RACING TOWARD A CURE FOR BLOOD CANCERS WITH NEW CARS (CAR-T CELL THERAPY)

Larry D. Anderson, Jr, MD, PhD

Internal Medicine Grand Rounds
University of Texas Southwestern Medical Center

March 9, 2018

This is to acknowledge that Dr. Anderson has disclosed a financial interest or other relationships with commercial concerns related directly or indirectly to this program. Dr. Anderson will be discussing “off-label” uses in his presentation.

Larry D. Anderson, Jr, MD, PhD
Associate Professor of Internal Medicine
Division of Hematology/Oncology
Director, Myeloma, Waldenstrom's, and Amyloidosis Program
Member, Hematologic Malignancies and Bone Marrow Transplant Program

Interests:
Multiple Myeloma
Waldenstrom's Macroglobulinemia
Amyloidosis
Cancer Immunotherapy
CAR-T Cell Therapy
Cancer Vaccines
Targets for T cell therapy of myeloma
Bone Marrow (Stem Cell) Transplantation

Purpose and Overview:
The goal of this discussion is to review the use of Chimeric Antigen Receptor (CAR) T-Cell Therapy in Hematologic Malignancies

Objectives:
At the conclusion of this lecture, the listener should be able to:
1). Describe the basic principles of how CAR T-Cell therapy is used to target cancer.
2). Identify 2 diseases that can be treated by FDA approved versions of CAR T-Cell Therapy.
3). Understand the toxicities and limitations of CAR T-Cell therapy
3). Review emerging data regarding the use of CAR T-Cell therapy in Multiple Myeloma.

INTRODUCTION

Cellular immunotherapy for hematologic malignancies is now being dominated by new techniques for adoptive transfer of genetically engineered T-cells expressing chimeric antigen receptors (CARs). CAR T-cells consist of a single chain variable fragment (scFv) of a monoclonal antibody, a spacer domain, a transmembrane domain, an intracellular signaling domain, and additional costimulatory domains to give the 2nd signal needed for T-cell function without relying on the cancer cell to provide it. Most of the clinical data available is regarding CD19-directed CAR T-cells for the treatment of B-cell acute lymphoblastic leukemia (B-ALL), chronic lymphocytic leukemia, and B-cell non-Hodgkin lymphoma. However, early data also looks very promising for Multiple Myeloma by targeting the plasma cell specific target antigen B Cell Maturation Antigen (BCMA). Results so far have been promising with impressive rates and depth of remissions not seen with any other therapy in highly chemo-refractory patients. However, CAR T-cell therapy is a complex multi-step process, and clinical trials so far differ in CAR construct used, composition of the cellular product, and CAR T-cell dose used. Randomized trials will be needed to conclusively evaluate the implications of these differences. CAR T-cell therapy is associated with significant neurotoxicity and potentially lethal cytokine release syndrome (CRS), both of which require specific management and often require ICU care. Improvements in CAR design may help to overcome toxicity, the effects of an immunosuppressive microenvironment, and antigen escape. This paper will explain the mechanism of action, summarize the clinical experience with this treatment modality so far, and explore future developments in the field.

TYPES OF IMMUNOTHERAPY

The main 4 subtypes of cancer immunotherapy include the following: 1). Monoclonal antibodies, 2). Checkpoint inhibitors, 3). Cancer vaccines, and 4). Adoptive cell transfer. Monoclonal antibodies were the first FDA approved immunotherapy for

cancer in 1997 with the approval of Rituximab, an anti-CD20 monoclonal antibody now used in most forms of B cell Lymphoma. Checkpoint inhibitors release the breaks on costimulation of T-cells by blocking either PD-1 (Pembrolizumab, Nivolumab) or CTLA4 (Ipilimumab).[1] Two of these therapies are approved for relapsed classic Hodgkin Lymphoma and are under investigation in many other hematologic malignancies. Cancer vaccines remain an area of active investigation but are limited by tumor induced immune dysregulation of the endogenous T-cells able to reach the tumor. Adoptive cell therapy has also been an area of investigation for many decades but did not have much success until the advent of molecular engineering of T-cell receptors. One form of genetically modified T-cell receptor therapy uses a gene encoding a T-cell receptor known to target a specific antigen. However, this is limited by the need for certain MHC expression and presentation of antigen in the cancer cells as well as requiring costimulation by the tumor cells. However, these obstacles are largely overcome by the more recent advent of Chimeric Antigen Receptor (CAR) T-cell therapy using a hybrid receptor with the extracellular domains of a single chain monoclonal antibody linked to T-cell signaling and costimulatory signaling built in to the same molecule. CAR T-cells are essentially a way of hijacking the immune system and forcing the T-cells to recognize and kill cancer cells.

