



INTERNATIONAL  
**MYELOMA**  
FOUNDATION

## The Potential of CAR-T Therapy and the Myeloma Patient Journey

**Discussion with IMF Nurse  
Leadership Board**

**September 28, 2018  
Las Vegas, Nevada**

IMF



**NURSE**  
LEADERSHIP BOARD



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## Overview

On September 28, 2018, 8 members of the International Myeloma Foundation (IMF) Nurse Leadership Board convened in Las Vegas, Nevada for their annual meeting, in concurrence with the American Society of Hematology's (ASH) Annual Meeting, to discuss the potential of anti-B Cell Maturation Antigen (BCMA) in the Relapsed/Refractory Multiple Myeloma (RRMM) patient-treatment journey.

The objectives of the discussion were to:

1. Obtain insights on key clinical data with anti-BCMA Chimeric antigen receptor T-cell (CAR T-cell) therapy, bb2121
2. Understand the patient-treatment journey and unmet needs for patients with RRMM
3. Gain insights into the management of patients on CAR T-cell therapy in the short-term and long-term, including the educational needs for oncology nurses, support, and resources based on their CAR T-cell experience in both the clinical trial setting and commercial setting with approved CAR T-cell therapies

## Introduction

Multiple myeloma (MM) is a relatively rare cancer affecting plasma cells in the bone marrow.<sup>1</sup> The abnormal growth of plasma cells can lead to low blood counts, bone and calcium complications, renal failure, and

various other immune system dysfunctions.<sup>1,2</sup>

Globally, between 1990 and 2016, MM incidence and death rates increased by 126% and 94%, respectively.<sup>3</sup> In 2016, there were 138,509 reported cases of MM and 98,437 deaths. The regions with the highest increases of MM cases were Australia, North America, and Western Europe. In the United States in 2018, incidence and death rates for MM are expected to increase by 14.6% and 13.6% respectively, compared to 2015 rates.<sup>4</sup> Approximately 30,770 new patients will be diagnosed and 12,770 patients will die from the disease (Figure 1). In addition, more men are diagnosed and die from MM than women.<sup>4</sup>

Due to advancements in diagnosis, treatment, and management of MM made in the past decade<sup>5</sup>, 50% of patients live at least five years after diagnosis.<sup>6</sup> While the disease remains incurable, novel immunotherapy approaches using genetically-engineered T-cells may be a promising treatment option for patients with RRMM.<sup>7,8</sup>

Chimeric antigen receptor T-cell (CAR T-cell) therapies use gene transfer technology to engineer T lymphocytes with synthetic receptors designed to target cancer cells independent of major histocompatibility complex molecules.<sup>9</sup> In the past year, the Food and Drug Administration (FDA) approved two CAR T-cell therapies for patients with leukemia and lymphoma. Kymriah (Tisagenlecleucel) is now FDA-

approved to treat children and adults with B-cell acute lymphoblastic leukemia and adults with B-cell non-Hodgkin lymphoma.<sup>10</sup> Yescarta (Axicabtagene Ciloleucel) is now FDA- approved to treat adults with B-cell non-Hodgkin lymphoma.<sup>11</sup>

Another CAR T-cell therapy currently undergoing study is bb2121, which targets B cell maturation antigen (BCMA) to redirect T cells to identify and eliminate myeloma cells.<sup>8</sup> Forty-three patients with RRMM are enrolled in the non-randomized, open label, multi-site phase 1 study of bb2121 (NCT02658929).<sup>8,12</sup> As of March 29, 2018, 21 patients were enrolled in the dose escalation cohort (dose levels  $50 \times 10^6$ ,  $150 \times 10^6$ ,  $450 \times 10^6$  and  $800 \times 10^6$  CAR T-cells) and 22 patients in the dose expansion cohort (dose range  $150$ - $450 \times 10^6$  CAR T-cells). Patients received lymphodepleting regimen of fludarabine and cyclophosphamide and one infusion of bb2121.

Overall, 8 of the 8 patients treated with  $450 \times 10^6$  CART T-cells with low levels of BCMA (0 to 50% of cells are BCMA positive) had a response. Ten of the eleven patients who expressed high BCMA ( $\geq 50\%$  BCMA positive cells) had a response. The median progression-free survival (PFS) for patients in the dose escalation cohort treated with  $\geq 150 \times 10^6$  CAR T-cells was 11.8 months. The median PFS for patients who received  $50 \times 10^6$  CAR T-cells was 2.7 months. In both the dose escalation and expansion phases, 16 patients who responded and evaluated for minimal residual disease (MRD) were MRD

negative at one or more timepoint with a median PFS of 17.7 months. Two patients with no response were MRD positive in the first month.

