4 Innovation

Summary statement

TALVEY™ is an innovative bispecific antibody targeting GPRC5D, a novel antigen with a distinct expression profile. It has received Breakthrough and Orphan drug designations from multiple countries, highlighting its unique potential in RRMM.

TALVEY™ has shown low treatment discontinuation rates and a favorable infection profile compared with BCMA-targeted bispecific antibodies. TALVEY™ preserves immune function due to limited GPRC5D expression on normal B-cell precursors or plasma cells, resulting in lower rates of severe infection with preservation of B-cell and immunoglobulin levels.

Unlike other approved bispecific antibodies, the pharmacokinetic profile of TALVEY™ allows for both QW and Q2W dosing from the initiation of therapy. Together with SC administration, which patients and providers prefer over intravenous administration, the less frequent Q2W dosing with TALVEY™ reduces the treatment burden by shortening the time for administration, reducing the need for active clinical intervention by the provider, and limiting healthcare resource use. Notably, some responders in MonumenTAL-1 who experienced AEs maintained efficacy after dose reductions, with a trend toward improved resolution of GPRC5D-related AEs, suggesting that dosing flexibility with TALVEY™ can enhance patient experience and convenience.

Due to its unique mechanism of action, TALVEY™ is demonstrating its potential as a first-in-class, versatile partner for sequencing (ie, therapy order) and combination regimens with other myeloma therapies. Recent findings from the TRIMM-2, RedirecTT-1, and MonumenTAL-2 studies highlight the strong therapeutic potential of dual-targeting with TALVEY™ combinations to maximize efficacy and overcome heterogeneous mechanisms of resistance, including in patients with EMD.[107-109] The relative preservation of immune function with TALVEY™ allows for effective combinations without exacerbating risks of serious infections.[77] Trials are exploring the potential of TALVEY™ in earlier lines of therapy, in patients with aggressive disease or high risk of progression, and in bispecific-exposed patients, with the goal of transforming the treatment landscape and pursuing a potential cure for patients with MM.

4.1 TALVEY™ Breakthrough and Orphan Therapy designations in Europe, the United States, China, Japan, and South Korea

Based on the efficacy and safety of TALVEY™ in the MonumenTAL-1 study and its novel GPRC5D target, TALVEY™ earned inclusion in programs that support the development of promising therapies: European Medicines Agency PRIority MEdicine (EMA PRIME) on January 29, 2021[110] and Orphan Drug in August, 2021[111]; US FDA Orphan Drug designation on May 3, 2021[112] and as a Breakthrough Therapy for the treatment of patients with RRMM, who have previously received ≥4 prior lines of therapy (including a PI, an IMiD, and an anti-CD38 antibody) on June 29, 2022[113]; Orphan Drug designations in Japan and in South Korea [114]; and Breakthrough designation in China. PRIME is awarded by the EMA to therapies that target a medical need for which limited treatment options exist.[115] Breakthrough Therapy designation by the US FDA or China's National Medical Products Administration is similarly awarded to potential new medicines for serious or life-threatening conditions, based on preliminary evidence that demonstrates substantial improvement over existing therapies.[116,117] Orphan Drug

designation is intended for potential treatments of rare, life-threatening diseases with a prevalence of <5 in 10,000 in the EU, <200,000 people in the US, <50,000 people in Japan, and <20,000 in South Korea.[111,118,119]

4.2 TALVEY™ is a novel, unique therapy that has shown robust efficacy and a clinically manageable safety profile for patients with RRMM

4.2.1 With an extended long-term follow-up of 30-38 months, patients with RRMM treated with TALVEY™ continue to demonstrate deep and durable responses, and tolerable safety with no new safety signals identified

