Celyad is a clinical-stage global leader in the development of chimeric antigen receptor (CAR)-T cell therapies for the treatment of cancer. The company is leading the next wave of CAR-T cell therapy development using a multifaceted approach that can be leveraged for the treatment of both hematological malignancies and solid cancers. In addition, the company is evaluating both an autologous (using the cells of the patient) and an allogeneic approach, also referred to as an off-the-shelf approach (based on cells from healthy donors), for the development of CAR-T therapies. The company’s clinical pipeline is also complemented by a portfolio of preclinical-stage candidates leveraging several technologies including short hairpin RNA (shRNA).

Celyad’s unique value proposition is its combination of a focus on novel natural killer group 2 member D (NKG2D)-based CAR-Ts, a robust intellectual property position in particular in the allogeneic field, and the company’s expertise in cell therapy manufacturing—with an in-house centralized good manufacturing practice (GMP) facility and the logistical capabilities to support global CAR-T cell therapy clinical trials and a potential commercial launch.

“Celyad has over a decade of experience in cell therapy development and manufacturing. Our strong focus on NKG2D biology allows us to today have a deep knowledge of the safety and potential of the target. Combined with our newly developed technologies, this will undoubtedly keep Celyad at the forefront of the CAR-T field and allow us to deliver novel therapies to cancer patients,” said Filippo Petti, CEO of Celyad.

Pan-cancer CAR-T cell strategy
Since CAR-T cells emerged on the cancer therapy scene with great promise for revolutionizing cancer treatment, a key challenge has been to expand their reach beyond a very limited number of tumor types. As conventional CAR-T cells are designed to recognize only one tumor antigen, their use is restricted to one type of cancer, potentially hindering the full potential of this novel modality.

Over the past four years, Celyad has been focused on addressing these limitations by developing an alternative approach centered around the natural killer (NK) cell’s activating receptor NKG2D. The receptor, which is naturally expressed on NK cells, plays an important role in the innate immune system’s ability to protect against infections and cancer. The receptor binds to eight different major histocompatibility complex class I-related ligands (MHC class I) polypeptide-related sequence A (MICA), MIBC and UL16-binding proteins 1–6) that are not typically expressed at the surface of most cells but that are induced in response to stress (for example, upon induction of the DNA damage pathway).

NKG2D ligands are highly expressed across many different types of tumor, including but not limited to acute myeloid leukemia (AML) and colorectal cancer (CRC). As such, NKG2D-based CAR-T cells could potentially address the vast majority of hematological malignancies and solid tumors. In addition, preclinical studies have shown that NKG2D CAR-T cells may have the ability to target not only the tumor cells but also the blood vessels that feed the tumors and the inhibitory cells that help tumors evade the immune system within the tumor microenvironment. This amplifies the direct antitumoral effect of the NKG2D CAR-T cells. In addition, NKG2D CAR-T cells may also trigger the generation of long-term cell memory against targeted tumors following induction of the host adaptive immune response—an effect reminiscent of traditional vaccination. Importantly, because NKG2D-based CAR-Ts can bind to several stress ligands, these CAR-T candidates offer minimal risk of clonal selection and tumor escape, a defense mechanism that tumors have developed to hide from first-generation CAR-T therapies that recognize only a single antigen.

Autologous approach: CYAD-01
Celyad’s lead clinical candidate for autologous CAR-T therapy, CYAD-01 (Fig. 1), is currently in phase 1 development for the treatment of relapsed or refractory (r/r) AML, myelodysplastic syndromes (MDS) and metastatic CRC (mCRC), both with or without concurrent administration of standard-of-care treatments (preconditioning chemotherapy).

In the studies without preconditioning, treatment with monotherapy CYAD-01 showed evidence of antileukemic activity in 60% of the patients and a complete response in 40%, providing confidence that the clinical effect was attributed to the NKG2D-based CAR-T. In solid tumors, CYAD-01 has also demonstrated a clinical benefit with disease stabilization observed across multiple dose levels of the treatment and good tolerability. Further data from CYAD-01 for both the treatment of r/r AML or MDS and mCRC are expected throughout 2019.

Allogeneic approach: CYAD-101
The barrier to the development of allogeneic therapies is overcoming graft-versus-host disease (GvHD), in which the donor T cells recognize the patient’s cells as foreign, resulting in attack of the healthy tissue. This event is attributed to the T cell receptor (TCR) at the surface of the donor cells recognizing human leukocyte antigen (HLA) on the patient’s tissues as foreign and instructing the T cells to attack.

Whereas many in the field have used gene-editing technologies such as transcription activator-like effector nucleases (TALENs), zinc finger nucleases or CRISPR–Cas9 to eliminate the TCR gene from the genome of the donor CAR-T cell, Celyad has focused on a means to modify TCR expression or function without editing the genome.

For instance, Celyad’s first non-gene-edited allogeneic candidate, CYAD-101, coexpresses the TCR inhibitory molecule (TIM) peptide plus the NKG2D–CAR utilized in CYAD-01. TIM acts as a competitive inhibitor to the CD3ζ component of the TCR and interferes with the ability of the TCR to signal, thus lowering the risk associated with the therapy to drive GvHD.

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Filippo Petti, CEO, Celyad
Initial results of the first cohorts of patients with advanced CRC treated with CYAD-101 are expected in mid-2019. “The TIM approach is a very elegant way to turn down the signaling of the TCR in an attempt at preventing the onset of GvHD while allowing tumor-specific killing through the CAR,” noted David Gilham, Celyad’s VP of research and development (R&D).

Next-generation shRNA-based allogeneic CAR-Ts

In parallel, Celyad has already embarked on the development of the next-generation CAR-T cell therapies that simultaneously target a tumor and specific genes via shRNA-mediated silencing. Celyad’s shRNA platform is the result of an exclusive agreement with Horizon Discovery Group for the use of its subsidiary Dharmacon’s SMARTvector shRNA technology. In the allogeneic setting, Celyad is developing an approach leveraging shRNA to silence the mRNA coding for the CD3ζ component of the TCR. The resulting reduction in TCR expression at the cell surface by shRNA is similar to that observed using gene-editing approaches to target the CD3ζ component, in particular CRISPR–Cas9 (Fig. 2).

In addition, an interesting aspect of the shRNA technology is that it dovetails nicely with Celyad’s ‘all-in-one vector’ concept, which allows for quick and efficient design of the company’s CAR-T candidates in a single-step process, leading to a ‘plug-and-play’ approach, thereby providing efficiencies across all segments of R&D and cell manufacturing.

“From our perspective, we have developed an shRNA platform that rivals gene-editing technologies for the design of allogeneic CAR-T therapies. The potential of this next-generation alternative to gene editing goes beyond our proprietary oncology programs and represents a great opportunity for us to grow our network of partners advancing CAR-T therapies in different therapeutic areas,” commented Petti.

Closing the production gap

A key challenge for the implementation of any CAR-T cell-based therapy is the manufacture and distribution of the cells. Celyad has more than a decade of expertise in cell therapy, including the treatment of over 350 patients through the company’s different trials with cells manufactured in-house. Celyad has its own manufacturing facility to independently improve and optimize the company’s streamlined processes. This results in the seamless and efficient reproduction of materials to advance the company’s pipeline from the preclinical stage through to clinical evaluation and eventually commercialization.

With a large storage capacity and the capability to globally supply cryopreserved drug products, Celyad is well positioned to execute the company’s clinical trials on a global scale. In addition, Celyad already has the capacity to supply materials to support the treatment of more than 1,000 patients annually for the company’s lead candidate CYAD-01.

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