

Cell Therapy

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Adoptive cellular therapies can sound like the stuff of science fiction.

A patient's own cells (or potentially donor cells) are modified in a lab and administered back to the patient to manipulate the immune system and treat, possibly cure, a disease. But with the approval of the first chimeric antigen receptor T-cell (CAR-T) therapies – Novartis' Kymriah and Gilead/Kite's Yescarta – this has become reality in a relatively short period of time. And the technology continues to develop at a rapid pace.

T-cell receptor (TCR) therapies are on the horizon, as well as allogeneic options that could expand the scope of diseases to be targeted and patients to be reached. Gene editing is opening up even more options. Still, even though technology continues to grow by leaps and bounds, there are challenges ahead.

There's much still to learn about patient responses, durability, improving safety and making the production processes easier and cheaper. There's also a lot to be gleaned from the commercial experience of the early cell and gene therapies – from manufacturing and patient experiences to payment models and reimbursement. Understanding the potential pitfalls will go a long way to ensuring future success.

The US FDA and other regulatory agencies are willing partners. FDA Commissioner Scott Gottlieb has repeatedly spoken about the “transformative promise” of regenerative medicine and ways to encourage innovation in the fields of cell and gene therapy. So with the first generation of products on the market to guide the way, and supportive regulatory partners, the time is right for new chapters on cell therapy.

Mary Jo Laffler

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Radically Changing Cancer Treatment and Costs – Medigene’s TCR Quest

► By Andrea Charles, *Editor of Custom Content, Pharma Intelligence*

Countless start-ups and established pharma companies are diving into the immunotherapy and regenerative medicine waters, working to connect with academics or to acquire CAR-T or TCRs from other groups. While big pharma and big biotech companies are flocking to immuno-oncology and seeking to build up infrastructure, Medigene follows a systematic discovery process in the TCR cell therapy space. Unlike many other firms, small or large, Medigene cultivates an in-house entrepreneurial start-up culture based on deep scientific expertise within the structures of an established biopharmaceutical company, says CEO Dolores Schendel.

Medigene has combined state-of-the-art science, bio-informatics, automation and robotic systems to build a growing TCR pipeline for own development and for its partner bluebird bio. With ongoing research to develop next-generation tools and find important patient-individualized therapy targets for those with high medical need, the company is navigating toward its goals – change cancer from an incurable disease to a controllable factor and to bring down production costs for highly innovative T cell therapies.



It's been a big year for cell therapy; how are you learning from regulatory and commercial experiences with Chimeric Antigen Receptor (CAR) T cell developers?

First and foremost, it's important to ensure approved products are making it to centers in the U.S. so they can deliver drugs to these patients now. We are starting to see the benefit from this in multiple centers. That's the ultimate proof-of-concept of this patient-individualized therapy being rolled out.

From the regulatory point of view, we can see from the CAR-T therapies that, first, market authorization was based on the treatment of surprisingly low number of patients. And it occurred in a very short period of time – less than

five years from when the Phase I/II trials were initiated. Second, accelerated procedures had been put in place at FDA, as these products were showing high levels of efficacy. So, the regulatory authorities were willing to move fast, together with the companies and manufacturers in order to get these products to patients as quickly as possible.

Here at Medigene, we're developing T cell receptor (TCR) modified T cells. Our trial of MDG1011, is the first such trial in Germany. So, we couldn't rely on other examples in Germany to understand what the regulatory authorities would require. We held scientific advice meetings with the authorities to shape what to include with respect to the production process, and how the TCR-modified cells should



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– CEO Dolores Schendel

be characterized. This was helped by the German authorities, which are known as one of the strictest in the world, to engage fully with our scientists during these meetings.

Commercially, prices for these therapies are still high at the moment, mainly due to the individualized nature of the manufacturing processes, but we can anticipate that over time automation and decentralization in the production of cell based therapies will become more commonplace. In addition, it may become possible to treat patients with fewer but more potent cells. If production sites can really be located close to or at hospitals where patients are being treated, the enormous logistic infrastructures that exist now will no longer be necessary. Taken together, those improvements have the potential to substantially reduce treatment costs over the years to come.

Advanced cell therapies are high tech products. How does that change your approach to development? Conversely, how does technology help aid development of this type of product?

In cellular therapy, the product is a process, which automatically puts you in the realm of manufacturing at the very beginning of the development process. You must have a robust cell manufacturing process in place that isn't just utilized one time to produce something that will then be

administered to multiple patients. The process must deal with variations of patient derived material from patient to patient and nevertheless result in a product that will consistently deliver the expected therapeutic benefit. We can benefit from the approaches in the CAR-T field, while relying on the very deep expertise that we have in T cell biology, accumulated out of an academic setting for over three decades. So, we know very much about these cells, how they behave and how they can be manipulated to have particular characteristics. This helps tremendously in setting up our own process for cell manufacturing.

For Paul-Ehrlich-Institute, PEI, the competent authority Germany for cell therapies like ours, we had to start working with a fairly mature manufacturing process, perhaps more extensively developed than required in other countries.

Alongside that, we have established a GMP simulation lab onsite. We believe that technologies now coming out of the field of robotics and automation will play a decisive role in the manufacturing of products in the next five to 10 years. We are very attuned to such possibilities and already start to experiment and work with such technologies, even as we launch our very first trial.

Also, we study how to improve characteristics of future cellular products, potential side effects are still a concern with

cellular immunotherapies, so we are working on methods to have better control of T cell activity, for example by inducible T cell receptors that can be turned on and off in patients as needed. We intend to present our first results on these new approaches at scientific conferences in the near future.

Taken together, our deep expertise in T cell immunology, combined with developing automation improvements have the potential to substantially reduce costs for cellular immunotherapies in the future.

Allogeneic versus autologous is an important issue with cell therapies. What are the prospects for an off-the-shelf option?

I think we have to consider one basic biological principle in allogeneic versus autologous cell therapies: allogeneic are foreign cells. They will be seen by the immune system of a recipient patient as foreign, as if you are transplanting a foreign organ, and the immune system will eventually reject those cells. We know from CAR-T therapies that persistence of the administered cells in patients is associated with clinical efficacy – the cells should stay around in the patients for longer periods of time. Up to this point, there has only been limited persistence of allogeneic cells. Some in the field suggest treating a patient in an acute stage of disease with allogeneic off-the-shelf agents could be used to bring the disease under control transiently or as a bridge to stem cell transplantation. That might provide a window of time to produce the autologous cell therapy, which would ultimately provide the long-term memory cells needed. Of course, costs would have to be reduced and the method simplified to think that a patient would actually receive two types of therapy. Therefore we see allogeneic approaches as complementary and not necessarily as alternatives to autologous cell therapy products at this time.

What would you say are the main advantages of a T cell receptor approach?

CAR-T cells, because they use an antibody fragment to dock the highly active T cell onto the tumor cell, can only recognize surface proteins. Whereas a T cell receptor has a chance to recognize small peptides that are brought to the surface by major histocompatibility complex (MHC) molecules from the intracellular space. Therefore, a T cell receptor can look inside a cell, so to speak, and see what's

reflected. So, there are many proteins that a tumor will upregulate, to give it growth and survival advantages, and this provides a differential window to target such molecules to be seen by T cell receptors.

There is another distinction between the CARs and the TCRs. With the T cell receptor therapy, you are taking a molecule and putting it in a cell that naturally uses such a receptor. That means the auxiliary signaling pathways, which are coupled to that T cell receptor, are all functioning independently and in parallel. Therefore, you have more regulation, you have potentially more power, and you have possibly a safer approach. CARs make an artificial signaling domain, pulling pieces from different pathways, splicing them together, and placing them physically in contact with the antibody molecule. It's more difficult to regulate activity with such a construct. I believe time will tell whether we will have better regulation and fewer side effects in the T cells using TCR-based approaches.

At Medigene, not only do we have this sophisticated discovery technology that allows us to generate many receptors for the same target in parallel, which gives us many possibilities, it's also all done in-house and we have already moved first projects into the clinical development stage.

How does Medigene differentiate from other TCR companies?

The major point that sets us apart from others is that we pull our T cell receptor sequences out of repertoires of normal healthy donors. Therefore, we use the basic principles of the immune system for inducing T cell responses *in vitro* and we get a repertoire of very diverse receptors to the same target structure. Next, we compare those and choose the best out of that very specific collection. Our receptors are not mutated in any way, they have all been circulating in the body of a healthy donor. And as we transfer only the DNA of the T cell receptor into the patient's T cells, rejection can't occur.

To find these receptors, we have automated the discovery process using sophisticated robotics systems and thus made functional high-throughput screening of T cell receptors a big part of our platform technology. One reason for that is: Cellular immunologists don't grow on trees. Therefore, we have said, "Let's take all the tedious work and put it in the hands of a robot. Let's do that as early as we can, so we can use our trained personnel for other, more elaborate steps in the process."

One question will be how long will a particular product remain on the market? It might change substantially in two or three years and therefore, there will be a dynamic in how these products improve over time.

And we have also genetic approaches that enable us to find T cell receptors for practically any antigen of choice. If there's an epitope in that antigen that can be presented by an MHC molecule, we can vary those MHC molecules within our allogeneic TCR-finding technology. This gives us great flexibility to produce receptors to targets for different tumor indications in different populations.

Many of the small start-ups and also some of the more established companies are working to find receptors from some other place, e.g. from academic groups and using those singular receptors to move forward. At Medigene, not only do we have this sophisticated discovery technology that allows us to generate many receptors for the same target in parallel, which gives us many possibilities, it's also all done in-house and we have already moved first projects into the clinical development stage.

How are you ensuring widespread and efficient application of TCRs?

Most of the T cell receptor therapies developed today are for patients that have one particular HLA molecule, HLA-

A*02:01. The reason is this particular allele of the MHC is expressed in about 50% of Caucasians, but representing far less than 50% of the overall world population. So, of course, you start with something that would give you a high number of patients you could treat. But what happens to all the patients who will not have HLA-A*02:01? These are still the majority of the worldwide population and you have to find T cell receptor products, that are able to treat those other patients. Through our special technologies, Medigene has the capability to achieve this and open the door to broaden the treatable patient populations.

How do you see cell therapy evolving over the next five to 10 years?

I think we're going to see tremendous growth in this field, because we can already measure it by the number of start-ups that are popping up. It's like a mushroom field in high season. We can anticipate large waves of innovation. Today's first-generation products will have a fast evolution. One question will be how long will a particular product remain on the market? It might change substantially in two or three years and therefore, there will be a dynamic in how these products improve over time. That will be a true particularly for solid tumor indications, where you have the challenge of ensuring that T cells can enter the tumor micro-environment, maintain their function and tackle the hostile setting tumors create for the immune system.

Big pharma and big biotech are recognizing this is an arena they want to play in. Novartis was the first to make that step. It's now marketing a product in the US and soon will be delivering products to patients in Europe. Other big pharma or big biotech players will probably look for means to acquire expertise and know-how as well as products and technologies from existing companies.

From a patient and medical point of view, cell therapy is on its way to further revolutionize cancer treatment becoming a standard treatment option, and tuning cancer more into a "chronic" if not even curable disease.

LIVING IMMUNOTHERAPIES

Medigene is developing highly innovative TCR-T immunotherapies to target various forms and stages of cancer.

Medigene's TCR-T therapies aim to arm the patient's own T cells with tumor-specific T cell receptors. The receptor-modified T cells are thereby able to detect and efficiently kill tumor cells. This immunotherapy approach aims to overcome the patient's tolerance to cancer cells and tumor-induced immunosuppression, by activating the patient's T cells outside the body (ex-vivo), genetically modifying them with tumor-specific TCRs and finally multiplying them. In this way, large numbers of specific T cells to fight the tumor are made available to patients within a short period of time.

- Focus on T cell-directed immunotherapies
- First TCR-T trial in Germany: Phase I/II trial with proprietary TCR-T therapy MDG1011 in acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and multiple myeloma (MM)
- Dendritic cell vaccines (DCs) in ongoing clinical phase I/II trial
- Collaboration on six TCR-Ts with bluebird bio, validating Medigene's technology
- Headquartered in Martinsried near Munich (Germany), with US-office in San Diego, California

Medigene AG (FSE: MDG1, ISIN DE000A1X3W00, Prime Standard, TecDAX) is a publicly listed German biotechnology company. For more information, please visit: www.medigene.com

Next-Generation CAR-Ts Tackle First-Generation Safety, Solid Tumor Challenges

► By Mandy Jackson

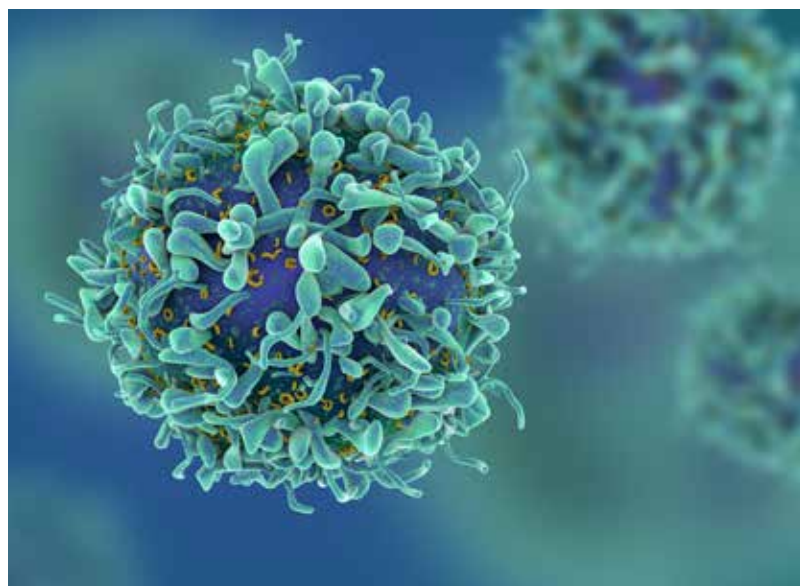
There are just two chimeric antigen receptor T-cell (CAR-T) therapies approved in the US, but dozens of companies already are clamoring to bring the next generation of CAR-T products to the market that address novel targets, improve toxicity and tackle the field's other big challenges.