Cytokine release syndrome (CRS), mostly grade 1/2, was reported in 63% of patients; 2 patients experienced grade 3 CRS that resolved in 24 hours. Twenty-one percent of patients (n=9) received tocilizumab, 9% (n=4) of patients received steroids with a median CRS duration of 6 days. For the 18 patients who received  $150 \times 10^6$  CAR T-cells, the CRS rate was 39% with no grade 3 adverse events (AEs). For the 22 patients who received  $\geq 150 \times 10^6$  CAR T-cells, the CRS rate was 82% and 9.1% of patients experienced grade 3 events. Fourteen (33%) of the 43 patients who received infusions experienced neurotoxicity and one patient experienced a grade  $\geq 3$  AEs. bb2121 is proving to be a promising treatment option for patients with RRMM.

The IMF Nurse Leadership Board's discussions focused on understanding the patient-treatment journey, as well as the educational needs of patients, caregivers, and providers. The Board also discussed infrastructure stabilization strategies for institutions to consider when bb2121 becomes FDA-approved for patients with RRMM.

## **The Patient Treatment Journey**

### **Overview of the Patient Journey**

The CAR T-cell therapy process involves a myriad of complex activities with varying

degrees of challenges<sup>13</sup> related to patient eligibility, timing, lack of infrastructure relating to the availability of apheresis units, observation of adverse events, and long-term monitoring after discharge.

The phases of the patient-treatment journey include (Figure 2):

- Patient selection
- Patient consent and education
- Patient screening
- Leukapheresis/apheresis collection
- Bridging and leukodepletion chemotherapies
- CAR T-cell infusion and inpatient monitoring
- Posthospital care and transition to long-term monitoring

### Patient Selection and Screening

The selection standards for patients with RRMM are not clearly defined, and there are variations in how different institutions discuss CAR T-cell therapy with patients and caregivers. While a physician can recommend or the patient can request CAR T-cell therapy, patients must also be eligible for the treatment. For patients with RRMM, eligibility for CAR T-cell therapy is dependent on whether the patient has been treated with three prior lines of therapy (eg, immunomodulatory agents, proteasome inhibitors, or CD38 targeting therapies), has had a relapse of disease, or has disease that has both relapsed and is refractory.<sup>14</sup> Providers need to be educated about the eligibility criteria for CAR T-cell

therapy. Considering the severity of the disease, providers must consider the time between patient's eligibility for treatment and when treatment is received.

Nurses are instrumental in navigating patients with RRMM through the treatment process. Once approved, nurses could ensure patients understand CAR T-cell therapy is another option to the patient's standard of care plan. It is also important for providers to manage expectations during discussions with patients, as MM remains incurable with this and other therapies.

### Leukapheresis/apheresis Collection and Shipment

Leukapheresis is the process where T cells are isolated and collected through apheresis.<sup>15</sup> Apheresis coordination and performance is time-sensitive and can be burdensome to both the patient and provider. For instance, some patients may experience adverse effects, such as nausea, fatigue, dizziness, or tingling sensation in the fingers and around the mouth.<sup>15</sup> Due to research demands and limited apheresis schedule at some institutions, bottlenecks in treatment often occur at this phase of the patient-treatment journey.

Potential solutions that may reduce some of the challenges of this phase include:

- Convening a meeting with physicians, nurses, pharmacists and other personnel involved with CAR T-cell therapy process, to set

appointments and assign specific apheresis collection days

- Utilizing a case manager who coordinates the apheresis collection dates and other treatment logistics
- Ensuring complete paperwork and other logistic items are received ahead of collection
- Developing a tracking system through EPIC or another electronic health record system for shipping cells for manufacturing. EPIC provides accurate and connected health information in real time<sup>16</sup> and can be used to track cell shipments and inform providers of the progress of CAR T-cell manufacture for each patient

### Bridging and Leukodepletion (lymphodepleting) Chemotherapies

Bridging chemotherapy may be given to control disease until the completion of the CAR T-cells manufacturing process.<sup>17</sup> Leukodepletion (lymphodepleting) chemotherapy is delivered to facilitate CAR T-cells expansion *in vivo* and may help to minimize disease burden before infusion of CAR T-cells in certain disease settings, but is not expected to meaningfully impact disease burden in RRMM patients.

