

4 Innovation

4.1 TECVAYLI™ FDA Breakthrough Therapy Designation for the treatment of RRMM

TECVAYLI was accepted into the European Medicines Agency's Priority Medicines scheme on January 29, 2021.⁹⁹ On June 1, 2021, TECVAYLI was granted a Breakthrough Therapy Designation by the US FDA for the treatment of patients with RRMM who have received at least 4 prior lines of therapy including a PI, an IMiD, and an anti-CD38 mAb.^{1,90} Breakthrough Therapy Designation is intended to expedite the development and regulatory review of a potential new medicine treating a serious or life-threatening condition based on preliminary evidence that demonstrates substantial improvement over existing therapies.⁹⁰ The designation was based on the outstanding efficacy TECVAYLI demonstrated in the phase 1/2 MajesTEC-1 study.⁸⁸ TECVAYLI then received accelerated approval from the US FDA on October 25, 2022.¹⁰⁰ TECVAYLI is a first-in-class BCMA×CD3 bispecific antibody offering transformative clinical benefits with convenience as an off-the-shelf therapy.

4.2 TECVAYLI™ targets BCMA, a recognized target for therapeutic intervention in RRMM

Preclinical models have demonstrated that BCMA-targeting effectively blocks MM cell proliferation and promotes malignant cell death.^{65,101,102} sBCMA is elevated in the serum of patients with MM and high levels are associated with increased disease burden and poor prognosis.^{65,101} BCMA overexpression and activation are associated with MM progression, and clinical models have validated BCMA as an effective target for therapeutic intervention in MM.^{58,65,78,82}

In MajesTEC-1, nearly 70% of evaluable patients who achieved at least a partial response demonstrated rapid reductions in sBCMA levels within 1 month after TECVAYLI treatment. The reduction in sBCMA levels were even more pronounced in patients who achieved deeper responses, with decreases from baseline of 80–90% in those who achieved ≥VGPR (**Figure 7**).⁸⁸

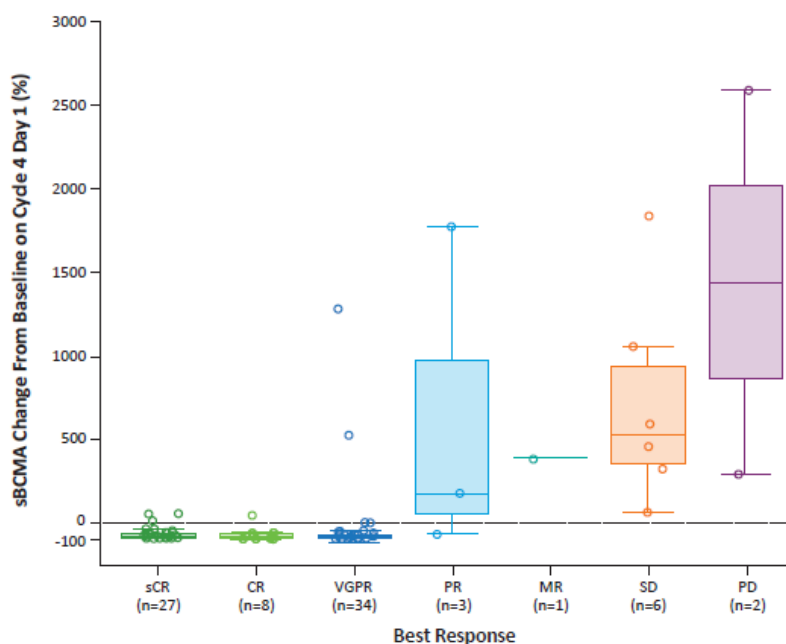


FIGURE 7: Changes in sBCMA after TECVAYLI treatment by response⁸⁸

These results further validate BCMA as an effective target in MM therapy and highlight the clinical utility of TECVAYLI's unique and effective MOA, complementing the deep and durable responses patients experience with TECVAYLI treatment to maximize clinical benefit.

