Astellasâ?? Peter Sandor on the Future of Immuno-Oncology

19.06.2023

Tags:

USA, Global, Astellas, Immuno-Oncology, Oncology, Immunotherapy, R&D

Astellas has steadily developed its immuno-oncology (IO) pipeline via both organic and inorganic means in recent years, with its early-phase IO projects now overseen by industry veteran Peter Sandor, the companyâ??s SVP and IO Primary Focus Lead. Sandor explains the variety of exciting IO approaches in development at Astellas, how the company is working with â?? and learning from â?? biotechs at the leading edge of IO innovation, and the data-driven translational strategies in place to ensure that as many of these therapies can eventually reach patients as possible.

Immuno-oncology (IO) is one of Astellasâ?? â??Primary Focusâ?? areas and has been pinpointed for its potentially significant role in the companyâ??s future. Why has the global group chosen to place this emphasis on IO?

It was not a case of waking up in the morning and choosing IO, but more of a continuous transition from our pre-existing approaches.

Astellas has built a leading role for itself in oncology, with approved products in prostate cancer, urothelial cancer, and acute myeloid leukaemia as well as a gastric cancer therapy for which we have recently presented phase 3 data. Through our strong heritage and experience in oncology, we have identified IO as a key area where we believe we have the potential to deliver transformative medicines for patients with limited treatment options.

As many as 80 percent of patients are estimated to be refractory (non-responsive) to immune checkpoint inhibitors or to relapse (fail to maintain a response) during treatment. We hope to significantly increase the 20 percent of patients that have strong, long-term survival rates and believe that new IO approaches can really deliver for patients.

The immune system attempts to eliminate viruses, bacteria, and dying cells which do not belong in a healthy body. However, cancer has been so difficult to treat because it has developed mechanisms to evade immuno-surveillance. We believe that new IO approaches have the potential to change the course of treatment for patients in need, delivering sustained, durable benefit for the patientâ??s long-term survival. As an example, new approaches, such as CAR-T and checkpoint inhibitors, have shown the immune system can be retrained to eliminate cancer, which is what makes IO such an exciting field. We must be mindful that these approaches are developed for selected patients with selected tumour types and are not considered a miracle solution for all cancers.

How has the companyâ??s IO approach evolved?

From very early on, there has been an understanding that the immune system is complex and that a single targeted approach would be insufficient. Therefore, we started to build multifunctional approaches so that a single drug could carry out multiple actions and attack the immune system from different angles.

In parallel, Astellas also shifted from a traditional asset-based oncology R&D strategy to a modality-based strategy, this allows us to learn more effectively how to work with complex technologies and efficiently generate a robust pipeline. When modalities are paired with the right biology, there is potential to create therapies with long-term benefits for patients with certain diseases.

How does Astellasâ?? IO pipeline look today and what are the assets or modalities that you are most excited about?

Bispecific immune-cell engagers offer great promise; they work by redirecting T-cells or other immune cells to target the tumour and training them to potentially offer the prospect of cure.

This is an exciting approach because â?? as weâ??ve seen from ongoing clinical trials â?? it can deliver meaningful clinical and preclinical effect (dependent on where we are in development) but also because these molecules are relatively easy to deliver.

There are many other companies utilising similar approaches, but we believe that our bispecific approach differentiates Astellas. Our solid clinical-stage pipeline has been built via strategic collaborations, for example with CytomX Therapeutics and Xencor on T-cell engaging bispecific therapies, combined with innovative internal programs. Our modality platform approach allows us to learn how and where to modify these technologies during preclinical development, as well as how to get the right doses to the right patients during the clinical stage.

Another important platform in our pipeline is allogenic cell therapy, which means that rather than using the patientâ??s own cells, therapies are derived from a single source of cells to treat many patients. This is an exciting field as it can be easily tailored to the needs of individual patients and adapted to multiple disease targets if designed properly.

We have begun to build a unique platform based on induced pluripotent stem cells (IPSC) whereby cells can be removed, reprogrammed as healthy cells, and reintroduced to a patient. We are also rapidly advancing a cancer cell platform that can be administered to any recipient without the need for human leukocyte antigen (HLA) matching. Combining our universal donor cell (UDC) technology (developed by Universal Cells Inc., a company acquired by Astellas in 2018) with our *convertibleC* AR system, we are developing a highly flexible, off-the-shelf IO cell therapy that can be used

repeatedly, for which we expect to see the first clinical program later in 2023.

Finally, we have a few other platforms which also represent highly differentiated approaches, including intravenously delivered oncolytic virus and antibody drug conjugate technology, which combines immunologic and traditional cell killing activities.