Lessons learned from patients receiving Tisagenlecleucel suggest, if disease progresses, bridging chemotherapy may be needed by some patients.<sup>17</sup> There are challenges with selecting an appropriate bridging therapy when patients have

relapsed or refractory disease. Prior therapy combinations may be attempted during the two-three weeks the patient is waiting for his or her infusion. CAR T-cell infusion dates must be carefully planned to allow for appropriate cycles of bridging and lymphodepleting chemotherapies.

### Infusion, Posthospital Care, and Long-term Monitoring

CAR T-cell may be a promising therapy option for patients with RRMM, however the potentially severe toxicities may limit its use.<sup>18</sup> The most common adverse event that occurs after treatment is Cytokine release syndrome (CRS). CRS is an inflammatory response produced by elevated cytokines and is associated with T-cell expansion and proliferation.<sup>7,15</sup> Patients who experience CRS require immediate attention and may be hospitalized for monitoring. Tocilizumab must be available for patients experiencing treatment-induced CRS. It is recommended that patients receive one or two doses of tocilizumab with advanced supportive care.<sup>19</sup> If the patient's CRS does not improve after a secondary dose of tocilizumab, corticosteroids or another immunosuppressive agent should be considered.<sup>18</sup>

Another common complication of CAR T-cell therapy is the occurrence of neurologic toxicities (neurotoxicity). Neurotoxicity may occur in patients receiving CAR T-cells in the absence of CRS and incidence varies between 0% to 50%. Clinical manifestations

in patients treated with CD19-targeted CAR T-cell for B-cell malignancies include headache, confusion, delirium, and seizures. Commonly used treatments include corticosteroids and interleukin-6 blockade.<sup>20</sup>

Criteria for discharging patients after treatment may include:

- 7 days after treatment - No CRS
- 14 days after treatment - A complete recovery from either CRS or neurotoxicity and manageable cytopenia (most patients may have cytopenia at 14 days) at discharge

Posthospital care and follow-up processes differ by institution, patient type, and therapy. If outpatients or discharged inpatients experience adverse events outside of regular clinic hours, the preference is for the patient to return to the academic institution's emergency room (ER). However, there are challenges that may result if CAR T-cell therapy patients are admitted to the ER (eg, patient receiving steroids).<sup>17</sup> It is imperative patients are educated about adverse events and provided with written information about who they should contact in case of an emergency.

The relationship between providers at academic institutions and community oncologists is critical to the patient's long-term care monitoring plan after treatment. Once the patient returns to his or her community oncologist, nurses at the academic institution should be informed

about the patient's progress by his or her caregiver and/or nursing staff at the community hospital. A one-page discharge summary letter outlining the posthospital care needs of CAR T-cell therapy patients could be used to facilitate dialogue between academic and community hospital providers.

Furthermore, psychological long-term follow-up should be addressed during disease monitoring since CAR T-cell therapy is different than standard of care and the psychological impact can be profound for patients. In standard of care treatment process, providers are a part of the social support system for patients with MM. The CAR T-cell therapy process, however, may involve fewer provider interactions. As a result, patients may experience depression and lack the coping skills to deal with these changes in treatment routine. Research is lacking to fully understand the psychological consequences of receiving this therapy. In the interim, palliative care support and face-to-face or electronic support groups may be useful options for patients with RRMM.

## **Education Needs of Patients, Caregivers, and Providers**

### **Patient and Caregiver Education Needs**

Patients and families can sometimes be overwhelmed with the amount of literature received after diagnosis. A specialized team of providers could provide educational materials (Table 1) to patients and

caregivers at the beginning and throughout the treatment process. This might reduce anxiety and fear patients experience after treatment. The educational tools may be in the form of traditional (books, pocket guides) and electronic mediums (websites, quick reference PDF documents). In addition, materials could include information about potential adverse events, long-term immunosuppression, and other sequelae (eg, cytopenia, infection, delayed onset CRS or neurotoxicity) patients may experience after treatment.

### **Provider Education Needs**

Providers require educational tools that are portable, easily accessible, and automatic. A more developed educational process is needed and should include traditional and electronic tools (Table 1) that streamline information needed to provide the most efficient standard of care practices.

Educational tools could be developed for each provider discipline that interacts with patients during the CAR T-cell therapy process. Disciplines include oncology, emergency room and intensive care physicians, neurologists, pharmacists, and nurses (eg, nurse practitioners, infusion nurses, staff nurses). Though CAR T-cell therapies are presently limited to specialized treatment centers<sup>21</sup>, awareness and interest in the therapy are growing. As a result, patients may seek care at their community institutions. There is an urgent need for community physicians and nurses to receive education about the CAR T-cell therapy process.

