The Case For CAR-T Grows As Responses Hold Up Longer Term

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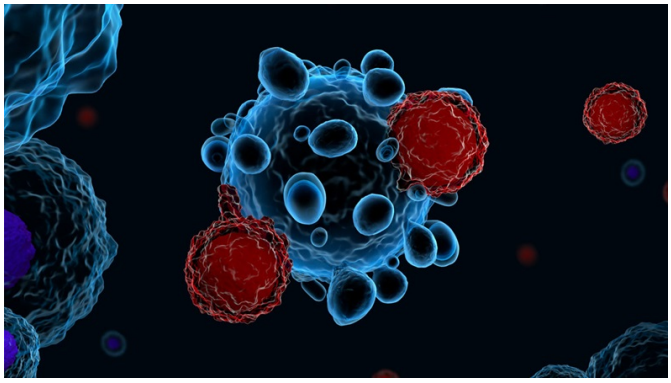
Executive Summary

Novartis and Gilead longer-term data show largely steady response and survival rates, shoring up the clinical and commercial case for their products and justifying continued investment in T-cell therapies. The CAR-T pioneers discuss their progress, including with allogeneic platforms, with *Scrip* at ASH.



As the first companies with commercial chimeric antigen receptor T-cell (CAR-T) therapies, Novartis AG and Gilead Sciences Inc., via its Kite Pharma Inc. subsidiary, are under pressure to show that the billions of dollars they have invested in these novel immunotherapies has been worthwhile.

While continuing to work through the challenges of bringing their autologous, CD19-targeting CAR-T products to market, the competitors are sharing longer term results to make the case for these costly, complicated therapies, including data presented at the recent American Society of Hematology (ASH) meeting in San Diego. Most of the relapsed and refractory leukemia and lymphoma patients who responded to treatment with Novartis' *Kymriah* (tisagenlecleucel) and Gilead/Kite's *Yescarta* (axicabtagene ciloleucel) have maintained their responses for 18 months or more.

"We're starting to deliver hope," Novartis Senior Vice President and Global Head, Cell & Gene Therapy Pascal Touchon told *Scrip* in an interview at ASH. "It's not yet there – ideally, we want three years, five years and so on – but this 18 months means that we have a very high level of complete remission and maintenance. We have the duration of response."

The US FDA approved Kymriah as a third-line or later treatment for relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) in pediatric and young adult patients in August 2017 with a supplemental approval in May of this year to treat adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in the third-line or later setting. (Also see "Novartis Beats CAR-T Competitors To The Pricing Punch With Kymriah Approval" - Scrip, 31 Aug, 2017.)

Data from the ELIANA trial evaluating Kymriah in pediatric ALL were presented at ASH showing that after 82% of 79 evaluable patients achieved complete response (CR) or CR with incomplete blood count recovery (CRi). the relapse-free survival rate at 24 months was 62% and the median duration of response and median overall survival (OS) had not been reached. Also, 98% of patients with a CR or CR1 were minimal residual disease (MRD) negative. The probability of OS at 12 months was 76% and at 24 months was 66%.

The overall response rate (ORR) at 19 months for 99 DLBCL patients in the JULIET study of Kymriah was 54%. Also, 54% of responders with a partial response (PR) converted to CR (15 out of 28 patients). The median duration of response has not been reached and the relapse-free probability has held steady throughout the trial – 66% at six months and 64% at both 12 and 18 months. Median OS was 11.1 months among all infused JULIET participants, but has not been reached for patients who've achieved CR. The OS probability was 48% at 12 months and 43% at 18 months.

"It's this kind of plateau in the response at about a 40% level that is really so important, because that means once you get that response rate, that remission, in most patients you maintain it," Touchon said.

The long-term response rates, he added, show that Kymriah – and CD19-targeting CAR-T therapies in general – can become the standard of care in relapsed/refractory leukemia and lymphoma.

CAR-T In Combination

Touchon also noted some small datasets presented at ASH that combined Kymriah with other cancer therapies to potentially improve CAR-T cell persistence and patients' responses.

For instance, among 14 pediatric patients – 13 with ALL and one with lymphocytic leukemia – who were treated with Kymriah followed by Merck & Co. Inc.'s *Keytruda* (pembrolizumab) or Bristol-Myers Squibb Co.'s *Opdivo* (nivolumab), the PD-1 inhibitors increased CAR-T cell expansion. The study conducted by the Children's Hospital of Philadelphia found that half of the patients achieved a partial or complete response, and investigators noted that the combination treatment strategy may be most beneficial for patients with early B-cell recovery or bulky extramedullary disease.

