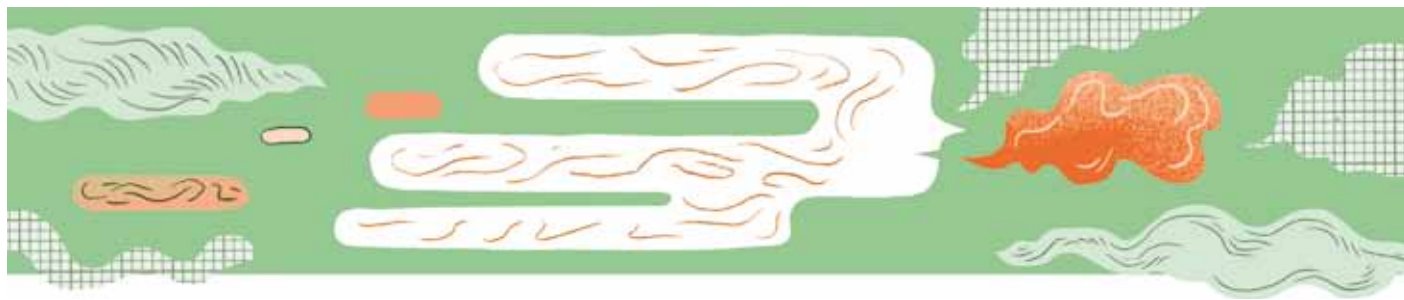
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# Csaba Dégi: Playing catch-up with the West

Csaba Dégi is all set to study how patients in Romania transition back into primary care after their treatment is over, as part of current international efforts to focus on the needs of survivors. That's something to be proud of, he tells **Janet Fricker**, given that as recently as ten years ago only a minority of patients in his country were even told they had cancer.

**E**motional and social distress require monitoring and attention just as much as the traditional 'vital signs' of temperature, pulse, blood pressure, respiration and pain. This sentiment – along with the emergence of the field of psycho-oncology – has its origins in the West. Csaba Dégi, a pioneer of psycho-oncology screening in Romania, has spent his career trying to put the philosophy into practice in his home country.

Dégi, who works as an associate professor in the Faculty of Sociology and Social Work at Babes-Bolyai University in Cluj-Napoca, argues that the right intervention at the right time can be the thing that enables people to continue living their lives in the face of a cancer diagnosis. "Cancer patients face a whole continuum of distress that ranges from low level distress that people can manage themselves to elevated distress, including clinically relevant depression and anxiety, that stops them functioning," he says. "Without support they become marginalised and experience a very lean survivorship."

In Romania, psychosocial provision for cancer patients is still regarded as something of a luxury rather than as an essential component of cancer care. Although more than 78,000

patients are newly diagnosed with cancer each year, only around 5% to 8% of them receive any professional psychological or social care. With studies estimating that between one and two out of every three cancer patients experience some level of psychosocial distress, there is clearly a huge unmet need.

Dégi attributes the shortage of professionals primarily to shortcomings in the National Cancer Control Plan, which makes no mention of psychosocial oncology care. Romania has no recognised accreditation programme for psycho-oncology training, he adds, with only around 20 psychologists and 10 social workers serving the country's four main cancer centres. "There's no official job title of 'psycho-oncologist', with the result that it's completely pot luck whether cancer patients have any access to the psychosocial services they so desperately need," says Dégi, who is all too aware that in poorly resourced countries funding of cancer treatment needs to take priority.

The situation in Romania is far from unique, however. Throughout the rest of Europe, Dégi adds, provision can be extremely patchy, with few countries fully integrating psychosocial oncology into their medical system. A survey



Attending a meeting with the Romanian minister of health in Bucharest this year, Csaba Dégi spoke stressing the importance of including psychosocial oncology care in the Romanian National Cancer Control Plan, which currently makes no mention of it

by the European Partnership for Action Against Cancer (EPAAC), involving 27 representatives of European countries, showed that only eight (fewer than one in three) reported having nationally recommended clinical guidelines for psychosocial oncology care, only 10 (fewer than two in five) had specific budgets for such a service, and only six (just over one in five) had an official certification programme for educating psychosocial oncology professionals (*Psychooncol* 2017, 26:523 – 30). Indeed, only the UK and Germany can be considered to have fully integrated psycho-oncology into mainstream services.

## Smart screening

After battling successive Romanian ministers of health to include psychosocial oncology in the national cancer programme, Dégi is now focusing his energies on promoting screening. It's urgently needed, he explains, because cancer care professionals all too often confuse clinical depression (feeling hopeless, helpless, worthless or suicidal) or anxiety disorders (phobic avoidance, agita-

tion and constant worry) with normal sadness. Dégi has decided to take a pragmatic approach by developing an innovative smart phone app – APSCO (Assessment of Psycho-Social and Communication needs in Oncology patients) – that patients can use at home to screen themselves for distress.

The app, based on the work of Alex J. Mitchell, from the University of Leicester, UK, consists of a visual system of five thermometers covering distress, anxiety, depression, anger, and the need of help, which cancer patients can use to rate how they are feeling on a scale of 0 to 10, similar to the way pain is reported. After calibrating the sensitivity and specificity of the app for use in the Romanian population, Dégi has settled on a cut-off value of any score above 4 as an indication patients require further evaluation.

“The app is needed because it's really hard for patients to judge whether they're experiencing normal suffering or require extra help,” says Dégi. “We want patients to use it at least once a week, as emotional distress isn't constant and can be triggered by different stages of the illness trajectory.”

Once distress has been flagged up, patients need to be

## Profile

further evaluated, he says, and they can then be offered a range of treatments, depending on levels of distress and co-morbidities, including supportive expressive therapy, solution-focused therapy, mindfulness, narrative, cognitive behaviours, and psycho-pharmacology. The app itself also includes a database of psycho-oncology resources in Romania and advice on meditation and guided relaxation.

### A question of justice

Dégi did not start out with the career of social work in mind, but instead attended theological high school with a view to training as a protestant priest. “I come from a tough background with lots of hardships. My parents were ambitious for us and realised that the main opportunity for education was through the seminary,” he says. Feeling disappointed with the church as an institution, Dégi instead chose to study for a Bachelor’s degree in social work at Babes-Bolyai University, in Cluj-Napoca.

“For me faith is about finding meaning in life, which provides peace of mind. I didn’t feel that this needed to take place in a theological framework and found social work connected me to values of being human and provided an outlet for my desire to fight social injustice,” he says.

While still at University, a defining moment in Dégi’s life was the death of his father János, at only 49 years old, from lung cancer. “The cancer was undoubtedly caused by exposure to industrial chemicals – virtually all of my father’s work colleagues from the factory died of cancer before the age of 54. The experience has meant that I understand first hand the isolation of cancer patients and the far-reaching effects that reverberate throughout their families,” he says.

### “I understand first hand the isolation of cancer patients and the effects that reverberate throughout their families”

Dégi started off working in child and family health, specialising in drug addiction, for his PhD in medical psychology at Semmelweis University, in Hungary. But he focused his attention on the emotional experiences of Romanian patients hospitalised with cancer. “I concentrated on the Romanian situation, because Hungary has a 40-year history of psycho-oncology,” he explains.

Getting access to cancer patients, he recalls, was ‘little short of a miracle’.

“Over the weekends cancer patients were kept in complete lockdown with no opportunities for visitors,” Dégi remembers. He had to rely on nurses, who had become convinced of the value of his work, to smuggle him in. “To me it was completely outrageous that dying patients were treated as nobodies, and locked out of society,” says Dégi, adding that the only support they were given was by priests, offering bible readings and prayer.

“I recognised that these people were really isolated, and wanted dialogue about their emotions, distress and fears. They wanted to talk through decisions they needed to take, like what to tell their children,” he says. An important early realisation was that ‘nice words’ were all very well, but changing systems requires good-quality evidence. “Although at heart I’m a patient advocate, I quickly realised that I needed to develop the mind-set of a researcher,” he says.

### Let the patient know

The issue around telling patients the truth about their diagnosis became an important aspect of his research after he became aware of how physicians and family members collaborated in a ‘conspiracy of silence’. “Revealing the diagnosis to cancer patients was felt to be too cruel, because you were taking away their hope. The prevailing view was that people coped better not knowing,” he says.

Dégi’s research showed that, in 2007 (before Romania joined the European Union), fewer than two in ten cancer patients were informed about their diagnosis (*Supportive Care Cancer* 2009, 17:1101-07), whereas by 2014, when disclosure had become a legal right, this had risen to more than nine in ten. Dégi and colleagues conducted a study to assess the difference disclosure made to patients’ mental health. They found that patients who were not informed about their cancer diagnosis were significantly more depressed, and had lower levels of problem-focused coping, compared to patients who were informed (*Psycho-oncology* 2016, 25:1418–23).

Disclosure, Dégi maintains, brings many benefits, including allowing the possibility for patients to have free and open communications with friends and family members about cancer. “It’s impossible for people to adjust to something they don’t understand,” he says. But despite the dramatic fall in non-disclosure levels in the second study, he found patients did not experience a corresponding improvement in quality of life. “Even though we were starting to communicate more openly about cancer, the problem was that there



were no services in place to help patients,” he says.

For Dégi the findings triggered painful memories about his father’s death. “We had taken the decision not to tell Dad about his diagnosis. But when he eventually figured out for himself that he had cancer, he felt terribly betrayed that we hadn’t shared the information with him. Sadly we never succeeded in restoring the trust between family members.”

In 2016, Dégi published his book *‘Psychosocial oncology needs: an absent voice in Romania,’* with the intention of providing a snap-shot of psycho-oncology care that could be used as evidence of the need to provide psychosocial oncology services in Romania. The book, which involved questionnaires and structured in-depth interviews, was unusual in being published from the outset in Romanian, Hungarian, and English. “I made the conscious decision to publish in three different languages to get the messages out to as many people as possible,” he says.

**“When he eventually figured out for himself that he had cancer, he felt terribly betrayed that we hadn’t shared the information with him”**

In his quest to bring about change Dégi, who describes himself as “naturally shy and introverted”, has needed to assert himself and become politically active. In 2016, he was a member of the steering group formed to develop the National Cancer Control Plan for 2016–2020, with special responsibility for psychosocial oncology care. “It’s been incredibly frustrating, because the new programme, which included a psychosocial action plan, was launched at a big event in Bucharest, but the document was never published and is still languishing on a shelf at the Ministry of Health,” he says.

The problem, he explains, is that Romania has had four different ministers of health in the last few years. “Every time I meet a new minister, I need to start from scratch explaining the importance of psychosocial oncology,” Dégi says. But he’s encouraged by the fact that, when palliative care was first introduced in Romania in the 1990s, there was little support from the national medical system, and yet by 2015 it had become an integral part of cancer care, with 115 specialists now employed in palliative care services.



With Anja Mehnert, head of the Psycho-Oncology Unit at the University of Leipzig, Germany, at an advanced psycho oncology training programme that Dégi organised for Romanian healthcare professionals

## Building capacity

With this optimistic outlook Dégi is mindful of the need to train the next generation of psychosocial oncologists and, in his current post in the faculty of Sociology and Social Work at Babes-Bolyai University, he runs an undergraduate course in oncology social work (20 students) a Masters in psycho-oncology (80 students) and a PhD programme in health sociology (three students).

But as he says, “there’s still a generation of oncologists in Romania who have had no training in communication skills.” To address this gap, he has been working with the International Psycho-Oncology Society (IPOS) to establish specialist training programmes in Romania. In 2013/14 he organised a series of training sessions for doctors and psychologists from the public health system, to improve their skills in conducting difficult communications – including breaking bad news and talking about intimacy and sexual life – and so far has trained 60 doctors and 40 psycho-oncologists. “We operate a cascading system, where the professionals we train offer local training to colleagues.”

Dégi was also influential in forming the Romanian Association for Services and Communication in Oncology, an organisation supporting cancer patients and their families that provides a data base of psychosocial services. “We connect the dots, helping patients navigate services, and push the psychosocial oncology agenda forward.”

## Profile

### An international player

Dégi talks about what an inspiration it was for him to meet many of the early pioneers of psychosocial oncology, including Lea Baidar, from the Hebrew University of Jerusalem, Maggie Watson, from the Royal Marsden Hospital in London, who edits the *Psycho-Oncology Journal*, and the late Jimmie Holland, from Memorial Sloan Kettering Cancer Center, in New York, who is widely recognised as the founder of psycho-oncology. “Jimmie told me that, in the 1960s, the psychosocial oncology situation in America was like Romania in 2007, before we joined the EU. People just didn’t talk about ‘the big C’. And just like me, but decades earlier, Jimmie did the research that built the evidence to show that there was a need for psychosocial oncology,” says Dégi.

Today Dégi increasingly contributes at an international level. He is an IPOS director, representing eastern European regions, he was part of the panel that drew up the psycho-oncology section of the ‘Essential Requirements for Quality Cancer Care’ published by ECCO (the European Cancer Organisation). He is especially proud of

having been recruited by Leslie Fallowfield, professor of psycho-oncology at Brighton and Sussex Medical School, in the UK, who has been hugely influential in the field, to facilitate a workshop training eastern European doctors to use more focused and open questions, show increased levels of empathy, and respond more appropriately to patient cues. “For me a big benefit of the course was that it gave me instant access to the Romanian oncologists that I’d been trying to reach to talk to about the importance of psychosocial oncology,” he says.

Next, Dégi plans to study the transition of cancer patients who have finished treatment, from cancer centres back into primary care. As with his other studies, the first part of the process will be to gather information, identify needs and then plan for change. “All my career I’ve been playing catch-up, doing studies 20 to 30 years later than my colleagues from the West. But this time I’m really excited to be taking part in an international research network that allows me to be in step with my colleagues from developed countries.”

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For a laugh



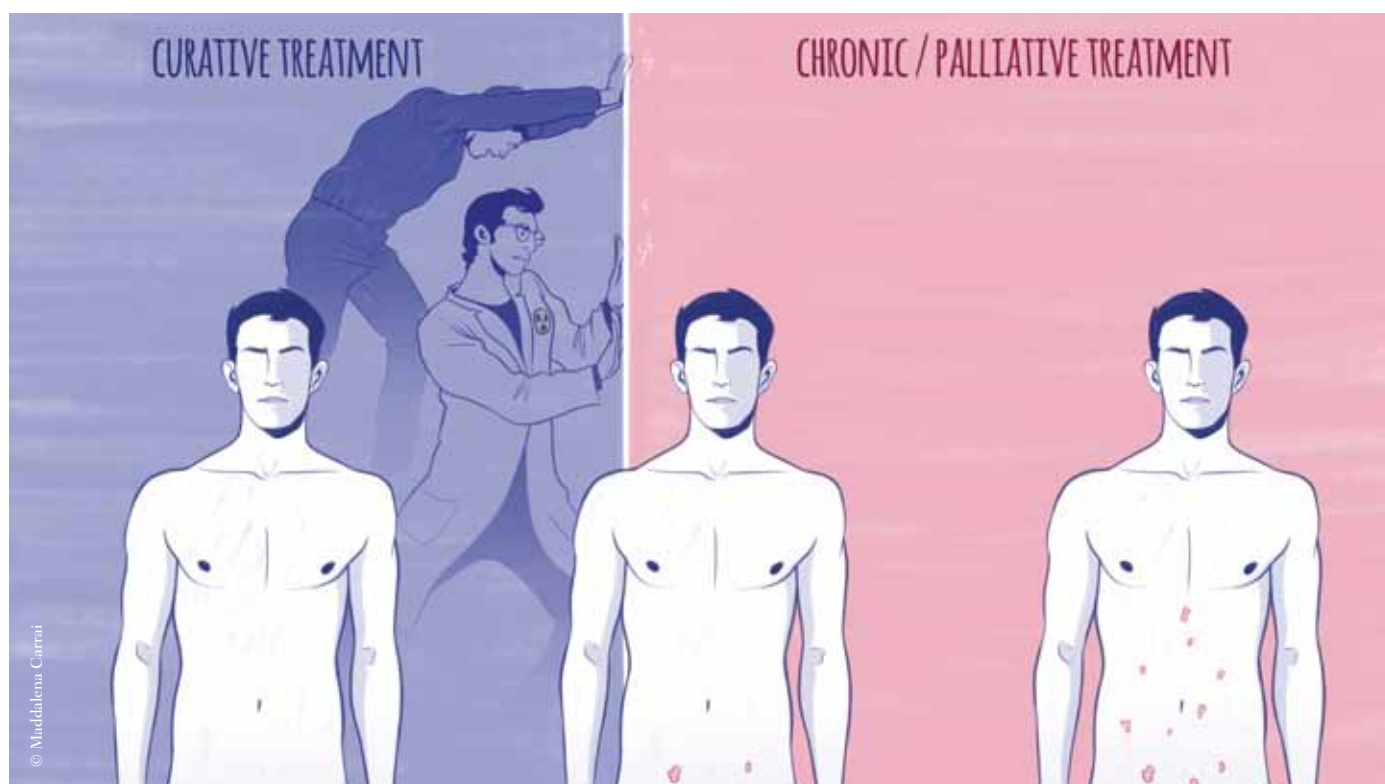
“Let’s just start cutting and see what happens.”

