Category

Best Startup

Product/Solution Name

Affini-T Precision Immunotherapy

Date of Approval

N/A

Indications

Our primary goal is to obtain second-line approvals in areas with significant unmet medical needs. Specifically, we are focusing on oncology indications where there is a high demand for effective treatments and limited options available to patients, such as those with colorectal cancer (CRC), pancreatic cancer (PDAC), and non-small cell lung cancer (NSCLC) who have failed previous treatments, including PD1/PDL1 inhibitors and chemotherapy. In our pre-Investigational New Drug (IND) interaction with the United States Food and Drug Administration (FDA), we communicated our plan to include patients who have undergone at least one prior line of treatment in our first-in-human trial. Ultimately, the decision on the indications we pursue will be guided by clinical data.

Therapeutic Categories

We are an adoptive cell therapy company and believe this modality holds great promise in treating patients with solid tumors, particularly in the context of autologous cell therapies. Affini-T recognizes the need to advance safe cell therapies that induce durable antitumor responses in patients. The importance of adoptive cell therapies becomes evident when considering the limitations of small molecule inhibitors, which target-specific oncogenic driver mutations like KRAS G12C. While these inhibitors have shown efficacy in patients with the targeted mutation, the majority of patients don't respond and many initial responders eventually relapse. The emergence of additional mutations in tumor cells often leads to treatment resistance to such small molecules.

T cell receptor (TCR)-engineered T cells (TCR-Ts) targeting KRAS mutations have the ability to recognize and kill tumor cells regardless of additional mutations, as long as the KRAS mutation is present. Unlike small molecules, cell therapies like TCR-Ts can bypass the selective pressures exerted by mutations and offer a potential solution for patients with KRAS mutations.

While allogeneic strategies may seem attractive for their cost reduction and global availability, autologous strategies have been clinically validated and are currently more established as an effective therapy. Advancements in manufacturing technologies have reduced the associated cost of goods. Recent studies in the allogeneic field have not led to durable antitumor responses where patients either do not respond to these therapies or, if they do, often relapse within a short period of time as the allogeneic cells fail to persist.

As such, Affini-T is pursuing an autologous adoptive cell therapy as this modality offers greater potential for inducing durable antitumor responses in patients. By overcoming the limitations of small molecule inhibitors and targeting specific mutations, such as KRAS mutations, adoptive cell therapies have the advantage of immediate killing and reduced susceptibility to treatment resistance mechanisms. Continued advancements in this field hold promise for meeting the high unmet needs of patients with solid tumors, providing more effective and long-lasting treatments.

Background information and need for solution/product

Affini-T, founded in 2020, is a biotechnology company focused on developing potentially curative therapeutics for patients with solid tumors. The company's primary objective is to address the urgent need for effective treatments for solid tumors, which often present significant challenges due to their complex nature and resistance to conventional therapies.

To achieve this goal, Affini-T has developed an innovative approach that revolves around targeting oncogenic driver mutations with a particular emphasis on mutant KRAS. KRAS is considered one of the most important proto-oncogenes involved in regulating cell division and proliferation, and its mutations, such as KRAS G12V and G12D, are prevalent in a large portion of solid tumor cases worldwide.

The company leverages three proprietary platforms, namely TAILOR TM, TUNE TM, and THRIVE TM, to harness the coordinated response of T cells. T cells play a crucial role in combating tumor progression by eliminating cancer cells and mitigating T cell exhaustion. Affini-T's therapies aim to provide a deep and durable remission for patients with solid tumors, offering the potential for curative outcomes.

One of the key advantages of targeting mutant KRAS with T cell therapies is that the tumor cells, dependent on the mutated KRAS for survival signals, continue to express the antigenic peptide on their cell surface. This feature enables sustained targeting of the tumor cells even in the presence of additional subclonal mutations. In contrast, small molecule inhibitors of KRAS G12C, which have shown initial responses in patients, often lead to rapid relapse due to alterations, for example, in the KRAS protein beyond the G12C mutation.

Small molecule inhibitors only partially inhibit mutant KRAS signaling, allowing selective pressure on the tumor cells. This pressure can lead to additional mutagenesis, enabling the tumor cells to circumvent the small molecule action and eventually develop resistance, escape, and relapse. Interestingly, patients treated with KRAS G12C small molecules have been observed to develop additional mutations, including sometimes KRAS G12V and G12D. This observation creates a new patient segment that can benefit from Affini-T's KRAS G12V or G12D TCR-T cell therapies.

Affini-T's T cell therapies offer the potential for increased durability compared to small molecule KRAS G12C therapies. By administering T cell therapies that target oncogenic driver mutations like KRAS, all tumor cells harboring that mutation may be eliminated. This approach directly attacks the underlying root cause of the cancer and deletes the cancer-driving cells themselves. Consequently, Affini-T believes that its therapies will demonstrate enhanced efficacy, potentially leading to curative treatments for patients with solid tumors.

Affini-T’s innovative science and drug development teams are joining forces to make a dramatic impact on patient outcomes with the goal of bringing curative therapies to a wider population.

Attached Files:

- AffiniT NonConfidential Corporate Presentation_June 2023_Prix Galien.pdf

History of the development of the solution/product

Developing Affini-T's solution involved a series of assessments and experiments to evaluate the activity and tolerability of its lead programs, which utilize A11 KRAS G12V and G12D TCRs, gene editing and synthetic biology.