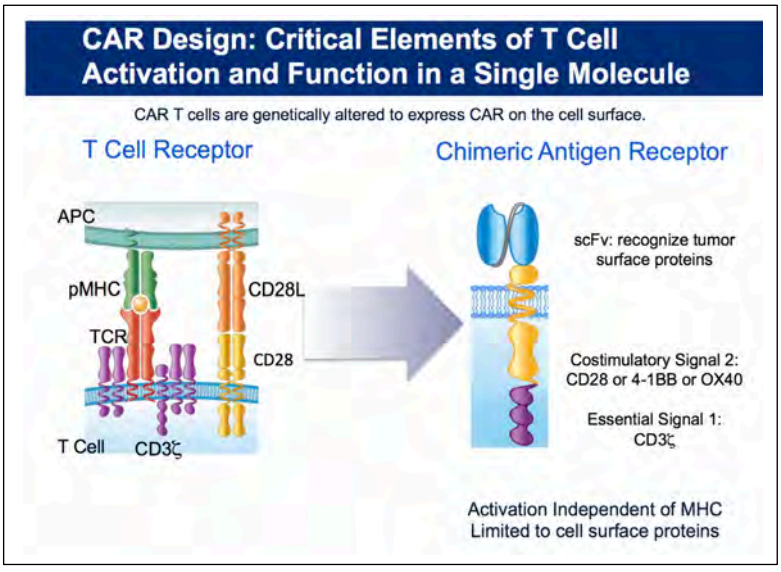

Figure 1: Native TCR vs CAR-T Receptor

CAR T-CELL THERAPY

Chimeric Antigen Receptor (CAR) T-Cell therapy is derived from the monster from Greek mythology the Chimera with the head of a lion and body of a monster. This is because the CAR receptor is half antibody and half T-cell receptor. The antigen being recognize depends on the CAR construct but so far the main 2 targets are CD19 (which is widely expressed in all B-cell malignancies other than Myeloma) and B Cell Maturation Antigen (BCMA, with expression limited to plasma cell and Myeloma).[2]

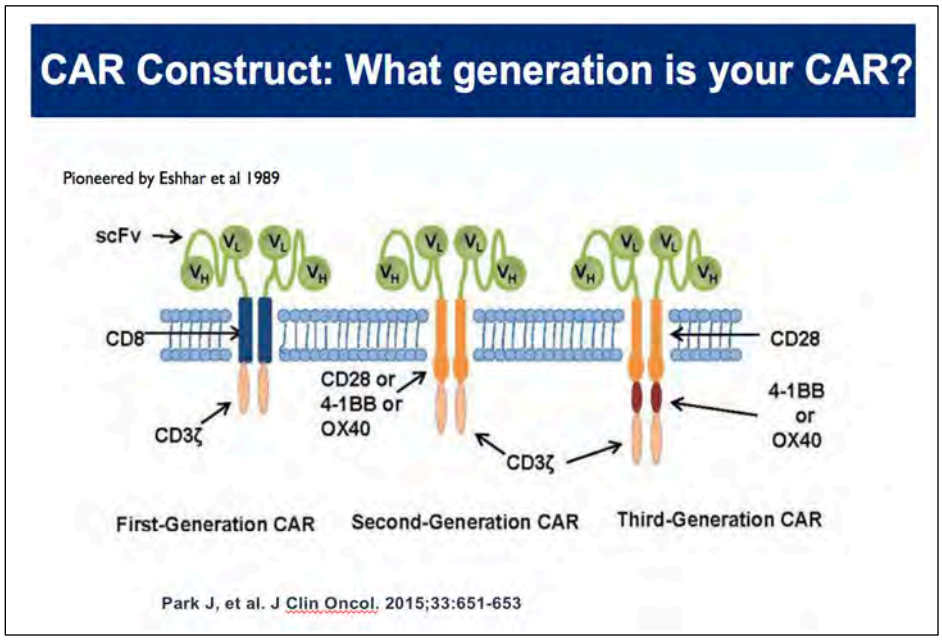

Figure 2: Three generations of CAR-T cells[3]

Most of the clinical data available is regarding CD19-directed CAR T-cells for the treatment of B-cell acute lymphoblastic leukemia (B-ALL), chronic lymphocytic leukemia, and B-cell non-Hodgkin lymphoma.[4,5,6,7] However, early data also looks very promising for Multiple Myeloma by targeting the plasma cell specific target antigen B Cell Maturation Antigen (BCMA).[8.] BCMA is an attractive target for Myeloma since it is not expressed by normal cells other than plasma cells. It is also almost universally expressed by Myeloma cells.

Figure 3. Chimera

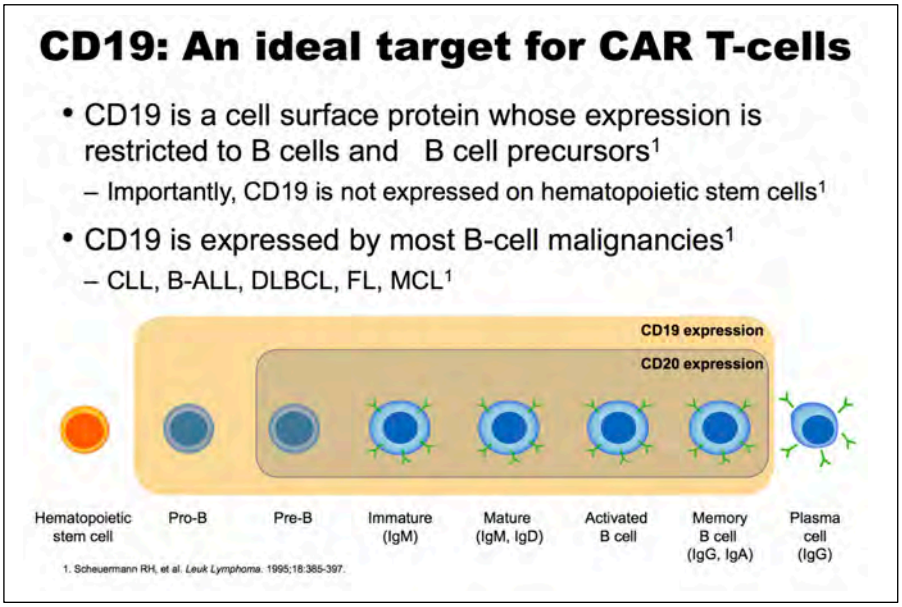

Figure 4: CD19 as a Target for CAR-T Therapy[9]

