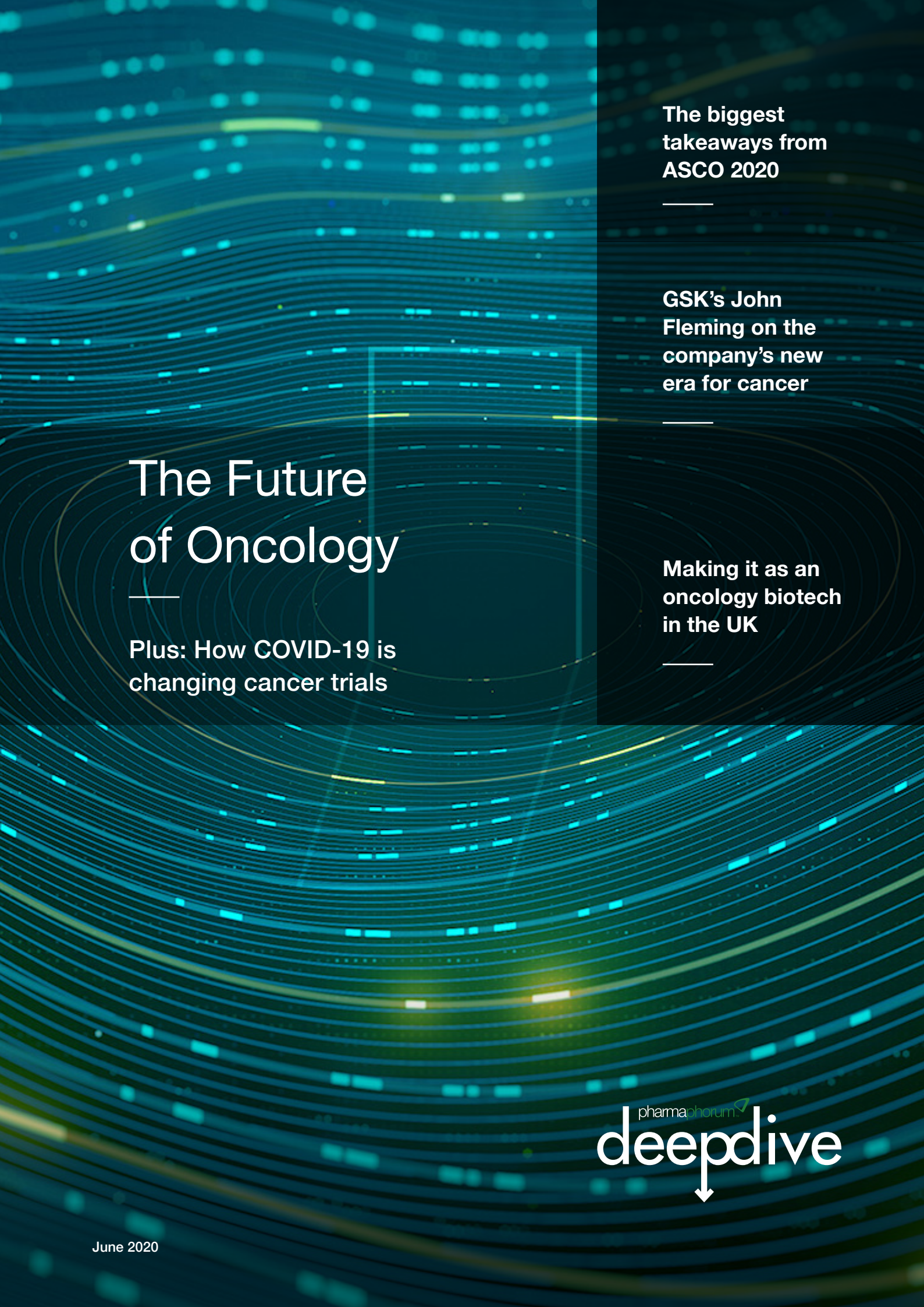



# The Future of Oncology

Plus: How COVID-19 is changing cancer trials

pharmaphorum deepdive

June 2020

# **Deep Dive:** The Future of Oncology

This year's ASCO might have been overshadowed somewhat by the COVID-19 pandemic, but the now-virtual conference didn't pull any punches, demonstrating that while coronavirus might be front and centre of everyone's minds, the desire to see real change in cancer treatment hasn't diminished.

In this issue, Jennifer Harris from Syneos Health discusses the biggest takeaways from the conference with Richard Staines. You can also read our full coverage of the event on pharmaphorum.com.

We also look beyond ASCO to get views from several cancer experts – including contributors from GSK, Accenture, ICON and Advanced Clinical – on how they think the future of oncology will play out.

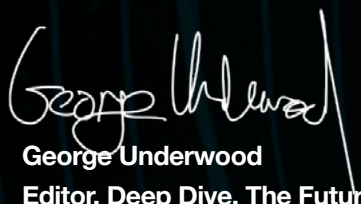
They cover a wide range of topics, but it's clear that they agree on several things – namely that the future of oncology research will be dominated by collaboration, innovative trials, and earlier planning. And that's not to mention their shared excitement surrounding approaches like immuno-oncology and cell & gene therapy.

Finally, several of our contributors also analyse how COVID-19 is affecting cancer trials, and what the industry can do to solve these issues.

I hope you're all staying safe in these unpredictable times!

I hope you enjoy the issue.

Kind regards,



**George Underwood**
**Editor, Deep Dive, The Future of Oncology**

**Next issue:**
**Communications & Commercialisation (September 2020)**
Plus:
• New innovations in digital health
• Listening to patients

**Catch up on recent issues:**

Market Access – June 2020

R&D Disruption – February 2020

Patient Engagement – November 2019

Digital Health – October 2019

pharmaphorum.com/deep-dive

# GSK's John Fleming on rethinking oncology from the ground up

What if we could look at cancer treatment from a completely fresh perspective? This is the philosophy GSK's UK country medical head for oncology, John Fleming, wants to bring to the company as it rethinks its approach to cancer.

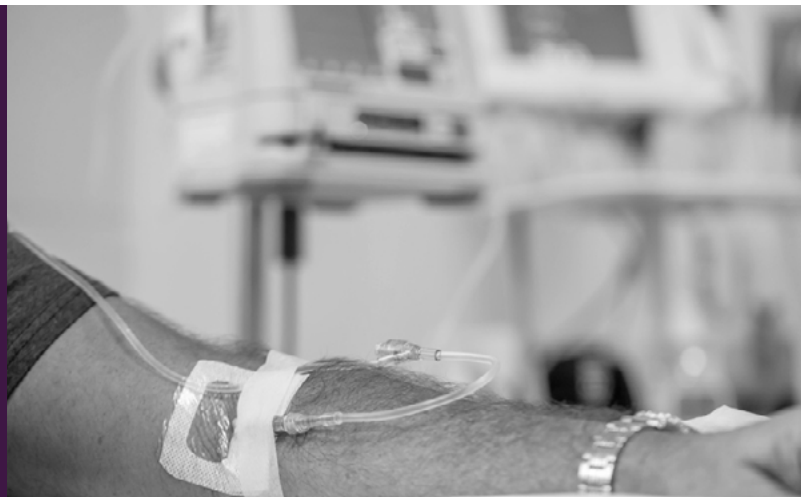
Fleming joined Novartis in 2015, when GSK divested its oncology portfolio to the Swiss firm. It might seem surprising, then, that his focus on cancer would bring him back to GSK – but, as Fleming points out, the company never truly left the oncology space, and it seemed to him to be the perfect place to help transform outcomes for people living with cancer.

"When people talk about GSK re-entering oncology, that's really a misconception," he explains. "The divestment involved a lot of second-to-market oral therapies, which didn't have the opportunity to be truly transformational and lead in their classes – so what was left behind was an R&D engine that was free to innovate and discover new molecular entities. It was a blank slate, if you will – an unencumbered starting point for us to look at fresh approaches and discover new modalities and classes of drugs.

"That's why I chose to return to 'GSK oncology 2.0' – because we have this opportunity to build with a start-up mindset at a large pharma."

With this 'blank slate', Fleming says the team can completely rethink their processes.

**"We're now bolting on medical affairs and the marketing infrastructure into our R&D – medical affairs at GSK is now involved three years prior to filing. We're also bringing patient groups into those earlier discussions."**



Fleming says he wants to re-orientate how the company looks at developing medicines and recognise that they are developing them for patients, not only prescribers.

"You need to start by talking to patient groups, not thinking up the programme first then going to them later. It should never be a question of 'them and us'. We should always be thinking about how we can work together to develop the best medicines – not just small incremental benefits in progression-free survival (PFS), but perhaps approaching functional cure in some cancers.

"If you're not in concert with patient organisations, you're already well behind the curve of innovation because you're setting things up which are not going to fly when they're brought into the real world."

## Accelerating the immune response

So, what kind of drugs does an 'unencumbered' company look at? Fleming says he is personally excited about the still-untapped potential of immunotherapy.

"We've had an explosion in immuno-oncology treatments that are essentially telling the immune system to take its foot off the brake and allowing it to mount a robust response against the cancer.

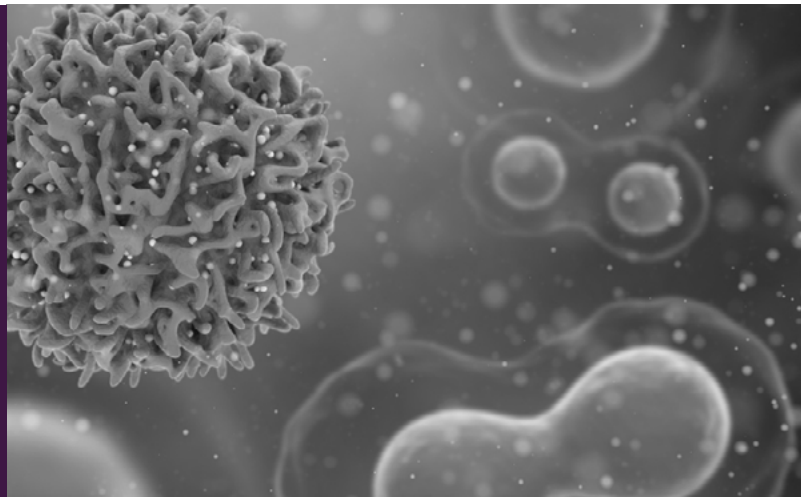
"With the next generation of immuno-oncology, rather than telling T-cells to release the brakes on the immune system, we're thinking about how we can move towards actually accelerating the immune system's surveillance against the cancer returning – an activated immune response."

This is an area GSK is looking into with research into inducible T-cell co-stimulatory (ICOS) receptors.

"It's a relatively new approach to treating cancer that essentially increases a patient's T-cell response by an order of magnitude, supercharging the attacks on the cancer.

"You could combine agonists with antagonists in certain patients and certain tumour types to great effect. You can phase one in and out on the impact of each drug on the cancer and aspire to actually titrate modulation of the immune system with just the right degree of response in each tumour type.

**"That's the potential of balancing agonism and antagonism – we want to move away from just breaking the shackles on the immune system to really doubling down on getting rid of the cancer."**



That's not to say approaches like these don't come with their own challenges – for example reduced population sizes.

"We're now looking at hyper-segmentation within cancer, not just based on tumour types or organ systems but also the genetic signatures of the cancer. This means there are smaller patient populations for studies, and you might have early data in phase 2 with no comparator arm showing a significant survival benefit.

"Regulators have been superbly agile in the way that they've embraced this in oncology to allow, in some instances, licenses to be granted from very immature data whilst additional safety and efficacy information is collected. But the need to recruit large numbers of patients to show you've got something statistically valid will remain a challenge in these smaller patient populations."

## From soloist to orchestra

Despite the challenges, Fleming hopes researchers can push forward towards real breakthroughs, not just in small niches of genetic signatures and specific subtypes of one mutation – but hopefully in innovation across solid and liquid tumours, looking at the commonality of mutations across phenotypes.

"PD-1 is a great example of this," he says. "it has been tremendously successful across a range of tumour types.

"You can't look for a one-size-fits-all approach in all tumours. That's clearly not going to work. On the other hand, if you can innovate across tumour types, that's going to be fantastic for many patients."

Another of GSK's agonist programmes that seeks to achieve that addresses the STING pathway (Stimulator of Interferon Genes).

"That can stimulate the immune system really broadly – producing type I interferon can mobilise a patient's adaptive immune response to cancer. That's another case of active cancer immunity, and active surveillance triggering a patient's inherent cancer-fighting responses.

**"Historically, some therapies have had to be injected into a tumour, which limits their breadth. In STING and other programmes we're looking at treatments being administered systemically, so you can target more tumours and more cancers."**

Fleming adds that as immuno-oncology matures, the industry will shift its therapeutic focus away from reliance on a few important pathways towards a wider perspective.

"The analogy I've heard is 'don't think soloist, think orchestra'. What music do you want to play? And what instruments do you need to play that music?

"That speaks to the power of combinations – not just two different medicines but actually combining medicines in one. We have some nice examples in our programmes of combining pathway inhibitors in one compound. Typically, when you suppress or target one pathway, another pathway will come to the rescue of the tumour clone, giving the cancer an escape mechanism. What if we could target both?"

## Closer collaboration

It's not just treatments that need to be acting as an 'orchestra', though – the industry and its partners need to be working in concert to truly make breakthroughs in oncology.

"We're looking at multiple alliances across oncology to address the sheer volume of potential combinations and then finding the truly transformational ones," Fleming says.

He adds that there is a need for closer collaboration between academia, industrial scientists and companies that will allow a two-way information flow and richer datasets to emerge.

**"The better the quality of the inputs and the better the quality of mining you can do in data, the better the outcomes. We need to get better at sharing across industry and academia. We will only succeed if we keep talking with academia, clinicians, patients and other stakeholders."**

Fleming says that, overall, he would like to see progress in oncology "going up in steps, rather than in a jagged line".

"To do that you need lateral thinkers in the room as well as pure scientists. It's about changing how you actually approach a tumour, rather than following on from where previous therapies have failed and fallen off.

"We almost need to forget what we've learnt and see if we can redesign how to kill a tumour cell. Who are the players? Well, it's your immune system. It's nutrition. It's your genetic make-up. We need to look at combinations and learn how to have that balance between agonism and antagonism to play the symphony rather than just be a soloist."

Because of this, he says he is optimistic about the future for this challenging disease space.

"I chose to rejoin this organisation to be part of what is hopefully a new dawn in oncology – where we're looking not at small incremental benefits in PFS to get another me-too on the market, but at actually addressing unmet needs for patients. What can we do that's going to really change the game in that tumour type?

"Rather than listening to what others are saying the direction of new therapies will be, we want to have a role in defining that and shaping it ourselves.

He adds: "In an organisation like ours, with the resources and the appetite to take smart risks, we have the privileged opportunity to define what that conversation can be and define what the future can be. That sounds grandiose, but we really want to be world leaders in oncology at GSK. We want the organisation to be catalysed around innovation, performance, and trust.

"I think we have a huge role to play with patients, with other top industry players, with academia and clinicians to define and then accelerate what the next innovation will be."

## About the interviewee

Dr John Fleming is the UK and Ireland oncology medical head for GSK. He has been in the pharmaceutical Industry since 2014 in local and global medical and commercial leadership roles across Oncology and Haematology at GSK and Novartis. Dr Fleming performed his undergraduate training at Imperial College London and spent nine years in clinical practice at London Teaching Hospitals prior to joining GSK Oncology.

## About the author

George Underwood is a senior member of the pharmaphorum editorial team, having previously worked at PharmaTimes and prior to this at Pharmafocus. He is a trained journalist, with a degree from Bournemouth University and current specialisms that include R&D, digital and M&A.

# ASCO 2020: Scientific advances & what's impacting doctors and patients

Despite going virtual due to the COVID-19 pandemic, Jennifer Harris, an immuno-oncology expert from Syneos Health, told pharmaphorum's Richard Staines that the 2020 American Society of Clinical Oncology (ASCO) meeting was full of groundbreaking research, as pharma finds new ways to harness the power of the immune system to fight cancer.

It's almost a decade since Bristol-Myers Squibb (BMS) ushered in the cancer immunotherapy revolution with the first approval of Yervoy (ipilimumab) in melanoma.

Since then, BMS and rivals, such as Merck & Co and Roche, have redefined care standards in both solid and blood cancers, and this year's ASCO showed how industry is refining treatment with existing therapies, as well as finding new ways to unleash the power of the immune system against cancer.

Like many other events, this year's ASCO went virtual due to the COVID-19 pandemic, but this enforced change did not prevent the emergence of some exciting new science, with immunotherapy a major focus for research.

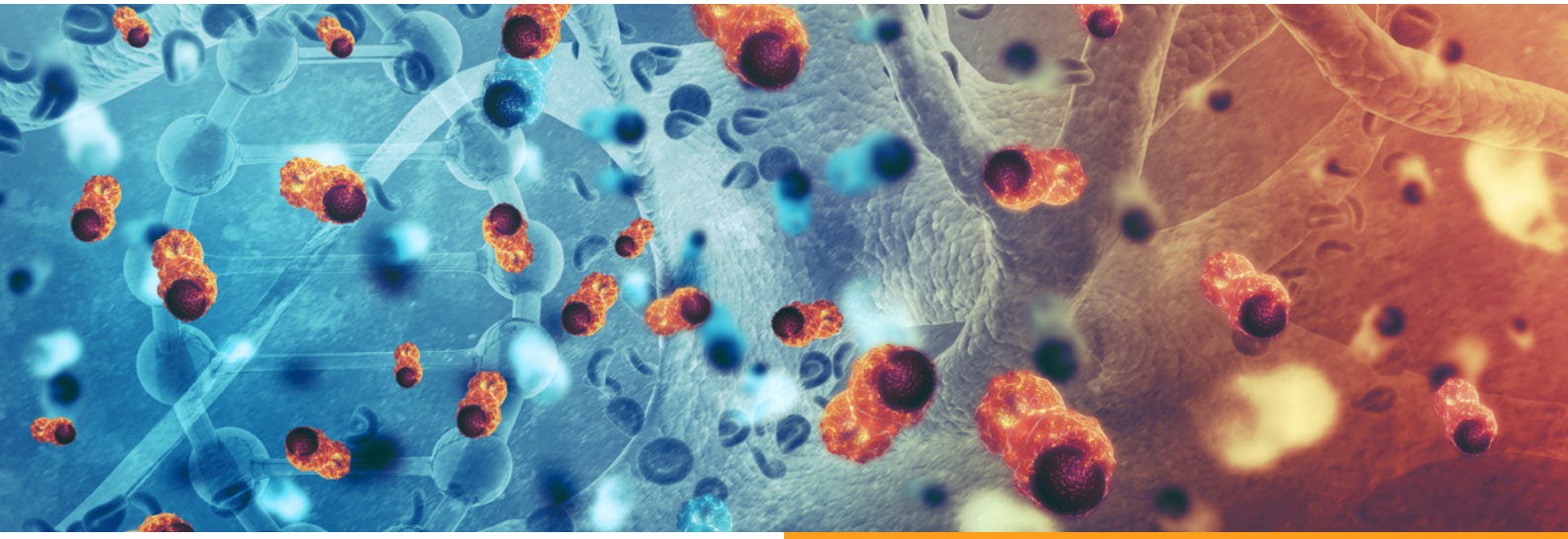
# New approach for checkpoint inhibitors

Since the approval of CTLA4-class Yervoy, PD-1/L1 checkpoint inhibitors have become standard of care in many forms of cancer, showing greater efficacy than chemotherapy and with fewer side-effects.