To evaluate the functional persistence of TCR-Ts, in vivo anti-tumor activity studies were conducted using established human cell xenografts. These studies aimed to directly assess the performance of the T cells in a relevant physiological context. Additionally, immunocompetent models and murine T cells were utilized to investigate armoring strategies that require interaction with an intact immune system.

The evaluation of activity and tolerability started with in vivo assessments using human cell line xenografts in an immunocompromised setting. This approach allowed for long-term evaluation of the engineered T cells' potential to persist and function effectively. Priority was given to models that naturally expressed the KRAS mutation and the specific HLA haplotype of interest. However, in cases where suitable models were not available, the deficient HLA haplotype was exogenously expressed, ensuring that MHC I surface expression was assessed at a physiologic level to maintain relevance.
For the A11 KRAS G12D TCR program, knock-in approaches were explored. These approaches involved replacing the endogenous TCR with the transgenic TCR, offering streamlined manufacturing and greater flexibility in product diversity. For both the A11 KRAS G12V and G12D programs, synthetic biology techniques were also employed, primarily using autochthonous and syngeneic tumor models. For instance, the FAS-41BB switch receptor was extensively analyzed in vivo using the FBL-leukemia model and the KPC model (LSL-KrasG12D/+; LSL-Trp53R172H/+; Pdx-1-Cre) -induced Pancreatic ductal adenocarcinoma (PDAC), which accurately recapitulates human disease.
The use of immunocompetent models allowed Affini-T to assess the interplay between its armoring strategies and an intact immune system, which is often critical for the efficacy of its approach. These comprehensive assessments and experiments contributed to the development and optimization of Affini-T's solution for providing potentially curative therapeutics for patients with solid tumors.

Why this solution/product is innovative, the broad implications for future research, and/or how it will improve the human condition

The solution provided by Affini-T is highly innovative and incorporates several differentiated scientific approaches to improve T cell fitness, persistence, and durability. These innovations have broad implications for future research and significant potential for those patients with high unmet medical needs.
Firstly, Affini-T utilizes the expression of naturally occurring potent and selective TCRs, which allows for the identification of highly active and tolerable therapies. Coordinating the CD4/CD8 T cell response is another key aspect, as it enables a deep and durable anti-tumor effector function. By integrating the CD8α/β co-receptor, the peptide/MHC recognition by the TCR is amplified, thereby enhancing the T cell response.
Coordinated CD4/CD8 T cell responses are facilitated by Affini-T's approach, leading to increased functional persistence of its therapies. This coordinated response involves the expression of selected TCRs and CD8α/β co-receptor chains, enabling CD4+ T cells to target and respond to the tumor. This response not only assists the responding CD8+ T cells but also modifies the inflammatory state by secreting cytokines into the tumor microenvironment, inducing an immune response.
Affini-T prioritizes novel armoring approaches to enhance both the early anti-tumor response and durability. Their integration of the FAS-41BB switch receptor into its products addresses the lack of T cell survival in the immune-suppressive tumor microenvironment. This switch receptor acts as a dominant negative signal, preventing FASL-induced death, and increases pro-survival signaling, proliferation/expansion and antitumor function. This approach has shown improved survival in aggressive cancer models.
To ensure product consistency and improve safety, Affini-T integrates nonviral and gene editing approaches in its future T cell therapies. These improvements not only decrease costs but also allow the delivery of larger payloads for arming T cells with novel functions. By eliminating randomly integrating transposons, retroviruses, and lentiviruses, the safety profile of the therapies can be enhanced.
Affini-T's collaboration with Metagenomi, a gene editing pioneer, enables Affini-T to make precise cellular edits with high selectivity, opening new avenues for multiplexed gene editing. Affini-T plans to

utilize gene editing approaches, such as deleting the endogenous TCR and knocking out inhibitory checkpoints, to improve T cell fitness, increase sensitivity, and enhance the efficacy of its cell therapy programs.

Finally, Affini-T has also established a robust cell manufacturing process to be able to provide patients with reliable and high-quality cell products with a swift turnaround time comparable to the leading approved CAR-T treatments. Affini-T's current manufacturing platform is a 10-day manufacturing process consisting of a leukocyte immunomagnetic enrichment step of a patient-collected leukapheresis sample followed by T cell activation and transduction with a single lentivirus encoding the transgenic TCR, CD8α/β coreceptor and a switch receptor. The transduced cells are then expanded in closed system culture vessels using serum-free media, then harvested and cryopreserved to enable shipment to clinical sites. The TCR-T cell drug product is stored in vapor phase liquid nitrogen and is ready to infuse at the patient bedside immediately upon thawing.

Overall, Affini-T's innovative solution combines various scientific advancements, including the expression of potent TCRs, coordinated CD4/CD8 T cell responses, selection of less differentiated T cells, armoring approaches, nonviral delivery and gene editing. These advancements have broad implications for future research in the field of T cell therapies and hold great potential to significantly improve the human condition by providing more effective and durable treatments for a broad range of solid tumors.

Please provide appropriate references (ie Pubmed links)

Please see attached posters/presentations, as well as a select publication list supporting Affini-T's scientific approach.

Attached Files:

- AFNT13.PDF
- AFNT11.PDF
- AFNT21.PDF
- AFNT22.PDF
- AFNT24.PDF
- AFNT212 ASGCT May.pdf