Long-term efficacy and safety data continue to highlight the overall clinical benefit of TALVEY™. In the MonumenTAL-1 study, high ORRs were maintained across cohorts over 38.2, 31.2, and 30.3 months of median follow-up for the QW, Q2W, and prior T-cell–redirecting therapy cohorts, respectively.[102] The ORRs were 74%, 70%, and 67%, with respective median PFS of 7.5, 11.2, and 7.7 months.[102] ORRs were consistent across high-risk subgroups except for patients with EMD.[46] The median OS was 34 months with QW dosing, not reached at 3 years with Q2W dosing, and 28 months in the prior T-cell–redirecting therapy cohort, with 36-month OS rates of 49.3%, 60.8%, and 44.6%, respectively.[102] This represents an important advancement over historical survival rates in triple-class exposed patients treated with standard of care (SOC) therapy. For example, the recent LocoMMotion study reported median OS of only 12.4 months in a similar population.[51] The safety profile of TALVEY™ was consistent with previous reports,[80] as overall rates of dose reductions and discontinuations due to AEs remained low (dose reductions: 15%, 10%, and 12%, respectively; discontinuations: 5%, 10%, and 5%, respectively). MonumenTAL-1 established GPRC5D as a valid target in MM, with selective expression and a protein structure that is complementary to BCMA, which has been targeted by recently approved myeloma therapies

GPRC5D is an established and validated target in MM and is primarily expressed in myeloma cells, with limited expression in normal human tissues.[78,120,121] BCMA expression is more broad in the immune compartment than GPRC5D, as it is found on normal, mature B cells and plasma cells.[122,123] BCMA is known to be an important regulator of normal B-cell maturation, proliferation, survival, and differentiation into plasma cells.[64,65,76,77,87,124-127] Therapies that target BCMA are associated with persistent B-cell aplasia and hypogammaglobulinemia.[65,68,76,128,129] In contrast, GPRC5D has no established role in the immune system and has more restricted expression in the immune compartment, with no or minimal expression on normal B-cell precursors or plasma cells.[76,77,87] The selective expression of GPRC5D, can potentially explain the lower infection rates, particularly severe infections, the quick and steady recovery of neutrophil counts, and the preservation of B cells and polyclonal immunoglobulin G observed with TALVEY™.[130]

GPRC5D is also a distinct clinical target from BCMA.[75,87] Both BCMA and GPRC5D have similar expression on normal CD138+ immune cells, and higher expression on MM cells; however, their expression patterns are independent of each other, and GPRC5D expression is therefore unaffected by BCMA loss.[75] Whereas the extracellular domain of BCMA can be cleaved by gamma-secretase, reducing target expression on myeloma cells and potentially acting as a "sink" for BCMA-targeting agents, GPRC5D has 7 transmembrane domains with a relatively short extracellular N-terminal domain, which is unlikely to be shed from target cells.[75,77,131] This distinct expression pattern compared with BCMA may increase sequencing and combination

options with TALVEY™ and complement the mechanisms of action (MOAs) of established agents including IMiDs and anti-CD38 antibodies and BCMA-targeted bispecific antibodies, including teclistamab.

4.2.2 TALVEY™ preserves immune function due to the expression pattern of the novel target GPRC5D

TALVEY™ has limited impact on humoral immunity compared with BCMA-targeting agents due to the more limited expression pattern of GPRC5D in the immune compartment.[129,130] In MonumenTAL-1, no reduction in normal CD19+ B cells was observed in patients treated with TALVEY™.[130] Additionally, immunoglobulin levels did not decrease over time, suggesting that B cells were producing functional antibodies **(Figure 4)**.[130] Hypogammaglobulinemia (immunoglobulin G<500 mg/dL or reported AE) occurred in 64.3% and 67.6% of patients in QW and Q2W cohorts, respectively, and relatively few patients received intravenous immunoglobulin (IVIG; 14.7% of QW and 13.1% of Q2W patients) for hypogammaglobulinemia.[130]