Cell therapies followed in their wake when CAR-T drugs were first approved in blood cancer – and pharma companies are continuing to raise standards with new approaches and new ways to improve on results with established therapies.

Jennifer Harris, vice president of immuno-oncology at Syneos Health Clinical Solutions, notes progress was on display at this year's event with a new kind of checkpoint inhibitor targeting TIGIT, short for T cell immunoreceptor with Ig and ITIM domains.

Roche's tiragolumab data showed that the tiragolumab/Tecentriq combination met both primary endpoints in the intention-to-treat population.



Compared with just Tecentriq there was an improvement in the objective response rate – 31.3% vs 16.2% – and an improvement in progression free survival (PFS) with a 43% reduction in risk of disease worsening or death.

An exploratory analysis showed that in people where at least half of tumour cells were expressing the PD-L1 biomarker, there was a clinically meaningful improvement in overall response rate (ORR) – 55.2% compared with 17.2%.

The improvement in PFS was also more marked in this group, with a 67% reduction in the risk of disease worsening or death – not reached versus 3.9 months – with the combination compared with Tecentriq alone.

The theory behind TIGIT is that targeting this checkpoint as well as PD-L1 will produce a stronger immune response than with a single therapy, something that Harris thinks has happened here.

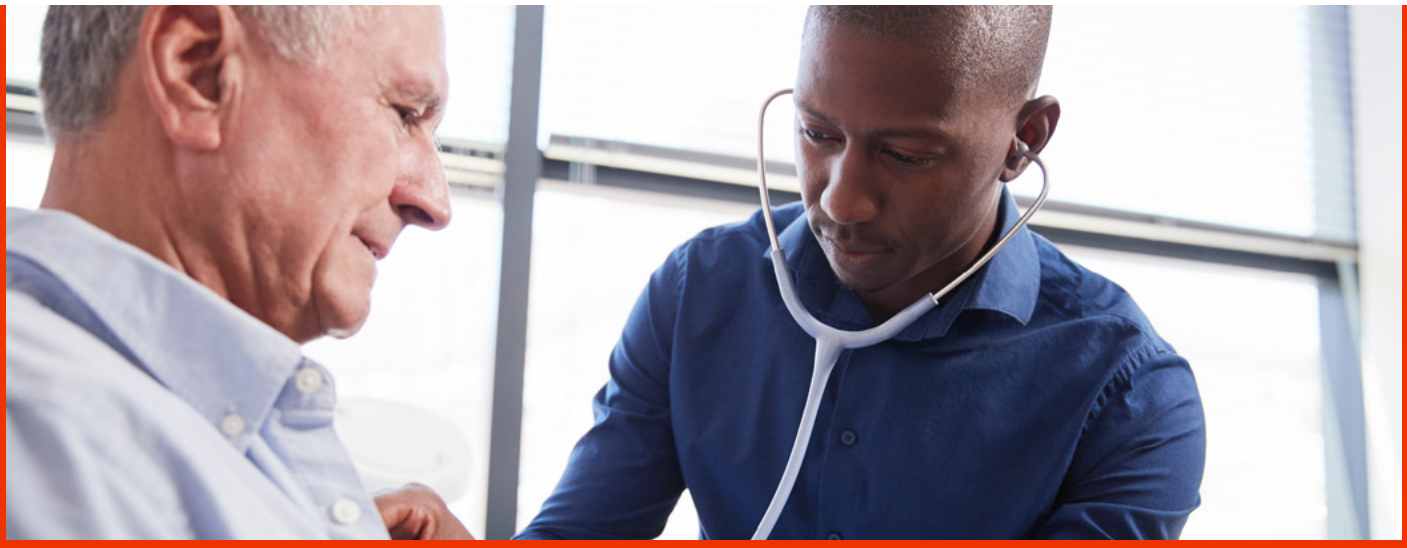
The data from the CITYSCAPE may suggest that the PD-L1 and TIGIT combination could have an advantage in terms of safety compared with the CTLA-4 and PD-1/PD-L1 dual therapies already on the market.

"I think that it goes to show that as of right now, the field is definitely looking at PD-1 as a foundational therapy, and then we're going to layer on additional checkpoints down the road," Harris says.

# Bispecifics approach

Bispecific antibodies, where the different ends of the giant "Y" shaped molecule target a different receptor, are also gaining in traction in clinical trials.

Macrogenics' MGD013, which targets both LAG-3 and PD-1, is addressing patients who had progressed following treatment with other checkpoint inhibitors, a group Harris says should be prioritised.



"The data has shown that 20% or 25% of patients that are going to respond to PD-1 therapy. The real, unmet need in the field, I think, is these patients that are either at primary resistance or whose tumours have become refractory," Harris says.

MGD013 has managed to produce responses in patients who had already failed to make headway with other checkpoint inhibitors.

The study also included a group where MacroGenics' antibody margetuximab was added to the regimen.

Margetuximab is essentially the antibody from Roche's Herceptin (trastuzumab), but with the "tail" of the Y-shaped molecule tweaked to produce a strong immune response.

At last year's ASCO it produced a marginal improvement over Herceptin in HER2-positive disease, but this trial suggests that it could work well as a way of priming the immune response produced from the checkpoint inhibitor.

# Biomarkers

According to Harris, this year's ASCO also demonstrated how the industry is making a steady approach towards therapies targeted at tumours or blood cancers based on their genetic characteristics rather than their place of origin in the body.

The key to this is identifying biomarkers found in cancer tissues but not elsewhere in the body – something that has already been achieved in a couple of approved drugs.

Merck & Co's Keytruda produced some intriguing results in colorectal cancer at ASCO, and other biomarkers are coming into play.

Those results were in tumours with a biomarker known as MSI-High, which is already targeted by Keytruda and is included on its FDA label.

But science is guiding pharma towards other biomarkers that have not yet been exploited: POLE/POLD1 is another potential target, which has attracted attention from a team at MD Anderson.

Another biomarker that was of interest at ASCO was LRP1B, which is the subject of research by a team at Duke University.

There's also the possibility of using biomarkers found in the blood, with research at ASCO highlighting circulating stromal cells, or CAMLs, as a way of detecting cancer.

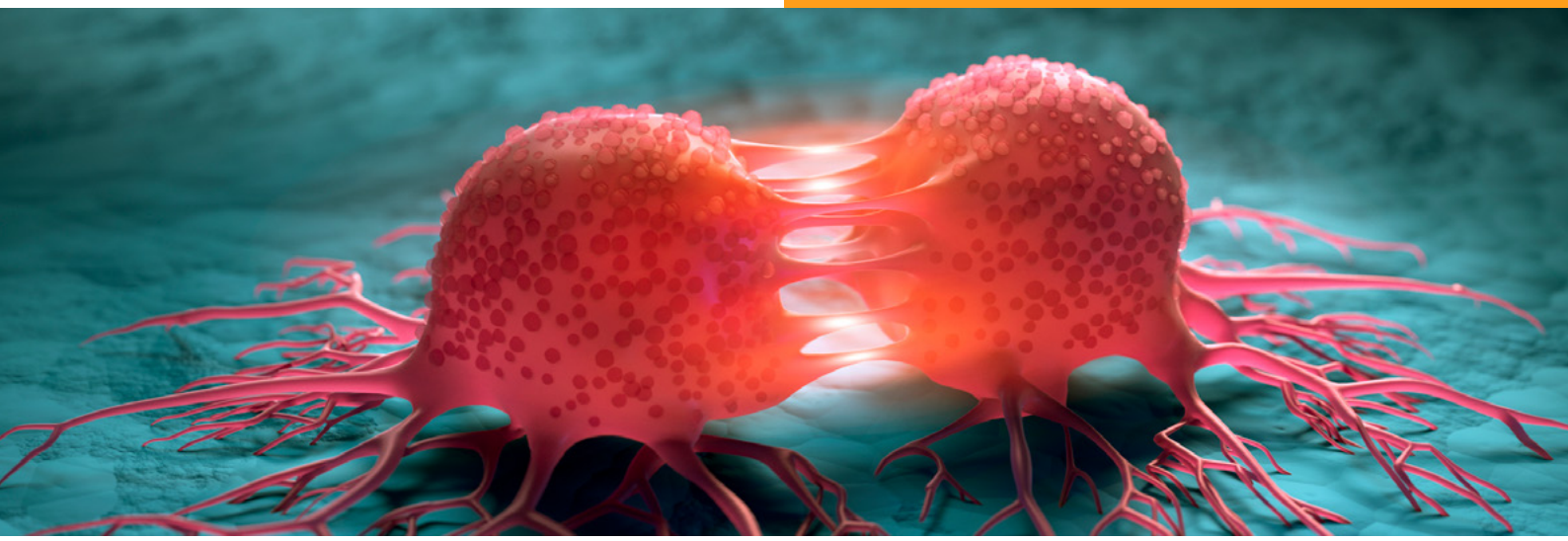
Soluble biomarkers are very attractive as they negate the need for invasive tissue biopsies. Companies such as GRAIL are exploring the potential of other blood-borne biomarkers, such as cell-free DNA circulating in the blood plasma.

Harris says: "We can't keep biopsying these patients over and over, especially if they have metastases in difficult-to-biopsy sites such as the brain or the liver."

The FDA also presented intriguing data about the role of the gut in effectiveness of checkpoint inhibitor regimes.

This trial involving 1,600 patients looked at four approved checkpoint inhibitor regimes and looked at whether use of antibiotics affected outcomes.

A control group with the same endpoints used standard chemotherapy or targeted therapies, and findings showed a statistically significant reduction in overall survival compared with those in the control group receiving the chemo or targeted therapy.



"Their conclusion was that – while they weren't recommending that antibiotics be withheld from patients that need them – antibiotics do induce negative outcomes for patients on immunotherapy, specifically checkpoint inhibitors," Harris says.

"They went so far as to say that they were advocating for antibiotic use to be used as a stratification factor in checkpoint inhibitor studies going forward."

In the future we may see more investigation into other factors that could be causing checkpoint inhibitors and immunotherapies to fail, such as differences in the area surrounding the tumours that could be preventing the immune system from mounting its attack.

This so-called tumour microenvironment has been a common topic of discussion at ASCO for the last few years, and according to Harris could play an increasing role in trial design in the future.

"We need to really look at negative predictors of checkpoint, not just positive predictors," she says.

# Evolving role of doctors and patients

Trial designs themselves also became a talking point in the oncology community during this year's meeting, as doctors navigate increasingly complex studies and findings that can be far more complex than the top-line summaries seen on the drug's label.

While simple trials with a control and a treatment group still do exist, in diseases such as lung cancer patients need to be stratified into different subgroup studies and often have several arms of treatment.

The case in point at ASCO 2020 was the CheckMate-227 trial, which was used to test BMS' combination of Opdivo and Yervoy in first line non-small cell lung cancer.

This trial had four different treatment arms, and produced results that, while supportive of the therapy, showed the drug combination was only working in a certain subsection of the population studied.

So on top of the complexity of a four-arm parallel trial there are also nuances regarding the drug's use that clinicians will have to take into account.

At the same time, patients continue to become more informed about results of trials through online searching. While this can prove beneficial in learning about novel treatments, clinicians must be wary of a potential digital divide and the implications it has for the quality of care patients receive.

"The patients that benefit are the ones that are savvy enough to go out and do their own research and ask the probing questions that lead the clinicians to dive a little deeper into the data," says Harris.

*To read additional oncology perspectives from Harris and her colleagues at Syneos Health visit syneoshealth.com/collaborate-for-a-cure/*

# About the interviewee

Jennifer Harris serves as head for the Immuno-Oncology (IO) business at Syneos Health.

In this role, Harris is responsible for IO strategy and scientific support for the project portfolio. Throughout her 25 year career focused in oncology, Harris has also held clinical positions at major academic centre, the NIH clinical centre and has held scientific roles within biotech and large pharma – focusing primarily on the rapidly expanding field of immuno-oncology.

# About the author

Richard Staines is Senior Reporter at pharmaphorum. He has been a journalist since the 1990s and has written for websites, newspapers and magazines. He has always had an interest in health, and has been focusing on the pharma industry since 2010, interviewing industry leaders and covering stories on topics including regulation, mergers and acquisitions, and the latest clinical developments.

# About Syneos Health

Syneos Health is the only fully integrated biopharmaceutical solutions organisation. The company, including a contract research organisation (CRO) and contract commercial organisation (CCO), is purpose-built to accelerate customer performance to address modern market realities. Created through the merger of two industry-leading companies – INC Research and inVentiv Health – it brings together approximately 24,000 clinical and commercial minds to help its biopharmaceutical customers shorten the distance from lab to life. Learn more at syneoshealth.com

# The pharma world at your fingertips

## Daily News from pharmaphorum

Direct to your inbox – insights and analysis on the big trends shaping healthcare and pharma, with a focus on:

- Sales and Marketing
- Digital
- Market Access
- Oncology
- Patients
- R&D

Sign up for our daily newsletter, visit https://bit.ly/33IccAB

# Adapting for the future of oncology

External pressures and rapid scientific advancements are changing oncology forever, and innovative trials are needed to keep pace. Experts Andreas Dreps and Martin Lachs from ICON give us their thoughts on the future of cancer research and tell us how the CRO is staying adaptive.

There is arguably no disease area more dynamic than oncology. Over the past few years, scientific advancements have fundamentally changed (and continue to change) how doctors view and treat cancer. It wasn't too long ago, for example, that immuno-oncology drugs seemed to dominate pharma news – but now much of the attention has moved towards the potential of T-cell therapies.

These rapid developments affect researchers as well as patients – and CROs like ICON have had to find innovative ways to remain adaptive and design trials that can push the boundaries of what is possible in cancer treatment.

For Andreas Dreps, ICON's senior vice president, oncology drug development, many of the most exciting developments in oncology are in the area of cell and gene therapy.

### Geographic Reach

98 locations in 40 countries with over 15,000 employees

### Core areas of expertise

We are a global provider of outsourced development and commercialisation services to pharmaceutical, biotechnology, medical device and government and public health organisations. We focus our innovation on the factors that are critical to our clients – reducing time to market, reducing cost and increasing quality. Our global team of experts has extensive experience in a broad range of therapeutic areas

### Year Established

1990

### Accolades

ICON has been recognised as one of the world's leading contract research organisations through a number of high-profile industry awards including CRO Leadership Awards (multiple categories), Forbes Best Employers for Diversity Award, PM360 Pharma Choice Gold Award, Scrip Best CRO Award, and Pharma Contract Services Company of the Year Award

### Company Goal

Our mission is to help our clients accelerate the development of drugs and devices that save lives and improve quality of life

### Motto/Ideology

At ICON we have built our reputation on enduring partnerships that are driven to advance medicine and make a difference in the world. Since our inception in 1990 we've strived to work as a 'trusted partner' to our clients, collaborating, innovating and finding new ways together to improve outcomes. It has been the lifeblood of our business and the vision that has shaped our strategy more than any other

“We’ve moved away from the sledgehammer approach of chemotherapy – which still has a significant role in the treatment of cancer – towards more targeted immuno-oncology, a subset of which is cell therapy,” he says.

“The results we’ve seen in cell therapy over the past few years have been quite stellar,” adds Martin Lachs, vice president, global project management at ICON, “particularly in liquid tumours such as lymphomas and leukaemias. Now we’re expanding into a broader range of tumour targets. The growth in the area is substantial, and when you’re looking at response rates of 60-70% – perhaps even 100% in some products – it’s hugely exciting.”

Nevertheless, cell and gene therapies present their own unique R&D challenges that CROs like ICON have had to adapt to.

“The logistics behind cell therapy are highly intense,” says Lachs. “Supply chains are no longer traditional – you have to take into account vein to vein chain of custody and cold chain shipment – and that means working with specialist groups who can facilitate all of those factors. The number of stakeholders involved in executing some of these complex trials has increased phenomenally.

“That means we’ve had to build in-house expertise to support that, both in clinical supplies but also in terms of feet on the ground in supporting sites.”

Dreps highlights biomarkers and precision medicine as others areas of oncology that are continuing to show amazing promise.

“With a biomarker you can identify the optimal target patient population very early on. Whereas 20 years ago chemotherapy agents were targeting many non-cancer cells with a lot of toxicities, we can now identify the subset of patients who express the targeted molecule and deliver a compound directly to the target.

“Biomarker testing for trials is becoming much easier and more widely used. That said, one of the challenges is that it makes clinical trials much more complex – meaning we might need innovative and novel trial designs like basket trials with multiple arms. As a sponsor, you have to look more into the molecular profiling of every patient and make sure that you have all the data available to select the right population.”

# Adapting for the future

As cancer treatment evolves in surprising and dramatic ways so must cancer research – and innovative, adaptive trial designs like these have become more popular in recent years as drug developers realise their potential.

“The changing nature of approaches to oncology means that we are more often looking at a molecular target rather than a specific cancer – e.g. you’re looking for any BRAF mutation or ALK mutation, which cut across the numerous tissue types,” says Lachs. “This is where adaptive trials are particularly useful.”

Adaptive trial designs include:

- Basket trials, which test how well a drug works in patients who have different types of cancer but all have the same mutation or biomarker
- Umbrella trials, which test how well a drug works in patients who have the same type of cancer but different gene mutations or biomarkers. The drugs being tested may change during the trial as new targets and interventions are found
- Platform trials, also called multi-arm, multi-stage (MAMS) trials, test several interventions against a common control group and allow for multiple treatments to enter or exit the trial over the course of the study

“We’re involved in all kinds of adaptive trials, because they are all different and they all have their place,” Lachs says.

“That said, while these innovative trials are very exciting, we also have to proceed with some degree of caution so as to balance complexity and timelines with anticipated trial outcomes.  We have conducted basket trials that have progressed over years and yielded little.”

Dreps adds that adaptive methodologies allow a much more flexible approach than traditional designs.

“A sample size re-estimation tool, for example, is a very flexible adaptive design that allows the sample size of the study to be reassessed mid-way through.

“One of the risks with oncology trials is treating too many patients with an ineffective new drug. If there are signals that the drug is very effective, you might not need to enrol more patients to demonstrate that you can add significant clinical benefit.

“Interim sample size reassessment aims to make sure that we only enrol as many patients as is needed. That will reduce costs and allow us to make earlier decisions, as well as increasing the probability of success.”