### **Commercialization of bb2121**

FDA approval of bb2121 will provide opportunities to improve standard of care practices and inform infrastructure stabilization strategies for academic institutions. However, the cost affiliated with developing a CAR T-cell therapy program and personnel capacity are examples of some key concerns that must be considered.

For instance, the transition from a clinical trial design to the commercial availability of CAR T-cell therapy may modify the types of personnel involved in the patient-treatment journey. Thus, institutions are encouraged to implement strategies learned from lymphoma and leukemia CAR T-cell therapy programs to inform treatment programs for patients with RRMM.

### **Closing Statements**

CAR T-cell therapy is a promising cellular immunotherapy approach to treat patients with RRMM.<sup>7</sup> Due to the novelty of this therapy for patients with RRMM, there are complexities about the patient-treatment journey that are not yet known.

Furthermore, the treatment journey can be a time-intensive, and psychologically burdensome process for patients and their caregivers.

Awareness and interest in the use of CAR T-cell therapy for patients with RRMM are increasing. It is critical that all provider disciplines that interact with patients during the CAR T-cell therapy process and after



discharge are properly trained. Providers ought to manage expectations during discussions with patients because MM remains incurable. Nurses must continue to

advocate for patients eligible for the therapy and provide the necessary education to properly inform patients and caregivers about this treatment option.

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**Figure 1 Multiple Myeloma Patients in the U.S. (2015 to 2018 Projections)**

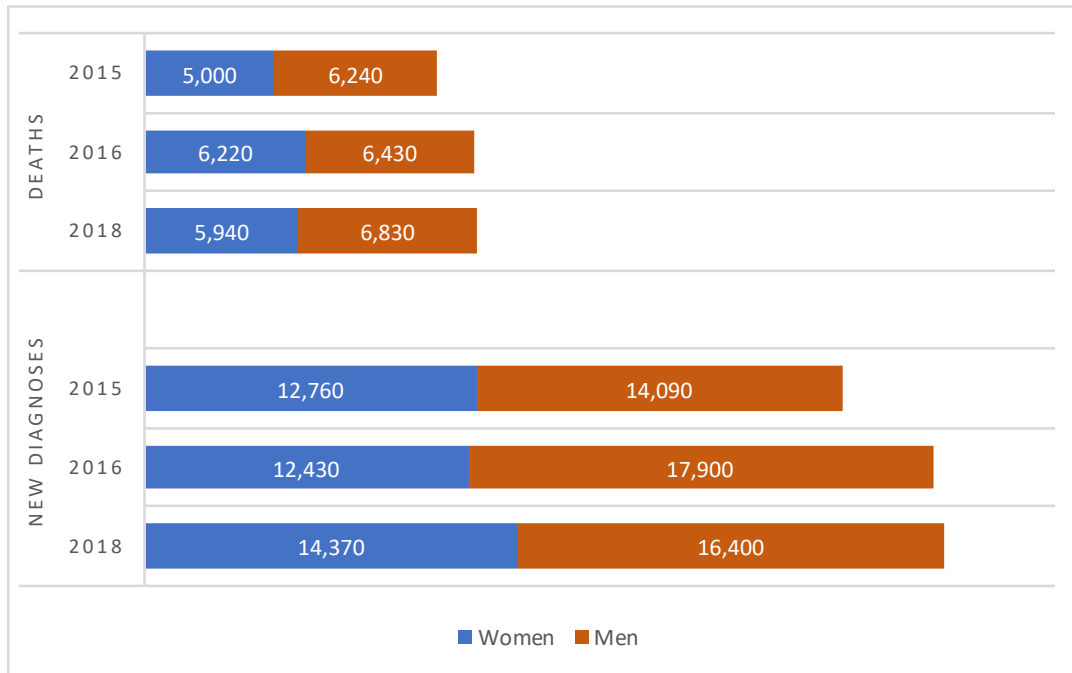
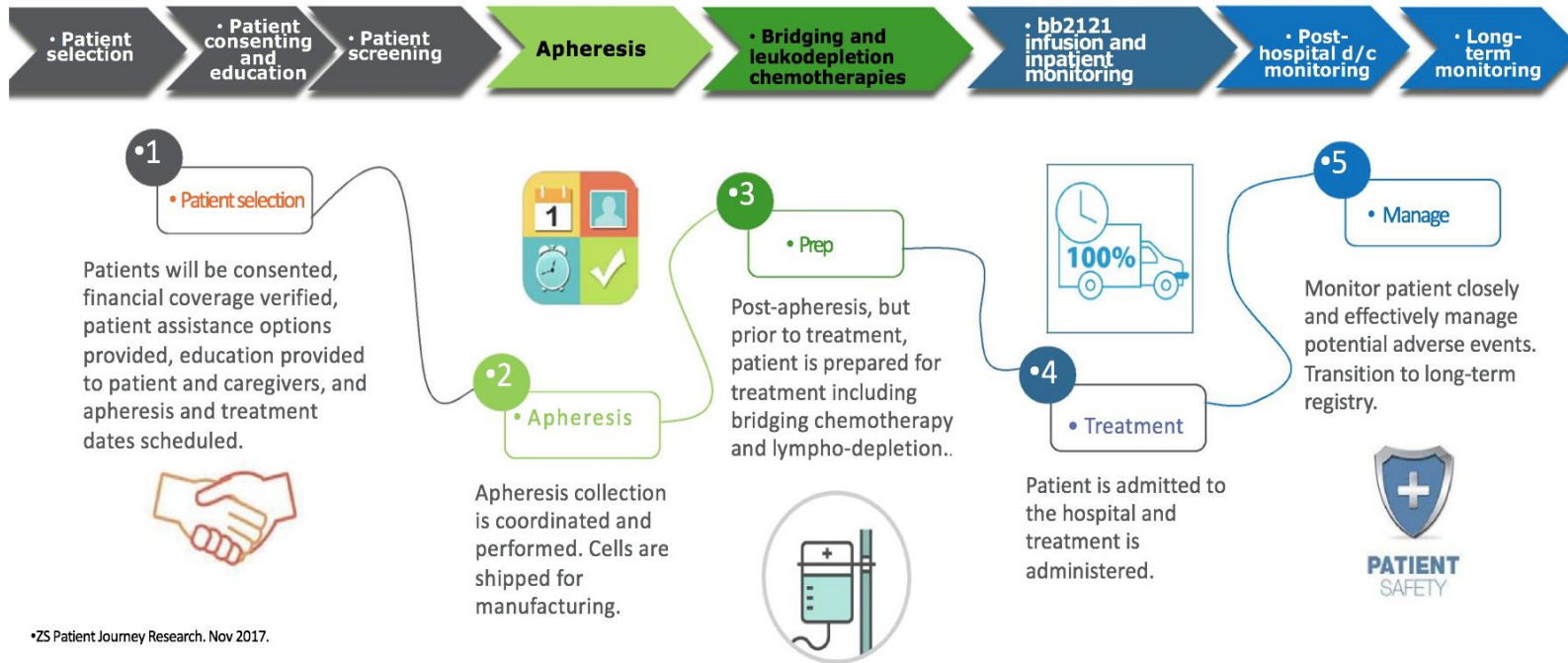


