Emanuele Ostuni â?? Head of Europe, Cell & Gene Therapy, Novartis Oncology

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Emanuele Ostuni, Novartis Oncologyâ??s head of cell and gene therapy for Europe, gives an overview of the introduction of the companyâ??s CAR-T therapy to Europe, the work still to be done to get this product to more patients who need it across the continent, and the future of cell and gene therapy in Europe, with Novartis as a key player driving an emergent field forward.

Can you give our audience an overview of your background and how you came to your current role as head of Europe Cell & Gene Therapy for Novartis Oncology?

I am a trained PhD chemist and started my professional life as a bench scientist at a startup before transitioning to McKinsey as a strategy consultant and then working for start-up companies in business development and as a founder/board member.

Eight years ago, I joined Novartis and spent most of the time since in Sandoz, the companyâ??s generics division, where I held, global, regional and country roles, mostly focusing on strategy and launch management. Those roles allowed me to spend a few years in Eastern European countries.

In late 2017, I took on my current role as European head for our oncology cell and gene therapy business.

Looking back, I realize how my experiences of navigating uncharted waters in a start-up and in emerging Eastern European markets have been invaluable. My current position entails a lot of pioneering work and an immense amount of unpredictability. A lot of this is caused by the fact that cell and gene therapies are scientifically highly complex and new to most healthcare systems and stakeholders.

Novartisâ?? cell and gene operations seem to stand alone from the rest of the organisation, even being mentioned as a â??focusâ?•. From an organisational perspective, why is it not so fully embedded?

Novartis Cell & Gene is separate and somewhat autonomous yet integrated at the same time. My role is the commercialization of CAR-T therapies in oncology and integrated into our world-leading Oncology unit. Other parts of the Novartis cell and gene portfolio â?? like a treatment for a rare form of blindness â?? are managed in Novartisâ?? pharma unit. Our gene therapy to treat spinal muscular atrophy sits with Avexis, a Novartis fully owned company.

The polarity between being separate and integrated requires some balancing. On the one side, we need to operate with high speed and great agility â?? which is not truly in the DNA of large organizations. On the other side, the amazing resources, history and knowledge of Novartis, especially in the area of haematology, offer unique advantages.

If we were to work in complete isolation, we would miss a fantastic opportunity to leverage the learning and position of the company. At the same time, if we were to operate just like any other franchise, we might lose our speed and agility.

This business requires a level of flexibility that is unheard of and unparalleled, even for us as a pharma company. To point out just one example â?? supply chain management. In CAR-T there are no medicine boxes or vials on the shelf that are delivered to pharmacies or hospitals. Each batch is only produced once we receive a patientâ??s cells. We need to operate in a completely integrated way with the companyâ??s supply service and manufacturing teams to ensure that there is the timely pick-up of a patientâ??s cells once she/he is considered treatment eligible. Once a patient is identified, the timely delivery of the final product to the physician and the patient becomes critical.

Novartisâ?? CAR-T product has been on the market for nearly two years now. Can you walk us through the journey it took to get to the first approval from the EMA and uptake by major European 5 markets? What lessons have you been able to draw from this process?

There are two words that come to mind: collaboration and learning.

We pioneered the therapy and the approval but had to do this by collaborating with many stakeholders. This journey started in 2012 with the University of Pennsylvania where the scientific and medical foundations for Novartis were laid when Emily Whitehead, a 6-year-old child, terminally ill with treatment-resistant leukaemia, was successfully treated with the CD19-CAR-T therapy that later on Novartis licensed in. Today, she is a healthy and happy teenager!

When we started the clinical trial program, we had to collaborate very closely with physicians and patients as well as manufacturing partners. As the therapy became more broadly used were learned together how to treat patients in a real-world setting, sharing information, and updating guidelines.

Throughout the journey we needed to collaborate with manufacturing partners, supply chain partners, patient organisations, regulators, policymakers and payers â??jointly we were building an understanding how to manage the complexity of the therapy on the one side and a sustainable access scheme on the other side. As with all pioneering journeys, we have to constantly be alert to learn from our steps and course-correct where necessary.

CAR-T therapies are still very new and to some degree represent uncertainty for physicians and patients, high prices for payers, and safety and efficacy concerns for regulators. How are you attempting to find answers for these issues?

Novartisâ?? CAR-T is a one-time therapy with a multi-year impact. In the beginning, many were not familiar with this new paradigm. We had to innovate collaboratively, learning what was and what was not working from other parties in order to deliver the therapy to patients in dire need of therapeutic options. Transparent collaboration with our partners in a learning mode is key to address these challenging questions without obvious answers.

