VALUATION INSIGHT
Life Sciences

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CAR-T Cancer Therapy: Linked Fortunes

INSIGHT: Despite their promise, CAR-T programs face substantial risks due to linked clinical fortunes and a future that is likely to involve fierce litigation.

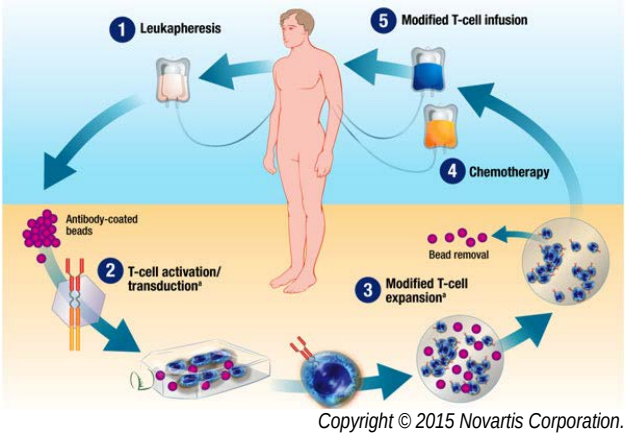
CAR-T Immunotherapy

Immunotherapies harness the power of the immune system to fight disease and are at the forefront of cancer treatment efforts. Chimeric Antigen Receptor T-cell (CAR-T) therapy is an experimental immunotherapy currently being tested on relapsed/refractory cases of blood-borne cancers, such as leukemia and lymphoma. "Unprecedented" remission rates up to 90% suggest immense potential.[1] Some researchers believe that CAR-T may be applicable to most, if not all, tumor types.

Cancer is the uncontrolled proliferation of abnormal cells. In healthy individuals, T-cells are responsible for identifying and destroying abnormal cells. Cancer cells' survival depends on their ability to evade detection and circumvent an immune response.

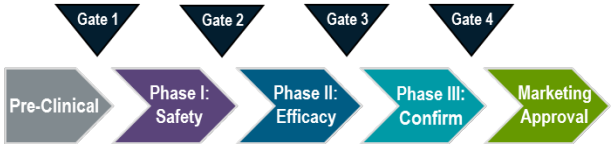
CAR-T allows an individual's own T-cells to be "reprogrammed" to recognize cancer cells as a threat and eliminate them. The process involves extracting T-cells from a patient's body, genetically engineering them to produce chimeric antigen receptors (CAR) that target a specific protein found on cancer cells, multiplying the modified T-cells in a lab, and then re-introducing them into the patient's body, where they further multiply and attack the cancer cells. (Process depicted below.)

Clinical trials for CAR T-cell therapies are currently underway. The frontrunners in this field—Juno Therapeutics, Novartis, and Kite Pharma—believe that they might obtain FDA approval for their lead candidates as early as 2017.



CAR-T Programs Face Clinical Risks Together

To gain FDA approval, CAR-T programs—like any new drug or therapy—must pass a series of clinical "gates" to prove safety, dosing, efficacy, and confirmation of results.

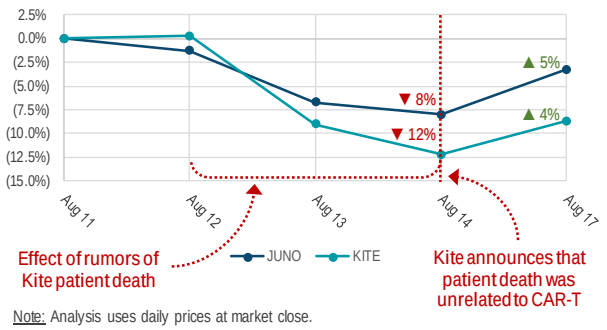


For CAR-T, this process is full of challenges. Along with its capacity to cure cancer comes risk of serious complications such as cytokine release syndrome (CRS), a potentially fatal inflammatory response that causes renal, pulmonary, and cardiac complications. CAR-T also is associated with neurologic toxicity (patients have died of cerebral edema) and increased infection risk. These issues highlight safety concerns and also raise questions about proper dosing, manufacturing, and protocols.

Despite distinct differences in their programs, CAR-T companies face these clinical challenges together. Bad news for one can be bad news for all. Based on a review of market data, it appears that prospects for two of the leading CAR-T companies—Juno and Kite—are especially interrelated. *[Novartis is excluded from this analysis due to the muting effects of diversification.]*

Rumors of a Kite Patient Death Affect Juno: In August 2015, rumors surfaced that a patient died in Kite's KTE-C19 phase 1/2 study for a CAR-T treatment for non-Hodgkin's lymphoma. In response, Kite's and Juno's stocks fell 12% and 8%, respectively. Once Kite announced that the death was unrelated to its therapy, both companies' stock rebounded. The NASDAQ Biotech Index remained flat during this period. This price movement reflects a market perception of clinical linkage among CAR-T programs.

