4 Innovation

4.1 TECVAYLI FDA Breakthrough Therapy Designation for the treatment of relapsed/refractory multiple myeloma

TECVAYLI was accepted into the European Medicines Agency's Priority Medicines scheme on January 29, 2021.[105] 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.[1,88] 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.[88] The designation was based on the outstanding efficacy TECVAYLI demonstrated in the phase 1/2 MajesTEC-1 study.[86] TECVAYLI then received accelerated approval from the US FDA on October 25, 2022.[106] 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 B-cell maturation antigen, a recognized target for therapeutic intervention in relapsed/refractory multiple myeloma

Preclinical models have demonstrated that BCMA-targeting effectively blocks MM cell proliferation and promotes malignant cell death.[72,107,108] sBCMA is elevated in the serum of patients with MM and high levels are associated with increased disease burden and poor prognosis.[72,107] BCMA overexpression and activation are associated with MM progression, and clinical models have validated BCMA as an effective target for therapeutic intervention in MM.[63,72,75,78]

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 7A**).[86] In a separate analysis, baseline sBCMA was identified as a predictive biomarker of response, with an inverse correlation between the 2 parameters such that as baseline sBCMA levels increase, the probability of responding to teclistamab decreases (**Figure 7B**).[109]

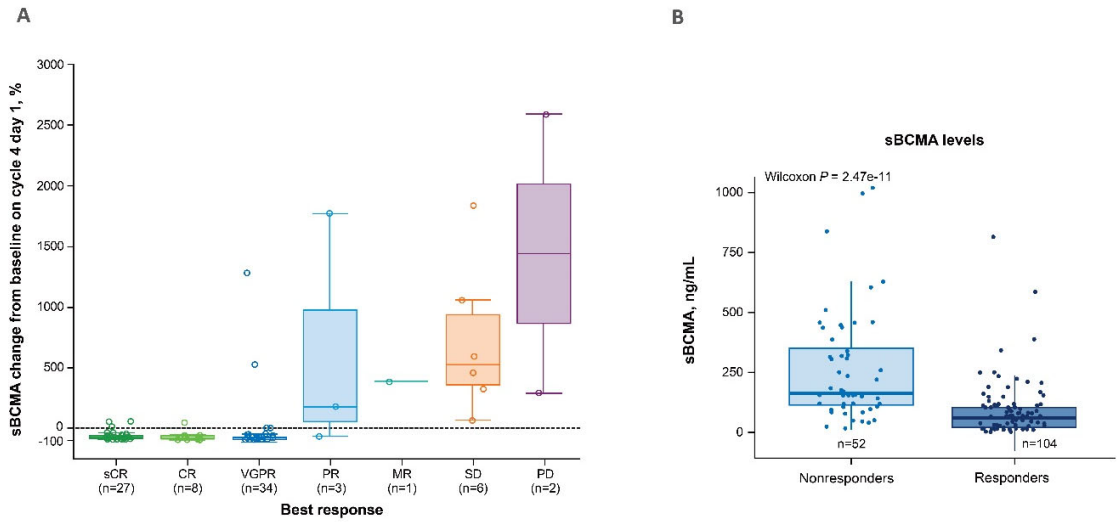

Figure 7: (A) Changes in sBCMA after TECVAYLI treatment by response[86] (B) sBCMA levels at baseline in responders and nonresponders.[109] CR, complete response; MR, minimal response; PD, progressive disease; sBCMA, soluble B-cell maturation antigen; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

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 relapsed/refractory multiple myeloma therapy with excellent efficacy

Currently, there is no single, clear SOC therapy for patients with TCE RRMM, with more than 100 different treatment regimens utilized in real-world settings.[110] 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 standard of care therapies

Data from ITCs between MajesTEC-1 and the prospective, noninterventional LocoMMotion and MoMMent studies showed that treatment with TECVAYLI resulted in improved outcomes over real-world physician's choice of therapy (RWPC). Adjusted comparisons showed that patients treated with TECVAYLI were 2.4-fold, 6-fold, and >100-fold more likely to respond, achieve ≥VGPR, and achieve ≥CR, respectively, compared with RWPC (**Figure 8**).[110]

