Avalon GloboCare Corp.
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Avalon GloboCare—expanding horizons in cancer immunotherapy and cellular medicine

Avalon GloboCare is a global leader in the development of transformative immune effector cell therapies. With 15 autologous and off-the-shelf cell therapy programs for a wide array of hematologic malignancies and solid tumors, Avalon is expanding horizons in cancer immunotherapy and cellular medicine.

Avalon GloboCare (NASDAQ: AVCO), a US-based developer of innovative and transformative cell-based technologies and therapeutics, has recently expanded its growing portfolio of cell therapy candidates through its recent acquisition of SenlangBio, the largest clinical cell therapy company in Northern China. Avalon's immune effector cell cancer therapy candidates include both autologous and next-generation off-the-shelf (universal) chimeric antigen receptor (CAR) T cell therapies (Fig. 1).

Over the past decade, immunotherapies, and in particular CAR T cell therapies, have radically changed the face of cancer care. Despite their success, there exist a number of challenges that prevent their wider implementation. Chief among the challenges are the limited therapeutic indications for CAR T cell therapies—B cell acute lymphoblastic leukemia (B-ALL), lymphoma and multiple myeloma (MM). These treatments have not been shown to be effective for solid tumors and continue to exhibit a relatively high rate of adverse effects and toxicities, including cytokine release syndrome (CRS) and CAR-related encephalopathy syndrome (CRES). In addition, current autologous CAR T cell therapies require extended manufacturing times (approx. two weeks), and utilize a viral vector and cold-chain transportation, which contribute to their high cost. To address these challenges, Avalon has developed a suite of platforms to advance next-generation CAR T cell therapies with more favorable characteristics for wider adoption.

Avalon's autologous CAR T cell therapies have already demonstrated promising, positive response rates in early clinical studies against relapsed and refractory (R/R) B and T cell leukemias and lymphomas, with excellent tolerability among patients.

The company is also developing universal, allogeneic CAR T cell therapy candidates using its γδ T cell–based universal CAR technology, a platform capable of cell expansion rates of more than 5,000-fold that could set a new standard in the cell therapy field. Avalon's lead CAR γδ T cell therapeutic candidates targeting relapsed and refractory acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), as well as multiple solid tumors, including pancreatic, gastric, and ovarian cancers, are slated to enter first-in-human trials in 2022.

With a GMP bio-processing and bio-manufacturing facility designed to generate clinical-grade cell therapy candidates, Avalon is poised to sustainably grow its portfolio of cell therapy candidates, expand opportunities for clinical trials worldwide, and manufacture its commercial-grade clinical therapies.

"At Avalon, we are driving innovative and high-impact cellular therapies through the vertical and horizontal integration of global healthcare resources," said David Jin, President and CEO of Avalon and co-CEO of SenlangBio. "Through our recent acquisition of SenlangBio, we will be able to rapidly expand our positive impact. Our core vision is to develop innovative and transformative immune effector cell therapies that will improve efficacy and quality of life for cancer patients around the world."

Controlling CAR density to minimize adverse effects

One drawback of CAR T cell therapies is the often debilitating and sometimes lethal side effects associated with overstimulating a patient's immune system. The sudden and sustained release of cytokines triggered by the treatment can cause CRS as well as CRES, two conditions requiring careful clinical management.

One strategy to significantly reduce the rate and intensity of these adverse events is to fine-tune the number of CARs expressed on the surface of the engineered CAR T cells. Evidence shows that this approach does not compromise the anti-tumor efficacy of the CAR T cells but greatly reduces the frequency and intensity of CRS and CRES among patients.

Avalon has developed an anti-CD19 CAR T cell therapy, AVA-SenI-1904B, in which CAR expression is driven by the MND promoter, which produces several-fold less CAR transcripts than EF1alpha, the conventional promoter used to drive CAR expression in currently approved CAR T cell therapies. As a result, the anti-CD19 CARs are present at a lower density on the surface of AVA-SenI-1904B.

AVA-SenI-1904B is in development for relapsed or refractory B-ALL. In a recently published study, AVA-SenI-1904B resulted in better anti-tumor efficacy in an animal model compared to EF1alpha-driven CAR T cells. In first-in-human studies, AVA-SenI-1904B exhibited a 97.2% (35/36) complete remission rate and only a 5.6% (2/36) rate of Grade 3 CRS among R/R B-ALL patients.

"These are early, but substantial and encouraging safety and efficacy data supporting the development of this and additional CAR T therapies using our novel promoter technology," said Jin. "We look forward to the continuing clinical development of AVA-SenI-1904B and to expanding the range of applications of this unique cell therapy candidate."

China's National Medical Products Administration (NMPA) recently approved an investigational new drug (IND) application for AVA-SenI-1904B to initiate a phase 1 clinical trial in cancer patients.