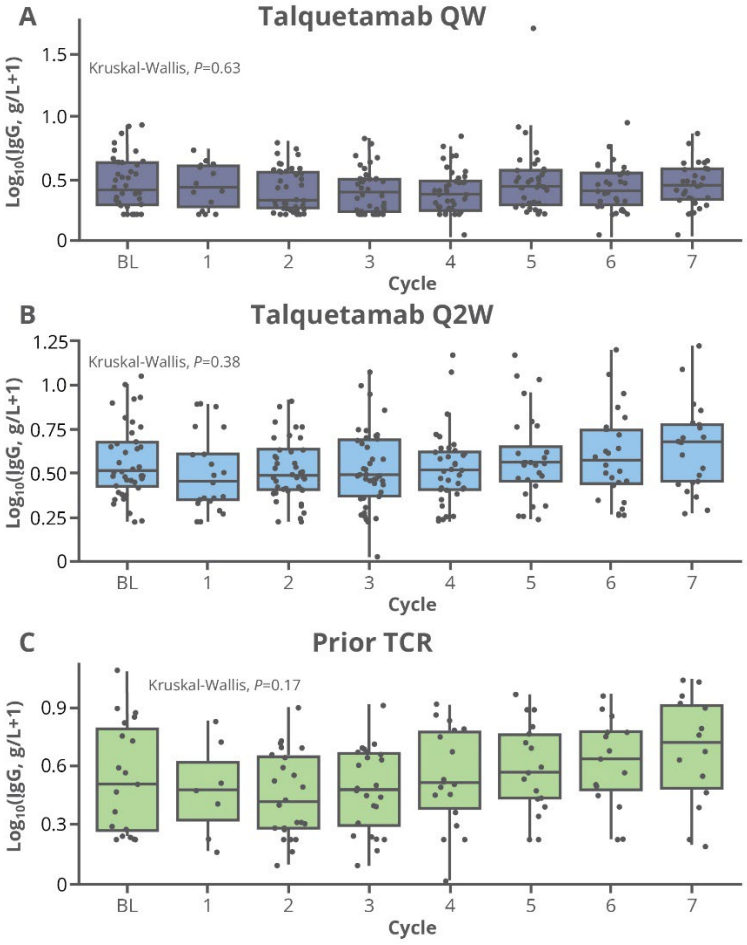

Figure 4. immunoglobulin G *levels were maintained over time in all cohorts in MonumenTAL-1.[130] IgG, immunoglobulin G; Q2W, every 2 weeks; QW, weekly; TCR, T-cell–redirecting.*

Notably, rates of serious (grade 3/4) infections with TALVEY™ were relatively low (15–20%), and the incidence of deaths due to infection was 1.4–2.1%.[130] In long-term follow-up data, across combined cohorts, new-onset grade ≥3 infections were mostly limited to early treatment cycles (**Figure 5**).[102] Multiple studies have found significantly lower rates of serious infections in patients receiving GPRC5D-targeting bispecific antibodies than BCMA-targeting bispecific antibodies, with which patients experience serious infections throughout treatment.[132-134] For example, a retrospective study of 229 patients in France found that rates of serious infections with BCMA-targeting bispecific antibodies were significantly higher than with GPRC5D–targeting bispecific antibodies (73% vs 51%), respectively.[133]

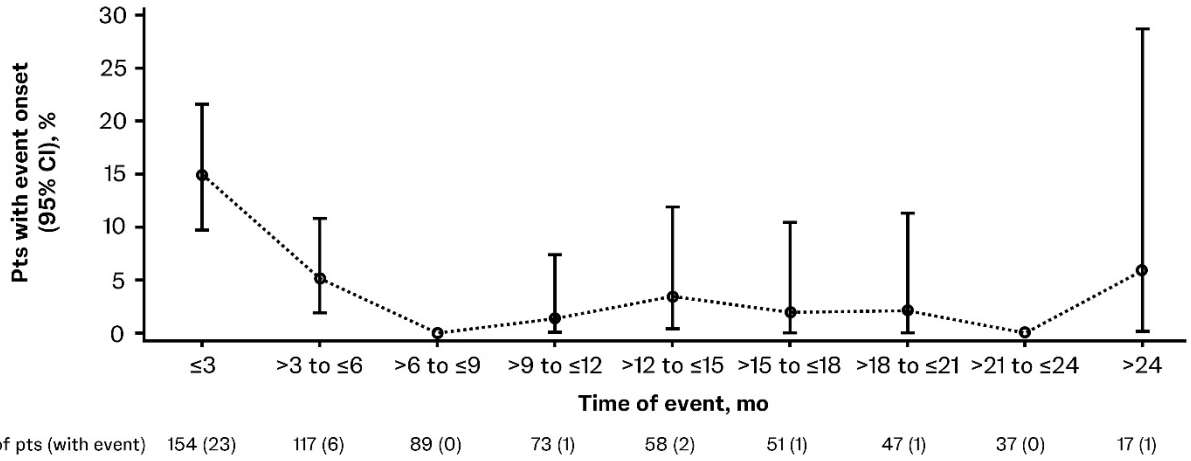

Figure 5. *New onset grade 3/4 infections in the 0.8 mg/kg Q2W cohort. pts, patients; Q2W, every 2 weeks.*