**Sandoz**  
in Oncology

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# Pushing the boundaries of curative treatment

*More patients with oligometastatic disease could benefit from local therapies*

Is there an early stage in the metastatic process at which the possibility of a cure remains open? **Marc Beishon** looks at the science, the opportunities opened up by new and more accurate imaging and treatment modalities, and the clinical evidence.

**C**an we cure any patients once their cancer has spread? It's a question that oncologists have been asking for some time, and are still asking. The prognosis for most advanced solid tumours remains gloomy and, in the majority of cases,

it is the metastases that kill.

Testicular cancer has, for many decades, been one of the rare exceptions to the rule, with effective chemotherapy regimens leading to survival rates of almost 75%, even among patients diagnosed with the most

advanced disease (stage 3c). Increasingly there is promise now with new immunotherapies in melanoma and lung cancer, but so far only in relatively few patients.

Apart from systemic therapies – which are the mainstays of treatment

for advanced cancers – surgery, radiotherapy, and other ablative techniques have also been used for a long time to treat and remove ‘mets’ in sites such as the liver, lung and brain, to relieve symptoms and/or extend life.

A minority of patients treated in this way have gone on to live a normal life span. The question is whether this proportion can be increased by bringing new biological knowledge, imaging and operative/ablative techniques to bear on what has become known as ‘oligometastatic cancer’ – a relatively recent term that means limited metastatic spread, usually to only one or two sites, which by definition is eligible for curative treatment.

‘Oligos’ is Greek for ‘few’, and the term oligometastasis typically refers to fewer than five mets, but there is no hard-and-fast definition, and the concept has been the source of a good deal of confusion and indeed scepticism that it represents any sort of definable clinical entity. As Socrates said, “The beginning of wisdom is the definition of terms.”

### What are we talking about?

The term ‘oligometastasis’ was first used by Samuel Hellman and Ralph Weichselbaum in a paper published in the *Journal of Clinical Oncology* in 1995 (vol 12, p8). In 2011, the same authors reviewed how thinking about the concept had developed over the intervening 16 years, in ‘Oligometastases revisited’ (*Nat Rev Clin Oncol* 2011, 8:378–82). Their proposal was that evolution of metastatic capacity has an intermediate status in which spread may be limited to specific organs, and mets might be present in small numbers – the clinical implication being that local treatments can be curative, as

borne out by studies on spread to the liver, lung, and adrenal gland.

But the key question they posed was the prevalence of oligometastasis – if more patients with this ‘status’ could be identified, maybe through new biomarkers and molecular diagnostics, then the curative population could rise. Access to better ways of treating such local tumours would also be important – the authors mentioned in particular stereotactic body radiotherapy (SBRT), which can treat mets in multiple organs in a patient, including some mets not eligible for surgery.

Fast forward again to 2018, and Weichselbaum was honoured at the ASCO meeting in Chicago, where he gave the annual Karnofsky lecture (an article based on his talk was published in the *Journal of Clinical Oncology*, doi:10.1200/JCO.18.00847). Here he had a more detailed answer to how common the oligometastatic state is, noting though that this is still hard to pick out of current literature. Some people say one in ten cases, others one in three – but his group had picked one in five, based on the first clinical trial they did.

Speaking about the US, he said: “If you look at the four most common cancers, 90,000 patients a year either developed oligometastases or presented with them. If we include less-common tumours, like sarcomas and renal cancer, where the presentation is frequently metastatic, this is more than 100,000 patients a year. So this subset of cancers would make the potentially life-threatening cancers more common than any cancer except lung cancer.”

Put in those terms, oligometastasis has the potential to be much

more important than “rare exceptions to the cancer metastatic paradigm”, as Hellman and Weichselbaum characterised conventional thinking in their 2011 *Nature* paper.

Like a lot of researchers, they are hoping to overturn that paradigm by understanding metastasis, and argue that it is a wide spectrum of disease in three respects: by the number of mets, by the organs they appear in and, importantly, by the pace at which they appear.

**Put in those terms, oligometastases could be much more important than the ‘rare exceptions’ they were initially characterised to be**

Weichselbaum argues that, contrary to many people’s conceptualisation of metastasis, the process is inefficient and often slow, as tumour cells have to detach and burrow into blood vessels and survive in the circulation and then move back out of vessels and colonise other sites, governed by genes and proteins.

One of the first studies they did found that the pace of recurrence of mets was a critical factor. In a set of patients with operable lung cancer, with between one and five mets at follow-up, there was a huge difference in survival for those who presented at a rate of fewer than 0.6 mets a year and those who developed more than 3.6 mets a year – it was mostly a difference between life and death.

### Precision in targeting oligometastases

It is the combination of imaging, local ablative techniques (especially stereotactic body radiotherapy), and development of biomarkers that is fuelling the work on oligometastasis.

#### Imaging

As a recent review by the imaging group of the EORTC (European Organisation for Research and Treatment of Cancer) reports, correct identification of oligometastatic disease is not trivial, and whole-body *in vivo* imaging is the only realistic current option for detection (*Eur J Cancer* 2018, 91:153–163). Advanced imaging modalities – especially using PET–CT – are starting to supersede standard ones (CT, MRI, bone scintigraphy). For example, a PSMA (prostate specific membrane antigen) tracer with PET–CT targets a protein expressed in prostate cancer (also expressed in other cancers such as kidney and liver). “It allows us to see affected lymph nodes and lesions we just couldn’t see a few years ago,” says radiation oncologist Alan Dal Pra. Piet Ost and colleagues, in their paper on the STOMP trial (see p 33), also note that the PSMA tracer, specifically <sup>68</sup>Ga–PSMA, holds great promise – they used choline PET–CT imaging in their study instead, which was the tracer available in Belgium at that time, but is outperformed by the PSMA tracer at low PSA levels. The PSMA–PET modality is now in wide use in many countries (see also review, *Eur Urol* 2018, 74:179–90, which found that using <sup>68</sup>Ga–PSMA PET altered management of about half of patients with metastatic prostate cancer).

#### Stereotactic body radiotherapy (SBRT)

EORTC, together with ESTRO (the European Society for Radiotherapy and Oncology), is conducting a ‘basket’

observational registry trial called OligoCare to collect outcomes on oligometastatic patients treated with SBRT (see slides at [bit.ly/OligoCare](http://bit.ly/OligoCare)). It is noted that SBRT is a standard of care, “despite a lack of hard evidence and despite huge uncertainties and variability in practice”, and that traditional clinical trials won’t provide all the answers. There are several machines that can deliver SBRT, including conventional linear accelerators, tomotherapy, cyberknife and MRI-guided radiotherapy, as well as gamma knife, which is used only for the treatment of cranial lesions. Along with surgery there are other local ablative approaches – in the liver, in both operable and inoperable settings, there is radiofrequency, selective internal radiation therapy (SIRT), portal vein embolisation, and embolisation using chemotherapy. But SBRT has found favour among many radiation oncologists for a range of tumour sites (see for example *Cancer Treat Rev* 2017, 52:22–32).

#### Biomarkers

Work on finding biomarkers that will identify which patients with oligometastases are likely to benefit from local intervention is in its early stages, and is allied to the large body of research on widespread metastatic disease, including on circulating tumour cells and DNA. In addition to the recent work on molecular subtyping of liver mets noted in the main text, there is research on microRNAs (miRNAs) as genetic probes for distinguishing between oligometastatic and polymetastatic (>5) lung cancer mets, as current imaging methods are said to be insufficient (see *Medicine (Baltimore)* 2018, 97:e10958). There has also been a study on gene signatures of lung mets from kidney cancer (*Int J Cancer* 2009, 125:474–482).

### Who should be eligible for intervention?

Researchers at a number of centres have since been looking at the clinical and biological factors that could determine whether a patient could have a good outlook from an oligometastatic intervention, and there has been a small number of randomised con-

trolled trials (RCTs). This year, Weichselbaum and colleagues published a paper that details molecular subtypes in colorectal cancer that can categorise patients into low-, intermediate- and high-risk groups for liver metastases (*Nature Comm* 2018, 9:1793).

Peter Naredi, a surgical oncologist at Sahlgrenska University Hospital, in Gothenburg, Sweden, and a specialist

in liver and gastrointestinal cancers, argues that immunotherapies, which are resulting in long-lasting durable responses in a minority of patients, are changing the perception of many in the oncology community about the curability of some metastatic disease. “But we have been talking about this with surgery for years,” says Naredi. “We can get long survival if we chose



the right cases, particularly for liver metastases that arise from colorectal cancer, and also from the much rarer neuroendocrine tumours.”

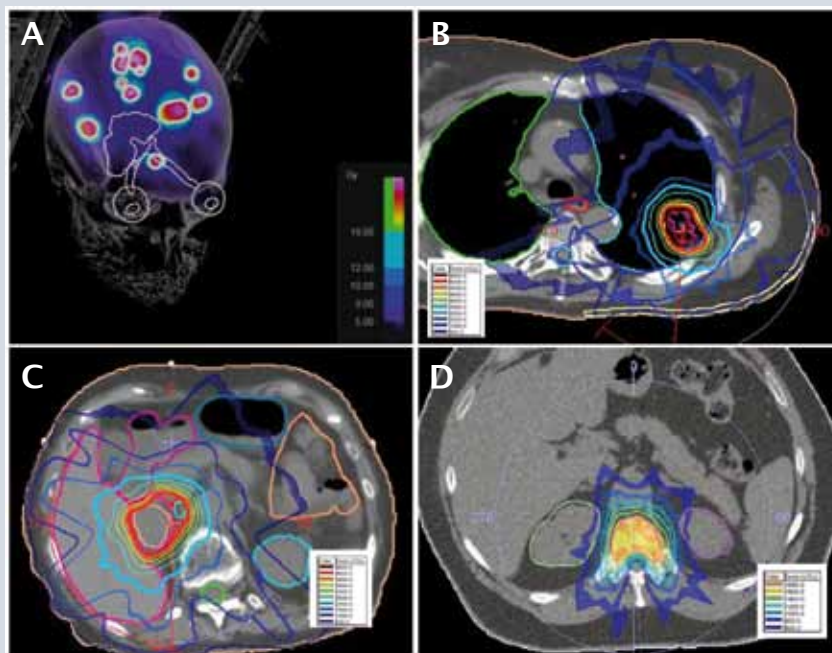
At present, he says, one in two patients deemed eligible for liver surgery has an excellent chance of five-year survival – but only if there are modern operative techniques that, for example, minimise bleeding, and excellent perioperative care, that can result in good quality of life. There is an existing knowledge base that, when coupled with multidisciplinary care, can provide this one-in-two chance, but Naredi says that, even in Sweden, patients living near a university hospital are more likely to be referred for such selection than those in out-lying hospitals. A study from the UK, he notes, looked at National Health Service hospitals and found a wide variation between rates of surgery for liver metastases. Notably, it also found that, where such surgery was done on colorectal cancer patients, outcomes were equivalent to those with stage 3 colorectal cancer (lymph node involvement but not metastatic) (see *Br J Surg* 2010, 97:1110–18).

There is a lot at stake. Naredi says about two in every five colorectal cancer patients develop liver metastases, and about one in five, or even one in four of them, should be eligible for surgery. That could be up to 10% of the colorectal cancer population. “If I say to patients they have a 50% or possibly better chance of five-year survival, they want that chance,” says Naredi.

## Guidelines, evidence and clinical trials

In mainstream clinical practice, Naredi considers that only colorectal/neuroendocrine liver mets have a sufficiently high level of evidence

## Precision planning for local treatment



Examples of stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) treatment plans for melanoma metastasis: A) SRS for multiple brain metastases; B) SBRT for lung metastasis; C) SBRT for adrenal metastasis; and D) SBRT for spine metastasis

Source: W Shi Radiation Therapy for Melanoma. In: WH Ward and JM Farna eds. (2017) *Cutaneous Melanoma: Etiology and Therapy* [Internet]. Brisbane (AU): Codon Publications, Chapter 8. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK481863/> doi: 10.15586/codon.cutaneousmelanoma.2017.ch8. Published under a Creative Commons licence

to justify curative surgical intervention. He mentions ongoing research using registry data on patient selection according to factors such as age and comorbidities, on the nature of the primary and metastatic tumours, and on adding drug treatment, such as using chemotherapy, to shrink tumours before surgery or to prolong life after surgery.

Naredi sees two main problems in current practice – a failure to refer patients to expert centres for assessment, and overtreatment by surgeons who perform non-evidence-based resections on metastases in a range of cancer types, such as pancreatic cancer. Guidelines are urgently needed

to rectify both problems, he says.

“There are a number of surgeons in Europe who are carrying out what is essentially futile surgery because they don’t want to tell the patient the truth, leading them to believe they can cure their cancer. We do have case reports on, for example, liver resections for pancreatic cancer, but we have seen no long-term survival. In my view it is wrong to do such surgery outside of clinical trials in cancers such as pancreatic and oesophageal, and national guidelines need to stress this.”

Naredi adds that there is emerging evidence for a middle category of cancers, such as breast, prostate, melanoma, sarcoma, and ovarian cancer,

to show that surgery (or stereotactic body radiotherapy and other ablative techniques such as radiofrequency) can be an option, where there is evidence of an oligometastatic state.

The field is also moving on to examining multimodal therapies, including chemotherapy, radiation, and new biological therapies, as well as surgery. But the less flashy, painstaking work involved in defining which groups of metastatic patients might benefit from different types of local ablative therapy already in mainstream use is quietly proceeding, says Naredi, even though it is not the type of work that is likely to hit headlines or make careers.

What all this also demands – from what should be a standard referral for liver mets, to the intermediate and cutting edge work – is working in multidisciplinary teams, as Naredi reiterates. In the metastatic setting, for a long time too many patients have been referred to isolated medical oncologists for the possibility of systemic therapy, but the wide choice of options for both curative and non-curative approaches, as detailed in numerous recent papers, demands an MDT that is on top of the current research. It should no longer be acceptable for patients diagnosed with metastatic disease to be referred automatically to management by medical oncology alone.

### Breast cancer

The MDT point was also highlighted in 2017 in an abstract in *The Breast*, written by a team at the Netherlands Cancer Institute, in Amsterdam, concerning questions raised about the best treatment for one of their patients – a 38-year-old woman who had triple-negative breast cancer and presented with two liver lesions six years after pri-

## The wide choice of options for both curative and non-curative approaches demands an MDT that is on top of current research

mary treatment (vol 36, p S60).

These included whether there are biomarkers to help select patients with oligometastatic breast cancer who might benefit from a multidisciplinary approach; the preferred method for local treatment (surgery, stereotactic radiotherapy, radiofrequency ablation, combinations); the extent of radiological remission following chemotherapy that should be required before proceeding to local treatment; and how the patient should be followed up. (The patient was treated with chemotherapy, followed by surgery, and at the time of publication she had been free of clinical or radiological signs of cancer for four years.)

The range of questions make clear that expert input from most of the core members of the multidisciplinary team needs to be brought to bear – medical oncologists, surgeons, radiologists (including interventional specialists), radiation oncologists, and pathologists.

There's a sense of frustration though at the slow pace of progress. The Amsterdam team notes that oligometastatic breast cancer was discussed at the 2008 meeting of the European School of Oncology Metastatic Breast Cancer Task Force (JNCI 2010, 102:456–63). That meeting called for prospective RCTs to gener-

ate robust evidence, and yet ten years on, the most recent guidelines from the Lisbon Advanced Breast Cancer (ABC) conference continue to say that, while curative treatment should be considered for selected oligometastatic patients, a prospective clinical trial is still needed.

