

# Teclistamab for Multiple Myeloma: Clinical Insights and Practical Considerations for a First-in-Class Bispecific Antibody

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**Abstract:** Teclistamab is a BCMAxCD3 bispecific antibody, the first approved for the treatment of relapsed or refractory multiple myeloma. Given its impressive efficacy in heavily pretreated patients and better accessibility compared to BCMA-directed CAR T cells, teclistamab is sure to become a staple of relapsed/refractory multiple myeloma therapy. Teclistamab carries a set of notable adverse effects including cytokine release syndrome (CRS), infections, and neurotoxicity for which providers must take unique precautions and prophylactic measures. Here, we review the preclinical and clinical data, which led to teclistamab's approval, important patient selection considerations, strategies for managing CRS and other side effects, and finally the future of bispecific antibody therapy in multiple myeloma.

**Keywords:** teclistamab, bispecific antibody, multiple myeloma, BCMA

## Introduction

Teclistamab (Tecvayli™) is a recently approved bispecific antibody and the first agent in its class for the treatment of multiple myeloma (MM). A humanized IgG<sub>4</sub> antibody composed of an anti-B-cell maturation antigen (BCMA) arm and an anti-CD3 arm, teclistamab recruits and activates endogenous T cells to kill myeloma cells.<sup>1</sup> Based on the results of the non-randomized Phase I/II MajesTEC-1 trial in which subcutaneous teclistamab produced a 63% overall response rate (ORR) in myeloma patients who progressed after standard proteasome inhibitor (PI), immunomodulatory drug (IMiD), and an anti-CD38 monoclonal antibody, conditional approval for teclistamab was granted in the EU on August 23, 2022.<sup>2,3</sup> Shortly thereafter, the FDA granted accelerated approval for teclistamab in the US on October 25, 2022.<sup>4</sup> At the time of this manuscript, teclistamab is authorized for the treatment of MM patients exposed to a PI, IMiD, and anti-CD38 drug (so-called “triple-class exposed”) and whose disease has progressed after at least 3 prior lines of therapy (LOT) in the EU or at least 4 prior lines in the US.

By redirecting T cells to target myeloma, teclistamab seeks to overcome the immune dysfunction that has long been recognized as a hallmark of MM. The progression of monoclonal gammopathy of undetermined significance (MGUS) to overt myeloma is marked by progressive alterations in both T cell quantity and quality which impair their tumor-specific activity.<sup>5</sup> Immune-based therapies such as monoclonal antibodies, CAR-T cell therapy, and antibody-drug conjugates (ADCs) reawaken the myeloma-killing potential of T cells and have proven their ability to generate deep responses despite IMiD and PI-refractory disease. Teclistamab is now the latest addition to an increasing arsenal of immunotherapies which weaponize cellular immunity to treat myeloma.<sup>6</sup>

Here, we will provide clinical insights into the use of teclistamab for relapsed/refractory multiple myeloma (RRMM), including appropriate patient selection and comparisons to other therapies approved in the same setting.

## Pharmacology and Mechanism of Action

Teclistamab targets BCMA, a 20.2 kDa transmembrane receptor encoded by the TNFRSF17 gene on chromosome 16p13 and which plays an essential role in long-term plasma cell survival.<sup>7,8</sup> Because BCMA is highly expressed on myeloma cells and normal plasma cells but is undetectable in hematopoietic stem cells and most non-hematologic tissues, it makes an attractive target for T-cell redirection.<sup>7,9</sup>

Teclistamab activates T cells against BCMA-expressing myeloma cells to promote release of perforins and granzymes and tumor cell lysis.<sup>10</sup> Activated T cells also release cytokines such as IL-2, IL-6, IL-10, and IFN $\gamma$  which contribute to their efficacy.<sup>1,11</sup> Preclinical studies have found no association between degree of BCMA expression on myeloma samples and teclistamab efficacy.<sup>10</sup> Rather, a high effector cell to target cell ratio is important for optimizing tumor cell lysis. Indeed, activating T cells in a high tumor burden environment promotes T-cell exhaustion and eventual loss of effector functions, limiting the efficacy of bispecific antibodies.<sup>12</sup>

