

Research Translating Immunotherapy Innovation into Earlier, Effective, and Durable Disease Control



Next Step in Immunotherapy Research: Early, Effective, and Durable Disease Control in Multiple Myeloma

T-cell redirecting immunotherapies, including chimeric antigen receptor (CAR) T-cell therapies and bispecific antibodies, have transformed the treatment of relapsed or refractory multiple myeloma.¹ Currently, these treatments share overlapping approval indications in the relapsed/refractory space, highlighting the importance of optimal selection and sequencing to maximize clinical efficacy.² Therefore, in multiple myeloma immunotherapy, proper treatment timing, sequencing, and long-term care are as important as the immunotherapy treatment used, as treatment advancements are becoming more strategic through identifying the right patient, treatment, and timing before cumulative disease and treatment compromise the opportunity for durable remission. Achieving that goal will require early referral, proactive supportive care, shared-care delivery, and biomarker development, along with clinical trials that measure treatment-free survival and quality of life alongside traditional efficacy endpoints.³⁻⁵

Since the first clinical approval in 2017, CAR T-cell therapy has emerged as one of the most powerful modalities for redirecting the immune response against cancer. Building on decades of foundational discoveries in T-cell biology and synthetic immune-engineering, CAR T-cell therapy has transformed the treatment of B-cell malignancies, resulting in durable remissions in patients with multiple myeloma.⁶ CAR T-cell therapies are moving earlier in treatment sequencing based on clinical studies, bispecific antibodies are generating randomized evidence in less heavily pretreated disease, and alternative antigen targets are creating viable options after B-cell maturation antigen (BCMA) exposure.⁷ At the same time, real-world data are showing that patients outside of clinical trials achieve durable benefit in clinical practice.⁸⁻¹³

The introduction of multiple BCMA-directed immunotherapies into the early-relapse setting has fundamentally changed treatment selection in multiple myeloma from a linear sequence of regimens to a strategic choice among highly effective modalities.¹⁴ CAR T therapy and bispecific antibodies each provide meaningful disease control but differ in the timing of treatment burden, toxicity profile, and logistical feasibility. Consequently, optimal therapy is no longer defined solely by treatment line but also by the integration of clinical trial evidence with patient fitness, disease biology, treatment urgency, and real-world access considerations.¹⁴ Shared decision-making is essential and therapy should be individualized in accordance with country-specific regulatory approvals and indications.¹⁴ As BCMA-directed therapies continue to move fast in the disease course and next-generation approaches emerge, including safer cellular therapies, in vivo CAR T therapy and multitargeted T-cell redirecting platforms, treatment sequencing will continue to evolve.¹⁴ The challenge for clinicians is no longer the absence of effective therapies but selecting the right therapy for the right patient at the right time.¹⁴

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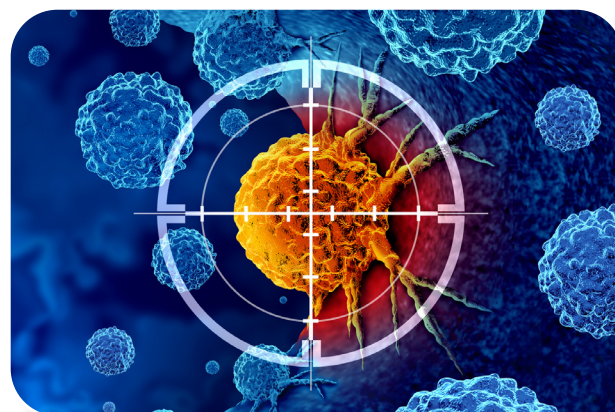
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Immunotherapy: Redefining Response in Relapsed or Refractory Multiple Myeloma



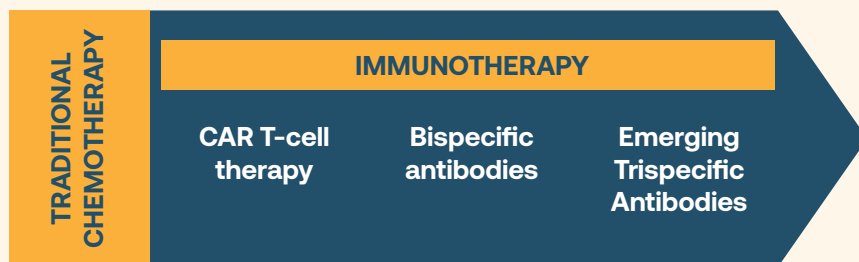
The central question in relapsed or refractory multiple myeloma is no longer simply whether a therapy can produce a response. Increasingly, clinicians and investigators are asking whether treatment can produce deep disease control, preserve function and quality of life, and create a meaningful interval without continuous therapy. The rise of immunotherapy has been one of the most significant drivers of this progress, as this shift reflects the impact of CAR T-cell therapies and bispecific antibodies, which have generated response depths and durations that were rarely observed in heavily pretreated disease only a few years ago.^{8,15-17} In the past, patients with relapsed or refractory multiple myeloma had poor survival outcomes,⁸ with median progression-free survival in heavily pretreated patients with refractory disease frequently being less than 6 months and median overall survival was often approximately 1 year.³ Advances in immune-based therapies have significantly improved outcomes for patients with multiple myeloma.¹⁶ CAR T-cell therapies and bispecific antibodies have transformed the therapeutic landscape for treatment outcomes in multiple myeloma, demonstrating unprecedented response rates in heavily pretreated patients, including refractory

The availability of BCMA-directed treatments means that antigen exposure, T-cell fitness, manufacturing time, infection risk, and patient preference must all be considered before treatment is selected.

disease following multiple prior lines of therapy.^{9,10,15,17,18} Recent studies included randomized data for the use of bispecific antibodies after one to three previous lines of therapy, mature follow-up of CART T-cell studies, growing real-world cohorts, and first clinical evidence that cellular therapy can induce sustained minimal residual disease

(MRD) negativity in high-risk relapsed multiple myeloma.⁹⁻¹³ Additionally, long-term follow-up data from CAR T-cell therapy clinical trials have provided data showing the possibility of a cure in selected patients.^{15,19} These new therapeutics are evolving multiple myeloma treatment beyond temporary disease control, but they also create new complexity. The availability of BCMA-directed treatments means that antigen exposure, T-cell fitness, manufacturing time, infection risk, and patient preference must all be considered before treatment is selected. Bispecific antibodies offer an off-the-shelf, scalable alternative to CAR T therapy, and clinical studies have demonstrated a substantial response in patients with heavily pretreated relapsed or refractory multiple myeloma as well as curative potential in selected patient populations.^{20,21} Trispecific T-cell engagers, which are designed to maximize tumor selectivity, limit antigen escape and prevent T-cell exhaustion, are the next evolution in immunotherapy for multiple myeloma.²²

Multiple Myeloma Care: Advancing Treatment at an Extraordinary Pace



- Unprecedented response rates
- Deep MRD-negative remissions
- Durable disease control without continuous treatment
- Longer remissions
- Improved quality of life

Real-World Treatment Patterns in Multiple Myeloma

A study was conducted to assess real-world treatment patterns and clinical outcomes among patients with relapsed or refractory multiple myeloma who received second-line, third-line, and fourth-line treatments.²³ Among the 3,910 patients who received second-line treatment, 42.6% went on to receive third-line treatment, and 20.4% went on to receive fourth-line treatment. The median age of patients who received second-line treatment was 70 years. Before second-line treatment, most patients had exposure to bortezomib (77.0%) and lenalidomide (70.0%).

The most common second-line treatment regimens ($\pm$ dexamethasone) were daratumumab + pomalidomide (7.7%), daratumumab + lenalidomide (7.6%), and daratumumab + bortezomib (6.0%). Daratumumab + pomalidomide was most common in third-line therapy (11.3%) and fourth-line therapy (8.3%). Median progression-free survival was 13.8 months in second-line, 8.1 months in third-line, and 7.0 months in fourth-line therapy. Median overall survival was 61.3 months in second-line therapy, 39.9 months in third-line therapy, and 30.7 months in fourth-line therapy. The predictors of worse outcome included higher International Staging System stage, frailty, high cytogenetic risk, and triple-class refractoriness. Overall, real-world treatment patterns for relapsed or refractory multiple myeloma were heterogeneous, and the increased use of the new therapies is necessary.

Most Commonly Used Second-line Treatment Regimes: Daratumumab Plus Pomalidomide, Lenalidomide, or Bortezomib²³

Bortezomib

A proteasome inhibitor that blocks structures in cells from breaking down important proteins, causing cancer cells to die²⁴

Daratumumab

A targeted monoclonal antibody therapy that attaches to CD38 markers on the surface of myeloma cells to flag them for destruction by the immune system²⁵

Lenalidomide

An immunomodulatory drug that helps the immune system attack cancer cells²⁶

Pomalidomide

A stronger immunomodulatory drug often used when treatments like lenalidomide stop working²⁷

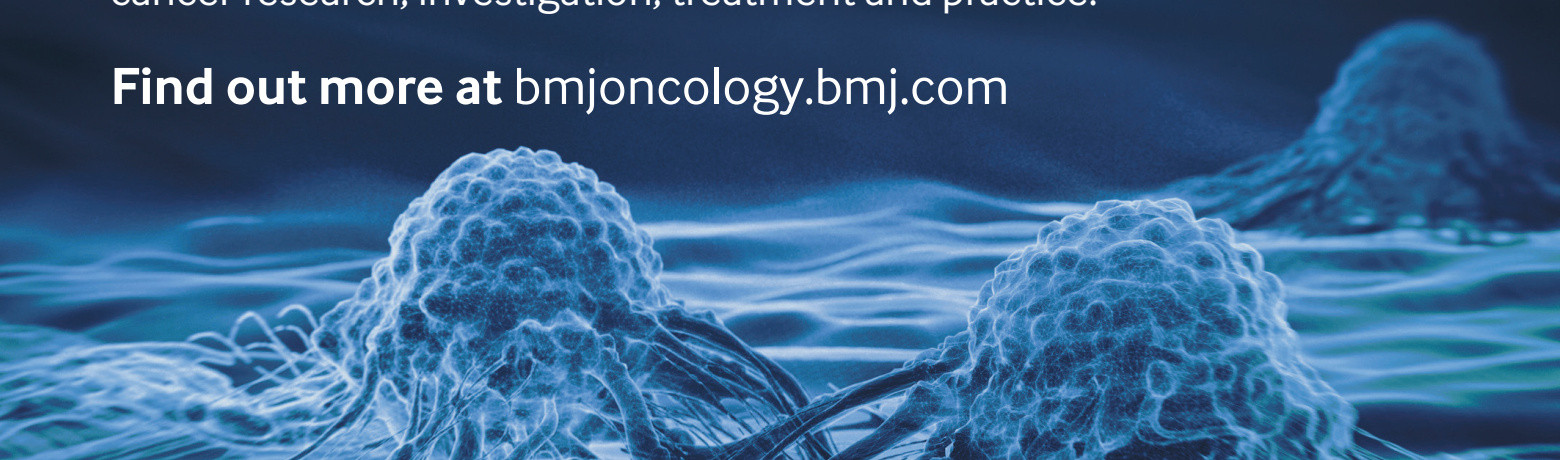
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Bispecific Antibodies: Expanding Access to Immunotherapy with Earlier-line Comparative Evidence