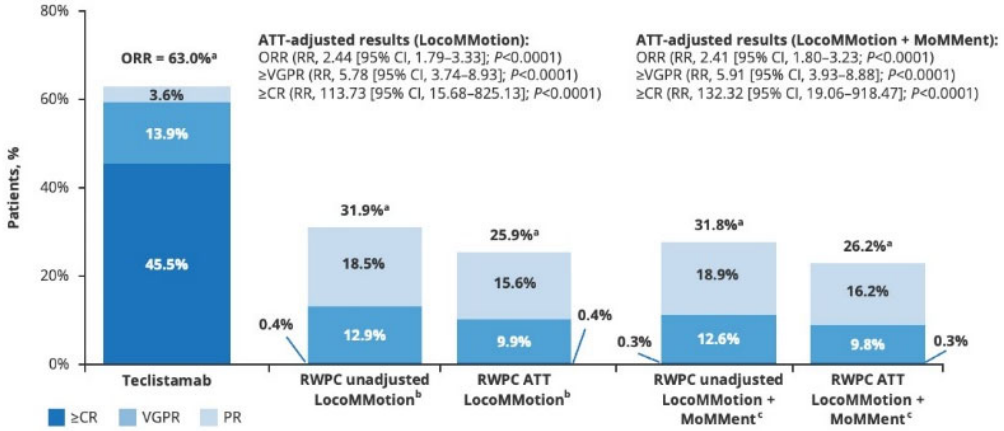

Figure 8: Response outcomes for TECVAYLI in MajesTEC-1 vs RWPC in LocoMMotion and LocoMMotion + MoMMent.[110] [a]ORR = ≥CR + VGPR +PR; may not sum appropriately as shown due to rounding. [b]Teclistamab versus LocoMMotion. [c]Teclistamab vs LocoMMotion + MoMMent. ATT, average treatment effect in the treated; CR, complete response; ORR, overall response rate; RR, response-rate ratio; RWPC, real-world physician's choice; VGPR, very good partial response.

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.[111,] 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.[111]

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.[112] Patients were 2-fold more likely to respond to treatment with TECVAYLI than with selinexor-dexamethasone and were 24-fold more likely to achieve ≥CR (**Figure 9**). Patients treated with TECVAYLI had significantly longer duration of response (HR [95% CI], 0.06 [0.03–0.14]; *P*<0.0001) and OS (0.55 [0.33–0.93]; *P*=0.0265) and numerically better PFS (0.61 [0.33–1.13]; *P*=0.1164).[113]

