3 History and development of TECVAYLI

3.1 Rationale for development of TECVAYLI

Although current SOC treatments have led to improvements in survival and HRQoL, patients still ultimately relapse, and outcomes decline with each successive line of therapy.[7,70] An ideal treatment would improve upon the efficacy of existing SOC therapies for RRMM, reduce treatment-related morbidity and mortality, improve HRQoL, and offer increased patient convenience.

3.1.1 Exploring options for immunotherapies in multiple myeloma

Novel targeted immunotherapies, such as bispecific antibodies, are being developed to help address the unmet need that remains after traditional SOC options have been exhausted. They work by helping to overcome the tumor evasion that occurs because of impaired immune surveillance against tumor antigens.[63,71-73] Bispecific antibodies have been developed to overcome some of the limitations of conventional mAbs to enhance therapeutic efficacy.[73] Bispecific antibodies target antigens on tumor cells and T cells, bringing the them into close physical proximity to result in killing of myeloma cells.[63,64,73]

3.1.2 Identification of a suitable target – What is B-cell maturation antigen?

Ideal antigens for immunotherapy are proteins that are highly expressed on tumor cells but have limited expression on healthy tissues.[73] BCMA regulates B-cell proliferation, survival, and maturation and differentiation into plasma cells.[63,72,74-77] BCMA is preferentially expressed on plasmablasts and differentiated plasma cells and is more abundant on myeloma cells compared with normal plasma cells.[63,72,74,76-78] BCMA has 2 agonist ligands, APRIL and BAFF, which are produced by bone marrow cells.[63,72,75-77] In MM cells, the binding of BCMA to these ligands activates multiple growth and survival signaling cascades via NF-κβ.[63,77] Soluble BCMA (sBCMA) can circulate in peripheral blood because of γ-secretase–mediated shedding from the cell membrane.[63,79]

3.2 TECVAYLI mechanism of action

T-cell redirecting bispecific antibodies are a novel class of immunotherapy for MM.[63] Teclistamab is a full-size bispecific antibody construct that is more stable and reduces nonspecific binding compared with single-chain variable fragment constructs.[63,66,67] TECVAYLI induces T-cell–mediated cytotoxicity via recruitment of CD3-expressing T cells to BCMA-expressing cells, leading to T-cell activation and subsequent target cell lysis via secretion of perforin and granzymes (**Figure 3**).[64,80]

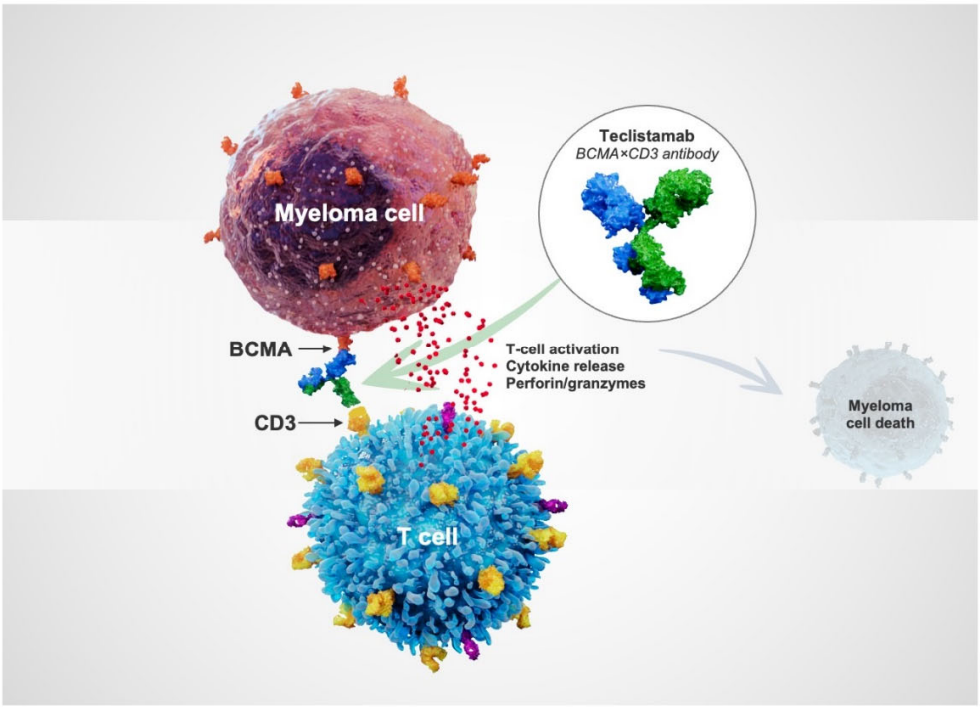

Figure 3: Teclistamab's MOA.[80] BCMA, B-cell maturation antigen.