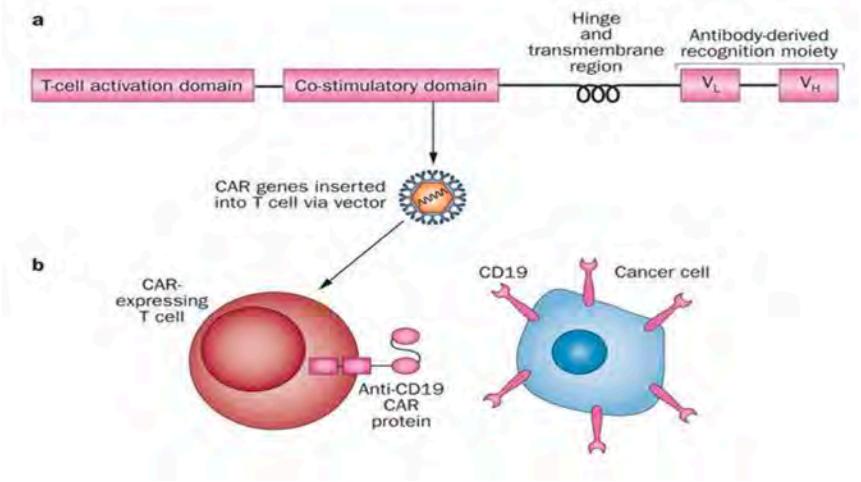

Figure 5: Viral transduction of CAR-T-Cells with anti-CD19 vector[10]

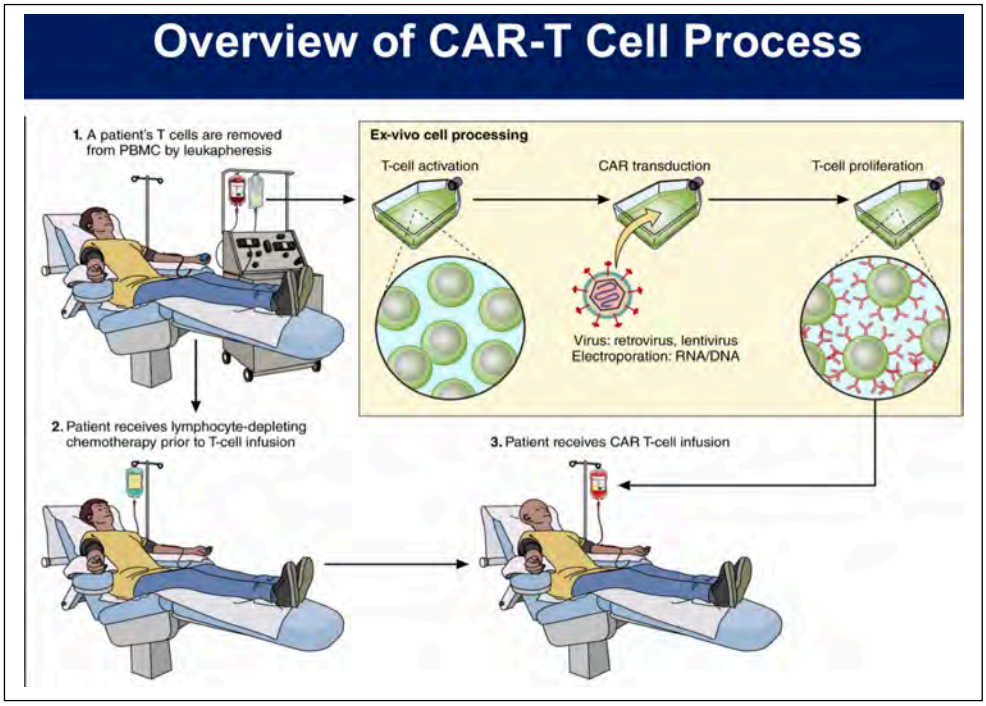

Figure 6: Overview of CAR-T Cell Process

CAR-T Therapy for Acute Lymphoblastic Leukemia:

Anti-CD19 chimeric antigen receptor (CAR) T-cells are the first FDA-approved cellular immunotherapy, and they have the potential to revolutionize the treatment of hematologic malignancies. The majority of patients initially respond to treatment, but much remains to be determined about numerous aspects of this therapy, including the durability of responses and the ability to produce and deliver complex cellular therapies across different geographical locations. Now, two forms of anti-CD19 CAR T-Cell therapy have been FDA approved, one made by Novartis (Tisagenlecleucel) that is approved for treatment of pediatric Acute Lymphoblastic Leukemia (ALL) through age 25. The other is made by Kite Pharma (Axicabtagene ciloleucel) that is approved for treatment of Diffuse Large B Cell Non-Hodgkin Lymphoma after 2 prior lines of therapy. These were approved based on Phase II data presented in several studies published in the *New England Journal of Medicine* provide further insight into the use of CAR T-cells.[4,5,6.] In the ALL trial Complete remission was observed in 83% of patients with a

median event-free survival (EFS) of 6.1 months and median overall survival (OS) of 12.9 months. Grade ≥3 adverse events included neurotoxicities in 42% of patients, and cytokine-release syndrome (CRS) in 26%, including one death.

Investigators reported a correlation between a low pretreatment disease burden (defined as <5% bone marrow blasts) and longer disease remission in ALL: median EFS was 10.6 months, with a median OS of 20.1 months in these patients compared with 5.3 months and 12.4 months, respectively, in patients with a high pretreatment disease burden (≥5% bone marrow blasts and/or extramedullary disease). Investigators noted that the extent of *in vivo* peak CAR T cell expansion was the best predictor of both short-term responsiveness and acute toxicities.