Poseida Therapeutics Inc. and **Celyad SA** spoke with *Scrip* about their first products in the clinic and initial results in a handful of patients, but the vast majority of CAR-T data at the American Association for Cancer Research (AACR) meeting April 14-18 in Chicago was preclinical research for emerging CAR-T candidates and novel constructs. Their developers aim to reduce the incidence and severity of cytokine release syndrome (CRS), improve the persistence and potency of engineered T-cells, get CAR-T therapies inside solid tumors, and deliver off-the-shelf (allogeneic) products derived from donor T-cells.

Both of the CAR-T therapies approved by the US FDA in 2017 – **Novartis AG's Kymriah** (tisagenlecleucel) and **Yescarta** (axicabtagene ciloleucel) from **Gilead Sciences Inc.** subsidiary **Kite Pharma Inc.** – are autologous products that involve reengineering relapsed/refractory leukemia and lymphoma patients' T-cells to attack their hematological malignancies. The one-time treatments have been curative in clinical trials enrolling patients whose cancer has progressed after multiple rounds of traditional therapies, but they also can cause severe neurotoxicity and CRS, which in some cases has been deadly. (Also see “Too Sick For CAR-T? Kite Reports Cerebral Edema Death” - *Scrip*, 8 May, 2017.)

Novartis and Gilead/Kite as well as their near-term competitors, such as **Celgene Corp.** and **bluebird bio Inc.**, have their own next-generation products in development, many of which use technology acquired or licensed from other companies. They have an intense appetite for technology – and an interest in early data like the research presented at AACR – that enables safer, more effective and allogeneic products.

Last year's Yescarta and Kymriah approvals, along with Gilead's \$11.9bn Kite acquisition and Celgene's \$9bn **Juno Therapeutics Inc.** purchase, increased the already robust



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investor interest in T-cell therapies and boosted the prospects for emerging CAR-T players. (Also see “Celgene Seeks CAR-T Leadership, Hematology Diversification With Juno Buy” - *Scrip*, 22 Jan, 2018.)

Poseida Advances Into Higher Dose Cohort

San Diego-based Poseida's first clinical CAR-T candidate is the autologous product P-BCMA-101, which targets BCMA for the treatment of multiple myeloma. CEO Eric Ostertag said initial activity in the first few patients enrolled in the company's dose escalation trial – presented at AACR – suggests better safety and efficacy than more advanced competing products that use lentiviral vectors for their manufacturing.

"We have other differences in the manufacturing process, but the non-viral technology allows us to, first of all, add a lot of components that competitors cannot add because of lack of cargo capacity," Ostertag said. Poseida's piggyBac DNA modification system allows for the inclusion of multiple components, including a safety switch to toggle CAR-T cells on and off as well as a gene that allows for positive selection.

"The latter is relevant to what we're seeing so far, both in animal models and now we're replicating that in the clinic, which appears to be a better therapeutic index than our competitors," he said.

Poseida's therapies are designed for purity, meaning that the T-cells infused back into patients are nearly 100% CAR-T positive, compared to lentiviral-manufactured products that appear to be about 10%-30% CAR-T positive. The piggyBAC manufacturing system also delivers a product with a very high percentage of stem cell T memory stem cells, including effectors that kill tumor cells.

"For our products, it's generally about 70% to 80% stem cell memory [and] in published data for competitor products, I've never seen anything more than about 15%. We know from animal models that can translate into better, longer durability," Ostertag said. "I don't think we have a long enough window yet on the patients we've treated in the clinic to know we've got advantages on durability."

Poseida's Phase I trial for P-BCMA-101 will enroll up to 40 relapsed or refractory multiple myeloma patients, starting with two initial three-patient cohorts testing a low and higher dose for safety before opening the study up to more patients. All three patients in the low dose cohort of 0.75×10^6 P-BCMA-101+ CAR-T cells/kg remain in the study. One person had a partial response for at least 10 weeks and signs of tumor regression have been observed in the other two patients, but none have experienced dose-limiting toxicities or CRS. The second cohort is enrolling patients now.

Ostertag noted that the first cohort's dose works out to be about 50m cells per patient, which is about the same as the cohort 1 dose for bluebird's BCMA-targeting CAR-T therapy bb2121, which is partnered with Celgene. (Also see "Bluebird Flies On 100% Response Rate For Anti-BCMA CAR-T" - *Scrip*, 6 Jun, 2017.) Even so, Poseida notes that no prior BCMA-targeting CAR-T has had responses lasting longer

than eight weeks at this dose level, according to published data, and CRS was observed in both responders and non-responders in the early stages of those studies.

"With the caveat that it's an early, first cohort at this dose, I would say that that's a truly unprecedented result - that we're getting efficacy across the board but without evidence of cytokine release," Ostertag said.

"The product is expanding and seems to be peaking at about three weeks - that may be part of the explanation for the lack of cytokine release, and another explanation is that we put in 100% pure product," he continued. "If you compare that to a lentiviral product at, for example, a 50m cell dose, they may have 30% pure product, which means they're actually putting in 50m CAR-T positive cells, but then another 100m CAR-T negative cells. And even though those CAR-T negative cells are from your own body ... those cells can still release cytokines."

Poseida's next product candidate to enter the clinic will be a PSMA-targeting CAR-T therapy for prostate cancer, for which the company will submit an investigational new drug (IND) application later this year or early next year. Next will be an allogeneic BCMA-targeting CAR-T following by another solid tumor program for which Poseida has not disclosed the target. The company recently closed a \$30.5m Series B venture capital funding round. (Also see "Finance Watch: VC Investment Soars In Q1, Putting Biopharma On Track For A Record Year" - *Scrip*, 15 Apr, 2018.)

Celyad's Three-Study Experiment

The Belgian firm Celyad has three Phase I clinical trials under way for its lead CAR-T candidate CYAD-01, which targets NKG2D and is administered via three separate injections - the THINK trial in relapsed or refractory acute myeloid leukemia (AML) and the SHRINK and LINK studies in metastatic colorectal cancer. CEO Christian Homsy said the goal of the three-study Phase I strategy is to determine the best path forward for a potential registrational trial. The study designs were presented at AACR.

THINK is testing CYAD-01 as a standalone treatment without a pre-conditioning chemotherapy regimen to evaluate safety and look for signals of efficacy. Celyad reported earlier this year that the first patient enrolled in the study had a complete response. Data from additional patients will be reported during or around the time of the American

Society of Clinical Oncology (ASCO) meeting June 1-5. Six patients have been treated with the low and higher dose, but the study will enroll up to 24 patients in the dose-escalation phase with up to 86 additional patients in the extension phase.

“No CAR-T therapies have ever been effective without chemo pre-conditioning,” Homsy said. “We know now that the safety profile of the standalone approach [for CYAD-01] is good and also that we have signs of efficacy that are promising.”

SHRINK is enrolling up to 40 colorectal cancer patients with potentially resectable liver metastases, including 21 in the extension phase, who will be treated with CYAD-01 and neoadjuvant FOLFOX chemotherapy. “The idea there is that those are patients that potentially have tumors that could become resectable and we need to see if we can get a clean setting for the patients post resection so that the patient has better overall survival,” Homsy said.

The LINK trial will enroll up to 18 metastatic colorectal cancer patients with unresectable liver metastases in the dose escalation phase. “We inject the hepatic artery to see if the injection of CYAD-01 close to the tumor or the organ would lead to a stronger effect without having toxicity on a systemic level,” Homsy said. “The first patient of that trial has just received three injections and we are waiting to get the readouts of those.”

The Celyad CEO noted that the company has not seen any neurotoxicity to date in the 20 patients that have received all three CYAD-01 injections and most cases of CRS have been grade 2 with one grade 3 and one grade 4 CRS event. “That’s encouraging [but] you need to put some conditions on that, because it is as a standalone treatment, and you would expect that part of the toxicities seen with other CAR-Ts are linked to the pre-conditioning approach,” he said.

Celyad will begin to report more data from its three ongoing CYAD-01 trials within the next few months with additional readouts by the end of 2018 and others around the first or second quarter of 2019.

In addition to CYAD-01’s novel target of NKG2D, the candidate also has a novel co-stimulatory domain – DAP 10 – rather than the 4-1BB and CD 28 domains used in most other known CAR-T therapies. Celyad presented preclinical

data at AACR showing that CAR-T cells expressing NKG2D are optimally stimulated by DAP 10.

The company is developing various technologies to improve the ability of CAR-T cells to get into solid tumors, to ensure the best target selection for CAR-T therapies, to increase CAR-T cell proliferation and to improve safety. “We think that we need to have a quite prolific approach to addressing those three problems together, because they are really intertwined,” Homsy said. (Also see “Celyad VP On IP Issues, Development Timelines For CAR-T Therapies” - *Scrip*, 26 Apr, 2017.)

Autolus Readies Next-Gen Version Of UCL/CRUK Program

Autolus Ltd. has made great strides since its founding in 2015 with £30m from Syncona and intellectual property from **University College London** (UCL) for CAR-T therapies against novel targets and with the potential for less toxicity. (Also see “New kid on the CAR-T block: Syncona/UCL form Autolus” - *Scrip*, 22 Jan, 2015.) The company raised a £40m (\$56m) Series B round in March 2016 to keep the CAR-T development momentum going. It then closed a \$80m (£59m) Series C in September 2017. (Also see “Autolus Raises \$80m To Take T-Cell Engineering To The Next Level” - *Scrip*, 26 Sep, 2017.)

And, as of March 5 of this year, the company plans to pursue an initial public offering in the US as it readies a next-generation version of AUTO6 – an autologous GD2-targeting CAR-T that’s being studied in a Phase I pediatric brain cancer clinical trial run by **Cancer Research UK** (CRUK). (Also see “Finance Watch: Biopharma IPOs Defy Broader Stock Performance Trends” - *Scrip*, 9 Mar, 2018.) Data for nine of the first 12 patients enrolled were presented at AACR.

No dose-limiting toxicities were observed in the first nine neuroblastoma patients, but for the first six patients AUTO6 was not detected in peripheral blood and no efficacy was seen. Among the three patients treated at dose level four, two patients had disease progression after day 28, but one patient experienced grade 2 CRS after day 5 and had evidence of tumor lysis after day 21. That patient had near complete tumor clearance in the bone marrow, but disease progression was observed after day 45. With evidence of a response to treatment, the study has advanced to dose level five.

While CRUK continues its study, Autolus says it is developing its next-generation product with programming modules to enhance efficacy via improved CAR-T cell persistence and to break through the layers of defense that cancers engage to evade T cell killing. The company plans to advance its new product into a Phase I/II trial and pursue studies for the treatment of both children and adults with solid tumors.

Other Company, Academic Data

San Diego-based **Fate Therapeutics Inc.** presented pre-clinical data for its allogeneic CAR-T candidate FT819 in a late-breaking poster session at AACR. The therapy, which is derived from a line of induced pluripotent stem cells (IPSCs), targets two receptors on cancer cells – CD19 and CD16 – to avoid antigen escape. The program was developed in collaboration with the Center for Cell Engineering at **Memorial Sloan Kettering Cancer Center**.

FT819 was shown in preclinical studies to target only CD19-positive tumor cells and not CD19-negative cells. It also, when combined with a CD20-targeting monoclonal antibody, targeted CD20-positive tumor cells through CD16 engagement. Fate said that developing FT819 from a master IPSC line allows for reduced manufacturing costs and production of an off-the-shelf product that can treat “many thousands” of patients.

Fate’s Vice President of Cancer Immunotherapy Bob Valamehr said during an April 16 media presentation that the company will advance FT819 into the investigational new drug (IND) application stage within the next 12 months.

In other next-gen CAR-T presentations at AACR:

- Researchers from the **University of Washington, Fred Hutchinson Cancer Research Center**, Seattle Cancer Care Alliance and the **Scripps Research Institute** presented early data from the first six patients treated with the first two doses of an autologous CAR-T therapy targeting ROR1 after lymphodepleting chemotherapy regimens containing cyclophosphamide in advanced non-small cell lung cancer (NSCLC) and triple negative breast cancer (TNBC). There were no dose-limiting toxicities and no severe cases of neurotoxicity or CRS, though three patients experienced grade 1 CRS. Two NSCLC and two TNBC patients had mixed responses with decreased disease burden at some metastatic sites at
- **Obsidian Therapeutics Inc.** presented preclinical data showing that its destabilizing domains (DD) – small protein domains that can stabilize a payload protein that’s engineered into a cell or gene therapy when the protein is added to enhance the therapy’s activity at the tumor site. The DD, and therefore the CAR-T product, is turned on when a readily available small molecule is administered to the patient or turned off when the patient stops taking the drug. Changing the small molecule dose also can increase or decrease a CAR-T therapy’s activity as needed to control efficacy and safety, Obsidian CEO Michael Gilman explained in December when the company revealed its \$49.5m Series A venture capital round. (Also see “*Start-Up Obsidian Gets \$49.5m To Determine How And When To Activate CAR-T Cells*” - *Scrip*, 6 Dec, 2017.) The poster presented at AACR described Obsidian’s creation of interleukin-12 (IL-12) and IL-15 cassettes containing the DD technology that can be inserted into CAR-T therapies.
- **Cellectis SA** also presented data related to IL-12 and IL-15 engineered into CAR-T therapies. In this instance, the



“No CAR-T therapies have ever been effective without chemo pre-conditioning,” Homsy said.

the first disease assessment between days 28 and 90. One TNBC patients treated with two CAR-T infusions maintained stable disease through at least day 56.

