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Building on points developed in his 2020 PharmaBoardroom interview, Professor Nicolaus KrÃ¶ger of the European Society for Blood and Marrow Transplantation (EBMT) outlines the progress made by the multi-stakeholder GoCART Coalition towards greater harmonisation of cell and gene therapy research in Europe, the challenges of integrating patient-reported outcomes into its registry, and his hopes for the future of the field.

Back in February 2021, the European Society for Blood and Marrow Transplantation (EBMT) held the 3rd European CAR-T-cell Meeting in collaboration with the European Haematology Association (EHA). What were the key takeaways from this congress?

Due to the COVID-19 pandemic, this yearâ??s meeting was held fully virtually but at next yearâ??s meeting in Nice, France, we will move to a hybrid in-person/online format. Local health authority restrictions cap the in-person numbers at around one thousand, but the level of interest is even higher, and many more people will attend virtually.

These annual CAR-T cell meetings are the result of a combined effort from EHA and EBMT, with whom we formed the GoCART Coalition. Given the novelty and competitiveness of the CAR-T field,

it made sense to join forces to create a win-win congress for patients, the pharmaceutical industry, health authorities, scientists/researchers, and national groups. Looking at the rapid progress made in the US and China around the development and approval of CAR-T therapies, it was important that all stakeholders in Europe came together under a single banner.

Over the past two years, we have stepped up our efforts to bring more CAR-T clinical studies to Europe. However, regulation presents a challenge, with different national requirements leading to a lack of harmonisation. The GoCART Coalition aims to create more awareness on the EU level of the need for greater harmonisation across Europe on approval processes, ethical terms, contracts, and data protection, thereby facilitating increased numbers of clinical trials in Europe. Having seen the potential for CAR-T cells in the lymphoma field at an earlier stage of the disease, for example, as well as other new indications coming up, more clinical studies are crucial.

This yearâ??s congress built on the topics discussed at previous events, with a focus on all underlying aspects of CAR-T, including the optimisation of manufacturing and harmonisation of different companiesâ?? accreditation processes. Of course, the meeting also looked at the rapidly evolving science, not only discussing conventional CARs, but dual, allogenic, and NK cell CARs as well as T cell receptors. This is now becoming a big scientific meeting with the participation of the KOLs driving the field forward.

Other interesting new initiatives include a special new training program for nurses as well as a prize for the best new study and a dedicated trainee session. The perspectives of health authorities are shared, as well as those of payers, as cost is becoming a big issue, especially in low- and middle-income countries which currently cannot afford these kinds of treatment.

Do you feel that, as the science develops, CAR-T is gaining more traction within Europe?

Yes, at least for clinicians. Europe is not behind the US and China in terms of the development of CAR-T cells or gene therapy. However, we do lag in translational science and the leap from lab to clinic, in my opinion, due to the complicated regulatory processes here. This is especially true for transnational studies. Compared to others, it always takes more time here in Europe to get approval from national regulatory bodies for new first in human trials using CAR-T.

One of the goals of the coalition was to set up a centralised data registry for CAR-T in Europe. Given the small number of patients involved, one might assume that the establishment of such a registry and the generation and cataloguing of real-world data would be more straightforward than in other, broader, areas. Is that the case? How is this registry progressing?

The registry is going well and now contains data from more than 2,500 patients with CAR-T cells. The data is not yet complete, but the patients are registered. However, one complication is competition with national regulatory bodies requiring dedicated registers in their own countries. This means that in several countries, there is a doubling up of reporting, which we want to avoid, because the centres can become overloaded with all the data requirements put upon them. We are now working with the national registries on transferring data to the EBMT registry, which aims to be the uniform European registry.

Is the data being entered into these registries in a standardised way or are you facing issues in this respect?

In the GoCART project we try to have all the data which is needed. However, with so many stakeholders there are many different demands around getting the data. The industry, scientific groups, and health authorities are all asking for different data, as are countries. For instance, Germany has specific requirements regarding data, as does Switzerland, and we try to include all this data into this registry. However, this means that the workload for the centres is increasing; so much data is now needed around areas like pre-treatment, lines of therapy, comorbidities, renal functions etc. This is problematic because it creates more workload for the Data Manager, but on the other hand, we want to ensure that every stakeholder is pleased.