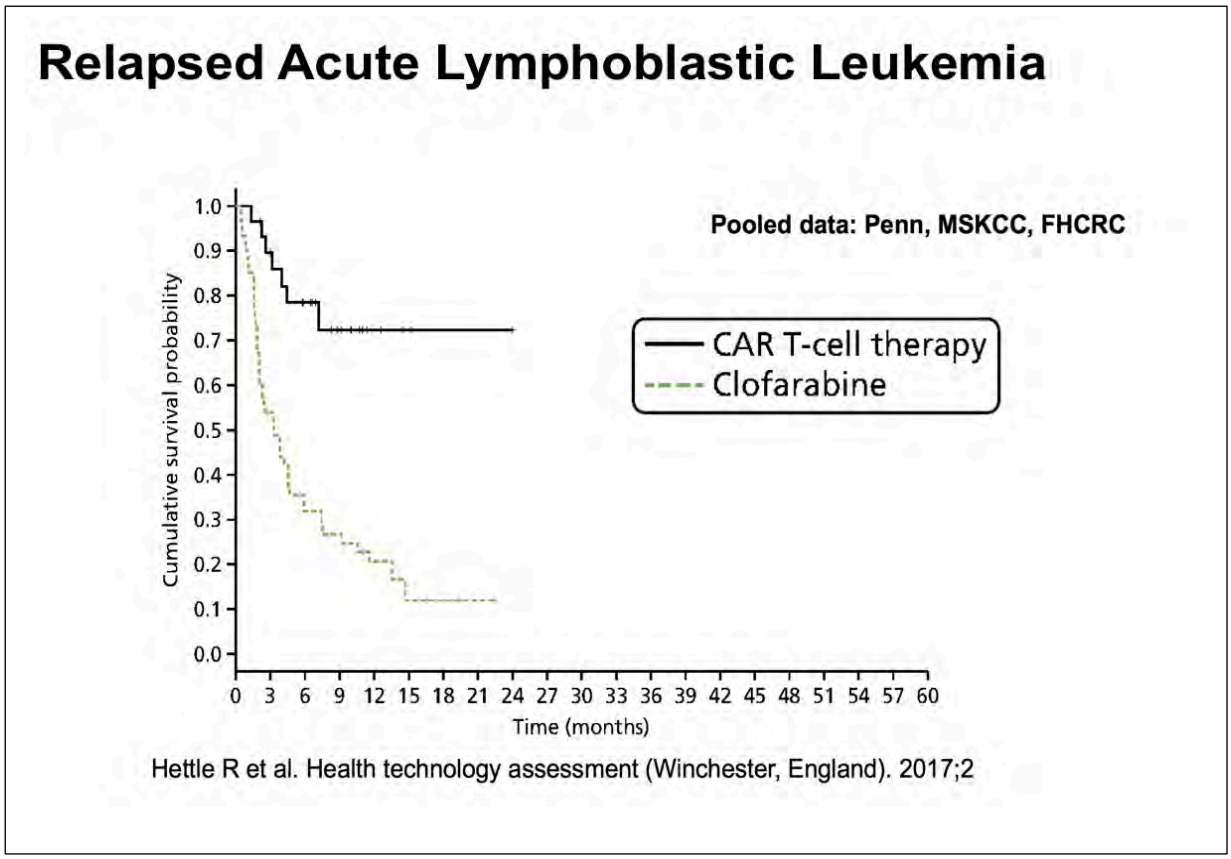

Figure 7: Overall Survival after CAR-T for ALL compared to historic control on a trial of Clofarabine

Analysis of the ongoing global phase I–II ELIANA trial, including data from 75 children or young adults (aged ≤25 years) with relapsed and/or refractory B-cell ALL showed that 81% of patients were in remission, with EFS and OS of 50% and 76% reported after 12 months of follow-up monitoring; 88% of patients had at least one grade 3–4 adverse event, with 37% of patients receiving tocilizumab for severe CRS and 13% having grade ≥3 neurotoxicities. Other notable aspects of this trial included the delivery of tisagenlecleucel to other centres in North America, Europe, Asia and Australia. Furthermore, investigators at several centres were able to deliver tisagenleclueucel infusions as an outpatient treatment. The findings of the ELIANA trial reveal both more sustained responses and a higher risk of adverse events. These differences in outcome might reflect differences in CAR design (tisagenlecleucel contains a 4-1BB domain, as opposed to a CD28 domain), and/or differences in the study population with adults, and in particular older adults, with B-ALL typically having inferior outcomes to those of children.

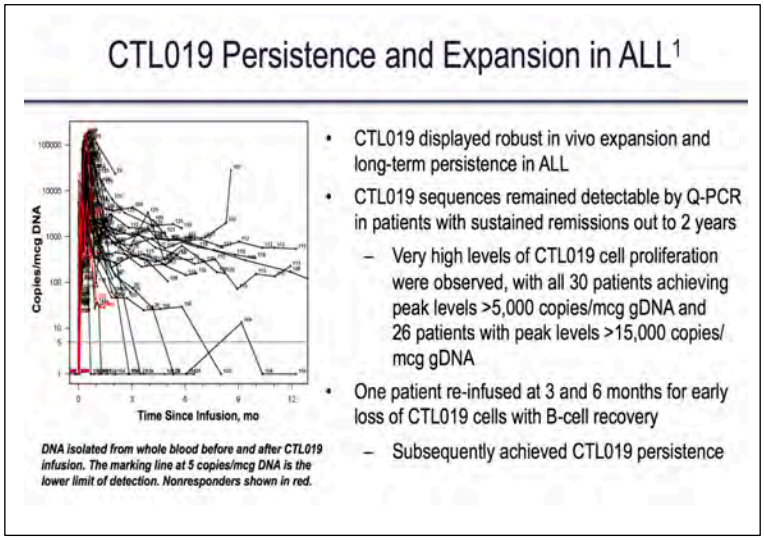

Figure 8: Persistence of CAR-T Cells in patients is important for sustained remissions[4]