Bispecific antibodies have changed the practical meaning of immunotherapy in multiple myeloma. These treatments are available off the shelf and, therefore, can be started without individualized manufacturing. Of the available bispecific antibodies, teclistamab, elranatamab, and linvoseltamab target BCMA and CD3, and talquetamab targets GPRC5D and CD3. The availability of these treatments provides an immediate T-cell redirecting option for patients who cannot wait for manufacturing, are not eligible for cellular therapy, or prefer a non-cellular approach.^{9,20,28-30}

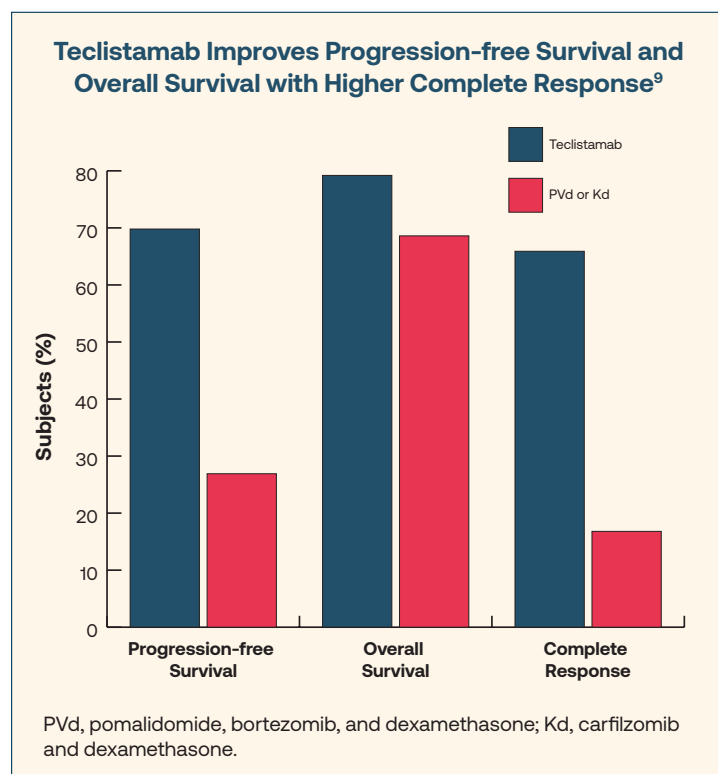
Data from clinical studies have demonstrated that bispecific antibodies generate robust anti-tumor responses, even in patients with advanced disease.^{32,33} Recent trials have reported overall response rates comparable to those seen with CAR T-cell therapies, particularly in patients who have received multiple prior lines of therapy.^{32,33} Importantly, bispecific antibodies have also shown activity in patients who have previously been treated with BCMA-targeted therapies, suggesting that they may play a role in later lines of treatment.^{32,33}

Moving bispecific antibodies earlier may improve response because patients have less refractory disease and more functional T-cells. It may also expose patients to longer periods of immune suppression. This tradeoff has increased interest in response-adapted or fixed-duration treatment, longer dosing intervals after response, and combination regimens that permit shorter exposure.²⁹⁻³¹ In a recent randomized study, subjects with relapsed or refractory multiple myeloma who had received one line, two lines, or three lines of therapy were randomized to receive teclistamab or the investigator's choice of pomalidomide, bortezomib, and dexamethasone (PvD) or carfilzomib and dexamethasone (Kd).⁹ A total of 296 patients were assigned to teclistamab, and 297 patients were assigned to PvD or Kd. Teclistamab significantly

improved progression-free survival compared with PvD or Kd (estimated 18-month progression-free survival, 69.8% vs. 26.9%). The percentage of patients with a complete response or better was higher with teclistamab than with PvD or Kd (65.9% vs. 16.8%). Overall survival was improved with teclistamab as compared with PvD or Kd (estimated 18-month overall survival, 79.2% vs. 68.6%).

Although bispecific antibodies have been proven effective in multiple myeloma and are being studied for use in earlier lines of treatment, these treatments are associated with challenges.³³ For example, cytokine release syndrome (CRS) is a common adverse event, and prolonged treatment with bispecific antibodies may lead to immune suppression, which increases the risk of infections in patients.³³ In addition, bispecific antibodies are often given continuously until disease progression or unacceptable toxicity is seen.³³ Specifically, in the recent study, CRS, mostly of grade 1 or 2, occurred in 66.0% of patients receiving teclistamab and grade 3 or 4 infection occurred in 41.6%.⁹

Approximate Overall Response Rates for Approved Bispecific Antibodies Reported in Pivotal Studies ³²	
Bispecific Antibody	Overall Response Rate
Teclistamab	63%
Elranatamab	61%
Linvoseltamab	71%
Talquetamab	74%



Earlier-Line CAR T-cell Therapy, the Importance of Immune Fitness, and Clinical Studies of Cilta-cel

The movement of CAR T-cell therapy from late-line rescue treatment toward earlier disease settings is one of the most consequential changes in multiple myeloma care. Earlier use of CAR T-cell therapy is supported not only by superior clinical outcomes compared with standard regimens, but also by a biologic rationale: patients treated after fewer lines of therapy generally have lower tumor burden, fewer cumulative cytopenias, less T-cell exhaustion, and a greater probability of reaching infusion without rapid clinical deterioration.^{8,16,34}

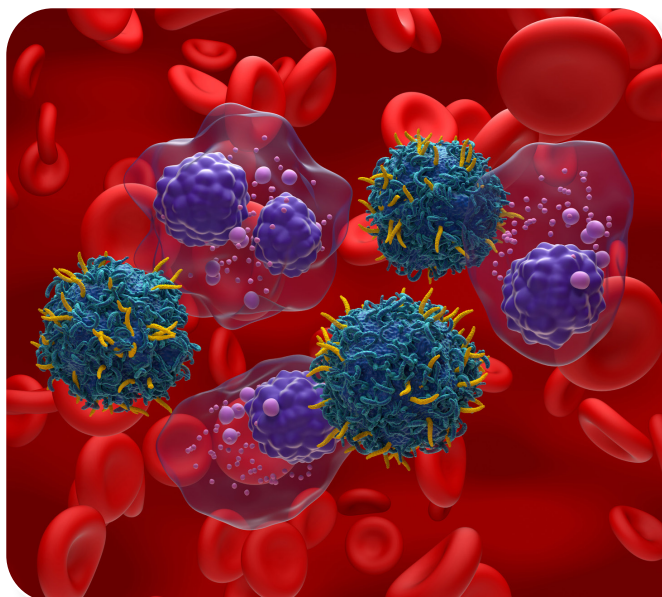
Cilta-cel is a BCMA-directed CAR T-cell therapy designed to recognize and eliminate BCMA-expressing malignant plasma cells.¹⁹ On the basis of the CARTITUDE-1 clinical trial, cilta-cel was initially approved in the US for patients with relapsed/refractory multiple myeloma after ≥ 4 previous lines of therapy.³ CARTITUDE-4 established the CAR T-cell therapy cilta-cel as an effective option for patients with lenalidomide-refractory multiple myeloma after one to three previous lines of therapy.^{8,35} Compared with physician's choice of standard regimens, cilta-cel produced a substantial progression-free survival advantage and higher rates of deep response and MRD negativity.^{8,35}

The importance of these clinical trial findings extend beyond efficacy data, they support the concept that immunotherapy should be considered for treatment



Immunotherapy should be considered for treatment while patients remain sufficiently fit to receive it, rather than reserved until later lines of therapy.

while patients remain sufficiently fit to receive it, rather than reserved until later lines of therapy after all other drug classes have been tried and failed.^{8,35} Earlier treatment may also improve the characteristics of the manufactured product. CAR T-cell expansion and persistence depend on the quality of the collected lymphocytes, the composition of the final product, and the relationship between effector-cell number and target-cell burden. Repeated exposure to alkylators, corticosteroids, proteasome inhibitors, immunomodulatory agents, and prior T-cell redirecting therapy may diminish immune reserve. Consequently, referral timing and the treatment given before leukapheresis can influence outcomes long before infusion occurs.^{34,36} To achieve earlier line use of CAR T-cell therapy, early referral should occur before CAR T-cell therapy becomes the immediate next treatment, providing time to confirm eligibility, obtain insurance authorization, plan leukapheresis, select bridging therapy, and address treatment logistics, such as transportation. Early referral is particularly important for those patients experiencing aggressive relapse, extramedullary disease, worsening cytopenias, or a short response to previous treatment.^{36,37}





Although cilta-cel expanded into use in earlier lines of treatment for patients with relapsed, lenalidomide-refractory multiple myeloma with ≥ 1 previous line of therapy on the basis of the CARTITUDE-4 clinical trial,^{19,38,39} long-term follow-up from CARTITUDE-1 has demonstrated the possibility of durable treatment-free remission and cure.¹⁹ CARTITUDE-1 trial evaluated cilta-cel in heavily pretreated patients with relapsed/refractory multiple myeloma who would have historically

had extremely poor outcomes and limited remaining therapeutic options.^{40–42} The study assessed overall survival, ≥ 5 -year progression-free outcomes, associated biomarkers, and safety. At study closeout, median progression-free survival was 34.9 months.⁴⁰ Median overall survival in CARTITUDE-1 exceeded 60 months in additional analyses, representing one of the most remarkable long-term outcomes observed in patients with heavily pretreated relapsed/refractory multiple myeloma. A post-hoc analysis was conducted to gain additional insight into those patients who had long-term clinical benefit (overall survival ≥ 5 years), with 61.3-month median follow-up.¹⁵ Twelve patients treated at a single center underwent serial MRD and positron emission tomography-computed tomography assessments, and all (100%) were MRD-negative (at least 10^{-5} threshold) and imaging-negative at year 5 or later after cilta-cel.¹⁵

If long-term remission rates improve further with earlier intervention, the role of CAR T-cell therapy in multiple myeloma could continue to transform treatment over the next several years. Additional research is ongoing, including CARTITUDE-5 and CARTITUDE-6. These trials are being conducted to evaluate whether CAR T-cell therapy with cilta-cel may eventually move into frontline treatment settings.