Smarter CAR T therapies for T cell malignancies

Developing CAR T cell therapies to treat T cell malignancies presents unique challenges because of the need for the CAR T cells to target and kill malignant T cells while sparing normal T cells. In addition to requiring the expression of an antigen specific to malignant T cells, a successful therapy requires the separation of healthy T cells from malignant T cells. Incomplete T cell separation can result in CAR-modified tumor cells. Residual expression of the targeted antigen on the engineered CAR T cells or the patient's healthy T cells can result in so-called 'fratricide' and T cell aplasia, respectively. Fratricide significantly reduces therapeutic efficacy, T cell aplasia can result in profound immunosuppression, and CAR-modified tumor cells result in contaminated product and reduced expansion of the CAR T cells.

Avalon has addressed these challenges by focusing on CD7, an antigen that Avalon researchers have shown is not expressed on T cells in the peripheral blood of T cell acute lymphoblastic leukemia (T-ALL) and T cell lymphoblastic lymphoma (T-LBL) patients. By selecting only CD7-negative T cells to generate autologous CAR T cells, Avalon's AVA-SenI-NS7CAR CAR T cell therapy candidate eliminates the fratricide effect, has no off-target risk, and exhibits durable activity in preliminary studies.

In a first-in-human investigator-led clinical trial, eight out of eight T-ALL and T-LBL patients achieved complete remission without developing any adverse effect greater than Grade 2 CRS. Avalon plans to file an IND application with the NMPA later in 2021 in preparation for a phase 1 clinical trial.

New targets for solid tumor–directed CAR T cell therapies

While existing CAR T therapies have been successful for patients with difficult to treat CD19-positive leukemias and lymphomas, attempts to treat solid tumors with CAR T cell therapies have thus far not shown enough efficacy to move them into larger trials. To better target solid tumors, Avalon is developing next-generation CAR T therapies that focus

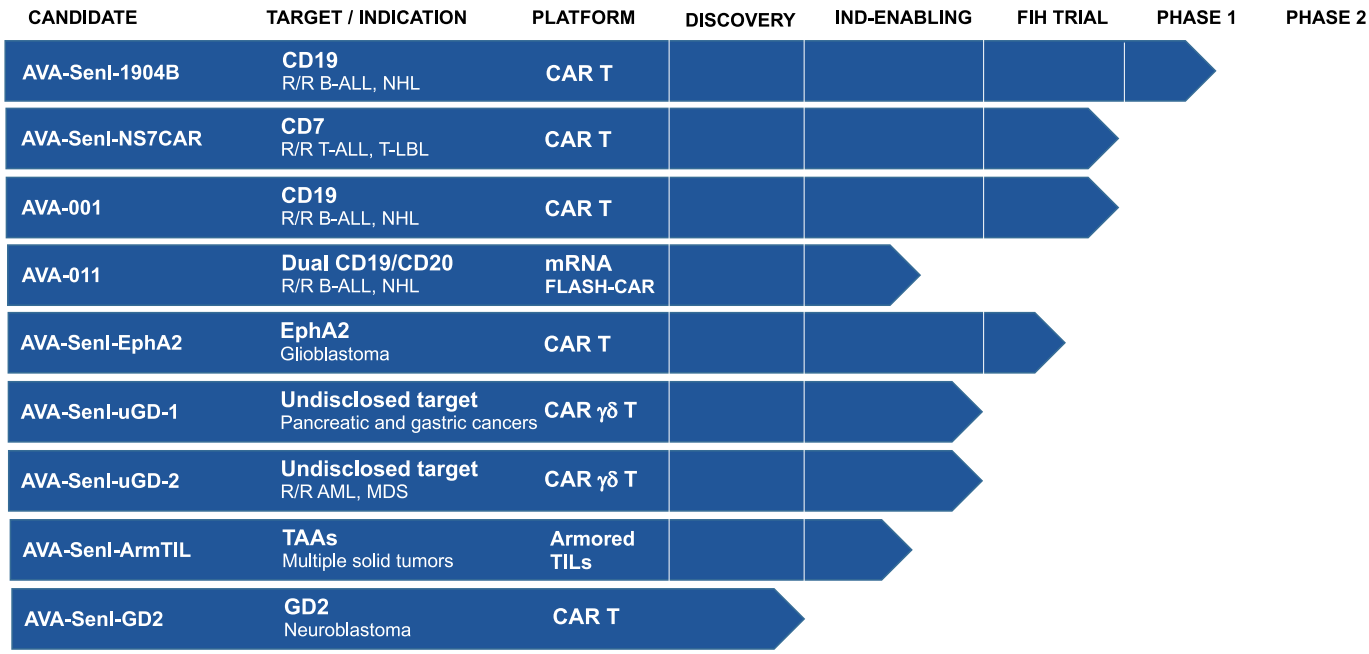

Fig. 1 | Avalon's pipeline of immune effector cell therapies. Avalon is developing a pipeline of transformative immune effector cell therapies that includes multiple autologous and universal cell therapy programs for a wide array of hematologic malignancies and solid tumors. AML, acute myeloid leukemia; B-ALL, B cell acute lymphoblastic leukemia; CAR, chimeric antigen receptor; FIH, first-in-human; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; R/R, relapsed or refractory; T-ALL, T cell acute lymphoblastic leukemia; T-LBL, T cell lymphoblastic lymphoma; TAAs, tumor-associated antigens; TILs, tumor-infiltrating lymphocytes.