CAR-T Therapy for Diffuse Large B Cell Non Hodgkin Lymphoma:

After approval for ALL, CAR-T-Cell therapy (Axicabtagene ciloleucel) has been FDA approved in 10/2017 for use in patients with Diffuse Large B-Cell Lymphoma or

primary mediastinal lymphoma or transformed follicular lymphoma after failure of at least 2 prior lines of therapy. Impressive response rates of 83% overall with 54% complete responses were seen in this heavily refractory population with traditionally a dismal prognosis in the Zuma 1 study.[6]

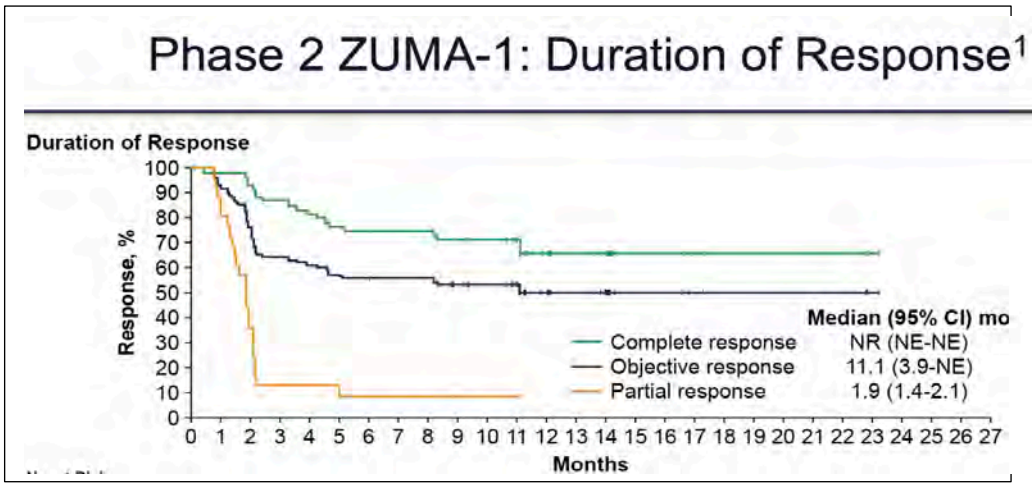

Figure 9. Duration of Response in DLBCL

Toxicity of CAR T-Cell Therapy

The main 2 side effects of CAR T-cell therapy are Cytokine Release Syndrome (CRS) and Cytokine Related Encephalopathy Syndrome (CRES). These are treated by symptom management for low grade symptoms, Tocilizumab monoclonal anti-IL6 therapy for moderate to several reactions, and steroids for severe reactions. CRS is a constellation of symptoms that occur when T cells engage and begin to proliferate in the body and lead to a general inflammatory response (IL-6 production). It is the main complication requiring hospitalization after CAR T-cell therapy. CRS and CRES are graded and treated in a stepwise fashion as in Figure 10 and 11.

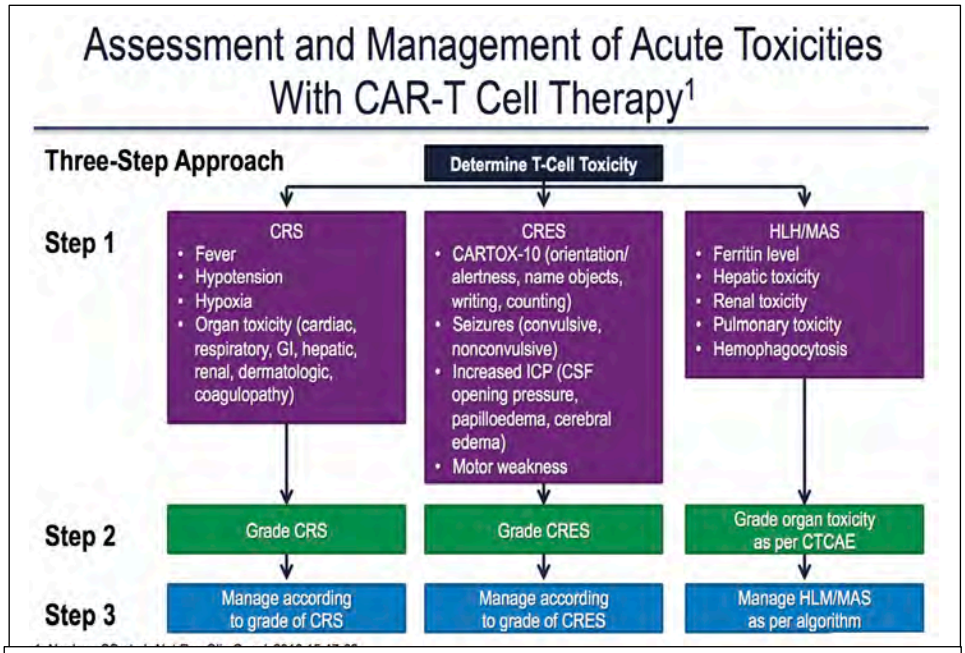

Figure 10. Grading of CRS/CRES[11]