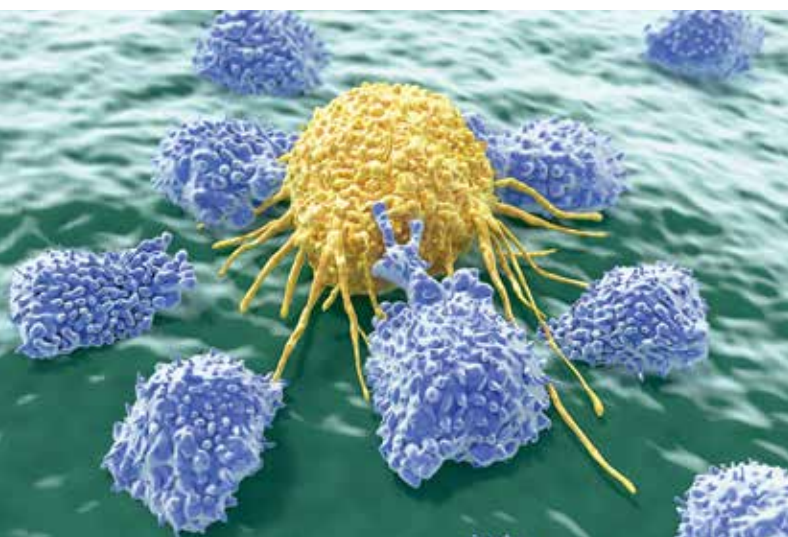
company described the use of IL-12 or IL-15 heterodimer expression cassettes to assist with the delivery of CAR-T cells into solid tumors. Cytokines have been explored previously as a means for delivering CAR-T cells into solid tumors, but that increases the therapies' toxicity. The Cellectis technology relies on endogenous promoters regulating PD-1 or CD25 to pull the CAR-T cells containing the cytokine-expressing cassettes into the tumor, so that exposure to IL-12 and IL-15 is local inside the tumor rather than systemic.

- Researchers from Washington University School of Medicine in St. Louis, Mo. showed preclinical research for an allogeneic CAR-T therapy targeting CD7 for the treatment of T-cell malignancies that was designed to prevent graft-versus-host disease (GvHD) from the donor T-cells. The clinicians used CRISPR/Cas9 gene editing to delete CD7 and the T-cell receptor alpha chain (TRAC) and found that the CAR-T was able to kill malignant cells better than an allogeneic CD19-targeting CAR-T used as a control while also generating no GvHD.
- **Aleta Biotherapeutics** in Natick, Mass. presented very early results for technology that uses a retargeting fusion protein (FP) or bispecific FP (biFP) to redirect CD19-targeting CAR-T cells to multiple other antigens in both hematological malignancies and solid tumors. The FP and biFP technology supported CAR-T cell activation and expansion, but the company is fine-tuning the technology to add multiple other features.
- Emeryville, Calif.-based **Eureka Therapeutics Inc.** and researchers from Memorial Sloan Kettering Cancer Center showcased their research focused on overcoming the tumor microenvironment (TME), which can be a barrier to CAR-T cells for solid tumors. The scientists engineered CAR-T cells to secrete PD-1-blocking single chain variable fragments (scFv), because the TME expresses ligands that bind inhibitory receptors on T-cells, such as PD-L1. Early studies show that the scFv strategy blocks PD-1 binding to PD-L1, thereby boosting CAR-T efficacy.
- **Brigham Young University (BYU)** researchers tackled the challenge of physical barriers to solid tumors and immunosuppressive conditions at the tumor site, which mute CAR-T therapy efficacy. They developed MOTO-CAR cells, which take advantage of the ability of macrophages to permeate almost any type of cell in the body. The BYU scientists created monocyte-derived human macrophages that were engineered to express a tumor-targeting receptor and secrete cytokines, ligands or chemokine receptors. The result was potent tumor cell killing in multiple cancer cell lines.
- **CRISPR Therapeutics AG** had a poster highlighting its first allogeneic CAR-T therapy, which involves the use of CRISPR/Cas9 gene-editing to edit donor T-cells so that they express CD70 from the space where TCR alpha constant region (TRAC) has been knocked out. The construct killed renal cell carcinoma tumor xenografts in mice and knocking out TRAC prevented GvHD.
- **Endocyte Inc.** and researchers at **Purdue University** worked together on a three-pronged approach for CAR-T therapies, which involve a CAR that expresses anti-fluorescein (anti-FITC) scFv instead of an anti-tumor ligand or self-antigen, a bispecific adaptor comprised of a FITC hapten linked to a tumor-specific ligand, and competitors that can interfere with the adaptor/CAR-T interaction with tumor cells. They presented data for their CAR-T candidate containing a folate-FITC known as EC17 in various folate receptor-positive tumor models. Treatment-related toxicity, including severe CRS, could be managed by administering competitors to the bispecific adaptor. Subsequent dosing of EC17 could reactivate the CAR-T cells. The preclinical studies showed that flexible dosing and treatment of CRS were possible without compromising anti-tumor activity or removing the CAR-T cells.
- Waltham, Mass.-based **Minerva Biotechnologies** intends to take its CAR-T targeting the growth factor receptor MUC1* (the cleavage product of full-length MUC1) into the clinic in the second or third quarter. The company presented preclinical safety and efficacy data, which showed that the candidate known as huMNC2-CAR44 stained more than 90% of breast, 83% of ovarian, 78% of pancreatic and 71% of lung cancer cells, but not healthy tissues. The huMNC2-CAR44 CAR-T cells also effectively inhibited tumor growth in mice.

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Immuno-Oncology Is Making Pharma Step Up Its Diagnostics Game

► By Alex Vadas



- Our understanding of the biology driving IO therapy responsiveness is being accelerated by next-generation sequencing profiling of solid tumors linked to clinical and outcomes data, with tumor mutational burden being the prime example.
- This acceleration creates challenges for biopharma, because the understanding (and validation across thousands of clinical samples) of immuno-oncology biology, pathways and biomarkers may simply outpace traditional pharma development.
- So what? The pharma industry will need to grapple with what type of biomarker strategy to pursue in IO. Standardization will be key, not only in which pathways and biomarkers to assess but also in defining standards around interpretation. Pharma must also work with industry partners to implement tests that fit better into therapeutic decision-making windows and health care economics.

Immuno-oncology represents a paradigm shift in cancer treatment, with the first wave of PD-1/PD-L1 checkpoint inhibitors such as *Opdivo* (nivolumab, from **Bristol-Myers Squibb Co.**) and *Keytruda* (**Merck & Co. Inc.**'s pembrolizumab) demonstrating cure-like performance in selected metastatic tumors such as non-small cell lung cancer (NSCLC) and melanoma.

This efficacy is driving significant checkpoint inhibitor adoption, and analysts project the class alone could represent a \$29 billion global market by 2022. In short, checkpoint inhibitors are providing hope to metastatic patients who were previously considered to be on a path to palliative care.

Despite their performance, checkpoint therapies have a number of shortcomings. For instance, response rates are still only 20% to 30% on average (although there is significant variance in published response rates by tumor type), and response times can be prolonged, which can be an issue for patients with advanced metastatic disease.

Checkpoint inhibitors also come with significant side effects, especially when used in the combination regimens (e.g., with anti-CTLA-4) that are ubiquitous in the industry. (Also see “*Combinations Continue To Drive Immuno-Oncology Deal-Making*” - *In Vivo*, 8 May, 2017.) Checkpoint inhibitors' cost (at up to \$150,000 per year for monotherapy) represents a significant burden to health care systems and payers. Furthermore, prior exposure to checkpoint therapy may render patients ineligible for other immuno-oncology clinical trials.

Today, PD-1/PD-L1 immunohistochemistry tests (IHCs) are available as companion or complementary diagnostics for many approved indications, yet their predictive power is considered limited in many situations. As such, while these IHCs are broadly ordered by clinicians, decisions to use checkpoint therapy may often be based on a lack of therapeutic alternatives coupled with substantial patient demand. This is creating significant need for improved diagnostics to predict response to checkpoint therapy, monitor response and support sustained usage.

Complex Biology

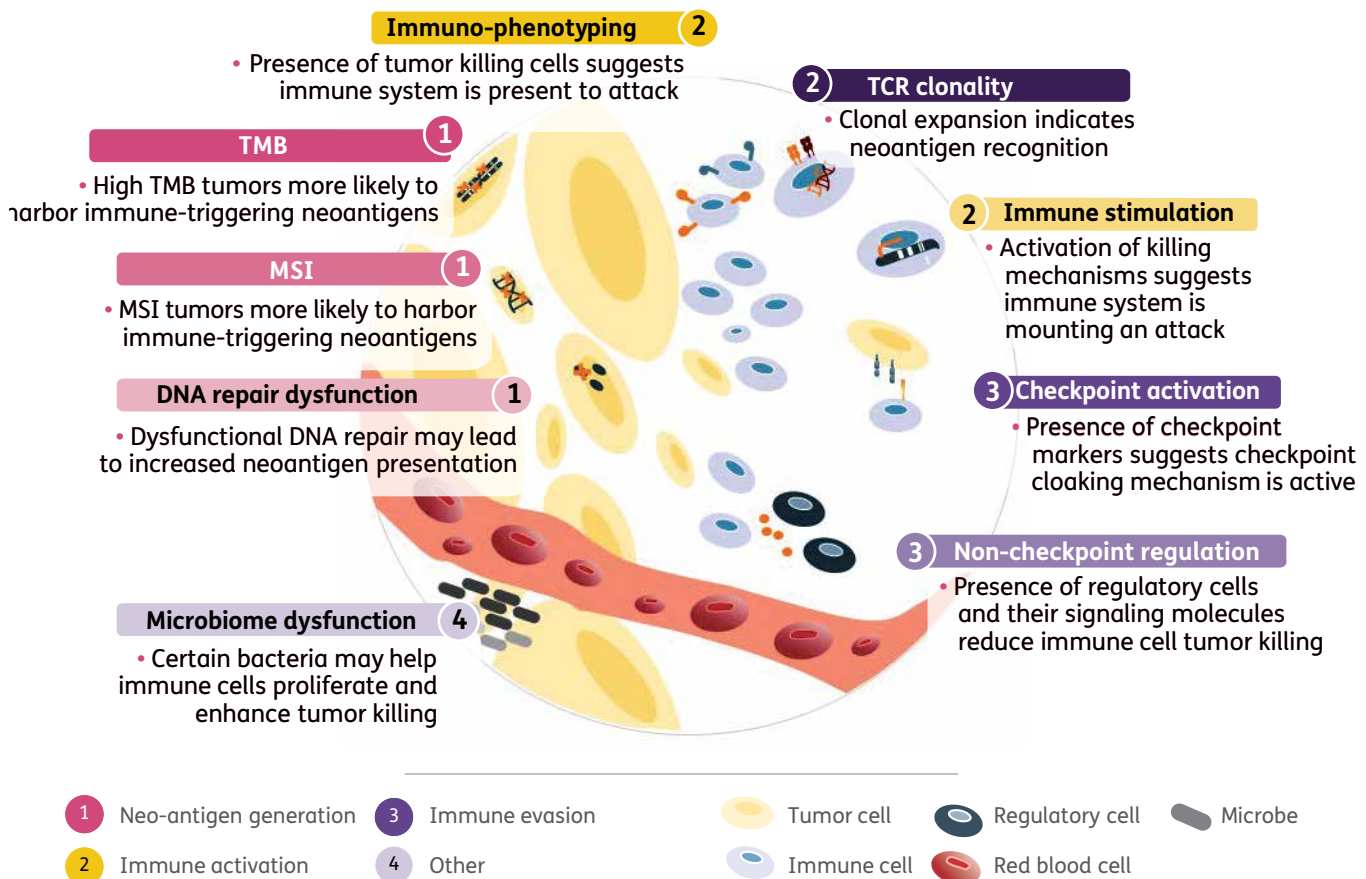
Cancer pathways are already complex, and when you layer in the need to understand the host's immune system and potentially the microbiome, the complexity is greatly enhanced. Furthermore, given the inherent heterogeneity of both the tumor and immune cells, understanding the biology may be required down to the single-cell level.

Through a systematic review of clinical trials involving checkpoint inhibitor therapies, we identified over 1,200 ongoing or completed clinical trials involving checkpoint inhibitors going back to 2011. We then mapped the biomarker activity covered in those trial protocols to develop insights on pathways and biomarkers under exploration by biopharma and academic sponsors. Based on this mapping exercise, immuno-oncology biomarkers in solid tumors were broadly categorized into four areas:

1. **Neo-antigen generation:** Tumor cells generate neo-antigens as a result of genetic alterations; these neo-antigens are recognized by immune cells (via their T-cell receptor), resulting in immune-cell activation.
2. **Immune activation:** Recognition of tumor cell neo-antigens leads to immune-cell proliferation and pathway activation.
3. **Immune evasion:** Tumors have mechanisms to evade immune system attack, including evading recognition (cloaking), such as in the PD-1/PD-L1 checkpoint mechanism, and recruiting regulatory cells to suppress immune cell-killing ability.
4. **Microbiome:** There is also emerging evidence on the role of the microbiome in checkpoint therapy responsiveness, although this is in the very early stages.

Exhibit 1

Overview Of Immuno-Oncology Pathways Under Exploration



Multiple pathways and biomarkers are being explored across categories. Neo-antigen generation trials are looking at TMB (tumor mutational burden), MSI (microsatellite instability) and DNA repair dysfunction. All three rely on the simple premise that the more mutated or genetically unstable a tumor, the more foreign it will look to the immune system. TMB's role in checkpoint therapy responsiveness emerged quickly from collaborative tumor profiling efforts by academia and clinical laboratories such as **Foundation Medicine Inc.** and has since garnered significant investment and attention, most recently from the positive results of partner Bristol Myers Squibb's Check-Mate 227 study. (Also see "Bristol's Opdivo/Yervoy Bid Will Show Whether Tumor Mutation Burden Is Ready For Prime Time" - Pink Sheet, 5 Feb, 2018.)

Looking at biomarkers by development phase highlights that while checkpoint activation biomarkers are the most represented pathway in Phase III trials, most other pathways are being explored across development phases.

Immune activation biomarkers are focused on measuring the presence of cancer-killing immune cells such as CD8+ T cells and the clonal expansion of those T cells, which suggests the immune system has recognized the cancer and is proliferating in preparation for tumor attack. Detection of killer immune cells has traditionally relied on immuno-phenotyping based largely on cell-surface markers, but recent activity also highlights interest in looking at HLA (human leukocyte antigen) genotypes and how they correlate with checkpoint therapy responsiveness. Expression of biomarkers correlated with immune pathway activation such as INF-gamma is also being explored as they are indicators of immune-mediated killing of cancer cells.