The Dutch team mentions that they are conducting their own prospective study, in which patients with oligometastatic breast cancer are treated with 'neoadjuvant' chemotherapy and maximal local therapy for all detected metastases and locoregional disease, and they advocate for pooling efforts to create a prospective registry for patients with oligometastatic breast cancer across Europe. The most urgent questions flagged up by the registry could then be investigated in an international trial led by the EORTC, they suggest.

### Prostate cancer

Prostate cancer is another area where interest is growing in identifying an intermediate or oligometastatic state between patients with localised disease and more widespread metastatic disease. "This is also because we have new imaging modalities that can detect lesions more accurately," says Alan Dal Pra, a radiation oncologist at the Sylvester Comprehensive Cancer Center, in Miami, Florida. "We also have the ability to treat the lesions with low toxicity, using stereotactic radiotherapy – just one to three fractions are needed," (see also box on imaging and SBRT, p 30).

Dal Pra points to a phase II RCT led by Piet Ost, at Ghent in Belgium, called STOMP, which reported this year (JCO 2018, 36:446–53; see figure opposite). It assigned 62 men with three or fewer metastatic lesions to either treatment of the lesions or

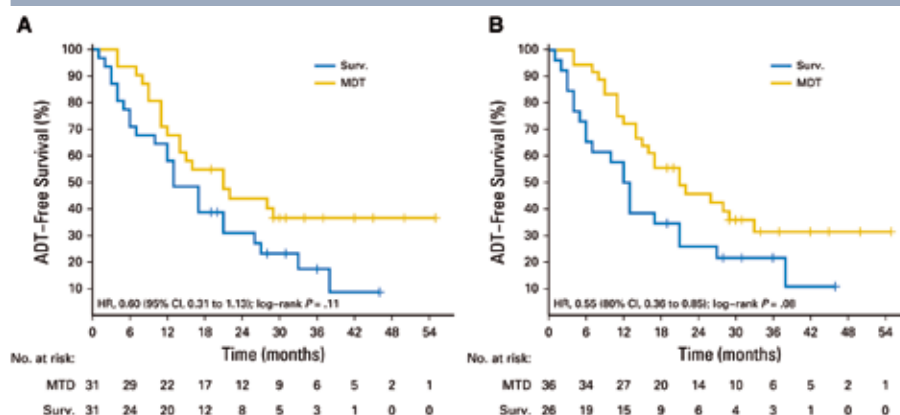
surveillance. The men were then monitored until they required androgen deprivation therapy (ADT), the standard therapy given when the cancer progresses. The median ADT-free survival time in the intervention group was more than 50% longer than that of the surveillance group, at 21 months compared with 13 months.

One remarkable finding, which Dal Pra also notes, was that the 35% of patients in the surveillance arm experienced spontaneous PSA declines (the marker used to gauge progression) without receiving any therapy, although for most this did not last. But it supports the concept of oligometastasis – that certain tumours have not fully developed their metastatic potential and show a slow natural history, say Ost and colleagues.

The prostate study also raises the question of lead time bias – whether intervening earlier does confer benefit or if survival would be the same. The results from the STOMP trial suggest that there is real benefit. The issue was discussed by clinicians in Greece in a paper, ‘Oligometastatic prostate cancer: is it real?’ (*J Cancer Prev Curr Res* 2017, 8:00295). Apart from aptly quoting Socrates on getting definitions right, they report that treating such mets does appear to decrease the need for subsequent palliative care – so it is a real state – and also that toxicity rates are low, which is another important factor in deciding whether to give local treatments. Other commentators, including Weichselbaum, have also noted the ‘immortal lead time bias’, in that it is selected patients who may do well in single-arm studies, and so well-designed RCTs are crucial (see *Nat Rev Clin Oncol* 2014, 11:549–557; and *J Targeted Therapies Cancer*, 2018, 27 April).

While the STOMP study may not sound as exciting as the immunother-

## Surveillance vs metastasis-directed therapy in oligometastatic prostate cancer



In the phase II multicentre STOMP trial, 62 men with asymptomatic prostate cancer with biochemical recurrence after primary treatment with curative intent, and three or fewer extracranial metastatic lesions, were randomised to surveillance or metastasis-directed therapy (MDT) of all detected lesions. The treatment was either by surgery or stereotactic body radiotherapy. The primary endpoint was androgen deprivation therapy (ADT)-free survival. ADT was started at symptomatic progression, progression to more than three metastases, or local progression of known metastases. At a median follow-up time of three years, the median ADT-free survival was 13 months (80%CI=12–17 months) for the surveillance group and 21 months (80%CI=14–29 months) for the MDT group (HR 0.60, 80%CI=0.40–0.90, log-rank  $P=0.11$ ). Quality of life was similar between arms at baseline and remained comparable at 3-month and 1-year follow-up. Six patients developed grade 1 toxicity in the MDT arm. No grade 2–5 toxicity was observed.

Figure A shows analysis by intention to treat; Figure B shows per protocol analysis. The surveillance arm (Surv.) is in blue, the metastasis-directed therapy arm (MDT) is in gold  
Source: Piet Ost, Dries Reynders, Karel Decaestecker, et al (2018) *JCO* 36:446–453. Reprinted by permission from the American Society of Clinical Oncology. © 2017 ASCO

apy stories, those in the oligometastatic field recognise it as an important step in realising the potential of such intervention, certainly in prostate cancer, and Ost and colleagues feel it justifies moving to a phase III trial.

A related and well-known trial, STAMPEDE, which is adding other therapies to hormone therapy, has reported survival benefits for localised low metastatic burden when radiotherapy to the prostate is added, and

the authors ask if there would be further benefit from additional radiotherapy to the oligometastases themselves.

Dal Pra adds that the Movember Foundation is funding an initiative under its sixth global action plan with at least 16 groups, including his own, to pool knowledge and samples from existing and planned trial work on treating intermediate spread prostate cancer. One of the problems with current research efforts, he notes, is



### Clinical trials

This selection of new and ongoing trials is from a total of about 80 that mention 'oligometastatic' or similar on ClinicalTrials.gov. There are several thousand trials concerning metastasis, some of which will also have relevance to oligometastasis, such as in ablative techniques.

**SARON** – phase III study on efficacy and safety of stereotactic body radiotherapy (SBRT) and conventional radiotherapy alongside standard chemotherapy in patients with oligometastatic lung cancer. Guys & St Thomas, and others, UK.

**CORE:** Phase II/III RCT in patients with breast, prostate or lung cancer comparing standard of care with or without SBRT for extracranial metastases. The Royal Marsden, London.

Multicentre adaptive phase II/III randomised trial of SBRT in oligometastatic castration-resistant prostate cancer patients. Jewish General Hospital, Montréal.

Standard of care with or without SBRT and/or surgery in limited metastatic breast cancer. Phase II/III trial at 136 international locations. NRG Oncology, Philadelphia.

**FORCE** – focal radiation for oligometastatic castration-resistant prostate cancer. Phase II RCT. University of Michigan Cancer Center, Ann Arbor.

**PEACE V:** Phase II RCT for salvage treatment of oligorecurrent nodal prostate cancer metastases. University Hospital, Ghent, and others in Belgium and Europe.

Phase II RCT on how well systemic therapy with or without local consolidative therapy works in treating participants with a solid tumour that has spread to one site. Banner MD Anderson Cancer Center, Gilbert, Arizona.

Single-arm prospective phase II study of SBRT for oligometastases from colorectal cancer. Cancer Hospital, Chinese Academy of Medical Sciences, Beijing.

**ORIOLE:** SBRT for prostate oligometastases randomised against observation. Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins, Baltimore.

Local therapies for oligometastatic lung cancer harbouring sensitising EGFR mutations. Memorial Sloan Kettering, New York.

Cohort study to explore prognoses of lung cancer patients with oligometastases. Multiple centres in China.

High-dose chemotherapy in oligometastatic homologous recombination deficient breast cancer. NKI-AVL, Amsterdam.

SBRT for inoperable lung and liver oligometastases from breast cancer. Istituto Clinico Humanitas, Milan.

Apatinib combined with SBRT in breast cancer oligometastasis. West China Hospital, Chengdu.

Chemoradiation +/- surgery versus systemic therapy for oesophageal or gastric cancer with oligometastases. MD Anderson, Houston.

that trial designs have a high degree of variability concerning the definition of oligometastasis, treatment technology, outcome measurement, and imaging methods. The aim of the Movember initiative is to build on retrospective and prospective clinical trials and invest in a complementary translational research project to answer critical clinical questions regarding tumour heterogeneity and treatment response.

### Melanoma

In melanoma, Don Morton at the John Wayne Cancer Institute in Santa Monica, California, has for many years carried out surgery on metastases and has shown good long-term survival, despite opposition from medical oncologists, notes Naredi. In 2015, the group at John Wayne reported on a 45-year history of cure for melanoma metastases to the abdomen, where they argued that, even in the era of immunotherapy for advanced melanoma, surgery still offered a better opportunity for long-term survival than systemic therapy ([www.facs.org/media/press-releases/2015/deutsch](http://www.facs.org/media/press-releases/2015/deutsch)).

### Lung cancer

In lung cancer, Weichselbaum reported on several papers, including a review in *The Lancet* on the use of stereotactic body radiotherapy (SBRT) to treat lung mets in a number of studies, showing that 20–30% of patients with limited disease were cured.

A later meta-analysis of lung cancer patients found an “astounding” near-50% five-year survival for a certain group. And Weichselbaum also noted several small RCTs, including one on lung cancer, which were stopped because the results were so much better in the ablative group

that the investigators thought it was unethical to continue.

That study was led by Puneeth Iyengar at the University of Texas Southwestern Medical Center, who has also co-authored a number of other papers including one in 2018 that reviewed oligometastatic and oligoprogressive lung cancer (*J Thorac Dis* 2018, 10:S2537–44).

It seems from this review, and from a rapidly growing list of papers on lung cancer, that the usual perception of all metastatic lung cancer as being incurable is being robustly challenged, but big knowledge gaps remain to be filled, and again this will only be advanced by research-oriented MDTs.

### Sarcoma

Another cancer type where it would be hard to imagine any treatment proceeding without MDTs is sarcoma, which has many subtypes and is highly complex. A number of groups have addressed oligometastatic disease in sarcoma, especially in the lung, where about half of soft tissue sarcomas metastasise.

### Head and neck cancer

A recent review of selected patients with recurrent/metastatic head and neck squamous cell cancer undergoing surgery or SBRT shows five-year survival rates of more than 20%, compared with median survival of about 10 months after first-line systemic treatment.

The authors say what is needed are revised imaging follow-up strategies to detect mets earlier; identification of predictive noninvasive biomarkers to guide treatment; assessment and corrections of biases in current studies; and, of course, RCTs (*Future Oncol* 2018, 14:877–889).

### A new era?

A point stressed by Weichselbaum is that there is merit in thinking further than just a few lesions. He and others are now pushing the boundaries to address more advanced conditions, which include the presence of more than five metastases, the presence of ‘oligoprogression’ – where some lesions are progressing and not stable – and even more widespread disease.

In his round-up of the brief number of RCTs, Weichselbaum mentioned one led by Theo Ruers, a surgeon at the Netherlands Cancer Institute, on the long-term effects of applying radiofrequency ablation plus chemotherapy as an aggressive method of treating up to nine inoperable colorectal liver mets, versus systemic therapy alone, finding a significant survival advantage in the ablation group (*JNCI* 2017, 109:djx015). This is the first such phase II trial.

There is also impressive news from a recent multicentre randomised phase II SBRT study, known as SABR-COMET, which reported recently at the annual meeting of the American Society for Radiation Oncology (ASTRO). It looked at the impact of adding SBRT to standard palliative care in patients with up to five mets from mainly breast, lung, colorectal, and prostate primaries. It found a greater than expected median survival in the SBRT arm of 41 months vs 26 months, and a doubling of progression free survival to 12 months. It is the first trial to demonstrate a survival benefit, says Dal Pra, and so helps address the lead-time bias issue. Nearly half (46%) of the patients treated with SBRT were still alive after five years, compared with 24% in the control group. A follow-up study will enrol patients with up to ten mets.

“Oligo is just a subset, a lower

bound of metastasis,” Weichselbaum says. “Now we want to see if maybe, combined with other therapies, we could treat 10 or 20. “So the conclusion is that some patients have oligometastatic disease and can be cured with ablative therapy. These patients can be identified through clinical features and molecular parameters. Some patients with oligoprogressive disease might be cured, and what about more widespread disease?”

**“Now we want to see if maybe, combined with other therapies, we could treat 10 or 20”**

That’s where immunotherapy, including T-cell therapies, possibly combined with radiation (which can stimulate the immune system), chemotherapy, and targeted therapies, may be coming into play, with the application of a lot of advanced thinking on molecular biology.

Perhaps the most important message from the work is that a systematic era of ‘metastatic-directed therapy’ (another MDT abbreviation) is emerging, as researchers put together risk classifications and appropriate multimodal treatments for patients who would have received only lines of drug therapy to control their advanced cancer. Landmark studies, such as that by Weichselbaum and colleagues on the molecular subtyping of liver mets, could also help convince the sceptics that we are dealing with real and unique entities in cancer.

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## ***Coming together on survivorship: an outcome of the ECCO 2018 European Cancer Summit***

**S**uccess can bring new challenges. Substantial progress has been made in improving survival for cancer patients across many (though not all) tumour areas. Earlier diagnosis and improved treatment approaches mean that, according to GLOBOCAN figures, there are now more than 30 million cancer survivors worldwide. But those cancer survivors face new challenges in their daily lives, which need attention. Not least of these relates to discrimination when seeking to access loans, mortgages, insurance and other financial services. Driven by Professor Françoise Meunier, Director of Special Projects at the European Organisation for Research and Treatment of Cancer (EORTC), the recent ECCO 2018 European Cancer Summit devoted its final day to considering how to address this particular injustice. Hearing from representatives of the youth cancer community, self-employed cancer survivors, and legal and academic experts, the scale and human impact of the financial discrimination problem for cancer survivors was made clear. However, more than this, the potential legal remedies that are immediately available to us were tantalisingly described.

In 2015 the French National Assembly instituted a new 'right to be forgotten' for cancer survivors. This means cancer survivors in France no longer have to tell insurers or loan companies they have had the disease when

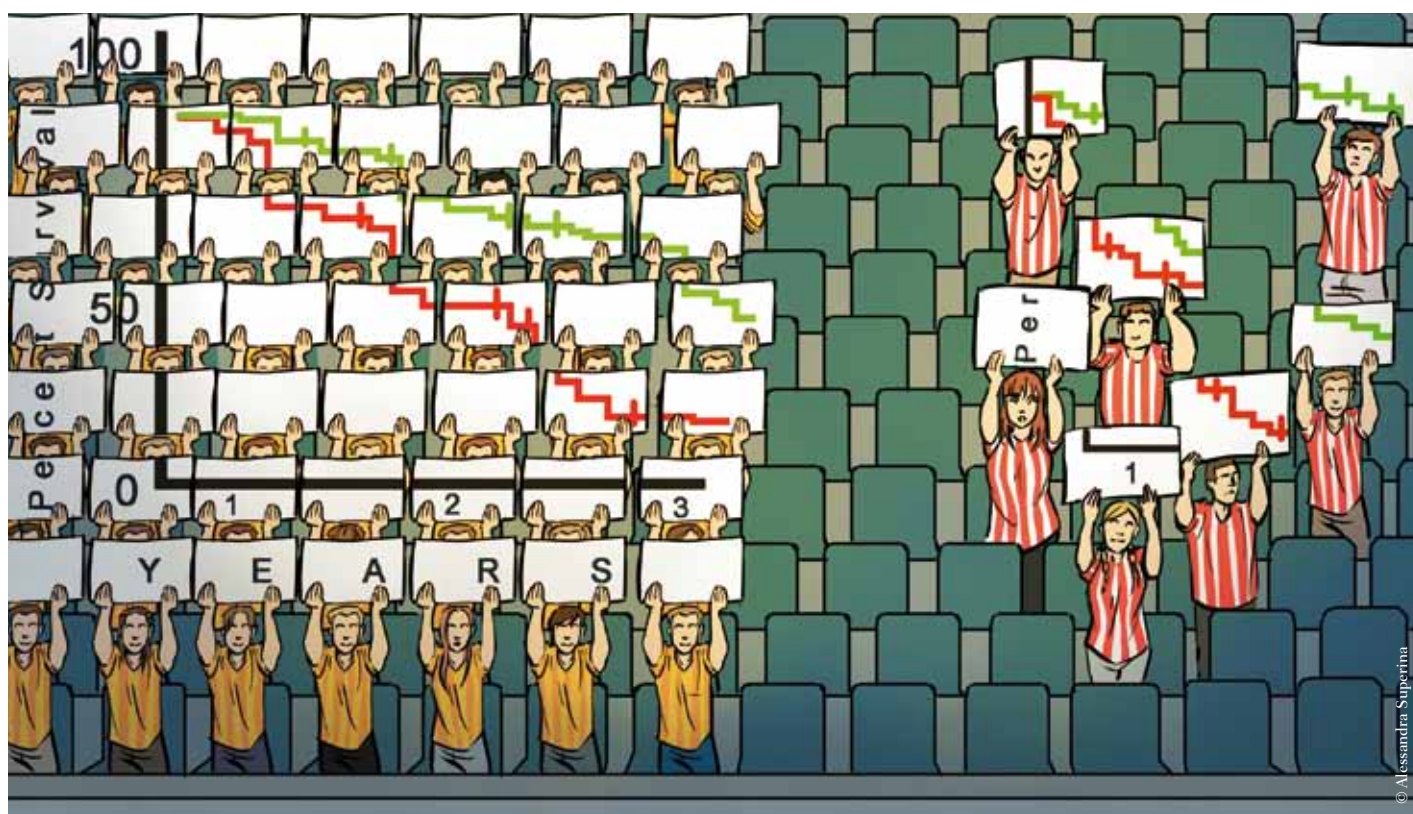
seeking access to financial services. This law benefits all former patients who have been cancer-free for 10 years, regardless of the type of cancer they suffered. Meanwhile, anyone who had cancer under the age of 18 does not need to inform insurers or loan agencies five years after their treatment ends.