4.2.3 TALVEY™ has 2 approved dosing schedules, QW and Q2W, with a favorable pharmacokinetic profile that allows biweekly dosing from the start

While other approved bispecific antibodies require QW dosing at initiation, TALVEY™ was approved for either QW or Q2W dosing from initiation of therapy.[58,81,135] The two doses of TALVEY™ were identified for investigation in the phase 2 portion of MonumenTAL-1: 0.4 mg/kg SC QW and 0.8 mg/kg SC Q2W.[78] Step-up doses of 0.01 and 0.06 mg/kg were administered prior to the first full weekly dose in the QW schedule, and step-up doses of 0.01, 0.06, and 0.3 mg/kg were administered prior to the first full dose in the Q2W schedule to reduce the risk of CRS.[78] The QW and Q2W dosing schedules have demonstrated comparable pharmacokinetics[78,136] and are the FDA approved dosing regimens for TALVEY™.

Together with SC administration, which patients and providers prefer over intravenous administration,[137] the option for less frequent Q2W dosing with TALVEY™ reduces the treatment burden by shortening the time for drug administration, reducing the need for active clinical intervention by the provider, and limiting overall use of healthcare resources.[138]

Notably, a subset of patients who achieved treatment response (partial response or better) in the MonumenTAL-1 study had their dose reduced, typically due to an AE. These patients demonstrated similar maintenance of response as those who did not reduce the dose, with a trend toward improved resolution of GPRC5D-associated AEs.[139] These results suggest potential flexibility to adjust dosing of TALVEY™ in patients who respond, improving the patient experience and convenience, while maintaining efficacy.

4.2.4 Indirect treatment comparisons demonstrate improved efficacy with TALVEY™ compared with other off-the-shelf current standard of care therapies

TALVEY™ has demonstrated clinical benefit in several efficacy outcomes compared with other approved off-the-shelf treatments in indirect treatment comparisons (ITCs).[140-143] ITCs are used to compare treatments and improve outcomes for patients in the absence of head-to-head clinical trials.[144-147] While it should be noted that residual or unmeasured confounding variables cannot be completely ruled out in ITCs, these studies attempt to balance baseline characteristics between patients in different trials across a range of clinically relevant prognostic factors.[140]

In an ITC evaluating TALVEY™ vs real-world physician's choice of therapy (RWPC) in the LocoMMotion and MoMMent studies, patients with triple-class exposed MM treated with RWPC had an ORR of just 27–37%.[148] Comparatively, patients receiving TALVEY™ had a substantially higher ORR of 70–74%, with an approximately 2.6-fold higher likelihood of achieving a response and a 30.8–52.2-fold higher likelihood of achieving a complete response or better.[148] Patients treated with TALVEY™ had significantly improved PFS and OS vs patients who received RWPC.[148]

A similar analysis in the real-world Flatiron database showed significantly improved PFS, OS, and time to next treatment (TTNT) with TALVEY™ vs RWPC in patients with triple-class exposed RRMM who received ≥3 prior lines of therapy.[141] In the QW and Q2W cohorts, median PFS was significantly longer in patients treated with TALVEY™ (7.5 vs 4.2 months and 11.2 vs 4.0 months, respectively), as was OS (32.1 vs 16.5 months and not reached vs 15.8 months, respectively). TTNT was 9.1 vs 5.0 months in the QW cohort and 11.7 vs 5.0 months in the Q2W cohort.[141]

TALVEY™ treatment was also associated with improved PFS, OS, and TTNT vs patients with similar baseline characteristics who received RWPC after participating in a daratumumab clinical trial.[143] In patients who received TALVEY™, median OS was not reached (QW and Q2W cohorts) vs RWPC (9.1 months and 10.1 months, respectively, in the comparison cohorts).[143]

In a matched-adjusted ITC of patients in MonumumenTAL-1 and the trials of selinexor + dexamethasone (sel-dex; STORM) or belantamab mafodotin (belamaf; DREAMM-2) who would meet the same inclusion criteria, patients treated with TALVEY™ had significantly better ORR and rate of complete response or better (≥CR), as well as longer DOR and OS vs sel-dex.[142,149] Versus belamaf, TALVEY™ had better ORR and rate of ≥CR, with a longer PFS.[142,149] Median OS in patients treated with TALVEY™ (QW and Q2W) was not reached vs 8.6 months for the sel-dex comparison cohort. TALVEY™ QW OS was 25.6 months and Q2W OS was 20.1 months vs 13.7 months for the belamaf cohort.[142,149]

