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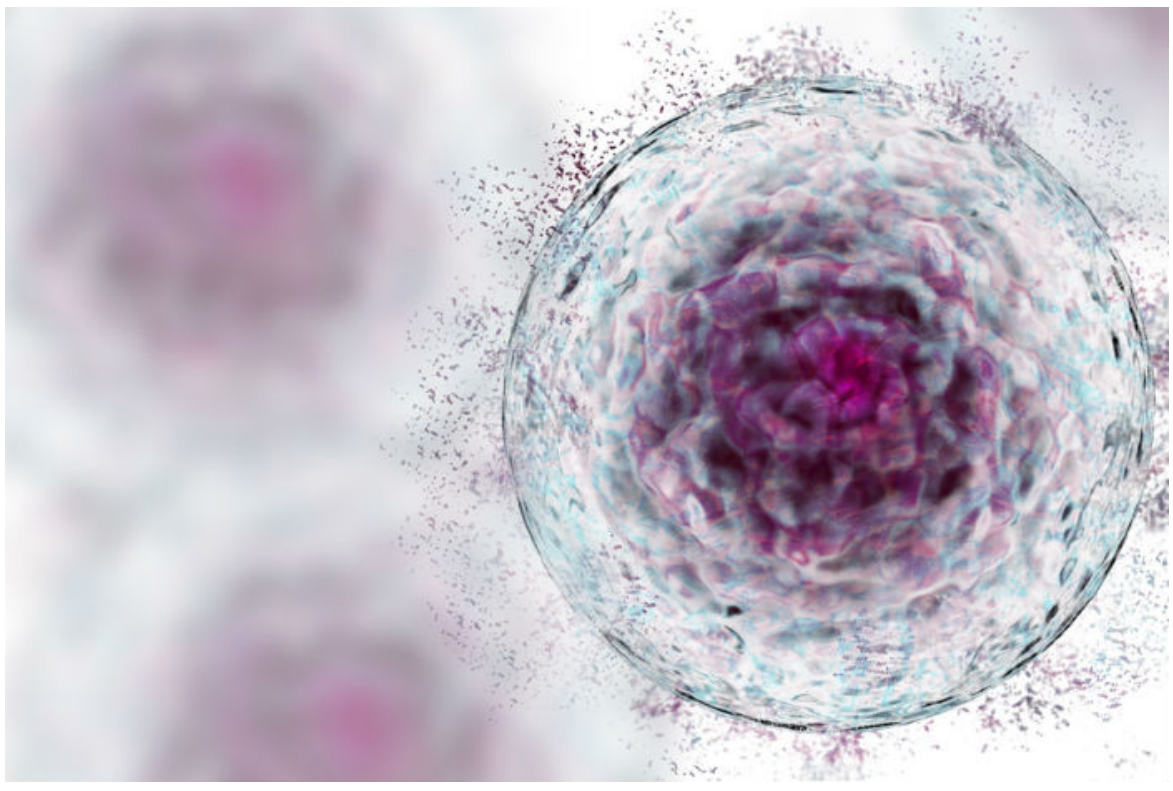
Industry keeps faith in finding solutions to bring stem cell and gene therapies to the masses



By Guy Martin

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Experts from the International Society for Cell and Gene Therapy (ISCT) told The Pharma Letter last month that the last 12 months had been the most important yet for advances in their field.

In reality, a lay onlooker might have guessed as much, as they have been in the limelight as never before since Kymriah (tisagenlecleucel) became the first therapy based on gene transfer technology to win approval from the US Food and Drug Administration (FDA) in August 2017.

That approval in B-cell precursor acute lymphoblastic leukemia (ALL) was swiftly followed by Gilead Sciences' (Nasdaq: GILD) Yescarta (axicabtagene ciloleucel), another chimeric antigen receptor T (CAR-T) therapy, receiving the nod in certain types of large B-cell lymphoma, an indication where it now faces direct competition from Kymriah after the Novartis (NOVN: VX) drug won a second approval last month.

In December 2018, Spark Therapeutics' (Nasdaq: ONCE) Luxturna (voretigene neparvovec-rzyl) also created a stir by becoming the first directly-administered gene therapy approved in the USA that targets a disease caused by mutations in a specific gene.

A field that is 'here to stay'

These regulatory milestones, and the fact that the new Kymriah approval came just before the ISCT met for its Annual Meeting in Montreal, added to a sense of momentum at the event and a realization that these therapies are now making a difference to the lives of growing numbers of patients.

“We couldn't have orchestrated it much better, that rolling out,” said Bruce Levine, who alongside colleagues at the University of Pennsylvania and the Children's Hospital of Philadelphia led research, development, and clinical trials of Kymriah.

“To have a second indication and an indication with 10 times more patients, I think it shows that CAR-T cell therapy, the field as a whole, it's here to stay.

“All of this has been built on work that has been happening for years, for decades in some cases,” Dr Levine said, and he predicted: “It's going to be a rampant evolution, branching out into different diseases, with combinations of approaches."

Within the next two years, there could also be CAR-T therapies approved for chronic lymphocytic leukemia (CLL) and multiple myeloma, too.

With the first indication for Kymriah in a young ALL patient group, it became the best option to treat around a third of the 3,100 Americans diagnosed with the rare cancer each year, but with the B-cell lymphoma approval and potentially those other two blood cancers added too, CAR-T therapies could reach tens of thousands of patients by 2020.