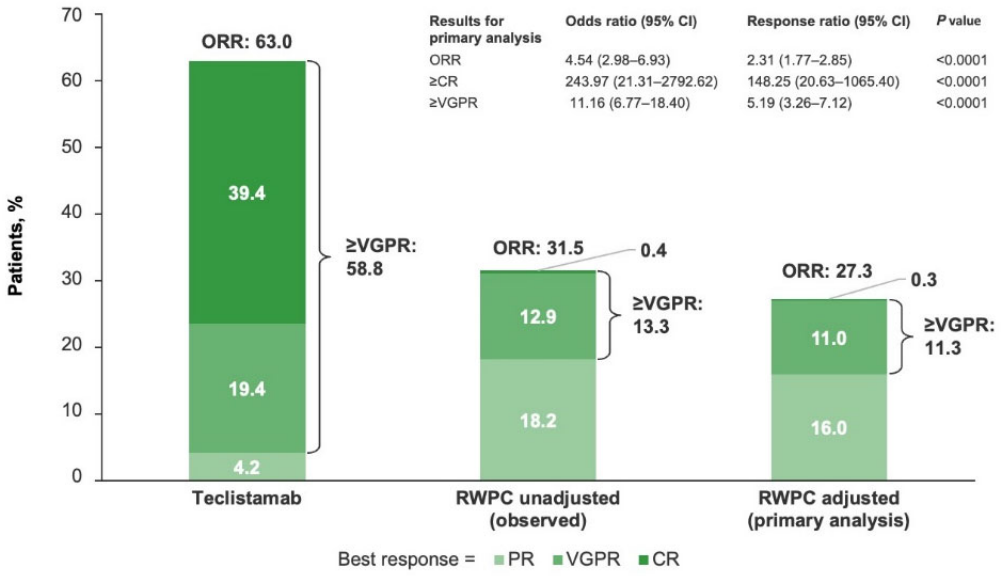

Figure 9: Response outcomes for TECVAYLI in MajesTEC-1 vs selinexor-dexamethasone in STORM part 2.[113] CR, complete response; ORR, overall response rate; PR, partial response; VGPR, very good partial response.

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

In a matched-adjusted indirect comparison of the MajesTEC-1 and MagnetisMM-3 studies, elranatamab, another approved BCMA-targeting bispecific antibody, demonstrated improved efficacy outcomes over TECVAYLI.[114] Patients treated with elranatamab had a significantly higher ORR (75.3% vs 63.0%) and significantly longer PFS (hazard ratio [HR], 0.59; 95% CI, 0.39–0.89). In an ITC comparing the MajesTEC-1 and LINKER-MM1 studies, linvoseltamab, a BCMA-targeting bispecific antibody currently in development, demonstrated improved outcomes over TECVAYLI.[115] Patients treated with linvoseltamab had significantly longer PFS vs TECVAYLI (not reached [NR] vs 10.1 [HR, 0.53; 95% CI, 0.33–0.86]) and rates of ≥CR (45% vs 32% [HR, 1.75 [1.17–2.62]) after matching. It is important to note, however, that the MajesTEC-1 pivotal population was enrolled during the peak of the COVID-19 pandemic, prior to availability of vaccines and guidelines for management of infections with BCMA therapies. Additionally, there is an unknown impact of subsequent therapies on overall survival: MagnetismMM-3 and LINKER-MM1 patients may have had greater accessibility to commercially available novel treatments that were not available to patients in MajesTEC-1.

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 line of therapy.[116] In addition to clinical efficacy and safety, it is vital to consider the impact novel treatments have on HRQoL.

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Treatment with TECVAYLI was associated with an overall improvement in patients' HRQoL in the MajesTEC-1 study.[117,118]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 meaningful improvement by cycles 4–12, and the proportion of patients reporting meaningful improvement in overall health (EuroQoL 5-Dimension 5-Level [EQ-5D-5L]) increased over time (**Figure 10**).

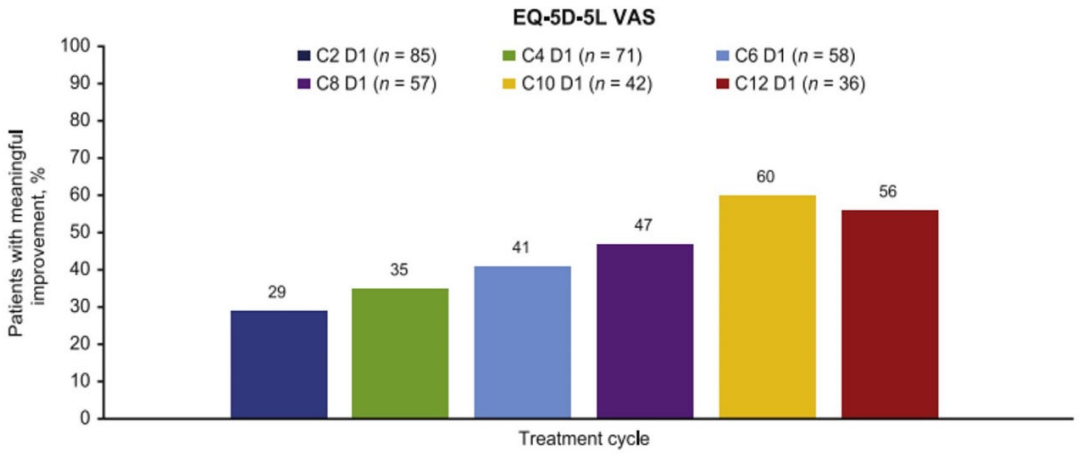

Figure 10: Improvement in HRQoL with TECVAYLI.[117] C, cycle; D, day; EQ-5D-5L, EuroQoL 5-Dimension 5-Level; HRQoL, health-related quality of life; VAS, visual analog scale.

