Sophisticated Flow Cytometry Assay Guides CAR T Dosing Strategy

SUMMARY

PPD Laboratories' biomarker lab developed a robust method to quantify CAR T cells that was used to determine the kinetics of CAR T cell therapy in a Phase I multiple myeloma trial.

OBJECTIVE

Our client needed a robust, accurate method to monitor the persistence of CAR T cells in a Phase I study that would test the safety and efficacy of its CAR T cell modality in relapsed/refractory multiple myeloma patients. The new method needed to achieve high levels of precision so it could be used to evaluate the persistence of CAR T cells to understand the adaptive T cell therapy. In addition, the samples needed to be analyzed in a laboratory with well-established quality control processes and quality assurance oversight.

Needed a sophisticated test to include an

ACCURATE, ABSOLUTE

Quantitation of the CAR T cells

BACKGROUND

The immune system is made up of several types of cells that work together to fight infections. Lymphocytes, divided into T cells and B cells, originate in the bone marrow and are the main cell type of the immune system. T lymphocytes migrate to the thymus to undergo their maturation and B lymphocytes mature in the bone marrow. When B lymphocytes respond to infection, they mature and transform to plasma cells. Plasma cells make the antibodies that help the body attack and kill foreign entities in the body. If plasma cells in the bone marrow become cancerous and grow out of control, they can produce a tumor in the bone called a plasmacytoma. If a person has more than one plasmacytoma, it is called multiple myeloma.

The most common multiple myeloma treatment typically has been chemotherapy, followed by a stem cell transplant. Since the disease is not curable and a patient may relapse, the goal of treatment is to create longer and extended spans of time during which the growth of cancerous cells does not progress.

Refractory myeloma is a condition in which the multiple myeloma is not responsive to therapy. This may occur in patients who never see a

Method to determine cellular kinetics for

Phase I study

response from their treatment therapies or in patients who have initially responded to treatment, but do not respond to treatment after a relapse.

Our client developed a new technology for the treatment of patients with relapsed/refractory multiple myeloma. A patient's white blood cells are harvested and certain T lymphocyte cells are extracted and activated to grow in the laboratory. Gene sequences for chimeric antigen receptors (CARs) are constructed to target a protein on the myeloma cell surface called a B-cell maturation antigen (BCMA) and are transferred into the patient's extracted T cell DNA using a lentiviral vector. The genetically engineered CAR T cells are designed to specifically target the cancerous plasma cells, utilizing the patient's own immune system to destroy the tumor.

The cell line is then expanded by cell culture in the laboratory. These genetically engineered cells express the receptors that can recognize the extracted proteins that are characteristic of the patient's multiple myeloma. Once the cell line has reached the target volume, the cells are re-infused into the patient.

STRATEGY

Our client developed a preliminary test to determine the presence of the CAR T cells by an isolated staining technique, but a simple test to include an accurate, absolute quantitation of the CAR T cells was needed to monitor the CAR T cells in the Phase I study.

PPD Laboratories' scientists utilized a single bead-enhanced cytofluorimetry (SBEC) assay to measure the CAR T cells.

By adding a known quantity of polystyrene fluorescence standardization beads to the cell suspension to serve as an internal control, the engineered cells could be accurately quantified. In addition, through well-controlled verification and validation studies, the assay was found to be repeatable and was deemed a suitable method.

RESULTS

Our scientists successfully adapted an established flow cytometry method to provide an accurate, absolute quantitation of the engineered CAR T cells for evaluating the persistence of CAR T cells. The assay was quickly validated as a fit-for-purpose lab developed test (LDT).

The PPD Laboratories biomarker lab has developed a partnership with this client that extends to other projects and various biomarker analytical technologies. Working closely with clients, PPD Laboratories provides trusted services and processes to maximize efficiencies for selecting the right approach to deliver the best solution for employing biomarkers during clinical trials across a wide range of therapeutic areas.

PPD Laboratories partners with clients to deliver the best biomarker solutions for their clinical trials