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Phase 3 Cilta-cel Studies in Patients with Newly Diagnosed Multiple Myeloma

CARTITUDE-5 (NCT04923893)

Clinical study testing the CAR T-cell therapy as an early treatment for newly diagnosed multiple myeloma

- **Patient Population:** Patients with newly diagnosed multiple myeloma who are not planned for an initial autologous stem cell transplant
- **Experimental Arm:** Induction therapy using bortezomib, lenalidomide, and dexamethasone (VRd) followed by a single infusion of cilta-cel
- **Control Arm:** Induction therapy with VRd followed by continuous maintenance treatment with lenalidomide and dexamethasone

CARTITUDE-6 (NCT05257083)

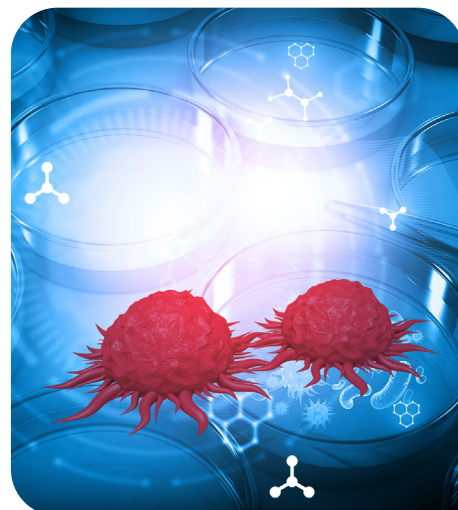
Clinical trial comparing CAR T-cell therapy with standard stem cell transplantation for newly diagnosed multiple myeloma

- **Patient Population:** Transplant-eligible adult patients with newly diagnosed multiple myeloma
- **Experimental Arm:** Induction therapy using DVRd (daratumumab, bortezomib, lenalidomide, and dexamethasone) followed by a single infusion of cilta-cel and subsequent lenalidomide maintenance
- **Standard Comparator Arm:** Induction therapy using DVRd, followed by high-dose therapy with autologous stem cell transplantation, DVRd consolidation, and lenalidomide maintenance

Working Towards a Cure for Multiple Myeloma Over the Next Decade

Although the possibility of functional cure for patients with multiple myeloma is currently limited to a subset of patients, requires longer follow-up, and needs clearer definitions, sustained MRD-negative, treatment-free remission after treatment with a single immune therapy is now an observable clinical outcome and a realistic direction for the future of multiple myeloma research over the next decade.^{3,12,15}

Multiple myeloma was historically thought of as incurable, with patients being at high risk of relapse and need prompt treatment to reduce the morbidity and mortality associated with the disease.²⁰⁻²² Therefore, multiple myeloma treatment focused on disease control and prolongation of survival through successive lines of treatment.^{8,15,16} However, recent advances in research and treatment free remissions following CAR T-cell therapy have improved survival outcomes and raised the possibility of achieving functional cure.¹⁹ A functional cure does not necessarily require proof that every malignant plasma cell has been eradicated, but it does describe sustained disease control without clinically meaningful progression, progressive organ injury, or an ongoing treatment burden that dominates daily life.^{3,19} As immunotherapies move to earlier lines of treatment, a larger proportion of patients may achieve deep responses, making the definition of functional cure increasingly important.^{3,38}



Common Features Associated With Functional Cure in Multiple Myeloma

Functional cure focuses on achieving a state where the myeloma doesn't negatively impact the patient's quality of life or lead to relapse, rather than achieving complete eradication of all myeloma cells.

Sustained MRD negativity
Long-term progression-free survival
Absence of active disease-related symptoms
No progressive organ damage
Minimal or no ongoing therapy
Preservation of quality of life

Long-term follow-up from CARTITUDE-1 provides a clinical framework for this concept. A subset of heavily pretreated patients remained progression-free for at least 5 years after a single cilta-cel infusion, and serial evaluations in a single-center subgroup showed sustained MRD and imaging negativity at year five or later. These findings do not establish a universal cure threshold, but they demonstrate that prolonged treatment-free remission is biologically and clinically possible in relapsed or refractory disease.¹⁵

There are common features associated with functional cure that include sustained MRD negativity and long-term progression-free survival.³ A useful definition should combine disease, treatment, and patient-centered outcomes. Sustained MRD negativity is an important component, particularly when confirmed over time and supported by imaging in patients with extramedullary or focal disease.⁴⁴ However, MRD alone does not capture treatment burden,

chronic toxicity, organ function, or quality of life. A patient who remains MRD negative but experiences persistent severe cytopenias, recurrent infections, or disabling neurologic effects may not experience the state that the term functional cure is intended to describe.⁴⁴

Novel immunotherapies, including BCMA targeting therapies, combined with refined diagnostics, imaging, and MRD assessment, functional cure is not just aspirational, but achievable over the next decade.⁴⁴ With decisive acts for treatment at diagnosis, optimization of treatment with the goal of sustained MRD negativity (10^{-6}) including imaging, and preservation of quality of life, then it is entirely plausible to see cure rates rise significantly within the next 5 to 10 years.⁴⁴ An important next step will be to refine the definition of which patients may already be “cured” with current treatment approaches.⁴⁴ Novel immunotherapies, may play a pivotal role by further deepening responses or rescuing patients at risk of relapse.⁴⁴ Cure is no longer a mirage but a horizon toward which multiple myeloma research and clinical practice must stride with courage and precision.

Key Steps in Multiple Myeloma Research and Treatment Working Towards a Cure

Primary Modality	Key Necessary Steps in Research and Treatment
Early diagnosis and line of treatment refinement	• Improve risk stratification in smoldering multiple myeloma • Predict progression and define when to intervene • Use functional imaging early to detect occult organ or focal disease
Maximal depth of response	• Achieve MRD negativity at sensitivity $\geq 10^{-6}$ validated by both marrow and imaging
Durability and synchronized treatment duration	• Define and validate standards • Standard risk (~2 years of sustained MRD negativity) • High risk (~3+ years) • Careful monitoring to detect relapse early and restart treatment if needed
Clinical trials with MRD-guided therapy	• Clinical trials with MRD-guided therapy decisions are needed • Trials should use MRD status (including imaging) to escalate, de-escalate, stop, or continue therapy • Trials should test duration of therapy required for cure
Safety, quality of life and fitness adaptation	• Ensure tolerable toxicity profile, including prophylaxis, supportive care, management of immune suppression • Incorporate frailty assessment, and adapt regimens for older or less fit patients • Collect patient-reported outcomes in clinical trials (quality of life and functional status)
BCMA Targeting Therapies	• BCMA targeting therapies may contribute to a true curative fraction in multiple myeloma as suggested by a growing body of evidence • Add to compelling data come from the CARTITUDE-1 study, whose 5-year update shows that approximately one-third of heavily pretreated patients remain treatment-free and progression-free • Study the possibility of long-term functional cure in a subset of individuals
Standardization of MRD assays	• Standardize MRD and imaging assays, and set common definitions • Support multicenter, randomized, MRD-driven trials • Ensure long-term data of ≥ 5 years are collected

Although no universally accepted definition for cure currently exists in multiple myeloma, long-term remission data from CARTITUDE-1 support the possibility that selected patients may achieve prolonged treatment-free disease control. Baseline characteristics, including the presence of high-risk cytogenetics and extramedullary disease, were generally comparable for the 32 patients who were progression-free for ≥ 5 years versus patients who had progressive disease by year 5.¹⁵ These data provided the first evidence that cilta-cel is potentially curative in patients with relapsed/refractory multiple myeloma,¹⁵ and continued research is demonstrating that a cure is possible for patients with the disease.⁴⁴

Treatment-free Interval: A Meaningful Outcome in Multiple Myeloma Treatment

A treatment-free interval in multiple myeloma is the length of time a patient spends off active systemic therapy between finishing one line of treatment and starting the next.⁴⁵ It is measured from the last dose of a current regimen to the first dose of subsequent therapy. Pausing active treatment

Treatment-free intervals can be achieved through advanced options like CAR T-cell therapies.

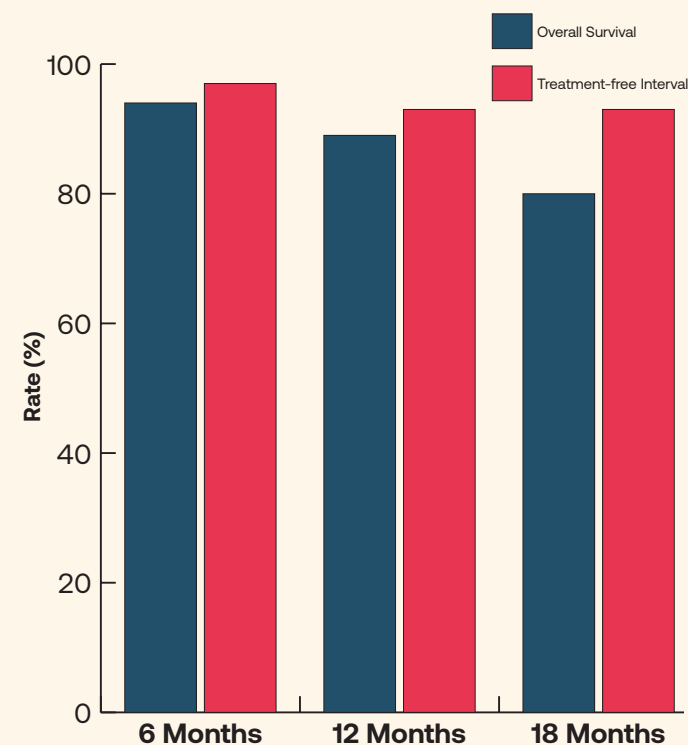
for patients with multiple myeloma reduces cumulative toxicity, lowers the burden of frequent hospital visits, and significantly improves patient-reported quality of life and functional well-being. Treatment-free interval is increasingly used in clinical trials and health economics as a critical measure of treatment efficacy and patient benefit beyond standard progression-free survival. Treatment-free intervals can be achieved through advanced options like CAR T-cell therapies (e.g., ide-cel and cilta-cel) as they provide one-time infusions that can establish deep remissions, yielding extended treatment-free interval periods in relapsed or refractory multiple myeloma settings. In addition, clinical protocols are actively studying response-adapted therapy stopping rules—such as pausing

treatment after achieving consecutive MRD-negative test results—allowing eligible patients to be monitored safely without continuous maintenance. Treatment-free interval in multiple myeloma is an important issue as it can allow patients to recover from toxicities and restore a good quality of life. It is, therefore, important to tailor the choice and duration of therapy to patients' priorities and individual needs.

CAR T-cell therapies are highly effective in terms of disease-free interval as well as allowing patients to be treatment free until the time of disease progression. In a real-world cohort (FREEDOMM claims analysis), adults patients (n=242) treated with cilta-cel after ≥4 prior lines of therapy showed favorable outcomes, with most patients remaining treatment-free and alive at 18 months post-infusion.¹³ At 6, 12, and 18 months, estimated treatment-free interval rates reached 94.0%, 89.0%, and 80.3% respectively, while overall survival rates for the same periods were 97.3%, 93.4%, and 93.4%.¹³ Although follow-up was limited and claims data have inherent limitations, treatment-free interval is especially relevant for a one-time therapy because it captures both disease control and freedom from continuous anticancer treatment.¹³



Rates of Treatment-free Interval and Overall Survival in Adults with Relapsed or Refractory Multiple Myeloma Receiving Cilta-cel after 4+ Previous Lines of Therapy¹³



For adult patients with RRMM who
have received a PI and an immunomodulatory
agent, and are lenalidomide-refractory

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INDICATIONS AND USAGE

CARVYKTI[®] (ciltacabtagene autoleucel) is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide.

WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, HLH/MAS, PROLONGED and RECURRENT CYTOPENIA, and SECONDARY HEMATOLOGICAL MALIGNANCIES

Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients following treatment with CARVYKTI[®]. Do not administer CARVYKTI[®] to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS), which may be fatal or life-threatening, occurred following treatment with CARVYKTI[®], including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with CARVYKTI[®]. Provide supportive care and/or corticosteroids as needed.

Parkinsonism and Guillain-Barré syndrome (GBS) and their associated complications resulting in fatal or life-threatening reactions have occurred following treatment with CARVYKTI[®].

Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS), including fatal and life-threatening reactions, occurred in patients following treatment with CARVYKTI[®]. HLH/MAS can occur with CRS or neurologic toxicities.