CD3 is expressed by all CD8+ and CD4+ T cells and enables polyclonal T-cell activation, expansion, cytokine production, and cell lysis.[81,82] Malignant cells, however, often downregulate or lose expression of major histocompatibility complex (MHC) molecules, and T-cell infiltration into the tumor can be poor.[83,84] Teclistamab helps to overcome these forms of tumor-mediated evasion from the immune system by binding to the CD3 receptor complex on T cells to mediate T-cell activation and redirection to BCMA-expressing myeloma cells without the requirement of MHC molecules.[64,84]

In vitro, teclistamab induced selective T-cell–mediated cytotoxicity of BCMA-positive cells, with robust T-cell activation as measured by surface expression of CD25 and CD107a on CD4+ and CD8+ T cells, respectively.[64] Teclistamab-mediated T-cell activation leads to the production and release of cytokines, perforin, and granzymes from both CD4+ and CD8+ T cells for subsequent lysis of myeloma cells.[64] 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.[85]

3.3 TECVAYLI clinical development program

TECVAYLI is approved for the treatment of RRMM after 4 or more prior lines of therapy in the United States and 3 or more prior lines of therapy in the EU and is being developed across a range of disease and treatment settings. The clinical development program includes studies of TECVAYLI both as a monotherapy and as part of combination therapies in RRMM (patients who have received 1 or more prior lines of therapy), NDMM (frontline or maintenance therapy and in patients who are both eligible and ineligible for ASCT), and early or smoldering MM. This

accelerated development plan was designed to bring TECVAYLI to as many patients with MM as possible at any stage of disease or treatment course.

3.3.1 MajesTEC-1

The MajesTEC-1 study was a phase 1/2, multicenter, open-label study of TECVAYLI monotherapy in patients with RRMM.[86,87] In the phase 1 part of the study, teclistamab was administered via intravenous infusion or subcutaneous injection in different dosing cohorts. A maximum tolerable dose was not reached, and the recommended phase 2 dose (RP2D) was determined to be a once-weekly subcutaneous dose of teclistamab 1.5 mg/kg preceded by step-up doses of 0.06 and 0.3 mg/kg. Patients could switch to every-other-week (Q2W) dosing if they achieved a partial response or better after at least 4 cycles in phase 1, or if they maintained ≥CR for at least 6 months in phase 2 (**Figure 4**).[86,87]

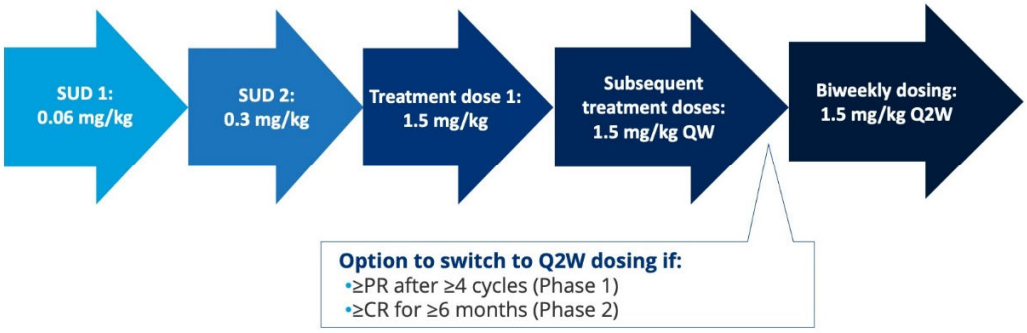

Figure 4: TECVAYLI RP2D dosing schedule. 2–4 days were allowed between step-up dose 1, step-up dose 2, and treatment dose 1. Patients could further switch to less frequent dosing with continued response on the Q2W schedule. CR, complete response; PR, partial response; Q2W, every other week; QW, weekly; RP2D, recommended phase 2 dose; SUD, step-up dose.