A part of safety concerns relates to the uniqueness of the therapy. As a patientâ??s own cells are the basis of the medicine, a so-called â??chain of identityâ?• is of paramount relevance. If ever two batches are incidentally interchanged, and patient A would receive patient Bâ??s cells, both are likely to die. So even something seemingly simple like the look of a product label becomes a significant question. For traditional therapies, the name of the product would suffice. But for Novartisâ?? CAR-T, a patientâ??s full name and date of birth become part of the batch ID â?? in Europe, this raised hitherto unknown data privacy challenges which we had to manage collaboratively with regulators.

Not surprisingly, the pricing conversations were complex. While payers consistently recognised the value of the product, they were not used to the concept of a one-time therapy with multi-year effect. Most of todayâ??s innovative therapies are for chronic disease management and payers are used to reimbursing over a period of time. Since every healthcare system has its own, unique aspects and we realized that cell and gene therapies are often a magnifying lens to existing problems and that we could not take the same approach in every system. Therefore, we collaborated with each payer to find solutions that matched their needs, as long as they could recognize the value of the therapy.

In addition, there were other new challenges that required that we and the systems adapt to match the situation. For example:

1. Given their complexity, todayâ??s commercial CAR-T therapies are only licensed for administration in specialized treatment centres. These hospitals are trained and qualified by Novartis. One of our biggest learnings was that clinics â?? which are usually clients â??onlyâ?• - become â??suppliersâ?• for pharma companies. They collect and provide the cells that are starting material for the final product. This fundamentally new relation requires specific regulations and a new, collaborative mindset.
2. Internally, we had to create new roles to appreciate all these different challenges, for example the experts who train and qualify the treatment centres or those who accompany the product ordering process throughout the whole manufacturing journey. We also had to develop an IT platform that allows physicians to place orders. Over the course of time, we have worked closely with physicians to continuously improve that platform. We are still working on that to

make sure it meets our needs.

In how many countries is Novartisâ?? CAR-T commercially present today?

One needs to differentiate between regulatory approval and reimbursement. On a global level, Novartisâ?? CAR T Therapy has received regulatory approved and is currently reimbursed in 23 countries. In Europe, the product has received centralized marketing authorization for all EU member states and is also approved in Switzerland. So far, we have also been able to achieve reimbursement agreements in 20 European countries.

Are patients scared when they are introduced to the concept of CAR-T therapy and the usage of their own cells? What has been the reaction?

Typically, the patients are amazed by CAR-T and understand what is a complex process rather well.

From our first contact with patient advocacy organisations, there was a huge amount of interest in the therapy. Especially in the beginning, this required also some expectation management as currently, only very few blood cancer patients are CAR-T eligible.

I have rarely heard about patients being concerned about genetic modification. We put a lot of effort into helping the community understand how CAR-T technology works, especially on helping people understand that genetic modification occurs outside of the patientâ??s body. People see this as science fiction becoming reality, which it is, even for the physicians among us.

In which part of the disease management cycle is Novartisâ?? CAR-T positioned? Is it the last possible solution?

We can only speak about the currently licensed indications. Today, our CAR-T therapy is approved for third-line use in two distinct forms of blood cancer. Third line means that patients underwent at least two other treatment options prior to CAR-T.

CAR-T therapies are administered once but give the hope of a long-term cure. Have you yet managed to gather any post-administration data to show whether this promise will hold true?

The word â??cureâ?? has to be used carefully. It is a one-time treatment with multi-year impact and evidence of the sustained efficacy is growing.

Our clinical trials have selected data from up to 24 months and there are now separate studies that go up to 48 months.

Looking at trial results after two years, the product is effective in 40 percent of lymphoma patients and in 66 percent of paediatric patients. Those clinical trial data are now complemented by real-world studies. So far, the curves of the clinical trial data and the curves of the real-world evidence (RWE) seem to match. Also, the medicineâ??s safety profile seems to improve in the real-world setting â?? probably due to the fact that physicians are learning how to work with this therapy and are more comfortable managing the side-effects.

We also have an obligation to track our CAR-T patients for 15 years after administration. That has started both in the US and Europe where we just announced a collaboration with the EBMT on building a registry and will continue.

How will this emergence of new RWE play into future discussions around the pricing of the product?

We have arrangements with some payers that are based on RWE on a patient or country basis. Part of our commitment is to work on that and establish a fair matching of pricing to the productâ??s value delivery. Our goal was not to have a â??one size fits allâ?? approach but to manage each payerâ??s varying needs. We wanted to make sure that we were fair to those needs as long as the value that the product delivers to patients, healthcare systems and society is recognised.

Europe presents a certain asymmetry by country in terms of GDP per capita and percentage of GDP dedicated to healthcare. How would you ensure that your CAR-T medicine, due to its pricing, does not become a solution that only countries with higher GDP can afford to integrate into their health systems?

We are present in 20 countries, including Croatia, Czech Republic, and Slovenia. Within Europe, we cover a great variety of geographies. The value that the product delivers to patients, their families and healthcare systems is the same. We have seen a lot of excitement from all countries in being able to make this product available to patients and in fact, we have also seen several cases of patients supported to travel cross-border in order to receive the therapy.