Prolonged and/or recurrent cytopenias with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery occurred following treatment with CARVYKTI[®].

Immune Effector Cell-associated Enterocolitis (IEC-EC), including fatal or life-threatening reactions, occurred following treatment with CARVYKTI[®].

Secondary hematological malignancies, including myelodysplastic syndrome and acute myeloid leukemia, have occurred in patients following treatment with CARVYKTI[®]. T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies, including CARVYKTI[®].

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Secondary endpoint: Overall survival

Median follow-up of 33.6 months

↓ 45% reduction in the risk of death
vs standard therapy (DPd or PVd)
(HR=0.55; 95% CI: 0.39-0.79; P=0.001)^{1‡§}

Primary endpoint: progression-free survival

Median follow-up of 15.9 months

59% reduction in the risk of disease progression
or death vs standard therapy (DPd or PVd)

(HR=0.41; 95% CI: 0.30-0.56; P<0.0001)^{||}



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(NCCN Guidelines®) for multiple myeloma after 1 prior therapy^{3||}

CARTITUDE-4 STUDY DESIGN

CARTITUDE-4 is a randomized, open-label, multicenter, controlled study evaluating the efficacy and safety of CARVYKTI for the treatment of adult patients with relapsed and lenalidomide-refractory multiple myeloma, who previously received at least 1 prior line of therapy including a proteasome inhibitor and an immunomodulatory agent. A total of 419 patients were randomized 1:1 to receive either CARVYKTI (n=208) or standard therapy which included daratumumab, pomalidomide, and dexamethasone (DPd) or pomalidomide, bortezomib, and dexamethasone (PVd) selected by physician prior to randomization based on patient's prior antimyeloma therapy (n=211). The primary efficacy measure was PFS analyzed based on the Intent-to-Treat Analysis Set.

2L=second-line; CAR-T=chimeric antigen receptor-T cell; CI=confidence interval; DPd=daratumumab, pomalidomide, and dexamethasone; HR=hazard ratio; NCCN=National Comprehensive Cancer Network® (NCCN®); PFS=progression-free survival; PI=proteasome inhibitor; PVd=pomalidomide, bortezomib, and dexamethasone; RRMM=relapsed or refractory multiple myeloma.

*Through October 2025.

†Through January 2026.

‡Median follow-up was 33.6 months in the Intent-to-Treat Analysis Set.

§Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable.

||Median follow-up was 15.9 months in the Intent-to-Treat Analysis Set.

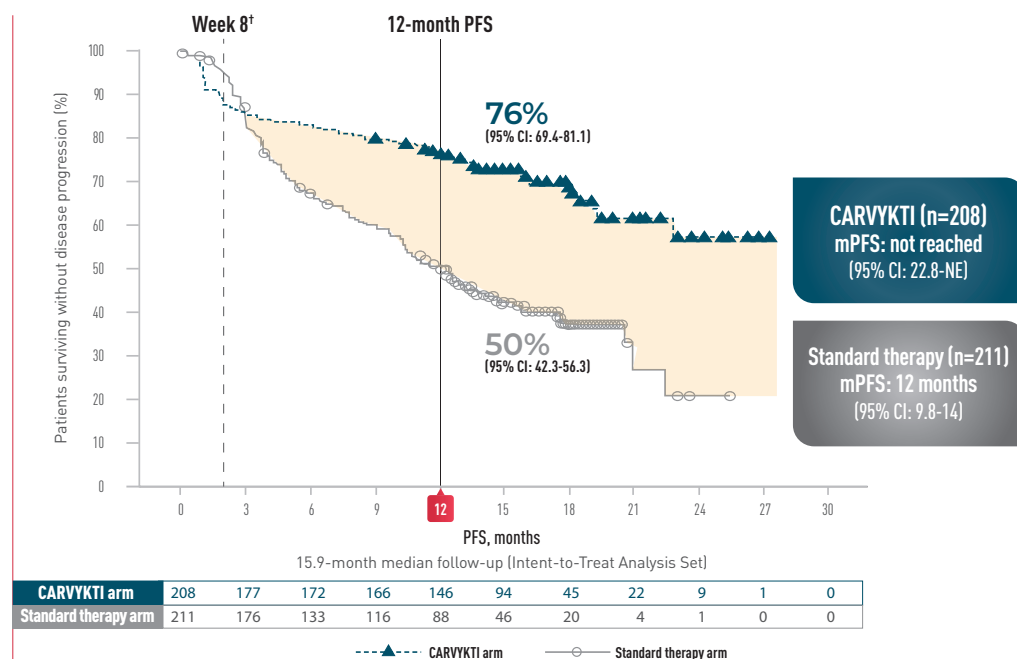
*Ciltacabtagene autoleucel (CARVYKTI®) is listed under "Therapy for Previously Treated Multiple Myeloma Relapsed/Refractory Disease After 1-3 Prior Therapies" as an option after 1 prior line of therapy, including an IMiD and a PI, and refractory to lenalidomide. Additionally, ciltacabtagene autoleucel (CARVYKTI®) is designated as Category 2A after 3 prior therapies³

Please read accompanying Brief Summary of the full Prescribing Information, including Boxed Warning, for CARVYKTI.

CARVYKTI SIGNIFICANTLY PROLONGED PROGRESSION-FREE SURVIVAL VS STANDARD THERAPY (DPd OR PVD)

INTENT-TO-TREAT/CARTITUDE-4 MEDIAN FOLLOW-UP OF 15.9 MONTHS

PROGRESSION-FREE SURVIVAL^{1,4*}



CARVYKTI demonstrated a

↓59%

Reduction in the risk of disease progression or death vs standard therapy (DPd or PVD)
(HR=0.41; 95% CI: 0.30-0.56; $P<0.0001$)^{†*}

Percentages rounded to nearest whole number.

CI=confidence interval; DPd=daratumumab, pomalidomide, and dexamethasone; HR=hazard ratio; mPFS=median progression-free survival; NE=not estimable; PFS=progression-free survival; PVD=pomalidomide, bortezomib, and dexamethasone.

*Median follow-up was 15.9 months in the Intent-to-Treat Analysis Set.

† A weighted log-rank test applied (0 for weeks 0-8, 1 after) because both arms used the same bridging treatment for 8 weeks.

SELECTED IMPORTANT SAFETY INFORMATION

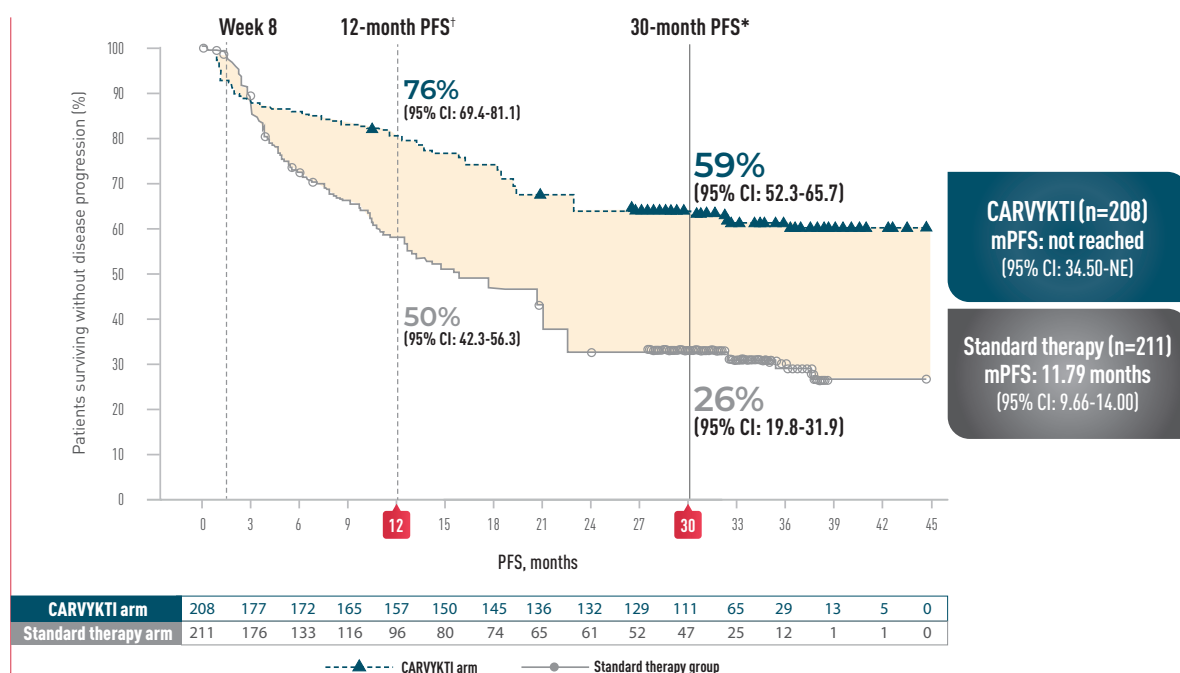
Fatal or life-threatening reactions occurred in patients following treatment with CARVYKTI[®], including Cytokine Release Syndrome (CRS), Parkinsonism, and Guillain-Barré syndrome, and their associated complications, and Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS). HLH/MAS can occur with CRS or neurologic toxicities. Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS), which can be fatal or life-threatening, occurred after treatment, before CRS onset, concurrently with CRS, after CRS resolution, or in absence of CRS.

MEDIAN PFS AT 3-YEAR FOLLOW-UP

INTENT-TO-TREAT/CARTITUDE-4 MEDIAN FOLLOW-UP OF 33.6 MONTHS

You are now viewing a subsequent follow-up analysis of the CARTITUDE-4 trial. This information is not included in the current USPI and the clinical significance is unknown. The data are presented here for descriptive purposes only.

PROGRESSION-FREE SURVIVAL^{1,2,4,5*}



71% Reduction In the risk of disease progression or death with CARVYKTI vs standard therapy (DPd or PVd) (HR=0.29; 95% CI: 0.22-0.39)^{5*†}

Percentages rounded to nearest whole number. These data are calculated from a weighted analysis.

CI=confidence interval; DPd=daratumumab, pomalidomide, and dexamethasone; FDA=U.S. Food and Drug Administration; HR=hazard ratio; mPFS=median progression-free survival; NE=not estimable; PFS=progression-free survival; PVd=pomalidomide, bortezomib, and dexamethasone; USPI=US Prescribing Information.

*Median follow-up was 33.6 months in the Intent-to-Treat Analysis Set.

[†] 12-month PFS values are derived from the USPI and are based on independent review committee (IRC) assessment of progression, FDA-requested analysis approach for PFS, and the 01 November 2022 data cutoff.

⁵ HR and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable, including only PFS events that occurred >8 weeks post randomization.

