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# Cleveland Clinic Clinical Rx Forum

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## Blenrep® for Relapsed or Refractory Multiple Myeloma

By: **Sonya Anderson, Pharm.D.**

**Background:** Multiple myeloma (MM) is a malignant B-cell neoplasm characterized by destructive proliferation within the bone marrow.<sup>1</sup> Dissemination throughout the bone marrow results in osteolytic lesions, pathologic fractures, and increased rates of osteoporosis. Additional complications include hypercalcemia, renal failure, anemia, and infections.<sup>2</sup> The approach to treatment is based on eligibility for autologous stem cell transplantation (ASCT). Primary therapy with ASCT is preferred over conventional chemotherapy due to superior response rates and progression-free survival.<sup>3</sup> Initial treatment with a three-drug regimen is preferred in both transplant-eligible and -ineligible patients.<sup>4</sup> Newly diagnosed MM is typically sensitive to a variety of drug classes including immunomodulatory agents (e.g., lenalidomide, pomalidomide, and thalidomide), proteasome inhibitors (e.g., bortezomib, ixazomib, and carfilzomib), and mono-

clonal antibodies (e.g., daratumumab, elotuzumab, and isatuximab). Despite lenalidomide or bortezomib-based maintenance therapy, most patients with MM, regardless of ASCT status, will eventually relapse.<sup>2</sup> On August 5<sup>th</sup> 2020, belantamab mafodotin-blmf (Blenrep®; GlaxoSmithKline LLC) received accelerated approval from the Food and Drug Administration for the treatment of adult patients with relapsed or refractory MM who have received at least four prior therapies (including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent).<sup>5</sup>

**Mechanism of Action:** Blenrep® is an afucosylated humanized IgG antibody-drug conjugate that targets B-cell maturation antigen (BCMA), a protein expressed primarily on MM cells.<sup>5</sup> The BCMA antibody is attached to monomethyl auristatin F (MMAF), a microtubule

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## Tecartus® for Mantle Cell Lymphoma

By: **Kerri Row, Pharm.D.**

**Background:** Mantle cell lymphoma (MCL) comprises approximately 2.5%–6% of B-cell non-Hodgkin's lymphoma cases.<sup>1</sup> It is considered an aggressive disease and has an overall median survival of 5 years; there is currently no curative therapy for these patients.<sup>2</sup> Treatment generally includes high-dose chemotherapy followed by autologous stem cell transplant (ASCT) if the patient is eligible. Even with intensive treatment regimens, there is still a high incidence of relapse and disease progression.<sup>3,4</sup> On July 24<sup>th</sup> 2020, brexucab-

tagene autoleucl (Tecartus®; Kite Pharma) received accelerated approval from the Food and Drug Administration for the treatment of adult patients with refractory or relapsed MCL.<sup>5</sup>

**Mechanism of Action:** Tecartus® is a genetically modified autologous T-cell immunotherapy treatment that binds to cells that express CD-19.<sup>5</sup> The patient's own T-cells are modified with a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing malig-

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inhibitor. This disrupts the microtubule network, resulting in cell cycle arrest and apoptosis. Blenrep® also exerts tumor cell lysis through antibody-dependent cellular cytotoxicity and phagocytosis.

**Clinical Trial:** The safety and efficacy of Blenrep® were evaluated in DREAMM-2, an open-label, two-arm, phase 2 trial.<sup>6</sup> Eligible patients had relapsed or refractory MM. These patients also had disease progression on or after receiving three or more prior therapies including an anti-CD38 monoclonal antibody, immunomodulatory drug, and proteasome inhibitor. Patients with mild to moderate renal dysfunction were excluded (eGFR 30 to 89 mL/min/1.73m<sup>2</sup>). Patients (n=223) were randomized to receive either Blenrep® 2.5 mg/kg or 3.4 mg/kg administered every 3 weeks intravenously until disease progression or unacceptable toxicity. The primary outcome was overall response. At baseline, the mean age was 65 years, with most patients having International Staging System stage II or III disease (77%) and prior ASCT (87%). High-risk cytogenetic factors were present in 27% of patients. In the 2.5 mg/kg cohort, 31% (97.5% CI: 20.8-42.6) achieved an overall response with 19% attaining a “very good” partial response or better. In the 3.4 mg/kg cohort, 34% (97.5% CI: 23.9-46.0) achieved an overall response with 20% attaining a “very good” partial response or better. The authors concluded that Blenrep® demonstrated anti-myeloma activity, particularly in those with relapsed or refractory heavily pretreated disease.