on cell targets such as erythropoietin-producing hepatocellular receptor tyrosine kinase class A2 (EphA2), a solid tumor-associated antigen expressed on glioblastoma cells, but not on non-cancerous, normal cells of the brain.

Avalon's anti-EphA2 CAR T is a first-in-class cellular therapy and the first ever EphA2-targeted CAR T with reported clinical trial data. Recently published preliminary results show that the therapy is well tolerated, and that the CAR T cells exhibit persistent activity over four weeks after initial dosing in patients.

Avalon's Flash-CAR—accelerated CAR manufacture

Avalon has developed an mRNA-based CAR platform (Flash-CAR) that dramatically reduces 'vein-to-vein' bio-manufacturing time from an average of two weeks for currently available CAR therapies to just one to two days. Key to Avalon's approach is the use of an electroporation step that efficiently introduces the mRNA construct of interest into the patient's T cells. This process can further be applied to the transformation and engineering of other effective immune cell types, such as natural killer (NK) cells or dendritic cells (DCs), that are also promising effector cell cancer immunotherapies.

The modified mRNA constructs include several elements that help increase both safety and efficacy. The construct includes a genetic safety switch and a number of other gene elements to enhance in vivo proliferation of CAR T cells, NK cells, DCs, and potentially other native immune cell types.

Avalon has developed this technology in collaboration with Arbele Limited and the University of Pittsburgh Medical Center. The company's lead Flash-CAR candidate, AVA-011, has completed preclinical testing and is in the IND-enabling process development stage to generate a clinical-grade cellular product in preparation for upcoming first-in-human clinical studies in the US and Asia.

Paving the way for universal access to CARs

The development of autologous CAR T cell therapies has been a boon for the treatment of cancer, yet the complexity involved in manufacturing the bespoke CAR T cells using self-derived individual patients' T cells has proven to be a major barrier for access. To solve these logistical issues, the cellular therapy industry has been working on allogeneic, universal CAR T cells engineered from T cells derived from a universal donor. Avalon has approached this challenge by focusing on the production of universal CAR T cells that would not only be easier, faster, and cheaper to produce, but that could also be used to treat both hematological malignancies and solid tumors. Avalon's strategy consists of harnessing the potential of γδ T cells, a subtype of T cells that express a unique T cell receptor composed of a γ-chain and a δ-chain, and that are preferentially involved in the infiltration and killing of tumors. γδ T cells, which are present in low abundance in the body, can mount both innate and adaptive immune responses. Utilizing a proprietary cell culture protocol, Avalon and SenlangBio's scientists have achieved a significant technical milestone of expanding these rare γδ T cells over 5,000-fold in culture to reach therapeutic and commercial scale.

Avalon's lead CAR γδ T cell therapy candidate is a potential breakthrough treatment for difficult to treat R/R AML and MDS as well as for multiple solid tumors including pancreatic, gastric, and ovarian tumors and for sarcomas. Avalon is performing the necessary IND-enabling studies and expects to enter first in human clinical trials in early 2022.

Forging a path toward innovative CAR partnerships

Avalon is establishing itself as a global leader in CAR T cell therapy development. A combination of innovative approaches—from novel cancer targets opening a path for CAR T cell–based interventions for solid tumors to next- generation CAR T cell manufacturing of autologous and universal therapies for cancer—and a determination to facilitate access to these novel therapies, define Avalon's ethos.

Backed by a unique research and development infrastructure that includes a 16,000 square-foot GMP facility consisting of five bio-production lines for autologous cell therapy products (5,000 unit-doses/year capacity) and two bio-production lines for allogeneic cell therapy products (10,000 unit-doses/year capacity), and a vertically integrated operation model that seamlessly integrates upstream innovative research, midstream bio-production, and downstream clinical and commercialization programs, Avalon is the partner of choice for academic and industry collaborators interested in developing the next generation of CAR T cell therapies.

Jin said "We are looking for clinical development partnerships with pharmaceutical and biotechnology companies that have a similar vision as us—that is, propelling effective, next-generation cellular therapies for cancer patients. Our ultimate goal is to advance and empower disruptive and transformative medical innovation that will positively impact the lives of cancer patients worldwide."

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