SELECTED IMPORTANT SAFETY INFORMATION (cont'd)

A numerically higher percent of early mortality was observed as compared to the control arm in CARTITUDE-4. Immune Effector Cell-associated Enterocolitis (IEC-EC), including fatal or life-threatening reactions, occurred following treatment. Prolonged and/or recurrent cytopenias with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery, and secondary hematological malignancies, including myelodysplastic syndrome, acute myeloid leukemia, and T-cell malignancies occurred following treatment.

cp-300288v6

Please read accompanying Brief Summary of the full Prescribing Information, including Boxed Warning, for CARVYKTI.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Increased early mortality. In CARTITUDE-4, a (1:1) randomized controlled trial, there was a numerically higher percentage of early deaths in patients randomized to the CARVYKTI[®] treatment arm compared to the control arm. Among patients with deaths occurring within the first 10 months from randomization, a greater proportion (29/208; 14%) occurred in the CARVYKTI[®] arm compared to (25/211; 12%) in the control arm. Of the 29 deaths that occurred in the CARVYKTI[®] arm within the first 10 months of randomization, 10 deaths occurred prior to CARVYKTI[®] infusion, and 19 deaths occurred after CARVYKTI[®] infusion. Of the 10 deaths that occurred prior to CARVYKTI[®] infusion, all occurred due to disease progression, and none occurred due to adverse events. Of the 19 deaths that occurred after CARVYKTI[®] infusion, 3 occurred due to disease progression, and 16 occurred due to adverse events. The most common adverse events were due to infection (n=12).

Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with CARVYKTI[®]. Among patients receiving CARVYKTI[®] for RRMM in the CARTITUDE-1 & -4 studies (N=285), CRS occurred in 84% (238/285), including $\geq$ Grade 3 CRS (ASTCT 2019) in 4% (11/285) of patients. Median time to onset of CRS, any grade, was 7 days (range: 1 to 23 days). CRS resolved in 82% with a median duration of 4 days (range: 1 to 97 days). The most common manifestations of CRS in all patients combined ($\geq 10\%$) included fever (84%), hypotension (29%) and aspartate aminotransferase increased (11%). Serious events that may be associated with CRS include pyrexia, hemophagocytic lymphohistiocytosis, respiratory failure, disseminated intravascular coagulation, capillary leak syndrome, and supraventricular and ventricular tachycardia. CRS occurred in 78% of patients in CARTITUDE-4 (3% Grade 3 to 4) and in 95% of patients in CARTITUDE-1 (4% Grade 3 to 4).

Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. CRS has been reported to be associated with findings of HLH/MAS, and the physiology of the syndromes may overlap. HLH/MAS is a potentially life-threatening condition. In patients with progressive symptoms of CRS or refractory CRS despite treatment, evaluate for evidence of HLH/MAS.

Confirm that a minimum of 2 doses of tocilizumab are available prior to infusion of CARVYKTI[®].

Of the 285 patients who received CARVYKTI[®] in clinical trials, 53% (150/285) patients received tocilizumab; 35% (100/285) received a single dose, while 18% (50/285) received more than 1 dose of tocilizumab. Overall, 14% (39/285) of patients received at least 1 dose of corticosteroids for treatment of CRS.

Monitor patients at least daily for 7 days following CARVYKTI[®] infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for at least 2 weeks after infusion. At the first sign of CRS, immediately institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids.

Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time.

Neurologic toxicities, which may be severe, life-threatening, or fatal, occurred following treatment with CARVYKTI[®]. Neurologic toxicities included ICANS, neurologic toxicity with signs and symptoms of Parkinsonism, GBS, immune mediated myelitis, peripheral neuropathies, and cranial nerve palsies. Counsel patients on the signs and symptoms of these neurologic toxicities, and on the delayed nature of onset of some of these toxicities. Instruct patients to seek immediate medical attention for further assessment and management if signs or symptoms of any of these neurologic toxicities occur at any time.

Among patients receiving CARVYKTI[®] in the CARTITUDE-1 & 4 studies for RRMM, one or more neurologic toxicities occurred in 24% (69/285), including $\geq$ Grade 3 cases in 7% (19/285) of patients. Median time to onset was 10 days (range: 1 to 101) with 63/69 (91%) of cases developing by 30 days. Neurologic toxicities resolved in 72% (50/69) of patients with a median duration to resolution of 23 days (range: 1 to 544). Of patients developing neurotoxicity, 96% (66/69) also developed CRS. Subtypes of neurologic toxicities included ICANS in 13%, peripheral neuropathy in 7%, cranial nerve palsy in 7%, parkinsonism in 3%, and immune mediated myelitis in 0.4% of the patients.

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS): Patients receiving CARVYKTI[®] may experience fatal or life-threatening ICANS following treatment with CARVYKTI[®], including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS.

Among patients receiving CARVYKTI[®] in the CARTITUDE-1 & -4 studies, ICANS occurred in 13% (36/285), including Grade ≥ 3 in 2% (6/285) of the patients. Median time to onset of ICANS was 8 days (range: 1 to 28 days). ICANS resolved in 30 of 36 (83%) of patients, with a median time to resolution of 3 days (range: 1 to 143 days). Median duration of ICANS was 6 days (range: 1 to 1229 days) in all patients, including those with ongoing neurologic events at the time of death or data cutoff. Of patients with ICANS, 97% (35/36) had CRS. The onset of ICANS occurred during CRS in 69% of patients, before and after the onset of CRS in 14% of patients, respectively.

Immune Effector Cell-associated Neurotoxicity Syndrome occurred in 7% of patients in CARTITUDE-4 (0.5% Grade 3) and in 23% of patients in CARTITUDE-1 (3% Grade 3). The most frequent ($\geq 2\%$) manifestations of ICANS included encephalopathy (12%), aphasia (4%), headache (3%), motor dysfunction (3%), ataxia (2%), and sleep disorder (2%).

Monitor patients at least daily for 7 days following CARVYKTI[®] infusion for signs and symptoms of ICANS. Rule out other causes of ICANS symptoms. Monitor patients for signs or symptoms of ICANS for at least 2 weeks after infusion and treat promptly. Neurologic toxicity should be managed with supportive care and/or corticosteroids as needed. Advise patients to avoid driving for at least 2 weeks following infusion.

Parkinsonism: Neurologic toxicity with parkinsonism has been reported in clinical trials of CARVYKTI[®]. Among patients receiving CARVYKTI[®] in the CARTITUDE-1 & -4 studies, parkinsonism occurred in 3% (8/285), including Grade ≥ 3 in 2% (5/285) of the patients. Median time to onset of parkinsonism was 56 days (range: 14 to 914 days). Parkinsonism resolved in 1 of 8 (13%) of patients with a median time to resolution of 523 days. Median duration of parkinsonism was 243.5 days (range: 62 to 720 days) in all patients, including those with ongoing neurologic events at the time of death or data cutoff. The onset of parkinsonism occurred after CRS for all patients and after ICANS for 6 patients.

Parkinsonism occurred in 1% of patients in CARTITUDE-4 (no Grade 3 to 4) and in 6% of patients in CARTITUDE-1 (4% Grade 3 to 4).

Manifestations of parkinsonism included movement disorders, cognitive impairment, and personality changes. Monitor patients for signs and symptoms of parkinsonism that may be delayed in onset and managed with supportive care measures. There is limited efficacy information with medications used for the treatment of Parkinson's disease for the improvement or resolution of parkinsonism symptoms following CARVYKTI[®] treatment.

WARNINGS AND PRECAUTIONS (cont'd)

Guillain-Barré syndrome: A fatal outcome following GBS occurred following treatment with CARVYKTI® despite treatment with intravenous immunoglobulins. Symptoms reported include those consistent with Miller-Fisher variant of GBS, encephalopathy, motor weakness, speech disturbances, and polyradiculoneuritis.

Monitor for GBS. Evaluate patients presenting with peripheral neuropathy for GBS. Consider treatment of GBS with supportive care measures and in conjunction with immunoglobulins and plasma exchange, depending on severity of GBS.

Immune mediated myelitis: Grade 3 myelitis occurred 25 days following treatment with CARVYKTI® in CARTITUDE-4 in a patient who received CARVYKTI® as subsequent therapy. Symptoms reported included hypoesthesia of the lower extremities and the lower abdomen with impaired sphincter control. Symptoms improved with the use of corticosteroids and intravenous immune globulin. Myelitis was ongoing at the time of death from other cause.

Peripheral neuropathy occurred following treatment with CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & -4 studies, peripheral neuropathy occurred in 7% (21/285), including Grade ≥3 in 1% (3/285) of the patients. Median time to onset of peripheral neuropathy was 57 days (range: 1 to 914 days). Peripheral neuropathy resolved in 11 of 21 (52%) of patients with a median time to resolution of 58 days (range: 1 to 215 days). Median duration of peripheral neuropathy was 149.5 days (range: 1 to 692 days) in all patients including those with ongoing neurologic events at the time of death or data cutoff.

Peripheral neuropathies occurred in 7% of patients in CARTITUDE-4 (0.5% Grade 3 to 4) and in 7% of patients in CARTITUDE-1 (2% Grade 3 to 4). Monitor patients for signs and symptoms of peripheral neuropathies. Patients who experience peripheral neuropathy may also experience cranial nerve palsies or GBS.

Cranial nerve palsies occurred following treatment with CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & -4 studies, cranial nerve palsies occurred in 7% (19/285), including Grade ≥3 in 1% (1/285) of the patients. Median time to onset of cranial nerve palsies was 21 days (range: 17 to 101 days). Cranial nerve palsies resolved in 17 of 19 (89%) of patients with a median time to resolution of 66 days (range: 1 to 209 days). Median duration of cranial nerve palsies was 70 days (range: 1 to 262 days) in all patients, including those with ongoing neurologic events at the time of death or data cutoff. Cranial nerve palsies occurred in 9% of patients in CARTITUDE-4 (1% Grade 3 to 4) and in 3% of patients in CARTITUDE-1 (1% Grade 3 to 4).

The most frequent cranial nerve affected was the 7th cranial nerve. Additionally, cranial nerves III, V, and VI have been reported to be affected.

Monitor patients for signs and symptoms of cranial nerve palsies. Consider management with systemic corticosteroids, depending on the severity and progression of signs and symptoms.

Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS): Among patients receiving CARVYKTI® in the CARTITUDE-1 & -4 studies, HLH/MAS occurred in 1% (3/285) of patients. All events of HLH/MAS had onset within 99 days of receiving CARVYKTI®, with a median onset of 10 days (range: 8 to 99 days), and all occurred in the setting of ongoing or worsening CRS. The manifestations of HLH/MAS included hyperferritinemia, hypotension, hypoxia with diffuse alveolar damage, coagulopathy and hemorrhage, cytopenia, and multi-organ dysfunction, including renal dysfunction and respiratory failure.

Patients who develop HLH/MAS have an increased risk of severe bleeding. Monitor hematologic parameters in patients with HLH/MAS and transfuse per institutional guidelines. Fatal cases of HLH/MAS occurred following treatment with CARVYKTI®.

HLH is a life-threatening condition with a high mortality rate if not recognized and treated early. Treatment of HLH/MAS should be administered per institutional standards.

Prolonged and Recurrent Cytopenias: Patients may exhibit prolonged and recurrent cytopenias following lymphodepleting chemotherapy and CARVYKTI® infusion.

Among patients receiving CARVYKTI® in the CARTITUDE-1 & -4 studies, Grade 3 or higher cytopenias not resolved by Day 30 following CARVYKTI® infusion occurred in 62% (176/285) of the patients and included thrombocytopenia 33% (94/285), neutropenia 27% (76/285), lymphopenia 24% (67/285), and anemia 2% (6/285). After Day 60 following CARVYKTI® infusion, 22%, 20%, 5%, and 6% of patients had a recurrence of Grade 3 or 4 lymphopenia, neutropenia, thrombocytopenia, and anemia, respectively, after initial recovery of their Grade 3 or 4 cytopenia. Seventy-seven percent (219/285) of patients had one, two, or three or more recurrences of Grade 3 or 4 cytopenias after initial recovery of Grade 3 or 4 cytopenia. Sixteen and 25 patients had Grade 3 or 4 neutropenia and thrombocytopenia, respectively, at the time of death.