## Clinical Data

Teclistamab was initially studied both intravenously and subcutaneously, with collective safety, efficacy, pharmacodynamic, and pharmacokinetic data supporting the subcutaneous route.<sup>13</sup> Current approval for subcutaneous teclistamab as monotherapy is based on results of the MajesTEC-1 trial. In this phase I/II study, 165 patients with RRMM who had at least 3 prior LOT including IMiDs, PIs, and anti-CD38 antibodies were treated with weekly subcutaneous teclistamab at the recommended Phase 2 dose of 1.5 mg/kg.<sup>3</sup> Patients received an initial step-up dose of 0.06 mg followed by a second dose of 0.3 mg/kg 2 to 4 days later, before initiating the standard weekly schedule after another 2 to 4 days. Despite enrolling a heavily pretreated population of 77.6% triple-class refractory patients with a median 5 prior LOT, responses were attained in 63% of patients. Extramedullary disease (EMD, defined as the presence of one or more soft tissue lesions that are not contiguous with bone), ISS stage III disease, and having  $\geq 60\%$  marrow plasma cells were each associated with lower response rates of 35.7%, 35.0% and 44.4%, respectively. Very good partial response (VGPR) or better occurred in 58.5% of patients and 39.4% had  $\geq$  complete response (CR) among whom 46% were minimal residual disease (MRD) negative at a sensitivity threshold of  $10^{-5}$ . Responses were durable with a median duration of 18.4 months, while medians for progression-free survival (PFS) and overall survival (OS) were 11.3 months and 18.3 months, respectively.

In MajesTEC-1, only one patient needed a dose reduction due to recurrent neutropenia, while 63% of patients skipped a dose due to adverse events (AEs) and two patients discontinued therapy due to AEs.<sup>3</sup> Overall, 94.5% of patients experienced grade 3 or 4 AEs which were primarily hematologic. Two-thirds of patients experienced grade  $\geq 3$  neutropenia, 32.7% grade  $\geq 3$  lymphopenia, 37% grade  $\geq 3$  anemia, and 21.2% grade  $\geq 3$  thrombocytopenia. Hypogammaglobulinemia occurred in 74.5% of patients (half of which received intravenous immunoglobulin (IVIg) at physicians' discretion) while infections of any grade occurred in 60% of patients and grade  $\geq 3$  infection in 22%. Other common nonhematologic toxicities included diarrhea (28.5%), fatigue (27.9%), pyrexia (27.3%), and injection site reactions (26.1%), of which the majority were grade 1 and 2. As with other T-cell redirecting therapies, cytokine release syndrome (CRS) was a common AE seen in 72.1% of patients, primarily with initial step-up doses or cycle 1.<sup>3</sup> Of the 119 cases of CRS, half required tocilizumab and only 1 case was grade  $\geq 3$ , meaning vasopressors or high-flow oxygen were required. Immune effector cell-associated neurotoxicity syndrome (ICANS) was seen in 5 patients (3%), frequently in conjunction with CRS. All ICANS events were grade 1 or 2 and tocilizumab and dexamethasone were the main supportive therapies used. Notably, 19 patients (11.5%) died from AEs, of which 12 were associated with the novel coronavirus disease (Covid-19) and ultimately 5 deaths deemed related to teclistamab by investigators. These patients experienced varying complications with progressive multifocal leukoencephalopathy in 1 patient, Covid-19 in 2 patients, liver failure in 1 patient, and streptococcal pneumonia in 1 patient.

Multiple combination trials with teclistamab are underway. Teclistamab has been combined with daratumumab (in TRIMM-2) and both daratumumab and lenalidomide (in MajesTEC-2) without major compounding toxicities limiting its use.<sup>14,15</sup> The Phase 1b TRIMM-2 study treated RRMM patients with a median 5 prior LOT with daratumumab and teclistamab.<sup>15</sup> The most common AEs were CRS in 54.5% (all grade 1 or 2), infections (51.5%, grade  $\geq 3$ : 24.2%), neutropenia (36.4%, all grade  $\geq 3$ ), thrombocytopenia (36.4%, grade  $\geq 3$ : 33.3%), anemia (36.4%, grade  $\geq 3$ : 24.2%), and

