

TECVAYLI™ (teclistamab-cqyv)

Category:

Best Biotechnology Product

Company Name:

Johnson & Johnson Services, Inc.

Product/Solution Name:

TECVAYLI™ (teclistamab-cqyv)

Compound/Tech Name:

Teclistamab-cqyv

Trade Name:

TECVAYLI™

Corporate Name:

Johnson & Johnson

Date of Approval:

2022-10-25

Indications:

TECVAYLI® (teclistamab) is a bispecific B-cell maturation antigen (BCMA)-directed CD3 T-cell engager with weight-based dosing and is the first bispecific antibody approved for use in patients with relapsed or refractory multiple myeloma (RRMM). In the United States, teclistamab is approved as a monotherapy for the treatment of adult patients with RRMM who have received ≥ 4 prior lines of therapy including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody (mAb). This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

In the European Union, teclistamab is approved as a monotherapy for the treatment of adult patients with RRMM who have received ≥ 3 prior therapies including a PI, an IMiD, and an anti-CD38 antibody, and have demonstrated disease progression on the last

therapy.

The recommended dose of teclistamab in the United States and European Union is 1.5 mg/kg weekly, preceded by step-up doses of 0.06 mg/kg and 0.3 mg/kg. Patients who have achieved and maintained a complete response or better (\geq CR) for a minimum of 6 months can switch to a reduced dosing frequency of 1.5 mg/kg every 2 weeks.

Therapeutic Areas:

Multiple myeloma (MM) is the second-most common hematologic malignancy and accounts for 1.8% of all new cancers in the United States. MM is characterized by uncontrolled proliferation of malignant plasma cells and overproduction of monoclonal immunoglobulin (M protein) in the bone marrow. The infiltration of these malignant cells into various organ systems gives rise to diverse clinical manifestations including bone disease, blood disorders, frequent infections, fatigue, neurological effects, and renal impairment, resulting in painful symptoms that can severely impact patients' quality of life. Nearly all patients with MM will eventually relapse or become refractory to treatment. Relapses may be symptomatic, defined by aggravated or new end-organ damage, and/or biochemical, defined by increases in disease-related markers such as M protein.

The prognosis for MM has improved in recent years, with a 5-year relative survival rate of 62.4%. While patients are experiencing better long-term outcomes, largely attributed to new, highly effective therapies, outcomes remain poor for patients with RRMM.

RRMM becomes increasingly difficult to treat with each relapse. Each remission period is typically shorter than the last as the tumor becomes more aggressive because of selective pressures and genomic instability, ultimately driving disease progression. The prospective LocoMMotion study assessed real-world clinical practice in triple-class exposed (TCE) patients with RRMM (patients who had received treatment with a PI, an IMiD, and an anti-CD38 mAb in prior lines) enrolled between 2019 and 2020 (ie, before the approval of teclistamab). The overall survival (OS) rate at 12- and 24-months was 53.4% and 33.7%, respectively, with a median follow-up of 26.4 months.

Not only do efficacy outcomes progressively decline with each additional line of therapy (LOT) in patients with RRMM, but treatment toxicities can accumulate over time, increasing the risk of

comorbidities or treatment discontinuation. Furthermore, symptom burden, comorbidities, and treatment toxicities contribute to poor health-related quality of life (HRQoL) in patients with MM that worsens with disease progression and increasing LOT. Therefore, there is a high unmet need for novel treatments that are more effective, well tolerated, and improve quality of life in patients with RRMM. The use of more advanced therapies in earlier lines to potentially delay or prevent relapse may help to improve patient outcomes and OS.

General Information File Document upload:

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Background information and need for drug / device:

The therapeutic landscape of MM is rapidly evolving, and the past few decades have given rise to several major treatment advancements (Figure 1). Three main drug classes comprise the current standard of care (SOC) for newly diagnosed MM: IMiDs, PIs, and anti-CD38 mAbs. Novel treatments including chimeric antigen receptor (CAR)-T cell therapies, selective inhibitors of nuclear export and T-cell redirectors are being developed to help address the unmet need that remains after traditional SOC options have been exhausted, as well as the need for more advanced treatment options that can be used in earlier LOT to prevent relapse.