How significant is the integration of patient-reported outcomes into the registry and what are some of the challenges around collecting and integrating them?

One of our ambitious goals is to include patient-reported outcomes in the registry, which we are now working on. However, regulatory and data protection issues can complicate this because we want to avoid having the names of the patients in the registries. Another challenge is collecting the data itself. Currently, quality-of-life questionnaires are handed out by physicians to patients, but many forget to do so. One idea would be to allow patients to upload their insights digitally direct to the registry and cut out the physician in the middle.

Data will presumably play a major role in advancing CAR-T therapies to earlier lines of treatment. Sponsors support a move from fifth/sixth line of treatment to second/third so that the patientsâ?? cells are not exhausted but patient groups assert that we need to follow the science and that insufficient data currently exists. What is your point of view?

I completely agree with the reservations of patient groups. Patients need to first be treated with medicine for which a strong evidence base has already been established before moving onto newer products for which less data exists such as CAR-T cells. More clinical studies on CAR-T as an earlier line of therapy are therefore needed for things to change; we should foster an environment where more trials are held and encourage patients to participate in them.

We should focus on evidence-based medicine and not be swayed by the hype. Patients are in a very delicate position if they are ill and if they read about something that could save their life, they will naturally want it. However, we should be honest and counsel our patients around what is based on evidence and what on hope. This is only fair.

Some patient groups have expressed concerns that the CAR-T patient journey is not particularly smooth at times and that there is a lack of clarity around which stakeholders are responsible for which elements of the journey. What are your thoughts?

It must be remembered that CAR-T cell therapy is still very new and that the progress that has been made on this front is, therefore, quite positive. Cell therapy with stem cells was developed by academia and represents a big change for the pharmaceutical industry. For drug companies, dealing with cells rather than drugs is a novelty; drugs have very clear specifications whereas with CAR-T we are talking about living organisms, where the dose of cells is never the same. It all depends on

how many cells you can collect, how many can be successfully transduced with genetic procedures, how many expand in the patient, and how many stay active in the patient over time.

Although stem cell transplants were first developed by academia, there now seems to be tension around how far academics can go in their own work with CAR-T. The industry seems to be suggesting that once indications are approved by the regulator, they can no longer be experimented with. What is your take on innovation within CAR-T and the role of academia and practitioners in relation to companies?

This is the basis of GoCART. CAR-T cells are new, and we are trying to develop and expand their uses in collaboration for the sake of patients. In the beginning, the CAR-T cell was an academic product developed in labs by scientists. Then companies jumped in and saw that this was a product for which there was a market. Now, the CAR-T cell products approved by the FDA and EMA have clear indications and are quite expensive. This means that they are indicated according to the label given by the regulatory bodies, but academics should work with the industry to develop these approved drugs for other currently non-approved indications, exploring the links between HIV and lymphoma for example, or looking at CNS patients. This would lead to investigator-initiated trials conducted in collaboration with companies that would provide the drug.

In addition to widening the indications, this will also let us do more specific studies. For instance, in most patients, the CAR T-cells will be rejected after a couple of days. What can we do to prolong the persistence? Is it beneficial to have a second dose after the first? How can we manage side effects better? How can we control neurotoxicity? How should we deal with so many things around the treatment itself? These are all important questions, which need to be addressed in collaborative clinical studies

What are your hopes for the future of the GoCART Coalition in 2022 and beyond?

I will step down as president at the end of my four-year term in 2022 to be replaced by Anna Sureda, but over the next five years, the optimum achievement would be to have a uniform registry in which everybody participates without any concerns. Currently, we still have some reluctance here.

The second would be to have a greater stakeholder acceptance that Europe is the right place to develop the CAR-T field in terms of production, studies, and collaboration with payers, health insurance, health authorities, academia, and industry. Through regular meetings and collaborations, a strong European position in cell and gene therapy can be established

I feel that CAR-T cells are just the beginning of cell and gene therapy and foresee massive expansion in the next few years for which collaboration is essential. Independent of GoCART, I hope that Europe will achieve greater harmonisation. We need to find a way to achieve cross-border harmonisation without impinging on countriesâ?? national identities and better serve patients.

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