diarrhea (36.4%, grade  $\geq 3$ : 3.0%).<sup>15</sup> One patient died from bacterial pneumonia considered unrelated to treatment. Responses were seen in 78% of patients across all dose levels while 21.7% attained  $\geq$ CR. The phase 1b MajesTEC-2 trial enrolled a less pretreated population with a median of 2 prior LOT (versus 5 in MajesTEC-1 and TRIMM-2).<sup>14</sup> With the triplet of teclistamab, daratumumab, and lenalidomide, common AEs included CRS (81.3%, all grade 1 or 2), infections (75.0%, grade  $\geq 3$ : 28.1%) neutropenia (75.0%, grade  $\geq 3$ : 68.8%), fatigue (43.8%, grade  $\geq 3$ : 6.3%), diarrhea (37.5%, all grade 1 or 2), and insomnia (31.3%, grade  $\geq 3$ : 3.1%). One patient died from Covid-19 which was considered unrelated to study drugs. The ORR across all dose levels was 89.7%, with longer follow-up time needed to assess frequency of deep responses.

These early data have demonstrated the feasibility and efficacy of teclistamab as a part of combination therapy. The ongoing randomized Phase 3 MajesTEC-7 will test teclistamab in the frontline setting by comparing daratumumab, lenalidomide, plus dexamethasone (per the phase 3 MAIA study) in newly-diagnosed myeloma patients without intent for transplant in first line to teclistamab, daratumumab, and lenalidomide.<sup>16</sup> Importantly, although historically in myeloma quadruplet and triplet regimens have generally outperformed doublets which have in turn outperformed monotherapy, the high response rates produced with teclistamab monotherapy in heavily pretreated patients call into question whether its utility would truly be improved in a combination regimen. As larger teclistamab-based combination studies are conducted, the potential for overlapping toxicities such as increased infection rates will need to be carefully monitored/addressed. We eagerly await the results of randomized studies to address this question.

## Patient Selection

As previously discussed, teclistamab is currently approved for triple-class exposed MM patients progressing after at least 3 or 4 prior LOT in the EU and US, respectively. Considering its high efficacy, ease of administration, and predictable toxicity profile without major non-hematologic organ toxicities, teclistamab is an option for both fit, younger patients and frail, older patients with comorbidities. CRS, though expected to occur in most patients, is fairly manageable with the IL-6 receptor inhibitor, tocilizumab, and rarely occurs after the dosage step-up phase.

Conversely, BCMA-directed bispecific antibodies as a class are associated with high rates of infections. A recent report pooled 1185 myeloma patients from 11 bispecific antibody monotherapy trials and noted higher rates of grade 3/4 infections among BCMA (30%) versus non-BCMA (11.9%) bispecific antibodies ( $p = 0.01$ , median follow-up 6.1 months), as well as higher rates of grade 3/4 neutropenia (25.3% versus 39.2%).<sup>17</sup> The high risk of infections while on teclistamab is an important long-term consideration, owing at least in part to the hypogammaglobulinemia produced by all anti-BCMA bispecific antibodies.<sup>18</sup> While respiratory tract infections (both viral and bacterial) are the most common, patients on anti-BCMA antibodies may also be at increased risk for fungal infections, urinary tract infections, skin infections, and CMV reactivation. Rates of severe infections may be lowered with IVIg administration, but nonetheless teclistamab may not be a good option in patients with a history of infectious complications.<sup>18</sup>

## Practical Considerations

As the first T-cell redirecting bispecific antibody approved for MM, teclistamab comes with a set of logistical hurdles unique to its class. Teclistamab is administered through subcutaneous injections with a 0.06 mg/kg step-up dose 1, 0.3 mg/kg step-up dose 2, and the first 1.5 mg/kg treatment dose separated by 2 to 4 days each. A roughly 7–10 day admission is recommended during these first three doses per the MasTEC-1 protocol, during which providers familiar with CRS and ICANS can monitor for and treat these frequent AEs with tocilizumab and/or steroids. Although neutropenia is common and can be mitigated with granulocyte colony stimulating factor (G-CSF), G-CSF is generally avoided during priming doses, first treatment dose, and active CRS. Because preclinical studies suggest that granulocyte macrophage colony stimulating factor (GM-CSF) and myeloid cells have a role in the development of CRS, G-CSF is avoided at these timepoints due to the potential for myeloid growth factors to stimulate or propagate CRS.<sup>19</sup> It is worth noting that fully ambulatory administration may become a reality in the near future with such mitigation strategies as tocilizumab pretreatment prior to bispecific antibody infusion, which in two recent bispecific antibody trials reduced cevostamab-related CRS from 90.9% to 35.7% and teclistamab-related CRS from 72.1% to 28.6% without impacting efficacy.<sup>20,21</sup>