Figure 2 Patient Journey Through the CAR T-Cell Therapy Process



**Table 1 Proposed Tools and Resources for Patients, Caregivers, and Providers**

<b>Tools and Resources for Patients and Caregivers</b>
A video depicting the CAR T-cell treatment process
A written guide on how to assess symptoms after treatment
A treatment calendar with directions, and words of inspiration for patients and families
A list of housing facilities patients and families could rent while receiving therapy away from home
A risks and benefits information sheet on CAR T-cell therapy
A take-home packet or interactive application that connects with the patient’s health care team
A one-page discharge summary letter about the CAR T-cell therapy process
<b>Tools and Resources for Providers</b>
The FACT accreditation program could be used to follow-up on patients receiving CAR T-cell therapy and track cellular products/infusions
REVLIMID REMS® program may be used to ensure all providers with a patient receiving CAR T cell-therapy are informed of signs and symptoms of CRS or neurotoxicity and management strategies to mitigate these adverse events
CAR T-cell therapy training videos distributed via YouTube, and/or other websites
Portable flip cards or prepopulated tools that are easily accessible
A process map identifying barriers and solutions for each phase of the patient-treatment journey
National predictive models that provide benefits of CAR T-cell therapy. Develop an algorithm based on Dr. Neelapu and colleagues’ multidisciplinary approach for monitoring, grading, and managing acute toxicities <sup>22</sup>
Fact sheet with information on the differences between transplant and CAR T-cell therapy
Best practice alerts <sup>23</sup> to identify CAR T-cell therapy patients in ER settings
Training offered by the <a href="#">Journal of Advanced Practitioner in Oncology</a> called “The Latest Advances In CAR T-Cell Therapy for Refractory and Relapsed Lymphomas and Leukemias”