Given that Astellasâ?? IO pipeline is predominantly at Phase I and the high failure rate of therapies at this stage of development, how many of these assets do you feel can realistically make it all the way to market?

Thatâ??s an important question and one I do not have a good answer for, itâ??s an industry-wide challenge. Unfortunately, the failure rate in oncology and especially IO is far higher than we would all like it to be. Translating discovery and preclinical data from animal models to human biology and clinical data is extremely hard and the highest failure rate is therefore in Phase I clinical studies.

We are committed to working to address this challenge and have made sizeable investments into translational research and science capabilities with humanised animal models that mimic the human response to these drugs more accurately. On top of this, we have huge capabilities in data management and data analytics, be it genomic, proteomic or clinical data management. When combined, we believe this is enabling us to become better at predicting what will happen in the clinic. However, there is still a lot to learn, meaning human Phase I studies are critical.

To what extent is the pricing and affordability of a potential drug a consideration at the early stage of development in which you work?

There is a balance to be struck to meet the unmet needs of patients from both a medical and commercial perspective. We of course operate in a market context, but decisions in drug discovery and preclinical development are primarily driven by scientific data.

In addition to costs, we also need to take efficacy, safety, and convenience into consideration when making decisions to serve the ultimate goal of ensuring that any drug which gets to market has a meaningful clinical benefit.

How closely do you and your early development team have to liaise with business development, given that Astellas has primarily grown its IO footprint via M&A and partnerships?

Very closely. We have an incredibly talented Business Development team which identifies opportunities. An expert cross-functional team then assesses them before making a decision. Most importantly, we look at how well the companies, their culture, commitment, and belief in certain aspects of oncology treatment match our vision and approach. This cultural and intellectual fit of any potential partner is crucial in these discussions.

Similarly, partner companies also have to evaluate how good a fit we, as a Big Pharma partner, are. They want to ensure that the development of their drugs will continue with the same philosophy with which they were created.

In what is a highly competitive field, how is Astellas differentiating itself and building up its reputation as an IO company?

Based on the feedback we receive from partners and other players in the industry, we have established a reputation as a committed company that has been creative in bringing technologies forward. It is all driven by our talent, which we have developed internally as well as via acquisitions and partnerships.

At Astellas, we have always been focused on developing IO projects or drugs that work differently and target different aspects of the cancer. We are also openly looking to build novel approaches into this. If you look at our dealmaking history over the past two years, we have conducted a fairly large number of smaller collaborations which focus on filling the gaps in our existing capabilities or platforms. In the future, this approach may evolve to include larger full-scale acquisitions.

Given that biotechs are driving most of the industry conversation and innovation, how would you characterise the role of multinational companies like Astellas moving forward?

Both small and large companies have strengths and weaknesses. Small and mid-cap biotechs focused on developing a single product or idea can move quickly to make decisions with great agility. However, at a certain inflection point they require the machinery of Big Pharma to take their drugs through clinical development as well as through the regulatory and commercialisation stages.

Smaller companies increasingly rely on external contract research organisations (CROs) for much of their early preclinical drug discovery work, but Astellas has been able to build these scalable capabilities in-house. Therefore, our own platforms can be deployed synergistically with those of the partner company to drive more value.

Additionally, large companies are often more bureaucratic and take longer to make decisions. However, Astellas is a learning organisation, meaning that bringing these smaller entities on board allows us to learn from them and create new approaches, processes, and governance to drive quicker decision making. As an example, we recently implemented a new R&D operating model which creates a very agile and fast matrix organisation which is laser-focused on, in our case, IO. This model is replicated in our other focus areas of research and development, including mitochondrial diseases, gene therapy, blindness and regeneration and targeted protein degradation, focusing our teams on a single goal.

What are you most excited for Astellas and the IO field more broadly over the next few years?

I expect that a lot of new data will start to flow from Astellasâ?? IO pipeline. This data, predominantly from preclinical development and Phase I trials has already started coming, and we are excited to see even more, especially around new solid tumour data with cancer cell therapy and antibody drug conjugate type approaches.

Beyond this, I expect that we will see much more progress on patient selection, especially in IO. We will start to understand and define patients who are more responsive to certain drugs as well as see more data and ideas come out of tumour microenvironment reprogramming to enable the effector cells and effector mechanisms to do their job better in the human setting.

Lastly, I hope we will build on promising data seen in melanoma and lung cancer with more IO programmes targeting earlier stage cancer, to maximize the value we can deliver for patients.

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