**Safety and Immunogenicity:** Common adverse effects (>15%) included keratopathy, decreased visual acuity, blurred vision, nausea, pyrexia, fatigue, and infusion-related reactions.<sup>5</sup> In the DREAMM-2 trial, the most common adverse events in both groups were grade I-II and III-IV keratopathies (2.5 mg/kg: 43% and 27%, respectively; 3.4 mg/kg: 54% and 20%, respectively).<sup>6</sup> These were also the most common reasons for treatment discontinuation and dose reductions (2.5 mg/kg: 1% and 47%, respectively; 3.4 mg/kg: 3% and 48%, respectively). No permanent vision loss was reported. While infrequent (<1%), formation of anti-belantamab mafodotin antibodies was reported.

**REMS Requirements:** Due to the risk for ocular toxicity, Blenrep® is only available through the Blenrep® Risk Evaluation Mitigation Strategy (REMS) program.<sup>7</sup> Hospitals and their associated clinics must be enrolled in the Blenrep® REMS program to dispense Blenrep®. Additionally, providers must be certified to prescribe Blenrep®. Certified providers who enroll patients in the Blenrep® REMS program need to counsel them about ocular toxicities. Before initiation of Blenrep®, ophthalmic examinations, including slit lamp and visual acuity exams, are conducted 3 weeks before the first dose. Follow-up ophthalmic examinations are conducted at least 1 week after the previous dose and within 2 weeks before the next dose. These

examinations must be documented and submitted before obtaining an Authorization Code, which is required for dispensing of Blenrep®. Patients are required to use preservative-free lubricant eye drops at least four times daily starting at the first infusion until the end of treatment. Contact lenses should be avoided.

**Dosing and Administration:** The recommended starting dose of Blenrep® is 2.5 mg/kg of actual body weight given intravenously every 3 weeks until disease progression or unacceptable toxicity.<sup>5</sup> Blenrep® should be discontinued in patients unable to tolerate a dose of 1.9 mg/kg. There are specific dosage adjustments based on the occurrence of corneal abnormalities, thrombocytopenia, infusion-related reactions, and other adverse effects listed in the package insert. More than one vial of Blenrep® may be required for a full dose; the dose should not be rounded down to avoid partial vials.

**Cost and Availability:** Blenrep® is available as 100 mg single-dose vials (NDC 0173-0896-01).<sup>5</sup> The average wholesale price per vial is \$9,932.40.<sup>8</sup> The estimated annual cost for a 70 kg patient is \$337,700.

**Formulary Status:** Blenrep® was added to the CCHS Adult Formulary restricted to the Department of Hematology/Medical Oncology for outpatient use only for on-label indication.

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nant cells. After binding to cells that express CD-19, the CAR activates signaling cascades that lead to T-cell activation, proliferation, and secretion of inflammatory cytokines and chemokines. This chain reaction leads to the targeting and killing of CD19-expressing cancer cells.