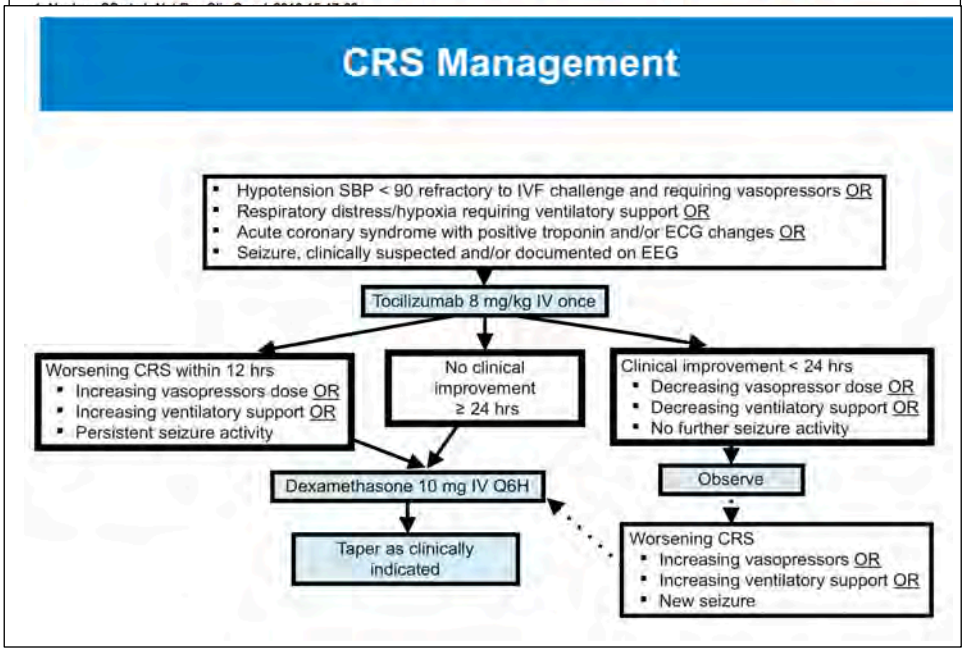

Figure 11. Treatment Algorithm for CRS

Neurotoxicity Symptoms and Signs:

Encephalopathy, somnolence, global aphasia, seizures, confusion, delirium, tremors, paralysis of limbs, incontinence. Onset of neurotoxicity may be biphasic: 1st phase (Days 0-5) – symptoms may appear with other CRS. 2nd phase (After day 5) – starts after CRS s/s have subsided. Neurotoxicity such as seizures may occur later even in 3rd or 4th week. Neurotoxicity typically lasts 2-4 days, but may vary in duration

from hours to few weeks. Its generally reversible. Corticosteroids treatment of choice in managing neurotoxicity. Tocilizumab might reverse neurological toxicity during 1st phase. Seizure prophylaxis is recommended with Keppra from Day 0-30 per protocol.

Anti-BCMA CAR-T-Cell Therapy for Multiple Myeloma:

4 Phase 1 studies have been presented:[12,13,14] NIH, U Penn, Chinese, and BlueBird Bio. LBA3001, the Chinese anti-BCMA CAR-T trial was presented at ASCO 2017 by Fan et al. They reported a 100% ORR, 33 out of 35 patients were in remission at 2 mo. The U Penn trial also reported promising results by Cohen et al at ASH 2016 with high ORR. Six out of 9 responded in U Penn in the active dose cohort. It is noted that patient #1 is now in sustained complete remission at 27 months out from the CAR-T infusion and had failed 12 lines of therapy prior to enrollment.

The NIH CART-BCMA, trial by Ali et al should that 3 out of 6 at higher dose levels had either VGPR or CR. Berdeja et al presented updated BlueBird Bio (Celgene) BB2121 results at ASH 2017 showing a 94% ORR, and a very impressive 56% CR in this heavily refractory Myeloma population. Of those evaluable, 90% achieved a molecular remission (Negative for Minimal Residual Disease)

Based on the phase 1 data, the BB2121 anti-BCMA CAR T-Cell therapy product is now under the FDA Breakthrough designation since 11/17/2017, and a Phase II KarMMa trial is underway to try to get this product FDA approved for Myeloma. UT Southwestern is one of 9 US sites and the only location in Texas invited to participate in this phase II study. However, it was also noted that 1 out of 15 patients in the Phase 1 study developed cerebral edema and subarachnoid hemorrhage. Therefore, the trial is now requiring a 2 week hospital stay for all patients on the Phase 2 study after CAR-T-BCMA infusion. The patients will also have to live within 30 minutes of the center for the next 2 weeks after discharge as well.