Catherine Bollard, a scientist at the Center for Cancer and Immunology Research at the Children's Research Institute and former president of the ISCT, said the field was currently "riding a wave of excitement and energy".

She served on the FDA Oncologic Drugs Advisory Committee that recommended the first approval of Kymriah, saying: "That definitely was a real milestone event that I think cannot be underestimated. Here is an autologous, gene-engineered T-cell product that got FDA approval. I never thought I would see that."

It is also an event that has blazed a trail with the further approvals since. But the path ahead is not without its hurdles.

Bespoke and labor-intensive

Cost is certainly a huge barrier. Novartis priced Kymriah at $475,000 for a one-time treatment in the pediatric ALL indication, a reflection of the fact that each dose is customized, created at the company's manufacturing facility in New Jersey, using an individual patient's own T-cells.

Once the cells are modified, the therapy is then infused back into the patient to kill the cancer cells.

This labor-intensive process and the amount of R&D work that has taken place perhaps make Kymriah's price more understandable, though they do not make it any more affordable, and expense has potentially contributed to sales being underwhelming in 2018's first quarter, at just $12 million.

In lymphoma, Kymriah and Yescarta are priced at $373,000, more than $100,000 cheaper than for the pediatric ALL indication, but still among the most expensive drugs ever marketed.

The Luxturna price tag is a jaw-dropping $425,000 per eye or $850,000 for both.

Whether these prices can be justified or not – the peer-reviewed journal of health policy thought and research, Health Affairs, claimed that the $475,000 Kymriah cost was too high by 197% – there is widespread acceptance that individually-tailored therapies like this come at great expense.

With that acceptance has come a shift in where some of the investment for these therapies is going.

Dr Bollard said: "I think now there's renewed focus, possibly driven by pharma, on the fact that we now need to push towards third-party, off-the-shelf cell therapeutics, to make cell therapy more like a drug, and fit the pharma model.

"It is proving that there are logistical challenges with the patient-specific product model, not insurmountable, but potentially challenging. For example, if you develop a 'home run' cell therapy for, say, lung cancer or colon cancer, how does this autologous model fit when you're now talking about significantly more patient numbers than the leukemia/lymphoma space?"

Investment still justifiable

If cost is responsible for the arrival of a roadblock moment, potentially when cell therapies come along for solid tumors or for other large patient groups, then Dr Bollard admitted to not knowing how the solution might play out, but she suspects that allogeneic therapies might be involved.

"I'm really just talking based on experience of discussions with pharma, who do seem more focused now on exploring the off-the-shelf cell therapies. And so, I am extrapolating from that, that there are challenges they're encountering in the patient-specific treatment model. My personal impression is that they're wanting to drive the off-the-shelf model as a priority."

So far, autologous treatments being tried in the solid tumor space have not actually done as well as in hematological malignancies, and it seems unlikely that a cell therapy will reach the market for this larger patient group in the next five years.

Even if there are delays, Dr Levine has faith that the industry and its partners will find ways of getting over the bumps in the road. Engineers are looking at ways of overcoming issues with supply chain and logistics, to name one example.

"What the clinical results and now the approvals have spurred is the investment by the tools and technology companies to come up with automated solutions, ways of reducing the labor needed to manufacture each product, so we will see improvements in that arena," Dr Levine

said.

“It's driven by the magnitude of the therapeutic effect. These are patients with no other therapeutic options save a stem cell transplant that carries with it substantial toxicity in the near term but also the long term, and if you look at the cost analysis of the first and second years post-stem cell transplant, and then out to five years, it’s higher than CAR-T therapy, even with management of CAR-T patients. So I think that justifies the investment in the technology going forward.”

Optimism prevails

Another factor is innovation that could come in pricing models, something that some companies are already subscribing to, including Spark Therapeutics, which has agreed for Luxturna to be made available under an outcomes-based rebate arrangement and an innovative contracting model that aims to reduce risk and financial burden for payers and treatment centers.

A further strong argument on the cost front is that single-treatment stem cell and gene therapies, with a one-off payment, are very different to other drugs for chronic conditions that have to be taken for years, or sometimes decades, to keep a disease at bay.

Patients can take heart from having an organization like the ISCT driving forward progress not just in research, but also in bench-to-bedside translation and ensuring broad access to the therapies that its members have dedicated much of their lives to making a reality.

Support for these aims is coming from regulators, too, in particular the FDA, and who better to have the final word than Peter Marks, director of the agency's Center for Biologics Evaluation and Research.

He said: “I believe that we are at one of those points where if we don’t, in the next few years, take very seriously the need to improve our manufacturing capabilities, we may be in a situation where the electronics industry was with computers at a point, where you won’t have them get out to the masses until you can actually make the products in a very scaleable, efficient way and bring down the cost.

“I’m incredibly optimistic that we have the scientific capabilities to get there. I don’t believe that there’s anything – there’s not some intrinsic block there, except that we haven’t put in as much effort as we need to to get over the hurdles to more efficiently to produce some of these products.

“So I’m incredibly optimistic, but we do have to pay attention to manufacturing.”

Biotechnology Feature Genetics Gilead Sciences Immuno-oncology In Depth Kymriah Novartis Oncology Stem Cell Therapy USA Yescarta