The aforementioned infection risk can be mitigated by anticipating hypogammaglobulinemia and treating patients with supplemental IVIg. Due to frequent treatment-related lymphopenia, *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis and viral prophylaxis against herpes simplex, varicella zoster, and, in at-risk patients, hepatitis B are recommended.

## Choosing Between Treatment Options in Late Relapse

Prior to becoming teclistamab-eligible, patients treated with standard myeloma regimens will typically be exposed to and/or refractory to the likes of carfilzomib, pomalidomide, daratumumab, and in some cases elotuzumab or isatuximab.<sup>22</sup> At this multiply relapsed stage, a number of agents are utilized, including selinexor, bendamustine, belantamab-mafodotin (belamaf), panobinostat, melphalan-flufenamide (melflufen), and BCMA CAR T-cells. Notably, the status of belamaf, panobinostat, and melflufen is currently in flux, withdrawn from the US market but still available in Europe. Matched indirect comparisons between teclistamab and selinexor-dexamethasone or belamaf have suggested higher response rates and deeper responses with the bispecific compared to these competing therapies.<sup>23,24</sup> Teclistamab's 63% ORR in MajesTEC-1 also compares favorably to response rates of panobinostat-based and bendamustine-based combinations in heavily pretreated patients which linger in the twenties to thirties.<sup>25–28</sup> Ultimately, the higher response rates with bispecific antibodies over standard regimens must be confirmed through randomized-controlled trials, as has been done with CAR T cells in the KARMMA-3 and CARTITUDE-4 studies.<sup>29,30</sup> The choice between teclistamab and anti-BCMA CAR T is another complex question.

## Teclistamab versus CAR T

When considering alternatives to bispecific antibodies like teclistamab, CAR-T cell therapy naturally comes to mind. Both bispecifics and CAR Ts are considered T-cell redirection approaches, but with the latter, immune cells modified ex-vivo to express chimeric antigen receptors are infused into patients in a form of immunotherapy called adoptive cell therapy. Currently, there are two approved CAR-T products for MM which are both BCMA-directed: idecabtagene vicleucel (ide-cel, ABECMA<sup>®</sup>) and ciltacabtagene autoleucel (cilta-cel, CARVYKTI<sup>®</sup>). Their approved indications mirror teclistamab's, meaning patients must be triple-class exposed and have  $\geq 3$  or  $\geq 4$  prior LOT in the EU and US, respectively.<sup>31–34</sup> Although both cilta-cel and ide-cel are second-generation CAR-T cells incorporating the 4–1BB co-stimulatory domain, in order to boost its affinity, cilta-cel has two BCMA-targeting domains instead of one.<sup>35</sup>

No trials thus far have directly compared teclistamab, ide-cel, and cilta-cel to one another head-to-head, though pertinent components of their respective studies are detailed in Table 1. All three therapies were trialed in primarily triple-class refractory patients with 5–6 prior LOT. Importantly, there was heterogeneity in the number of patients with EMD, known to predict poorer outcomes with T-cell redirecting therapies, with baseline EMD present in 13.4% of CARTITUDE-1, 17.0% of MajesTEC-1, and 39.1% of KarMMA patients.<sup>3,35,36</sup> Teclistamab and ide-cel produced grossly comparable response rates (63.0% vs 73.4%, respectively) and PFS (11.3 vs 8.8 months, respectively).<sup>3,36</sup> In contrast, in the CARTITUDE-1 study cilta-cel boasted a remarkable 97.9% ORR with median PFS 34.9 months.<sup>37,38</sup> Although the ability of cilta-cel to achieve a median PFS more than triple teclistamab's and ide-cel's is difficult to ignore, no definite conclusions can be drawn without a direct comparison. Early reports of real-world cilta-cel data have found a lower 80% ORR in a population with more EMD (35%) and prior BCMA therapy (14%) than CARTITUDE-1.<sup>39</sup>