4.2.5 Due to its novel MOA, TALVEY™ has the potential to be a versatile first-in-class sequencing and combination partner with complementary therapeutic agents

Combining or sequencing agents with distinct targets and MOAs has been used to address multiple subclonal groups, induce deeper responses, and reduce the risk of developing refractory disease.[150] As a novel therapy targeting GPRC5D, TALVEY™ may be a versatile combination partner for agents with different targets, with the potential to improve efficacy without increasing toxicity.[77] GPRC5D is expressed on different subsets of immune cells than other myeloma targets such as CD38 or BCMA, and its expression is unaffected by BCMA loss.[75,77] Targeting GPRC5D also spares components of the immune system that other therapies, including anti-BCMA and anti-CD38 therapies, deplete via off-tumor effects.[68,128-130] As a result, combining TALVEY™ with these other agents is unlikely to substantially increase immune-related toxicities, such as infection, compared with monotherapy.[77,130]

TALVEY™ may also be a key element to improve outcomes in patients with high-risk features, such as EMD. This subgroup patient population has historically worse outcomes compared with the overall study population, especially a shorter durability of response and PFS.[20,69-71,73,74] Although the introduction of bispecific antibodies and CAR-T have somewhat improved outcomes in these patients over historical norms, response rates in patients with EMD are generally below 50% for bispecific antibodies, and median PFS is less than 14 months with CAR-T, much poorer than the outcomes for patients without EMD.[37,38,79,151,152] Due to the versatility of the MOA, TALVEY™ improves efficacy outcomes in patients with EMD in combination with the BCMA-targeted bispecific antibody teclistamab, and risk of infections remains manageable. ORRs with TALVEY™ + teclistamab were nearly 79% in this difficult-to-treat EMD population, which is better than the responses observed in the RRMM population with the monotherapies.[38,79,108] Median PFS was longer than 15 months, and 75% of patients with EMD who received teclistamab + TALVEY™ survived over 12 months.[108]

4.2.6 TALVEY™ provides novel sequencing options after BCMA-targeted therapies

BCMA-targeted CAR-T therapy and bispecific antibodies have improved outcomes for patients with RRMM; however, most patients eventually relapse.[38,152] Patients can develop multi-drug resistance following exposure to the major classes of MM therapy, limiting their potential treatment options as re-exposure to the same antigen-targeting therapy can predispose patients to inferior outcomes.[49,153] These patients require new modalities that are designed to overcome resistance, either through new targets and MOAs or multi-modal strategies leveraging complementarity with existing options.[49] TALVEY™, with its novel GPRC5D target, allows for sequential antigen switching following BCMA-targeted T-cell–redirecting therapy to overcome resistance due to loss or downregulation of the previously targeted antigen.[154,155]

Patients who have been exposed and/or are resistant to the 4 major classes of MM therapy (PI, IMiD, anti-CD38 antibody, and BCMA-targeted T-cell–redirecting therapy) are a new class of patients with poor outcomes and limited therapeutic options.[156-158] TAVLEY has shown high efficacy in these patients with an ORR of 67% and median PFS of 8 months.[46,159] The ORR with TALVEY™ was particularly high (>71%) following BCMA-targeted CAR-T therapy.[46,159] Studies are currently being planned to evaluate the use of TALVEY™ as consolidation therapy following BCMA-targeted CAR-T cell therapy (https://clinicaltrials.gov/study/NCT06066346).