Delegates at the ECCO 2018 European Cancer Summit formed a united view that this inspirational action by France should be replicated across Europe. The Summit passed, by large majority, a resolution stating:

*"By 2025, in respect to accessing financial services, the right of cancer survivors not to declare their cancer 10 years after the end of the active treatment and 5 years if they had cancer under 18, should be codified across European countries."*

Momentum to see concrete lobbying action to bring the resolution into reality has been immediate. Youth Cancer Europe recently launched in the European Parliament a call to action on combatting financial discrimination against cancer survivors, quoting the resolution. Furthermore, a new implementation working group, chaired by Professor Françoise Meunier, has now been constructed convening representatives from a range of key advocacy societies to oversee advocacy activities. I am delighted by these developments. It is exactly the kind of convergence of energy and effort required to see the shadow of cancer banished for all survivors. Quality of life considerations for patients do not finish at the end of treatment. As a cancer community our compassion and action for survivors' needs must go further.

The full text of the resolution on Survivorship (Financial Discrimination) passed at the ECCO 2018 European Cancer Summit is posted on the ECCO website [bit.ly/ECCO\\_financial-discrimination](http://bit.ly/ECCO_financial-discrimination)



# How should we assess the efficacy of new treatments in rare tumours?

Traditional approaches to generating clinical evidence rely on recruiting large numbers of patients into trials. **Paolo Bruzzi** reflects on the challenges of designing and analysing clinical trials in rare cancers, and reviews the potential for using alternative trial designs and Bayesian statistical approaches to build robust evidence where patient numbers are small.



*This grandround was first presented by Paolo Bruzzi, from the Institute for Cancer Research, Genoa, Italy, as a live webcast for the European School of Oncology. Paolo Casali, from the National Cancer Institute – IRCCS Foundation, Milan, Italy, posed questions raised during the e-grandround presentation. It was edited by Susan Mayor. The webcast of this and other e-sessions can be accessed at [e-eso.net](http://e-eso.net).*

**T**he rarity of some cancers poses a challenge in conducting clinical trials with sufficient numbers to provide adequate power to assess the effects of a novel therapy. Rare cancers include: rare histologies in frequent sites, such as breast cancer with a squamous histology; cancers at rare sites, such as uveal melanoma; and cancers with both rare histologies and rare sites, such as astrocytomas and most sarcomas. Rarity is set to become a more general issue in cancer research, with growing interest in rare cancer conditions, increased recognition of rare presentations, such as skin metastases, and increased identification of molecular variants of many common tumours.

The 'statistical mantra' applied to clinical trials is that a study must have adequate size to provide adequate power to reduce the risk of false-positive or false-negative results, and to obtain precise estimates of the effects of the experimental therapy being investigated. The aim is to demonstrate a minimal difference that is considered clinically worthwhile, to a level of statistical significance ( $\alpha$ ) usually set at 5% (which means that out of 100 trials comparing treatments with identical effect on the primary endpoint, 5 will show a statistically significant difference by chance alone – that is they'll provide a false-positive result). The power of a study (usually 80%–90%) indicates the probability it will obtain a statistically significant result, if the difference between the effects of the two therapies is the desired one.

The minimal clinically worthwhile difference is usually a risk reduction, including mortality risk. The sample size needed in cancer trials for breakthrough drugs in early disease, based on cumulative mortality from 10%

Number of events needed to show benefit	
Risk reduction (1-HR)	Required no. of events
-10%	2830
-20%	635
-30%	252
-40%	125
-50%	71
-60%	43

The number of events (eg deaths or tumour progressions) required to have an 80% chance of demonstrating risk reduction to a 5% level of statistical significance depends on the size of benefit offered by the drug. The risk reduction offered by most cancer drugs is at the lower end of the scale, requiring larger trials sizes to generate the evidence

to 70%, is 500 to 5000 patients. In advanced disease, with cumulative mortality of 50% to 90%, the sample size required is 300 to 1000 patients. International co-operation is needed to gather a sufficient number of patients for a trial to have adequate size, but this may not be possible for some very rare cancers.

The assumption that a study must have an adequate size based on traditional statistical parameters can lead to the unjustified assumption that trials with small size are of poor quality.

### Establishing therapeutic standards in very rare tumours/conditions

Where there are no trials, treatment of a rare tumour type may be based on 'expert opinion', although it is important to question what this is based on, or may be guided by indirect evidence. However, therapeutic standards can also be based on 'small' trials.

There are four key questions to consider when designing a small trial:

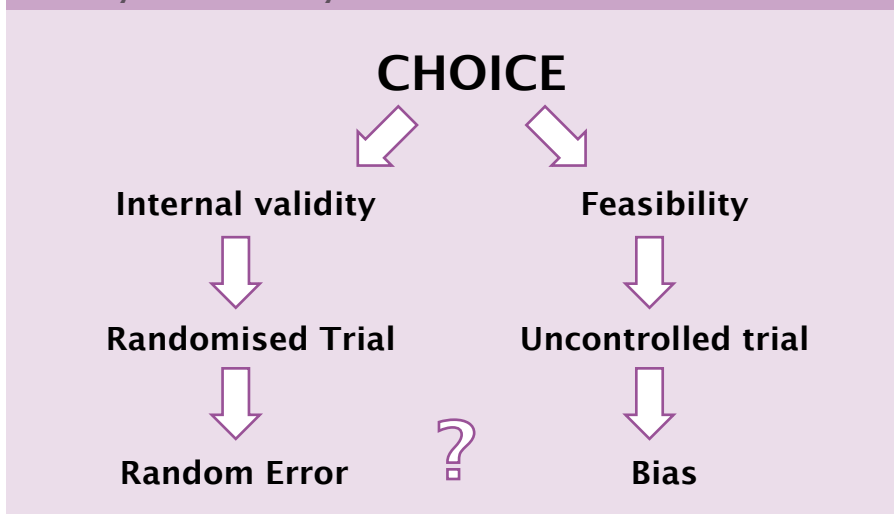
- ☐ Phase II or phase III?
- ☐ Randomised or uncontrolled?
- ☐ What are the endpoints?
- ☐ Conventional or unorthodox statistics?

### Phase II or phase III trials?

If the number of patients is inadequate for a standard phase III trial, then it may be possible to run a phase II trial. There are several examples of phase II trials carried out in rare cancers over the past few years that have contributed important new information to their treatment and led to registration of new drugs based on comparing response rates against historical data. For example, a phase II, single-group trial of PD-1 blockade in advanced Merkel-cell carcinoma showed a median progression-free survival of nine months, compared to a historical value of three months (*NEJM* 2016, 374:2542–52).



### Efficacy trial in a very rare condition



### Randomised or uncontrolled trials?

There are several false beliefs about randomised trials, including the myth that randomised trials require large numbers of patients, while uncontrolled trials do not. Second, some mistakenly think that uncontrolled trials do not require a statistical plan. The reality is that an uncontrolled trial, even one with appropriate statistical planning, is not necessarily the best option where patient numbers are small.

To conduct an efficacy trial in a rare condition, researchers must choose between internal validity – in which case a randomised trial is required – and feasibility – which means an uncontrolled trial (see figure above). Whichever type of trial is carried out, it is important to recognise and minimise sources of error. There are two types of error in any trial:

- Sampling error – due to chance. Preventing sampling error requires an increase in sample size.

- Bias – due to errors in selection of groups, assessment of outcomes or statistical analyses, which distort the evaluation of any associations observed. Methods to reduce bias include randomisation, masking (such as double blinding) and intention-to-treat analysis (all patients who were enrolled and randomly allocated to treatment are included in the analysis and are analysed in the groups to which they were randomised).

The benefits of an uncontrolled trial in a rare cancer are that it enables more patients to receive the new treatment being investigated, and it is easier to recruit patients.

A randomised trial provides unbiased estimates of treatment effects, but makes it more difficult to enrol patients, and fewer patients receive the new treatment being investigated.

It is important to remember that sampling error and bias are independent. Increasing sample size in the presence of bias can be misleading, because it gives researchers more confidence in a wrong result. Statis-

tical methods deal mainly with sampling error but provide little help with bias.

If the expected, or necessary, treatment effect is large but not outstanding, then a randomised clinical trial, if ethically acceptable, is the best way to assess a new drug even in rare diseases. The advantages are validity and credibility, but the disadvantage is a moderate loss in power.

The problem is that there is often no standard treatment for a rare cancer, which may mean the control group is untreated, leading to issues around ethics and acceptability. As a consequence there may be situations where a randomised controlled trial may not be the best approach, or should be avoided for ethical reasons.

These include: when the prognosis with standard therapy is poor, or there is no therapy; when an experimental therapy is not very toxic; or when there is plausible efficacy for the experimental therapy, based on uncontrolled trials in the cancer being studied, randomised controlled trials in different stages of the same cancer, randomised trials in other cancers with the same biology, or dramatic effects having been observed in other cancers.

For example, the tyrosine kinase inhibitor imatinib was initially investigated in a large randomised controlled trial in chronic myeloid leukaemia (CML). The size of the effect was sufficient to suggest that randomised trials in rarer cancers were unethical, so the drug was evaluated in a much rarer cancer, gastrointestinal stromal tumour (GIST), with a large uncontrolled trial, and then with case series in other very rare indications, including dermatofibrosarcoma protuberans, plexiform

neurofibromas, and chordomas.

New paths are emerging for investigating novel drugs (see figure opposite) that start with large randomised controlled trials in common cancers. These provide proof of principle and data on toxicity. The next step is uncontrolled but formal trials in other, often rare, cancers that share the same drug target. It is important to develop the best methodology for conducting uncontrolled trials, which should be rigorous and transparent and take account of biases, with much better selection and use of historical controls. Finally, a new drug can then be investigated in even rarer conditions with the same target with off-label use in individual cases.

## Endpoints in cancer trials

There are two main types of endpoint in cancer trials: 'true' endpoints, including overall survival and validated quality-of-life scores, and surrogate endpoints, such as response rate and progression free survival.

None of these surrogate endpoints have been validated in rare cancers. However, objective response is reproducible and consistently associated with clinical benefit in solid tumours even without a control group, so is a preferred endpoint.

Progression free survival is sensitive to the type and timing of assessments and is meaningless without a control group, so always requires historical control data. Use of any surrogate endpoint in trials for rare cancers is acceptable only if the new treatment is associated with dramatic changes in prognosis, ideally in the long term.

## New paths to drug use

**Large RCT in a frequent cancer with the target – Proof of principle – Toxicity**

**Uncontrolled (but formal) trial(s) in other (rare) cancers with the target**

**Off-label use in individual cases with the target**



## Conventional or unorthodox statistics?

It is important to consider the expected frequency or probability of the event or observation being measured in a trial, given the hypothesis underpinning the trial. The statistical foundation of a randomised trial is based on the null hypothesis: that there is no difference between the two treatments being compared. Randomisation ensures that any differences between treatment groups are due to chance, and allocating treatment on a double-blind basis prevents bias in assessments. The trial tests whether the observed results are compatible with the null hypothesis that the two treatments being compared are identical.

With conventional (frequentist) statistics, the advancement of knowledge in medicine is based on assuming that the dominant theory is true (i.e. the standard treatment is better) until sufficient evidence becomes available against this. Only evidence collected within one or more trials aimed at falsifying the dominant therapy can be used.

The problem is that outstanding efficacy is seldom observed with new drugs in cancer, so this makes large trials necessary to show that the new treatment is more effective. In addition, this approach cannot make use of external evidence or evidence in favour of an alternative hypothesis. This means that any knowledge or results outside the primary analysis of a clinical trial is ignored in the trial's design and analysis.

There are several recent developments in the design and statistical analysis of clinical trials to overcome these limitations, including: surrogate endpoints; new types of systematic review; and adaptive trials. Bayesian statistics provide one of the most important developments in trial analysis.

The concept of Bayesian probability is based on considering the probability that a hypothesis is true, given observation and prior knowledge. Frequentist probability looks at the probability of an observed difference based on the assumption that the experimental therapy being tested in a trial does not work. In contrast, Bayesian probability considers the

probability that the experimental therapy works or does not work, given the observed difference and prior knowledge.

It is commonly thought that frequentist probability is objective and provides a 'hard' approach to analysing experiments, while Bayesian probability is subjective and 'soft'. This is incorrect. They are simply different approaches to the meaning of probability and, most importantly, to the use of prior evidence, which is a key difference between conventional frequentist and Bayesian approaches. Frequentist probability makes no use of prior knowledge, whereas Bayesian probability makes considerable use of what is already known.

The disadvantages of Bayesian statistics are that they are considered to be somewhat subjective, arbitrary, and amenable to manipulation, with the fear that pharmaceutical companies could register drugs based on marginal benefits from trials. However, the conceptual advantages are that they reflect human reasoning, or 'common sense'. The approach is focused on estimates of effect. It provides a conceptual framework for medical decision-making and, most importantly, is transparent because it makes explicit any assumptions made during interpretation of results.

There are practical advantages to using Bayesian statistics to analyse studies in rare tumours. There is no need to set the sample size in advance, facilitating adaptive trial designs in which patients are enrolled until there is sufficient evidence in favour or against efficacy. Where strong *a priori* evidence is available and trial results are in agreement with this evidence, then a smaller sample size is sufficient and a trial can be stopped earlier, when appropriate.

The critical factor for the use of

Bayesian statistics is the availability of prior evidence, which should be transformed into a probability distribution. This evidence should be based on objective information using meta-analysis techniques drawing on a range of sources including randomised trials, biological and pre-clinical studies, case reports, uncontrolled studies, studies with surrogate endpoints, and studies in other similar cancers or in different stages of the same cancer.

Current approaches often make use of rational but informal integration of available knowledge. In contrast, use of Bayesian methods facilitates formal, explicit, and quantitative integration of available knowledge, using verifiable quantitative methods, sensitivity analyses and a focus on summary effect estimates.

In conclusion, a trial in a rare cancer requires more careful planning and protocol preparation than a trial for a more frequent cancer, because standard trial design and analysis techniques cannot be used. The design and methodology and the statistical analysis must be planned carefully in advance, making optimal use of available evidence.