The pivotal cohort was comprised of 165 patients from phase 1 and 2 of MajesTEC-1 who received teclistamab at the RP2D dose.[86] Results from this cohort formed the basis of the breakthrough therapy designation and accelerated approval from the United States FDA for TECVAYLI as a monotherapy for patients with RRMM who had received at least 4 prior lines of therapy including a PI, an IMiD, and an anti-CD38 mAb.[1,88] The European Commission (in August 2023) and the United States FDA (in February 2024) approved TECVAYLI for a reduced

dosing frequency of 1.5 mg/kg once every 2 weeks in patients with RRMM who have achieved and maintained ≥CR for a minimum of 6 months.[89,90]

Patients in the pivotal cohort of MajesTEC-1 were heavily pretreated and had received a median of 5 prior lines of therapy.[86] At median 30.4-month follow-up (clinical cut-off: August 22, 2023), 104/165 patients responded, giving an ORR of 63%. Responses were deep: 98 (59.4%) patients achieved a ≥VGPR, and 76 (46.1%) patients achieved a ≥CR (**Figure 5**). In addition, 48 of 56 patients evaluable for minimal residual disease (MRD) were MRD negative (85.7%). The median duration of response was 24.0 months; median duration of response in patients who achieved ≥CR was not reached. Medians for PFS and overall survival (OS) were 11.4 months and 22.2 months, respectively.[24]

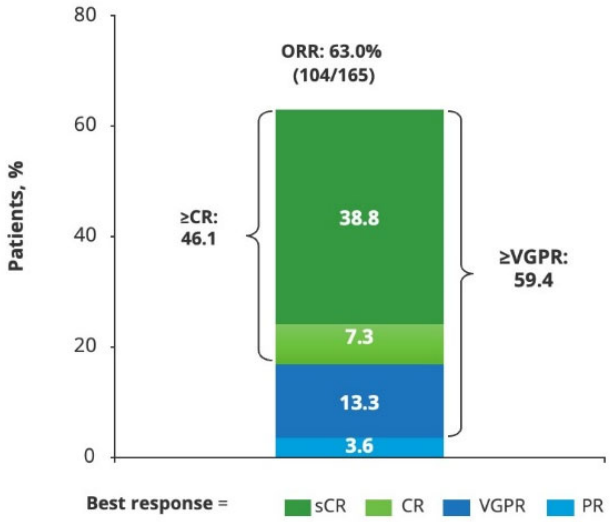

Figure 5: TECVAYLI overall response rate at 30.4-month median follow-up.[24] CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

Responses to teclistamab were also consistent across most clinically relevant subgroups, including those who were aged ≥75 years, had high-risk cytogenetic abnormalities, or had penta-drug refractory disease.[86, 91] Lower response rates were observed in patients with EMD, who are historically challenging to treat,[92] as well as those with International Staging System stage III disease and those who had ≥60% bone marrow replacement by plasma cells; however, a small sample size and wide confidence intervals make these data challenging to interpret.[86] Notably, the ORR was higher in patients who received 3 or fewer prior lines of therapy compared with those who received more than 3 prior lines (74.4% vs 59.0%), suggesting that teclistamab may be an effective treatment earlier in the disease course.[86,93]

TECVAYLI also demonstrated a safety profile with toxicity that is largely manageable.[86,94] Adverse events (AEs) were common but clinically manageable in MajesTEC-1. Hematologic AEs included neutropenia (71.5%), anemia (55.2%), thrombocytopenia (41.8%), and lymphopenia (36.4%). Infections occurred in 78.8% of patients, including 55.2% with grade 3/4 infections.[86,95] Overall, the frequency of infections is consistent with the increased susceptibility to immunodeficiency associated with MM and the immunosuppressive effects of prior therapy.[96] The rate of new-onset grade ≥3 infections generally decreased over time in MajesTEC-1, potentially due in part to switching to less frequent dosing schedules or differences in management strategies such as immunoglobulin replacement and infection prophylaxis.[97] The incidence of investigator-assessed neurotoxicity was 14.5%, with 5 patients experiencing a total of 9 events of immune effector–cell associated neurotoxicity syndrome (ICANS); all ICANS events were grade 1/2 and fully resolved.[86] Cytokine release syndrome (CRS) occurred in 72.1% of patients, and all events, except 1, were grade 1/2. CRS was managed with implementation of 2 step-up doses; premedication with a steroid, an antihistamine, and an antipyretic; in-hospital monitoring; and other supportive measures, including tocilizumab and corticosteroids.[98] Median time to CRS onset was 2 days, and all CRS events fully resolved after a median duration of 2 days (range, 1–9 days).[1,86,94]