4.3 TECVAYLI™ offers a new approach to RRMM therapy with excellent efficacy

Currently, there is no single, clear SOC therapy for patients with TCE RRMM, with more than 90 different treatment regimens utilized in real-world settings.²⁰ The treatment options that are currently available and utilized in real-world clinical practice have demonstrated relatively poor clinical outcomes. TECVAYLI has demonstrated a significant improvement in efficacy compared with other off-the-shelf treatments, as shown by several indirect treatment comparisons (ITCs). In the absence of head-to-head clinical trials, ITCs are used to compare treatment options and improve outcomes for patients.

4.3.1 Indirect treatment comparisons demonstrate improved efficacy over other off-the-shelf current SOC therapies

In the LocoMMotion study, an ORR of just 30% was observed in patients with TCE MM treated with real-world physician's choice of therapy (RWPC).²⁰ Data from an ITC between MajesTEC-1 and LocoMMotion showed that treatment with TECVAYLI resulted in improved outcomes over real-world SOC treatments.¹⁰³ Adjusted comparisons showed that patients treated with TECVAYLI were 2.3-fold more likely to respond compared with RWPC and were 148.3-fold more likely to achieve ≥CR (**Figure 8**).

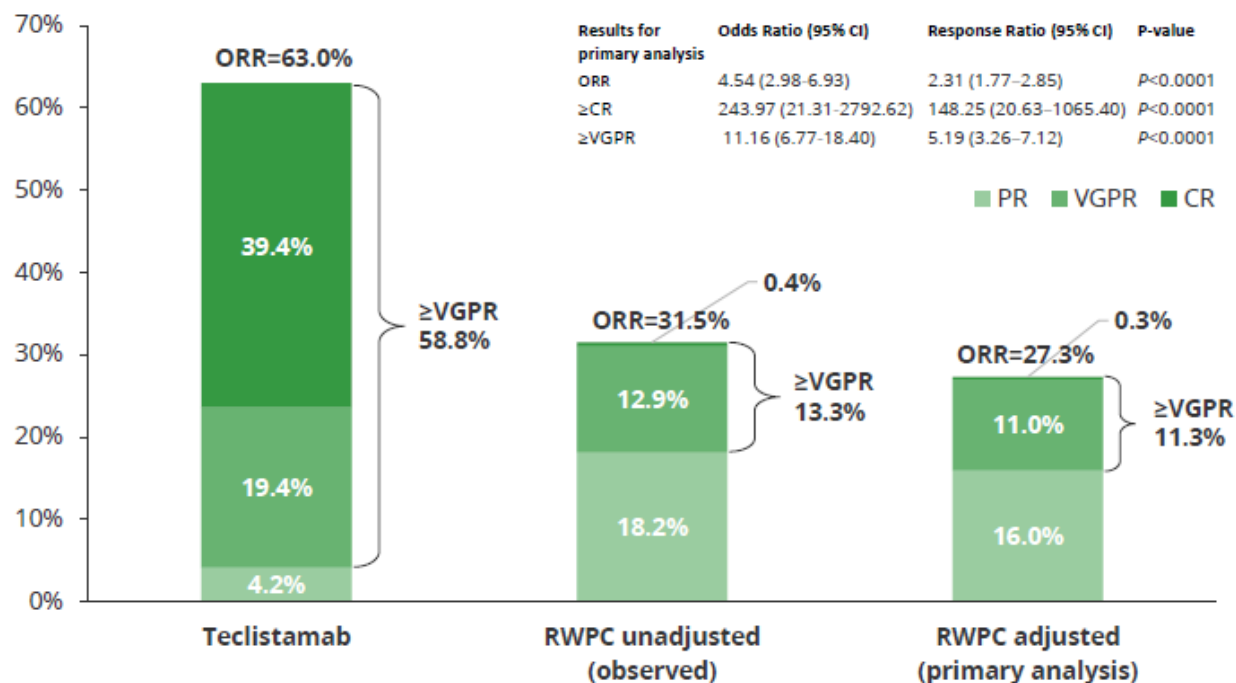


FIGURE 8: Response outcomes for TECVAYLI in MajesTEC-1 vs RWPC in LocoMMotion¹⁰³

Similarly, in an ITC of patients from MajesTEC-1 vs patients with MM from the Flatiron Health Database, TECVAYLI improved outcomes over real-world SOC, demonstrating a numerically better OS and statistically significant improvements in PFS and time to next treatment.¹⁰⁴ In addition, OS, PFS, and time to next treatment were significantly improved with TECVAYLI over RWPC in a cohort of patients from a long-term follow-up of 4 clinical trials of daratumumab in patients with TCE RRMM.¹⁰⁵