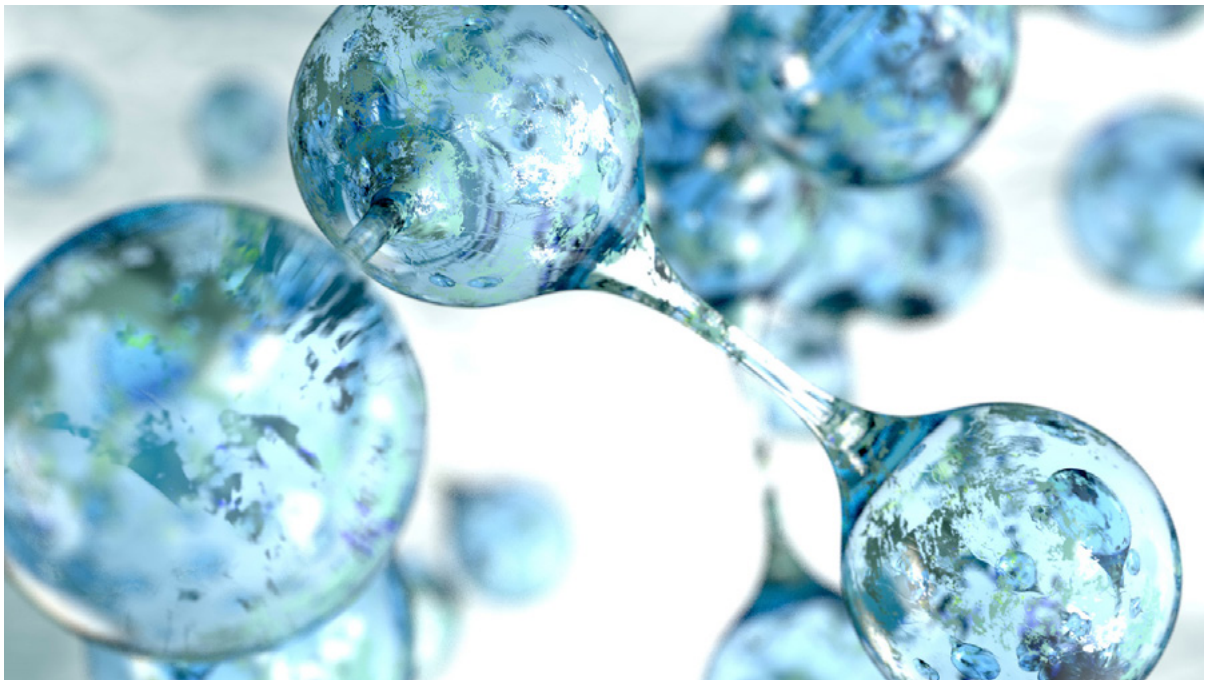
Of course, CROs also have to adapt their businesses to the increased complexities these trial designs bring.

“This involves both building expertise and creating new systems to be more flexible in coping with changes which are required for these protocols – for example taking into account that in basket studies cohorts will drop in and out as the trial progresses,” says Lachs.

“We’ve had to set up our data systems flexibly to facilitate rapid change, but we’ve also had to become much more adept at obtaining data rapidly to facilitate making decisions based on that data, so that we can progress with new arms of the study.”

Dreps adds that it’s important the company employs people with knowledge and expertise in the adaptive trial designs.

“We will likely start seeing biostatistics experts helping us in creating new trial designs more often – which allows us to expedite the entire process and do analysis to decide whether or not to proceed very early on.”



In general, earlier engagement with all stakeholders is becoming increasingly important in order to increase productivity and success.

“More and more we are trying to identify early on the potential candidates for a trial from a pool of pre-screened patients,” Dreps says. “This might require much closer collaboration with investigator networks – as well as the use of data from a patient population that has already received one line of pre-treatment, where the molecular profile is already available.”

Part of this, Lachs adds, is ensuring that ICON is always working in partnership with database platforms, so that the company can build in flexibility.

“Data is going to be an evolving picture,” he says. “We continue to adapt our data collection and our endpoint protection processes to keep pace with the increasing complexity. We’re well set up to do that because of our in-house expertise, and we have an extensive staff training programme for oncology, which we’re constantly reviewing and revising.”

# Cancer research post-COVID

Many would argue that the biggest catalyst for change in cancer research has been the COVID-19 pandemic, which has forced a shift towards remote monitoring, virtual arms and other uses of digital tools as global lockdowns reduce the ability of patients to go to clinics.

Lachs, however, says it’s still too early to tell whether these changes will be permanent.

“I think everybody will have a slightly different take on it,” he says. “COVID has certainly brought to the fore discussions on how you operationalise trials. I don’t think it is at this point having any impact on trial design or endpoint selection, but there’s very healthy discussion going on about running trials differently, right from the patient experience through to how we manage data.

“Thinking about patient centricity, for example, some patients may be fearful to go into hospitals as a result of the COVID-19 situation, and those that do are finding the number of appointments available are reduced to ensure social distancing. You can see that there’s a benefit to the patient if they have to go into the clinic less – perhaps once every two months instead of once every four weeks. We just need to make sure we’re not compromising safety.

“All that is on the table and is being feverishly discussed. The actual application of it might be a bit slower.”

Lachs believes that the permanence of these changes will be contingent on a number of things.

> “If we have another wave or a prolongation of the current wave, I think we are going to be forced into more rapidly changing the way we do trials. If things quickly go back to normal, people will be less compelled to change.”

He says, though, that there will always be a mixed model in oncology.

“The complex requirements of oncology studies – radiology, scans, imaging etc. – can’t be done in an individual’s living room. Neither can earlier phase studies that require hospitalisation for PK sampling.

“Hospitals also have to be amenable to having other bodies being part of the assessments and conduct of clinical trials, both from an economic and logistics point of view.

“Realistically, we have to know that the crisis is not going to completely turn over oncology studies to become completely different from how they are now. It’s going to be an adjunct as much as anything else.”

Nevertheless, Lachs says ICON has made sure to be geared up for increasing virtualisation in trials.

“For example, last year we acquired Symphony Clinical Research, a provider of in-home and alternate site services. We also work with a number of telemedicine platforms, and we have people within our group devoted to the virtualisation of trials.”

# Working with regulatory bodies

The other key factor in being prepared for these changes is making sure regulators are aligned with drug developers and will be open to more innovative trial designs.

“We keep in regular contact with the regulatory bodies to bring ourselves up to speed with regards to their thinking,” says Dreps. “It also gives us the opportunity to discuss our ideas on how to develop new trial designs.”

Dreps and Lachs note, however, that not all regulators are aligned on how to approach adaptive designs – in their experience, for example, the FDA has been more open than the EMA to innovative ways of approaching research.

“We’ve also got to consider Japan’s PMDA and the Chinese NMPA, because they’re also substantial markets, and they’re not all aligned,” says Lachs.

“COVID-19 has in some ways been surprising in marking out what different agencies are permissive of in terms of how we go about conducting clinical trials. For example, the EMA has been more restrictive about remote monitoring or remote access to data than the FDA have – partly due to data protection and GDPR considerations.

“Overall survival has always been the backbone to approvals in oncology, and we anticipate that it will be that way for some time to come. But it’s changing to some degree and I think the FDA is currently more progressive in that regard.”

# The future of oncology

Dreps notes that, above all else, the most critical driver of change is our increasing understanding of the molecular biology of cancer.

“More or less every week we identify a new target, we learn more about pathways, about how to interact with these pathways and potentially how to stop cancer growth. This means the molecular profiling of patients will play a more and more important role.

“Most likely, this will also result in a situation where a new drug is only targeting a very small subset of patients. In contrast to 10 years ago where you normally had to design a trial with thousands of patients, today you often only need a few hundred participants.

“Molecular profiling might eventually allow us to identify those patients who will benefit from a new treatment very early on, such that you need only a very small group to demonstrate significant clinical benefit.”

“The elucidation of our immune system and immunology in general is growing exponentially,” adds Lachs. “Cell therapy is built on the idea of stem cell therapy; the idea of using the body’s own immune systems and immune cells isn’t that new, but the amount of information we’re learning as we do more trials is causing an exponential growth in understanding. That’s going to continue to gain pace.

“I think the actual re-purposing of stem cells – which is currently in the foothills of its development – is really going to take hold and have a major impact on the outcomes for cancer patients.”

Advances in technology are likely to have a similar impact.

“Our ability to use quantum computing to process huge amounts of data rapidly may actually facilitate more synthetic trials so that we can be even better at prediction, especially in combinational trials, where we can see what the best combinations might be,” says Lachs. “That means you can have a more focused approach to the real clinical trials, and it also cuts development time, cuts costs and improves outcomes.

“That’s an area ICON has been looking into for a few years – for example we were involved in the Cancer Moonshot Program headed by Joe Biden – but that concept still needs to be developed further.

“Let me be clear – you’re not going to get approval on the basis of some computer modelling. Rather, it’s about pointing us in the right direction. I think that’s yet to really take hold but I do see it as a real development, and our interest is in no way diminished. We need to have the best technology available for that but we also need to have an appropriate way of getting data, and data is expanding on a daily basis.”

Likewise, predictive analytics and artificial intelligence will help researchers analyse the huge amount of data becoming available.

“That can help us identify new clinical hypotheses to test and expedite enrolment by identifying protocol-ready patients,” says Dreps. “It’s hard to say how long it will take, but this will also become a major driver to improve the development of oncology drugs.”

Lachs again stresses the importance of early engagement with clients to all aspects of drug development.

“The earlier you engage with developers and help them design studies and take into account all the points we’ve discussed, the better. The divide between designing, conceptualising, and operationalising trials is going to blur – and we still need to keep endpoints and even pricing considerations in mind. Our continued investment in technology which supports that is going to be important.

“Meanwhile, with the increasing complexity of molecular targets and data, the relationship between CROs, pharmas and investigator sites needs to become less transactional. We need to be more embedded with what our principal investigators are doing and be a part of that operation.

“All those things need to be brought together and we have that capability and capacity within ICON.”

# About the interviewees

Martin Lachs is vice president, global project management at ICON. With over 28 years' experience in clinical development, Lachs has worked across a number of therapeutic areas whilst specialising in oncology. He is based in the UK and heads up ICON's Oncology and Cell Therapeutics Project Management Group, lending operational and indication expertise across a group of over 260 international project management staff globally, dedicated to oncology and cell therapy drug development. Lachs has worked in developing key oncology site networks in the US and the UK and in 2020 was a member of a clinical trial review panel for University of Sydney affiliated hospitals.

Andreas Dreps is senior vice president, oncology drug development at ICON. Dr Dreps has over 25 years of clinical research and development experience in a variety of solid tumours and haematology diseases including breast, NSCLC, SCLC, pancreatic, gastric, ovarian, colorectal, head & neck and prostate cancers. He is co-author of the EMA submission dossier of Paclitaxel for ovarian cancer and the FDA/EMA Taxotere submission dossier for breast cancer and NSCLC. Prior to joining ICON, Andreas held positions at BMS, Aventis Medical, Merck/Serono and was responsible for the clinical development of Taxol, Taxotere, Campto and Gliadel, among others.

# About ICON

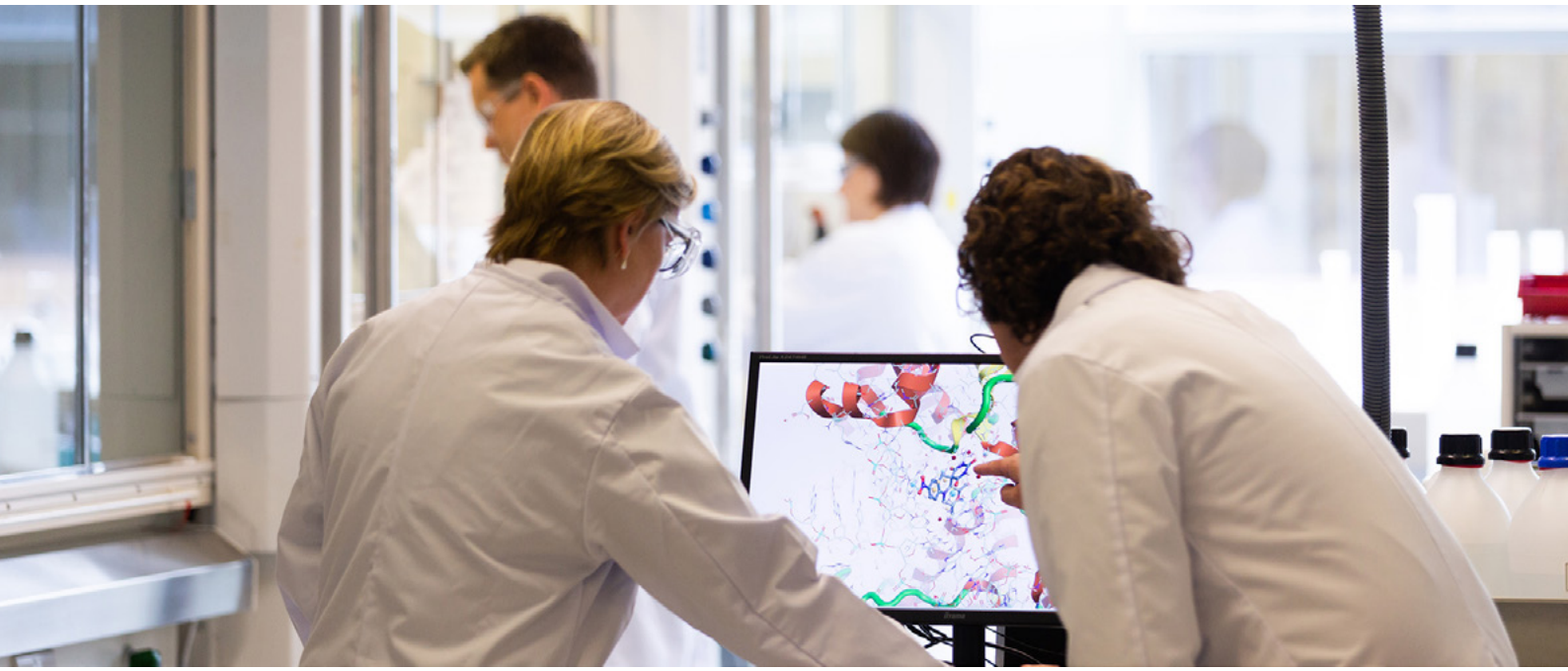
ICON plc is a global provider of outsourced development and commercialisation services to pharmaceutical, biotechnology, medical device, government and public health organisations. ICON supports programs across all stages of drug and device development, from endpoint selection and PRO development, through clinical trials, to post-approval and scientific publication. ICON delivers integrated market access, pricing, communications and health economics solutions to demonstrate product value and support brand success around the globe. For more information visit, www.ICONplc.com/access

ALDERLEY PARK

*53° 16' 46" N 002° 14' 12" W*

# MAKING IT AS AN ONCOLOGY BIOTECH IN THE UK

**We speak to R&D experts to find out how oncology biotechs can get the support they need to be successful in the competitive UK ecosystem**



There has never been a more exciting – or more daunting – time to be an oncology biotech. Amazing breakthroughs in cancer science mean there's no shortage of opportunities in this space – but this also results in fierce competition, and cancer researchers face extra challenges on top of the difficulties posed to any biotech operating in the UK.

"It's very difficult for any biotech to navigate the UK's complex innovation system right now," says Dr Kath Mackay, managing director of Alderley Park, the UK's largest single-site life science campus. "It can be hard for a company to understand who they should be talking to for funding and support. There are a lot of agencies and groups out there, and if you're new to the field, navigating that and working out what's best for you can be a challenge."

She says it's also important to find the right partners.

***"It's very rare for a company in this space to be doing everything themselves – few have expertise in all parts of the discovery and development pathway. They need to outsource and embrace open innovation."***

Mackay says she sees a role for the government in providing "clear and sustainable funding" for biotechs.

"In the life sciences sector there's a particular issue around the lack of patient capital and the funds needed to advance a therapy into the clinic through a rigorous programme of multi-site clinical trials.

"There's a role for both the public and the private sector to support that sustainable investment. In the current model, if companies miss a milestone or a milestone is delayed, valuation rapidly decreases. That is very detrimental to a company. There's a need for long-term patient investment that isn't quite resolved yet."

# Early doors

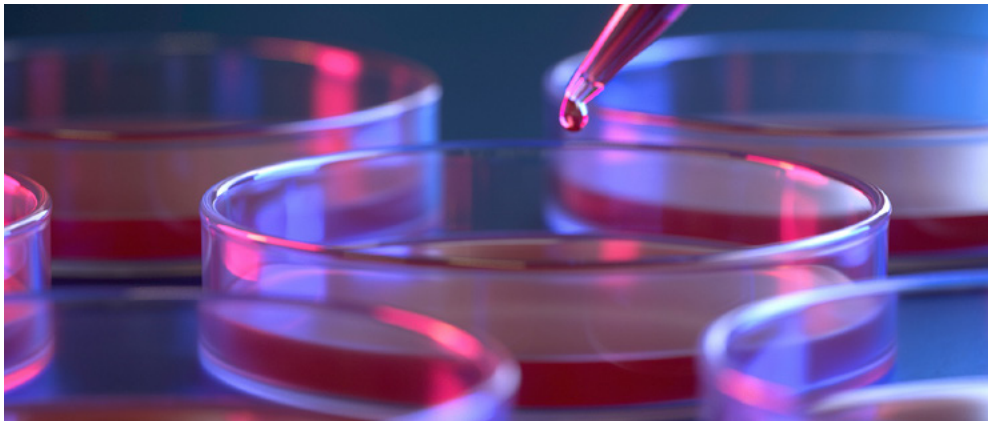
Oncology biotechs face additional challenges on top of this thanks to the complex nature of the disease area.

"The oncology market remains huge," says Mackay. "It's attractive for businesses to go into this area, but it's also an unbelievably competitive field.

"The failure rate in oncology remains extremely high. We still need better approaches, and better pre-clinical models for every aspect of the process."

Luckily, she says, the situation is improving.

"There are many great organisations working closely with their clients to develop new models and approaches, not just to get drugs to the clinic faster, but to do so with an increased chance of delivering patient benefit.



***"The UK has great strength in that pre-clinical CRO piece – the work that the Medicines Discovery Catapult is doing at Alderley Park, for example, is absolutely fundamental to some of that. They need to be supported in their remit to be able to help companies get through some of these technical challenges."***

Allan Jordan, director of oncology drug discovery at Sygnature Discovery (who help their clients discover novel oncology medicines from their sites at Alderley Park and BioCity in Nottingham), says that supporting companies to think holistically about a drug candidate's future as early as possible in the development process is key to mitigating the chance of failure.

"Education is still needed in some areas, but we are seeing more and more companies realise that early planning and engagement with stakeholders is the most sensible, commercially relevant and patient-meaningful way to do what we do," he says.

"The risks of failure are high enough as it is – I've seen compounds get all the way through pre-clinical development and start to move towards the clinic before people realise that either the patient population doesn't exist or they're so heavily pre-treated that they won't respond – thankfully I think that is happening less and less. We're becoming much more astute in that area, much more aware of patient selection, patient stratification, and using that knowledge to drive our drug discovery programmes to enable success, not just in the preclinical stage but also further down the line."

Jordan says that one thing the COVID-19 pandemic has taught the industry is that access to clinical trials can be much more responsive than it has been in the past.

"We've seen with COVID trials that regulatory approval, ethics approval, access to patients and entry into the clinic for novel vaccines, biologics, small molecules, or repurposed agents can be done much faster and more efficiently than it has been done in the past.

***"One of the questions going forward will be how we learn from that and apply it, not just to oncology trials, but to clinical trials in general – such that we can get our medicines into the clinic and deliver patient benefit much more efficiently."***

Steve McConchie, CEO of Aptus Clinical, a full service clinical CRO based at Alderley Park that specialises in the design, conduct and delivery of clinical trials, adds that this 'efficiency' partly involves getting science into the clinic as "quickly and cost effectively" as possible – but it's important to note that there's a difference between 'speed' and 'haste'.