3.3.2 Other ongoing and future studies

A robust clinical development program is in place to explore the use of teclistamab for all patients with MM at any stage of disease or treatment course. The results of the pivotal cohort from the MajesTEC-1 study have demonstrated the exceptional efficacy of TECVAYLI as a monotherapy for patients with heavily pretreated RRMM. Initial subgroup analyses from MajesTEC-1 suggested that ORRs were higher for those patients who had received 3 or fewer prior lines of therapy (vs more than 3 prior lines of therapy) and support the use of TECVAYLI in earlier lines of therapy.[86] The emerging immune profile of TECVAYLI monotherapy is being evaluated to understand whether using clinical combinations of TECVAYLI can favorably modulate the immune response to improve clinical efficacy with translational data from MajesTEC-1.[99] Clinical response was associated with a higher baseline frequency of peripheral T cells and a higher baseline frequency of naive CD8+ T cells. A longer PFS was observed in patients with a low frequency of programmed cell death protein 1 (PD-1)+/CD8+ and Treg/CD4+ T cells in the periphery and those with a low frequency of CD25+/CD4+ and CD38+/CD4+ T cells in the bone marrow. These data indicate that patients who do not respond to TECVAYLI have an unfavorable baseline immune profile suggestive of T-cell dysfunction or exhaustion, supporting clinical combinations of teclistamab with immunomodulatory agents such as daratumumab or checkpoint inhibitors.

TECVAYLI in combination with other agents and in earlier lines of therapy are being investigated in several ongoing and future clinical trials (**Figure 6**).

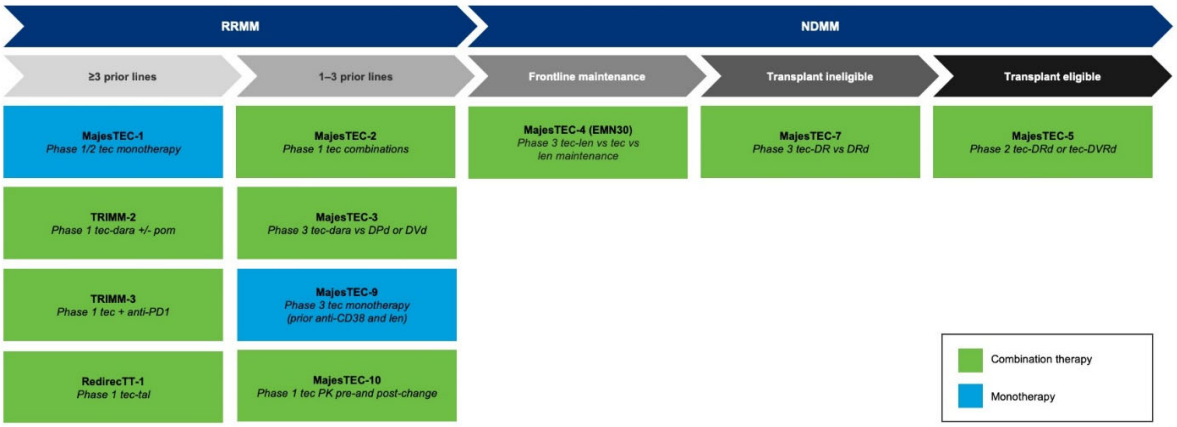

Figure 6: TECVAYLI clinical development program. dara, daratumumab; DPd, daratumumab, pomalidomide, and dexamethasone; DR, daratumumab and lenalidomide; DRd, daratumumab, lenalidomide, and dexamethasone; DVd, daratumumab, bortezomib, and dexamethasone; len, lenalidomide; PK, pharmacokinetics; pom, pomalidomide; tal, talquetamab; tec, teclistamab.