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 mechanism of action that has the potential to enhance antimyeloma effects when combined with complementary therapeutic agents

Combination regimens that include agents with distinct targets and MOAs are being increasingly used to remove multiple subclonal tumor cell populations, induce deeper responses, and reduce the risk of developing refractory disease.[119] Combinatorial approaches are hypothesized to yield synergistic efficacy with manageable safety profiles.[85] 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.[120] 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.[120] The combination of teclistamab and daratumumab has been shown to upregulate CD38+/CD8+ T cells and proinflammatory cytokines, suggesting the potential for synergistic effects and enhanced efficacy.[101] Initial results from the weight-based cohort of 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%.

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.[49,50,121] 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.[121]

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.[109] 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.[122] The phase 1b TRIMM-3 study is evaluating TECVAYLI in combination with cetrelimab, a PD-1 inhibitor, in patients with RRMM.

The first-approved GPRC5D×CD3 bispecific antibody, talquetamab, has shown promising efficacy in patients with RRMM. Simultaneously targeting 2 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.[123] The phase 1b RedirecTT-1 trial reported high ORRs in patients who received teclistamab in combination with talquetamab, including in patients with extramedullary plasmacytomas.[103]

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.[124] At median follow-up >1 year from the safety run-in cohort 1 of the phase 3 MajesTEC-7 study, teclistamab in combination with daratumumab and lenalidomide demonstrated a manageable safety profile and promising efficacy in patients with NDMM who are transplant ineligible/not intended for ASCT.[99]

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-naive. 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.[67,125,126] 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%).[58,86] 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.[127] 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.[128] TECVAYLI is manufactured by the validated DuoBody® platform, a robust method to produce highly stable, full-length bispecific antibodies on a commercial scale.[81] 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.[129] 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.[130,131] Additionally, subcutaneous dosing offers lower hospital and clinical costs and healthcare resource utilization compared with intravenous administration.[129,130] The convenience of subcutaneous therapies increases overall satisfaction reported by patients and healthcare providers.[132,133] 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.

4.5.3 Option for flexible dosing

The European Commission (August 2023) and United States FDA (February 2024) have approved TECVAYLI for a less frequent dosing frequency of 1.5 mg/kg Q2W in patients with RRMM who have achieved and maintained a ≥CR for a minimum of 6 months.[89,90] In the MajesTEC-1 study, patients who switched to less frequent dosing maintained deep responses. In addition, new-onset grade ≥3 infections generally decreased over time, approximately coinciding with the timing of switch to Q2W dosing schedules.[134] The approval of biweekly dosing may further enable healthcare providers to meet the needs of individual patients who want more flexibility in their dosing schedules, with the opportunity for future studies to continue optimizing the convenience and benefit-risk profile of TECVAYLI.[90]

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4.5.4 Ongoing innovation

The convenience of subcutaneous administration, reduced healthcare resource utilization and costs,[129] and a unique MOA, make TECVAYLI highly conducive to combination therapy, increasing its transformative utility in MM therapy. Data from the MajesTEC-1 study have helped 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.

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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 first approved BCMA×CD3 bispecific antibody for the treatment of TCE RRMM, with weight-based dosing and the longest study follow-up of any bispecific antibody in MM. With superior clinical outcomes, immediate availability, and high combinability, TECVAYLI is establishing a new SOC that is transforming the existing therapeutic landscape and creating a foundation for future treatments, potentially leading to curative regimens for patients with MM.