"Sometimes just taking a little bit of time to understand what you're doing and why you're trying to do it is time well spent," he says, "because you can charge into a first-in-human study and waste time and money there if it doesn't recruit or doesn't get the right results."

Meanwhile, 'cost effective' can mean understanding the best use of the resources the biotech has, and where the limits are.

"By 'cost effective' we mean doing the right experiments at the right time to get the right science to the right patient in an optimal way. If you do that then you use your cash in the most efficient manner."

McConchie adds that, ultimately, early hurdles with patient recruitment, ethics committees and regulatory agencies can often be solved by "following the science and putting the patient at the centre of everything you do".

"If you focus on the patient, and the strategic/scientific reason of why there's value to the patient, the ethics committee will be happy with it, the regulatory authorities will be happy with it, and your investigators will agree to it and will be passionate about trying to recruit participants.

"You can sit in an ivory tower and come up with a scientifically amazing trial in melanoma, but if it doesn't fundamentally engage the early-phase clinician who has got the patients in front of them it's not going to go anywhere fast."

# Standing out from the crowd

Medical conferences like ASCO (which, for the time being, are mostly virtual) remain key opportunities for biotechs to find partners and garner interest – although the larger events can be daunting for the smaller companies asked to present alongside some of the biggest players in the industry. So how can biotechs stand out?

McConchie says that this is another area where focusing on science can be extremely helpful.

“The biggest asset a biotech has is its science – that’s what we are all passionate about, and it’s what investigators are passionate about.

“You can’t have a massive stand at ASCO, you can’t do all of the things that some of the larger organisations can do, but what you do have is your science. Again, I think interacting with investigators at a scientific level is really important, because leveraging science for the benefit of patients is what unites us all. That’s how you build those key relationships.”

# Working in the UK ecosystem

Despite the many challenges facing biotechs, Mackay and Jordan both stress that the UK has a vibrant ecosystem for oncology.

Jordan says that having the NHS as a fully integrated health service is “the jewel in the crown” of this environment.

“The networks that exist within the NHS – such as the Experimental Cancer Medicine Centres, expert clinicians, and a communications network across the country that can assign patients to clinical trials, even if they’re not necessarily running in that particular centre – are a huge asset. I don’t think anything like that exists to the same extent in many places around the world. There’s a huge opportunity in those networks to make the UK a global leader in clinical trials.

“That gives us a great baseline to work from. From there we need to encourage greater engagement from the biotech community to strengthen and deepen those networks – turning them into a real force for patient benefit – and get companies to place clinical trials in the UK where that support exists, rather than taking them elsewhere, such as the US, which seems to be a common way forward.”

Meanwhile, Mackay highlights the plethora of small businesses and biotechs at Alderley Park working in this area, supported by the wider ecosystem.

***"We have a lot of activity across all the different types of therapeutics – small molecules still have a role, targeted antibody treatments have been highly dominant, and immuno-oncology and cell and gene therapies, which are considered by many to be the most promising areas of research in cancer therapeutics, are still on the rise."***

She adds that cell and gene therapies are an area of "great strength" for the UK.

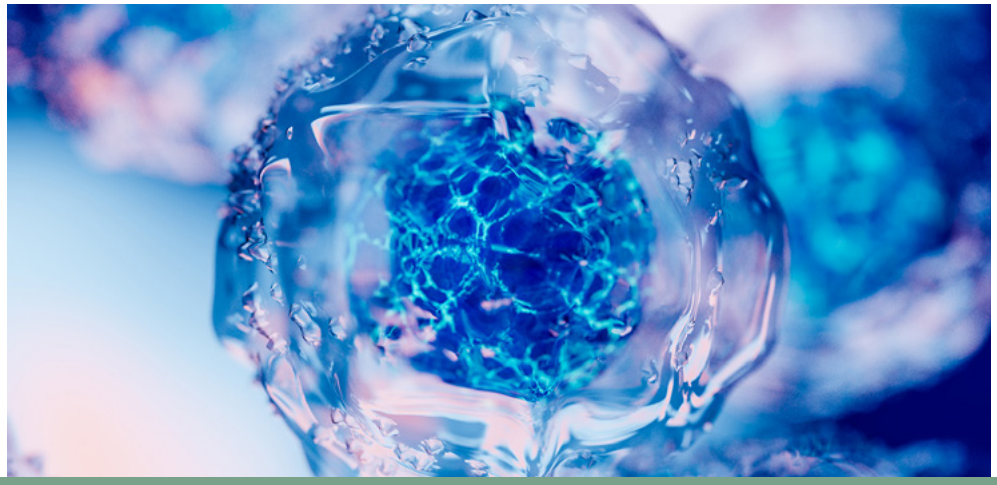
"A lot of investment has gone into supporting development of novel CAR-T cell therapies, which are now licensed for use in the UK. There has been a deliberate and sustained investment from the UK government to support the cell therapy field and we're starting to see returns on that now."

Mackay notes that biotechs working in these specialist areas often require more targeted support, such as in manufacturing cell therapies.

"If we really want these novel treatments to be scaled, then that support needs to be continued because the manufacturing challenges are very different to those in developing a small molecule drug. A lot of research and funding is needed to facilitate widespread use and commercialisation.

"There needs to be a lot of support for helping these new types of therapies onto the NHS – it will require changes to every aspect of the pathway, from lab to bedside."

Mackay says that while this support has been good so far, it needs to be "rolled out to the next stage".



***"While the government has led initiatives to start that work, it's just the start. There needs to be wider engagement from the NHS. It can't seep top-down from the government – various hospital trusts have got to work together, working closely with the wider health system."***

She adds that the UK also needs to encourage more innovation and entrepreneurialism if biotechs are to get more cancer medicines into development and eventually to patients.

McConchie concludes: "At the end of the day, drug development is a team sport. Companies need to engage with scientists, academia and with the service sector to be successful – I think a lot of people don't realise how amazing the service sector here is. You can get anything you need.

"There are a lot of great individuals and organisations that can help you on the journey. I think we're very lucky in the UK to have such a vibrant ecosystem that can help anyone at whatever stage of the journey they're on. You just need to reach out and develop those relationships."

## About the interviewees

Dr Kath Mackay is managing director of Alderley Park, home to the UK's largest single-site life science campus. Her responsibilities include stimulating new business ventures and managing further development of the Park. Mackay joined Alderley Park in 2019 from Innovate UK. In her most recent role there, Mackay was director for ageing society, health and nutrition, and part of the executive management team.

Steve McConchie is CEO of Aptus Clinical. After obtaining a PhD in Biochemistry, McConchie spent 25 years in a variety of clinical development roles with AstraZeneca where he gained valuable global experience in the delivery of numerous oncology and haematology clinical development programmes. Since forming Aptus Clinical with former AZ colleagues, he and his expert teams have continued to support a broad range of life science and biotech clients with the design, conduct and delivery of innovative early phase clinical studies in oncology.

---

Allan Jordan is director of oncology drug discovery at Sygnature Discovery. His role includes scientific oversight of the oncology projects within Sygnature and the strategic development and enhancement of capabilities and expertise in oncology. Jordan started his career as a medicinal chemist at RiboTargets (now Vernalis). After ten years in the lab, he joined Cancer Research UK (CRUK) as head of chemistry in the Manchester Institute Drug Discovery Unit.

## About Alderley Park

ALDERLEY PARK

*53° 16' 46" N 002° 14' 12" W*

Alderley Park is a place where world leading science, innovation and stylish living come together to create a place like no other.

Part of Bruntwood SciTech, a 50:50 joint venture between leading property company Bruntwood and Legal and General, Alderley Park is currently undergoing a £247 million investment. Home to the internationally recognised Mereside life science campus, the Park offers more than 1m sq ft of high specification lab space, a range of scientific services and an accelerator delivering a comprehensive programme of business support for start-ups and scale-ups. It is also home to a vibrant and fast-growing community of over 60 established and 150 pre start-up companies.

Follow news from the park on Twitter or LinkedIn.

Advanced Clinical

# Solving immuno-oncology trial challenges in the COVID-19 era

The COVID-19 pandemic has placed immense stress on healthcare provision, but the emergency may also make major advances in cancer treatment even more relevant – if studies can continue to improve

The last decade has seen a sustained period of progress in cancer treatment with the emergence of immuno-oncology as a serious therapeutic option in the years since the US Food and Drug Administration's 2010 approval for Dendreon's pioneering Provenge.

Today, many other mechanisms have built on the ground broken by Provenge. Leading the way have been checkpoint inhibitors of PD-1/PD-L1 and CTLA-4, the leading products of which have already been phenomenally successful.

However, immuno-oncology is a field that doesn't stand still and, after 10 years of change, more advances are anticipated as understanding improves about how the various immuno-oncology treatments available and in development work, both on their own and in combination.

Now, widely heralded as the future of oncology, immuno-oncology's favourable safety profile and beneficial treatment characteristics may also see it take on greater relevance in light of the COVID-19 pandemic.

Improvements are needed to the way immuno-oncology drugs are studied, and a host of different pharmaceutical companies are ramping up their clinical research efforts to test these types of drugs in different settings, combinations and treatment lines.

# Immuno-oncology trends

As pharmaceutical companies train their research efforts on unmet needs in oncology, some standout applications are being seen as new immuno-oncology medicines help patients with hard-to-treat cancers to live longer.

According to Dr Pavel Tyan, therapeutic area lead, oncology at global contract research organisation Advanced Clinical, unmet medical need is the main driver for all oncology drug development, but especially for immuno-oncology. He notes: "Metastatic melanoma used to be seen as an incurable and deadly disease. Now, with immunotherapy, we see it as a controlled disease or even potentially curable."

Immuno-oncology has also made some large steps forward in a number of other cancers in terms of overall survival and progression-free survival – importantly, without increasing toxicity. Indeed, the perception of certain tumour types is undergoing huge changes, based on these therapies' performance, including in hard-to-treat diseases, like pancreatic cancer or prostate cancer.

Andres McAllister is chief medical officer at BioInvent, a Swedish life sciences company that specialises in immuno-oncology. He says: “Interestingly, in the area of immunotherapy the first trials had to be done in very advanced disease. Now you see those targets moving into earlier stage disease. For instance, in lung cancer, stage three is now being addressed with immunotherapy. I think that will be the trend, to see earlier stage disease being treated with immunotherapy. You will see neoadjuvant therapy used as part of the treatment paradigm.”

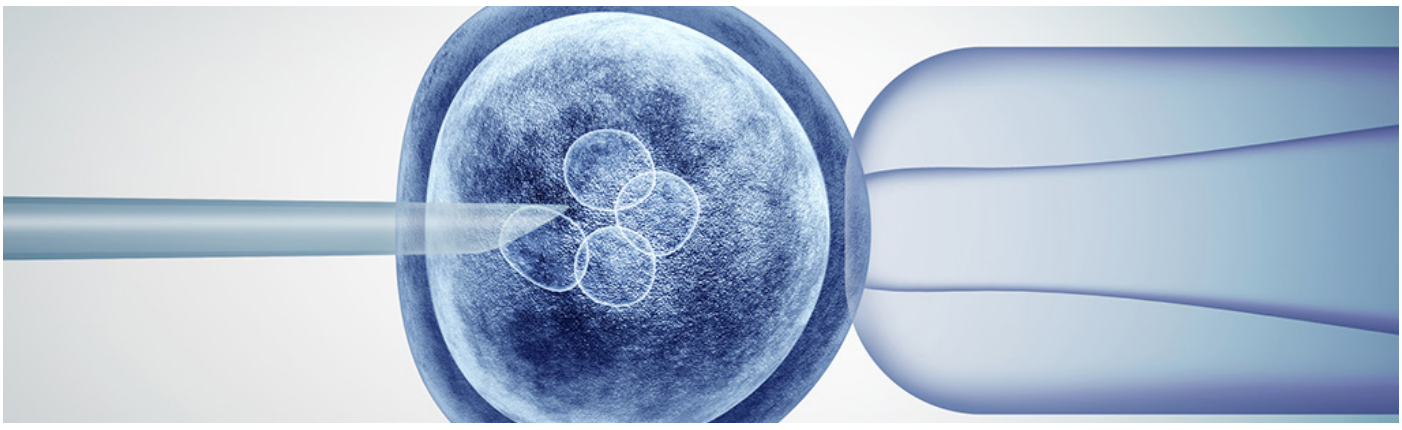
Looking at the current treatment options, particularly for advanced metastatic tumours, he sees the next few years bringing greater understanding of the role of combinations of immunotherapy with other agents such as chemotherapy and radiotherapy. “There is a lot to do here that hasn’t yet been done and it’s likely to come in the next few years,” says Andres.

## Treatment advances

The striking advances made to date in immuno-oncology have primarily come from treatments focused on two targets – PD-1/PD-L1 and CTLA-4 – which both negatively regulate the T-cell immune function to increase activation of the body’s own immune system.

PD-1, or programmed cell death protein 1, and its associated programmed death-ligand 1 (PD-L1) have so far proved most profitable for the pharmaceutical industry. Merck & Co’s Keytruda (pembrolizumab) and Bristol Myers Squibb’s (BMS) Opdivo (nivolumab) were the first two PD-1 inhibitors to come to market and have each built blockbuster brands that brought annual sales in 2019 of $11.1 billion and $7.2 billion respectively from melanoma, lung cancer, stomach cancer, liver cancer, and head and neck cancer. Meanwhile, a smaller number of drugs have been developed to target CTLA-4 (cytotoxic T-lymphocyte- associated protein 4), most notably BMS’ Yervoy (ipilimumab).

In addition, the PD-1/PD-L1 and CTLA-4 inhibitors, the other prominent immuno-oncology class are the CAR-T (chimeric antigen receptor T-cell) therapies, whose complicated route of administration involves a patient’s own T-cells being harvested, modified to fight his or her cancer and then injected back into the patient’s body. The first CAR-T to be approved in the US was Novartis’ Kymriah (tisagenlecleucel) in acute lymphoblastic leukaemia in 2017, followed by Gilead’s Yescarta (axicabtagene ciloleucel) in lymphoma.



These advances are being extended by the beginnings of a new wave of tumour-agnostic drugs – led by Roche's Rozlytrek (entrectinib), Bayer's Vitrakvi (larotrectinib) and Keytruda.

Hand-in-hand with these treatment advances have come new ways to diagnose and look at cancer with biomarkers, as diagnosis and treatment become ever more interconnected.

Pavel explains: "Previously, we just looked into the cancer histology and whether or not it showed adenocarcinoma, sarcoma or any other type of tumour. Then, based on that, we decided what kind of drugs will be useful. Biomarkers are a different approach. We can see if specific tumours are hybrids or over-express specific biomarkers, even regardless of the histology of tumour types. So, there is a shift in how we see the tumour.

> "The histology itself is still an important factor, but it no longer means as much now as it once did. For example, lung cancer was previously considered a single disease, but now it is seen as a family of diseases of which there are numerous different types of biomarker-based treatment strategies and approaches."

Meanwhile, at BioInvent they have spent the last five years exploring mechanisms of resistance to immunotherapy. Andres explains: "If you look at, for instance, mechanisms of resistance in T-cell-driven cell theory, such as PD-1, PD-L1 and CTLA-4, all of those things basically step on the brakes of the immune responses against cancer, but that is all part of the adaptive immune response. An area where people haven't really looked is the innate immune response."

The company is exploring ways of using Fc gamma receptor proteins to enhance cancer immunotherapy by targeting these proteins which, BioInvent says act as 'antibody checkpoints'.

## Immuno-oncology and COVID-19

Amid these medical advances the current global COVID-19 has had a major impact on cancer and clinical trials, affecting treatment and oncology patients in a number of different ways.

The significant pressure and increased workload due to the massive hospitalisations of COVID patients has led to the re-profiling of many hospitals and departments including oncology clinics for treating patients with the COVID infection. Consequently, many diagnostic and treatment procedures have been cancelled or postponed around the world, including as many as 2.3 million cancer surgeries according to one study.

The real impact could be much wider, according to Pavel. "Not only surgeries, but also the medicinal treatments have been affected as the majority of them require either visits to clinics or overnight stays and there is also an increased risk of severe COVID disease due to the toxic

anticancer therapy. Also, as they are patients from a high-risk group due to multiple organ system dysfunctions, especially those with advanced disease, they must be isolated from others as much as possible. The global oncology community is concerned about the rise of cancer cases and the increase of the portion of advanced disease in the near future."

Clinical trials in oncology, as in other therapy areas, have also been affected, with about 170 studies suspended due to COVID-19, according to a report by Evaluate Vantage.

In many oncology trials the number of participants that have completed, or are in the process of completing, a study has decreased, while the number of protocol deviations being registered has increased. As well as sending clinical trial costs higher, the pandemic can have other impacts on studies.

Pavel explains: "COVID-19-related deaths could potentially affect survival endpoints in some studies. Both survival and PRO-based endpoints are affected due to the enormous stress, anxiety and fear oncology patients are now experiencing."

Immuno-oncology may also come into its own at this time, given the benefits that it has traditionally shown over chemotherapy – particularly combinations of chemotherapy agents – and other more traditional cancer treatments, in terms of its safety profile.

"The recently published TERAVOLT study has confirmed that the chemotherapy was an additional risk factor for the development of COVID disease compared to immuno-oncology or target therapy," Pavel says. "Even though cancer immunotherapy is not intended to treat infections, I think it has the same vector and works in the same direction towards boosting the patient's immune system rather than abating it as chemotherapy does.

> "We also see some similarities between the COVID manifestations and cytokine release syndrome, which is one of the expected complications of anticancer immunotherapy. The immune modulator cancer drug tocilizumab is one of the drugs being tested as a treatment for COVID-19."

Immunotherapy has also been found to have a durable treatment response in patients after just a few courses of therapy, for example in cases where patients can't continue with their treatment. The drugs reveal the cancer to the body's immune system, turning it against the cancer and, when treatment stops, the immune system can continue killing the cancer itself. That, Pavel says, is in contrast to cytotoxic chemotherapy, which can only kill tumour cells when treatment is ongoing and can do nothing to prevent the cancer relapsing after the chemotherapy is stopped.

## Clinical trial challenges in immuno-oncology

As advanced as the use of immuno-oncology appears to be today, there is still plenty more to learn about these medicines. One of the most pressing issues to assess is how to ensure they are as effective as they can be, which increasingly requires testing combinations of different drugs to look for synergistic effects.

Pavel explains: "Combinations of immuno-oncology treatment are still a relatively unexplored area for us. One of the main challenges they present is in terms of their toxicity, as we don't know much about it. So how do these two different types of immunotherapy interact with each other? We need to know whether or not there will be overlapping toxicity or additional toxicity, for example."

For all types of immuno-oncology studies trial design is a challenge. It requires sponsors to move on from traditional clinical trial designs that were invented for chemotherapy and look to the unique characteristics, features and responses of immuno-oncology.

"The old standards may not always be applicable for a new immunotherapy or combinational therapy," says Pavel. "More and more sophisticated trial designs are needed, especially for early phase and dose escalation trials, and often they'll need to be based on adaptive trial principles rather than conventional ones."

As part of this, he says, pharmaceutical companies will need to think carefully about how to set optimal timings for initial responses, dose escalation and trial duration. “Another question is how to choose correct endpoints and assessment criteria for these trials. This makes a huge impact on a study design, development strategy and also on the cost of a drug.”