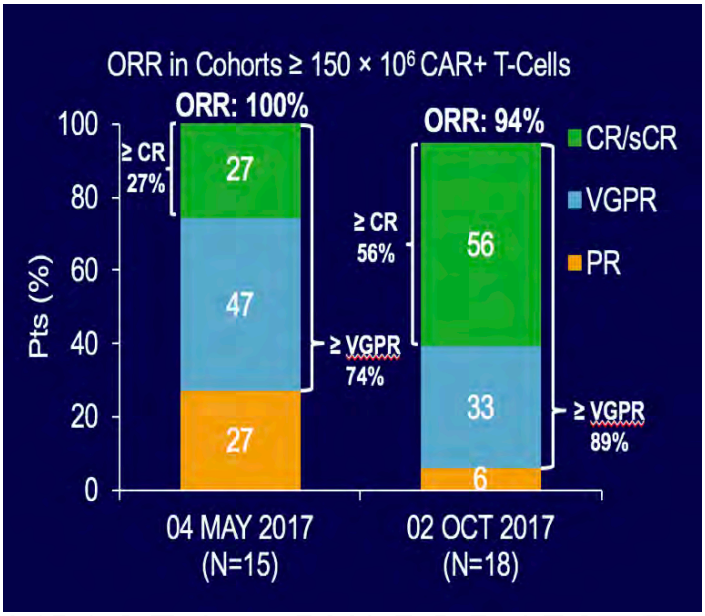

Figure 12. BlueBird Bio Phase 1 CAR-T-BCMA Responses at ASCO 2017 vs ASH 2017

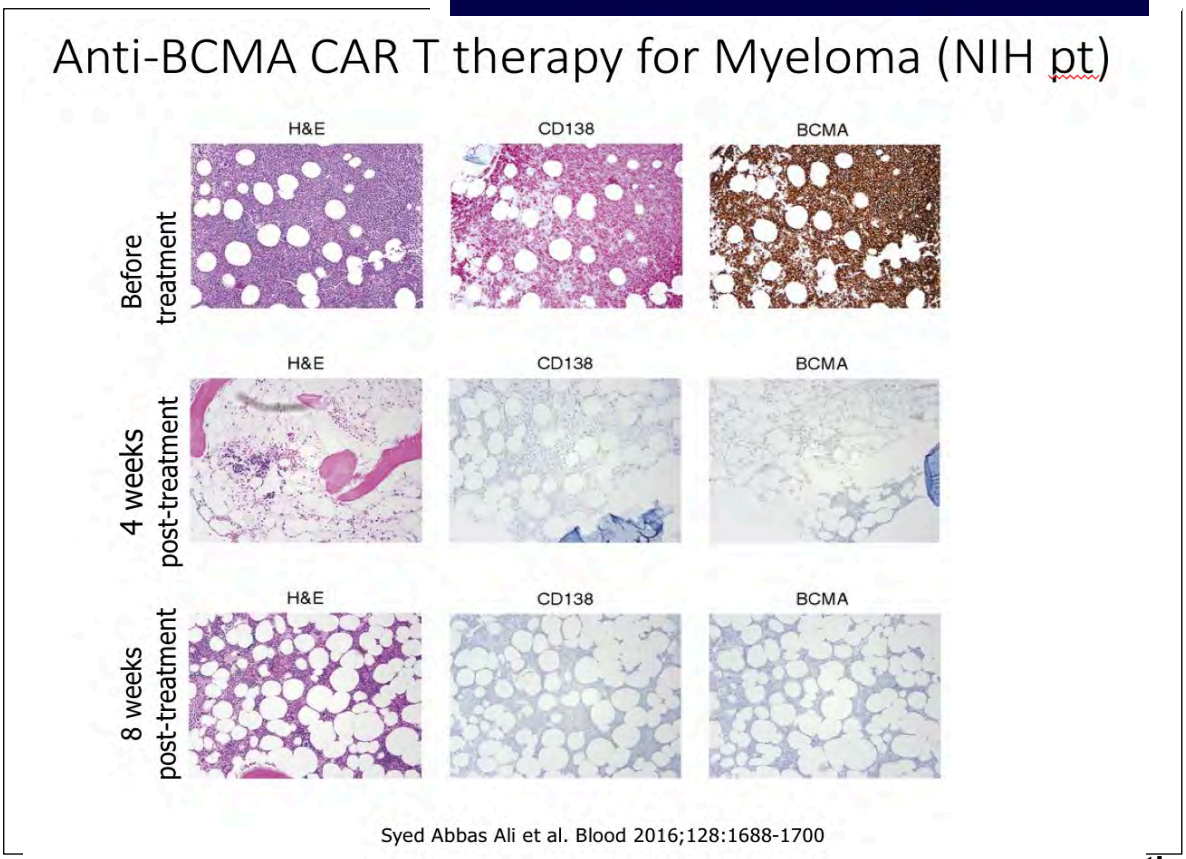

Figure 13. Bone Marrow Response of NIH patient on Phase 1 study of anti-BCMA CAR-T Therapy showing complete eradication of Myeloma.