"We see combination with checkpoint inhibitors as a way to improve response rate." – Novartis Cell & Gene Therapy Head Pascal Touchon

"We have started a study already in lymphoma combining Kymriah with pembrolizumab," Touchon said. "We see combination with checkpoint inhibitors as a way to improve response rate, and especially to maintain response for the expansion of the T-cells, and to avoid the exhaustion of the T-cells."

In another early dataset at ASH, Novartis' next-generation CD19-targeting CAR-T therapy CTL119 generated CRs in almost all of the 19 adults with chronic lymphocytic leukemia (CLL) enrolled in an ongoing Phase I study. Patients already were being treated with AbbVie Inc./Johnson & Johnson's BTK inhibitor *Imbruvica* (ibrutinib) and continued therapy during the trial, but they had not reached CR after at least six months of treatment prior to entering the study.

Morphologic CRs were observed in the bone marrow of 17 patients at three months and 15 of these patients were MRD negative; of 14 patients assessed at three months, 43% were in CR.

"These impressive results suggest that combining CTL119 cells with ibrutinib increases the CR rate," Biomedtracker said in a Dec. 2 analysis. "The 43% CR rate for CTL119/ibrutinib compares well to Kymriah (CTL019) monotherapy, which previously reported a 28.5% CR rate."

Touchon noted that "we are going to start the Phase II study in CLL early in '19 with the aim to show that when you combine Kymriah with ibrutinib, which is a standard of care now in CLL, you can achieve complete remission, because ibrutinib by itself does not achieve complete remission in many patients."

Kite Presents Longest-Term CAR-T Data

Gilead's Kite subsidiary reported the longest-term data to date for a CAR-T therapy at ASH for Yescarta, which the FDA approved in October of last year as a third-line or later treatment for DLBCL.

Two-year results for Yescarta from 101 DLBCL patients in the ZUMA-1 study showed an overall response rate of 83%, with a 58% CR rate. Kite reported that 39% of patients remained in response with a median follow-up of 27.1 months, and 93% with an ongoing response at 12 months remained in response at 24 months. While the median duration of response was 11.1 months, the company said the median duration of CR and the median duration of OS were not reached.

"It was a very important presentation to us, and I think it's really demonstrating that the promise of CAR-T cells is being realized," Kite Pharma Global Head of Cell Therapy Development Jeff Wiezorek told *Scrip*.

> **"The really gratifying thing to see is, even with 27 months follow-up, we have not yet reached the median overall survival." – Kite Cell Therapy Head Jeff Wiezorek.**

Based on an analysis of the SCHOLAR-1 study published in 2017, Wiezorek noted that survival for the DLBCL population represented in ZUMA-1 would be about six months without Yescarta treatment.

"The really gratifying thing to see is, even with 27 months follow-up, we have not yet reached the median overall survival ... and almost 40% of the patients are still in remission," he said. "To me, this is

kind of what the promise of CAR-T has always been – to induce durable remissions with a single treatment – and this is what we're seeing."

Wiezorek also pointed to some real-world data for Yescarta – a set of 300 patients and another set of 100 patients – that showed similar responses to those seen in ZUMA-1 with similar rates of cytokine release syndrome (CRS) and neurotoxicity, both of which tend to occur within the first few weeks of treatment and can be severe, or even deadly. (Also see "Too Sick For CAR-T? Kite Reports Cerebral Edema Death" - Scrip, 8 May, 2017.)

"As often happens with the practice of medicine outside of a trial, there were a sizable number of patients that would not have been eligible for ZUMA-1, just because of poor performance status or poor renal function or cardiac function – about a quarter or a third of the patients [in the real-world setting] – and even including those patients, we're still seeing similar outcomes," he said.

Like Novartis, Kite is studying ways to deepen responses and move Yescarta into earlier lines of therapy. The company's ZUMA-7 trial is the first randomized CAR-T study and it is testing Yescarta in second-line treatment of DLBCL after a relapse following Genentech Inc./Biogen's *Rituxan* (rituximab) plus chemotherapy (R-CHOP).