*Question: Can genetic subgroups be considered in a similar way to rarer cancers? Is precision medicine inevitably more imprecise, from a statistical point of view, because of small numbers?*

*Answer: The more you try to tailor a treatment to individual patients, the less evidence you have because the patient numbers are smaller. I think that Bayesian reasoning has always been used in clinical medicine, drawing on information from a range of settings, including nonrandomised trials, case series and past experience with patients. In molecular subsets of*

*tumours we should make explicit use of Bayesian reasoning, using all information available from different settings. This is the core of Bayesian reasoning: what is the possibility that this drug works in this group of patients?*

*Question: Regulators sometimes suggest setting up clinical registries of patients with rare cancers as a source of external controls, which we often lack when we plan uncontrolled studies. Are there methodologies for doing this?*

*Answer: I think patients referred to specialist centres should have their data included in registries. There is a good example of this kind of registry in Italy, but it has not yet provided cases that are useful for proving efficacy. What we need to do is select data from unselected registries for cases that are comparable to those included in trials, and we need unselected historical controls. It is important to remember that, when we introduce a new treatment, the prognosis of subgroups changes. For example, cases of sarcoma today do not have the same prognosis as patients seen 10 years ago. The best approach is to maintain a population registry and to be able to abstract cases eligible for a new drug from that population base. Artificial intelligence could be used to interrogate large databases to identify historical controls.*

### Further reading

A consensus position on a set of methodological recommendations for clinical studies in rare cancers, developed by Rare Cancers Europe, co-authored by Paolo Bruzzi, was published in the *Annals of Oncology* (2015, 26:300–6).

To comment on or share this article, go to [bit.ly/CW84\\_RareCancers-TrialMethodology](http://bit.ly/CW84_RareCancers-TrialMethodology)



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Within the frame of its goal to improve the quality of life of women and men living with advanced breast cancer worldwide, the ABC Global Alliance has organized an event at the EU Parliament to increase awareness about working rights of cancer survivors and advanced cancer patients.

**A write-up of the event will be available at  
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# Breasts, cancer, and relationships: changing attitudes in central and eastern Europe

Breast cancer impacts on the way a woman sees herself and on how she is seen by her partner and society in general. It's getting easier to talk about, but are these conversations also happening in central and eastern Europe?

**Pawel Walewski** reports.

**W**hen Magda learned she had breast cancer, she felt it couldn't have happened at a worse time. She was coming up to 30, and had recently parted ways with her fiancé. "My

first thought was that I would lose my breast and no man would look at me ever again. I was going to forget about sex altogether."

Magda lives in Warsaw, Poland. She was right about losing the

breast – in fact she ended up having both her breasts removed. She was wrong, however, about what the loss of her breasts meant for her prospects of future relationships.

A few years on she met Peter



and they got married, and started a family. Access to expert counselling allowed them to have the conversation about how he felt about her body, and helped build the mutual trust and confidence that is an essential foundation for any relationship. “I was terribly afraid that he would leave when I stopped being attractive to him,” Magda recalls, “but it turned out that it was a much smaller problem for my husband than for me.”

The issues at the heart of Magda’s story – breast cancer, body image, sexuality, self-perceptions, the perceptions of others, and how hard it can be to talk about all of this – are common to societies across Europe. Recent decades have seen an increasing interest in exploring these topics in the professional and mass media, creating a virtuous circle in which it becomes easier to conduct these conversations in private and also to advocate for improving the counselling available to cancer patients through their health services.

But how far have these changes been limited to western European cultures? Do taboos against discussing cancer or sexuality at a personal level, and assumptions about gender roles, remain more of a problem in the countries and cultures of central and eastern Europe?

Agnieszka Jagiello-Gruszfeld is an oncologist from the Cancer Centre and Institute of Oncology in Warsaw, Poland. She has no doubts that perceptions of breast cancer in the country are changing: “It used to be a larger taboo topic, so women also lived with this stigma in the family. Husbands were only responsible for the logistics: they would bring their spouses to clinics, and they would

pick them up after chemotherapy, almost as if cancer was not a part of their deeper relationship.”

Today, she says, she frequently sees couples at her consultations, and stories like Magda’s are not unusual. Many women are over-fearful about the impact a mastectomy might have on their desirability and sexual relations, she says. “When couples are sitting across the desk, the male partner often reprimands his wife or fiancée: ‘What are you worried about? Don’t even think that I might be dissatisfied! Your health is the most important thing to me’.”

**“Women may fear they are being rejected when the problem may be their partner is not sure how to respond to the struggle they are going through ”**

Mariola Kosowicz, a psycho-oncologist from the same Warsaw cancer centre, agrees with her colleague, that women sometimes fear they are being rejected, when the problem may simply be that their partner is not sure how they should respond to the struggle she is going through. She cites the example of a woman who phoned in to her live radio broadcast, who complained that, ever since she had been diagnosed with breast cancer, her husband would not even touch her.

“I asked if she had talked to him

about it. The woman replied that she hadn’t. She believed that if her husband did not want to touch her, it was clear he would not change his mind. I advised her to ask him what he was afraid of. Did he feel aversion, or maybe he was just afraid to put his wife in an uncomfortable situation? Maybe he didn’t want to give an impression that he was only thinking about sex.”

That’s not to say that such fears are never justified or rooted in reality. Kosowicz cites the case of a woman who brought her husband to a consultation to tell him that, once the surgery was over, he would no longer be able to make love to her in the position he liked best without causing her pain. When the man asked his wife why she had not said anything about this at home, recalls Kosowicz, she reminded him of the time she did not want to make love, and he told her off, saying she had to remember other women would want to. “This fear was now back.”

“This disease is a test of how couples deal with a crisis,” says Kosowicz. “If a relationship is mature and built on something more than physical attraction, one can immediately see a different bond between the partners.”

### A widespread problem

How many relationships fail the test is difficult to know, but advocates across the region believe the problem is widespread.

Stanislava Otasevic is president of the breast cancer advocacy group Europa Donna, in Serbia. She says, “No statistics in this field are available, but it’s not rare that relationships become deeply damaged.”

Donjeta Zeqa, her counterpart in Albania, points out that failed relationships cannot anyway be measured simply in terms of separations and divorces. “In Albania people care about the opinions of others, and sometimes couples stay together just to not let others talk about them.”

“Typical Balkan mentality!” she adds.

## **“Some men help their wives with housework, but only on rare occasions do they understand what the wives expect from them emotionally”**

Alena Kallayova, a medical professional who works with the Slovakian breast cancer patient advocacy group OZ Amazonky, says that the situation is particularly bad in the smaller towns and in rural areas. “We have information showing that many women feel ashamed of their disease, and even their closest relatives do not talk to them about it. They feel they are not a part of the local community anymore.”

Her point is echoed by Otasevic. “In my country [Serbia], women treat the disease as their fault, and they worry that they wouldn’t be attractive to their partners,” she says. “Even medical professionals diagnosed with breast cancer prefer to speak about it to their fellow females,” adds Otasevic, who has

herself worked as a health professional for almost 30 years.

Anna Kupiecka from Warsaw understands that feeling. When she was diagnosed in her mid-40s with an aggressive breast cancer requiring a mastectomy, she felt it would be best to part ways with her partner. “Since it was so difficult for me to live without a breast, I was sure that he would not be able to bear it, and that’s why I preferred to let him go,” she says.

She believes that the image of a strong heroic woman is one many feel they should live up to, even when they have a serious illness – coping with demanding jobs, caring for their homes, raising the children, and still playing the chief caring role in relation to their partner, advising them to get screened for cancer themselves. “They won’t admit to anyone that they also cry, feel pain, or fatigue.”

Zeqa, from Albania, argues that her country’s macho culture makes it difficult for women to feel they can talk to their partners about their breast cancer. “Generally, in the Balkans, the global phenomenon of gender inequality reveals itself in highly normalised practices of domestic violence against women, rape shaming, enforced economic dependence via unequal resource distribution, and many other historical and contemporary dimensions. In this condition, women in Albania sometimes feel frightened to talk about breast cancer with the partner.”

Kallayova argues that, in Slovakia, the men often do try to help out, within the boundaries of what is seen as ‘their role’, but they often fall short when it comes to providing emotional support. “Some men help their wives with housework,

such as shopping, cleaning, cooking, as they feel that they are the head of the family, but only on rare occasions do they understand what the wives expect from them emotionally and psychologically, taking active interest in their treatments,” she says.

Her point is echoed by Elena Volkova, a breast cancer survivor from Moscow, Russia. “Our men know how to support their women who have a headache, but they have no idea what to say if someone has breast cancer. People don’t know how to talk openly – what to say, and when.”

This may not be so surprising, as Otasevic from Serbia comments, because “family members do not have the opportunity to learn what their roles are, and how they should behave.”

She argues that the educational system has an important role in educating girls and boys about gender relationships, and says the church could also influence behaviours for the better if it chose to, though currently, she says, “the Church does not pay attention at all in this field.”

## **“People don’t know how to talk openly – what to say and when”**

Zeqa says that, in Albania, Europe Donna often collaborates with churches and mosques, so that priests and imams encourage frank conversations between men and women with breast cancer. “Of course nothing can happen magically,” she agrees. “Everything needs time and hard work.”



### Doctors don't ask

Her point about time and hard work may hold as true for the culture of medicine as it does for society at large. While Magda and her partner did get the benefit of counselling many years after her diagnosis, the topic was never mentioned at the time of her treatment. She felt the focus was on saving her life, and it had seemed inappropriate for her to broach such a personal subject. Her doctors did not ask. Looking back on it, she wonders why.

Zbigniew Izdebski, from the Department of Counselling and Sexology at the University of Zielona Gora in Poland, believes the answer is obvious: “Most doctors have never been trained in sexology. They don’t know what the norm is, what to ask, or how. This topic makes them feel awkward, so if the patient does not

dare to speak up, they will not be the first to raise it.”

Lack of time tends to be the reason most commonly given by doctors for failing to address this issue, says Izdebski. Oncologists have too little time to spend with each patient, and need to limit themselves to what they feel are the most important matters in order to find time for everyone. But they also feel they lack the expertise needed to offer help and advice in this area.

### Investing in psychosocial care

One solution would be to invest in specialist counselling services such as psycho-oncology, which patients can access directly or by referral from their oncologist. Recent decades have seen an expansion of this spe-

cialism, but countries of eastern and central Europe are generally lagging behind, according to a 2014 survey conducted by the International Psycho-Oncology Society within the framework of the European Partnership for Action Against Cancer (*Psycho-oncology* 2017, 26:523–30).

**“The network of psychological advisers is weak, old fashioned, and not up to the job... Women don’t find the support they need”**



Of the 27 countries for which data was supplied, 21 included psychosocial oncology care in their national cancer plan, but only five of these countries were from central and eastern Europe (Czech Republic, Estonia, Hungary, Lithuania and Slovenia). Of these, only Estonia and Slovenia reported having specific budgets for the service.

While these findings give some indication of disparities in provision of psychosocial care across Europe, they will also reflect disparities in how far such services have been formally integrated into cancer plans. The Profile article on Romanian psycho-oncologist Csaba Dégi in this issue of *Cancer World*, 'Playing catch-up with the West', gives some insight into the obstacles to making progress on this front (p 22).

There are also issues of quality. The same survey indicated that, of the eight countries that reported having published or nationally recommended guidelines covering psychosocial oncological care, none were from eastern or central Europe. A separate study conducted five years earlier had found that only seven countries in Europe recognised the need to improve their psychosocial oncology care, and had a method for evaluating the plan, its objectives and outcomes, of which Estonia was the only one from central or eastern Europe (*Psycho-Oncology* 2012, 21:1027–33).

The absence of guidelines and quality control is likely to translate into substandard services. Otasevic comments, for instance, that in Serbia, the network of psychological advisers is weak, old fashioned, and not up to the job. "Women don't find the support they need," she says.

Elena Volkova, treated for breast cancer in Moscow, gives an equally

## I'm a partner, what can I do?



Bartosz Polinski spends a lot of time advising men on how they can talk to their partners who've been diagnosed with breast cancer, so they can better share the monumental task of learning about the disease and the treatment options, and navigating through the Polish cancer care system.

Bartosz is not a psychologist. He's an IT specialist who took up the cause of his sister Agata, after she was diagnosed with breast cancer aged 27, and her boyfriend at the time left her. (Ironically her boyfriend was a psychologist. "Today it might amuse me, but back then I was not happy," she says.)

Using his professional experience in managing complex projects, Bartosz

threw himself into the task: searching Google for credible information; reading and summarising clinical reports, which Agata herself found too stressful to do by herself; seeking expert second opinions; accompanying his sister to consultations; and disarming the proverbial 'bombs' that he says the Polish oncological care system would throw at them.

The partnership almost fell apart, however, over differences about what they were trying to achieve. For Bartosz, maximising his sister's chances of survival was all that mattered, while Agata placed a high premium on avoiding a mastectomy, and insisted that her brother could not advocate for her unless he backed up her priorities, "Because this is a problem that concerns my body."

Today, Bartosz and Agata jointly run Alivia, a Polish foundation that seeks to educate cancer patients and give them the tools and means to make decisions regarding their own health, based on reliable information.

The foundation, and especially Bartosz himself, frequently receives calls from men seeking information about how to care for partners diagnosed with breast cancer. They often feel embarrassed, says Bartosz, asking whether it is fair for them to disturb the wall of privacy their partner hides behind. But these guys, says Bartosz, are just like him: task-oriented, with a managerial approach to life. "If something has to be taken care of, they want to be the first to do it."

scathing account of the quality of psychological 'support' she received. "The psycho-oncologists we have in the clinics are not very good. I tried to speak with some of them and they were not interested in patients. They just say everyday phrases like: 'How do you feel now, calm down, everything happened already, you just need to think about your family, your kids,

your life... and so on'. They speak in that way, as if you are going to die. They don't believe you can live a happy and long life after cancer. This is the main problem. I think that only when a woman believes in herself, can she be happy with her partner."

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## ***The focus of my leadership***

Last October, at the ESSO38 Congress in Budapest, I took over the Presidency of the European Society of Surgical Oncology for a term of two years.

The surgical oncologist is in the centre of cancer care, leading the multidisciplinary cancer management teams, and surgeons have a pivotal role in diagnosing and treating cancer patients. Surgical oncology is an independent subspecialty with its own curriculum, fellowship, and specialty examination (UEMS Board). As part of the ESSO Strategic Plan I intend to focus my leadership objectives around:

- Surgical oncology European accreditation,
- Certification of surgical oncologists and breast cancer surgeons,
- Global collaboration with partner societies,
- Promoting diversity in surgical oncology leadership,
- Mentoring young surgical oncologists and promoting the introduction of new educational methods and social media.

In Europe we have only 12 countries with a national surgical oncology society, and surgical oncology is recognised as a subspecialty in only one in three European countries. The accreditation of surgical oncology is performed by a variety of bodies, including national institutes, ministries and regional health boards. There is no universal and unique training and accreditation system in surgical oncology and breast cancer surgery across Europe. Together with its partner societies, ESSO has a key role in promoting and working on certification. It is my strong belief that patients should be treated by accredited cancer surgeons, no matter where in Europe they live.

The Global Forum of Cancer Surgeons was formed under the auspices of the Society of Surgical Oncology (USA) in 2017. It aims to work with global cancer advocacy groups and organisations to address the lack of surgical leadership and

inequalities in surgical care for cancer patients. ESSO is a founding member of the Global Forum, and intends to further develop its goals and mission to provide a voice for cancer surgeons.

In my tenure I intend to further promote diversity in our leadership. Diverse surgical leadership promotes co-operation and decreases conflict. It has even been reported that mixed surgical teams lead to less medical error. I am proud to say that the ESSO leadership has already a 30% female representation, and that proportion will continue to grow.

ESSO offers a platform for young surgical oncologists, the ESSO Young Surgeons and Alumni Club (EYSAC), with benefits such as career support, networking, fellowships, courses, and masterclasses. My intention is to expand this towards comprehensive mentoring of young surgeons working in cancer care. A web-based survey of the ESSO-EYSAC community regarding the quality of life of surgical oncology residents across Europe showed a positive screening for depression in 51% and burnout in 25% of the respondents, with a lack of mentorship. It is our society's duty to continue to assess the young ESSO community, to raise awareness and to talk about the problems. I am keen to promote combining clinical activity with research and academic interests to increase job satisfaction, and to promote mentorship programmes addressing all complex problems related to a career in surgical oncology.

By developing close links with patient support organisations, my view is that cancer care should be patient led. Patients all across Europe should have access to specialists, trained and accredited in surgical oncology.

The new ESSO Board for 2018–2020 is keen to work towards these goals together, and prepared to face the 'grand challenges' in surgical oncology: "The surgeon should not only act as a technician but as a real scientist, being able to understand the results of basic and clinical research beyond the surgical domain," (Umberto Veronesi, 2012).