The LocoMMotion and MoMMent studies found that outcomes were poor in patients with heavily pretreated RRMM who were exposed to prior BCMA-targeted T-cell–redirecting therapy.[51] An

ITC that evaluated the comparative effectiveness of TALVEY™ in these patients vs RWPC showed superior efficacy of TALVEY™ after BCMA T-cell–redirecting therapy, with better ORR (65.3% vs 22.2%, RR=3.03; 95% CI, 1.66–5.54; P<0.0003), PFS (HR=0.30; 95% CI, 0.17–0.52; *P*<0.0001), and OS (HR=0.37; 95% CI, 0.20–0.70; *P*=0.002) vs RWPC.[160] Additionally, a subgroup analyses was performed in patients with prior BCMA CAR-T and BCMA bispecific antibodies. ORR was 70.9% and 56.0%, respectively, in patients treated with TALVEY™ and 40.0% and 12.5%, respectively, in patients who received RWPC.[160] PFS and OS were longer with Tal vs RWPC for patients with prior BCMA CAR-T and those with prior BCMA bispecific antibodies.[160] These results support TALVEY™ as a novel, highly effective treatment option not only for BCMA-naive patients, but also for patients with prior exposure to BCMA T-cell–redirecting therapy including CAR-T and bispecific antibodies.

4.2.7 TALVEY™ provides versatile sequencing options before BCMA-targeted therapies

Similar to BCMA-targeted CAR-T and bispecific antibodies, TALVEY™ is a T-cell–redirecting therapy.[161] Among patients who received BCMA-targeted CAR-T following TALVEY™, the ORR was 78%, while those who received bispecific antibodies had an ORR of 58%.[162] This suggests that using TALVEY™ prior to other T-cell–redirecting therapy does not substantially raise resistance to these therapies despite engaging T cells in a similar manner.[162] TALVEY™ also preserves the function of normal B cells during treatment, which may help maintain immune fitness for subsequent immunotherapy.[77,163]

4.2.8 TALVEY™ would potentially provide versatile combination options with anti-CD38 antibodies and immunomodulatory agents

Many patients with RRMM are exposed early in treatment to effective agents that can affect resistance mechanisms and raise the risk of infections in later lines of therapy, including anti-CD38 antibodies and IMiDs.[47,48,164] For example, many patients in later lines of therapy may have prior exposure to daratumumab because it is an effective treatment option both for patients with newly diagnosed MM and patients with RRMM, and has been approved for use as front-line therapy in patients who are ineligible for autologous stem cell transplant.[165,166] The early use of these agents leads to multi-drug resistance to effective treatments, limiting options as patients progress through successive lines of therapy.[50] These newer treatments, while providing better disease control, also elevate infection risk due to their effects on therapeutic targets in the immune system.[164] TALVEY™, which preserves humoral immune function, is a versatile combination partner with complementary therapeutic agents that has the potential to address this unmet need.

TALVEY™ + daratumumab
Immunosuppressive cells that express CD38 are associated with decreased immune function and earlier disease progression.[167] In addition to its direct effects on myeloma cells, the anti-CD38 antibody daratumumab depletes CD38-expressing nonplasma cells, including myeloid-derived suppressive cells, regulatory B cells, and a subpopulation of regulatory T cells that robustly suppress T-cell proliferation[167]. Daratumumab may also increase T helper and cytotoxic T cell absolute counts.[167] The combination of TALVEY™ and daratumumab has been studied in TRIMM-2.[107] Initial results showed high ORRs (>71%) with over 15 months of follow-up.[107]

Promisingly, the ORR was high (80%) with TALVEY™ (Q2W schedule) + daratumumab in patients who became refractory to prior anti-CD38 therapy in the TRIMM-2 study, and ORR was

79% in patients who had prior T-cell–redirecting therapy.[107] Normal B cells were not depleted despite the combination of 2 immunotherapies, and rates of serious infections remained relatively low (<26%).[107]

TALVEY™ + pomalidomide
Pomalidomide is an IMiD that enhances T-cell and NK-cell activity and inhibits monocyte production of proinflammatory cytokines, in addition to direct cytotoxic effects.[168] Preliminary data from MonumenTAL-2 showed TALVEY™ + pomalidomide was tolerable, demonstrating a relatively low rate of severe infections (<23%) and promising efficacy (ORR >84%) with this immune-based doublet, with over 11 months of follow-up.[169] Recent long-term follow-up data continued to show promising efficacy, with a high ORR of 88.6% in all patients receiving TALVEY™ + pomalidomide. Robust responses were observed in subgroups, including those with high-risk cytogenetics (77.8%), prior CAR-T therapy (100%), and prior pomalidomide treatment (100%).[109] TALVEY™ + pomalidomide showed a rapid, deep, and durable response, a longer median follow-up of 16.8 months, and a 12-month PFS rate of 72.6%.

