

The Cancer Drug Development Forum champions the importance of multistakeholder collaboration in the search for new cancer drugs. Managing director Professor Heinz Zwierzina talks *Health Europa Quarterly* through the challenges ahead

Challenges and opportunities in cancer drug development

The Cancer Drug Development Forum (CDDF) was set up in 2001 to accelerate the development of innovative, effective and cost-efficient oncology drugs and deliver them to patients as quickly as possible. To this end, the Brussels-based organisation provides a single platform for academia, industry, regulatory authorities, payers and patient advocates to come together to consider how best to create the kind of scientific, commercial and regulatory environment necessary for the development of anticancer medicines.

Through dedicated meetings and workshops, the Cancer Drug Development Forum provides a confidential, open environment for stakeholders to take stock of achievements, look ahead to new challenges, and brainstorm new solutions in everything from personalised medicine to paediatric oncology and companion diagnostics.

Here, managing director Heinz Zwierzina, a professor of medical oncology at Innsbruck University, Austria, discusses the recent boom in cancer drug development, the challenges behind immunotherapy, and the problems with clinical trial design.

More drugs have been approved within oncology than in any other therapy area since 2000 - to what would you attribute this progress?

We have learned so much about molecular biology in the meantime that we are now able to define targets that we didn't know about before. There are so many targets – some of them druggable, some of them not. The oldest is



BCR/ABL in chronic myeloid leukaemia; HER2 expression in breast cancer is another example.

Ultimately, it is thanks to breakthroughs in molecular biology, methodology and genomics that these targets have been defined.

Cancer is increasingly coming to be understood as not just many but thousands of different diseases; how will this complicate drug development in the future?

Take lung cancer as an example: lung cancer used to be two disease entities – non-small cell and small cell lung cancer. The latter has now become a variety of entities. Some express ALK, in which case the respective drug can be given, others express EGFR in a mutated way, which is also druggable. Some express ROS1, another oncogene, while others express different targets, drugs for some of which are currently under development. In other words, we can no longer talk simply about non-small cell lung cancer, we

have to talk about ROS1-positive lung cancer or ALK-positive, EGFR mutation-positive, and so on.

Complicating this further are immunotherapeutic approaches, to which not all non-small cell lung cancer types respond. Some cancers have an extremely high expression of PD-1 and tend to respond very well to therapy, but others with a very low PD-1 expression tend to respond less well. Yet they may also respond. What we need, then, is more well-defined targets but also more biomarkers. That's the crux of the matter.

Meanwhile, the usual drug development programmes, which are derived from cytotoxic agents, are quite old-fashioned. Typically, the endpoint for a Phase I clinical trial is toxicity, for Phase II it's response, and then in Phase III we check whether the new drug would be more effective than existing ones. Because the targets we have are so rare – ALK is expressed in perhaps 5% or 6% of non-small cell lung cancers – it has become very hard to run a Phase III trial. For even rarer targets, there simply aren't enough



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patients. Developing a drug using this I, II, III structure for a very rare cancer is near impossible – especially for a small company.

This means that the European Medicines Agency, the Food and Drug Administration and other regulatory authorities then have to approve a drug based on a very limited number of people included in a trial, and using historical comparisons is of course a challenge for them.

What are your thoughts on the so-called 'seamless design' of clinical trials? Might this pose a solution to the challenges facing cancer drug development?

That is one possible solution that may help, but when there are so few patients it will still be very difficult. For example, other programmes concentrate on the molecular phenotyping of patient tissue. We enrolled more than 200 patients in such a programme in collaboration with Caris in Arizona, but each patient with a specific molecular profile is an individual patient, and finding others with the same profile in Europe is difficult. These complex profiles require completely new drug development programmes because they are so very individualised.

It's also a matter of cost efficiency. If we cannot define patients with a high probability of response, we'll get nowhere with the health technology

assessments (HTAs). We simply can't treat all patients with a PD-1 inhibitor when we know that only a subgroup would respond, especially considering the high cost of immunotherapy. To come back to my favourite topic, then, we need more biomarkers to define which patients have a high probability of response (or non-response). The best example here is trastuzumab, which is used to treat breast cancer in patients with a high HER2 expression. Nobody would use it to treat the other 75% of patients who don't express HER2. We need to develop more of these biomarkers.

How is the CDDF working to support and accelerate cancer drug development?

The Cancer Drug Development Forum is the only multistakeholder group to bring together all the respective parties around one table – industry, academia, regulatory authorities, and patient advocacy groups. At a recent meeting on biomarker development in Brussels, Belgium, we also included the payers or insurance companies in our discussions.

Our meetings are very open-minded and really encourage people to speak up and state their views on specific issues. That's hugely important in cancer drug development because the view of someone working in HTA is very different than that of someone working in academia, and both need to be heard if our efforts are going to be successful.

Looking to the future, where do you believe the next breakthrough in cancer drug development will lie?

I believe that we are only at the beginning of immunomodulation as a therapeutic tool. There was, unfortunately, a drug that failed recently – the IDO inhibitor. This looked very promising in Phase II but was negative in Phase III. What does that tell us? If there are patients who respond in Phase II, then the drug must be effective in certain patients, but if it then dilutes the population in a huge Phase III without a biomarker, it might be negative. This is a very tricky, complex issue in drug development, because as soon as a Phase III fails, the drug is off the market and companies are no longer interested in it.

Again, this comes back to needing better biomarkers. Already, there are so many different drugs in development in immuno-oncology, and once the biomarkers are there, this will only continue to grow.



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