**Table 1** Comparison of Approved T Cell-Redirecting Therapies

Agent	Trial	%EMD	%Triple-Class Refractory	Median LOT	ORR	Median PFS	CRS, Any Grade (Grade $\geq 3$ )	ICANS, Any Grade (Grade $\geq 3$ )
Teclistamab (Tecvayli)	MajesTEC-1 <sup>3</sup>	17%	77.6%	5	63.0%	11.3	72.1% (0.6%)	3% (0%)
Ide-cel (ABECMA <sup>®</sup> )	KarMMA <sup>36</sup>	39.1%	84.4%	6	73.4%	8.8	84% (5%)	18% (3%)
Cilta-cel (CARYKTI <sup>®</sup> )	CARTITUDE-1 <sup>37,38</sup>	13.4%	87.6%	6	96.9%	34.9	95% (4%)	17% (2%)

In addition to efficacy, safety is an important issue when comparing CAR T products and teclistamab. At just 3%, the ICANS rate observed with teclistamab was noticeably lower than was seen with ide-cel and cilta-cel, at 18% and 21%, respectively.<sup>3,36,37</sup> CRS rates with teclistamab (72.1%) were also slightly lower than with ide-cel and cilta-cel (84% and 95%, respectively).<sup>3,36,37</sup> Indeed, while both bispecific antibodies and CAR T cells cause CRS, CRS appears to generally be more frequent, last longer, and necessitate more prevalent tocilizumab use with CAR T cells than with bispecifics.<sup>40</sup> Furthermore, CAR T cells also have the potential to induce cytopenias that persist for many months in a subset of patients, a thus far incompletely understood phenomenon initially recognized with the use of CD19 CAR T cells in lymphoma.<sup>41,42</sup> Patients who are older, more heavily pretreated, and have had prior transplants are at higher risks for developing these prolonged cytopenias.<sup>43</sup>

Lastly, when choosing between teclistamab and either ide-cel or cilta-cel, the logistical hurdles CAR T's pose must be taken into account. Manufacturing autologous CAR-T cells is a laborious process, which takes about one month from time of cell collection to infusion, with rare but not non-existent failure rates.<sup>36</sup> Although bridging therapies are used during this period to control disease progression, in the KarMMa 12 enrolled patients (8.6%) failed to receive ide-cel while in CARTITUDE-1 16 (14.2%) failed to receive cilta-cel due to progression, withdrawal, or death.<sup>35,36</sup> Furthermore, an ongoing shortage of BCMA CAR-T manufacturing slots has meant that many patients who qualify for them are unable to get timely access to the products.<sup>44,45</sup> Prior to the approval of cilta-cel, patients awaited ide-cel treated for a median of 6 months, with only 25% of waitlisted patients receiving a leukapheresis slot for commercial ide-cel, 50% instead enrolling in clinical trials, and 25% dying or enrolling in hospice.<sup>46</sup> Among waitlisted patients, younger patients and those who had previously received stem cell transplantation were more likely to receive CAR-T therapy.<sup>47</sup> For patients who are eventually treated with ide-cel or cilta-cel, an approximately 2-week admission is generally required to monitor for and manage anticipated CRS and ICANS.

When taken together, these important differences can help to distinguish patients for whom teclistamab is most appropriate from patients who make strong CAR T candidates. As an off-the-shelf product, teclistamab is the clear choice for patients experiencing rapidly progressive disease in need of short-term control. For younger, fitter patients who are at lower risk for prolonged cytopenias, can tolerate potential waiting periods for CAR T, and can tolerate their higher CRS and ICANS risks, cilta-cel may be their best chance at a deep, multiyear response. Additionally, either CAR T product will be a good fit for patients young and old for whom the potential for a treatment-free period is strongly desired. Conversely, as a regularly administered treatment, teclistamab may be preferable for more frail patients prone to AEs or those prioritizing quality of life, for whom teclistamab treatment can be delayed or discontinued as needed based on tolerance. Finally, teclistamab remains an essential option for all patients who are simply unable to access CAR T cells due to logistical hurdles such as geographic location or limited supply.