TALVEY™ + daratumumab + pomalidomide
Preclinical data suggest that the immunomodulatory effects of daratumumab, an anti-CD38 antibody which depletes CD38-expressing cells,[167] and pomalidomide, an IMiD that enhances T cell and NK cell activity and has direct cytotoxic effects[168] may potentiate the efficacy of TALVEY™.[76] In the phase 1b TRIMM-2 study, ORRs of >76% were observed in patients who received TALVEY™ + daratumumab + pomalidomide, with >55% of patients achieving a complete response or better.[170] Promising ORRs were also observed in patients with prior exposure to CAR-T therapies (83.3%), patients who were refractory to prior bispecific antibody therapy (82.8%), and patients who were refractory to prior pomalidomide (81.0%).[170] The safety profile of the triplet regimen was also similar to the safety profile observed following TALVEY™ monotherapy.[76,170]

TALVEY™ + daratumumab + lenalidomide
Daratumumab (an anti-CD38 antibody) may increase T-helper and cytotoxic T-cell absolute counts.[167] Lenalidomide is an established IMiD and current standard-of-care in patients with newly diagnosed MM, with direct on-tumor apoptotic activity.[171] Both of these agents have been studied in an immune-based triplet alongside TALVEY™ in the MonumenTAL-2 study in patients with newly diagnosed MM.[172] High ORRs were observed (>96%) and high proportions of patients achieved a very good partial response or better (>80%). With a median follow-up of 5.8–13.2 months, this triplet was tolerable and no patients discontinued the study due to AEs.[172]

4.2.9 The efficacy of dual-antigen targeting with TALVEY™ + teclistamab was transformative for patients with EMD in the largest dedicated study to date

EMD is a particularly complex, aggressive form of MM in which plasmacytomas have become embedded in soft tissue independently of bone marrow, and it is associated with a heterogeneous group of high-risk cytogenetic markers and aggressive disease features.[70,173,174] Despite the introduction of novel therapies, there is no consensus on EMD management, prospective studies in patients with EMD are lacking, and prognosis for these patients has remained dismal compared with those without EMD.[19,173,175] In the LocoMMotion and MoMMent studies evaluating current standard treatments in patients with EMD, ORR was 32.5%, median PFS was 4.6 months, and the median patient died within 15 months.[20]

Teclistamab is a BCMA-targeting bispecific antibody approved for treatment of patients with RRMM.[135] Combining teclistamab with TALVEY™ allows for simultaneous immunotherapy targeting GPRC5D and BCMA, 2 distinct, independent antigens that are expressed on a majority of myeloma cells.[176] Dual-targeting may maximize tumor eradication in heterogenous cell populations and prevent potential resistance due to loss of a single antigen.[177] Results from the phase 1b-2 RedirecTT-1 study showed promising efficacy of this combination in patients with RRMM, with 72% and 74% of patients achieving a response with teclistamab + QW TALVEY™ and Q2W TALVEY™, respectively.[177] In the subgroup of patients with EMD, ORR was 61% and the likelihood of continuing to have a response at 18 months was 82%.

On the strength of these data, a phase 2 study was conducted in 90 patients with RRMM and EMD, the largest dedicated interventional study in EMD to date.[108] ORR was 79% for all patients with EMD, 83% among patients who had prior anti-BCMA CAR-T therapy, and 75% for those with prior bispecific antibody therapy.[108] The 9-month DOR, PFS, and OS rates were 75%, 64%, and 80%, respectively. Overall, the combination of TALVEY™ and teclistamab demonstrated high efficacy, particularly when compared with SOC in patients with EMD in the LocoMMotion and MoMMent studies (ORR 32.5%, median PFS 4.6 months, and median OS 14.8 months) or with TALVEY™ and teclistamab monotherapies (ORR 43%-44%), and the safety profile of the combination was consistent with the respective monotherapies.[20,108,177] These results highlight the clinical benefit of treating with 2 bispecific antibody therapies that target 2 different antigens.[108]

4.2.10 Ongoing innovative development for TALVEY™ in patients with earlier lines of therapy

Given the promising efficacy and the lack of overlapping toxicities of TALVEY™ + daratumumab ± pomalidomide in patients with RRMM who have been exposed to ≥3 lines of therapy, the MonumenTAL-3 trial will evaluate the combination vs a standard approved therapy (daratumumab, pomalidomide, and dexamethasone [DPd]) in patients with RRMM exposed to ≥1 prior lines of therapy who are lenalidomide refractory.[178]