TECVAYLI has also shown substantial clinical benefit over the approved treatment of selinexor-dexamethasone in an ITC of MajesTEC-1 with part 2 of the STORM trial.¹⁰⁶ Patients were 2-fold more likely to respond to treatment with TECVAYLI than with selinexor-dexamethasone and were 23.3-fold more likely to achieve \geq CR (**Figure 9**). Patients treated with TECVAYLI had significantly longer DOR (HR [95% CI], 0.06 [0.02-0.13]; $P<0.0001$) and OS (0.56 [0.33-0.94]; $P=0.0285$) and numerically better PFS (0.60 [0.32-1.11]; $P=0.1049$).¹⁰⁶

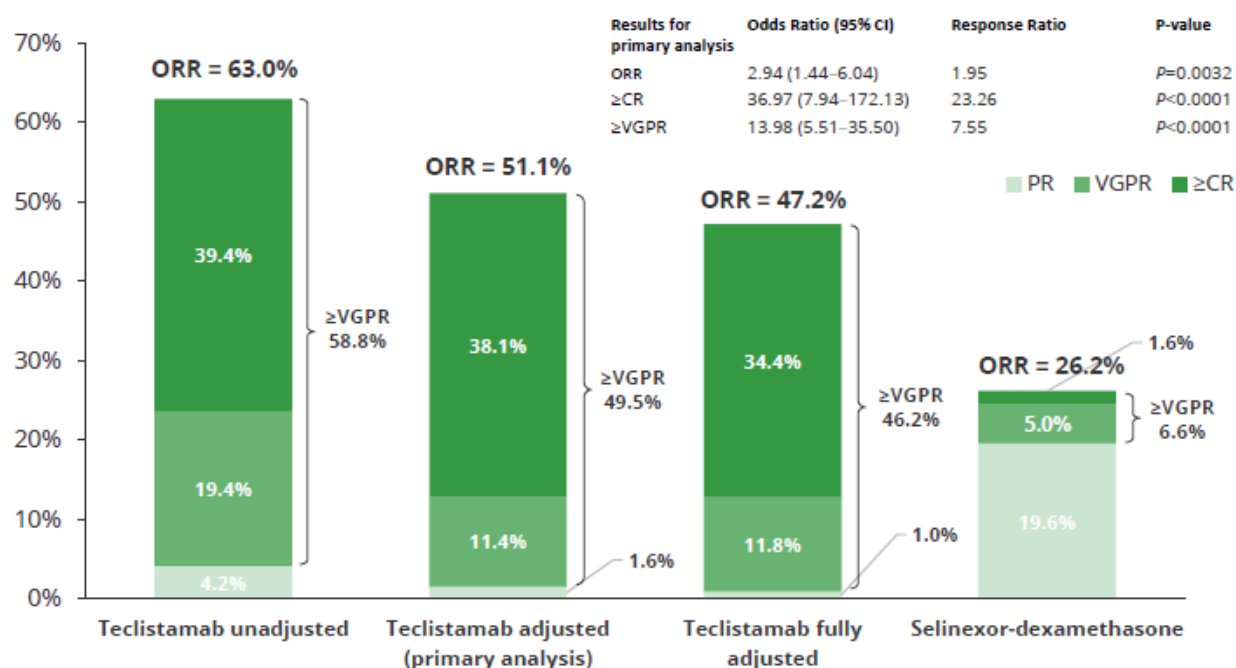


FIGURE 9: Response outcomes for TECVAYLI in MajesTEC-1 vs selinexor-dexamethasone in STORM part 2¹⁰⁶

These data signify a paradigm shift in MM treatment, with TECVAYLI standing out as the clear SOC of choice for superior clinical outcomes.