**Clinical Trial:** The safety and efficacy of Tecartus® were evaluated in the pilot clinical trial ZUMA-2 which was a phase 2, multicenter, single-arm trial in adult patients with relapsed or refractory MCL.<sup>6</sup> Adult patients (≥18 years) were enrolled if they had confirmed MCL that was either relapsed or refractory to up to five previous regimens for MCL; these regimens included an anthracycline or bendamustine-containing chemotherapy regimen, rituximab, and a Bruton's tyrosine kinase (BTK) inhibitor such as ibrutinib or acalabrutinib. Patients were excluded if they had active or serious infections, prior history of an ASCT, or evidence of central nervous system disease or disorders. The primary endpoint was the percentage of patients with an objective response (including complete or partial responses). Tecartus® was successfully administered to 60 patients; out of these 60 patients, 90% of them received the recommended  $2 \times 10^6$  CAR-T cells, while the remaining patients received lower doses. Among these patients, who had at least 7 months of follow-up, 93% (95% CI: 84-98) in the primary efficacy analysis had an objective response and 67% (95% CI: 53-78) had a complete response. At a median follow-up of 12.3 months, 57% of the 60 patients were in remission. At 12 months, the estimated progression-free survival and overall survival were 61% and 83%, respectively. Cytokine release syndrome (CRS) occurred in 91% of the patients, with a median time to onset of 3 days. No patients died from CRS or neurologic events during the trial. The authors concluded that Tecartus® is an effective treatment option in patients with relapsed or refractory MCL after BTK inhibitor therapy failure.

**Safety:** Common adverse effects (>20%) included fever, hypotension, encephalopathy, fatigue, and tachycardia.<sup>5,6</sup> In the ZUMA-2 trial, the most common adverse events were CRS, infection, cytopenia, and hypogammaglobulinemia.<sup>6</sup> Infections occurred in 56% of patients; of these, grade III or higher infections occurred in 32% of patients. Grade III-IV cytopenias after 90 days were found in 26% of ZUMA-2 trial patients, including neutropenia (16%), thrombocytopenia (16%), and anemia (12%). Additionally, 16% of the patients in ZUMA-2 experienced hypogammaglobulinemia.

**REMS Requirements:** Due to the risk of CRS and neurological toxicities, Tecartus® is only available through the Yescarta® and Tecartus® Risk Evaluation Mitigation Strategy (REMS) program.<sup>7</sup> Hospitals must be enrolled with the Yescarta® and Tecartus® REMS program to dispense Tecartus®. Enrolled hospitals must have on-site, immediate

access to tocilizumab, with a minimum of two doses available for each patient for infusion within 2 hours after Tecartus®. Healthcare providers who prescribe, dispense, or administer Tecartus® must be trained to manage CRS and neurologic toxicities. Patients must be given a Patient Wallet Card to indicate that they have received Tecartus®.

**Dosing and Administration:** The dose of Tecartus® is  $2 \times 10^6$  CAR-positive viable T cells per kg, with a maximum of  $2 \times 10^8$  cells, infused intravenously over 30 minutes.<sup>5</sup> Before administration the patient identifiers on the Tecartus® cassette and infusion bag must be verified and the patient should be pre-medicated with acetaminophen and diphenhydramine. Systemic corticosteroids may interfere with the efficacy of Tecartus® and must be avoided. Before use, Tecartus® should be stored frozen in the vapor phase of liquid nitrogen ( $\leq -150^\circ\text{C}$ ;  $-238^\circ\text{F}$ ) Once thawed, it should be administered within 30 minutes, but may be stored at room temperature ( $20^\circ\text{C}$  to  $25^\circ\text{C}$ ;  $68^\circ\text{F}$  to  $77^\circ\text{F}$ ) for up to 3 hours.

**Pharmacist Considerations:** Patients should be monitored in the hospital for at least 7 days following infusion for CRS and neurologic events.<sup>7</sup> Once discharged, they should remain within a 2-hour driving distance from the hospital for at least 4 weeks and not drive or operate heavy machinery for up to 8 weeks after receiving Tecartus®.

**Cost and Availability:** The average annual cost of therapy is approximately \$380,000. Tecartus® is supplied as an infusion bag (NDC 71287-219-01) containing approximately 68 mL of frozen suspension of genetically modified autologous T-cells in 5% DMSO and human serum albumin.<sup>5</sup> Each Tecartus® infusion bag is individually packed in a metal cassette (NDC 71287-219-02).

**Formulary Status:** Tecartus® was added to the CCHS Adult Formulary restricted to the Department of Hematology/Oncology and Bone Marrow Transplant.

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