## Managing CRS and ICANS from Teclistamab

The mainstays of CRS management are the IL-6 receptor antagonist, tocilizumab, and corticosteroids which are both reasonable frontline options. Though a number of additional immunosuppressive agents may be considered for refractory cases (Table 2), these interventions are rarely required with bispecific antibodies and thus experience with agents like anakinra and etanercept are primarily in CAR Ts.<sup>48–51</sup> Tocilizumab is highly efficacious for terminating CRS as well as for preventing recurrences and is typically the first agent used for teclistamab-related CRS. Side effects of tocilizumab include neutropenia (60%), headache (17%), diarrhea (8%), and a potential for increased rates of serious infections.<sup>52</sup> Grade 1 CRS (fever without hypotension or hypoxia) is treated supportively with acetaminophen, though tocilizumab is increasingly utilized at this stage to prevent progression to more serious manifestations. In MajesTEC-1, median time from administration of tocilizumab to resolution of CRS was 1.0 day.<sup>48</sup> Patients receiving tocilizumab for their first CRS event were also far less likely to experience a second event (20.0% vs 62.2% in those who did not).<sup>48</sup> Higher grades of CRS should be treated with tocilizumab or steroids along with supportive interventions for hypotension or hypoxia including fluid resuscitation, vasopressors, and supplemental oxygen when appropriate. Patients who experience recurrent or persistent CRS events may be re-dosed with tocilizumab for up to 3 total doses per day. Although tocilizumab has a long concentration-dependent half-life of close to one week (160.2 hours) after just one 8 mg/kg dose which reaches 241.8 hours after three doses, redosing primarily serves to increase serum concentrations of tocilizumab and total drug exposure.<sup>53</sup>

**Table 2** Agents Utilized for Cytokine Release Syndrome

Agent	Starting Dose	Target/Mechanism	Pros/Cons
Tocilizumab	8 mg/kg	IL-6 receptor	Pros: No direct effect on T cell viability, <sup>54</sup> efficacious with large body of evidence Cons: Poor CNS penetration, high cost
Corticosteroids	Grade I CRS – dexamethasone 10 mg PO/IV daily Grade 2/3 CRS - dexamethasone 10–20 mg IV every 6 hours Grade 4 - methylprednisolone 1–2 g IV daily	Varied mechanisms including downregulating inflammatory pathways and inducing lymphocyte apoptosis	Pros: Efficacious with large body of evidence, low cost Cons: Potential to hamper efficacy of T-cell redirection
Anakinra	100–200 mg SC q8h	IL-1 receptor	Pros: Preserves T cell function, <sup>55</sup> crosses blood-brain barrier and may be effective for both CRS and ICANS <sup>56</sup> Cons: Limited data for CRS treatment
Siltuximab	11 mg/kg x1	IL-6	Pros: Comparable efficacy to tocilizumab in small retrospective studies, <sup>57</sup> long half-life (21 days) Cons: Limited data compared to tocilizumab, high cost
Etanercept	25 mg SC BIW	TNF- $\alpha$	Pros: Efficacious for TNF- $\alpha$ -driven CRS, <sup>51</sup> well-established safety in other settings (RA) Cons: Limited data for CRS treatment
Sarilumab	400 mg IV x1	IL-6 receptor	Pros: Same target as tocilizumab, potential substitute in shortages Cons: Clinical data primarily in COVID-19
Ruxolitinib	5 mg BID	Janus kinase 1 and 2	Pros: Preserves T cell viability <sup>58</sup> Cons: Limited data for CRS treatment
Etoposide	150 mg/m <sup>2</sup> IV BIW	Topoisomerase II	Pros: Preferred for CRS with hemophagocytic lymphohistiocytosis (HLH) Cons: Myelosuppressive, kills activated T cells <sup>59</sup>
Emapalumab	1 mg/kg IV BIW	IFN $\gamma$	Pros: Preferred for CRS with hemophagocytic lymphohistiocytosis (HLH) Cons: Data in CRS limited to case reports