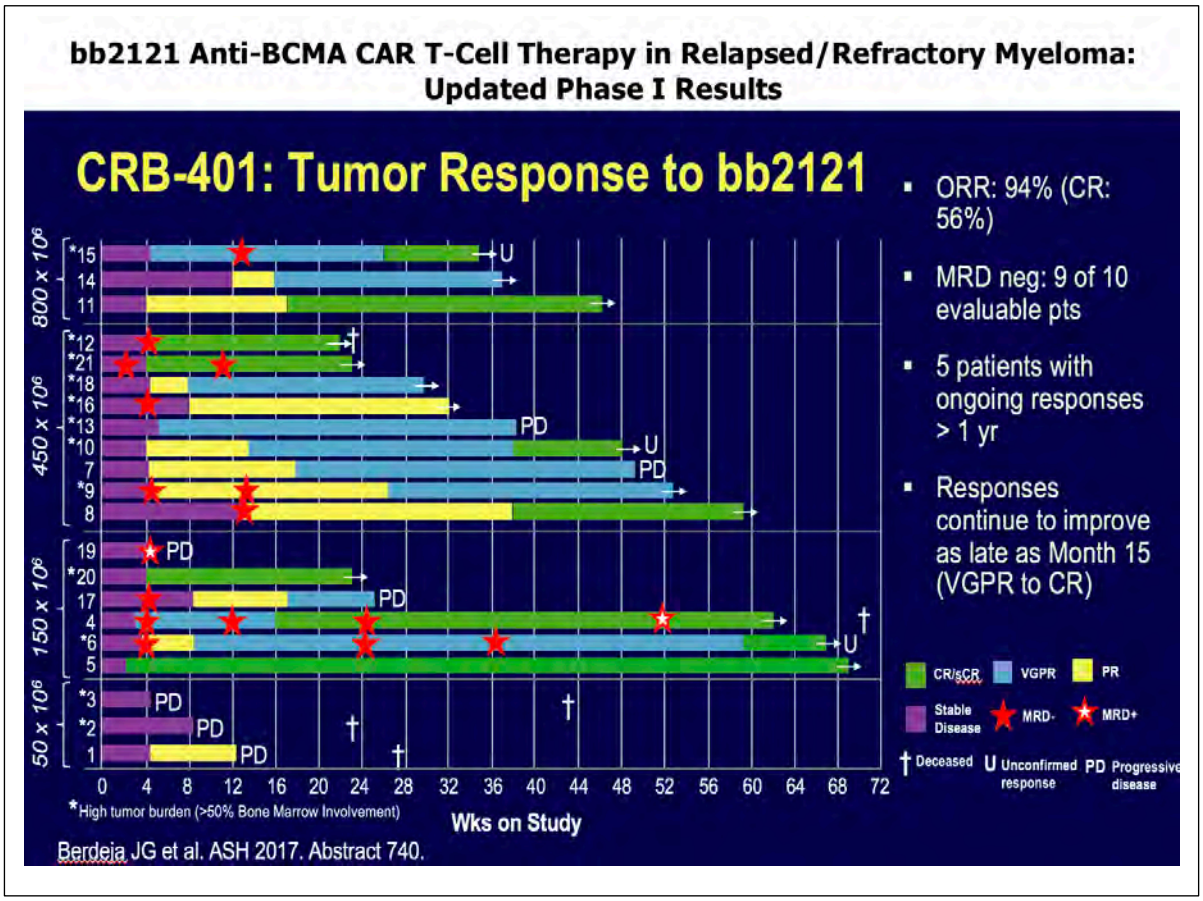

Figure 14. Phase 1 CAR-T-BCMA Responses at ASH 2017 by Swimmer's Plot

CONCLUSIONS AND FUTURE DIRECTIONS

This is a new Era of exciting treatment options for Hematologic Malignancies. Some diseases that never had an option for a cure may now have that option (Myeloma, FL, Chemo-refractory ALL/DLBCL)

Antigen Escape remains an issue. One way to overcome this may be to infuse 2 different CAR T-cell products (CD19 and CD22, etc). Another way could be combining 2 specificities in the same "tandem" CAR molecule to force the T-cells to recognize 2 different targets from the same CAR.[15]

Another potential pitfall is CAR T-cells is lack of persistence due to clonal exhaustion or anergy. One way to counteract this would be to re-infuse more CAR T-Cells. A better way may be to isolate central memory CAR T-cells that have self-renewal capacity to persist indefinitely in the patient.[16] Even if the CAR T-cells persist they may lack efficacy due to lack of cytokine stimulation. One way to overcome this would be to engineer TRUCKs (T cells redirected for universal cytokine-mediated killing) which secrete IL-12 and support killer functions of the T-cells.[15]

One criticism of CAR T-cell therapy is the very high price tag. However, when one considers the many years of constant expensive therapy that one normally receives for Multiple Myeloma the one time large price tag may actually be an overall savings. Furthermore, others are working on "off the shelf" versions of CAR T-cells that can be universal donor T-cells that are MHC matched with the patient and therefore not rejected. This would save on time and effort and expense of personalized production of T-cells for each patient and could potentially drive down the cost of the procedure.

Another exciting area that CAR T-cell therapy is going is treatment of solid tumors. There are early phase trials underway in a variety of solid tumors.

In summary, CAR T-Cell is now an FDA approved option for therapy of relapsed Acute Lymphoblastic Leukemia and relapsed Diffuse Large B Cell Lymphoma. We have also seen exciting results in other tumors such as Myeloma and predict adoptive cellular immunotherapy will continue to change the standard of care for therapy of hematologic malignancies.

REFERENCES:

1) Mehta-Shah N, et al, Management of relapsed/refractory classical Hodgkin Lymphoma in transplant-ineligible patients. *Blood* 2018
2) Ali SA, et al, T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma. *Blood* 2016
3) Park et al, Are all chimeric antigen receptors created equal? *Journal of Clinical Oncology* 2015

4) Maude, S. L. *et al*. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N. Engl. J. Med.* **378**, 439–448 (2018)
5) Park, J. H. *et al*. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *N. Engl. J. Med.* **378**, 449–459 (2018)
6) Neelapu SS et al, Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lyumphoma. *N Engl J Med.* 2017
7) Schuster SJ et al, Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. *N Engl J. Med*. 2017.
8) Ali SA et al, T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma. *Blood* 2016
9) Scheuerman RH et al. CD19 antigen in leukemia and lymphoma diagnosis and immunotherapy. *Leukemia Lymphoma* 1995.
10) Kochenderfer JN et al, Treating B-cell cancer with T cells expressing anti-CD19 chimeric antigen receptors. *Nat Rev Clin Oncol* 2013
11) Neelapu SS et al, Toxicity management after chimeric antigen receptor T cell therapy: one size does not fit all. *Nat Rev Clin Oncol.* 2018
12) Fan et al, LBA3001 Results of CAR-T-BCMA in Myeloma, *JCO* 2017
13) Cohen et al, CAR T-Cell Therapy for Myeloma using BCMA at U Penn, *Blood* 2016
14) Berdeja et al, Updated on BB2121 therapy of Myeloma, *Blood* 2017
15) Hartmann J et al, Clinical development of CAR T cells – challenges and opportunities in translating innovative treatment concepts. *EMBO Mol Med* 2017
16) Wang X et al, Phase 1 studies of central memory-derived CD19 CAR T-cell therapy following autologous HSCT in patients with B-cell NHL. *Blood* 2016