Monitor blood counts prior to and after CARVYKTI® infusion. Manage cytopenias with growth factors and blood product transfusion support according to local institutional guidelines.

Infections: CARVYKTI® should not be administered to patients with active infection or inflammatory disorders. Severe, life-threatening, or fatal infections occurred in patients after CARVYKTI® infusion.

Among patients receiving CARVYKTI® in the CARTITUDE-1 & -4 studies, infections occurred in 57% (163/285), including Grade ≥3 in 24% (69/285) of patients. Grade 3 or 4 infections with an unspecified pathogen occurred in 12%, viral infections in 6%, bacterial infections in 5%, and fungal infections in 1% of patients. Overall, 5% (13/285) of patients had Grade 5 infections, 2.5% of which were due to COVID-19. Patients treated with CARVYKTI® had an increased rate of fatal COVID-19 infections compared to the standard therapy arm.

Monitor patients for signs and symptoms of infection before and after CARVYKTI® infusion and treat patients appropriately. Administer prophylactic, pre-emptive, and/or therapeutic antimicrobials according to the standard institutional guidelines. Febrile neutropenia was observed in 5% of patients after CARVYKTI® infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids, and other supportive care, as medically indicated. Counsel patients on the importance of prevention measures. Follow institutional guidelines for the vaccination and management of immunocompromised patients with COVID-19.

Viral Reactivation: Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients with hypogammaglobulinemia. Perform screening for Cytomegalovirus (CMV), HBV, hepatitis C virus (HCV), and human

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

immunodeficiency virus (HIV) or any other infectious agents if clinically indicated in accordance with clinical guidelines before collection of cells for manufacturing. Consider antiviral therapy to prevent viral reactivation per local institutional guidelines/clinical practice.

Reactivation of John Cunningham (JC) virus, leading to progressive multifocal leukoencephalopathy (PML), including cases with fatal outcomes, have been reported following treatment. Perform appropriate diagnostic evaluations in patients with neurological adverse events.

Hypogammaglobulinemia can occur in patients receiving treatment with CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & -4 studies, hypogammaglobulinemia adverse event was reported in 36% (102/285) of patients; laboratory IgG levels fell below 500 mg/dL after infusion in 93% (265/285) of patients. Hypogammaglobulinemia either as an adverse reaction or laboratory IgG level below 500 mg/dL after infusion occurred in 94% (267/285) of patients treated. Fifty-six percent (161/285) of patients received intravenous immunoglobulin (IVIG) post CARVYKTI® for either an adverse reaction or prophylaxis.

Monitor immunoglobulin levels after treatment with CARVYKTI® and administer IVIG for IgG <400 mg/dL. Manage per local institutional guidelines, including infection precautions and antibiotic or antiviral prophylaxis.

Use of Live Vaccines: The safety of immunization with live viral vaccines during or following CARVYKTI® treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during CARVYKTI® treatment, and until immune recovery following treatment with CARVYKTI®.

Hypersensitivity Reactions occurred following treatment with CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & -4 studies, hypersensitivity reactions occurred in 5% (13/285), all of which were ≤2 Grade. Manifestations of hypersensitivity reactions included flushing, chest discomfort, tachycardia, wheezing, tremor, burning sensation, non-cardiac chest pain, and pyrexia.

Serious hypersensitivity reactions, including anaphylaxis, may be due to the dimethyl sulfoxide (DMSO) in CARVYKTI®. Patients should be carefully monitored for 2 hours after infusion for signs and symptoms of severe reaction. Treat promptly and manage patients appropriately according to the severity of the hypersensitivity reaction.

Immune effector cell-associated enterocolitis (IEC-EC) has occurred in patients treated with CARVYKTI®. Manifestations include severe or prolonged diarrhea, abdominal pain, and weight loss requiring parenteral nutrition. IEC-EC has been associated with fatal outcome from perforation or sepsis. Manage according to institutional guidelines, including referral to gastroenterology and infectious disease specialists.

In cases of refractory IEC-EC, consider additional workup to exclude alternative etiologies, including T-cell lymphoma of the GI tract, which has been reported in the post marketing setting.

Secondary Malignancies: Patients treated with CARVYKTI® may develop secondary malignancies. Among patients receiving CARVYKTI® in the CARTITUDE-1 & -4 studies, myeloid neoplasms occurred in 5% (13/285) of patients (9 cases of myelodysplastic syndrome, 3 cases of acute myeloid leukemia, and 1 case of myelodysplastic syndrome followed by acute myeloid leukemia). The median time to onset of myeloid neoplasms was 447 days (range: 56 to 870 days) after treatment with CARVYKTI®. Ten of these 13 patients died following the development of myeloid neoplasms; 2 of the 13 cases of myeloid neoplasm occurred after initiation of subsequent antimyeloma therapy. Cases of myelodysplastic syndrome and acute myeloid leukemia have also been reported in the post marketing setting. T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies, including CARVYKTI®. Mature T-cell malignancies, including CAR-positive tumors, may present as soon as weeks following infusions, and may include fatal outcomes.

Monitor lifelong for secondary malignancies. In the event that a secondary malignancy occurs, contact Janssen Biotech, Inc., at 1-800-526-7736 for reporting and to obtain instructions on collection of patient samples.

ADVERSE REACTIONS

The most common nonlaboratory adverse reactions (incidence greater than 20%) are pyrexia, cytokine release syndrome, hypogammaglobulinemia, hypotension, musculoskeletal pain, fatigue, infections-pathogen unspecified, cough, chills, diarrhea, nausea, encephalopathy, decreased appetite, upper respiratory tract infection, headache, tachycardia, dizziness, dyspnea, edema, viral infections, coagulopathy, constipation, and vomiting. The most common Grade 3 or 4 laboratory adverse reactions (incidence greater than or equal to 50%) include lymphopenia, neutropenia, white blood cell decreased, thrombocytopenia, and anemia.

Please read enclosed full Prescribing Information, including Boxed Warning, for CARVYKTI®.

cp-258862v11

REFERENCES:

1. CARVYKTI [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Data on file. Janssen Biotech, Inc. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma V.5.2026. © National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed January 9, 2026. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **4.** San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or standard care in lenalidomide-refractory multiple myeloma. *N Engl J Med.* 2023;389(4):335-347. doi:10.1056/NEJMoa2303379 **5.** Mateos MV, San-Miguel J, Dhakal B, et al. Overall survival with ciltacabtagene autoleucel versus standard of care in lenalidomide-refractory multiple myeloma: phase 3 CARTITUDE-4 study update. Presented at the 21st International Myeloma Society (IMS) Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil. Oral Presentation. **6.** ABECMA® [Prescribing Information]. Summit, NJ: Bristol-Myers Squibb, Inc.

FOR YOUR ADULT PATIENTS WITH RRMM WHO HAVE RECEIVED A PI AND AN IMMUNOMODULATORY AGENT, AND ARE LEN-REFRACTORY

HOPE FOR SURVIVAL GROWS WITH CARVYKTI AS EARLY AS 2L¹

THE ONLY CAR-T WITH A PROVEN LONG-TERM OS BENEFIT IN 2L+ RRMM^{1,6}

Secondary endpoint: OS (median follow-up 33.6 months)

45%

Reduction

In the risk of death
vs standard therapy (DPd or Pvd)

(HR=0.55; 95% CI: 0.39-0.79; $P=0.001$)^{1*†}

Primary endpoint: PFS (median follow-up 15.9 months)

59%

Reduction

In the risk of disease progression or death
vs standard therapy (DPd or Pvd)

(HR=0.41; 95% CI: 0.30-0.56; $P<0.0001$)^{1‡}

OVER 140 CARVYKTI TREATMENT CENTERS THROUGHOUT THE US²



FIND THE ONE NEAR YOU

Data rates may apply.

2L=second line; CAR-T=chimeric antigen receptor-T cell; CI=confidence interval; DPd=daratumumab, pomalidomide, and dexamethasone; HR=hazard ratio; len=lenalidomide; PI=proteasome inhibitor; PFS=progression-free survival; Pvd=pomalidomide, bortezomib, and dexamethasone; OS=overall survival; RRMM=relapsed and/or refractory multiple myeloma.

*Median follow-up was 33.6 months in the Intent-to-Treat Analysis Set.

†Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable.

‡Median follow-up was 15.9 months in the Intent-to-Treat Analysis Set.

Johnson & Johnson

LEGEND
BIOTECH

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Please read accompanying Brief Summary of the full Prescribing Information, including Boxed Warning, for CARVYKTI.

WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, HLH/MAS, PROLONGED and RECURRENT CYTOPENIA, and SECONDARY HEMATOLOGICAL MALIGNANCIES

Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients following treatment with CARVYKTI. Do not administer CARVYKTI to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids [see Dosage and Administration (2.2, 2.3) in Full Prescribing Information, Warnings and Precautions].

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), which may be fatal or life-threatening, occurred following treatment with CARVYKTI, including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with CARVYKTI. Provide supportive care and/or corticosteroids as needed [see Dosage and Administration (2.2, 2.3) in Full Prescribing Information, Warnings and Precautions].

Parkinsonism and Guillain-Barré syndrome (GBS) and their associated complications resulting in fatal or life-threatening reactions have occurred following treatment with CARVYKTI [see Warnings and Precautions].

Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS), including fatal and life-threatening reactions, occurred in patients following treatment with CARVYKTI. HLH/MAS can occur with CRS or neurologic toxicities [see Warnings and Precautions].

Prolonged and/or recurrent cytopenias with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery occurred following treatment with CARVYKTI [see Warnings and Precautions].

Immune Effector Cell-associated Enterocolitis (IEC-EC), including fatal or life-threatening reactions, occurred following treatment with CARVYKTI [see Warnings and Precautions].

Secondary hematological malignancies, including myelodysplastic syndrome and acute myeloid leukemia, have occurred in patients following treatment with CARVYKTI. T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies, including CARVYKTI [see Warnings and Precautions].

INDICATIONS AND USAGE

CARVYKTI is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Increased Early Mortality

In CARTITUDE-4, a randomized (1:1), controlled trial, there was a numerically higher percentage of early deaths in patients randomized to the CARVYKTI treatment arm compared to the control arm. Among patients with deaths occurring within the first 10 months from randomization, a greater proportion (29/208; 14%) occurred in the CARVYKTI arm compared to (25/211; 12%) in the control arm [see Clinical Studies (14) in Full Prescribing Information]. Of the 29 deaths that occurred in the CARVYKTI arm within the first 10 months of randomization, 10 deaths occurred prior to CARVYKTI infusion, and 19 deaths occurred after CARVYKTI infusion. Of the 10 deaths that occurred prior to CARVYKTI infusion, all occurred due to disease progression, and none occurred due to adverse events. Of the 19 deaths that occurred after CARVYKTI infusion, 3 occurred due to disease progression, and 16 occurred due to adverse events. The most common adverse events were due to infection (n=12).