3.3.2.1 Monotherapy in relapsed/refractory multiple myeloma

An additional cohort of patients in the phase 2 part of the MajesTEC-1 study is ongoing that includes patients with prior exposure to BCMA-targeted therapies including antibody-drug conjugates and CAR-T cell therapy. Initial results from this cohort demonstrated that TECVAYLI monotherapy elicits an overall response rate of 52.5%, with 47.5% of patients achieving ≥VGPR and 30.0% achieving ≥CR (N=40).[100]

The use of TECVAYLI monotherapy after 1–3 prior lines of therapy is being explored in the randomized, phase 3, open-label, multicenter MajesTEC-9 study (NCT05572515). Prior therapies must include an anti-CD38 mAb and lenalidomide, which represents an increasingly relevant patient population. Patients will be randomized 1:1 to receive either teclistamab at the RP2D or investigator's choice of either pomalidomide, bortezomib, and dexamethasone or carfilzomib and dexamethasone. Enrollment is ongoing.

3.3.2.2 Combination therapy in relapsed/refractory multiple myeloma

MajesTEC-2 is a phase 1b, multicohort study designed to assess TECVAYLI in various combinations after prior treatment with at least 1–3 prior lines of therapy (NCT04722146). Six cohorts will assess teclistamab in combination with daratumumab and pomalidomide (regimen A); daratumumab, bortezomib, and lenalidomide (DVR) in 21-day cycles (regimen B); nirogacestat, a selective γ-secretase inhibitor (regimen C); daratumumab and lenalidomide (regimen E); or DVR in 28-day cycles (regimen F).

The phase 1b TRIMM-2 study is evaluating a combination of TECVAYLI and daratumumab (+/- pomalidomide) in patients with RRMM who have received at least 3 prior lines of therapy or were double-refractory to a PI and an IMiD (NCT04108195). Initial results at median 8.6-month

follow-up demonstrated an ORR of 76.5% among the 51 response-evaluable patients with 70.6% achieving ≥VGPR.[101]

TRIMM-3 is a phase 1b study of TECVAYLI in combination with a PD-1 checkpoint inhibitor in patients with RRMM who have received at least 3 prior lines of therapy (NCT05338775).

MajesTEC-3 is a randomized, phase 3, open-label, multicenter study evaluating the efficacy and safety of TECVAYLI in combination with daratumumab in patients who have received 1–3 prior lines of therapy including a PI and lenalidomide (NCT05083169). Patients will be randomized 1:1 to receive either TECVAYLI + daratumumab or investigator's choice of either daratumumab-pomalidomide-dexamethasone or daratumumab-bortezomib-dexamethasone. Enrollment began in October 2021 and is ongoing.[102]

The RedirecTT-1 trial is an ongoing phase 1b study assessing TECVAYLI in combination with talquetamab, a GPRC5D-targeting bispecific antibody, in patients with TCE RRMM (NCT04586426). Talquetamab has previously demonstrated promising efficacy in patients with RRMM as a monotherapy. Simultaneously targeting 2 different myeloma antigens has the potential to improve outcomes by overcoming mechanisms of tumor resistance, such as antigen escape. 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]

3.3.2.3 Frontline multiple myeloma therapy

The phase 3 MajesTEC-4 study will assess the efficacy of TECVAYLI in combination with lenalidomide vs TECVAYLI alone vs lenalidomide alone as frontline maintenance therapy for patients with NDMM (NCT05243797). Lenalidomide is an established SOC therapy for MM and is hypothesized to enhance or improve the efficacy of other immunotherapies through synergistic effects. Enrollment opened in May 2022 and is ongoing.

The phase 3 MajesTEC-7 study is designed to evaluate TECVAYLI in combination with daratumumab and lenalidomide (DR) compared with daratumumab-lenalidomide-dexamethasone (DRd) for patients with NDMM who are ineligible for stem cell transplantation (NCT05552222). Enrollment is ongoing. Initial safety results from the safety run-in cohort demonstrated a manageable safety profile with early efficacy of teclistamab + DR in patients with transplant-ineligible/not intended NDMM.[104]

The phase 2 MajesTEC-5 study will evaluate the safety and efficacy of TECVAYLI in combination with DRd with or without bortezomib as induction therapy in patients with transplant-eligible NDMM (NCT05695508). The study will also evaluate TECVAYLI in combination with daratumumab and lenalidomide as maintenance therapy.

Additional studies will advance TECVAYLI further towards earlier lines of treatment, with the ultimate goal of replacing ASCT as frontline SOC therapy.