# The patient advocates will see you now

## *Cancer groups trial the AIDS model for interacting with industry*

It's easy to say you are patient centred – until you are asked to spell out what that means in terms of your processes and practice. Last summer 11 patient groups invited nine pharmaceutical companies to join in a frank discussion about how to make 'patient centred' a reality. **Anna Wagstaff** reports on how it went.

**“M**ost of us in this room will have participated in pharma advisory boards. They're nice. You get to see faces you haven't seen for a while – a bit like family reunions. But the topics covered are rarely the ones

we feel address the main needs and wants of patients. And there is no follow up, so we never know what the outcomes are. That has to do with the fact that we do not set the agenda, and we are not the ones who send out the invitations.”

Ananda Plate, chief executive of Myeloma Patients Europe, was addressing around 100 European myeloma advocates, gathered at their 2018 AGM, to make the case for changing the way they interact with industry in favour of a model devel-

oped by the HIV/AIDS community.

The traditional pharma advisory boards she was referring to are meetings convened by companies, typically at the instigation of marketing departments, to help them with issues that crop up in developing a product, generating data, and creating educational and promotional materials.

The new approach she was advocating – community advisory boards, organised and driven by patient advocates – operate in the reverse direction. Their function remains to enable advocates to offer expert advice to companies. But their aim is to assist companies in their efforts to most effectively meet the needs of the patient community. It is the advocates who choose the topics on the agenda, and it is they who invite companies to send representatives with the expertise and authority to discuss how both sides can work better together to help achieve shared goals.

In June, Plate got her first taste of what that means in practice, as a key organiser and participant in the first ever haematology community advisory board (Hem-CAB), which took place in Stockholm, immediately after the European Hematology Association congress.

Formally convened by Myeloma Patients Europe, the meeting brought senior representatives from nine pharmaceutical companies active in haematology together with leading people from 11 advocacy networks, covering leukaemias, lymphomas, myelomas, and myelodysplastic syndrome as well as some non-malignant blood disorders. The companies contributed equally to cover the costs of the meeting.

The agenda was developed by the advocates and addressed three top-

ics of especial concern to patient communities:

- Increasing patient engagement at all stages of industry research and development
- Strengthening the quality of evidence generated by patient organisations, and using it to improve industry decision-making
- Legal compliance issues that hinder effective collaboration between patient organisations and industry.

Invited to the table were company representatives who had the authority to conduct meaningful discussions on these topics. They were offered the opportunity in advance to make suggestions for the agenda.

The discussions aimed at agreeing actions to try to move forward on the topics being addressed. To ensure all sides felt they could speak frankly, the details of the discussion remain confidential. The key point, however, is that they are minuted and act as a 'to-do' list for both sides, who will have to report back to the next CAB meeting on what they did to follow up on commitments made at the meeting, and what impact those actions had. A redacted set of minutes agreed by all sides are made publicly available to allow patient communities and the public to get a general idea of what was discussed and decided. These are précised here (see boxes), and can be read in full on the CML Advocates Network website, [bit.ly/Hem-CAB\\_Report](http://bit.ly/Hem-CAB_Report).

The success of the initial Hem-CAB can only be judged in the light of what changes are implemented in practice as a consequence. But the fact that this CAB happened at all testifies to the growing maturity of patient advocacy. It also provided a valuable learning experience for

people on both sides of the table, and offers a template that other cancer patient communities can adapt to their own needs.

### Born from necessity

The CAB model was developed by HIV/AIDS advocates in the US, as part of their legendary battle to put the interests of the patient community at the centre of efforts to tackle the epidemic. European CABs (ECABs) have been run by the European AIDS Treatment Group (EATG) since the early 1990s.

That community-led approach remained confined to AIDS advocates until 2016, when, with help and encouragement from EATG activists, it was introduced into the cancer community by the CML Advocates Network (chronic myeloid leukaemia), which now convenes CML CABs twice a year.

CML advocates had been immersing themselves in the science and organisation of treatments and trials since STI-571 – later named Glivec – started offering them a lifeline nearly 20 years ago. They developed the concept of evidence-based advocacy and, for 16 years, have been meeting with clinicians and drug developers for catch-up sessions, while training new layers of advocates across Europe and beyond.

Other cancer advocacy groups have been watching and learning, but none can yet match what the CML advocacy community has built, as Plate readily admits.

“For quite some time we had followed the CABs that were out there in the HIV community and CML community, and we were quite keen to replicate this in myeloma,



but were not sure whether we were ready yet from our community side, so we decided to watch and see what was happening,” she says.

As it turned out, the myeloma network did not have to go it alone. “Within the haematology and the cancer community there was a shift towards everyone trying to collaborate and avoid duplication, and join forces and so on. So we came up with this idea of having a cross-disease CAB.”

Within the haematology community, the catalyst was the establishment of EuroBloodNet, the European Reference Network for rare blood diseases, which under EU rules must have a patient advocacy group, which provides representatives to the EuroBloodNet board. These seven advocates “formed the brain of the Hem-CAB,” says Plate.

A parallel move toward greater collaboration had been happening over the same period within the wider cancer advocacy movement. A group of 21 European/international cancer patient advocacy organisations joined forces as WECAN (Workgroup of European Cancer patient Advocacy Networks) to “collaborate, align and develop joint projects of the European cancer patient community towards all stakeholders, and to provide a resource for the participants and external organisations.”

One of their early projects involved engaging collectively with pharmaceutical companies to reduce the burden created by differing and often unfair requirements their legal departments impose regarding the terms on which their companies can support the work of patient groups (see [wecanadvocate.eu/rapp](http://wecanadvocate.eu/rapp) and [mpeurope.org/legal\\_agreements/](http://mpeurope.org/legal_agreements/)).

These developments formed the

## Who was at the table?



Present at the Haematology Community Advisory Board on the patient side were the seven representatives elected to the patient advocacy group of EuroBloodNet, the European Reference Network for rare haematological diseases, together with delegates from the 11 advocacy umbrella groups listed below:

ALAN, [acuteleuk.org](http://acuteleuk.org) – acute leukemia

CML Advocates Network, [cmladvocates.net](http://cmladvocates.net) – chronic myeloid leukaemia

CLL Advocates Network, [clladvocates.net](http://clladvocates.net) – chronic lymphocytic leukaemia

EFAPH, [efaph.eu](http://efaph.eu) – European Federation of Associations of Patients with Haemochromatosis

EHC, [ehc.eu](http://ehc.eu) – European Hemophilia Consortium

ITP Support Association, [itpsupport.org.uk](http://itpsupport.org.uk) – immune thrombocytopenia

International MDS Alliance/MDS UK, [mdspatientsupport.org.uk](http://mdspatientsupport.org.uk) – myelodysplastic syndrome

Lymphoma Coalition Europe, [lymphomacoalition.org](http://lymphomacoalition.org) – lymphoma

MPN Advocates Network, [mpn-advocates.net](http://mpn-advocates.net) – myeloproliferative neoplasms

Myeloma Patients Europe, [mpeurope.org](http://mpeurope.org) – myeloma

PNH European Alliance, [pnhuk.org](http://pnhuk.org) – paroxysmal nocturnal haemoglobinuria

Thalassaemia International Federation, [thalassaemia.org.cy](http://thalassaemia.org.cy) – thalassaemia

Present from the industry side, with two representatives each, were: Alexion, Celgene, Janssen, Jazz Pharmaceuticals, Novartis, Pfizer, Servier and Takeda. In addition, the meeting was supported by AMGEN who could not send a representative on that date.

backdrop to the Hem-CAB. “We felt we were a community strong enough to have a united voice and go for it. It was not possible before, because everyone was working in their own world and duplicating and doing everything that everyone else was doing and spending money in a crazy way for exactly the same things,” says Plate.

“We wanted to run a CAB, we knew there were topics that were cross disease, that were not drug-specific, so no commercially sensitive stuff being discussed; no reason for companies not to speak openly. So we decided to give it a try.”

## It takes two to tango

CABs can only work if both sides see value in participating. And while companies are always happy to declare themselves to be patient-centred, not all welcome patient advocates having input into how they conduct their businesses, while others have simply been less exposed to this sort of engagement.

Plate sums up her perception of the range of experience on the industry side.

“You had three categories. The well-prepared – you could tell that these people had been at a CAB before, and

### What they agreed: Patient engagement in R&D



Patient organisations said there are only a small number of documented cases where the input provided by the patient organisations has influenced decision-making in industry R&D, and they felt that the insights of patient experts and patient organisations could be included more systematically and effectively by industry researchers, e.g. in terms of defining research priorities and trial designs, as well as contributions to data safety monitoring boards and to clinical trial participants. One proposal discussed was the implementation of a 'scorecard' system that would allow patient organisations to monitor the patient involvement practices of companies, and would also allow companies to keep track of their own performance in this area. All agreed that a more structured approach to the input of the patients' opinions was needed. Also, more involvement in the identification of needs was required so that these needs can be focused on subpopulations and groups. The patient groups said they want to be included in protocol review for phase II and III trials, but not necessarily phase I. Data safety committees and investigator meetings should also include patient representatives. As a platform for collaboration, CABs by invitation of the patient organisations were seen to be one of the most effective platforms to bring in patient experts' skills and knowledge, rather than any other affiliation with the company or otherwise.

came with clear positions and questions; others, who tried to get away with generic, non-specific statements, and discovered they couldn't; and some who had no idea what they were getting into, and obviously felt quite uncomfortable not being in control of the agenda."

The three companies – Takeda, Novartis and Janssen – that agreed to speak to *Cancer World* about what they got out of the meeting were among those with previous experience of the CAB model.

### Multiple companies

This, however, was one of the first community-driven meetings they had attended that involved several companies all sitting in the same meeting. The opportunity this offered to hear

what others are doing across the spectrum of haematological diseases was an important plus point, says Sanja Njelic, Head of Patient Affairs for these patient communities at Takeda. "It enabled us to engage with patients with different haematological malignancies, as well as with the companies who have a similar strong interest in the haematological malignancy setting. There was a huge opportunity to discuss big topics of mutual interest."

"I think that is a unique aspect of this meeting," agrees Louise Huneault, who holds a similar brief at Novartis. "Every company did their little eight-minute presentation, so it was interesting for us to see what other companies were doing and get some ideas of best practice that we may also wish to consider, moving for-

ward. It was very enlightening from that perspective."

### A systematic dialogue

Daniel de Schryver, their counterpart at Janssen, was there primarily to present his positive experience of working with HIV/AIDS ECABs for the best part of two decades, and to encourage all the companies to embrace this approach.

The great thing about the CAB model, says De Schryver, is that it is not managed by the industry.

"The approach is the other way around, and therefore more systematic, by definition, because the agenda is put in a regular way by patient advocates, not depending on your own calendar, as a company. It is more regular, and in my opinion it is a good approach. The success stories are clear."

"It's the sustained conversations that are critical," says Huneault. Her experience of the twice yearly CML CABs is that the companies and the patient groups commit themselves to a list of actions. "When we meet again we report back on the progress that we have made; the barriers that we've run into; other things that have cropped up that we need to discuss."

"This is why a critical success factor to this model is sustained and regular contact that has actions attached to it. Otherwise it's just some nice talk."

The CML model has delivered this, says Huneault, and she is confident that that Hem-CAB will do so too, especially as some concrete actions were suggested at the first meeting.

### Common issues

Companies have a clear interest in getting feedback and advice in relation to their own specific products, but those discussions cannot be done within a multicompany meeting for

reasons of commercial confidentiality. The strong attendance at this first Hem-CAB meeting indicated that companies could also see value in discussing common issues regarding how to better align the industry actions with what patient communities want.

“The dialogue was extremely constructive because the agenda items were very relevant and there was a very collaborative atmosphere,” says Takeda’s Njelic. The big issues, including patient engagement in research and development, access to care, and digital solutions, are cross-cutting topics that will be increasingly important in the future, she argues. “Only by moving together with other healthcare stakeholders in a systematic way can we start to move the needle. So CABs provide an important platform for figuring out how we can work together to tackle these issues and also come out with some viable solutions that are acceptable to all.”

For Janssen’s de Schryver, it’s a no brainer. The healthcare environment is focused increasingly on outcomes and on value, he says, so if you want to succeed, you need to be working with patients to understand what they value and how they rate outcomes.

“We are doing this because we believe it is the right thing to do, not from a sort of ethical, moral perspective, but because it will bring better solutions and provide better outcomes. We are convinced.”

### A question of trust

Trust issues may also have been a factor companies weighed up in deciding the value of attending the meeting – did they trust the advocates to organise a constructive conversation, and would the meeting help build advocates’ trust in them? Novartis’s Huneault makes the point that pharmaceutical companies are

### What they agreed: Patient-generated evidence



Patient organisations wanted to know from the companies how they take advocacy-generated evidence into account, and what evidence industry needs from patient organisations to effectively influence their own decision making. They asked how patient organisations and industry can collaborate towards a more systematic methodology on the generation of patient evidence. The participants acknowledged the fact that patient communities generate different evidence from what companies or researchers may collect and generate, and their research has different motivations. This unique information needs to be incorporated into industry processes.

Also, a closer feedback loop is needed between industry, research and patient groups. Currently, patients contribute to research in many different ways, but find it difficult to access the results or outcomes. The CAB model was recognised as a feasible avenue towards better integration of all stakeholders’ work.

Several company representatives urged patient organisations to develop and improve their publishing practices. Indeed, patient organisations have not been systematic enough in publishing and disseminating their results and research findings, even if the quality of such research matches international scientific standards. Also, patient organisations believe that they can do as good a job as agencies hired by pharmaceutical companies to do the kind of research that collects patient needs and generates patient evidence.

An important proposal and agreement at the meeting concerned the possible establishment of a ‘research institute’ or ‘office’ by patient organisations, which could be responsible for the coordination and pooling of patient-generated evidence, its dissemination and authoring, and which could also control the ownership of data so generated. There was agreement that patient organisations should increase their capacities in this area by building better infrastructure/collaborative models in a way that allows for good data collection and proper analysis and publication in peer-reviewed journals for all stakeholders to use as a reference.

used to having challenging conversations with payers and health technology assessors, but not with the patient community. “This is new. Challenging conversations with empowered patients who are very knowledgeable – patient opinion leaders – this is a different stakeholder.” Companies need to send representatives who are “able to manage what may be a chal-

lenging conversation and respond appropriately,” she adds.

It is also in the interests of the patient advocates to build industry confidence that the discussions will be constructive and in good faith. In this regard, the involvement of the CML Advocates Network paid off. Jan Geissler, a co-founder of the CML Advocates Network, organises



## Patient Voice

the CML CABs and played a leading role in developing the Hem-CAB agenda and bringing companies on board. “There were no concerns from our side, because of knowing and trusting those who were organising the CAB,” says Takeda’s Njegic. She appreciated the efforts Geissler made to consult company delegates over the objectives and expected outcomes of the meeting.

If anything, the board meeting was a bit too polite, says Huneault. “In the one-to-one CABs we’re past the honeymoon stage. We’re now rolling up our sleeves and really getting down to the topics of true interest, and the patients are very persistent in not letting the sticky issues off the agenda. The conversation is very fruitful, very honest, very transparent.”

She hopes that Hem-CAB will go the same way, “so that we can get into the nitty gritty.”

### Did it work out?

“I thought they did pretty well,” says Tamas Bereczky, a veteran of the AIDS ECABs who had offered his advice and experience to the Hem-CAB and was present as minute taker.

“I enjoyed the honesty and the fact that company reps could sit at the same table and talk. I think that was a great achievement that hardly ever happens. Hem-CAB was able to successfully create this neutral space, which is what we always preach, where people can meet and talk about things that matter – about science and policy. I like the fact that the agenda was controlled by the community and they could keep to the point, and maintain a high-level conversation around issues that matter. I was very happy to see that.”

De Schryver, from Janssen, was

also pleased with how the meeting went. “The patient advocates had really prepared their case. They were very united, they were organised, they were singing from the same songbook, and with a clear vision.

“And I felt there was willingness [on behalf of the companies] to say, ‘OK we are listening to you and these things can make sense.’ My takeaway was that most of them were convinced. Smaller companies said, ‘We don’t know yet, because we don’t know how we can do that.’ That’s a fine detail. I felt most companies were agreeing and saying ‘let’s find out how.’”