Corticosteroids can also be used for teclistamab-related CRS and are significantly cheaper, but have a number of drawbacks.<sup>60</sup> Steroids can suppress T cell proliferation and induce apoptosis, hampering bispecific antibody efficacy, an effect not seen with tocilizumab.<sup>54</sup> Furthermore, unlike tocilizumab, steroids did not reduce the rate of CRS recurrence in MajesTEC-1, with 77.8% of patients treated with steroids alone experiencing subsequent CRS events.<sup>48</sup>

Prophylaxis against CRS is not standard practice at the time of writing. However, premedication with tocilizumab is being actively studied with a recent study of tocilizumab pretreatment prior to the FcRHxCD3 bispecific, cevostamab, reducing CRS incidence from 90.9% to 35.7% without impacting efficacy.<sup>20</sup> If rates and severity of CRS events can be sufficiently abrogated with such premedication approaches, initiation of teclistamab and other T-cell redirecting therapies may move to the ambulatory setting.

Teclistamab-related ICANS is far less common than CRS, occurring in just 3% of treated patients with no grade  $\geq 3$  events in MajesTEC-1.<sup>3</sup> ICANS is graded according to the 10-point Immune Effector Cell Encephalopathy (ICE) score, which tracks

orientation, writing, language, and attention.<sup>61</sup> Steroids and supportive care are the mainstays of ICANS management. Tocilizumab has poor central nervous system penetration and can actually raise IL-6 levels in the cerebrospinal fluid, potentially worsening ICANS.<sup>62–64</sup> With grade 1 ICANS, seizure prophylaxis with levetiracetam should be initiated while dexamethasone can be considered.<sup>65</sup> For grade 2 or higher ICANS, patients should receive full neurologic evaluations along with high doses of steroids (potential regimens include 10–20 mg dexamethasone IV every 6 hours for grades 2–3, 1–2 g IV methylprednisolone daily for grade 4) with a rapid taper once symptoms improve.<sup>61</sup>

## The Future of T Cell-Engaging Antibodies in Myeloma

Teclistamab continues to be actively studied in numerous monotherapy and combination therapy trials (see Table 3). Additionally, numerous other bispecific antibodies are under active clinical investigation (details in Table 4). Many target other antigens expressed by myeloma cells such as GPRC5D, FcRH5, and CD38, while some bispecifics such as alnuctamab and forimtamig have been manufactured with a ratio of two myeloma antigen-binding domains to one CD3-binding domain to improve affinity and efficacy. Multiple trispecific antibodies targeting either two different myeloma antigens and one T cell antigen or vice versa are in preclinical development.

Many ongoing bispecific antibody trials seek to combine them with agents that may enhance their activity, commonly partnering them with anti-CD38 antibodies, IMiDs, checkpoint inhibitors, cereblon E3 Ligase Modulating Drugs (CELMoDs), or even other bispecifics as with teclistamab and talquetamab in RedirectTT-1.<sup>66</sup>  $\gamma$ -secretase inhibitors, which inhibit cleavage of membrane BCMA, are also being tested in combination with BCMA-directed bispecifics like elranatamab in ManetisMM-4 (NCT05090566). Other studies are testing the utility of bispecific antibodies as maintenance therapy after autologous stem cell transplant, including MajesTEC-4 which compares maintenance teclistamab plus lenalidomide to lenalidomide alone and MagnetisMM-7 which compares maintenance elranatamab to lenalidomide.<sup>67,68</sup> Lastly, the