4.3.2 TECVAYLI™ provides clinically meaningful improvements in patient reported outcomes

Patients with MM have burdensome symptoms such as pain and fatigue that adversely affect their HRQoL, which deteriorates further with each additional relapse and LOT.¹⁰⁷ In addition to clinical efficacy and safety, it is vital to consider the impact novel treatments have on HRQoL.

Treatment with TECVAYLI was associated with an overall improvement in patients' HRQoL in the MajesTEC-1 study.¹⁰⁸ Patient reported outcomes, including those for pain, global health status, and emotional functioning, demonstrated improvements over baseline following treatment with teclistamab. Notably, reduction in pain scores occurred as early as cycle 2, with significant improvement by cycles 4–8, and the proportion of patients reporting meaningful improvement in overall health (EQ-5D-5L) increased over time (**Figure 10**).

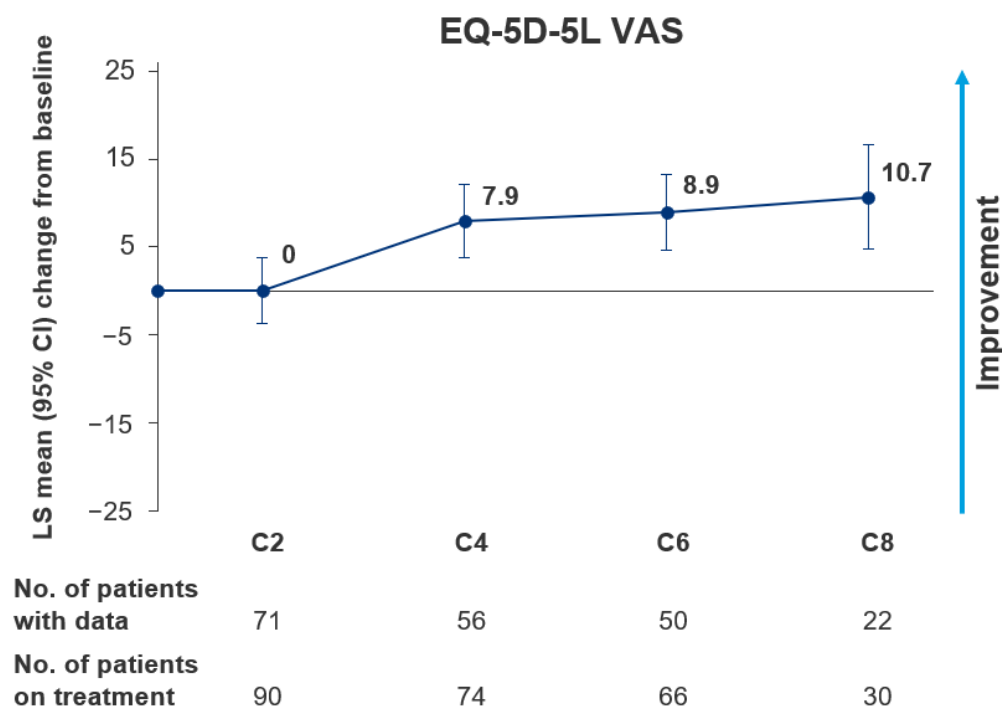


FIGURE 10: Improvement in HRQoL with TECVAYLI¹⁰⁸

The sustained improvements in HRQoL with TECVAYLI complement its outstanding clinical benefits and further underscore its utility as a new and transformative SOC therapy for patients with RRMM.

4.4 TECVAYLI™ has a novel MOA that has the potential to enhance anti-myeloma effects when combined with complementary therapeutic agents

Combination regimens that include agents with distinct targets and MOAs are being increasingly used to remove multiple sub-clonal tumor cell populations, induce deeper responses, and reduce the risk of developing refractory disease.⁷⁶ Combinatorial approaches are hypothesized to yield synergistic efficacy with manageable safety profiles.⁸⁷ TECVAYLI combinations, including in earlier lines of therapy, are being investigated in several clinical trials to identify optimal doses and treatment regimens.