Cytokine Release Syndrome

Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with CARVYKTI. Among patients receiving CARVYKTI for relapsed or refractory multiple myeloma in the CARTITUDE-1 and CARTITUDE-4 studies (N=285), CRS occurred in 84% (238/285), including ≥ Grade 3 CRS (ASTCT 2019) in 4% (11/285) of patients. The median time to onset of CRS, any grade, was 7 days (range: 1 to 23 days). Cytokine release syndrome resolved in 82% with a median duration of 4 days (range: 1 to 97 days). The most common manifestations of CRS in all patients combined (≥ 10%) included fever (84%), hypotension (29%) and aspartate aminotransferase increased (11%). Serious events that may be associated with CRS include pyrexia, hemophagocytic lymphohistiocytosis, respiratory failure, disseminated intravascular coagulation, capillary leak syndrome, and supraventricular and ventricular tachycardia [see Adverse Reactions].

Cytokine release syndrome occurred in 78% of patients in CARTITUDE-4 (3% Grade 3 to 4) and in 95% of patients in CARTITUDE-1 (4% Grade 3 to 4).

Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. CRS has been reported to be associated with findings of HLH/MAS, and the physiology of the syndromes may overlap. HLH/MAS is a potentially life-threatening condition. In patients with progressive symptoms of CRS or refractory CRS despite treatment, evaluate for evidence of HLH/MAS [see Warnings and Precautions].

Confirm that a minimum of two doses of tocilizumab are available prior to infusion of CARVYKTI.

Of the 285 patients who received CARVYKTI in clinical trials, 53% (150/285) patients received tocilizumab; 35% (100/285) received a single dose, while 18% (50/285) received more than 1 dose of tocilizumab. Overall, 14% (39/285) of patients received at least one dose of corticosteroids for treatment of CRS.

Monitor patients at least daily for 7 days following CARVYKTI infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for at least 2 weeks after infusion. At the first sign of CRS, immediately institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids, as indicated in Table 1 in Full Prescribing Information [see Dosage and Administration (2.3) in Full Prescribing Information].

Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time [see Patient Counseling Information].

Neurologic Toxicities

Neurologic toxicities, which may be severe, life-threatening or fatal, occurred following treatment with CARVYKTI. Neurologic toxicities included ICANS, neurologic toxicity with signs and symptoms of parkinsonism, GBS, immune mediated myelitis, peripheral neuropathies and cranial nerve palsies. Counsel patients on the signs and symptoms of these neurologic toxicities, and on the delayed nature of onset of some of these toxicities. Instruct patients to seek immediate medical attention for further assessment and management if signs or symptoms of any of these neurologic toxicities occur at any time [see Patient Counseling Information].

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies for relapsed and refractory multiple myeloma, one or more neurologic toxicities occurred in 24% (69/285), including ≥ Grade 3 cases in 7% (19/285) of patients. The median time to onset was 10 days (range: 1 to 101) with 63/69 (91%) of cases developing by 30 days. Neurologic toxicities resolved in 72% (50/69) of patients with a median duration to resolution of 23 days (range: 1 to 544). Of patients developing neurotoxicity, 96% (66/69) also developed CRS. Subtypes of neurologic toxicities included ICANS in 13%, peripheral neuropathy in 7%, cranial nerve palsy in 7%, parkinsonism in 3%, and immune mediated myelitis in 0.4% of the patients [see Adverse Reactions].

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

Patients receiving CARVYKTI may experience fatal or life-threatening ICANS following treatment with CARVYKTI, including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, ICANS occurred in 13% (36/285), including Grade ≥ 3 in 2% (6/285) of the patients. The median time to onset of ICANS was 8 days (range: 1 to 28 days). ICANS resolved in 30 of 36 (83%) of patients with a median time to resolution of 3 days (range: 1 to 143 days). The median duration of ICANS was 6 days (range: 1 to 1229 days) in all patients including those with ongoing neurologic events at the time of death or data cut off. Of patients with ICANS 97% (35/36) had CRS. The onset of ICANS occurred during CRS in 69% of patients, before and after the onset of CRS in 14% of patients respectively.

Immune Effector Cell-associated Neurotoxicity Syndrome occurred in 7% of patients in CARTITUDE-4 (0.5% Grade 3) and in 23% of patients in CARTITUDE-1 (3% Grade 3).

The most frequent ≥2% manifestations of ICANS included encephalopathy (12%), aphasia (4%), headache (3%), motor dysfunction (3%), ataxia (2%) and sleep disorder (2%) [see Adverse Reactions].

Monitor patients at least daily for 7 days following CARVYKTI infusion for signs and symptoms of ICANS. Rule out other causes of ICANS symptoms. Monitor patients for signs or symptoms of ICANS for at least 2 weeks after infusion and treat promptly. Neurologic toxicity should be managed with supportive care and/or corticosteroids as needed [see Dosage and Administration (2.3) in Full Prescribing Information]. Advise patients to avoid driving for at least 2 weeks following infusion.

Parkinsonism

Neurologic toxicity with parkinsonism has been reported in clinical trials of CARVYKTI.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, parkinsonism occurred in 3% (8/285), including Grade ≥ 3 in 2% (5/285) of the patients. The median time to onset of parkinsonism was 56 days (range: 14 to 914 days). Parkinsonism resolved in 1 of 8 (13%) of patients with a median time to resolution of 523 days. The median duration of parkinsonism was 243.5 days (range: 62 to 720 days) in all patients including those with ongoing neurologic events at the time of death or data cut off. The onset of parkinsonism occurred after CRS for all patients and after ICANS for 6 patients.

Parkinsonism occurred in 1% of patients in CARTITUDE-4 (no Grade 3 to 4) and in 6% of patients in CARTITUDE-1 (4% Grade 3 to 4).

The manifestations of parkinsonism included movement disorders, cognitive impairment, and personality changes [see *Adverse Reactions*].

Monitor patients for signs and symptoms of parkinsonism that may be delayed in onset and managed with supportive care measures. There is limited efficacy information with medications used for the treatment of Parkinson's disease for the improvement or resolution of parkinsonism symptoms following CARVYKTI treatment.

Guillain-Barré Syndrome

A fatal outcome following GBS occurred following treatment with CARVYKTI despite treatment with intravenous immunoglobulins. Symptoms reported include those consistent with Miller-Fisher variant of GBS, encephalopathy, motor weakness, speech disturbances, and polyradiculoneuritis.

Monitor for GBS. Evaluate patients presenting with peripheral neuropathy for GBS. Consider treatment of GBS with supportive care measures and in conjunction with immunoglobulins and plasma exchange, depending on severity of GBS.

Immune Mediated Myelitis

Grade 3 myelitis occurred 25 days following treatment with CARVYKTI in CARTITUDE-4 in a patient who received CARVYKTI as subsequent therapy. Symptoms reported included hypoesthesia of the lower extremities and the lower abdomen with impaired sphincter control. Symptoms improved with the use of corticosteroids and intravenous immune globulin. Myelitis was ongoing at the time of death from other cause [see *Adverse Reactions*].

Peripheral Neuropathy

Peripheral neuropathy occurred following treatment with CARVYKTI.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, peripheral neuropathy occurred in 7% (21/285), including Grade ≥ 3 in 1% (3/285) of the patients. The median time to onset of peripheral neuropathy was 57 days (range: 1 to 914 days). Peripheral neuropathy resolved in 11 of 21 (52%) of patients with a median time to resolution of 58 days (range: 1 to 215 days). The median duration of peripheral neuropathy was 149.5 days (range: 1 to 692 days) in all patients including those with ongoing neurologic events at the time of death or data cut off [see *Adverse Reactions*].

Peripheral neuropathies occurred in 7% of patients in CARTITUDE-4 (0.5% Grade 3 to 4) and in 7% of patients in CARTITUDE-1 (2% Grade 3 to 4).

Monitor patients for signs and symptoms of peripheral neuropathies.

Patients who experience peripheral neuropathy may also experience cranial nerve palsies or GBS.

Cranial Nerve Palsies

Cranial nerve palsies occurred following treatment with CARVYKTI.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, cranial nerve palsies occurred in 7% (19/285), including Grade ≥ 3 in 1% (1/285) of the patients. The median time to onset of cranial nerve palsies was 21 days (range: 17 to 101 days). Cranial nerve palsies resolved in 17 of 19 (89%) of patients with a median time to resolution of 66 days (range: 1 to 209 days). The median duration of cranial nerve palsies was 70 days (range: 1 to 262 days) in all patients including those with ongoing neurologic events at the time of death or data cut off [see *Adverse Reactions*].

Cranial nerve palsies occurred in 9% of patients in CARTITUDE-4 (1% Grade 3 to 4) and in 3% of patients in CARTITUDE-1 (1% Grade 3 to 4).

The most frequent cranial nerve affected was the 7th cranial nerve. Additionally, cranial nerves III, V, and VI have been reported to be affected.

Monitor patients for signs and symptoms of cranial nerve palsies. Consider management with systemic corticosteroids, depending on the severity and progression of signs and symptoms.

Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, HLH/MAS occurred in 1% (3/285) of patients. All events of HLH/MAS had onset within 99 days of receiving CARVYKTI, with a median onset of 10 days (range: 8 to 99 days) and all occurred in the setting of ongoing or worsening CRS. The manifestations of HLH/MAS included hyperferritinemia, hypotension, hypoxia with diffuse alveolar damage, coagulopathy and hemorrhage, cytopenia and multi-organ dysfunction, including renal dysfunction and respiratory failure.

Patients who develop HLH/MAS have an increased risk of severe bleeding. Monitor hematologic parameters in patients with HLH/MAS and transfuse per institutional guidelines. Fatal cases of HLH/MAS occurred following treatment with CARVYKTI [see *Adverse Reactions*].

HLH is a life-threatening condition with a high mortality rate if not recognized and treated early. Treatment of HLH/MAS should be administered per institutional standards.

Prolonged and Recurrent Cytopenias

Patients may exhibit prolonged and recurrent cytopenias following lymphodepleting chemotherapy and CARVYKTI infusion.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, Grade 3 or higher cytopenias not resolved by day 30 following CARVYKTI infusion occurred in 62% (176/285) of the patients and included thrombocytopenia 33% (94/285), neutropenia 27% (76/285), lymphopenia 24% (67/285) and anemia 2% (6/285). After Day 60 following CARVYKTI infusion 22%, 20%, 5%, and 6% of patients had a recurrence of Grade 3 or 4 lymphopenia, neutropenia, thrombocytopenia, and anemia respectively, after initial recovery of their Grade 3 or 4 cytopenia. Seventy-seven percent (219/285) of patients had one, two or three or more recurrences of Grade 3 or 4 cytopenias after initial recovery of Grade 3 or 4 cytopenia. Sixteen and 25 patients had Grade 3 or 4 neutropenia and thrombocytopenia, respectively, at the time of death [see *Adverse Reactions*].

Monitor blood counts prior to and after CARVYKTI infusion. Manage cytopenias with growth factors and blood product transfusion support according to local institutional guidelines.