**“I enjoyed the honesty and the fact that company reps could sit at the same table and talk. I think that was a great achievement that hardly ever happens”**

Sanja Njegic, from Takeda, believes that the collaborative atmosphere will have encouraged other company representatives, with less experience of working with patient advocates, to get more involved in similar initiatives.

“I think it had a very positive snowball effect. Companies have a different organisational maturity when it comes to patient engagement – some of us have been working with patients for 10 years; others just came into the picture. For example, those who were not involved in the WECAN initiative

on legal agreements indicated that they were very interested in being part of that.”

Within Takeda she has already started to work with legal colleagues on actions arising from the meeting. “We definitely started to work on the simplification of some of those legal contracts that we have with patient advocates.” She has also strengthened discussions with the company’s R&D team about the right way to involve patient advocates systematically, from a European perspective. The emphasis in CABs of involving people with key roles not just in patient affairs, but also the legal and medical side of the company, helps speed up internal processes, adds Njegic.

Huneault of Novartis also highlights progress with concrete actions. “We came up with some really good ideas together in terms of how we might tackle some of the issues that were brought forward in the Hem-CAB.” This includes the potential to use more patient-led evidence from such things as surveys and patient preference studies. “The haematology community are very advanced, and they are generating their own evidence to move the scientific conversation forward. We are very excited about this and were keen to have a discussion with the patient community about how we develop models where we can help build their capacity.”

### A good start

Patient advocates were also positive about the meeting. Plate was proud of how the patient advocates performed. “There will always be patient advocates who are more quiet and shy, because they are not used to the setting. The moderator

[an expert with experience from the European AIDS Treatment Group] tried to open them up, and shut up the ones who spoke too much. He did a good job.” Also important was the advocates’ pre-meeting the previous evening – another tip from the HIV community. “That was super helpful, because after that we were all very aligned.”

However, Plate adds a note of caution. “I was happy, but it will be easier to answer when we sit down at the next CAB and see what has changed. We had some very well prepared industry reps in the room. But we had others who seemed to think this was just a tick-box exercise. We don’t want someone just sitting there saying pretty words.”

She stresses, however, that both sides have responsibilities. “The whole burden shouldn’t just be on industry. On our side it is hard enough to get a group together that knows enough to talk in depth about everything and be able to put time into what we want to discuss.”

MPE is now planning to organise single-company myeloma CABs sometime in 2019, and has been piloting a patient advocacy training course.

Sophie Wintrich was at the Hem-CAB on behalf of patients with myelodysplastic syndrome. She has been chief executive of MDS UK Support Group for 10 years and is on the board of the (global) MDS Alliance. She is also adopting a ‘wait and see’ policy before pronouncing on what was actually achieved, but felt very positive about the way it went, and the possibilities it could open up.

Wintrich particularly appreciated being able to discuss issues that matter to her patient community with a group of senior company representa-

## What they agreed: Compliance issues and legal challenges



The patient organisations asked each of the companies about: how to create an environment where a trusted and safe collaboration is possible without overburdening the patient groups with excessive regulation; what approach each company takes to strike an acceptable benefit/risk balance; and what the patient community can do, on its side, to reduce compliance hurdles for industry. Some companies have already started a process to streamline their internal processes and documents. Other companies have now been made aware of the challenges.

Addressing this issue has been the focus of the WECAN Project on Reasonable Legal Agreements (see [wecanadvocate.eu/](http://wecanadvocate.eu/) and [mpeurope.org/legal\\_agreements/](http://mpeurope.org/legal_agreements/)), which was initiated by the patient community in oncology, working in collaboration with a workgroup of legal and compliance officers from multiple companies. Both sides at the Hem-CAB agreed that the WECAN project is in a unique position to identify the key interests of patient organisations and advocates that need to be protected when signing agreements with the pharmaceutical industry. Companies that are not yet involved in this project were urged to join.

The discussion also included some considerations around the fair market value of, and remuneration for, the work of patient experts and patient organisations. This is a particularly sensitive issue in some settings in Europe, which is further complicated by different industry rules and standards. This topic will be discussed further with the Hem-CAB stakeholders in future meetings, based on a proposal currently being worked out by WECAN.

One proposal concerned the setting up of a training course or capacity building resource from patients to companies to educate case workers and decision makers in different industry departments about the real-life applicability of legal and compliance processes in patient advocacy. Other actionable points from this part of the meeting included inviting legal and compliance persons to the next Hem-CAB meeting, putting together a catalogue of hurdles and challenges, developing contracting templates (WECAN is working on relevant guidelines), and organising a ‘roadshow’ by patient groups for companies to discuss current challenges.

tives who are tuned into the European regulatory environment and cultural attitudes. Her experience has been that, even when companies are headquartered in Europe, decisions on trial surveys or protocols are driven by US perspectives.

“They tell us they’ve checked with patient advocacy groups, but they’ve

checked with US groups, and the US groups are not as involved or advanced in terms of their ‘critical friend’ attitude towards industry. We advocates in the EU interact with industry in a slightly different way.”

The CAB offered a great opportunity to tackle tricky issues, she adds,

such as the compliance contracts companies expect patient advocates to sign. “So that was an opportunity to put it on the table openly and realise we are all struggling with the same thing, and if we as patient groups give you the opportunity to say it, you may then feed that back internally to your colleagues and hopefully improve matters.”

“Above all”, says Wintrich, “it was a great learning environment, for both companies and advocates. Advocates could show companies that they expect the same best practices from everyone, while companies could voice their frustrations with the patient advocacy world.” It was also a welcome opportunity to learn from other advocates.

**“So that was an opportunity to put it on the table openly and realise we are all struggling with the same thing”**

Her one reservation is the extent to which discussions within the Hem-CAB filter into the wider consciousness and practice of the companies. “I’ve spoken to other people in some of the companies since, and they are not aware of the Hem-CAB.”

Wintrich is very interested in exploring the possibility of an MDS-only CAB, but needs time to build capacity among advocates. “We are still making baby steps in that regard,” she says. As she points out, the CML community has an advantage of being younger on average and less debilitated by disease.

The MDS Alliance will also need to consider the divide between the US and EU mentalities. “It may only work with European participants,” she says. “I think the US ones would feel a little uncomfortable.”

For Michael Rynne, board member of the chronic lymphocytic leukaemia CLL Advocates Network, the big issue for patients is access to prognostic tests prior to treatment as well as access to the newer drugs. This is a problem not only in his home country Ireland, but across much of Europe. Access issues were not on the agenda for the first Hem-CAB, and would probably need to be tackled company by company because each drug is different and there is a need for commercial confidentiality.

Nonetheless Rynne gained a huge amount from the Hem-CAB. “I learnt that even though there are differences in diseases, there are similarities in how we interact with pharma. What was interesting on a European level was that patients organisations can work together, looking at the same goals, whether pharma were there or not. When pharma were involved, we were able to ask questions, and I was asking on behalf of all the advocate organisations. And I thought that was a very good concept.”

Having access to more senior company representatives, who were able to answer questions and make commitments, made a big difference. “I’ve been involved with the CLL network since 2014. Fairly often we have phone conversations with local representatives. We often ask the companies about how it’s coming along, and they never give a straight answer, probably because they don’t know. We haven’t really entered that space where we can ask, ‘When is this drug going on compassionate access?’ That’s the space we want to be in. So

we need to be able to talk to the senior people.”

Rynne believes the CLL Advocates Network will use what they learned from this experience to improve the quality of their interactions with industry. “What I came away with is that we now know that pharma want to work with us, so it is a question of how we can work together to make things run a lot easier.”

### Highly recommended

Would these patient advocates recommend the CAB model to other cancer patient groups?

“Absolutely,” says MPE’s Plate. “It’s a way of making sure that the needs and wants of patients are addressed, and to put pressure on important topics in a more systematic way. This is a effective way of turning around the system and doing it from the patient point of view. It’s also a good way to train the community. I absolutely recommend it.”

“It’s the way to go,” agrees EATG’s Berezky. Training and capacity building will be needed to develop layers of advocates who can adequately discuss trial protocols, biomarkers, quality of life measures and survey techniques. As he points out, patient advocates are driven by the powerful motive of wanting to stay alive. “Learning, self-education and self-empowerment are a brilliant way to cope.”

Is years of experience and expertise a requirement to get involved? Certainly not, says Berezky. “This is a process. You cannot expect the patients to sit in these meetings, all of them, with the same standard of knowledge. It is just happening now, as we speak.”

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# When more sleep won't do it: tackling cancer-related fatigue

Cancer-related fatigue affects many people, before, during and after treatment. It can have a seriously debilitating impact on lives, but effective interventions have so far proved hard to find. **Sophie Fessl** explores what might be causing the condition, and asks healthcare providers and patients about how they manage it.

**“B**efore cancer, I did not know fatigue. Now, I live my life at half energy and am very tired and depressed on a daily basis. My healthcare providers just told me to get used to my new life, and I found myself alone to deal with new problems.”

Fatigue, the mental and physical exhaustion described here in the words of a woman with breast cancer, is one of the most common side effects of cancer, and affects people before, during and after cancer treatment. Although many people with cancer suffer from fatigue, the causes are poorly understood, and there is no drug to effectively treat it.

Fatigue may affect anyone at any stage of the disease, any type of cancer, treated by any modality. And while fatigue usually improves after treatment, in around one third of cases fatigue persists for months or years, and may even turn into a chronic condition, with devastating implications for the person's quality of life.

In a study of people with cancer who had received chemotherapy, almost all who reported fatigue felt that it

prevented normal life (*The Oncologist* 2000, 5:353–360). A more recent study found that many feel that their doctors either fail to grasp the seriousness of the problem, or if they grasp it, they still had no effective treatment or advice to offer (*Support Care Cancer* 2011, 19:363).

The experience of Paul Senior, who has been living with advanced, incurable prostate cancer for the past six years, is a case in point. “On a good day, I can go out, read a book. On a bad day, I want to do nothing. I might watch a bit of TV, but that is all I'm fit for. The worst for me is brain fog, or ‘muzzy headedness’ as I describe it. As someone who was an academic for most of my life, the fact that sometimes I can't think, act or read is frustrating.”

Healthcare providers are aware of the problem, he says, “but find it rather more difficult to offer solutions.”

For Natalija Sintler, who is on hormone therapy for breast cancer, fatigue affects both work and family life: “I had to reduce my daily working hours from eight hours to four hours. But these four hours leave me as tired as an eight- or ten-hour day left me before. When I get home, I crave rest in the middle of the day, which I didn't before.



My lack of energy affects my partnership, motherhood, friendship and my job.”

Natalija sought help from her doctors, and was not impressed by their response. “[They] all offered treatments focused on the cancer only. They left me without answers on how to deal with my lack of energy, and just told me to get used to my new life. I wish my doctor had listened when I told her about my fatigue, but she didn’t have time. And at some point, you stop asking and find other sources of help.”

So how can healthcare providers do better to manage this common, and often severe, side effect of cancer and cancer treatment, and what can patients themselves do to alleviate the impact of fatigue on their lives?

Dave Balachandran, director of the Sleep Center at the MD Anderson Cancer Center in Houston, argues that healthcare providers’ attitude to cancer-related fatigue (CRF) now is where attitudes towards pain were a decade ago: “Ten to fifteen years ago, cancer patients were told to just accept pain, because we can’t do much about it. But there has been a huge change in mindset. We now ask patients routinely about pain, and rightly so. With fatigue right now, we are at

**“On a good day I can go out, read a book. On a bad day I want to do nothing”**

a point where physicians tell patients to just accept CRF as a chronic illness. But this is where we specialists come in. We say that, yes, fatigue is common with cancer, but there is more to it, and we need to strategise on treatment modalities. We don’t just draw up our hands and say ‘sorry, you just have to deal with it’, especially in the long term.”

### What causes cancer-related fatigue?

Balachandran emphasises the importance of distinguishing cancer-related fatigue from the problem of sleep disruption. “Sleepiness is defined and measured as the tendency to fall asleep. In the fatigue clinic, we offer patients with fatigue the option to objectively quantify their tendency to fall asleep.





### Natalija Sintler, treated for breast cancer “I wish my doctor had listened”

“I received chemotherapy for breast cancer last August, and radiotherapy in October. Now I receive hormone therapy. With the therapy, fatigue arrived. My work leaves me very tired and, when I get home, I crave rest. But I have an eleven-year-old daughter, so I can't just take naps when I want to. My fatigue has changed me. My family and friends couldn't adapt to the new me, and frankly, neither could I.

“My doctors operated, poisoned, and burnt the tumour out of my body, and when treatment was finished, it was like ‘Mission completed!’. Two months after the end of treatment, my doctor sent me back to work. When I told her about my fatigue, she prolonged my sick leave by one month.

“Nobody told me where to find help, or offered ways to deal with my lack of energy, so I searched for support. Psychotherapy has helped me to cope with my problems. I also practice yoga on a daily basis, which helps me to feel better in my body. I spend more time in nature, walking, jogging, and hiking. As I walk, slowly new energy arrives. Mindfulness-based stress reduction has helped to calm my mind, sleep better, and cope with stress. I now accept times of fatigue as time for rest.

“Europa Donna has been a great support community. I feel that I can only get useful advice from someone who has had the same experience. Stories by others bring on a new perspective, and I realise now that it is more about the quality of what I do than about the quantity.”

If they score highly, we refer them to the sleep centre, where we test sleep quality. So we tease out the sleepiness component, which we can indeed treat. But people with fatigue don't necessarily want to sleep. And while there are validated scales to measure fatigue, the mental and physical exhaustion that comes with it is hard to quantify.”

At a symptom level, we know that fatigue is associated with a variety of conditions connected with cancer, including anaemia, deconditioning, pain, depression, and anxiety, says Balachandran. Nutrition is also a big issue for patients with cancer, he adds. “But also cancer treatment itself, especially immunotherapy, causes fatigue. And co-morbid illnesses, such as liver and kidney disease or diabetes also contribute. When we see what contributes to fatigue in a patient, we can strategise treatment.”

What is going on at the biological level is less well understood, however. A recent review of current controversies in the pathophysiology of cancer-related fatigue argues that inflammation probably plays a major role (*Support Care Cancer* 2018, 26:3353–64). Cytokines convey to the brain that an infection has occurred, and induce feelings of ‘sickness’. These feelings lead to changes in behaviour, i.e. ‘sickness behaviour’, such as tiredness, exhaustion, depression, and loss of appetite, which are seen as part of a body's normal adaptive response to infection, enabling the body to prioritise clearing the pathogens.

“Cytokines play a role in cancer, and the same changes to the immune system occur,” explains Balachandran, “we see an increase in cytokines such as TNF $\alpha$  and  $\gamma$ -interferon.

‘Sickness behaviour’ is similar to cancer symptoms such as fatigue.” However, there is more to cancer-related fatigue than just the immune system, he says.

Other mechanisms that may be at play include the disruption of the hypothalamic-pituitary-adrenal axis, which normally regulates the release of the hormone cortisol in response to stress. Cancer, or its treatments, may cause endocrine changes that induce fatigue. Other hypotheses, which may not be mutually exclusive, but could well be connected or act in concert, propose that the dysregulation of the circadian rhythm and of serotonin, as well as activation of the vagal afferent nerve, contribute to fatigue.

For Ollie Minton, Macmillan Consultant and honorary senior lecturer in palliative medicine at St. George's University Hospital in London, who has co-authored a Cochrane Collaboration review on pharmacological treatments for cancer-related fatigue, this lack of understanding of the causes is to blame for the difficulty in treating the condition. “Until we know what is causing cancer-related fatigue, all we have to treat CRF are non-specific interventions.”

### Ask and tell

In the US, the National Comprehensive Cancer Network (NCCN) has been publishing annually updated guidelines for treating cancer-related fatigue since 2000. These offer guidance for screening as well as recommendations for interventions. Ann Berger, Professor and Dorothy

Hodges Olson Endowed Chair in Nursing at the University of Nebraska, Omaha, leads the panel tasked with the annual updates. For her, the NCCN guidelines are a step in the right direction: “Interventions for cancer-related fatigue have been tested for the past 25 years. We have come a long way since then, but there is still a long way to go. Our goal in treating CRF according to evidence-based guidelines is of course to help patients have a good quality of life. If a patient suffers from severe fatigue, we may be able to bring it to a moderate level, so that they continue cancer treatment and enjoy life.”