These are crucial questions to answer correctly within such a competitive and crowded environment and, as further trials are required, their importance will only increase.

As Pavel confirms: “We will see more and more immuno-oncology combination trials because, even if we know that immuno-oncology is quite an effective treatment, especially in certain types of tumours, there is still resistance to immuno-oncology drugs. In research now, we look to see how to overcome this resistance and how to make these effective drugs even more effective.”

## Still more to do

This is a fascinating time for immuno-oncology research, as pharmaceutical companies work hard to test their drugs in optimal settings, combinations and treatment lines, with the aim of building on the area’s early advances to make immuno-oncology treatment even more effective.

As part of those efforts the industry has more work to do in tackling hard-to-treat cancers and there are ongoing challenges to be overcome in making clinical trials more patient-centric, both of which have been long-term issues for research.

Progress will come, but the additional trial issues raised by the COVID-19 pandemic are certain to continue providing companies with additional obstacles to navigate, at least for the short to medium term.

Nevertheless, while there is still more work to do, the future for immuno-oncology trials, and the treatments they result in, is bright. As Andres notes: “Immunotherapy of cancer has changed the way cancer patients are treated today for the most part. There are still a few areas where that hasn’t happened yet, but it will.”

Download the Trends in Immuno-Oncology white paper from Advanced Clinical

# About the interviewees

**Pavel Tyan, therapeutic area lead, oncology, Advanced Clinical**

Pavel has over 20 years' experience working in hospital, pharmaceutical and clinical research roles and has degrees in General Medicine, General Surgery and Medical Oncology; he is an active member of American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO).

**Andres McAllister, chief medical officer, BioInvent**

Andres is a doctor in Medicine and Surgery from the Universidad del Rosario (Bogotá) and holds a PHD from the Pasteur Institut/Université Paris. He has been with BioInvent since 2017. He has performed academic work at the Pasteur Institut and the University of California, San Francisco, on cancer immunotherapy.

**Graham Belgrave, senior vice president, head of european operations, Advanced Clinical**

Graham Belgrave has over 35 years of experience leading pharmaceutical development across clinical operations (phases I-IV), outsourcing and contract management, project, programme and vendor management. During that time, he has held senior management roles overseeing clinical operations, outsourcing and vendor management at global pharma and biotech companies.

# About Advanced Clinical

Advanced Clinical is a global clinical research services organisation that provides CRO, FSP, quality and validation, and strategic resourcing services for biopharmaceutical and medical device organisations. Our mission is to deliver a better clinical experience.

To learn more, visit www.advancedclinical.com.

PODCAST

# Catch up on the series so far

Hear about biotech strategy, digital disruption, biosimilars, marketing teams and much more.

**Listen Today!**
https://pharmaphorum.com/podcast/

pharmaphorum™
bringing healthcare together

accenture

# Clinical decision support tools will help oncologists manage complexity

Making treatment decisions is a tough choice for oncologists: a therapy might save or significantly extend one patient's life but not deliver the desired outcome for another patient. Reaching this decision involves weighing a variety of data – from clinical trials to the patient's medical background – and with the advent of more personalised oncology, the sheer volume of data that needs to be considered is growing exponentially.

When we speak to oncologists, the most consistent feedback we hear is that the complexity of information is increasing and we need support to access it faster, more efficiently and in a more targeted manner.

Consider how precision oncology will fundamentally change the way cancer patients are treated. First, instead of looking at the organ of the cancer's origin only, doctors are going to pay more attention to the patient's genomic characteristics and the medical history when deciding on the most effective cancer therapy. With next-generation sequencing technologies now broadly available, it is easier than ever before to understand the genomic variants of a cancer. We expect many new therapies based on the molecular profile of a tumour to come to the market in the next three to five years; for some indications it could be two or three times as many therapies compared to today.

All the 'new' data that is becoming available is driving therapeutic decisions in oncology.

It is therefore legitimate to ask: could oncologists be overwhelmed by the amount of data available to them? The short answer is: if limited to only today's standard tools and practices, if they aren't already, they will be very soon.

In the near future, oncologists will need to embrace digital solutions, such as Clinical Decision Support (CDS) systems, to manage the complexity. Based on algorithms and extensive computing power, CDS tools can structure and filter clinical data to help physicians make more informed treatment decisions faster.

However, according to our recent research with 130 oncologists from the US and Europe, only one fifth of oncologists routinely use CDS tools today. We expect that number to significantly increase and CDS to become a standard tool for tumour diagnosis in the coming years. Furthermore, we believe that these tools will contribute to the breakthrough of precision oncology as they help physicians choose individual therapies for patients over standard treatments and do so with a reduced margin of error.

The main objective of CDS tools is to structure and filter information so the physician will only have to analyse data relevant to a specific case. Depending on the task – either diagnosis or assisting in treatment decisions – the way the CDS tool supports the physician is different. In the first case, CDS are significantly reducing the risk of human error by 'spotting' things even the most experienced oncologists might overlook or at least need a second opinion for.

When it comes to deciding on the right treatment, CDS is not replacing the physician's authority but rather provides and classifies relevant information that allows the specialist to make an even better and more informed decision. For example, CDS tools display the appropriate clinical evidence. As a medical director at a breast cancer centre points out: "These recommendations solicit our thoughts and I feel like we can be better doctors and can deliver better, more precise care."

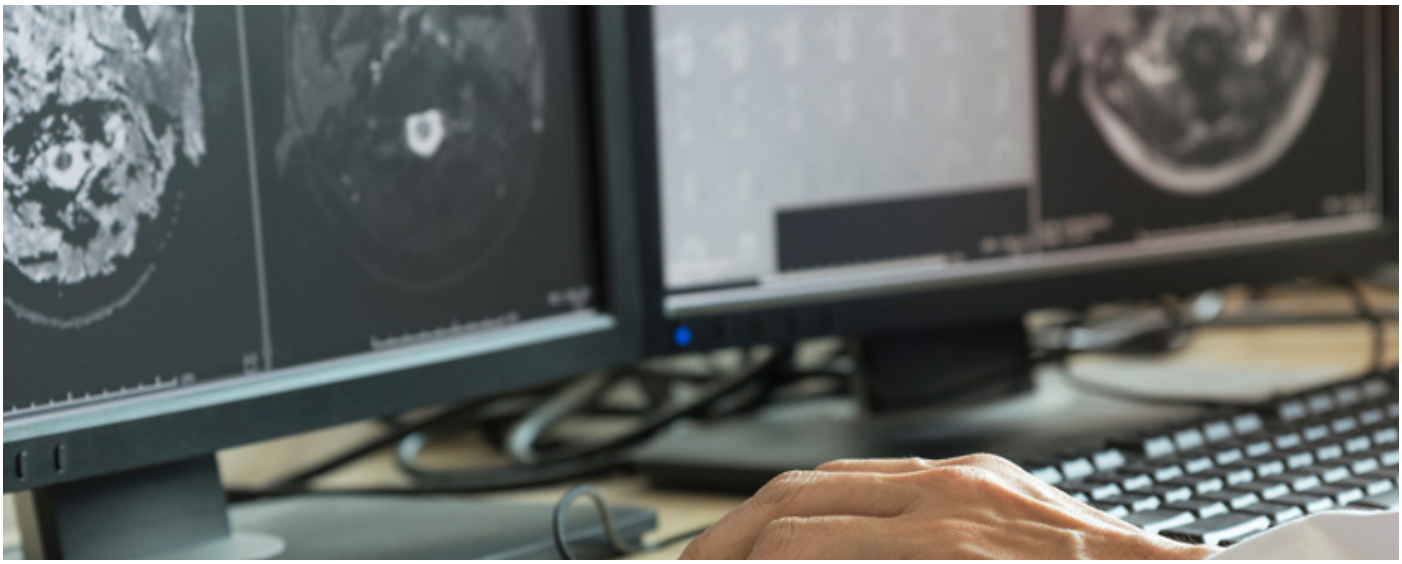
This feature becomes even more important as the number of possible therapy options increases once oncologists start considering genomic profiling for their patients. One medical centre assistant professor argues that, as treatment options are "going to get more granular and more detailed, it's good to have a lot of treatment support". This allows oncologists to use non-standard treatments with more confidence or focus on the findings of a clinical trial for a particular sub-population.

So why isn't it used more now?

The complaint we've heard from physicians is that too much useless data is thrown at them and that CDS tools aren't always very good at understanding the context in which decisions need to be made by physicians. A lung cancer specialist illustrates this perfectly: "If you have a patient who's a smoker, I get a pop up saying 'Did you screen them for lung cancer?' I am a lung cancer doctor. All my patients have lung cancer."

One-size-fits-all CDS tools simply ask too many questions or require too much effort by the physicians to get the user experience right. Instead of reducing complexity and saving time for the physician, one-size-fits-all CDS tools have the opposite effect in reality: they require physicians to filter much more information themselves as they need to carefully consider which click is important and which is not. The more the physician has a role in triggering the right information, the less likely the physician will use the tool – it needs to happen in the background.

But it will – with improved algorithms and more real-world data being fed into these tools, CDS will become even more accurate in the future. Consequently, CDS tools will become the standard application in diagnostics. They are more likely to get the diagnosis 100% right compared to even the most experienced oncologist who might only be at 99%. CDS tools need to improve by requiring less front-end physician input than they do now.



To be clear, CDS systems are in the end just tools. The most effective therapy might not always be the best treatment option for the patient. Quality of life, for example, is a dimension that is hardly considered by algorithms although it is a very important aspect for patients who are going through cancer therapy. It is the patient and the doctor deciding together what the right approach is in an individual situation. But arming both the patient and physician with the best possible information to help make that decision is crucial.

To learn more about what oncologists say they need, read our full research report The Future Is now: How to Drive Precision Oncology

# About the authors

Dr Boris Bogdan, medical doctor by training, is a partner at Accenture Switzerland and globally leads Accenture's Precision Oncology and Personalised Healthcare Practice. His passion is to envision the future of healthcare. Prior to joining Accenture, Dr Bogdan was an entrepreneur and part of McKinsey. He has published numerous publications on the pharmaceutical industry and is author of the books Valuation in Life Sciences and Medrevolution.

---

Dr Sandra Dietschy-Künzle is a senior principal in Accenture's Life Sciences practice with more than 10 years of experience in the healthcare industry and in-depth expertise on drug development in the field of oncology. Prior to joining Accenture, Dr Dietschy-Künzle held positions at a biotech company and has worked as an equity analyst for the healthcare sector. She has supported the development of oncology assets from early research into late clinical development. She holds a PhD in Natural Sciences from the University of Zurich.

# About Accenture

Accenture is a leading global professional services company, providing a broad range of services in strategy and consulting, interactive, technology and operations, with digital capabilities across all of these services. We combine unmatched experience and specialised capabilities across more than 40 industries — powered by the world's largest network of Advanced Technology and Intelligent Operations centers. With 509,000 people serving clients in more than 120 countries, Accenture brings continuous innovation to help clients improve their performance and create lasting value across their enterprises. Visit us at www.accenture.com

Medscape
Oncology Global

# How to increase haematologists' and oncologists' confidence with new treatments

A new whitepaper from Medscape highlights the difficulties haematologists and oncologists face in keeping up with rapid developments in treatment. We speak to the company's Katie Lucero and Victoria Harvey-Jones to find out how independent medical education is changing to help HCPs increase their confidence in treating cancer patients.

It's an exciting time to be a haematologist/oncologist, with new clinical data emerging and new drugs being approved at a stunning pace. But this comes at a price – physicians sometimes struggle to keep pace with the mountains of data, and the resulting implications for clinical practice and the patient sitting in front of them.

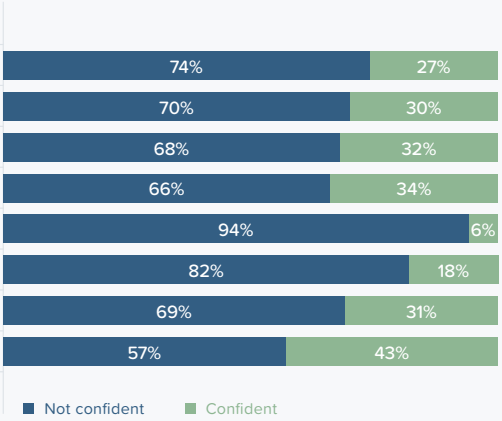
Decision making is becoming particularly difficult for haematologists/oncologists in the community setting – who treat more than 50% of all cancer patients in Europe. Community haematologists/oncologists can also see patients who present with every type of solid tumour, as well as haematological malignancies.

A Medscape confidence-based assessment of European Union haematologists/oncologists found that, when selecting from eight different treatment choices for a patient with relapsed/refractory multiple myeloma, only 43% of them were confident in their choice, at best (see figure 1).

*Figure 1: Decision-making for a relapsed/refractory case of multiple myeloma*

A 60-year-old male with multiple myeloma, no cytogenetic abnormalities, and otherwise healthy without significant comorbidities, achieved complete response after initial induction therapy (bortezomib/lenalidomide/dexamethasone) followed by ASCT. He was placed on maintenance therapy of lenalidomide for 1 year. After 1 year, he relapsed. What would your next treatment decision be for this patient?

| Decision | Percent | Count |
|---|---|---|
| Bortezomib/lenalidomide/dexamethasone | 29% | 35 |
| Carfilzomib/lenalidomide/dexamethasone | 37% | 44 |
| Daratumumab/bortezomib/dexamethasone | 38% | 45 |
| Daratumumab /lenalidomide/dexamethasone | 30% | 36 |
| Elotuzumab/lenalidomide/dexamethasone | 14% | 17 |
| Ixazomib/lenalidomide/dexamethasone | 15% | 18 |
| Ixazomib/pomalidomide/dexamethasone | 14% | 17 |
| Daratumumab/pomalidomide/dexamethasone | 26% | 31 |




*Source: Medscape Oncology Global 2019 (Behavioral Insights: Practicing Hematologists'/Oncologists' Search for Evidence)*

"The space is filled with options, some of which may work better given patient preferences or characteristics," says Dr Victoria Harvey-Jones, associate director of clinical strategy at Medscape Oncology Global. "Haematologists/oncologists need the right education at the right time to help make decisions in which they feel confident."

She adds that time is another challenge.

"Pressures are mounting on physicians in several different ways and finding the time to not only keep up to date with all the available data, evolving guidelines and clinical protocols, but to also consider how these impact their patients is challenging. Collectively this adds to the complexity of making continuous treatment decisions for each patient they see, as well as the confidence that they have in making those decisions."

Dr Katie Lucero, director of outcomes and insights at Medscape Education Global, says that patient pressures may also contribute to this lack of confidence.

"With the availability of information about treatments and patient experience 24/7 via the internet, patients come armed with their own idea of what treatment should be along with their personal goals for treatment.

"Triangulated with the need to stay up to date because of the fast pace of the latest evidence and institutional protocols for treatment, this situation creates a complex system for making treatment decisions and having confidence in those decisions."

As noted by Medscape's whitepaper, *Behavioral Insights: Practicing Hematologists'/Oncologists' Search for Evidence to Empower Clinical Decision-Making*, the gap between physicians knowing what they're doing and feeling comfortable with what they're doing is growing wider.

# Finding mastery in clinical practice

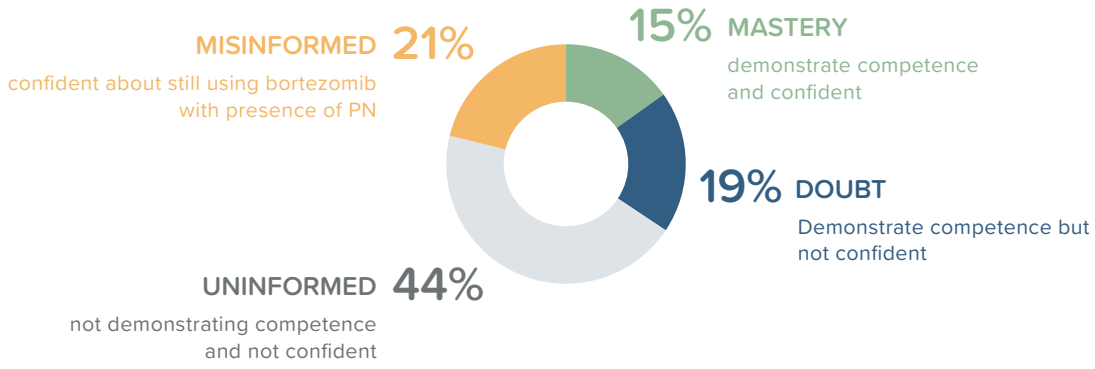
The whitepaper also showed that very few haematologists/oncologists demonstrated mastery – defined as showing both competence and confidence – in making treatment decisions with the presence of an adverse effect.

In fact, only 15% demonstrated mastery when answering a case-based question regarding a patient with multiple myeloma who presented with severe peripheral neuropathy (figure 2).

Meanwhile, 44% of those surveyed demonstrated neither competence nor confidence – 21% were misinformed and were confident about continuing to use an agent that was not recommended for use in patients with this condition.

*Figure 2: Confidence-based assessment of a multiple myeloma patient presenting with severe peripheral neuropathy*

**Only 15% of hematologists/oncologists are demonstrating competence and report confidence**




*Source: Medscape Oncology Global 2019 (Behavioral Insights: Practicing Hematologists'/Oncologists' Search for Evidence)*

Lucero says these results likely come down to “a lack of education and experience”.

“In this case the treatment was linked with a particular adverse event. The majority of survey respondents were community haematologists/oncologists, so it is plausible that they had not encountered such an adverse event before, and it didn’t jump out at them when they read the case.

“Obviously surveys do have limitations in that they are not as high stakes as the real world, so although research shows case vignettes are correlated with and good indicators of real world practice, they may not motivate information-seeking in the same way. For example, if one was unsure in the real world, they might seek additional information.

“It’s unlikely that during the survey, they sought additional information to answer the questions. So that 15% is a conservative estimate but still reflective of the small percentage who could recall the correct answer with confidence.”