"This is attempting to replace autologous transplant, which has been a mainstay of large-cell lymphoma treatment for decades," Wiezorek said. "This is randomizing CAR-T cells versus salvage chemotherapy followed by transplant."

ZUMA-12 will test Yescarta versus R-CHOP in the first line in DLBCL patients that are considered high-risk and unlikely to respond to the standard-of-care chemotherapy regimen. ZUMA-2 in mantle cell lymphoma and ZUMA-5 in follicular lymphoma are ongoing, but nearing the end of patient enrollment.

Meeting Commercial Challenges Head On

Kymriah and Yescarta have been on the market in the US for more than a year in their initial indications, but sales remain under-whelming. The companies continue to train cancer treatment centers to administer the products and manage their side effects, including CRS and neurotoxicity, while dealing with the additional challenges of manufacturing and reimbursement.

Touchon noted that Novartis has told investors it would be a five-year path to blockbuster sales for Kymriah as the company works closely with doctors and treatment centers to make sure they are administering CAR-T therapies and treating adverse events appropriately. Treatment centers must be specially certified to do both under the Kymriah and Yescarta labels.

Touchon said certified health care providers have impressively managed Kymriah's side effects in the commercial setting, so far, and have been able to treat some patients on an outpatient basis, rather than admitting all patients to the hospital.

What has been more challenging has been manufacturing and reimbursement for the autologous CAR-T therapies. Novartis set a wholesale acquisition cost (WAC) of $475,000 for Kymriah in pediatric and young adult ALL

Novartis Beats CAR-T Competitors To The Pricing

with a $373,000 WAC in DLBCL; the latter matches Kite's price tag for Yescarta in DLBLC.

Kymriah generated just $20m in sales during the third quarter, bringing this year's total to $48m, with one Novartis executive noting that the July-to-September period's sales still were above expectations given ongoing manufacturing challenges. (Also see "Eight Things To Know From Novartis' Third Quarter Call " - Scrip, 18 Oct, 2018.) Novartis noted during its second quarter call that cell variability was of particular concern for Kymriah when manufactured for DLBCL patients – the larger of the product's two markets. (Also see "Cosentyx Carries Novartis Sales But Kymriah Manufacturing Gives Cause For Concern" - Scrip, 18 Jul, 2018.)

Punch With Kymriah Approval

By Mandy Jackson

31 Aug 2017

Novartis got a leg up on its competition Aug. 30 with an earlier-than-expected approval for *Kymriah* in pediatric ALL, ending the CAR-T pricing mystery with its $475,000 price tag, which the company is positioning as a relative bargain.

Read the full article here ›

"We had some challenges in having a release of Kymriah as a commercial product at the end of the [manufacturing] process, even though in most cases this product could still benefit the patient," Touchon said.

In such instances, he explained, the FDA has allowed Novartis – at the request of treating physicians – to release the reengineered cells as an investigational product so that patients still may benefit from Kymriah. The therapy in those cases is provided at no cost to patient.

"We have been working over the last few months actively on that" manufacturing issue, Touchon said. "We've identified the root cause analysis there. We are adapting and improving our process." He indicated that Novartis also has filed for approvals to change a part of the Kymriah manufacturing process that will improve the percentage of viable T-cells in the final product going forward.

In terms of reimbursement in the US, Touchon said Novartis has seen commercial health plans find a way on a patient-by-patient basis to approve payment for Kymriah. The company also has seen Medicaid reimbursement for covered pediatric ALL patients, providing the product at no cost via the Kymriah Treatment Access Program (KTAP) for children and young adults who could not attain Medicaid reimbursement.

The story has been different for adult DLBCL patients covered by Medicare, however, as the Centers For Medicare & Medicaid Services

City Of Hope's Joseph Alvarnas On CAR-T Real-World Use, Reimbursement

By Mandy Jackson

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City of Hope hematologist/oncologist Joseph Alvarnas shares his perspectives on how CAR-T therapies are requiring new models of health

(CMS) struggles to adjust its reimbursement procedures to cover the cost of a one-time, autologous therapy administered in most cases as an inpatient treatment. CMS is trying to figure out a way to classify CAR-T therapies for appropriate reimbursement, but until that system is put in place, treatment centers struggle to get Medicare to pay for these products. (Also see "CAR-T In Medicare: Add-On Payments But No New Bundle Planned For 2019 " - Pink Sheet, 5 Aug, 2018.)

care delivery and engagement with more kinds of stakeholders, during an interview at the recent ASH annual meeting.

