Clinical Development of a Non-Gene-Edited Allogeneic BCMA-Targeting CAR T-cell Product in Relapsed or Refractory Multiple Myeloma


BACKGROUND

Multiple myeloma (MM) remains largely incurable. Despite demonstrated efficacy of current therapies, most patients eventually relapse due to persistence of therapy-resistant plasma cell clones in the bone marrow. Autologous chimeric antigen receptor (CAR) T cell therapy directed against the B-cell maturation antigen (BCMA), a protein that is expressed on MM cancer cells, has shown impressive objective response rates in patients with advanced MM. Clinical grade manufacturing of autologous CAR T cells has limitations including the need for suboptimal production time, patient-to-patient variability, and variable immunophenotypic variability of T-cells isolated from patients with advanced disease. Allogeneic CAR T cell products, whereby cells from healthy third-party donors are used to generate an "off-the-shelf" product, have the potential to overcome some of these issues.

CYAD-211 is an "off-the-shelf" non-gene edited allogeneic anti-BCMA CAR T-cell product which uses an Allo-A-One vector approach (Figure 1) to co-express:

- A CAR made by the in vivo fusion of a BCMA-specific single-chain variable fragment (scFv) with the extracellular hinge, transmembrane domain of CD8β, and the intracellular domains of CD3ζ and CD28.
- A single optimized short hairpin RNA (shRNA) to down-regulate the expression of the T cell receptor (TCR) CD3ζ-subunit, thereby limiting the TCR expression on the surface of the donor T-cells, preventing their allosreactivity with the normal host tissue cells and potential risk of life-threatening graft-versus-host disease (GVHD).
- A truncated human CD34 membrane protein as an identification and selection marker.

CYAD-211 is Celyad Oncology’s first allogeneic CAR T candidate using shRNA through an Allo-A-One vector approach.

PRECLINICAL RESULTS

The shRNA targeting CD3ζ incorporated in the CYAD-211 vector efficiently knockdowns cell surface TCR expression to undetectable levels in the final CAR T cell product (Figure 3A) concurrent with inhibiting functional T cell responses to TCR activating stimuli (Figure 3B).

Upon co-capital with the BOMX-expressing multiple myeloma cell lines RPMI-8228, OP-M2 and KMS-11, CYAD-211 cells produced high amounts of interferon-gamma (IFN-γ) and exhibited potent cytotoxic activity, in contrast to control cells produced from the same donors, bearing only the selectable marker or the selectable marker and the shRNA targeting CD3ζ without the BCMA-targeting CAR (Figure 4).

The anti-tumor efficacy of CYAD-211 was further confirmed in vivo in xenograft MM models using the KMS-11 (Figure 5A) and RPMI-8228 (data not shown) cell lines. Immunodeficient (NSG) mice injected with vehicle or control T-cells succumbed to tumor with a median survival of 35 and 43 days, respectively, while mice injected with CYAD-211 cells remained alive until the end of the trial, illustrating effective anti-tumor activity of CYAD-211 cells.

No demonstrable evidence of GVHD when CYAD-211 was infused in sublethally irradiated NSG mice, the gold standard preclinical model of GvHD. While mice injected with CYAD-211 cells did not show any evidence of weight loss, the first sign of GvHD in this animal model, and survived until the end of the experiment (day 69), mice injected with control T-cells generated from the same donor manifested weight loss as of Day 23 and median survival of 32 days (Figure 5B, 5C). These results demonstrate that CYAD-211 cells effectively protect against induction of GVHD.

IMMUNICY-1 STUDY

- The first-in-human study evaluating CYAD-211, the open-label Phase I IMMUNICY-1 study (NCT04613557), has been initiated and first patient to be enrolled in November 2020.
- Study design:
- Dose escalation segment with a 3×3 design evaluating three dose levels (DL) of CYAD-211: 3×10⁷, 1×10⁸ and 3×10⁸ to define the recommended dose; 6 patients will be enrolled in total at each DL.
- DLTs of CYAD-211 were selected based on previous studies with autologous anti-BCMA CAR T cell products and studies with gene-edited allogeneic CAR T cell products.
- Potential higher DLS of CYAD-211 might be evaluated if the maximum tolerated dose is not reached.
- Treatment schedule (Figure 2):
- Single infusion of the allogeneic CYAD-211 anti-BCMA CAR T cell product at Day 1 administered after a non-myeloablative preconditioning chemotherapy.
- Preconditioning chemotherapy consisting of 300 mg/m² cyclophosphamide and 30 mg/m² fludarabine daily for 3 days (CyFlu, at Days -5 to -3) aims to improve expansion of CYAD-211 cells and subsequently their persistence and clinical activity.
- Key inclusion criteria:
- At least 1 prior treatment regimen
- At least 1 response to a prior treatment regimen
- Potential disease that should include exposure to immunomodulatory drug (IMiD) and proteasome inhibitor (PI)
- Either alone or in combination
- CYAD-211 demonstrated robust anti-tumor activity in vitro and in vivo concurrent with lack of allosreactivity in preclinical models in vivo.

CONCLUSIONS

CYAD-211 is the first non-gene edited allogeneic CAR T cell product based on shRNA technology, incorporating a BCMA-targeting scFv and a shRNA targeting the CD3ζ subunit of TCR complex.

CYAD-211 demonstrated robust anti-tumor activity in vitro and in vivo concurrent with lack of allosreactivity in preclinical models.

The preclinical data supported the initiation of the first-in-human study (IMMUNICY-1) with CYAD-211 in October 2020.

The IMMUNICY-1 clinical study seeks to provide proof of principle that single shRNA-mediated knockdown can generate fully functional allogeneic CAR T cells in humans without GVHD-inducing potential.

We anticipate that subsequent generations of this technology will incorporate multiple single gene-shRNA treatments. Minimizing the enhancements required for the therapy within a single vector (All-In-One vector) provides significant manufacturing advantage, necessitating single transduction and single selection step.

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1. New York University Langone Health, New York, NY; 2. Antwerp University Hospital, Antwerp, Belgium; 3. H.Lee Moffitt Cancer Center, Tampa, FL; 4. AZ Delta, Roeselare Belgium; 5. Institut Jules Bordet (ULB), Brussels, Belgium; 6. Celyad Oncology, Mont-Saint-Guibert, Belgium

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