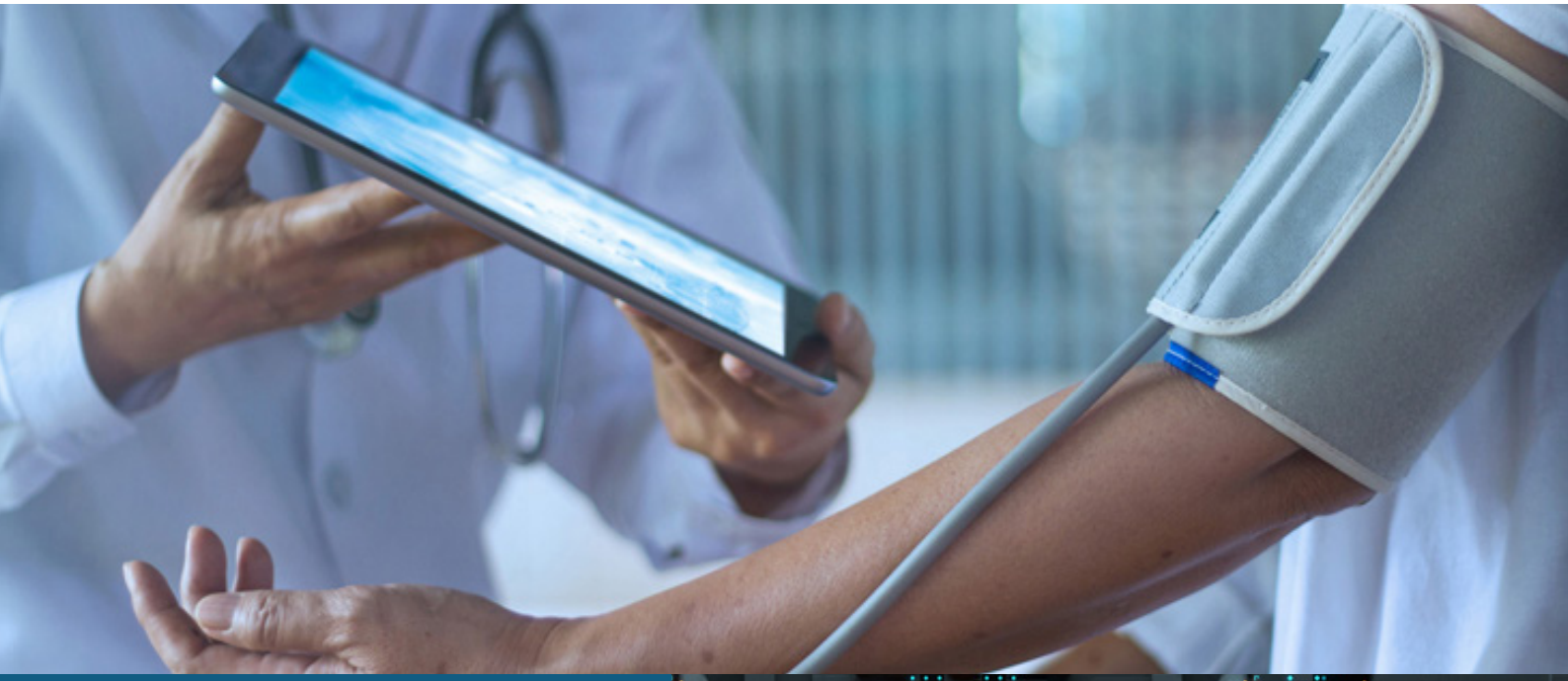
Harvey-Jones adds: “Community haematologists/oncologists never know what they will be presented with next in the clinic and the more nuanced the patient presentation the more challenging it is for the clinician to make treatment decisions.”

# Providing knowledge and confidence

Lucero says the results suggest that, because of the multitude of treatments available that may be effective in multiple myeloma, haematologists/oncologists need continuing medical education (CME) to truly understand how to apply evidence to practice.

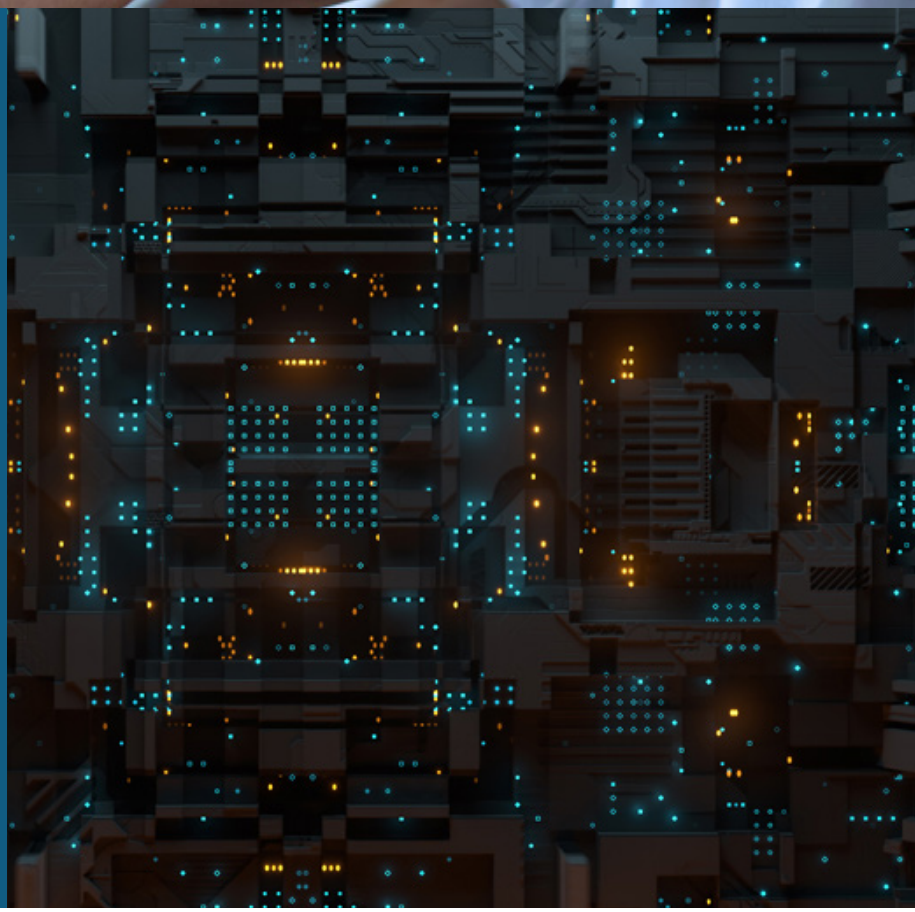
“Behavioural theories and research generally point to the importance of confidence in behaviour change. Confidence is typically obtained from vicarious learning – watching others successfully enact the behaviour, through skills practice, and knowledge acquisition. Adding formative feedback (immediate feedback after practicing) adds an additional bump to learning and confidence.

"We see that when competence improves or is reinforced (i.e. confirmation of current decision-making) from education, there is also an increase in confidence. Confidence gains are largest when there is improvement in competence, but there are still significant gains from experiencing reinforcement. If one does not demonstrate any competence from the activity via assessment, that is linked with lower starting confidence and non-significant increases in confidence from pre to post."



The whitepaper shows that education has a consistent impact on knowledge, competence, and confidence – average relative increases in knowledge/competence in clinical trial data, treatment decisions, and patient management resulting from CME activities in acute myeloid leukaemia, multiple myeloma, and chronic lymphocytic leukaemia were 20%, 25% and 28%, respectively.

Importantly, although baseline knowledge and competence consistently decrease in the wake of market events from the previous quarter, subsequent evidence-based education increases the knowledge and evidence-based decision making of the learners.



Harvey-Jones says that case-based education is important for community haematologists/oncologists.

"While a review of available data is useful, expert opinion and translating these data into practical application using case-based learning is critical. Community-based haematologists/oncologists want to know how to apply the multitude of available clinical data, so they can transfer their knowledge of that data into confident and optimal decision-making that ultimately has a positive impact on patient outcomes."

"Case-based education allows skills practice which can build confidence and make for a more effective clinician when coupled with the best information," Lucero adds. "Case-based can be done through text, audio, video, and simulation, so it's possible to implement in almost any format."

"Case-based learning is more exciting and can enliven topics that might otherwise not be engaging," notes Dr Sagar Lonial, chief medical officer, Winship Cancer Institute of Emory University, quoted by the report.

# The digital future of education

Flexibility in format is a key point – with Medscape's study finding that over 75% of learners identified convenience and content quality as important factors in choosing a learning activity.

"There is definitely a trend for preference of more bite-size lengths of content – such as two 15-minute segments versus one 30-minute segment," Lucero says.

Harvey-Jones notes that this is partly driven by changing demographics among HCPs.

"Some years ago, we reached a digital tipping point where most practicing physicians are now 'digital natives' and are often going online for their education rather than seeking face to face opportunities."

Lucero predicts that medical education in this area will continue to trend towards digital, expedited, of course, by the effects of the COVID-19 pandemic.

"The 80% or more of physicians who regularly attend live meetings each year will have to get that information elsewhere. Digital information is more vital now than ever, and I see the innovation in digital exponentially growing. There will be more innovative live stream platforms and enduring formats."

"The COVID-19 pandemic really has highlighted the presence of conflicting information available. This means clinicians need to have trusted, up-to-date, scientific sources of information to feel confident in what they are consuming and utilise the best evidence in practice."

Further data from a 2020 McKinsey report suggests that 93% of physicians expect to use digital tools for clinical-decision support the same amount, greater or significantly greater after the COVID-19 crisis. Furthermore, 90% of physicians say they will engage with remote learning tools the same amount, greater or significantly greater after COVID-19.

"We know that haematologists/oncologists get information that impacts their practice from a multitude of sources beyond online education – including scientific journals, live meetings, clinical/medical news, colleagues, and pharma," says Lucero. "If the information is important to the extent that not using it may cause harm, then it must be available at the point of care. That's what makes online very powerful. Making the same information available in many different formats is one way to reach clinicians with the right information at the right time."

Dr Lonial agrees: “CME is most valuable when presenters provide clinical context regarding real-world situations rather than just regurgitating study data. This type of CME can be done at live meetings and recorded for online presentation. CME is used over and over again by people who can’t be at live meetings.”

He says that it is important to recognise that “most digital sources of medical information are not peer reviewed”. Conversely, he says, non-biased, evidence-based, peer-reviewed CME, “provides a lot of credibility”.


“Medical journals are late to the game,” Dr Lonial adds. “Press releases get attention but may not drive practice changes. [There is a] fairly fluid area of treatment in multiple myeloma… things change quickly. Because data is presented at conferences… practice changes often precede actual label changes.”

While the whitepaper showed that 47% of practice changes were driven by medical journals, online CME also has the advantage of being able to cover late-breaking developments reported at conferences – recorded and interpreted for rapid online delivery.

“The types of digital education will also evolve,” says Harvey-Jones, “becoming more innovative and interactive to maintain that important scientific exchange between teacher (the expert) and learner (the community physician) that provides value during those face to face educational opportunities that may become less frequent.”

# The power of digital

Harvey-Jones adds that a blended approach to learning will continue to be important and this is key for engaging all kinds of physicians.

“It’s important to provide education in a variety of formats, such as text-based, video-based or simulation, and at the time that suits physicians the most. Haematologists/oncologists get their information from a multitude of different sources such as online news articles, guideline updates, medical journals, expert opinions – it’s important to have these available to them.

“We also need to ensure that the content is convenient and of high quality – short, bite-sized pieces of education are becoming increasingly popular and it’s important to make sure that the data is contextualised for what it means for daily clinical practice and the patients sitting in front of them.”

A recent study by the FDA and Medscape, published in *Pharmacy Practice*, has also shown that digital CME combined with Targeted Short Form Messages can often offer the biggest benefit for HCPs.

The problem identified was inappropriate clinical behaviour in the face of a black box warning concerning fluoroquinolones. The study design exposed only high-volume prescription writers of fluoroquinolones to one of three behaviour modification strategies: CME, Targeted Short Form Messages, or a combination of both.

The study looked at 320,478 prescribers of fluoroquinolones, 28,000 of whom were “high decile” prescribers.

The results found that all arms showed a statistically significant impact on clinical behaviour with CME alone, and with CME plus messaging yielding the greatest impact.

The authors noted that they were able to “target clinicians who may have been compromising public health, reach them, and have a positive impact on their behaviour”.

Since then, the role of digital CME has become even more important in light of COVID-19 and the resulting lack of face to face learning opportunities, thanks to its ability to increase the confidence of haematologists/oncologists in making informed treatment decisions for their patients.

*To read the full whitepaper download it here.*

# About the interviewees

Katie Lucero is director of outcomes and insights at Medscape Education Global. She has nearly 20 years of experience in research and evaluation in developmental psychology, public health, health outcomes, and education (K-12 and CME). Prior to Medscape, she was director of research and evaluation for McREL International where she was responsible for designing, pursuing, and managing education evaluation and research studies, including government projects.

Victoria Harvey-Jones is an associate director of clinical strategy at Medscape Oncology Global where she designs impactful physician education to improve patient outcomes. She has spent the last 10 years in the medical education and communications industry. She previously helped found touchIME, the Independent Medical Education division at Touch Medical Media, where she was the head of medical and editorial.

# About Medscape

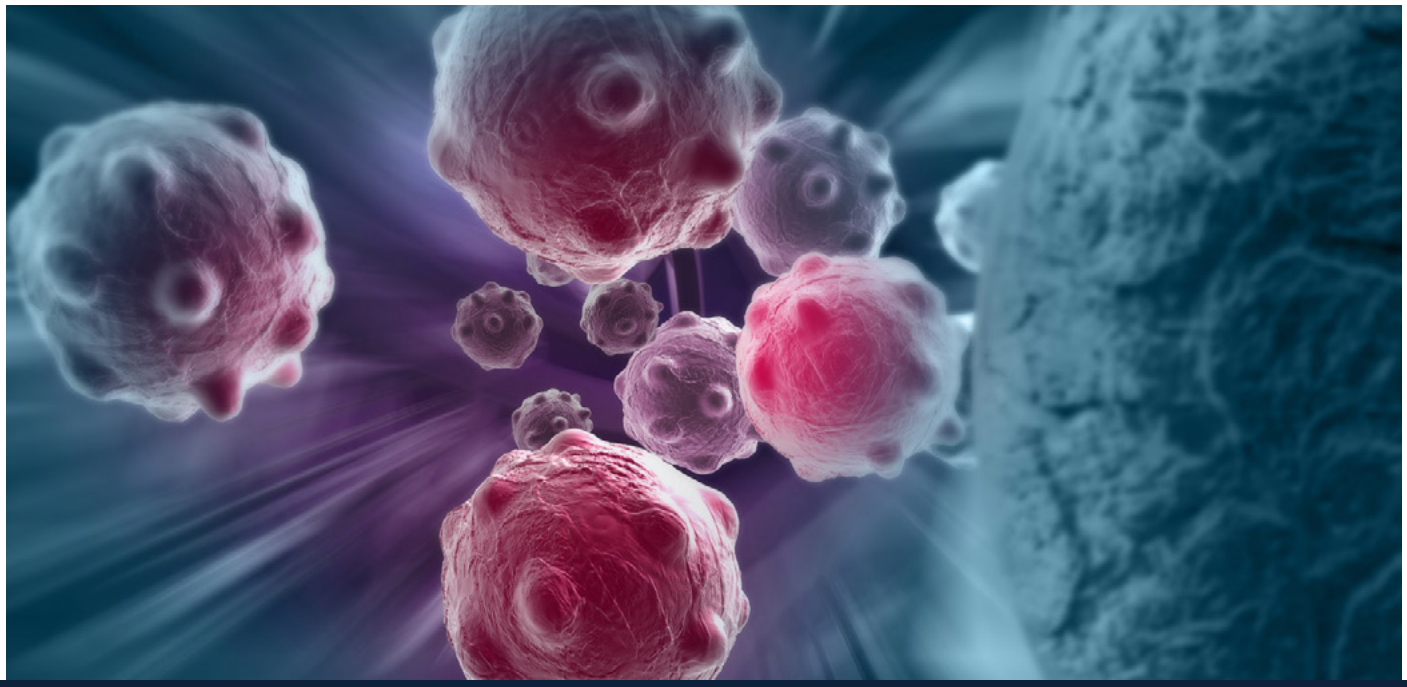
For over 25 years, Medscape Education has been a trusted and essential resource for healthcare professionals throughout their careers, growing into the global healthcare provider it is today, reaching 4.7 million physicians worldwide with the news, resources and education they need in over 30 therapeutic areas. Medscape Oncology Global enjoys a unique and unparalleled relationship with its vast, active member community of oncologists around the world. With a shared commitment to improving cancer care, Medscape Oncology Global provides ubiquitous access to learning resources across multiple channels, offering a variety of personalised, evidence-based, and clinically relevant educational solutions to support the entire oncology care team and improve patient outcomes.

To learn more, please contact Stephen Dunn, executive director, Medscape Oncology Global, at sdunn@webmd.net / +44 (0)203 802 1146

OPEN HEALTH

# Helping HCPs navigate the ever-evolving advanced cancer landscape

OPEN Health's Christine Drewienkiewicz, Sara Black and Annie Rankin on advances in modern oncology and how pharma can help ensure maximum patient benefit



Every year, the American Society of Clinical Oncology (ASCO) shares the latest potentially practice-changing research at its annual meeting and, despite the COVID-19 pandemic, this year was no exception. Cancelling the most important congress in the oncology calendar was not an option so, for the first time in its 55-year history, ASCO went fully virtual in 2020.

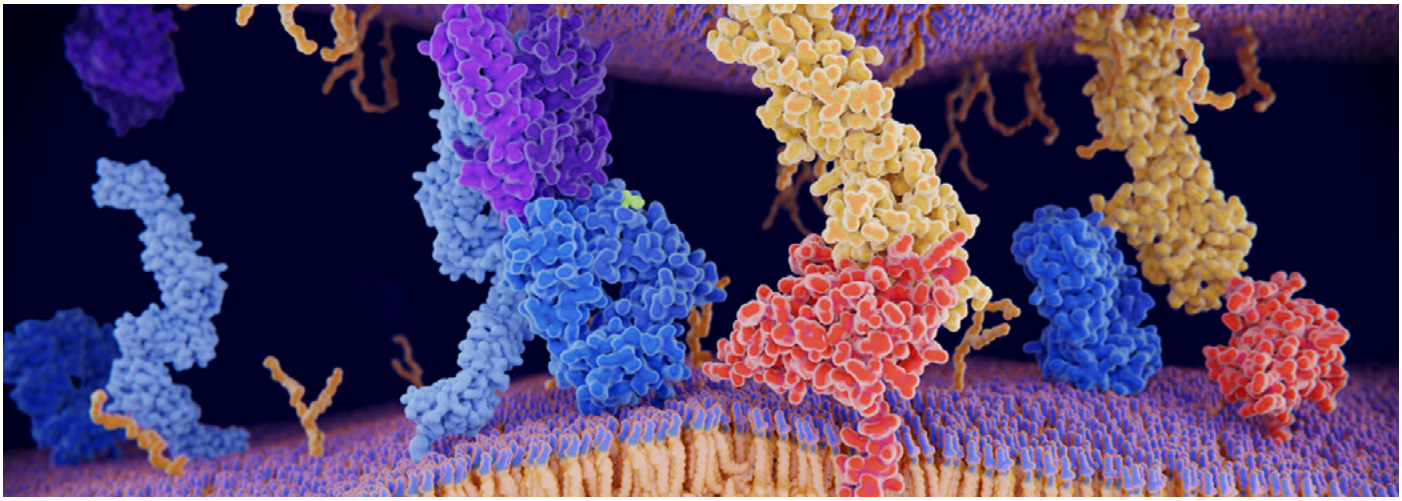
This presented an opportunity to rethink how pharma, researchers, healthcare professionals and patients communicate, to enable all stakeholders to keep up with developments – particularly important in an era when each new development can help change at least some types of advanced cancer from a lethal to a more chronic disease.

# Today's trends in cancer therapy

The considerable improvements in the prognosis for patients with advanced disease in the past 20 years has been led by breakthroughs in our understanding of the molecular drivers of cancer. This understanding has fuelled the development of therapies that target cell signalling, angiogenesis and the host immune response.

**Cell signalling:** Many cancers are driven by genetic mutations that upregulate molecular signalling pathways promoting survival and proliferation; by blocking these pathways, therapies have been developed that can disrupt this process.