But cancers have cloaking mechanisms, and this drives the need to look at immune evasion biomarkers, which today focuses primarily on checkpoint activation. The current wave of cancer immunotherapies relies on the disruption of the PD-1/PD-L1 checkpoint interaction, and measuring PD-1 or PD-L1 expression is often correlated with inhibi-

tor response. The industry is also beginning to look into the role of the microbiome in PD-1/PD-L1 inhibitor therapy responsiveness, as it may represent an important use case in microbiome-based diagnostics.

Clinical Trials Are Increasingly Assessing Multiple Biomarkers

The sheer growth in trial numbers is impressive, but there is another important trend to call out, which is the number of unique biological pathways/biomarkers being assessed per trial. (See Exhibit 2.)

Since 2015, there has been notable growth in trials measuring two or more pathways as part of the trial design, and this trend appears to be accelerating, with some trials looking at four or more pathways. It is important to note that while many trials may not specify a biomarker, many require tumor biospecimens as an enrollment criterion, suggesting that biomarkers may be explored and even submitted to regulators regardless of what is specified in the trial protocol. It is also important to mention that merely highlighting interest in exploring a particular pathway or biomarker as part of a clinical trial does not necessarily lock in a biomarker as part of the drug label.

Biomarkers Assessed Are Broadening Beyond PD-1

Checkpoint activation biomarkers (PD-1/PD-L1) have seen the most activity and sustained growth, as they are directly related to the mechanism of action of checkpoint inhibitor therapies. However, exploration of other pathways and biomarkers is occurring in parallel. Trials looking at immune activation biomarkers, including immune stimulation, immuno-phenotyping (this includes tumor infiltrating lymphocyte [TIL] counting) and TCR clonality, have exploded since 2015 and are now being explored in 40% of biomarker-specified trials initiated in 2017.

Neo-antigen generation biomarkers have also grown significantly since 2015, with emphasis on MSI and TMB. MSI (for which Merck & Co gained the industry's first biomarker-defined drug label) activity is the highest of the two, but it is also a more established biomarker, whereas TMB, which has gained prominence in the past year, is already being explored in registration trials by a number of biopharma players, including **Roche** and Bristol-Myers Squibb.

Since 2015, there has also been an uptick in assessing non-checkpoint regulatory biomarkers, such as IDO and

Exhibit 2

Number Of Biological Pathways Assessed In Checkpoint Inhibitor Clinical Trials

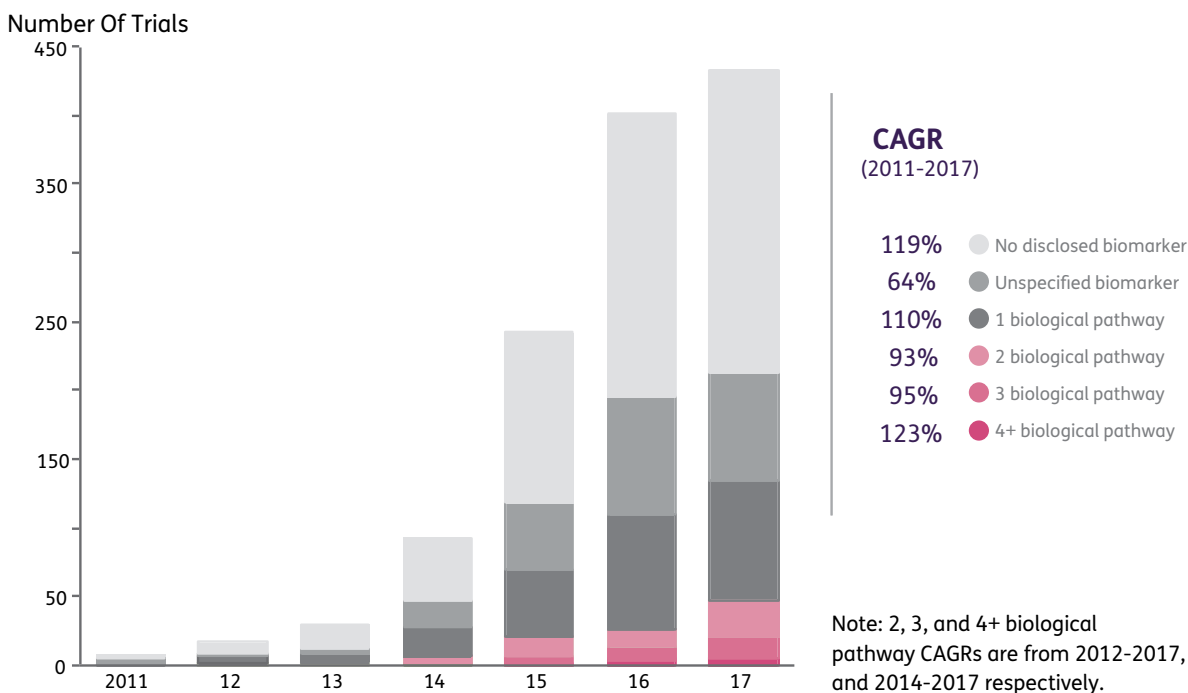
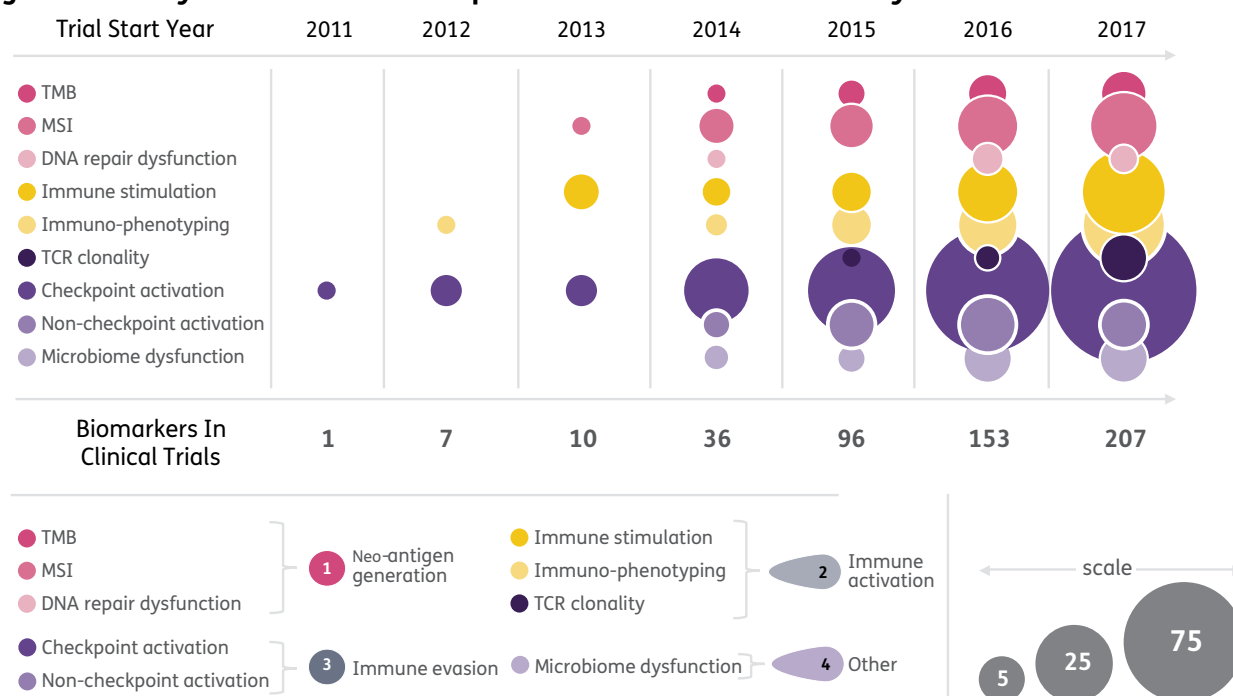


Exhibit 3

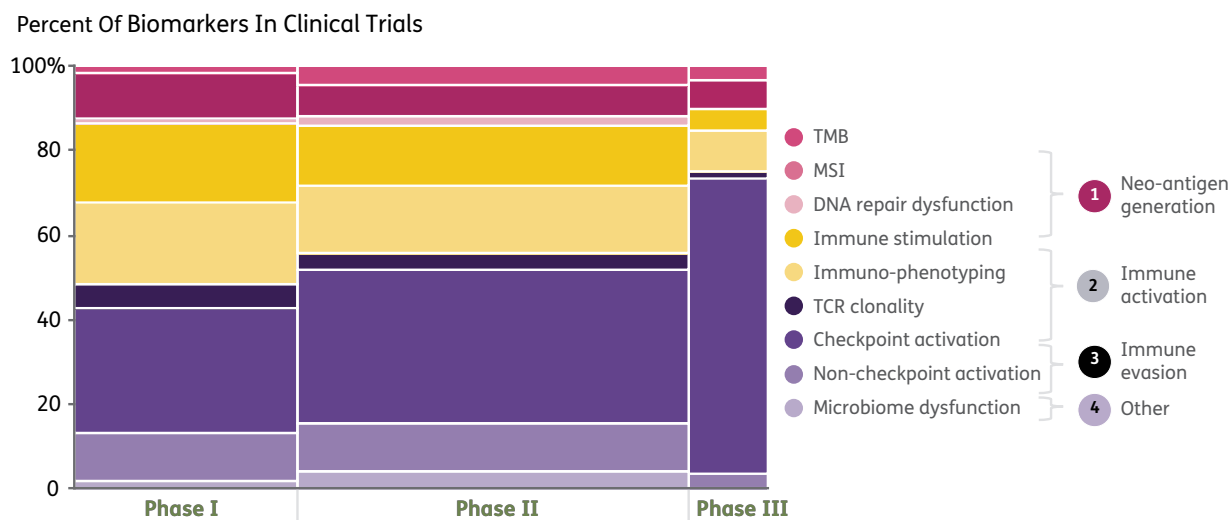
Biological Pathways Assessed In Checkpoint Inhibitor Clinical Trials By Trial Start Year



Notes: CAGRs may vary from start year of 2011-2014 but end Nov. 2017; does not include 13 retrospective studies without a known start date; includes double counting of trials if trial has more than 1 biological pathway interrogated.

Exhibit 4

Biological Pathways Assessed In Checkpoint Inhibitor Clinical Trials By Development Phase



Notes: Excludes 2 biomarker-specific studies, leveraging real-world evidence; includes double counting of trials if trial has more than 1 biological pathway interrogated.

FOXP3 (representing 8% of clinical trials initiated in 2017). And although still small today, there is a clear interest in assessing the microbiome's role in checkpoint therapy trials (<3% of trials initiated in 2017). (See Exhibit 3.)

Looking at biomarkers by development phase highlights that while checkpoint activation biomarkers are the most represented pathway in Phase III trials, most other pathways are being explored across development phases. (See Exhibit 4.)

Biomarkers Are Being Explored Across Tumor Types

Not surprisingly, overall trial activity is highest in NSCLC and melanoma, as these are indications where the first checkpoint therapy approvals were awarded. But there is also meaningful trial activity in other solid tumors such as breast, head-and-neck, renal, colorectal (CRC), bladder and even liquid tumors. Interestingly, biomarkers are being explored across all tumor types, with CRC over-indexing relative to other tumors (due to the well-established link between MSI in CRC), whereas HCC (hepatocellular carcinoma), pancreatic and gastric cancers are under-indexing on a relative basis.

The industry needs to go through this current R&D wave to really understand which biomarker strategies work best by tumor type and indication.

Ultimately, with few exceptions, it appears that most tumors will benefit from biomarker analysis to predict checkpoint inhibitor responsiveness. That said, the industry needs to go through this current R&D wave to understand which biomarker strategies work best by tumor type and indication. (See Exhibit 5.)

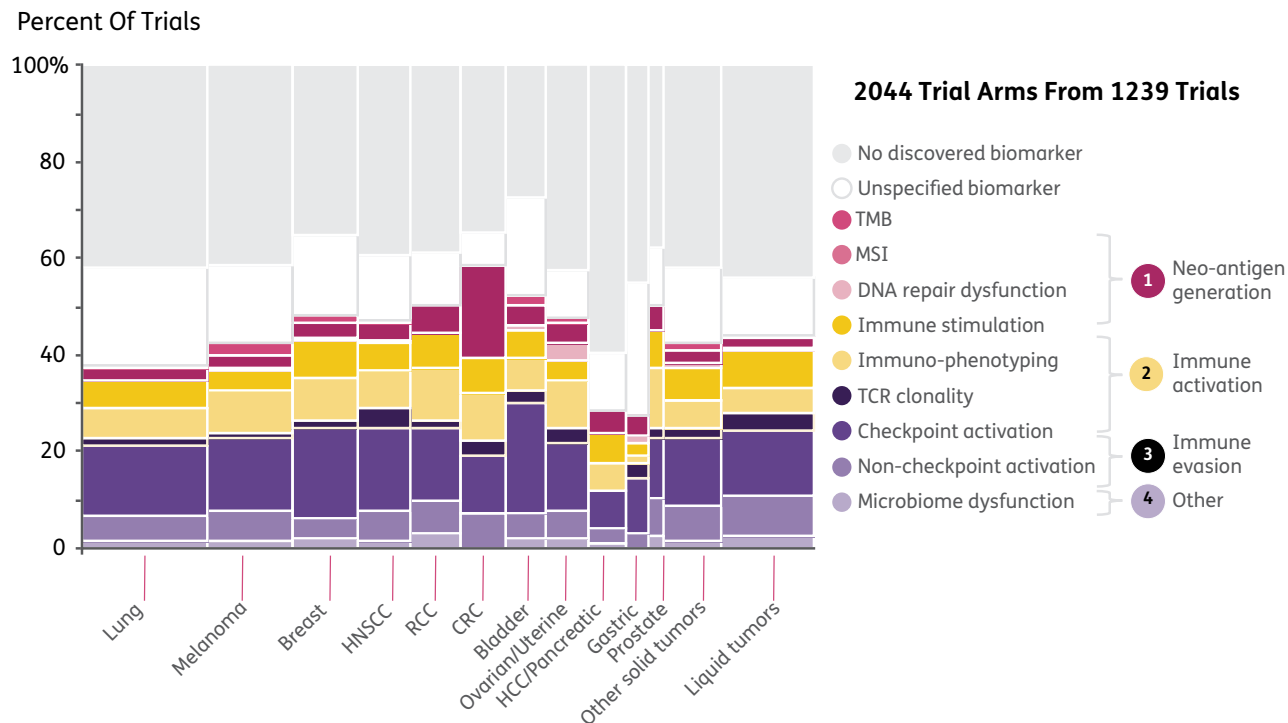
A possible future outcome may be that many pathways and biomarkers will need to be assessed regardless of tumor type, to tailor IO therapy to patients by looking at the underlying biology of the tumor, the host immune system and even the microbiome.