Read the full article here ›

Gilead/Kite Experience Not Complicated By Manufacturing Issues

Wiezorek said Gilead and Kite are "pleased" with the Yescarta launch to date. The product brought in $75m in third quarter sales and $183m in the first nine months of this year. (Also see "Gilead's Yescarta Growth Continues, But Momentum Slowed" - Scrip, 25 Oct, 2018.)

"We've been able to qualify the largest number of centers; we're at 70 in the US," Wiezorek said. "We recently had the European approval. We're moving towards 20 sites to be approved in Europe." (Also see "Gilead And Novartis Unveil EU Marketing Plans For CAR-T Therapies, But Hurdles Remain" - Scrip, 28 Aug, 2018.)

He noted that "the manufacturing has been a strength of ours, I think, from the very beginning. At the outset, we put a lot of emphasis on building a robust manufacturing platform. It initially started at [our partner] the National Cancer Institute (NCI), and then we optimized it for multi-center trials."

"Most of this is manufactured from what we call T-cell Factory III near [Los Angeles International Airport (LAX)] in El Segundo that can manufacture up to 4,000 to 5,000 patient doses a year, but we have several other T-cell factories in the area and are looking to expand to other regions as well," Wiezorek said.

Kite's manufacturing facilities support both commercial and investigational products, since the company has four CAR-T and T-cell receptor (TCR) therapies in the clinic, including Yescarta in a Phase II indolent non-Hodgkin lymphoma study, a Phase I study in combination with Roche/Genentech's PD-L1 inhibitor *Tecentriq* (atezolizumab) in DLBCL, and a Phase III study in second-line DLBCL.

"We have another combination planned with Pfizer Inc.'s 4-1BB agonist," Wiezorek noted in addition to the Tecentriq study that's already under way. "The idea there is to agonize the 4-1BB ligand on the surface of the T-cell and that will hopefully further promote expansion of the cells."

Combinations with an anti-CD20 monoclonal antibody are also being assessed as a means for preventing relapse, with plans to eventually develop a dual-targeting CAR-T against both CD19 and CD20, he said.

Kite's other clinical programs include KTE-X19, a CAR-T that also targets CD19 and is in Phase

II in mantle cell lymphoma (MCL) and Phase I for pediatric and adult ALL. Also, the B-cell maturation antigen (BCMA)-targeting candidate KITE-585 is in Phase I in multiple myeloma – a target in the CAR-T field with many competitors, including several that presented data at ASH.

However, Jefferies analyst Michael Yee said in a Dec. 3 note about Gilead that there are low expectations for Kite's BCMA-targeting candidate ahead of the first set of clinical data anticipated in early 2019. Yee predicted that Gilead "does not want a 'me-too' and instead will wisely seek attractive differentiation internally and externally, such as a dual antigen approach ... or other strategies to 'leap-frog' the fast-followers or me-toos in BCMA, which are mostly all pretty similar."

Poseida, Legend/Janssen Look To Snag Celgene/Bluebird's BCMA Crown

By Mandy Jackson

04 Dec 2018

Poseida and Legend/Janssen aim to develop CAR-T therapies with improved efficacy and safety, and both programs delivered updates at ASH for BCMA-targeting CAR-T candidates in multiple myeloma that could challenge Celgene/bluebird's lead in this field.

Read the full article here ›

New T-Cell Therapies, Allogeneic Possibilities For Kite

KITE-718, a TCR candidate against MAGE A3/A6 is in Phase I to treat patients with solid tumors. The target is overexpressed in lung, bladder and other cancers. A second solid tumor TCR candidate targeting HPV-16 E7, which Kite is taking over from the NCI, is expected to enter the clinic in 2019.

Yee noted that Gilead's acquisition of Cell Design Labs Inc. at the end of 2017 and its collaboration with Gadeta BV also have the potential to boost Kite's CAR-T capabilities in solid tumors. (Also see "Gilead Acquisition Of Cell Design: The Next Logical Step" - Scrip, 8 Dec, 2017.) and (Also see "Deal Watch: Gilead Continues To Add To IO Armamentarium In Collaboration With Gadeta" - Scrip, 20 Jul, 2018.)