In breast cancer, Herceptin (trastuzumab) was the first monoclonal antibody to target a specific cell receptor, in this case HER2, overexpression of which had until then been a marker of particularly poor prognosis. Similarly, the management of chronic myeloid leukaemia was transformed by Glivec (imatinib), which was the first kinase inhibitor to be licensed in cancer and paved the way for a whole class of small molecules targeting different parts of the cell-signalling cascade in different cancer types.



**Angiogenesis:** Without their own blood supply tumours cannot grow larger than a pinhead, but many tumours are able to recruit cells involved in blood-vessel development to create their own vasculature.

The key to this process is vascular endothelial growth factor (VEGF) and its receptors, which are the target for a number of therapies, such as Avastin (bevacizumab) and Sutent (sunitinib).

**The host immune response:** Usually, the body's own immune system destroys mutated cells, but cancers are able to avoid this process by signalling to immune cells to switch off.

For many years, there was a hope that it would be possible to harness the immune system to treat cancer, but with little success until the recent development of immune checkpoint inhibitors – therapies that control communication between tumour and immune cells or that stimulate immune response essentially, by removing the 'brakes' applied by the cancer on the immune cell.

This approach has been particularly effective in melanoma, where Yervoy (ipilimumab) and Opdivo (nivolumab) have set new standards, and it is also being applied in many other types of cancer.

## Unmet need in oncology

These targeted therapies have changed the treatment landscape for patients with advanced cancer, in many cases offering the possibility of several lines of active therapy, with each new development extending survival beyond the boundaries ever dreamt of 20 years ago. Nonetheless, except in rare cases, they cannot completely eradicate the tumour, which will sooner or later develop resistance, requiring a new treatment approach.

Tumour resistance is a reflection of both heterogeneity between cells within a tumour mass and the availability of redundant signalling pathways within cells, which can come into action when the main survival pathway is blocked by a targeted therapy. The challenge, therefore, and the ultimate goal of cancer research, is to understand the individual network of factors that may contribute to tumour survival in each patient in order to offer a tailored treatment approach to maximise antitumour activity.

At the same time, adverse events need to be minimised to mitigate any impact on the patient's quality of life. Although targeted therapies have been designed to have tumour-specific effects, they can still be associated with many side effects, often affecting the skin, gastrointestinal tract, blood vessels, and other organs. Such toxicities can substantially restrict a patient's daily work and leisure activities, while even mild symptoms, if persistent, can have a big impact on the patient's overall health and energy levels. These toxicities may necessitate treatment interruptions or dose reductions, potentially reducing the effectiveness of the treatment, or may even result in the patient stopping treatment altogether.

## Addressing these needs: looking to the future

Meeting these combined needs of optimising antitumour activity and minimising adverse events requires multidisciplinary collaboration between research, oncology, pathology, radiology, surgery and the pharmaceutical industry, with all stakeholders keeping the patient at the centre of their focus. Collaboration between and within research groups and industry will maximise resource use and help focus activities on areas that are most likely to have a practice-changing effect.

The first step is diagnostic assays that can identify tumours most likely to respond to specific treatments. These assays need to be reliable and consistent (that is to say,

sensitive and specific), use accessible technology that has rapid turnaround times, and be minimally invasive, e.g. by using 'liquid biopsies' (i.e. based on circulating tumour cells or DNA fragments in blood samples), rather than traditional invasive biopsy to remove tissue from the tumour itself. Liquid biopsies can be repeated more frequently than tumour biopsy, improving assessment of treatment response and disease progression.

Coupled with increasingly accessible next-generation sequencing, liquid biopsies can provide a more comprehensive picture of tumour heterogeneity and allow multiple mutations to be identified in one go. The ultimate goal is a point-of-care device that can be used in the oncologist's office for on-the-spot tumour analysis and treatment planning.

Another major focus is optimal combinations of different targeted therapies, or targeted therapies and other treatment approaches (chemotherapy, surgery or radiotherapy) to minimise or overcome resistance. By targeting a range of molecular drivers at once and blocking redundant pathways, combination therapy can restrict the survival of clonal populations that are not dependent on any one particular pathway.

Most recently, the finding that some tumours are more likely to respond to immuno-oncology than others has prompted research into how to turn immunologically 'cold' tumours, which lack T-cell infiltration, into 'hot' ones, for example using bispecific antibodies that target receptors on both the tumour and immune cells or chimeric antigen receptor (CAR) T cells.

Finally, focusing on the whole patient rather than just the cancer in order to help them live well, with and beyond cancer, has emphasised the importance of recognising the adverse-event profile of each treatment in order to pre-empt and manage toxicities before they become treatment limiting. Crucial to this approach is good patient communication and education, enabling them to recognise and appropriately respond to adverse events and be an informed participant in their own treatment decisions.

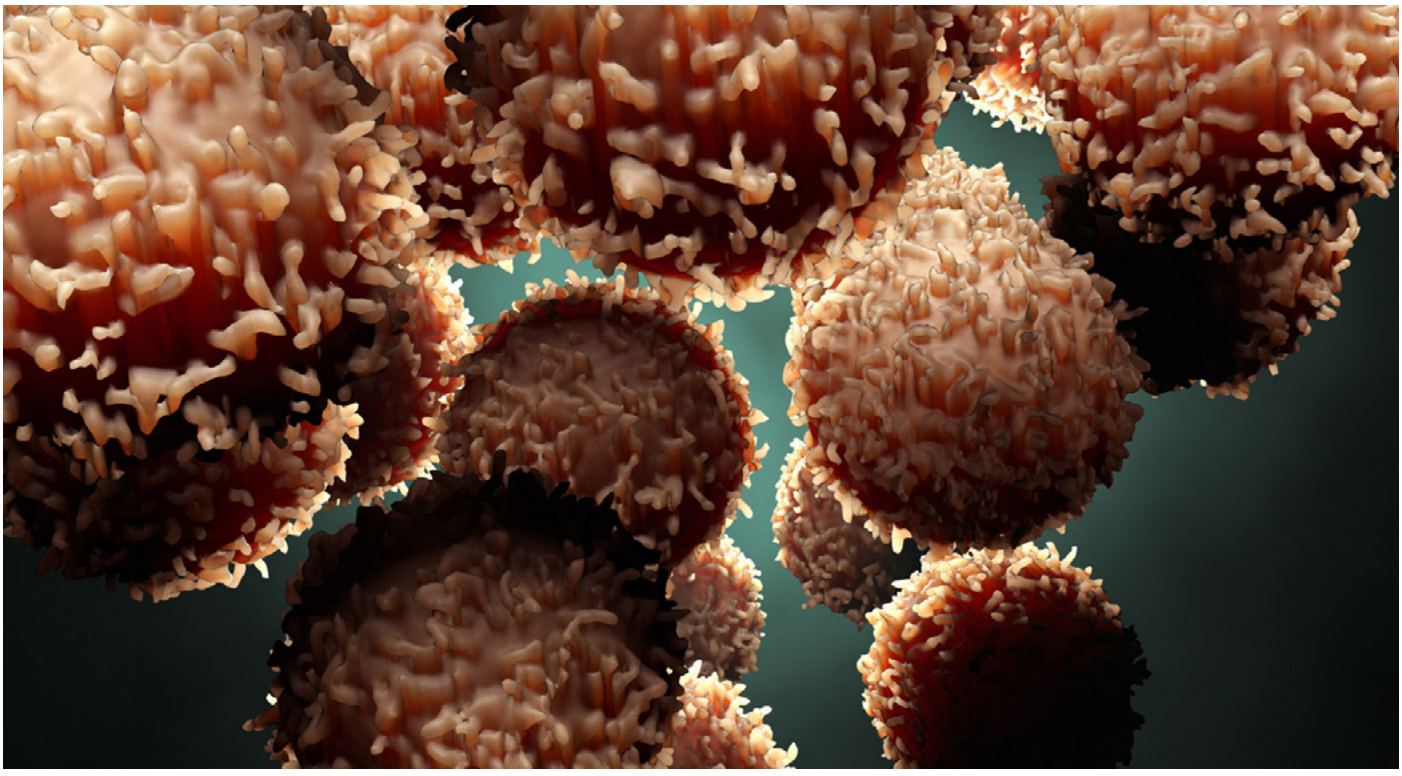
# Knowledge management in oncology

More than 2,200 abstracts were selected for presentation at ASCO 2020 alone, illustrating the scale of the challenge faced by those trying to keep up with the latest developments.

With the COVID-19 pandemic prompting a surge in virtual interactions, the options for communication have now expanded exponentially, increasing the number of ways in which data can be shared with the aim that at least one route will reach the relevant audience (akin to the redundant pathways used by tumour cells described above). However, the flipside of this approach is that there is now more 'noise' than ever, making it harder for healthcare professionals to find the information that they need.

Face-to-face meetings will always have a central place in medical communications. Most healthcare professionals still agree that such meetings are one of their main ways of networking with colleagues, learning from experts and staying up to date. What is important is that these meetings offer a broad range of education, ideally across disciplines to foster multidisciplinary collaboration and provide most benefit for hard-working professionals who are increasingly restricted in how much time they can commit to professional development.

Peer-reviewed primary publications are the most widely accepted standard of evidence that forms the basis of treatment decisions. For the benefit of the whole research community, it is crucial that the results of all research, whether positive or negative, is made public to minimise unnecessary duplication of effort and increase the overall knowledge pool. Nonetheless, this approach does increase the amount of literature available and the time required to assimilate it. To aid readers, many journals now offer multimedia supporting information, such as graphical or video abstracts, which can help to highlight the clinical relevance of research.



# Conclusions

At a time of unprecedented advances in oncology, it is crucial that research findings are accessible to and actually accessed by all stakeholders. It is only then that we can hope to evolve clinical practice and improve patient outcomes. To do this there are many communication vehicles available – from traditional publications to face-to-face meetings to online platforms, and all have their place in the communications mix.

Clearly, as suggested by this year's digital-only ASCO meeting, online channels are likely to punch above their weight in 2020 and the COVID-19 crisis has provided valuable learnings about the best way to use virtual and digital communications. The coronavirus pandemic has certainly forced healthcare professionals and the wider population to rapidly upskill themselves about digital communications technologies.

The rate of change in oncology today can be bewildering, so it is imperative that the pharmaceutical industry supports healthcare professionals and that everyone works together to explore the most clinically relevant lines of research and ensures that knowledge is effectively shared in order to change the management of people with cancer for the better.

## About the authors

Sara Black is a principal medical writer at OPEN Health Medical Communications. With nearly 30 years' experience in scientific publishing and medical education, she has a wealth of expertise in medical communications, particularly in oncology, and is an ISMPP Certified Medical Publications Professional

Christine Drewienkiewicz is a scientific services director at OPEN Health Medical Communications. Christine has over 28 years' of experience in medical communications, scientific strategy and publishing, working across multiple therapy areas including oncology.

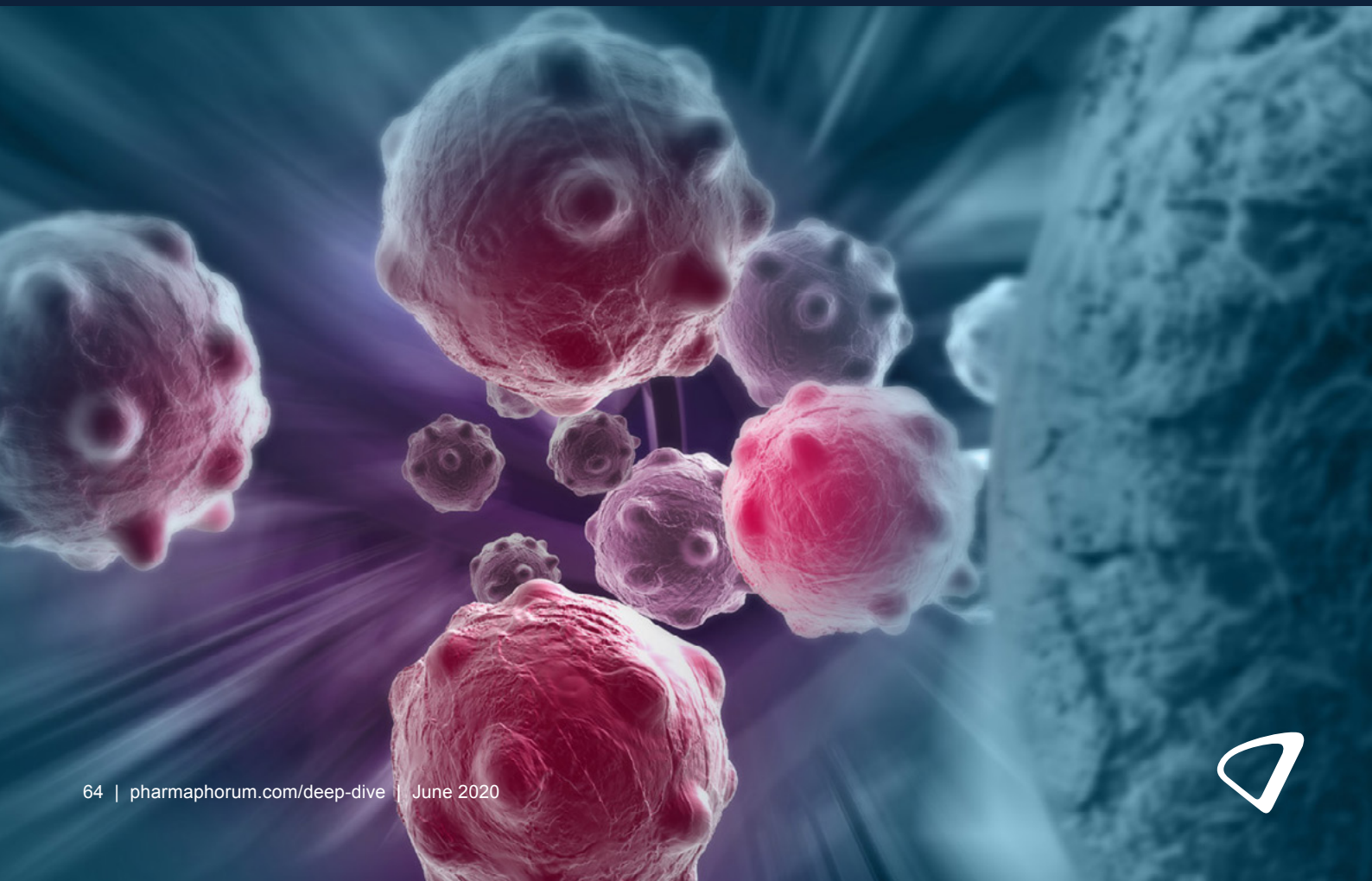
Annie Rankin is a strategic partnerships director at OPEN Health Medical Communications. Annie has worked exclusively in healthcare communications for over 10 years partnering with our medical affairs clients to drive meaningful outcomes against their strategic needs.

## About OPEN Health

OPEN Health is a family of expert practices working in partnership to drive positive change in healthcare communications and market access globally. It all started with a vision for improving the lives of patients, worldwide. The OPEN Health vision has manifested with the integration of experts from Pharmerit and Peloton Advantage to create a new unique entity equipped to be a global leader in HEOR, market access, medical and patient brand communications and digital services.

For more information visit:

OPEN Health Group ›



# Commercialising innovative new medicines

OPEN HEALTH

As pharmaceutical ingenuity hits new heights, ensuring that patients gain access to innovative medicines requires a unique combination of evidence generation and communication

Working with all stakeholders to generate evidence that communicates value, from early phase development to launch and reimbursement, is essential in therapy areas including oncology.

These are challenging times for the pharmaceutical industry as it navigates an oncology landscape offering an increasing array of new ways to target and treat cancer.

The rise of ever-more personalised treatments for different tumour types, a greater understanding of the mutations that cause cancers and the increasingly central role of combination therapies are just some of the factors that make this a particularly complicated and competitive space.

Consequently, there is a greater than ever need for pharma to partner with agencies whose multidisciplinary teams understand the clinical aspects of advanced technologies, in oncology and other therapy areas, have the methodological expertise to address those challenges, and can also have those discussions from a commercial and marketing perspective.

## Geographic Reach

700+ people in 15 locations across 6 different countries including the US, the UK, the Netherlands, Germany, India and China

## Clients

200+ current sponsors

Working with 90% of the top pharma brands

## Publications

1,200+ peer-reviewed publications

## Core areas of expertise

- Real-world evidence and data analytics
- Patient-centred outcomes
- Modelling and meta-analysis
- Strategic market access
- Multichannel medical education
- Publications planning and delivery
- Internal training
- Patient engagement
- Patient and brand communications
- Digital and creative

## Therapeutic focus

Experience in a wide range of therapy areas, including oncology, endocrinology, rare disease, cardiology, neurology, pulmonology and genetics

## Our mission

Improving the lives of patients, worldwide

The integrated group of practices at OPEN Health were brought together to meet these needs through a suite of services aimed at identifying and addressing evidence gaps and delivering world class value communications across a wide range of media.

"Commercialisation of new technologies in oncology requires expertise in both health economics and outcomes research (HEOR) and medical communications," says Dorinda Hickey, joint managing director at OPEN VIE. "Development of a compelling value proposition supported by robust evidence generation planning is essential in order to be able to communicate value, demonstrate cost-effectiveness and secure patient access to treatment.

"In the absence of randomised controlled trial evidence due to small patient numbers, it is important to be able to demonstrate incremental clinical benefit and value using real world-evidence, health informatics, modelling and meta-analysis to capture not only clinical endpoints, but also economic and humanistic outcomes.

"Real world-evidence, health informatics, modelling and meta-analysis are key levers that pharma needs to gain positive health technology appraisal outcomes. Data collection over the long term, particularly through patient registries or retrospective analyses, is often also needed to demonstrate an overall survival benefit as proof that the surrogate markers used for health technology assessment (HTA) are adequate."

## Pharma's key oncology needs in HEOR and medical communications

For over a decade, oncology has experienced a sustained period of scientific innovation that has seen the emergence of personalised treatments and immuno-oncologics that train the body's own immune system to fight a tumour, and cell and gene therapies. Together these advances make oncology a hugely exciting therapeutic area.

But, as the nature of oncology innovation becomes ever more complex, so too does the task of proving the worth of new and innovative medicines, particularly when it comes to first collecting the necessary data to support a drug during HTA discussions and then communicating those outcomes to healthcare professionals.

It's not enough to just release new data and hope that it will make its mark in a clinical world that can often be overwhelmed with new study readouts to digest.

"Companies need to be actively publishing their data and assisting healthcare providers and payers in understanding the complex data and evidence generation methodologies behind it," says Dorinda. "It's important that the industry can simplify and explain all of the different technologies and methodologies that are used, so that the value messages for products resonate with clinicians."

Aside from randomised controlled trials, evidence generation methodologies used for HTA submissions and value communications include observational research such as primary data collection including patient surveys, medical chart reviews, or registries and secondary data analytics, systematic literature reviews, meta-analysis and health economic modelling. Patient-centred methodologies including qualitative interviews, social listening exercises, and patient preference studies can help contribute to the interpretation of this data from a patient's perspective.

Rosemary Jose is director of strategic market access at Pharmerit – an OPEN Health Company, and she explains how the expanded OPEN Health Group, which merged the medical communications business of Peloton Advantage in 2018 and Pharmerit's HEOR and market access business to the group earlier this year, can also assist with the communication element of pharma's data needs in oncology.