Multiparameter Diagnostic Modalities Will Be Critical

Given the number and types of biomarkers explored (DNA, RNA, protein), multiple diagnostic modalities are

Exhibit 5

Biological Pathways Assessed In Checkpoint Inhibitor Clinical Trials By Tumor Type



Notes: Liquid tumors include lymphoma, leukemia, myeloma and other liquid tumors; includes double counting of trials if trial has more than 1 biological pathway interrogated.

being employed, including next-generation sequencing (NGS), quantitative polymerase chain reaction (qPCR), **NanoString Technologies Inc.**'s *nCounter*, IHC and flow cytometry. NGS (covering both DNA and RNA sequencing) appears to be poised to address the majority of IO biology and pathways, and its increasing prominence in tumor profiling in metastatic disease could position the technology as a front-runner in IO diagnostics. However, high-parameter flow cytometry and IHC are also expected to be important IO diagnostic tools in the long run given their ability to detect expressed proteins at the single-cell level. (See *Exhibit 6*.)

Another notable point in the IO diagnostics space is the emergence of multi-parameter RNA expression and single-cell NGS. Multi-parameter expression analysis has the potential to include multiple areas of IO biology and pathways, essentially covering both immune activation and evasion. And because both tumors and the immune system are marked by their cellular heterogeneity (due to the genetic

instability of tumors and the adaptability of immune cells to new threats), the need for single-cell NGS is also gaining prominence in research.

Interestingly, TMB also represents a new situation where diagnostics companies have forged the path and biopharma has followed suit.

Although the cost to assess multiple biomarkers to predict checkpoint responsiveness may represent a step-change from the single biomarker companion diagnostics associated with most targeted therapies, the clinical and economic need associated with tailoring the use of checkpoint inhibitors will likely support this added cost.

It is important to note that many diagnostic enablers, including platform companies such as **Illumina Inc.**,

Exhibit 6

Overview Of Biomarkers And Modalities In IO Diagnostics

Biological pathway		System	Analyte		Example biomarkers	Key diagnostic modalities	
1. Neoantigen generation	TMB	Tumor cell	Somatic mutation density	DNA	TMB	NGS	
	MSI		Short tandem repeats		Mismatch-repair status	NGS qPCR	
	DNA repair dysfunction		Mutations in DNA repair gene		HRRm, POLE GA	NGS qPCR	
2. Immune activation	Immune stimulation	Immune cell	Expression of immune cell activation markers	RNA protein	IFNg, TNFa, CRP, cytokines	NGS qPCR nCounter	IHC Flow
	Immuno-phenotyping				CD8, CD4, CD3, CD25, HLA	NGS qPCR nCounter	IHC Flow
	TCR clonality		Clonal population analysis of variable region	DNA	TCR regions	NGS	
3. Immune evasion	Checkpoint activation	Tumor and Immune cell	Expression of checkpoint immune evasion markers	RNA protein	TC: PD-L1, PD-L2, TAA, Ki67 IC: CTLA-4, PD-1, LAG-3	NGS qPCR nCounter	IHC Flow
	Non-checkpoint regulation				TC: IDO IC: FOXP3	NGS qPCR nCounter	IHC Flow
4. Other	Microbiome dysfunction	GI/stool	Microbiome composition and genetic diversity	rRNA	16s rRNA	NGS	

Thermo Fisher Scientific Inc., HTG Molecular Diagnostics Inc. and **NanoString**, as well as clinical laboratories such as **Foundation Medicine**, **OmniSeq LLC** and **Caris Life Sciences**, are developing immuno-oncology diagnostic solutions that span multiple biological pathways and are actively partnering with pharma. (See Exhibit 7.) **OmniSeq**, a clinical laboratory associated with **Roswell Park Cancer Institute**, now offers *Immune Report Card*, which looks at pathways across neo-antigen generation, immune activation and immune evasion. A recent commercial partnership between **OmniSeq** and **Laboratory Corp. of America Holdings** has the potential to significantly expand access to **OmniSeq's** *Immune Report Card* by leveraging **LabCorp's** extensive channel.

NGS And Big Data Are Accelerating The Biomarker Innovation Cycle

Against this backdrop, there is an acceleration in the biomarker innovation cycle driven by the comprehensive genomic profiling of tumors using NGS. **LEK Consulting**

estimates that 10% to 20% of metastatic patients receive NGS profiling in the US today, and that number could increase two to three times in the next three to five years (which represents hundreds of thousands of patient cases annually).

Many of the NGS providers are building large data sets incorporating genomics, clinical and outcomes data which is enabling identification and retrospective validation of new biomarker associations directly from real-world clinical cases. This activity has the potential to validate new biomarker associations backed by a significant number of patient cases (often dwarfing what is feasible with traditional clinical trials). Supported by this strength of evidence, it is expected that guidelines and clinical adoption of these biomarkers will follow quickly. Conceptually, this represents the application of big data in precision genomic medicine.

However, as highlighted earlier, this is no longer purely conceptual. The rapid rise of TMB represents a paradigm shift.

Exhibit 7

Leading Diagnostic Companies In IO Diagnostics

		Platform companies						Specialty labs			
Company overview	Diagnostic platforms used	Roche	Illumina	Thermo Fisher Scientific	Qiagen	Nano-String	HTG Molecular	Caris	Foundation Medicine	HalioDx	OmniSeq
		NGS qPCR IHC	NGS	NGS qPCR Flow	NGS qPCR	nCounter	NGS	NGS IHC ISH	NGS	nCounter IHC	NGS qPCR IHC
1. Neoantigen generation	TMB	✓	✓	✓	✓	✗	✓	✓	✓	✗	✓
	MSI	✓	✓	✓	✓	✗	✓	✓	✓	✗	✓
	DNA repair dysfunction	✗	✗	✓	✗	✗	✗	✓	✓	✗	✗
2. Immune activation	Immune stimulation	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓
	Immuno-phenotyping	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓
	TCR clonality	✓	✓	✓	✓	✗	✗	✗	✗	✗	✗
3. Immune evasion	Checkpoint activation	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓
	Non-checkpoint regulation	✗	✗	✗	✗	✓	✓	✗	✗	✓	✓
4. Other	Microbiome dysfunction	✗	✓	✓	✓	✗	✗	✗	✗	✗	✗

TMB isn't even a definable genomic biomarker in the traditional sense. TMB is affiliated not with a specific gene or pathway, but rather with an observation that tumors with a relatively high frequency of mutations (high TMB) tend to respond better to checkpoint inhibitors (thought to be due to increased neo-antigen presentation). Interestingly, TMB also represents a new situation where diagnostics companies have forged the path and biopharma has followed suit. This stands in significant contrast to other targeted therapies where biomarkers and their associated complementary/companion diagnostics were largely validated by biopharma-sponsored pivotal trials.

TMB is also creating a virtuous discovery cycle that may only continue churning out new and more nuanced biomarker associations. NGS is required to measure TMB, and as TMB becomes more routinely adopted it is an important driver to continued NGS adoption. Furthermore,

NGS panel sizes continue to grow, and digitization of health-care data by players such as **Flatiron Health Inc.** and **COTA Inc.** is enabling the creation of massive minable data sets.

The Road Ahead

There is a long road ahead for the IO diagnostics space to mature. As discussed earlier, the science and supporting evidence need to be developed, and there are many directions in which they could go. Will it end with a reductionist biomarker strategy reliant on a few highly predictive biomarkers, or will it end with a more comprehensive biomarker strategy that looks at many pathways in concert? Certainly, the biology of IO therapies, which relies on the interaction between a dynamic tumor and the immune system suggests the more comprehensive strategy may prevail in the long run, but it will take time for that to materialize.

Separately, the industry needs to drive standardization, not only in pathways and biomarkers assessed, but also in defining standards around interpretation, including defining thresholds for what constitutes a biomarker-high or biomarker-positive result. Standardization and concordance across sample types assessed will also need to be worked out, including understanding cell heterogeneity (for both tumor and immune cells) and discriminating between tissue-based samples and those derived from biofluids including CTCs, peripheral immune cells, cell-free components, exosomes and so forth.

There will need to be cooperation and collaboration across the industry, and looking at other diagnostics markets, a reasonable assumption suggests three to five major competitors will emerge as leaders.

The industry will also ultimately want to consolidate testing into a standard set and will not support a different test for every therapeutic option under consideration. This means there will need to be cooperation and collaboration across the industry, and looking at other diagnostics markets, a reasonable assumption suggests three to five major competitors will emerge as leaders.

Access to novel diagnostic approaches will also need to be addressed. Today, many of the emerging IO diagnostic tests require specialized instrumentation and operators, may take many weeks to process and are not well-reimbursed. Clearly, as the industry scales, this will need to change and fit better into therapeutic decision-making windows and health-care economics.

Biopharmaceutical companies will need to adapt in this new fast-paced biomarker environment. Trying to stay abreast of the biomarker landscape in a sequential fashion

with each new biomarker approval may put companies into endless catch-up mode.

An alternative strategy could be to proactively assess multiple pathways and biomarkers at the outset, leveraging basket trials with fast conditional approvals to match therapeutic options to each patient's unique (and ever changing) biomarkers.

Organizationally, biopharmaceutical companies will need to change across many functions. Deeper embedding of biomarker/diagnostics groups into development and commercial functions will be required. Business development activity with diagnostics partners will need to focus on broader collaborations with a focused set of diagnostic companies, with the ultimate goal of creating industry-standard diagnostic solutions.

Market access and pricing functions will also need to consider how evolutionary biomarker strategies impact pricing and reimbursement of both the IO diagnostics and therapeutics.

Regulators will do well to enable such forward-thinking approaches. Just like the immune system, the industry needs to adapt to enable IO companion therapies and diagnostics to reach their full potential.

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INTERVIEW: Measured Launch, Long Future For Gilead CAR-T In Europe

► By Eleanor Malone

Gilead Sciences Inc. and **Novartis AG** are poised to simultaneously launch Europe's first CAR-T therapies within the next couple of months following the expected approval from the European Commission of Gilead's *Yescarta* (axicabtagene ciloleucel) and Novartis' *Kymriah* (tisagenlecleucel). Both therapies received a positive opinion from the European Medicines Agency's drug evaluation committee, the CHMP, on June 29, paving the way for approval in early September. Both are recommended for relapsed or refractory diffuse large B-cell lymphoma (DLBCL), while *Yescarta* is also recommended for primary mediastinal B-cell lymphoma and *Kymriah* for B-cell acute lymphoblastic leukemia.

While *Yescarta* and *Kymriah* have both been launched in the US already, the timing and the indications were different. *Kymriah* won approval first for the small indication of pediatric acute lymphocytic leukemia in August 2017 while *Yescarta* was approved in October for adults with relapsed or refractory large B-cell lymphoma. *Kymriah* won its second indication, for adults with r/r large B-cell lymphoma, in May 2018. Novartis was able to take advantage of being the only CAR-T therapy provider on the market in its crucial first months after launch, while Gilead enjoyed a wider market to itself during its initial launch.

In the EU, however, the therapies are competing for the same DLBCL patients and will both become available at the same time, making the market dynamics more competitive. There are around 7,700 patients across Europe with DLBCL who are refractory to other therapies or relapsed, i.e., who may be potential candidates for CAR-T therapy.

As the two competitors embark on the final stage of their launch preparations, *Scrip* spoke to Michael Elliott, vice president of medical affairs in Europe at Gilead Sciences, about the company's launch plans and longer-term strategy in cell therapy.



Michael Elliott,
VP medical affairs,
Europe, Gilead Sciences

Steady Not Speedy

Downplaying those competitive dynamics, Elliott emphasized that Gilead was not venturing to forecast sales or numbers of patients to be treated in the launch phase. "We'll be in a much better place 12 months down the track to be more solid on predictions," he said, underlining rather that "we're quite happy for it to go at a steady pace rather than too rapid a pace." He noted that in the first seven-eight months on the US market "we've opened all the sites we would have predicted and still opening more sites, and certainly patients have come in and gone through at the rate we would have

expected. It's early days but so far everything's working."

The reason for the measured approach to launch relates in large part to the safety challenges that are known to be associated with CAR-T therapy. There are two serious syndromes that can be triggered by therapy and result in the need for patients to be treated in intensive care: cytokine release syndrome and neurotoxicity.

These require careful education and preparedness at sites delivering the therapies for the syndromes to be managed properly, noted Elliott. "It's really important the site, the physicians, the nurses, the pharmacists and the ICU are well aware and can manage those when they come up. And it's also critical that the patients know, because if they go home and either one of those syndromes occurs later than we would predict [i.e., after the first 10-14 days], they and their carer have to make sure that they connect back straight away to a hospital." He added: "We've shown in clinical trials as well as in our early US experience that things can be managed, but it's important that everyone's aware."

First Launch Markets

Gilead will focus initial commercial launch efforts in four markets: the UK, France, Germany and Austria. In those countries, the company is working to have enough sites offering the treatment "to make sure patients have access to a site. It won't be every transplant center, but there will

be proximity to somewhere that does.” It is also working on referral-in systems to give patients at other centers access to the therapy. Initial launch will begin as soon as the European Commission gives its approval.

However, the competitive challenge vis-à-vis Kymriah is one that is still difficult to quantify. For example, whether sites will decide to offer just one CAR-T therapy – Kymriah or Yescarta – or whether they may offer both, remains to be seen.

“This will be the first test of that, because in the US the approvals were at different times. It could be either: we’ve talked to quite a few of the hospitals. I think maybe the preference would be to work with one company and their system, but it may be that some units want to do their own internal comparison. It’s part of us working with the hospitals to tell them everything about Yescarta and how it should be used, and then they’ll make their decisions.”