4.4.1 TECVAYLI™ in combination with immunomodulatory agents

CD38+ immunosuppressive cells are associated with decreased immune function and disease progression.¹⁰⁹ Daratumumab depletes immunosuppressive regulatory cells that express CD38, including myeloid-derived suppressive cells, regulatory B cells, and a subpopulation of Treg cells that robustly suppresses T-cell proliferation. Daratumumab may also increase T helper and cytotoxic T-cell absolute counts.¹⁰⁹ The combination of teclistamab and daratumumab has been shown to upregulate CD38+/CD8+ T cells and pro-inflammatory cytokines, suggesting the potential for synergistic effects and enhanced efficacy.⁹⁷ Initial results from the TRIMM-2 study demonstrated that the combination of TECVAYLI + daratumumab was well tolerated and had promising clinical activity. At median 8.6-month follow-up, the ORR was 76.5% and in patients with prior anti-CD38 mAb exposure, the ORR was 73.7%.

TECVAYLI™ (teclistamab-cqyv) US Prix Galien submission. June 26, 2023.

Lenalidomide, as an IMiD, directs tumor cell apoptosis, stimulates effector immune cells, reduces immunosuppressive cells, and may enhance or improve the efficacy of other immunotherapies, such as TECVAYLI.^{44,45,110} TECVAYLI is being explored in combination with lenalidomide in the multicohort, phase 1 MajesTEC-2 study (regimen D) for patients with RRMM. The phase 3 MajesTEC-4 trial will further evaluate the efficacy of TECVAYLI + lenalidomide by comparing it to teclistamab alone and lenalidomide alone as maintenance therapy in patients with NDMM.¹¹⁰

Translational data from MajesTEC-1 showed that patients who did not achieve a clinical response had a higher baseline frequency of T cells expressing markers associated with T-cell exhaustion or dysfunction, such as PD-1, an immune checkpoint marker.⁹⁵ PD-1 overexpression is associated with both an immunosuppressive environment and progressive disease, and PD-1 inhibition has shown anti-tumor activity in combination with other immunomodulatory agents.¹¹¹ The phase 1b TRIMM-3 study is evaluating TECVAYLI in combination with cetrelimab, a PD-1 inhibitor, in patients with RRMM.

The novel GPRC5D×CD3 bispecific antibody, talquetamab, has shown promising efficacy in patients with RRMM.¹¹² Simultaneously targeting two different validated myeloma target antigens is hypothesized to improve outcomes by overcoming antigen escape or other mechanisms of resistance and potentially reducing the risk of relapse.¹¹³ The phase 1b RedirecTT-1 trial is exploring the combination of TECVAYLI with talquetamab in patients with TCE RRMM.

4.4.2 *TECVAYLI™ in combination with multiple agents*

Combining the cytotoxic and immunomodulatory actions of multiple immunotherapies may synergistically enhance efficacy. Initial results from MajesTEC-2 regimen E demonstrated that the combination of TECVAYLI-daratumumab-lenalidomide resulted in deep and durable responses in patients with RRMM.¹¹⁴ The phase 3 MajesTEC-7 study will further explore this fully immune-based triplet in comparison with daratumumab-lenalidomide-dexamethasone in transplant ineligible patients with NDMM,¹¹⁵ as patients may have a more favorable immune profile in earlier lines of therapy.⁹⁵

The multicohort MajesTEC-2 study is exploring combinations with other immunomodulatory SOC therapies that may have complementary effects when used in combination with TECVAYLI across different lines of therapy. Regimen A will evaluate teclistamab-daratumumab-pomalidomide in patients with RRMM who have received 1–3 prior lines of therapy including a PI and lenalidomide. Regimen B will assess TECVAYLI in combination with DVR in 21-day cycles in patients with NDMM or RRMM who are lenalidomide-naïve. Regimen F will evaluate TECVAYLI in combination with DVR in 28-day cycles in patients with NDMM.