**Table 3** Ongoing Trials of Teclistamab in Myeloma

Agent(s)	Disease Setting	Phase	Clinical Trial ID	Status
Teclistamab	RRMM, $\geq 3$ prior LOT	I/2	NCT04557098	Recruiting
Teclistamab vs Rd	High risk smoldering myeloma	2	NCT05469893	Recruiting
Teclistamab vs Pvd or Kd	RRMM, 1–3 prior LOT	3	NCT05572515	Recruiting
Teclistamab or talquetamab with PD-I inhibitor	RRMM, no further established therapies	I	NCT05338775	Recruiting
Teclistamab with various therapies (multi-armed): daratumumab, lenalidomide, pomalidomide, bortezomib, nirogacestat	NDMM or RRMM	I	NCT04722146	Active, not recruiting
Maintenance teclistamab with lenalidomide and teclistamab alone vs lenalidomide after ASCT	NDMM	3	NCT05243797	Recruiting
Teclistamab with daratumumab with/without pomalidomide and talquetamab with daratumumab	RRMM, $\geq 3$ prior LOT	I	NCT04108195	Active, not recruiting
Teclistamab with daratumumab vs DPd or DVd	RRMM, 1–3 prior LOT	3	NCT05083169	Recruiting
Teclistamab with daratumumab, lenalidomide, dexamethasone with/without bortezomib	NDMM	2	NCT05695508	Recruiting
Teclistamab with daratumumab, lenalidomide vs DRd	NDMM	3	NCT05552222	Recruiting
Teclistamab with talquetamab	RRMM, no further established therapies	I/2	NCT04586426	Recruiting

**Abbreviations:** Rd, lenalidomide, dexamethasone, Pvd, pomalidomide, bortezomib, dexamethasone, Kd, carfilzomib, dexamethasone, DPd, daratumumab, pomalidomide, dexamethasone, DVd, daratumumab, bortezomib, dexamethasone, DRd, daratumumab, lenalidomide, dexamethasone.

**Table 4** Clinical Trials of T Cell-Engaging Antibodies (Monotherapy)

Agent	Targets	Configuration	Phase	Clinical Trial ID	Status
Talquetamab	GPRC5D×CD3	1:1	II	NCT04634552	Recruiting
Elranatamab	BCMA×CD3	1:1	II	NCT04649359	Active, not recruiting
Alnuctamab (CC-93269)	BCMA×CD3	2:1	I	NCT03486067	Recruiting
Forimtamig (RG-6234)	GPRC5D×CD3	2:1	I	NCT04557150	Recruiting
Linvoseltamab (REGN5458)	BCMA×CD3	1:1	I/II	NCT03761108	Active, not recruiting
ISB-1342	CD38×CD3	1:1	I	NCT03309111	Recruiting
Cevostamab	FcRH5×CD3	1:1	I	NCT03275103	Recruiting
ABBV-383	BCMA×CD3	2:1	I/II	NCT03933735	Active, not recruiting
Lava-051	CD1d×Vδ2-TCR chain	1:1	I/II	NCT04887259	Active, not recruiting
TNB-383B	BCMA×CD3	2:1	I/II	NCT03933735	Active, not recruiting
Y150	CD38×CD3	1:1	I	NCT05011097	Recruiting
EMB-06	BCMA×CD3	2:2	I/II	NCT04735575	Recruiting

appropriate duration of bispecific antibody therapy is an important question yet to be answered. The current approach of treating until progression with teclistamab and other bispecifics increases the cumulative risk of AEs while potentially contributing to T-cell exhaustion; investigation of the effectiveness of a time-limited approach to bispecific antibody therapy will be paramount.

## Conclusion

The approval of teclistamab no doubt represents the first of many imminent approvals for bispecific T-cell engaging antibodies in MM. In the multiply relapsed setting, teclistamab monotherapy provides an effective therapeutic option for triple-class refractory patients. Compared to the currently limited supply of BCMA-directed CAR T cells, teclistamab is more accessible logistically and can be more expediently initiated for patients with rapidly progressive disease. While CRS is generally predictable and manageable with tocilizumab, the increased infectious risk for patients receiving teclistamab must be carefully considered. We anticipate the results of ongoing combination trials that may identify ideal partners that may enhance bispecific antibody efficacy. In the near future, the role of bispecific antibodies like teclistamab may also extend to an earlier LOT or post-transplant maintenance.

## Disclosure

Dr Joshua Richter reports personal fees from Janssen, during the conduct of the study; personal fees from Janssen, personal fees from Karyopharm, personal fees from Sanofi, personal fees from BMS, personal fees from Abbvie, personal fees from Adaptive Biotechnologies, personal fees from Genentech, personal fees from Pfizer, personal fees from Takeda, outside the submitted work. The authors report no other conflicts of interest in this work.

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