In the US, sites have tended to start small, with just one patient, then another, and “once they get the system running they can if necessary have an increased flow of patients,” Elliott said. “The advice really is that the profile is as the label would say regarding efficacy and safety, so start a little bit slowly for the first weeks or months, so that all of your staff, the whole system in the hospital, whether it’s the intensive care or the pharmacy, is trained up on the system, and then moves to routine care. Dealing with very sick patients isn’t uncommon in intensive care, so they know how to manage, it’s just not normal to be managing this level of severity for patients with DLBCL.”

In Europe also, the company will be very involved with working with all the stakeholders in the process to prepare them for using this novel therapy: “it’ll be a staged rollout, nothing like a regular pharmaceutical rollout,” noted Elliott.

Gilead will also begin working in larger countries with slower reimbursement systems on giving patients treatment via expanded access programs in advance of reimbursement agreements.

Payer Interest

Elliott said that there had been a lot of interest from both payers and departments of health across the continent, particularly following US approval. “It was well known that these therapies were coming and there was an understanding of both the huge advantages, the scientific breakthrough and the potential to get patients to a function cure, as well as the

challenges, which include safety and potential cost.”

He predicted there would be a mixed approach to reimbursement across the EU, but expected “we’ll be able to find a good and fairly quick solution in most if not all countries across Europe.” Gilead is in the middle of discussions over different pricing and reimbursement options. “There’s a will on all sides – patients, healthcare professionals, payers, ourselves – to make sure we get this to patients. Working on innovative therapies, usually the value argument is pretty strong.”

One significant piece of the jigsaw is the manufacturing and supply logistics: each individual patients’ cells must be taken to Gilead’s European processing center in Amsterdam before being shipped to the manufacturing site in Santa Monica, California and then being returned to the patient in question. Still, for 99% of cells taken from patients the manufacturing is a success, Elliott noted. In 2020, a larger primary manufacturing site is to be opened in Amsterdam, enabling all production to be done within Europe. Elliott was sanguine about the challenges of Brexit, saying “the worst case is that you’ll need some more import/export licenses for the cells,” which the company would obtain.

Future Outlook

The launch of CAR-T therapies is a major step forward in cancer treatment, but it is early days for cell therapy still. “If you wind 10 years forward into the future you’ll see a number of things,” Elliott said. “First of all, the hospitals themselves will be able to manufacture the cells, so there won’t be any of this shipping around the world, or even shipping around Europe, to have manufacturing. You’ll also see many more tumor types addressed. We’re starting with the hematological tumors, so DLBCL and so on, but then we’ll move to solid tumors probably in the next five or so years.

“With this targeted approach, whether it’s CAR-T or going for T-cell receptors, I think in 10-15 years’ time you’ll see these therapies all manufactured within a hospital and treating many different tumor types.” Elliott noted that Gilead is “engaged across that whole spectrum” both with ongoing programs and recent deals (from the \$11.9bn acquisition of **Kite Pharma Inc.** to the purchase of **Cell Design Labs Inc.** and a pact with **Sangamo Therapeutics Inc.**). “Our aspiration is to very much be a leader in this area of cancer therapy,” he concluded.

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Competitive Strategies Critical As EMA Decides On Kymriah And Yescarta

► By Neena Brizmohun



Launch plans and pricing for what are set to become Europe's first CAR T-cell therapies are at the fore as the European Medicines Agency this week decides whether to recommend marketing approval for **Novartis's Kymriah** (tisagenlecleucel) and **Kite's Yescarta** (axicabtagene ciloleucel).

Based on their clinical profile to date, the two advanced therapies are likely to receive a positive opinion this week from the EMA, according to Ollie Spray, a company analyst at Informa's PharmaVita. Both products were approved in the US last year, with Novartis beating Kite to the market.

Kite had originally been expected to get the first CAR T-cell (chimeric antigen receptor T cell) therapy to the EU market. The **Gilead Sciences** company had submitted its EU marketing authorization application (MAA) for Yescarta in July 2017, months before Novartis filed its MAA for Kymriah – this happened last November. Both applications had been granted

fast-track review, but Kite's MAA recently reverted to the standard review timetable because, the company said, the EMA wanted more time to understand the data supporting the application. (Also see *"EU CAR-T Race Tightens After Yescarta Reverts To Standard Review"* - Pink Sheet, 23 Apr, 2018.)

"It may be that negotiations result in a settlement that states payment will only be made for those patients that get cured, as is the case for Kymriah in ALL (acute lymphoblastic leukemia) in the US,"

"Kymriah is now likely to gain approval in the EU alongside Yescarta," Spray said, adding that both products, assuming they are indeed approved, are likely to be launched at around the same time.

"With the two drugs looking similar in terms of efficacy and safety in diffuse large B-cell lymphoma (DLBCL), the launch dates would have been an important differentiating factor for these companies," Spray told *Scrip*. "Crucially, companies that launch their products first are able to set the benchmark for price, upon which companies planning subsequent launches will have to adapt."

Negotiations for reimbursement across the EU member states are going to be interesting, Spray said, noting the EU market is "much less likely to pay the high prices we have seen for both products in the US."

"It may be that negotiations result in a settlement that states payment will only be made for those patients that get cured, as is the case for Kymriah in ALL (acute lymphoblastic leukemia) in the US," he said. "Other forms of discounting, such as rebates may also be negotiated."

The EMA's drug evaluation committee, the CHMP, is scheduled to adopt an opinion on the MAAs for Yescarta and Kymriah at its latest plenary meeting, which runs from June 25-28. The indications for which the companies are seeking approval overlap in the DLBCL space. Novartis is seeking approval of Kymriah in the treatment of B-cell ALL and DLBCL. Kite wants Yescarta to be used in the treatment of DLBCL, primary mediastinal B-cell lymphoma (PMBCL) and transformed follicular lymphoma (TFL). (Also see "*Aimovig And Tegsedi In Raft Of Products To Get EMA Thumbs up*" - *Pink Sheet*, 1 Jun, 2018.)

The CHMP's opinion on whether or not the products should be approved will be made public by the EMA on June 29, if not sooner by the companies.

Significant Discounts

According to Zach McLellan, an analyst at Informa's Data-monitor Healthcare, it is likely that "significant discounts will need to be negotiated in order for these regimens to reach the markets in the EU."

"For DLBCL, both drugs were launched in the US at a WAC [wholesale acquisition cost] price of \$375,000," McLellan said. "It's important to note that, in terms of Kymriah, this is an indication-specific price. Kymriah is available to treat ALL, but at a WAC of \$475,000. Indication-specific price negotiations, as well as associated costs for hospitaliza-

tions, could factor into approval and eventual reimbursement decisions."

According to Spray, physician familiarity is also an important factor in the success of these highly complex and novel therapies. "A period of exclusivity would have given physicians time to become familiar with the product that was launched first, disincentivizing them to prescribe any subsequently approved treatments which they have not had experience with," he explained.

McLellan added that manufacturing and logistical impacts on availability, patient characteristics and the success of ongoing awareness and training campaigns to improve physician familiarity with the products are also likely to impact the outlook for these medicines.

The DMHC analyst noted that comparing the treatments was difficult due to the complexity of the molecules involved and the obvious caveat of cross trial comparison. "If we attempt this in DLBCL, responses to both CAR-T treatments in their targeted segmentations of relapsed/refractory patients are impressive, fairly durable, and somewhat similar. Both drugs are also associated with significant toxicity that often requires active intervention and hospitalization."

There is some differentiation, McLellan continued. "Kymriah has shown higher rates of Grade $\frac{3}{4}$ CRS [cytokine release syndrome], whereas Yescarta is associated with higher Grade $\frac{3}{4}$ neurological events, both hallmark adverse events with CAR-T treatment."

A Tight Race

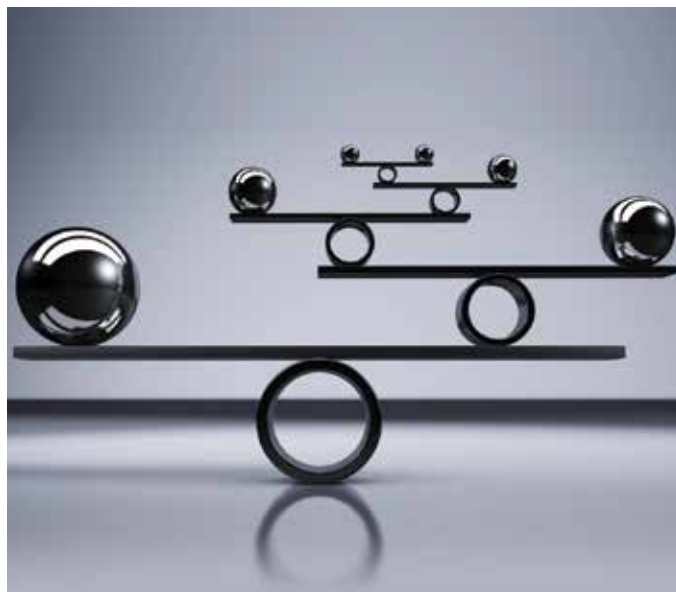
Regarding Novartis's and Kite's race for EU approval, Kite's MAA reverted from regulatory review under an accelerated assessment to a standard review timetable around a couple of months ago. An accelerated assessment cuts the review time from within 210 days to within 150 days (not counting clock stops for companies to address any questions from the EMA).

CHMP opinions on whether or not products should be approved are sent to the European Commission, which usually delivers a legally binding decision within 67 days.

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PAYING FOR GENE THERAPY: Will Pharma Be First In Line?

► By Jennifer Tedaldi and Adriel Koschitzky



- In evaluating the prospect of a wholesale payer exodus from reimbursing these new costly medicines, the signal to watch for is the totality of the budget impact, not the sticker price itself.
- Of four alternative pricing models evaluated, only one – manufacturer-managed financing – appears to have practical application in the “real world” setting.
- So what? There is a risk that failure to resolve payment barriers to gene and cell therapy could slow or prevent investments in other potentially transformative therapies now in the biopharma pipeline, as well as create new reputational burdens for innovators.

The first-ever US gene and cell therapy approvals of 2017 suggest that the industry stands on the brink of a fundamental shift in the way transformative therapies will be financed and accessed by patients. In quick order that acknowledged the clinical merits of the science, the FDA approved the first directly administered gene therapy, *Luxturna* (voretigene neparvovec-rzyl), as well as the first two CAR-T therapies, *Kymriah* (tisagenlecleucel) and *Yescarta* (axicabtagene ciloleucel).

What makes these therapies noteworthy is that we can call them potentially curative. They’re administered just once, or over a very short time period, but have long-term clinical benefits, and may be able to eliminate, reverse or stop the progression of a disease.

The prices needed to secure the commercial viability of gene and cell therapies, especially for small manufacturers, may not align with what health care systems are willing or able to pay.

However, commercialization has been challenging, in large part because today’s biopharma funding models are not designed to value or afford this innovation.

Under the US’ current funding model, drug costs are incurred immediately, but the value of gene and cell therapies is established only over time – actually a lifetime. This complication is compounded by the fact that many patients switch insurance carriers every few years. This means that the party paying the bill may never reap the benefits.

Moreover, the prices needed to secure the commercial viability of gene and cell therapies, especially for small manufacturers, may not align with what health care systems are willing or able to pay. So far, financial analyst perspectives on the value of these therapies have significantly exceeded what payers and the public at large instinctively perceive as acceptable.

Now that there is an accepted path to regulatory approval, health systems are on the spot to address these structural and financial disparities and find the right balance between affordability and innovation. ([A#PS122976]) If the balance skews toward incentivizing innovation over ensuring affordability, there's no guarantee that everyone who could benefit from these therapies will receive them. There's also little certainty that maintaining the financing status quo on payment systems will be sufficient to preserve the financial position of self-insured employers, catastrophic insurance carriers and even fully insured health plans. On the flip side, if we prioritize affordability over innovation, there's no guarantee that manufacturers will invest in developing potentially curative therapies over the long term.

A few manufacturers have acknowledged that the development of gene and cell therapies isn't worth it financially. **GlaxoSmithKline PLC**, for example, has announced that it plans on divesting its rare disease portfolio, including its European approved gene therapy, *Strimvelis*. But other companies are betting big, and there are more than 15 additional gene and cell therapies in late-stage development for which FDA approval could be sought in the next few years. Some of these therapies are being developed to target more prevalent, high-impact diseases like hemophilia.

The essential question for the industry: will this exciting new wave of potential cures end up producing a much-

needed disruption of an outdated funding model, one that is ill-suited to meet the rising expectations of clinicians, regulators and patients alike?

Current Funding Approaches




Given the limited number of gene and cell therapies currently indicated to treat ultra-orphan populations, most payers and health systems are continuing to rely on traditional funding and management approaches. Traditional funding mechanisms, however, pose serious cost challenges for therapies that are administered just once, or over a very short period of time, and have high up-front exposure to payers (see *Exhibit 1*).

Let's look at how traditional funding mechanisms have made it challenging for hospitals to use CAR-T therapies, which are administered in the inpatient setting, for now. Under current funding mechanisms, when new drugs are administered inpatient, hospitals often don't receive specific reimbursement for the drug and therefore may end up financially underwater.

As part of our research, we asked a senior pharmacy director at a major hospital that's also fully integrated as its own payer. "We've been watching," he said. "We decided not to sign up to be a center of excellence [for CAR-T therapies]. Our neighbors did, though, and all of their heavy lifting is being done at the level of the head of contracting and

Exhibit 1

The Most Important Funding Challenges For Provider Organizations, Payers And Patients

	STAKEHOLDER	KEY FUNDING CHALLENGES
	Hospitals and health systems	<ul style="list-style-type: none"> • Reimbursement potentially below cost (inpatient administered therapies) • Short-term cash flow issues due to potentially delayed reimbursement • Time and energy required to secure reimbursement
	Payers (including self-insured employers)	<ul style="list-style-type: none"> • Short-term budget impact and short-term business focus (quarterly reports to Wall Street, annual employer bidding cycle) • Potential for wasted spend due to uncertainty on long-term outcomes • High margins for buy and bill therapies: even a few points of markup can be substantial on a high-priced therapy or technology
	Patients	<ul style="list-style-type: none"> • Affordability under coinsurance plan designs, especially for Medicare patients • Coverage delays or lack of coverage

SOURCE: ZS Associates

grants. They told me that they're using these drugs before they're sure they'll get paid. We're a large system, but we can't afford to do that, nor can most other hospitals in this country afford to do so. We need to be cautious. We need reassurance that there is a proper channel to bill."