"What the medical communications team offers is excellence in publication planning, which pharma increasingly needs to use earlier in the product life cycle. Strategically planning which conferences and journals to target, and when to do so should be done in parallel with the HEOR activities. Being able to do both of these, through OPEN Health's mergers with Peloton and Pharmerit, allows us to be a strategic partner for HEOR and medical affairs along the product life cycle."

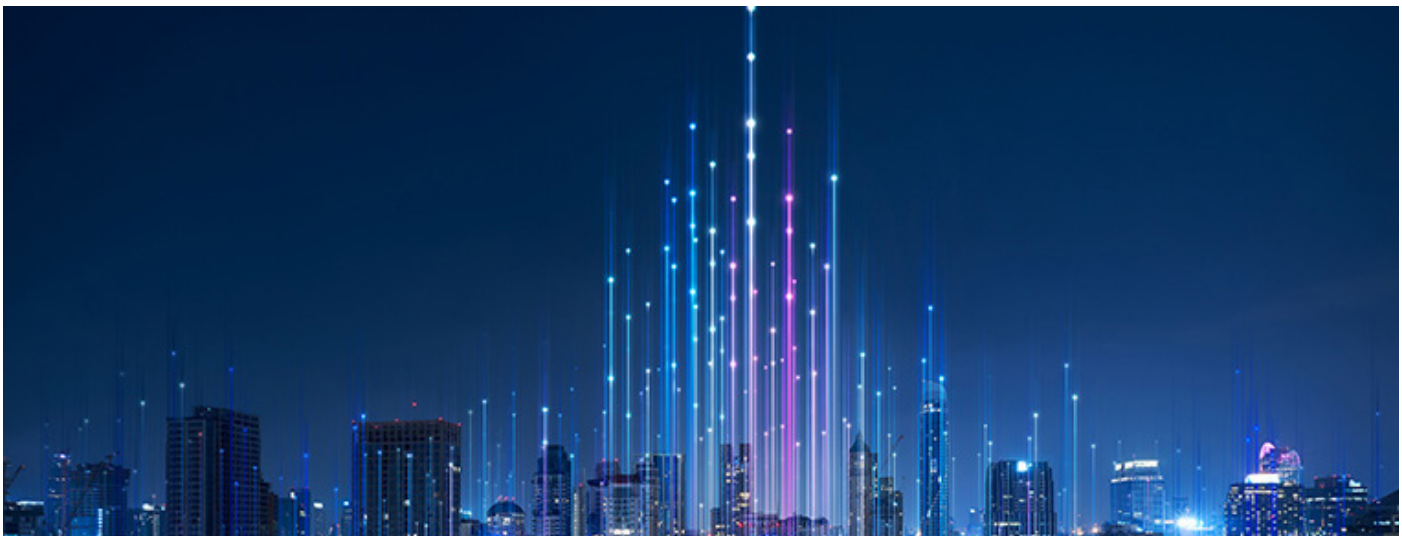
Marja Hensen, director of strategic market access at Pharmerit – an OPEN Health Company, adds: "Education and training are equally important. We do not stop at delivering the evidence, publications or communication tools. We train the stakeholders to effectively get the message across. Especially in the field of innovative oncology, where clinical trial data can be limited and innovative methodologies are increasingly used to demonstrate value, this becomes even more important in the future."

The effective communication of evidence and outcomes that the company can deliver is an important asset to its clients – in oncology as well as in other therapeutic areas. The way that the group's HEOR solutions solutions apply complex and innovative methodologies to evidence generation and cost-effectiveness demonstration, and then combine them with effective expertise in medical communications, is hugely valuable for pharmaceutical companies. It has proven benefits in successfully explaining what new innovations mean for medical practice and how they can benefit patients.

## Cross-border HTA considerations

Beyond healthcare professionals (HCPs), payers constitute another key stakeholder for pharmaceutical companies, and they're a group that pays particular attention to innovation in therapy areas like oncology, where big therapeutic advances often require major financial investments.

In looking to meet payers' needs, one of the areas in which a strategic approach to market access is necessary relates to cross-border considerations. Different countries' pricing and reimbursement systems, whether through direct price referencing or the influence of high profile HTA bodies like Germany's IQWiG and NICE in the UK, are increasingly interconnected. At the same time each country also has its requirements that add up to a complex global HTA environment, with local nuances, that brings with it clear considerations for pharmaceutical companies about the kinds of companies with which they should partner. It takes a multidisciplinary team to understand the market, be able to deliver and interpret the science, and provide strategic support around the comprehensive value of therapies.



"Geographical expertise is extremely important because, although the strategy is often driven from the top down or cascaded down from the global team, every market has different requirements. A strategic partner should have an idea of how a global cross-functional team works and also understand what the local markets require," says Rosemary.

On an individual level, payers may need their own cost-effectiveness studies, comparative clinical effectiveness research or budget impact analyses, but there's also a trend for countries to go beyond reference pricing models of influence to direct collaborations around stronger price negotiation or managed entry agreements and value based pricing. We also cannot ignore joint clinical assessments that are being conducted through the EUnetHTA initiative, as discussions continue about how HTA in Europe can be harmonised. Moreover, as there is a movement towards greater patient centricity worldwide, it is important to have experts who understand how to engage with patients as champions of their own condition in the drug development, approval, and commercialisation process.

"This is what makes OPEN Health a strategic partner – the fact they recognise the nuances of how these different requirements can be met and how we can develop that one common dossier or submission that addresses everybody's needs, and how to address the challenges this approach might create," Rosemary adds.

## Strengths of the combination of OPEN Health, Pharmerit and Peloton

Tackling the evidence, communications and access environment for commercialising innovative new medicines demands a special type of agency partner, and the new combination of OPEN Health, Pharmerit and Peloton has some key differences from other HEOR companies or med comms agencies.

"With the skills to cover the whole development process from early phase research through to launch and reimbursement, we provide a full-service offering in the commercialisation process for innovative new medicines, working with all stakeholders, physicians, patients, and payers, communicating the value of new treatments, and securing positive health technology appraisals and system funding," Dorinda explains.

The integration of Pharmerit into the group earlier this year has strengthened its global footprint as well as the range of its core capabilities, from health economics and real world evidence to patient-centred outcomes to strategic access reimbursement and medical affairs supported by digital communications.

As Rosemary notes: “We can do so much more as a single combined entity. On the one hand, there are synergies across the strategic market access teams, where we can work cohesively to generate compelling value propositions. On the other hand, complementary elements have come together, for example, of value communications with digital solutions. Or for instance, publication planning, with a focus on health economics and outcomes research. Or, HEOR and market access with digital training solutions. The possibilities are endless.”

The company isn’t siloed – either across locations or teams, so it’s easy for different parts of the whole entity to come together for a particular project, bringing all of their specialist expertise and knowledge. The teams are working in an integrated way across different specialties/centres of excellence and many consultants have experience working across different types of projects. The benefit this brings to pharma is that the group is able to look at the product’s evidence generation and communication with a bird’s-eye view, making it a truly strategic and global partner.

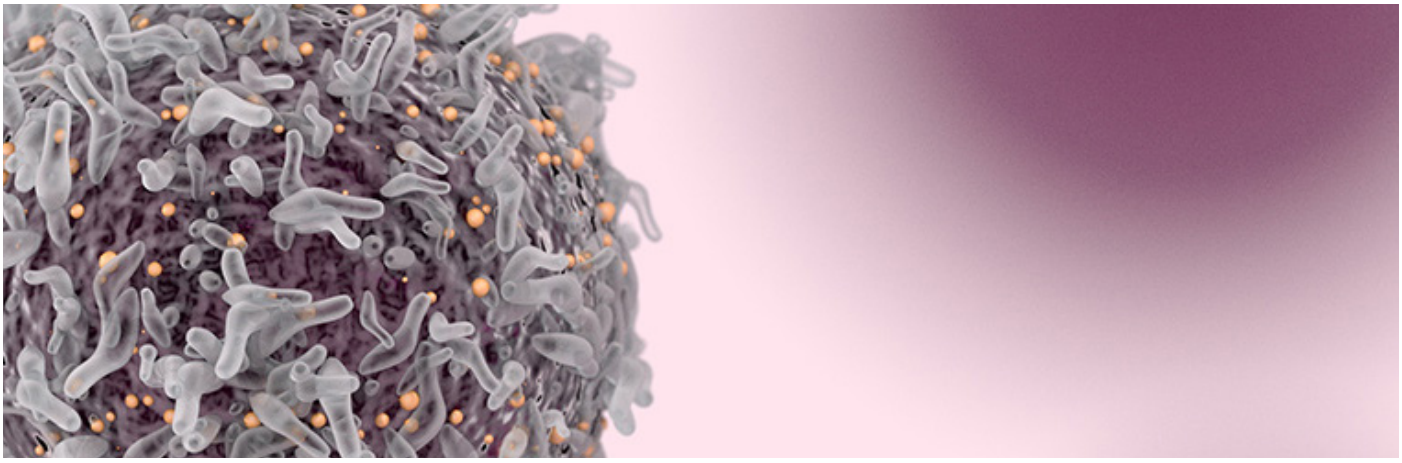
Dorinda explains: “We work a lot with different patient groups to make sure that they have a voice and that they can get access to new and innovative treatments. Our work on HTA submissions, for instance, may involve long-term follow-up of patients to prove that, for example, gene therapies and cell therapies actually work. So, we’ve seen first-hand the importance of working not only with patients to generate data but also as co-creators to ensure that, at the stage of reassessment, these products continue to be funded.”

## Mapping the patient journey in melanoma and Hodgkin’s Lymphoma

Patient journey studies have been one of the areas where the combination of OPEN Health, Pharmerit and Peloton has successfully contributed to improving patient outcomes.

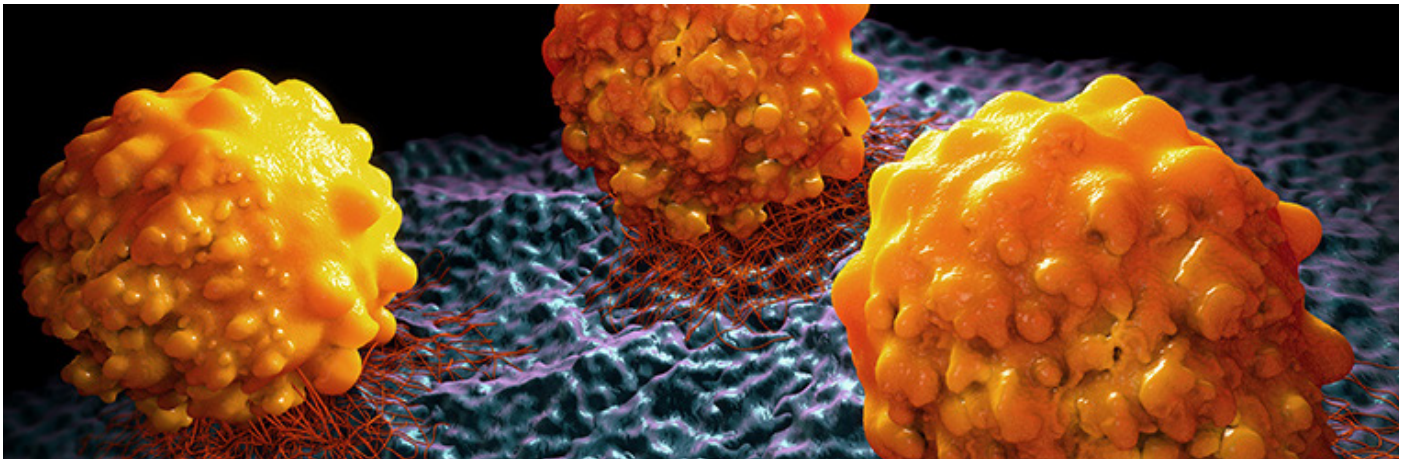
One case saw the Group working in melanoma to support HTA submissions to the Pan-Canadian Oncology Drug Review Committee (pCODR), which gives recommendations and evidence to the Canadian Agency for Drugs and Technologies in Health (CADTH).

pCODR had requested that the patient voice be included in the application for coverage for a product in advanced melanoma, but no quality of life data had been collected during clinical trials for the product.



To overcome this, OPEN Health worked to gain patient-centred descriptions of symptoms, disease and treatment burden, diagnosis/treatment journey and healthcare resource utilisation. This involved a literature review, an advisory board with KOLs, clinicians and patients, a series of in-depth interviews with patients, caregivers, healthcare professionals, and finally the coding and analysis of the interview transcripts.

This comprehensive approach made it possible for the sponsor to successfully submit new data to pCODR showing that its product aligned with patient values.



Meanwhile, in a separate study OPEN Health illustrated the global patient journey in Hodgkin's Lymphoma (HL), illuminating the emotional journey for HL patients, carers, and HCPs from pre-diagnosis to treatment maintenance in three different markets.

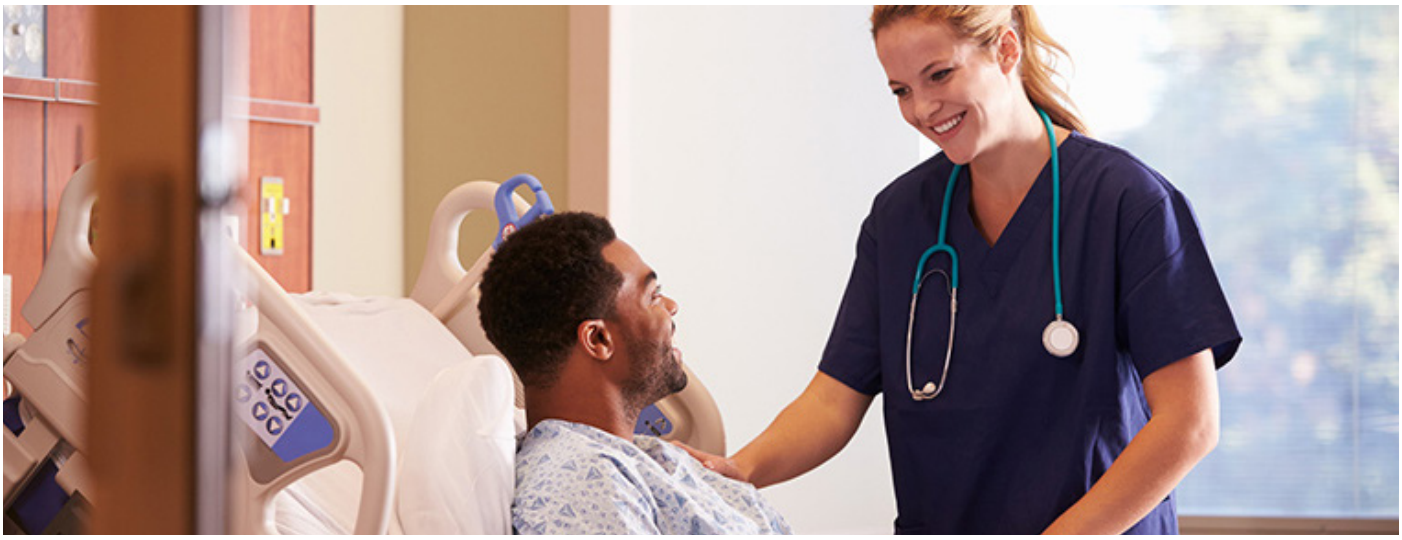
To do this, OPEN Health produced a visual and easy to understand mapping of the patient journey in HL that highlighted the emotional dissonance between treatment stakeholders, as well as simplifying and bringing clarity to the treatment journey for HL patients, carers and HCPs.

The interactive resource identified the unmet needs, key leverage points and tactical solutions around which new services could be developed to improve patient care, support HCPs and ultimately improve real world outcomes.

The sponsor was able to leverage this new knowledge to achieve a competitive advantage by developing differentiated tools and services to support patients and HCPs and the Patient Journey Map was used as the primary business planning tool.

# Working to improve patients' lives

OPEN Health works closely with many different patient groups to make sure that they have a voice and to help them to gain access to new and innovative treatments. This can involve including their voice in discussions about payment mechanisms or long-term follow up, for example, gene therapies and cell therapies to build a body of evidence showing they work.



To do this the growing OPEN Health Group can call upon a combination of medical communications, publications planning, real-world evidence, health informatics and data analytics using artificial intelligence. As Dorinda notes: "We have a combination of engagement skills across physicians, payers, and patients, supported by digital expertise, which bring complex ideas about innovative medical treatments to life and makes them meaningful and easier to communicate."

## About the interviewees

Dorinda Hickey is joint managing director of OPEN VIE. She has over 15 years' experience in market access consulting; specialising in pharmaceutical pricing and reimbursement, healthcare policy analysis, clinical advocacy, payer engagement and value communications. Prior to consulting, Dorinda spent many years in the pharmaceutical industry where she held positions in sales, marketing and market access including business unit and country management.

Rosemary Jose is director in the Strategic Market Access Center of Excellence at Pharmerit, and is based out of the Rotterdam office, the Netherlands. Rosemary has over 14 years of experience across the pharmaceutical industry, including more than 12 years in market access and health economics, both in global and consulting roles – leading strategic projects, managing international clients and mentoring multi-cultural teams.

Marja Hensen is director of strategic market access at Pharmerit. She has presented work at conferences including ISPOR, EFIC, ESH and EHA. Marja authored articles in Expert Review of Hematology, Diabetes Research and Clinical Practice, Haematologica and Applied Health Economics and Health Policy. She holds a MSc degree in Biomedical Sciences from the University of Leiden. She joined Pharmerit in 2006 and since then performed and led a large number of projects.

## About OPEN Health

OPEN Health is a family of expert practices working in partnership to drive positive change in healthcare communications and market access globally. It all started with a vision for improving the lives of patients, worldwide. The OPEN Health vision has manifested with the integration of experts from Pharmerit and Peloton Advantage to create a new unique entity equipped to be a global leader in HEOR, market access, medical and patient brand communications and digital services.

For more information visit:

OPEN Health Group ›

Stay informed

# Get future editions of Deep Dive

**Insights and analysis on the big trends shaping healthcare from pharmaphorum.**

*Deep Dive* magazine brings you the knowledge and expertise of the top minds in the industry, backed by our team of specialist healthcare journalists, and presented in an innovative, interactive format. Each issue focuses on a specific topic.

Upcoming themes:

- **Communications & Commercialisation (September 2020)**
  Plus: VR & AR in healthcare
  • Listening to patients
- **Digital Health Innovation (October 2020)**
  Plus: New R&D strategies
  • New models for market access
- **Patients & Partnerships (November 2020)**
  Plus: 2020 in review and predictions for 2021

**Keep up to date with what you need to know.**

Sign up to receive complimentary future editions of *Deep Dive* magazine direct to your inbox, as soon as they are published.

Subscribe to Deep Dive, visit https://bit.ly/33lccAB

# Contacts

**Editorial team**
George Underwood
editorial@pharmaphorum.com

**Sales team**
advertising@pharmaphorum.com

**Design**
Mike Hammerton
Mike Smith

A pharmaphorum media publication



www.pharmaphorum.com

pharmaphorum media ltd, Third Floor, Rosemount House, Rosemount Avenue, West Byfleet, Surrey KT14 6LB, UK
Tel: +44 (0)1932 339 264