Juno and Kite: Relative Price Movement
Due to Rumors of Kite Patient Death in August 2015



Note: Analysis uses daily prices at market close.

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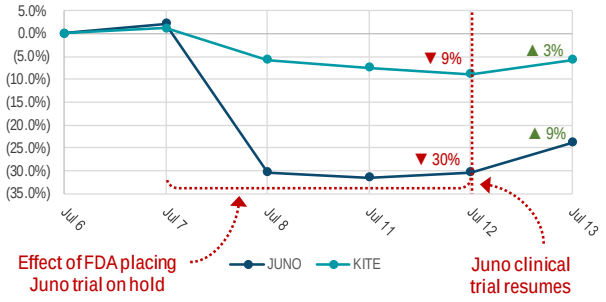
Juno's Clinical Trial Woes Affect Kite: In July 2016, the FDA halted Juno's phase 2 trial for a CAR-T leukemia treatment following three patient deaths. Juno's and Kite's shares dropped 30% and 9%, respectively. A few days later, the FDA removed the hold, determining that the deaths were due to the combination of Juno's treatment with the chemotherapy drug fludarabine. News of the trial resuming caused Juno's stock price to increase 9%. Kite saw a parallel increase of 3%. Again, the NASDAQ Biotech Index remained flat during this period.

Juno and Kite: Relative Price Movement
Due to Juno Clincal Trial Issues in July 2016



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FDA Pushes to Centralize CAR-T Trial Data: In March 2016, the FDA proposed new databases to consolidate CAR-T trial information. This move is expected to improve its ability to evaluate safety concerns. The data collected would focus on toxicity issues and manufacturing practices in a particular class of CAR-T therapies (anti-CD19). The databases would allow the FDA to analyze a larger sample size of patient data, build risk models, and provide safety advice to sponsors. The FDA indicated that participation would be voluntary.

Perception of Clinical Linkage Increases Market Risk for All: The perception of clinical linkage among CAR-T programs increases market risk for the entire cohort. CAR-T companies do not have control over the processes or outcomes of others' studies, and negative results can impact all. Issues with a single trial could affect the cost and availability of capital and the pace and cost of clinical trials for every CAR-T company. Consequently, CAR-T program valuations should not be done in isolation. Instead, they require a broad assessment of the progress and risks of all CAR-T programs in the field.

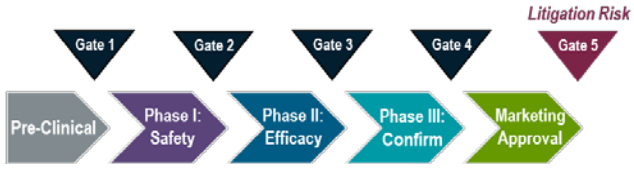
IP Ownership Issues Could Trigger Litigation

In part due to their shared trajectories, CAR-T companies will likely find themselves entangled in IP ownership disputes. More than 10 research institutions have been involved in the development of CAR-T and have actively partnered with companies pursuing therapies. Although positive for scientific advancement, widespread collaboration also clouds IP rights. What begins as collaboration may well lead to litigation.

For example, two groups working on anti-CD19 CAR-T therapies—Novartis/Penn and Juno/St. Jude—already litigated over their early collaboration, ultimately settling their differences with an agreement that includes millions of dollars in payments and mid-single-digit royalties.[2] Interestingly, even in the midst of that litigation, Sloan-Kettering, which helped launch Juno, moved forward with a clinical study of CARs in collaboration with Penn, Juno's litigation adversary.

The groups discussed above are far from alone in the anti-CD19 space. As of mid-2016, there were 36 anti-CD19 therapies involving more than 15 different sponsors. This represents one-third of the 105 engineered T-cell therapies under FDA review.

The risk of IP litigation among CAR-T companies serves as an additional "gate" on the path to commercialization. (See below.) This is a looming risk, and it is unclear which entities possess the strongest rights.



Accordingly, there is the potential that future litigation could lead to a substantial redistribution of value among competitors in the CAR-T space. This would be a playbook that we have seen before with cardiac stents, which led to an industry-wide battle and over a billion dollars changing hands as a result of litigation.

Notes:
[1] Dr. Noelle Frey, of the University of Pennsylvania, as cited in an American Society of Clinical Oncology (ASCO) article dated July 10, 2016.
[2] Juno Therapeutics, Inc. Form 8-K dated April 4, 2015.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