A number of approaches are either in use or under consideration to alleviate hospital funding challenges for CAR-T therapies (see *Exhibit 2*). Overall, we see some progress, including the potential for new diagnosis-related groups specific for CAR-T therapies, but there are significant issues still to be addressed.

In particular, Medicare recently assigned outpatient reimbursement rates to hospitals, aligned to standard hospital markups, if hospitals use CAR-T therapies in the outpatient setting. However, these rates are associated with minimum patient co-pay amounts in the \$80,000 to \$100,000 range.

While neither deal is likely to result in meaningful savings, they may be a signal that the needle is starting to move in outcomes-based agreements, at least in the context of these types of therapies.

By law, patients' financial out-of-pocket exposure is capped below these amounts, but deductibles and out-of-pocket limits can be high. Despite legal caps on patient out-of-pocket amounts, cost sharing for Medicare patients may be prohibitive and cannot be offset by co-pay support programs from manufacturers.

A variety of approaches are also in use or under consideration to alleviate payer funding challenges for gene and cell therapies (see *Exhibit 3*).

Outcomes-Based Deals

Let's take a closer look at the pay-for-performance agreements negotiated last year for Kymriah and Luxturna. While neither deal is likely to result in meaningful savings, they may be a signal that the needle is starting to move in outcomes-based agreements, at least in the context of these types of therapies.

For example, the Centers for Medicare and Medicaid Services (CMS) will only pay for Kymriah if the patient responds within the first month. The probability of an unsuccessful outcome at 30 days for a drug that showed an 83% overall remission rate in a clinical trial is low. One could argue that **Novartis AG** is limiting its risk by choosing a short-term time frame, and thus is not yet addressing the true payer uncertainty of longer-term efficacy.

One of the major challenges for outcomes-based deals for curative therapies in the US is legislation requiring that Medicaid gets the "best price." What this means is that if a manufacturer offered, say, a 100% rebate for patients who don't respond to the therapy, the company would be required to offer the product to Medicaid for free, even for patients who do respond. And many of the gene therapies target small groups of patients with significant Medicaid representation.

From this lens, the selection of a 30-day time line for Kymriah may be more interesting than it first appears: if the patient doesn't respond within a month, it's possible that Novartis may not need to invoice the CMS at all. According to the director of contracting at a large payer, "It looks like a 'no sale, no record of payment' and, therefore, a 'no best price implication' deal."

A Kymriah Precedent?

Novartis' Kymriah deal with the CMS may therefore be paving the way for manufacturers and other industry partners to waive Medicaid's best price requirement for gene therapies. A best price waiver will be particularly important in making longer-term, outcomes-based deals with multiple rebate opportunities more attractive.

We see this issue playing out in the outcomes-based Luxturna deal between Harvard Pilgrim and **Spark Therapeutics Inc.**: Harvard Pilgrim has a rebate collection opportunity at 30 to 90 days (linked to the trial assessment time frame) and then again at 30 months. Thirty months, not surprisingly, is around the average amount of time that a member stays in a plan. Although the specific magnitude of the rebate is confidential, best price legislation effectively puts a cap on the size of the rebate.

Harvard Pilgrim Senior VP and Chief Medical Officer Michael Sherman, who was at the negotiating table with Spark Therapeutics, told us: "Of course we wanted more [rebates] than we got, but [Medicaid] best price got in the way. Even

Exhibit 2

Current Approaches In Use Or Under Consideration To Alleviate Hospital Funding Challenges For CAR-T Therapies In The US, When Administered Inpatient

APPROACH	OVERVIEW	SPECIFIC EXAMPLES	HOSPITAL ISSUE DESIGNED TO ADDRESS	REMAINING ISSUES TO ADDRESS
New technology add-on payments (NTAPs) or Medicare outlier payments	<ul style="list-style-type: none"> • NTAPs: Medicare reimbursement above typical inpatient rates, such as diagnosis related group (DRG) or per diem rates, for new therapies deemed as breakthroughs • Outlier payments: additional Medicare reimbursement for patient cases incurring extraordinarily high costs above a defined threshold amount 	<ul style="list-style-type: none"> • Both Novartis and Gilead have applied for NTAPs for Kymriah and Yescarta 	<ul style="list-style-type: none"> • Reimbursement potentially below cost 	<ul style="list-style-type: none"> • Doesn't fully address hospital cost burden: historically, NTAPs only pay a fraction of the total cost of care above the DRG amount • Difficult to secure
New drug-specific DRGs or new bundled payment models	<p>Medicare options under consideration:</p> <ul style="list-style-type: none"> • Develop new CAR-T specific Medicare DRGs • Use current bone marrow transplant bundle for CAR-T hospital reimbursement 	<ul style="list-style-type: none"> • CMS is currently evaluating these options for 2019 • Some commercial plans have started to use specialized case rates for hospital reimbursement of CAR-Ts, carving out drug reimbursement from associated medical services, focusing on a select number of certified treatment centers 	<ul style="list-style-type: none"> • Reimbursement potentially below cost • Short-term cash flow and budget impact • Reimbursement time and energy 	<ul style="list-style-type: none"> • Can take several years to secure • A new DRG for all future gene and cell therapies may not align with Medicare's stated priority of encouraging lower drug prices • Payment for non-specialized services may be at risk, if more funds are allocated to highly specialized services
Reinsurance	<ul style="list-style-type: none"> • Catastrophic coverage above a pre-defined total amount • Hospital-managed funding reserves 	<ul style="list-style-type: none"> • Some, but not all, hospitals have reinsurance mechanisms in place 	<ul style="list-style-type: none"> • Short-term cash flow and budget impact 	<ul style="list-style-type: none"> • Sustainability: stop loss premiums may rise and become unaffordable

SOURCE: ZS Associates

Exhibit 3

Current Funding, Distribution And Contracting Approaches In Use Or Under Consideration To Address US Payer Funding Challenges

APPROACH	OVERVIEW	SPECIFIC EXAMPLES	PAYER ISSUE DESIGNED TO ADDRESS	REMAINING ISSUES TO ADDRESS
Insurance model: stop loss or reinsurance	<ul style="list-style-type: none"> Catastrophic coverage above a pre-defined total amount 	<ul style="list-style-type: none"> Self-insured employers Insurance companies Some hospital systems 	<ul style="list-style-type: none"> Short-term cash flow and budget impact 	<ul style="list-style-type: none"> Sustainability: stop loss and overall premiums may rise and become unaffordable, especially for smaller self-insured employers
Funding model: amortized through a manufacturer or designated specialty pharmacy (SP)	<ul style="list-style-type: none"> Payers have the option of paying up front, with a discount, or paying in installments with interest, like a mortgage 	<ul style="list-style-type: none"> No concrete examples yet, but Spark Therapeutics has made an amortized payment proposal to the CMS for <i>Luxturna</i> GSK used an amortized payment plan in Europe for <i>Strimvelis</i> 	<ul style="list-style-type: none"> Short-term cash flow and budget impact 	<ul style="list-style-type: none"> Portability: the average patient switches insurance every three years Financial risk to carry liability for a patient no longer insured Any type of loan is cost additive, not reductive
Distribution and payment model: payer or SP purchases drug directly, instead of the provider “buying and billing” the payer for the drug	<ul style="list-style-type: none"> Payer or SP manages distribution and pays provider administration and handling fees 	<ul style="list-style-type: none"> Express Scripts (ESI) for <i>Luxturna</i> Some private plans, including Express Scripts and Harvard Pilgrim, are using this model with <i>Luxturna</i> 	<ul style="list-style-type: none"> “Buy and bill” markup Providers also benefit as they don’t have to front the cost of an \$850,000 drug 	<ul style="list-style-type: none"> Doesn’t fully address cash flow issues Not always possible for inpatient drugs
Payer/manufacturer contracting model: pay for performance	<ul style="list-style-type: none"> Payment contingent upon efficacy outcome 	<ul style="list-style-type: none"> CMS: Kymriah Harvard Pilgrim: <i>Luxturna</i> 	<ul style="list-style-type: none"> Uncertainty regarding long-term efficacy 	<ul style="list-style-type: none"> Medicaid “best price” rules Limited savings if efficacy aligns with clinical trial experience

SOURCE: ZS Associates

with the Medicaid best price ceiling, the alternative was no deal at all. I know it’s a small population and that we may not see significant savings, and it was a lot of work, but it’s important to send a message to other companies and get some momentum going so that we can get best price waivers for future gene therapies.”

Harvard Pilgrim has built a market position and brand repu-

tation around these types of outcomes-based deals, and not just for curative therapies. The real question is whether we’ll see more of these deals in the short term from other payers.

Payers are more interested in outcomes-based deals for cell and gene therapies than they are in other circumstances. These deals have the potential to address a real problem: the uncertainty of long-term outcomes and the high up-

Exhibit 4

Summary Of Amortized Funding Models For Gene Therapies Theorized In ICER's 2017 White Paper On Gene Therapies

CONSUMER LOAN	THIRD-PARTY FINANCING	MANUFACTURER MANAGED FINANCING	GOVERNMENT FINANCING
Patients take out a personal loan to enable upfront payment for the treatment outside of regular health insurance	Payer receives a loan from a financial institution to enable upfront payment to the manufacturer	Manufacturer offers an installment payment option allowing the payer to pay for the treatment in period installments	Payer receives a loan from the government to enable upfront payment

SOURCE: ZS Associates

front costs. However, unless the best price issue is addressed, we're unlikely to see many more-specific examples in the short term. Payers' savings opportunity will need to be large enough to justify the work required.

As an executive at a large payer told us: "Today, finding an ROI on an outcomes-based contract for a gene therapy is like finding a unicorn. So far, they've just been a splash out in the public domain creating a warm and fuzzy feeling. They're a way to take some heat off the manufacturer in the press for looking greedy on their price, and to show proof of concept, but these require a lot of bandwidth to operationalize. We have to prioritize what's going to deliver the return, and that is always a guaranteed short-term cost savings."

The problem with the short-term focus on guaranteed cost savings is that at some point there will be diminishing returns. Steps need to be taken to make outcomes-based deals more practical, such as investing in third-party-administered databases to track outcomes. Spark Therapeutics and several other curative therapy developers are actively working with patient advocacy groups and legislators to waive the best price legislation, but there's more work to be done.

Amortized Funding Models

There has been a great deal of discussion recently about amortized funding models as a potential solution. For example, a 2017 gene therapy white paper from the Institute for Clinical and Economic Review (ICER) theorized a number of options (see Exhibit 4).

Let's start with the first model: consumer loans. Our view is that such models are highly unlikely to succeed. Fifty-seven percent of Americans have less than \$1,000 in savings, and many patients with inherited genetic diseases are on Medicaid. Who would underwrite a direct-to-consumer loan for a multimillion-dollar drug?

While a manufacturer may trust that a large health plan would be good for a multimillion-dollar loan, would a smaller plan like Oscar Health also be?

The second and fourth models, which involve payers taking out loans from either banks or the government, are also unlikely to succeed. Even if such models alleviate short-term acute cash flow concerns, any type of loan is cost additive, not reductive. In addition, most payers, self-insured employers and hospital systems already have financial reserves or catastrophic insurance for unexpected and major costs. As a medical director at a regional plan explained, "Let's suppose that we, as a publicly traded company, take a loan for a gene therapy. This would get rated as subordinate corporate debt. We'd probably need to carry it on our balance sheet as a liability, which can hurt our stock price. That's why it's more attractive for us and our self-funded employer clients to use stop loss carriers because it's not an ongoing liability: it's an annual expense."

The third model, manufacturer-managed financing, is

more interesting. A manufacturer could choose to manage the financing themselves or partner with a large specialty pharmacy both for drug distribution and payment system management. Payers would have a variety of payment options, including payment in full or different “down payment” options with associated interest levels.

Our perspective is that this third model has the most practical potential for the CMS specifically, but significant challenges remain in applying such a model for private commercial payers, who deal with frequent membership turnover. Private payers have major concerns about becoming contractually responsible for paying for patients who could switch health plans prior to the deal’s end date. As a pharmacy director at a national plan told us, “Bottom line: it’s not prudent or good management for an insurance company to carry liability for patients who aren’t paying premium. That’s asking me to break the gold standard of insurance.”

Biopharma companies also will need to assess whether they truly want to get into the lending business. While a manufacturer may trust that a large health plan would be good for a multimillion-dollar loan, would a smaller plan like Oscar Health also be? Is the US government good for a multimillion-dollar loan? A manufacturer would also need to assess whether they are structured to take on financial liability to account for financial risk and manage the associated financial regulatory implications. Small biopharma companies may find manufacturer-managed financing more challenging than large companies would.

A health policy professor recently theorized some sort of industry-wide mechanism that would allow for portability of an annuity payment, such that the responsibility to pay followed the patient. Legislative action would be needed to require all health plans to participate; practically speaking, this is highly unlikely. Even if concerted policy action made this type of legislation a reality, private payers and state government payers still would have major concerns. As a medical director said, “I can’t imagine calling up competitor plans and haggling over practicalities of transferring liability, even if the government said I had to. It would conflict with our competitive strategies and come with a ton of compliance and legal red tape.”

On The Horizon: A Tipping Point?

One of the reasons we haven’t seen more innovation in funding of gene and cell therapies is their novelty. To date,

the overall budget impact has been relatively limited. However, if we look at the growing pipeline of gene and cell therapies, budget impact concerns may become acute cash flow problems for smaller, self-insured employers, provider groups and catastrophic insurance carriers.

ZS recently asked several payers about any triggers that could be an impetus for change in gene and cell therapy funding models, wondering whether we’ll see a specific price level, total budget impact or a gene therapy removed from the market, or even major insurance market disruption.

**“There’s an element of getting desensitized to these prices like people do to continued news of violence in the media”
– Michael Sherman**

A medical director at a large plan responded: “I just have this feeling in my gut that there’s very little in this world that would justify more than \$1 million. I don’t know. Maybe \$2 million? But even if it were more expensive – say, \$4 million – and the data were really good, we can’t say no. We’d all get ripped apart in the press if the system didn’t work to get these cures to all patients for whom the evidence clearly supports a benefit.”