The crucial first step is identifying when fatigue is a problem, says Berger. “Patients need to report fatigue, but they need to know that fatigue is not just ‘something that comes with cancer and treatment’, which they have to accept. And nurses need to ask about, and need to record, fatigue levels. Patients bring up pain, we want people to bring up fatigue as well.”

When a cancer patient reports fatigue at a moderate to severe level, the NCCN guidelines, which are also used in the UK, strongly recommend physical activity as intervention – once other contributing factors like pain, anaemia, or nutrition are ruled out or treated. This is a departure from previous practice, says Berger: “Oncology nurses used to teach cancer patients to rest and not assume their daily activities. Now, guidelines recommend that cancer patients on treatment stay as active as they were before treatment.”

For patients both on active treatment and post-treatment, recommendations are to take 150 minutes of moderate-intensity exercise, broken into chunks, such as walking for 30 minutes on five days a week. “This is the most general intervention that seems to work for all patients in alleviating cancer-related fatigue,” says Berger. A Cochrane Systematic Review, published in 2012, supports that assertion, concluding that aerobic exercise is beneficial for people with cancer-related fatigue.

### Reality check

How realistic is the expectation that patients on cancer treatment comply with such a recommendation? JiaHui Gan, senior physiotherapist at Milford Hospital, under the Royal Surrey County Hospital, says that even in-patients can reach such a level of activity: “Moderate-intensity exercise means that the person should feel that completing the exercise or activity is ‘somewhat hard to hard’, but not ‘too hard’.

“In a healthy person, or after treatment, that would mean fast walking, cycling or swimming. In an in-patient or out-patient setting, we assess the complexity of CRF and how much effort a patient needs to put in to reach the recommended ‘feeling’. And this could be as basic as engaging in activities of daily living, like getting up from bed, walking around the room or the ward, or to the hospital restaurant, if a patient has severe fatigue and is deconditioned. If a patient does this daily, they can easily achieve the recommended exercise protocol of 150 minutes a week.”

**“Nurses need to ask about and record fatigue levels. Patients bring up pain, we want people to bring up fatigue as well”**

Replacing that half-hour walk with a pill is not yet possible. While several pharmacological options for treating fatigue have been trialled, none have given oncologists a ‘cure-for-all’. Pharmacological interventions may help in some cases, says Minton: “Ritalin, for example, may be given to patients with advanced cancers. But on the small evidence base for it, I’m not confident to prescribe it routinely. We do not have any drugs that we can routinely recommend.”

### Mateja Veber, treated for breast cancer “Talking helps”

“After working for four hours, I go to sleep immediately and stay at home in the afternoon. I cannot play with my two daughters anymore, I cannot work. My life is not the same as before. “Fatigue is a big problem for me. My legs hurt, my muscles and bones hurt. But my oncologist and personal doctor help me, and I receive psychological help.

“Talking with them and meditation help me.

“I would recommend to other patients who suffer from fatigue to talk a lot, especially to friends who have the same cancer.”





### Sally Jenkins, living with neuroendocrine cancer “Fatigue is both physical and psychological”

“The effects of fatigue are quite profound. Previously, when I was tired, I’d just grit my teeth, keep on going, and get rest once it was possible. But if I take this approach with cancer-related fatigue, I feel very ill and have to stay in bed for two days to recover. I cannot be spontaneous anymore, I have to plan when and what I’ll do. But if the tumours say ‘no, you are too tired’, I have to ditch my plans. The physical fatigue controls you.

“Fatigue rules my life. Having a long-term condition that will never be cured leaves us NET [neuroendocrine tumours] patients not only with the physical effects from therapy and the tumour burden, but also with a psychological fatigue. Psychological support is necessary to be able to accept the situation and maximise quality of life – to enjoy the good things and not regret what had to be given up.

“We now have a specialised NET service in south Wales, which is absolutely wonderful. I feel very well cared for. But before, without a dedicated service, fatigue was not a priority. When I mentioned it, I met an attitude of ‘oh well, it’s just part of the condition’. As a NET patient, you don’t look ill, so people might think that you are simply lazy, and this attitude extended to some healthcare providers.

“I know now how to manage my physical and psychological fatigue. I’ve found yoga extremely useful as it allows me to work within my limits. And my yoga teacher is very understanding when I fall asleep in class – they put a blanket over me, I snooze for ten minutes, and then continue with the exercises. I couldn’t do that in an aerobics class! Personally, I recommend recognising your own limits, then accepting and working within them. This approach allows me to maintain a reasonable quality of life, but it is not the same quality of life as before the diagnosis.”

The evidence for complementary medicine is also thin: “Vitamins and ginseng have been tested, but trials haven’t shown anything. Ginseng for CRF was tested in small trials that were not terribly effective. It may be that there is an active ingredient in ginseng, but not knowing what risks all sorts of interactions.” Nevertheless, Minton argues that eventually, drugs could complement the toolkit for treating fatigue: “Ideally, we would like to give fatigued patients something that makes them feel better and more active. Then we would encourage them to exercise.”

## Empowering patients to manage fatigue

Balancing exercise with rest is important for fatigued patients especially on days when fatigue is strong, emphasises Gan. She also recommends alternative ways of increasing activity levels, including yoga, tai-chi, and meditation, so long as the patient enjoys doing them – as many do (see for instance the testimonies of Natalija Sintler and Sally Jenkins). “Yoga and mindfulness-based stress reduction are evidence-based interventions for CRF patients on active treatment and post treatment,” Berger agrees. “Mindfulness can calm the emotional status and distress, while psychosocial interventions such as cognitive behavioural therapy and psycho-education are also good for treating fatigue.”

These approaches are helping Sintler: “I practice yoga on a daily basis, which helps me to feel better in my body. I spend more time in nature, walking, jogging, and hiking. As I walk, slowly new energy arrives. Mindfulness-based stress reduction has helped to calm my mind, sleep better, and cope with stress. I now accept times of fatigue as time for rest.”

Zuzana Ondrusova, a psychologist practising in Slovakia, seeks to help patients find their own coping strategies. “First, patients need to know what is going on with their fatigue, and why there is no easy way to help them with a pill. Then I try to lead my patients to find where to put this condition in their lives. But they have to find themselves what fits them. I hear from some patients that they need to be more careful, that they need slightly more time for doing things. Dealing with fatigue is also about priorities, taking yourself seriously and fulfilling the needs of your own body and mind.”

While cognitive therapy and behavioural therapy have proven benefits for patients with cancer-related fatigue, and are recommended by the NCCN, the need for therapy often exceeds the availability of qualified therapists.

Clinical psychologist Bram Kuiper turned to digital technology to address this gap. The former head of the Centre for Psycho-Oncology at the Helen Dowling Institute, in the Netherlands, founded a social enterprise ‘Tired of Cancer’, which developed the ‘Untire’ app to scale up cognitive behavioural therapy and mindfulness-based cognitive therapy.

### Paul Senior, living with prostate cancer “Brain fog is the hardest”

“I’ve been living with cancer, and cancer treatment, for over six years. Fatigue for me is not constant: it sometimes peaks, and then it weakens again. What affects me the most is the brain fog. Sometimes, I cannot pick up a book without it feeling like a strain – I can’t focus, can’t concentrate. I also experience tiredness, sleep disturbances and anxiety.

“My healthcare providers are aware of the problem of fatigue, but I think they find it rather more difficult to offer solutions. They listen to me and provide advice, but there is no easy solution. I’m also not pushing this aspect too much. At my appointments, I’m most anxious about the progress of my disease and most interested that my doctors get the treatment of my cancer as right as they can.

“Fatigue has just become part of my life, part of me now. I deal with it myself, and with the help of nurses, friends and the Prostate Cancer UK online community. Peer support is invaluable, as they are extremely knowledgeable from their own experience.

“I struggle with anxiety. I try to identify the source of anxiety and avoid it, and if I cannot avoid it, work through it by talking with my friends and with the help of mindfulness techniques. Mindfulness exercises help to calm my anxiety down, I feel better since using them.”



“Untire is a self-management tool for patients with cancer-related fatigue,” says Kuiper. “Everybody has his own journey, so we do not know the specific reason why any one patient is and stays fatigued. We give patients the tools to figure it out, including simple education about fatigue, recommendations for physical activity, tools to help patients learn how to manage energy, and advice and tips from positive psychology.”

Gan agrees that technology can be very helpful for building up activity levels, citing as examples pedometer counts on smart phones, or apps such as Untire and the UK NHS ‘Couch to 5K app’, which helps people work towards running five kilometres. However, apps are not a universal solution, says Gan: “We encourage our patients to self-manage, but we are not expecting them to do it all by themselves. If fatigue levels are high and persist, patients should get support and join an individual or group exercise programme for people with cancer.”

### Target the cause

While exercise is currently the most strongly recommended intervention for treating cancer-related fatigue, Ollie Minton wants something better. “Recommending exercise is a generic, ‘this will make you feel better’, public health message. The size of the effect of exercise on fatigue is small, but there is no harm in it, so it makes sense to recommend

it.” Minton’s hopes lie with science: “We need to find the mechanism causing fatigue. The mechanism is really not understood, especially not compared to how much targeted oncology treatment has moved on. Fatigue management needs to get to this targeted level.”

### “We could use this data to identify proper markers for fatigue. The technology to do this exists”

Minton would like to see not only a quality-of-life arm included in all oncology trials, but also a comprehensive testing of blood markers and genome profiles: “As a matter of routine, we should have more patient-reported outcome measures in all trials, not just scan results. Patients on trials should be asked about their consent to blood samples, which could then be looked at to see what happens when people report more fatigue or more pain. We could use this data to identify proper markers for fatigue. The technology to do this exists, but we need a whole load more samples and data to be collected. And of course funding – costs are involved, but I think this is worth it.”

To comment on or share this article, go to [bit.ly/CW84\\_Fatigue](https://bit.ly/CW84_Fatigue)





# 7<sup>TH</sup> ACCELERATE PAEDIATRIC ONCOLOGY CONFERENCE

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**COURSES AND SEMINARS**

## In the Hot Seat



# Lena Sharp

## President of the European Oncology Nursing Society



The European Oncology Nursing Society is a pan-European organisation dedicated to the support and development of cancer nursing. It recently completed a landmark research project – RECaN – aimed at increasing recognition of the value and contribution of cancer nursing across Europe. **Cancer World** asked EONS president Lena Sharp what they learned and why it matters.

**Cancer World:** Recognition for specialist cancer nursing is clearly important to nurses. Does it matter to patients?

**Lena Sharp:** The fact that so many countries do not recognise cancer nursing as a speciality and therefore don't offer specialist training is a big problem for patients. It deprives them of access to cancer nursing competence, such as psychosocial support and symptom management. It also affects their safety. In some countries, nurses with no, or minimal, education in cancer care prepare, administer and monitor complex cancer drugs. We also know from the RECaN project that cancer nurses are less inclined to report errors in countries where they have less recognition.

**CW:** What did you learn from the project?

**LS:** From a systematic review, based on 351 papers [Int J Nurs Studies 2018, 86:36-43], we learned that the nursing contribution to cancer care and cancer research

is significant and varied: nurses are producing high-quality, innovative and cutting edge research, and nurse-led interventions are increasing in frequency and complexity. The preliminary results of a meta-analysis show that there can be benefits in terms of the quality, no safety concerns and also economic benefits from having nurses rather than physicians leading certain cancer services.

The RECaN project also compared cancer nursing across four different countries – Estonia, Germany, the Netherlands and the UK – and found significant differences regarding tasks, roles, education, responsibilities, autonomy, safety culture and recognition.

**CW:** What are the hurdles to achieving better recognition of cancer nursing and enabling nurses to contribute more to care across Europe?

**LS:** A big hurdle, and the hardest one to change, is hierarchical structures in healthcare. These structures strongly



impact the culture in an organisation, which affects important quality factors such as patient safety. In the RECaN study, we found clear signs of hierarchical impact in the countries with little recognition of nursing.

In Germany, for instance, most nurses do not have university education, but those who do, and complete a Masters in nursing, find the salary increment that applies for *all* other healthcare professionals on obtaining their Masters does not apply to them! There is a forceful lobby against higher education for nurses in Germany. The German nursing organisations strongly contest the argument that ‘compassion’ alone is all it takes to provide effective and safe care, but they meet very little interest from political or other stakeholders.

What is interesting is the contrast with the Netherlands, which borders on Germany, and where national guidelines stipulate that all cancer drugs should be delivered by oncology nurse specialists. Dutch cancer nurses have a recognised career path and are required to complete a two-year cancer nursing programme based on a national curriculum.

Estonia, another of the countries in the RECaN project, has had a similar structure and culture to Germany, but it’s encouraging to see that beginning to change. When EONS first visited Estonia in May 2017, we met with different stakeholders, including hospital leaders, to discuss recognition and the need for specialist training for cancer nurses. The response was very positive and we are very happy that the first Masters programme in nursing started in September 2018, with 120 nurses currently in the programme.

**CW:** *How important is cancer education for EONS?*

**LS:** We recently published the EONS Cancer Nursing Education Framework, which is important on two levels. At a practical level it helps universities across Europe to shape cancer nursing programmes. At a broader level, by describing and explaining the competencies of cancer nursing, it helps increase recognition of cancer nursing as a specialism that has a positive impact on the lives of people affected by cancer. This in turn strengthens the argument that cancer nursing should be recognised by the cancer community, and by national- and European-level policy makers, as a profession with specialised training and qualifications available across the continent.

The collaboration with the European School of Oncology is important here. The ESO–EONS Eastern Europe and Balkan region joint Masterclass in Cancer Nursing (Budapest, September 2018) was the first educational

event based on the new EONS framework. It worked really well and the plan is to base all EONS educational events around the Cancer Nursing Education Framework.

**CW:** *Why does EONS prefer the term ‘multiprofessional’ to ‘multidisciplinary’?*

**LS:** Medical oncology, radiotherapy, surgery, pathology, radiology are all disciplines within medicine. Nursing is not. Medics and nurses are professionals with different disciplines, and nursing has its own specialist disciplines, including cancer nursing. Very often the term ‘multidisciplinary’ is used to describe the medical members of a multidisciplinary team, with nursing lumped in among them – very often at the end. We feel this hinders recognition of cancer nursing as a distinct profession.

**CW:** *Cancer care will increasingly take place in community settings. Is EONS part of conversations about how this will happen?*

**LS:** Absolutely! We welcome the stronger role of primary care in cancer care for nursing and other professions. This is one of the reasons why we prefer the broader term ‘cancer nurse’, because our specialist nurses don’t just care for cancer patients being treated in an oncology setting, but also in primary and palliative care settings. This move towards more community and home-based care is reflected in the EONS Cancer Nursing Education Framework, which covers competencies in cancer nursing from primary prevention to early detection, treatment, rehabilitation, and palliative and end-of-life care.

*To comment on or share this article, go to [bit.ly/Cw84\\_HotSeat\\_LenaSharp](http://bit.ly/Cw84_HotSeat_LenaSharp)*

Lena Sharp, RN, PhD, was elected president of the European Oncology Nursing Society in 2017. She is the Head of the Regional Cancer Centre, Stockholm–Gotland, in Sweden. She teaches regularly at nursing schools and postgraduate nursing courses, she has been a faculty member for the annual ESO–EONS Masterclass in Oncology Nursing for many years, and was the project lead for the EONS Cancer Nursing Education Framework published in 2018.

Prior to taking up her post at the Regional Cancer Centre, Lena Sharp was the chief nursing officer and patient safety coordinator at the Department of Oncology at Karolinska University Hospital. Her main focus in research is patient safety, communication, leadership and cancer care organisation.





# 16<sup>th</sup> St. Gallen International Breast Cancer Conference 2019

Primary Therapy of Early Breast Cancer  
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*June 19<sup>th</sup>-21<sup>st</sup> 2019*  
*Hotel Nicolaus*



June 20<sup>th</sup> - **Pathology Day**  
Early diagnosis in aggressive tumours

June 20<sup>th</sup> - **Patient Day**  
Patient-stakeholder engagement

June 21<sup>st</sup> - **Scientific Conference**  
Tackling tumour heterogeneity: Biological,  
Laboratory, Clinical and Regulatory Implications

June 21<sup>st</sup> - **Accreditation and Designation Session**  
Using quality systems and comprehensiveness  
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June 22<sup>nd</sup> - **OECD General Assembly 2019**



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# Advanced Breast Cancer

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