Multiple Myeloma **NEWS**

NORTHSIDE HOSPITAL CANCER INSTITUTE
IMMUNOTHERAPY PROGRAM

SPRING 2019 ISSUE

Multiple Myeloma and B-cell Maturation Antigen (BCMA): Different Routes to Attack a New Target

Over the last two decades, outcomes of multiple myeloma (MM) patients have shown remarkable improvement due to incorporation of therapies such as immunomodulatory drugs (IMiDS), proteasome inhibitors and monoclonal antibodies (Daratumumab and Elotuzumab). Despite recent treatment advances for MM, most patients are expected to relapse, as the disease is still considered incurable. The outcome of patients failing the above-mentioned drugs remains extremely poor, with an estimated survival of less than one year. It is therefore clear that further treatment approaches are needed for relapsed refractory MM.

Advances against MM have come at an especially rapid pace, with six new drugs approved in the last six years. However, the arrival of a new generation of immunotherapies is accelerating progress even more. Today, a range of immune-based treatments have been designed that marshal the immune system to attack cancer. The immune-based treatments are now available to patients with relapsed/refractory myeloma on clinical trials. Although there are a number of possible myeloma antigens that may serve as targets for immunotherapies, BCMA has become the leading candidate for many upcoming clinical trials.

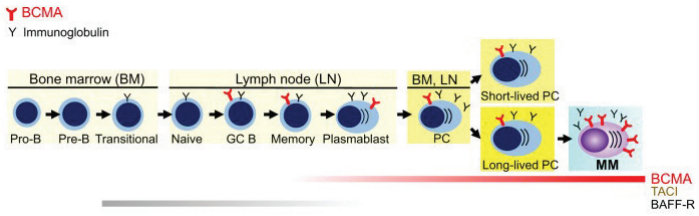
Rationale for Targeting BCMA in MM

BCMA is a type III transmembrane that belongs to the tumor necrosis factor receptor (TNFR) superfamily. It critically regulates B-cell proliferation and survival, as well as maturation and differentiation into plasma cells. BCMA is induced on late memory B-cells and is present on all plasma cells, which makes it an ideal target for therapeutic modalities aimed at treating plasma cell malignancies. Studies from BCMA-knockdown mice further indicate that BCMA is most important for long-lived PC survival but is dispensable for overall B-cell homeostasis. BCMA mRNA and protein are more highly expressed on malignant than normal plasma cells. Furthermore, soluble BCMA levels are increased in MM patients and is correlated with disease status and prognosis. BCMA and its ligands are integral for growth and survival of malignant plasma cells in MM supporting the notion of targeting BCMA as a novel MM therapy.

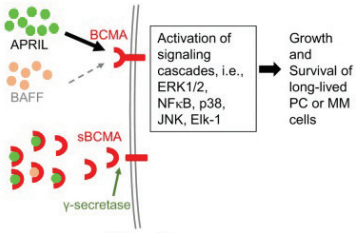
Several approaches to target BCMA have now been developed for potential clinical use. A number of studies that utilize many of these approaches are now available at Northside Hospital Cancer Institute (NHCI).

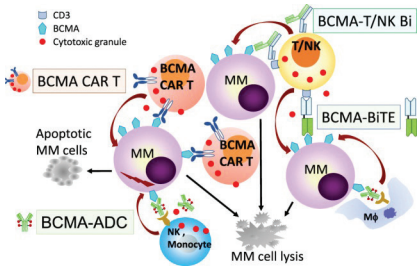
Multiple Myeloma Clinical Studies at NHCI and the Blood and Marrow Transplant and Cellular Immunotherapy Program at Northside

Antibody-Drug Conjugate against BCMA[1]



GSK2857916 is a humanized and IgG1 monoclonal antibody with high affinity to BCMA, which uses non cleavable linker, maleimido-caproyl (mc) and antimitotic agent monomethylauristatin F, as a payload.





The DREAMM2 study is a phase II, open-label, randomized, two-arm study to investigate the efficacy and safety of two doses of the antibody drug-conjugate GSK2857916 in participants with multiple myeloma who had three or more prior lines of treatment, are refractory to a proteasome inhibitor and an immunomodulatory agent and have failed an anti-CD38 antibody **(clinicaltrials.gov/NCT03525678)**.

(continued on next page)

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Multiple Myeloma Clinical Studies *(continued)*

Bispecific T-cell Engager, clinicaltrials.gov/NCT03269136

PF-06863135, is a bispecific T-cell engager consisting of a heterodimeric full-length bispecific antibody comprised of one BCMA biding arm and one CD3 binding arm paired through hinge maturation technology.

CAR T-cell Therapy Against BCMA, clinical trials.gov/NCT03651128

Adoptive transfer of genetically modified T-cells to recognize tumor antigens has been proven to be a very effective modality in treating non-Hodgkin lymphomas and acute lymphoblastic leukemia. By using similar techniques of gene modifications, CAR T-cells can be manufactured to target BCMA with multiple ongoing anti-BCMA CAR T-cell therapies showing impressive clinical activity. **BB2121, a BCMA targeted CAR T-cell**, is being evaluated in the KarMMa-3 trial: A Phase 3, Multicenter, Randomized, Open-label Study to Compare the Efficacy and Safety of bb2121 Versus Standard Triplet Regimens in Subjects with Relapsed and Refractory Multiple Myeloma (RRMM) (KarMMa-3).

Additional details regarding each of these studies will be forthcoming. In the meanwhile, to refer relapsed and refractory patients with MM who may be potential candidates for these trials, please contact Dr. Solh at 404-255-1930 or Stacey Brown, NHCI/Leukemia Clinical Research Manager, at 404-780-7965 or stacey.brown@northside.com.

[1]Cho S, Anderson K, Tai Y. Targeting B-cell Maturation Antigen (BCMA) in Multiple Myeloma: potential uses of BCMA-based Immunotherapy. *Front Immunol.* 2018;9:182.

BMTGA Physicians

(L-R) Drs. H. Kent Holland, Asad Bashey, Melhem Solh, Scott Solomon and Lawrence Morris

To make a Multiple Myeloma referral, or to speak with a physician, please call (404)-255-1930.

Website info: **Northside.com/immunotherapy** and **bmtga.com/immunotherapy-program-at-northside**