An interesting theme emerged from these payer discussions: an instinctual feeling of what price is acceptable, either subconsciously or consciously shaped by the highest price levels seen to date. The instinctual – and practical – sticker shock is real, and often outweighs rational discussions of “value-based prices,” like we saw with *Sovaldi* (sofosbuvir).

Let’s consider the price levels that early-stage gene therapy companies need to secure to attract enough capital to get their therapies to market. From this perspective, a drug may very soon launch at a price that generates sticker shock, to a degree far beyond what the industry has seen to date.

Michael Sherman at Harvard Pilgrim responded: “As much as I hate to say this, \$750,000 is the new \$300,000. Soon, \$1.5 million may be the new \$750,000, and then \$2 million may be the new \$1.5 million.” He paused for a moment and then added, “There’s an element of getting desensitized [to

these prices] like people do to continued news of violence in the media.”

Shortly after conducting our interviews, analysts at Leerink Partners LLC increased their estimate of the likely prices for the new hemophilia A gene therapies to \$1.5 million, and possibly \$2 million.

Practically speaking, it's probably not going to be a single, very high price that triggers a major change. The true signal that an evolution in our funding approaches has finally arrived may be the totality of budget impact, especially if it's sustained. Not all of the gene therapies in late-stage development are for orphan diseases.

For example, what if premiums for stop loss coverage become so much more expensive that some self-insured employers choose to forego it? And then the following year, the financial health of a few of these employers takes a public beating, as a result of back-to-back claims for multimillion-dollar drugs? What if employers can no longer afford to self-fund their coverage, fully insured plans start taking on the sickest patients, and overall insurance premiums go up by more than 100% over the next few years?

A few private payers have wondered about the possibility of the government taking full responsibility for curative therapies, as is the case in many other countries. The government would set reimbursement and coverage criteria and potentially even negotiate prices. Drug price negotiation has been on the CMS wish list for a while now, but all efforts to do so in the US have failed to date. And Congressional Budget Office projections indicate savings from negotiations would be negligible over time.

The Path Forward

Despite the seeming deadlock, there are a number of approaches that could help promote the continued development of potential cures and long-term patient access:

- **Ensure a strong policy focus from early stages of development, and engage early with the CMS and commercial payers on policy and billing issues.** A strong policy focus and savvy are critical for curative therapies and likely will differentiate the commercial winners and losers. In the short term, we should continue to build the momentum that companies such as

Spark Therapeutics and **bluebird bio Inc.** are creating to secure Medicaid best price waivers for gene therapies. Highly focused and coordinated policy engagement will be needed to make policy changes like drug-specific Medicare DRGs or amortized payment options a reality for the CMS. A drug company working alone isn't going to prevail: providers, drug companies, health plans and employers will need to come together and convince the CMS that we need to make changes that allow the whole system to function more effectively. Manufacturers, payers, employers and patient advocacy groups need to work together to enact meaningful legislative change. For curative therapies that require an inpatient stay for drug administration and patient management, getting hospitals to use these drugs and securing reimbursement for them is a substantially more complex process than for typical specialty drugs. Manufacturers need to engage early with the CMS and commercial payers on complicated billing and coding issues to ensure that each step of the treatment and management protocols can be billed. When appropriate, manufacturers need to think through a variety of alternative inpatient funding models like NTAPs, new DRGs and new types of payment bundles to alleviate hospitals' cost burdens.

Where substantial cost savings opportunities exist, economic value should be at the forefront of curative therapy value stories.

- **Develop specialty distribution models.** The payers we spoke with are very interested in specialty distribution models such as the one we've seen Express Scripts Holding Co. use for Luxturna. These types of models, which reduce provider cash flow issues and payers' need to pay a markup through a "buy and bill" model, are feasible for outpatient-administered drugs and work well within the current system. Expect to see this approach used more frequently as more outpatient-administered curative therapies are approved.
- **Provide payers with advanced notice.** In alignment with legislated 21st Century Cures Act standards,

manufacturers can seek appropriate opportunities to proactively provide payers with information, including on appropriate patient profiles, to help understand and forecast budget impact. Where substantial cost savings opportunities exist, economic value should be at the forefront of curative therapy value stories. We can imagine how this may play out with the new gene therapies in development for hemophilia. The list prices for factor VIII therapies, the drugs currently used to treat hemophilia, are about \$300,000 to \$450,000 a year, and they're taken over a patient's lifetime. A story about a new curative therapy that centers on minimal budget impact due to reduction in factor VIII use would be compelling, especially if coupled with agreement about which drug payments are offset by reductions in factor VIII use in the real world.

- **Ensure evidence development programs have a long-term focus.** Real-world evidence and postmarketing commitments to support durability of efficacy and safety will be critical to address concerns about the long-term value. New approaches and economic models to help extrapolate short-term trial data and understand the potential need for re-treatment also will help.
- **Broaden the definition of gene therapy value.** ICER may have under-weighted some of the long-term societal value of improved vision in its determination that Luxturna isn't cost-effective. Manufacturers need to be smart and start early in their efforts to determine which of their drug's benefits are most likely to be undervalued by traditional assessment approaches, to identify a broader ecosystem of expanded drug benefits, to identify which stakeholders – outside of payers – may receive the most value, and take a multi-stakeholder approach to value communication. Manufacturers also need to work with payers to help them develop organizational goals that have a longer-term focus.
- **Develop transparent pricing frameworks.** Practically, this needs to be led by manufacturers but also vali-

dated by independent third parties. ICER has made a start, but we need to avoid looking at each drug in a vacuum: a value-based price for each individual therapy in the pipeline may not align with the finite amount of money available to pay for all of them over time. Pricing approaches that take this tension into account could go a long way as part of a collaborative solution. The conflict between the need for a profit incentive to fund research on major scientific innovation and the ability to pay for such investigative work is, at its core, an ethical one. Manufacturers may consider consulting with health ethicists at major universities as part of developing pricing frameworks for these types of therapies and being more vocal about their commitment to developing potential cures.

For curative therapies to reach patients successfully, there's much that has to change in a system that was built for maintenance therapies – the non-cures. The industry as a whole needs to rise to the challenge; otherwise, there's no guarantee that everyone who can benefit from these cures will receive them. And the political backlash from that scenario will hit the innovative industry's reputation – first and last. There's also a high risk that the commercialization challenges met by the first few gene therapies may prevent long-term investment in developing other transformational therapies. After all, the pricing and funding decisions that we make in the early days of the new therapeutic paradigm will have far-reaching effects on patients' ability to access potential cures for years to come.

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Regenerative Medicine Financing Sees Uptick in the Second Quarter of 2018

► By Patricia Reilly, Vice President, Intelligence Alliances and Unification, Pharma Intelligence

One of the top stories of this second quarter of 2018 has to be the uptick in the number of IPOs filed by regenerative medicine companies. The total number of filings in the first half of 2018 has jumped from previous years, exhibiting investors' continuing confidence in the advanced therapies sector. Companies that filed in Q2 include: MeiraGTX, Autolus, AVROBIO, and Magenta. These companies join Homology Medicines, Genprex, Unum Therapeutics, and Solid Biosciences in IPO filings for 1H 2018.

The second quarter also began with the high-priced acquisition of AveXis for \$8.7 billion as Novartis builds its gene therapy portfolio. GI Partners agreed to purchase the Cord Blood Registry, a cord blood stem cell collection and storage company, from AMAG Pharmaceuticals, Inc. for \$530

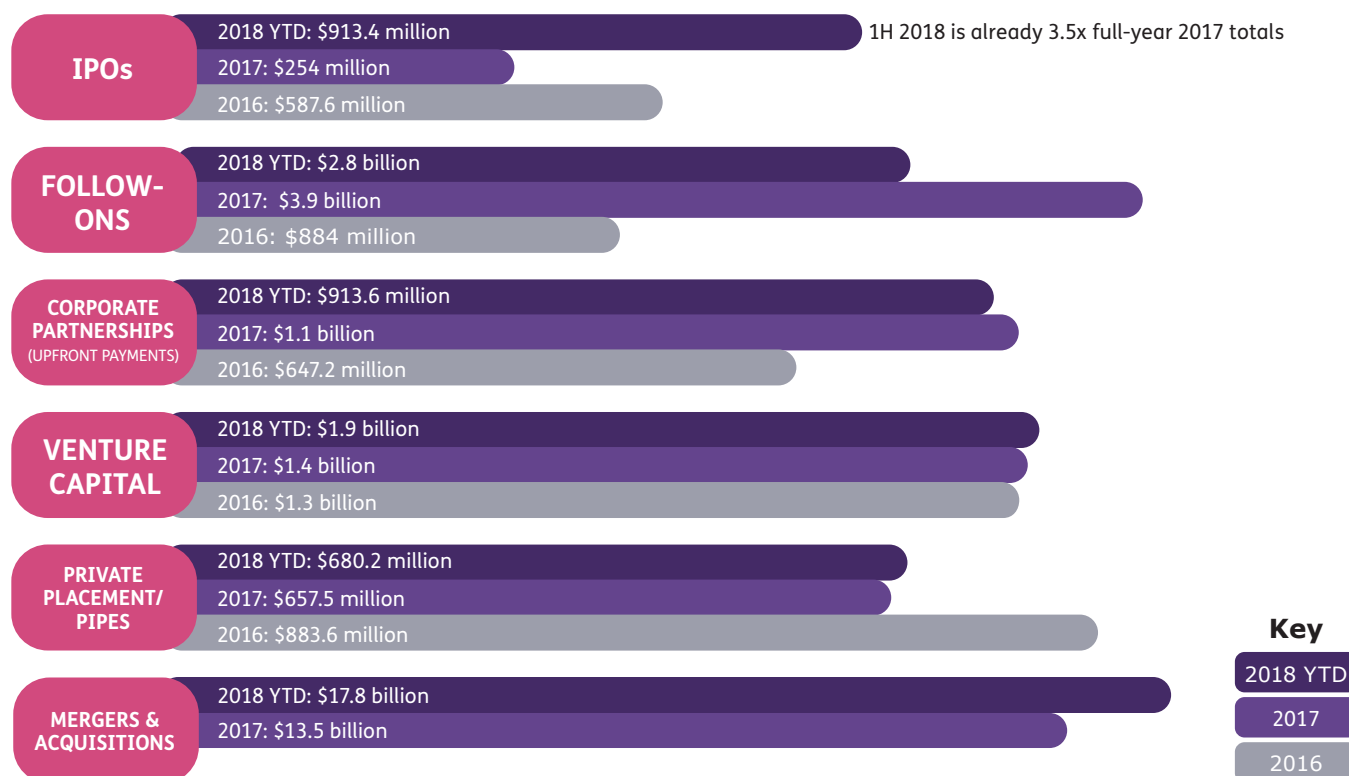
million in an all cash transaction that is expected to close in the third quarter.

Rounds of financing were also successful and plentiful. In Series A rounds, Tmunity raised an additional \$35 million; Allogene launched, raising \$300 million; and Beam Therapeutics launched and raised \$87 million. Freeline and Precision Bio raised \$116.6 million and \$110 million, respectively, in Series B rounds. Biocytogen raised \$65 million and Decibel landed \$55 million in Series C rounds.

Other financing rounds were equally valuable. Sangamo closed a follow-on public offering that raised \$230 million, while Cellectis announced a closing of \$163.7 million in a follow-on public offering. uniQure N.V. raised \$147.49

Exhibit 1

Total Global Financings by Type, by Year



Source: Medtrack 2018

million, Vericel raised approximately \$74.8 million, and MediGene AG raised \$37.91 million. Celyad also announced a closing of a global offering netting approximately \$54.5 million in private placement of shares. TapImmune announced their intent to raise \$70 million from private placement of shares, while Intrexon expects to raise \$100 million in a public offering.

In partnerships this quarter, Sigilon received an upfront payment of \$63 million from Eli Lilly to develop engineered iPSCs to become insulin-producing beta cells. Milestones could go as high as \$410 million. bluebird bio expanded its partnership with Medigene for two additional TCR targets worth \$250 million each in a licensing deal could raise a potential \$1.5 billion for Medigene and tiered royalty payments. Editas earmarked \$125 million to the Broad Institute for first refusal on genome editing inventions





developed in this sponsored research agreement. Humacyte and Fresenius Medical Care announced a global strategic partnership supported by a \$150 million equity investment.

And finally, there were four new RMAT designations granted this quarter: Nightstar Therapeutics for a gene therapy to treat choroideremia; Caladrius Biosciences for the CD34+ cell therapy targeting refractory angina; Voyager Therapeutics's gene therapy for Parkinson's disease; and Abeona Therapeutics's second RMAT, this one for the company's ABO-102 gene therapy to treat MPS IIIA.

This sector continues its clinical and commercial uptick, as more investors and other stakeholders take notice. The second half of the year likely holds additional accomplishments for the field.

Exhibit 2

Total Global Financings by Type, by Year

			
TOTAL GLOBAL FINANCINGS	GENE & GENE-MODIFIED CELL THERAPY	CELL THERAPY	TISSUE ENGINEERING
\$4.1 Billion raised in Q2 2018 164% increase from Q2 2017	\$2.7 Billion raised in Q2 2018 124% increase from Q2 2017	\$2.2 Billion raised in Q2 2018 416% increase from Q2 2017	\$421 Million raised in Q2 2018 526% increase from Q2 2017
\$7.9 Billion raised YTD 2018 79% increase year-over-year	\$5.8 Billion raised YTD 2018 133% increase year-over-year	\$4.2 Billion raised YTD 2018 83% increase year-over-year	\$784 Million raised YTD 2018 25% increase year-over-year

*Total amount raised represents sector-wide figures; please note that some companies utilize technology from more than one technology group. As a result, the total financings amount does not equal the sum of the raises of the individual technology groups.

** Figures do not include M&A transaction totals.

Source: Medtrack 2018



Excerpted from: Alliance for Regenerative Medicine's Q2 2018 Data Report
https://alliancerm.org/wp-content/uploads/2018/08/ARM_Q2_2018_Web.pdf



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