Treatment selection becomes increasingly limited as patients progress through successive lines LOT. This is particularly problematic for those who become TCE. Recycling of previously used agents and regimens is widespread in later LOT where remission durations are shorter and relapses more frequent. In the real-world LocoMMotion study of patients with TCE RRMM, 91 unique treatment regimens were received by 248 patients at enrollment, including PIs in 54.4%, IMiDs in 48.8%, and anti-CD38 mAbs in 9.7% of patients. Treatment recycling contributes to the poor outcomes observed in patients with RRMM, as demonstrated by the 33.7% OS rate at 24 months and lack of deep and durable responses in LocoMMotion (ORR was 29.8% [95% CI: 24.2-36.0]; median DOR was 7.4 months [95% CI: 4.7-12.5]).¹⁶ Thirty-two (12.9%) patients achieved a very good partial response (VGPR) and just 1 patient (0.4%) achieved CR. The median progression-free survival (PFS) and OS were 4.6 and 13.8 months, respectively. Results from the retrospective MAMMOTH study in patients with RRMM who were refractory to an anti-CD38 mAb showed similarly poor survival outcomes, with a median PFS of 3.4 months and median OS of 9.3 months after salvage therapy. Many patients were re-treated with drugs previously used in earlier LOT. The recycling of prior treatments was also reported in a study of >5,000 Medicare beneficiaries with TCE RRMM.³⁸ Among the 1,672 patients who initiated a new therapy, 97 different monotherapy and combination regimens were observed. Nearly one-quarter of the patients were treated with a PI and an anti-CD38 mAb despite prior exposure to these drug classes. The median time to discontinuation of the new therapy was 3.3 months and 41% of the patients died during the study period.

The approval of new immunotherapeutic approaches have helped transform the treatment landscape for RRMM by addressing the key unmet need for therapies that improve upon the efficacy of existing SOC therapies, are well tolerated, improve HRQoL, and offer increased patient convenience.

Teclistamab is the first approved BCMA-targeting, off-the-shelf, bispecific antibody that has demonstrated deep and durable responses and clinically meaningful improvements in HRQoL in heavily treated patients with RRMM, effectively changing the expected outcomes of patients with MM. Data from additional clinical studies and real-world clinical practice have contributed to a growing body of evidence on the potential of teclistamab in improving outcomes for patients in early relapses as well as in

combination with other potent antimyeloma therapies.

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History of the development of the solution/product:

BCMA, a recognized target for therapeutic intervention in RRMM, regulates B-cell proliferation, survival, and plasma cell maturation and differentiation, and is highly expressed on MM cells compared with normal plasma cells. Teclistamab is a full-size BCMA bispecific antibody that induces T-cell-mediated cytotoxicity by recruiting CD3-expressing T cells to BCMA-expressing cells, leading to T-cell activation and subsequent cell lysis of BCMA+ cells via secretion of perforin and granzymes (Figure 2). Bispecific antibodies are a novel class of immunotherapy for RRMM that overcome some limitations of conventional mAbs, which only bind to one antigen and may fail to elicit a strong immune response.

In preclinical studies, teclistamab induced selective T-cell-mediated cytotoxicity of BCMA+ cells, with robust activation of CD4+ and CD8+ T cells. Similarly, teclistamab induced T-cell activation and MM cell lysis in bone marrow aspirates from patients with MM, both with and without prior treatment exposure.

Teclistamab demonstrated rapid, deep, and durable responses in patients with TCE RRMM enrolled in 3 registrational studies/cohorts: the pivotal cohort of patients from the phase 1/2 MajesTEC-1 study; the China cohort of MajesTEC-1; and the Japan phase 1/2 MMY1002 study. At a median follow-up of 29.2 months in the pooled population (N=217), the overall response rate (ORR) was 66.4%; 63.6% of patients achieved a \geq VGPR and 49.8% achieved a \geq CR.⁵² The median DOR, PFS, and OS were 26.7, 15.1, and 26.3 months, respectively. Of note, most patients in the pivotal MajesTEC-1 cohort enrolled during the first peak of the COVID-19 pandemic. A post hoc analysis showed that DOR, PFS, and OS were prolonged in this cohort after censoring for COVID-19 deaths.