4.5 Improving patient convenience with TECVAYLI™

The clinical efficacy of any therapeutic is of utmost importance, but it is essential for a treatment to also be available and convenient in order to be truly effective for patients. TECVAYLI delivers on all 3 aspects with exceptional efficacy, immediate availability, and convenient administration.

4.5.1 Off-the-shelf therapy with immediate availability

TECVAYLI is readily available for same-day administration and does not require additional procedures, such as lymphodepletion, or time-consuming and costly manufacturing logistics that are involved in the production of CAR-T cell therapy.^{62,116,117} For example, the BCMA-targeting CAR-T cell therapy, ide-cel, demonstrated a similar ORR to that of TECVAYLI in their respective pivotal trials for patients with RRMM (73% vs 63%).^{55,88} The time between apheresis and infusion of the CAR-T cell product, however, can take approximately 1 month, and patients may experience disease progression in the interim.¹¹⁸ A recent study showed that patients spent a median of 6 months on a waiting list for apheresis, with only 25% going on to receive treatment and 25% moving to hospice care.¹¹⁹ TECVAYLI is manufactured by the validated DuoBody® platform, a robust method to produce highly stable, full-length bispecific antibodies on a commercial scale.⁸⁴ TECVAYLI has demonstrated exceptional clinical efficacy in patients with RRMM and is readily available for those patients who cannot afford to wait.

4.5.2 Subcutaneous administration

TECVAYLI is administered as a subcutaneous injection, which is the preferred route of administration over intravenous infusion reported by patients and providers.¹²⁰ Subcutaneous delivery is fast and simple. As less time is spent in infusion centers, the treatment burden is reduced for both the patients and providers, and there is often an option for outpatient administration.^{121,122} Additionally, subcutaneous dosing offers lower hospital and clinical costs and healthcare resource utilization compared with intravenous administration.^{120,121} The convenience of subcutaneous therapies increases overall satisfaction reported by patients and healthcare providers.^{123,124}

Collective safety, efficacy, pharmacokinetic, and pharmacodynamic data supported the weekly subcutaneous RP2D of TECVAYLI in the MajesTEC-1 study, delivering outstanding efficacy with tolerable safety. Intermittent and alternative dosing schedules for TECVAYLI are also being explored for increased convenience without compromising efficacy. For example, some patients in the MajesTEC-1 study who have achieved a sustained response have switched to a less frequent dosing schedule; these data have been submitted for regulatory approval in the USA and EU supporting a labeling update to allow every-other-week dosing. The reduced cost and complexity of subcutaneous administration, in addition to a unique MOA, makes TECVAYLI highly conducive to combination therapy, increasing its transformative utility in MM therapy.

4.5.3 Ongoing innovation

Data from the MajesTEC-1 study has helped to establish TECVAYLI as a new SOC therapy for MM. Its robust clinical efficacy and high combinability demonstrate that TECVAYLI has the potential to revolutionize the therapeutic landscape of MM and beyond by expanding treatment options across all lines of therapy, both as a monotherapy and in a variety of combination treatments. Studies are also planned to explore the use of TECVAYLI alone or in combination in patients with early/smoldering MM.

5 Conclusions

Over the past few decades, the MM therapeutic landscape has evolved considerably with the emergence of current SOC therapies. However, patients continue to relapse and cycle through these treatments, giving rise to a growing population of patients with TCE RRMM. It is becoming increasingly clear that treatments with novel MOAs are urgently needed for this difficult-to-treat patient population. TECVAYLI is the only approved BCMA×CD3 bispecific antibody with a personalized, weight-based, and flexible dosing schedule for the treatment of TCE RRMM, offering time and hope to patients with RRMM. With superior clinical outcomes, immediate availability, and high combinability, TECVAYLI represents a new SOC that is transforming the therapeutic landscape, giving rise to potentially curative regimens for patients with MM.