Hospitals and doctors play an incredible role in the journey of CAR-T therapies by the necessity of particular infrastructure, training and certification. How do you select the hospitals and doctors that are eligible? What has been the level of motivations to support these new kinds of therapies?

From the very beginning of our commercial journey, we have seen tremendous interest from physicians and hospitals. The number one question we heard is â??when can we use the product?â?•

This is not a therapy that can be administered lightly. As I tell my friends who are doctors themselves, this is not something that they were taught in medical school. It is truly new science.

The decision for selecting and preparing a centre has a lot to do with its infrastructure, the number of patients it sees, and its ability to guarantee certain quality standards. In all countries, we are working collaboratively with Ministries of Health and with relevant professional societies to provide a set of rules for centres and the characteristics that make them eligible to administer CAR-T.

I like to compare CAR-T treatment to heart transplants as especially in the beginning, only a few hospitals with specialised staff and equipment can carry out these procedures. It is important that we are able to guarantee quality for patients in order to ensure the best management of possible side effects or complications.

Novartis CEO Vas Narasimhan is very keen on artificial intelligence and advanced technologies across all possible company operations. To what extent do these new technologies stand to impact your work in cell and gene therapy?

I see a big short-term impact in the manufacturing processes, how we manage them, and how we correlate patient outcome data with manufacturing inputs and outputs.

These technologies can also help in terms of supporting physicians with patient management and side effect management to enable patients to spend as short a time in hospital as possible.

What are your priorities in cell and gene oncology for the next two to three years?

There are multiple tumour types that may be treated with cell therapies and CAR-T. We are expanding the number of haematology malignancies that we fight with the existing CAR-T as well as rapidly evolving and innovating the manufacturing platform for our currently approved and other CAR-T products. Novartis has invested a tremendous amount in establishing multiple manufacturing sites all over the world in order to be able to provide the therapy for years to come and for all patients globally. Another priority is innovating the manufacturing process to make it faster and more efficient.

We are in this for the long-run. We are looking to reduce side-effects, increase safety and efficacy, and finally expand to solid tumours so that we can provide solutions to more patients.

Given the pricing issues around CAR-T, at what point do you foresee these products becoming something closer to mainstream and being adopted more widely?

As with all pioneering innovations, it is important to commit for the long run. We made a good entry in the cell and gene space with offering CAR-T therapies for paediatric and adult blood cancers. We do see this becoming a more accepted and broader larger-scale therapy mode for many tumours, starting with other hematologic malignancies and hopefully eventually solid tumours.

Novartis was the first Big Pharma company to invest in this space, but now many other large and smaller companies get on board. There is also a huge amount of venture investment firms entering the space. They are carefully observing the commercial impact we are having and finding that this field is worth investing in.

With all innovations, there are peaks and valleys, but the innovation in this field is going very quickly â?? faster than in many other areas. We are likely to see drastic improvements in all aspects of the therapy in the next few years.

What would you like to share to industry sceptics about your journey and the journey of Novartis within cell and gene therapy? What do you see as Novartisâ?? role as a pioneer in this field?

It is both exciting and challenging. Innovation is here, it is happening at a fast speed and that is fantastic from a patient perspective. We bring to the table the know-how of how to turn a very interesting scientific experiment into a therapy; a skill sometimes lacking in biotech companies.

We also have a role in shaping the environment with regulators and policymakers. Like us, they are also stepping into the unknown. The most valuable thing that we can do in this new space is to take a learning approach to what we do. By definition, not everything that we do is going to work 100 percent of the time. We have to try new things, learn from them, scrap them if they do not work and try something new. That approach is as important in the labs as it is in the regulatory and policy space.

I am sure we will put in place some policies and regulatory approaches that may not have the desired effect. We need to have the humility to look back on that and be able to change our approach.

What do you see as the true impact of CAR-T therapies?

It is really important to step back and recognise the wonder of it all. We have come so far and should not forget how amazing it is that we are now able to genetically engineer patient cells, put them back into the patient, remove cancers for a long time, and give these patients a new lease of life.

It is important that we appreciate it, celebrate it and at the same time do not take it for granted and think that this approach will work for every single tumour in every single patient. It is a balance of great hope and at the same time the reality that it will take time for these approaches to work in broader groups of patients.

What are your ambitions for the rest of 2020?

We are doing everything we can to maintain supply in these uniquely challenging times. While COVID19 changes the world day by day, cancer does not care about social isolation and cancer patients are one of the most vulnerable communities. Our mission has to continue and we are doing our utmost to keep the supply of the product unaffected. In mid-2020 we are going to have some important milestones with more manufacturing sites coming on board and clinical trials finishing to give more patients hope.

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