The MonumenTAL-6 trial is evaluating the combinations TALVEY™ + pomalidomide and TALVEY™ + teclistamab vs standard approved therapies (EloPd, elotuzumab, pomalidomide, and dexamethasone; PVd, pomalidomide, bortezomib, and dexamethasone) in patients with RRMM who have received 1–4 prior lines of therapy including an anti-CD38 and lenalidomide.[179]

5 Conclusions

Despite advancements of recently approved therapies, including BCMA-targeting CAR-T and bispecific antibodies, most patients with MM continue to relapse and cycle through treatments.[2,50,180] As newer, more effective therapies are increasingly used in earlier lines and in combinations, patients are becoming exposed and refractory to treatments earlier in disease.[181] Use of these agents leads to multi-drug resistance to effective treatments, limiting options as patients progress through successive lines of therapy since re-exposure to the same antigen-targeting therapies results in inferior outcomes.[49,50,153] The risk of infections, which are the leading cause of the observed morbidity and mortality in patients with MM are also increased due in part to persistent immunosuppression with current therapies.[13,14,164] Patients require therapies with new modalities and targets that are designed to overcome resistance and complement existing options.[49]

TALVEY™, with its novel GPRC5D target, allows for sequential antigen switching following BCMA-targeted T-cell–redirecting therapy to overcome resistance due to loss or downregulation of the previously targeted antigen.[154,155] Moreover, the therapeutic target of TALVEY™, GPRC5D, has limited expression in normal immune cells (eg, B cells) and immunoglobulin levels are generally maintained in treated patients. The preservation of immune components with TALVEY™ results in a lower rate of serious infection compared with BCMA-targeting therapies. This suggests that TALVEY™ can potentially be combined with other immunotherapies for effective disease control without increasing the risk of infections.[107,130] TALVEY™ therefore addresses the unmet need for an innovative, highly effective therapy that can be used as monotherapy, in sequential antigen switching strategies to overcome treatment resistance, and/or in dual-targeting combinations with other myeloma therapies to maximize tumor eradication and prevent resistance in heterogenous cell populations.

Notably, TALVEY™ monotherapy has demonstrated a median OS of 34 months with QW dosing after a median follow-up of 38 months, while the median OS was not reached at a median follow-up of 31 months with Q2W dosing.[102] TALVEY™ has demonstrated high ORRs and durable responses in patients with RRMM who are triple-class exposed, with consistent ORRs across most subgroups of patients, including those with high-risk disease characteristics.[46,100,103] Long-term safety outcomes with TALVEY™ monotherapy were consistent with previous reports; discontinuation rates due to AEs remained low and no new discontinuations occurred due to GPRC5D-related AEs.[46,102] Furthermore, as a GPRC5D-targeting therapy, TALVEY™ is effective in patients that have been previously treated with BCMA-targeting therapies, particularly CAR-T therapy. BCMA-targeting therapies also remain effective as subsequent therapy in patients who have received TALVEY™, suggesting that antigen switching is an effective strategy to overcome resistance to BCMA.[159,162] In addition to TALVEY™ being an effective therapy, it also improves health-related quality of life in patients with historically poor outcomes. TALVEY™ can be administered SC with a Q2W dosing schedule from the start of treatment, which contributes to convenience and reduces resource use.[82,137,138]

In combinations, TALVEY™ has shown promising efficacy in a number of difficult-to-treat patient populations characterized by heterogeneous, aggressive disease features, including patients with EMD and patients refractory to early-line therapies such as daratumumab. The safety profile with TALVEY™ in combination with daratumumab and/or IMiDs was consistent with individual agents, which suggests a nonoverlapping safety profile, further highlighting the ability

of TALVEY™ to be a versatile combination partner. The versatility to safely combine TALVEY™ in a dual-targeting approach with the BCMA bispecific antibody teclistamab has led to transformative efficacy, with a manageable risk of infections, in patients with difficult-to-treat EMD.[108]

Ongoing clinical studies will evaluate use of TALVEY™ in patients in earlier lines of therapy and inform optimal combination regimens with other myeloma therapies.