Responses to teclistamab in MajesTEC-1 were consistent across most clinically relevant subgroups, including patients who were aged \geq 75 years, had high-risk cytogenetic abnormalities, or had penta-drug refractory disease. Notably, the ORR was higher in patients who received \leq 3 prior LOT versus those who received $>$ 3 prior LOT (74.4% vs 59.0%), suggesting a trend toward improved efficacy from later- to earlier-line settings. Teclistamab was also associated with an overall improvement in patient-reported outcomes for pain, global health status, and emotional functioning. Teclistamab has demonstrated a clinically manageable safety profile in patients with TCE RRMM. In a long-term follow-up of MajesTEC-1 (median 30.4 months), the most common adverse events (AEs) were cytopenias (neutropenia, 71.5%; anemia, 55.2%) and infections (78.8%; grade 3/4, 55.2%), consistent with increased susceptibility to immunodeficiency associated with MM and the immunosuppressive effects of prior therapy. There were no changes in cytokine release syndrome (CRS; 72.1%, 0.6% grade

3) or immune effector cell-associated neurotoxicity syndrome (ICANS; 3.0%, all grade 1/2) during follow-up, and new onset grade ≥ 3 infections declined over time, possibly due to transition to Q2W dosing and increasing use of immunoglobulin replacement therapy. Dose reductions ($<1\%$) and discontinuations ($<5\%$) due to AEs were infrequent.

Based on the positive results of MajesTEC-1, teclistamab was granted Breakthrough Therapy Designation by the US Food and Drug Administration and accelerated approval as the first BCMA-targeting bispecific treatment of TCE RRMM.

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Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition:

Teclistamab is the first approved BCMA \times CD3 bispecific antibody and has demonstrated substantial activity in $>15,900$ patients with RRMM treated worldwide in the commercial setting. Teclistamab has shown rapid, deep, and durable responses with a manageable safety profile in a diverse global clinical cohort, including patients from the pivotal MajesTEC-1 study. Baseline soluble BCMA (sBCMA) level was associated with lower response rates in MajesTEC-1, further validating BCMA as an effective target in MM and highlighting the clinical utility of teclistamab's unique and effective mechanism of action (MOA). In addition, several indirect treatment comparisons have demonstrated substantially improved outcomes with teclistamab over current off-the-shelf, SOC treatments.

While clinical efficacy is of utmost importance, it is also essential for treatments to be available off-the-shelf and convenient in order to be truly effective for patients. Teclistamab delivers on all 3 aspects with exceptional efficacy, immediate availability, and subcutaneous administration with personalized weight-based dosing and the option of flexible biweekly dosing in patients with \geq CR for ≥ 6 months. Compared with intravenous infusion, subcutaneous dosing reduces costs and health care resource utilization, reduces treatment burden for patients and providers, and there is often an option for outpatient administration. Due to the risk of CRS and neurologic toxicity, the US Prescribing Information recommends hospitalization for teclistamab step-up dosing. However, a phase 2 study found that administering prophylactic tocilizumab before teclistamab in the outpatient setting reduced CRS risk, with one patient of 16 (6.3%) experiencing CRS. In 2025, the National Comprehensive Cancer Network guidelines were updated to include that prophylactic tocilizumab may be considered prior to the first dose of teclistamab to reduce the risk of CRS. Several real-world studies also demonstrated the feasibility and safety of teclistamab administration in the outpatient setting.

Several studies are exploring the use of teclistamab as monotherapy in earlier LOT and

in combination with various SOC therapies and novel agents (Figure 3). The combination of teclistamab with other therapies may enhance antimyeloma activity and overcome resistance through multiple, complementary MOAs. Preliminary efficacy/safety results are shown in the Table.

In RRMM, teclistamab monotherapy is being assessed in patients treated with 1-3 prior LOT in the phase 3 MajesTEC-9 and phase 1 MajesTEC-10 studies. Teclistamab combinations with different SOC agents are being evaluated in patients with ≥ 3 prior LOT (phase 1 TRIMM-2) and patients with 1-3 prior LOT (phase 1 MajesTEC-2, phase 3 MajesTEC-3). Studies of teclistamab combinations with other novel immunotherapies are also underway, including talquetamab, the first-approved GPRC5D \times CD3 bispecific antibody (phase 1/2 RedirecTT-1) and a programmed cell death receptor-1 (PD-1) inhibitor (phase 1 TRIMM-3).

In newly diagnosed MM, teclistamab combinations are being evaluated as induction therapy and maintenance therapy in the phase 2 MajesTEC-5 study or as maintenance therapy in the phase 3 MajesTEC-4 study. The phase 3 MajesTEC-7 study is evaluating teclistamab combinations in transplant-ineligible/not intended patients.

Teclistamab represents a new SOC for MM that has the potential to revolutionize the therapeutic landscape by expanding treatment options across all LOT, both as a monotherapy and in a variety of combination treatments.

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