With long-term partner NCI, Gilead also is investigating the potential for a T-cell therapy targeting neoantigens as a treatment for solid tumors.

"Eighteen months ago, we thought that this [neoantigen program] was pure science fiction, and it just kind of goes to show you how quickly the technology is evolving," Wiezorek said.

This program involves analysis of patients' tumor samples to tease out each individual's specific neoantigens, which will be the targets for the patient's reengineered T-cells. The NCI scientist who developed this candidate has shared preliminary data with Kite that convinced the company to make it a priority program following completion of the ongoing proof-of-concept study. Yee noted that data are expected from the NCI study in late 2019 or early 2020.

While autologous T-cell therapies got Kite off the ground, their complex and costly manufacturing results in a lag time between removing cells and infusing them back into patients, many of whom have

no time to waste waiting for treatment. That's why Kite and partner Sangamo Therapeutics Inc. are also working on allogeneic technologies for off-the shelf treatments derived from donor T-cells. (Also see "Gilead Partners With Sangamo For Gene Editing As It Builds Up Kite's Cell Therapy Platform" - Scrip, 22 Feb, 2018.)

"Our collaboration with Sangamo was really built around this allogeneic platform, so we are focusing there; we have dedicated teams working on the allogeneic platform," Wiezorek said. "We'll have a bit more information about that coming up in 2019, but that's something we're doing in parallel."

Kite is working with induced pluripotent stem cells as well, as a renewable source of T-cells for allogeneic therapies that are even further away from the clinic.

Novartis Explores Getting Treatments To Patients Faster

Touchon said Novartis is looking at allogeneic approaches, but noted the company is also exploring ways to get its autologous CAR-T therapies to patients faster.

"One way to improve that is to improve the logistics, improve the manufacturing process, to make it faster and closer to the patient, and we are working actively there," he said. "We are very confident that all the work and investment we make into improving manufacturing and logistics will lead to a much easier journey for the patient and the physicians, to give autologous CAR-T."

Novartis partnered with Intellia Therapeutics Inc. in 2015 specifically to develop allogeneic CAR-T therapies. (Also see "Novartis to use gene editing tool with CAR-T therapies" - Scrip, 7 Jan, 2015.) Intellia's gene-editing technology uses a CRISPR/Cas9 construct, while Gilead's partner Sangamo is developing zinc finger nuclease gene-editing technology.

However, Touchon argued that allogeneic T-cell therapies actually are more difficult to develop and manufacture than autologous products, despite the relative simplicity of manufacturing multiple doses of CAR-T products from a single donor cell source. Donor T-cells need more than one genetic change to become therapeutic gene-edited CAR-T cells for allogeneic products, but Novartis has the technology and is working on the best, most efficient way to do that, he said.

"The challenge with allogeneic CAR-T is that today, the results that have been shown so far, are showing lack of persistence of the allogeneic CAR-T in the body, and that makes sense, because they are still considered as foreign and they're being eliminated by healthy cells," Touchon said. "So, if they don't persist, then it's no surprise that the efficacy is not as persistent as it is the case with autologous."

That doesn't mean allogeneic CAR-T therapies will never work, but it may be that they're viewed as a bridge to stem cell transplant instead of a cure, he added.

For now, Kymriah remains a big focus for Novartis' CAR-T portfolio.

"Kymriah now is an approved product, so we can move an approved product into new indications or into earlier lines of treatment," Touchon said. "We have eight programs starting right now for Kymriah around new indications like follicular lymphoma, like adult ALL, like CLL."

Second-line DLBCL, first-line pediatric ALL in very high-risk patients, and combination therapy regimens are in the Kymriah pipeline. Novartis also is pursuing new targets with its partner the University of Pennsylvania and via the Novartis Institutes for BioMedical Research Inc. (NIBR), such as a BCMA and CD19 dual-targeting CAR-T and a CD22 candidate, as well as new constructs, including a regulatable CAR-T that can be turned on and off as needed.

"We have four new CAR-Ts that will go to the clinic next year [and] we have one more which will go to the clinic … by the end of this year," Touchon said. "It's really a very active program right now for Novartis."

Editor's Note: This article was updated on Dec. 21 to note that Gilead/Kite's T-Cell Factory III has capacity to make 4,000 to 5,000 doses per year, not 45,000. Also, 70 treatment centers in the US have been certified to administer Yescarta, not 60.