Infections

CARVYKTI should not be administered to patients with active infection or inflammatory disorders. Severe, life-threatening, or fatal infections, occurred in patients after CARVYKTI infusion.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, infections occurred in 57% (163/285), including $\geq$ Grade 3 in 24% (69/285) of patients. Grade 3 or 4 infections with an unspecified pathogen occurred in 12%, viral infections in 6%, bacterial infections in 5%, and fungal infections in 1% of patients. Overall, 5% (13/285) of patients had Grade 5 infections, 2.5% of which were due to COVID-19. Patients treated with CARVYKTI had an increased rate of fatal COVID-19 infections compared to the standard therapy arm [see *Adverse Reactions*].

Monitor patients for signs and symptoms of infection before and after CARVYKTI infusion and treat patients appropriately. Administer prophylactic, pre-emptive and/or therapeutic antimicrobials according to the standard institutional guidelines. Febrile neutropenia was observed in 5% of patients after CARVYKTI infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids and other supportive care, as medically indicated.

Counsel patients on the importance of prevention measures. Follow institutional guidelines for the vaccination and management of immunocompromised patients with COVID-19.

Viral Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients with hypogammaglobulinemia.

Perform screening for Cytomegalovirus (CMV), HBV, hepatitis C virus (HCV), and human immunodeficiency virus (HIV) or any other infectious agents if clinically indicated in accordance with clinical guidelines before collection of cells for manufacturing.

Consider antiviral therapy to prevent viral reactivation per local institutional guidelines/clinical practice.

Reactivation of John Cunningham (JC) virus, leading to progressive multifocal leukoencephalopathy (PML), including cases with fatal outcomes, have been reported following treatment with CARVYKTI [see *Adverse Reactions*]. Perform appropriate diagnostic evaluations in patients with neurological adverse events.

Hypogammaglobulinemia

Hypogammaglobulinemia can occur in patients receiving treatment with CARVYKTI.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, hypogammaglobulinemia adverse event was reported in 36% (102/285) of patients; laboratory IgG levels fell below 500 mg/dL after infusion in 93% (265/285) of patients. Hypogammaglobulinemia either as an adverse reaction or laboratory IgG level below 500 mg/dL, after infusion occurred in 94% (267/285) of patients treated. Fifty six percent (161/285) of patients received intravenous immunoglobulin (IVIG) post CARVYKTI for either an adverse reaction or prophylaxis [see *Adverse Reactions*].

Monitor immunoglobulin levels after treatment with CARVYKTI and administer IVIG for IgG <400 mg/dL. Manage per local institutional guidelines, including infection precautions and antibiotic or antiviral prophylaxis.

Use of Live Vaccines

The safety of immunization with live viral vaccines during or following CARVYKTI treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during CARVYKTI treatment, and until immune recovery following treatment with CARVYKTI.

Hypersensitivity Reactions

Hypersensitivity reactions occurred following treatment with CARVYKTI.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, hypersensitivity reactions occurred in 5% (13/285), all of which were ≤ Grade 2. Manifestations of hypersensitivity reactions included flushing, chest discomfort, tachycardia, wheezing, tremor, burning sensation, non-cardiac chest pain, and pyrexia.

Serious hypersensitivity reactions, including anaphylaxis, may be due to the dimethyl sulfoxide (DMSO) in CARVYKTI. Patients should be carefully monitored for 2 hours after infusion for signs and symptoms of severe reaction. Treat promptly and manage patients appropriately according to the severity of the hypersensitivity reaction.

Immune Effector Cell-associated Enterocolitis

Immune effector cell-associated enterocolitis (IEC-EC) has occurred in patients treated with CARVYKTI [see *Adverse Reactions*]. Manifestations include severe or prolonged diarrhea, abdominal pain and weight loss requiring parenteral nutrition. IEC-EC has been associated with fatal outcome from perforation or sepsis. Manage according to institutional guidelines including referral to gastroenterology and infectious disease specialists.

In cases of refractory IEC-EC, consider additional workup to exclude alternative etiologies, including T-cell lymphoma of the GI tract, which has been reported in the postmarketing setting [see *Warnings and Precautions and Adverse Reactions*].

Secondary Malignancies

Patients treated with CARVYKTI may develop secondary malignancies.

Among patients receiving CARVYKTI in the CARTITUDE-1 and CARTITUDE-4 studies, myeloid neoplasms occurred in 5% (13/285) of patients (9 cases of myelodysplastic syndrome, 3 cases of acute myeloid leukemia, and 1 case of myelodysplastic syndrome followed by acute myeloid leukemia). The median time to onset of myeloid neoplasms was 447 days (range: 56 to 870 days) after treatment with CARVYKTI. Ten of these 13 patients died following the development of myeloid neoplasms; 2 of the 13 cases of myeloid neoplasm occurred after initiation of subsequent antineoplastic therapy. Cases of myelodysplastic syndrome and acute myeloid leukemia have also been reported in the post marketing setting.

T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies, including CARVYKTI. Mature T-cell malignancies, including CAR-positive tumors, may present as soon as weeks following infusions, and may include fatal outcomes [see *Boxed Warning, Adverse Reactions*].

Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Janssen Biotech, Inc. at 1-800-526-7736 for reporting and to obtain instructions on collection of patient samples.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described in the WARNINGS and PRECAUTIONS section reflect exposure to CARVYKTI in 285 patients with relapsed or refractory multiple myeloma: one randomized, open-label with 188 patients in CARTITUDE-4 and one single-arm, open-label study with 97 patients in CARTITUDE-1.

CARTITUDE-4

The safety of CARVYKTI was evaluated in CARTITUDE-4, a randomized, open-label multicenter study, in which patients with relapsed and lenalidomide refractory multiple myeloma received CARVYKTI meeting the product specifications (N=188) or standard therapy (N=208) [see *Clinical Studies (14) in Full Prescribing Information*]. Patients with known active or prior history of central nervous system involvement, patients who exhibit clinical signs of meningeal involvement of multiple myeloma and patients with a history of Parkinson's disease or other neurodegenerative disorder, were excluded from the trial. Patients received CARVYKTI at a median dose of 0.71×10^6 CAR-positive viable T-cells/kg (range: 0.41 to 1.08×10^6 cells/kg). The median age of the 188 participants was 62 years (range: 27 to 78 years); 40% were 65 years or older, and 57% were male; 76% were White, were 9% Hispanic or Latino, 8% were Asian, and 3% were Black.

The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was 0 in 56%, 1 in 44%. For the details about the study population, see *Clinical Studies (14) in Full Prescribing Information*.

The most common nonlaboratory adverse reactions (≥20%) included pyrexia, CRS, hypogammaglobulinemia, musculoskeletal pain, fatigue, upper respiratory tract infection, diarrhea, viral infections, headache, hypotension, and nausea.

Serious adverse reactions occurred in 34% of patients. The most common nonlaboratory serious adverse reactions (≥5%) were pneumonia (9%), viral infection (6%), CRS (6%), and cranial nerve palsies (5%).

Table 1 summarizes the adverse reactions that occurred in at least 10% of patients treated with CARVYKTI.

Table 1: Adverse reactions observed in at least 10% of patients treated with CARVYKTI (N=188) and standard therapy (N=208) in CARTITUDE-4

System Organ Class (SOC) Preferred term	CARVYKTI N=188 Any Grade (%)	CARVYKTI N=188 Grade 3 or higher (%)	Standard Therapy N=208 Any Grade (%)	Standard Therapy N=208 Grade 3 or higher (%)
Gastrointestinal disorders	-	-	-	-
Diarrhea ^a	27	3	27	2
Nausea	20	0	18	1
Constipation	10	0	21	1
General disorders and administrative site conditions	-	-	-	-
Pyrexia	79	5	16	1
Fatigue*	28	3	50	3
Edema ^b	11	1	20	1
Pain*	10	1	14	<1
Immune system disorders	-	-	-	-
Hypogammaglobulinemia ^c	94	9	72	<1
Cytokine release syndrome	78	3	<1	0
Infections and infestations	-	-	-	-
Upper respiratory tract infection*	25	1	40	5
Viral infection*	23	4	31	6
Bacterial infection*	15	6	17	4
Pneumonia*	14	9	18	11
Metabolism and nutrition disorders	-	-	-	-
Decreased appetite	10	0	5	0
Musculoskeletal and connective tissue disorders	-	-	-	-
Musculoskeletal pain*	34	2	47	4
Nervous system disorders	-	-	-	-
Headache*	23	0	13	0
Encephalopathy ^d	11	2	4	1
Respiratory, thoracic and mediastinal disorders	-	-	-	-
Cough*	15	0	18	0
Hypoxia	12	3	1	1
Vascular disorders	-	-	-	-
Hypotension*	23	4	3	0

* Represents multiple related terms.

^a Diarrhea includes Colitis, and Diarrhea

^b Edema includes Face edema, Generalized edema, Localized edema, Edema peripheral, Periorbital edema, Peripheral swelling, Pulmonary edema, and Scrotal edema.

^c Hypogammaglobulinemia includes subjects with adverse event of hypogammaglobulinemia and/or laboratory IgG levels that fell below 500 mg/dL following CARVYKTI infusion or standard therapy.

^d Encephalopathy includes Amnesia, Bradyphrenia, Confusional state, Depressed level of consciousness, Disturbance in attention, Immune effector cell-associated neurotoxicity syndrome, Lethargy, and Psychomotor retardation.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with CARVYKTI include the following:

- *Blood and lymphatic system disorders*: coagulopathy* (5%), febrile neutropenia (2%), lymphocytosis (2%)
- *Cardiac disorders*: tachycardia* (5%), cardiac arrhythmias* (3%)
- *Gastrointestinal disorders*: abdominal pain* (6%), vomiting (5%)
- *General disorders and administration site conditions*: chills (6%)
- *Immune system disorders*: HLH (1%)
- *Infections and infestations*: gastroenteritis* (7%), sepsis* (9%), urinary tract infection* (5%), fungal infection* (3%)
- *Investigations*: c-reactive protein increased (6%)

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- **Metabolism and nutrition disorders:** hypophosphatemia (10%), hyperferritinemia (7%)
- **Neoplasms benign, malignant, and unspecified (incl cysts and polyps):** hematologic malignancy^a (3%)
- **Nervous system disorders:** dizziness* (9%), cranial nerve palsies* (9%), motor dysfunction^b (9%), peripheral neuropathy* (7%), sleep disorder* (6%), tremor (4%), aphasia* (3%), ataxia* (3%)
- **Psychiatric disorders:** delirium* (2%), personality changes* (2%)
- **Renal and urinary disorders:** renal failure* (5%)
- **Respiratory, thoracic and mediastinal disorders:** dyspnea* (10%)
- **Skin and subcutaneous tissues:** rash* (7%)
- **Vascular disorders:** hemorrhage* (9%), hypertension (7%), thrombosis* (3%), capillary leak syndrome (1%)

* Represents multiple related terms

^a Hematologic malignancy includes Myelodysplastic syndrome, Acute myeloid leukaemia and T-cell lymphoma

^b Motor dysfunction includes Bradykinesia, Coordination abnormal, Dysgraphia, Extrapyramidal disorder, Micrographia, Muscle spasms, Muscular weakness, and Parkinsonism

Laboratory Abnormalities

Table 2 presents the most common Grade 3 or 4 laboratory abnormalities based on laboratory data, occurring in at least 10% of patients.

Table 2: Grade 3 or 4 laboratory abnormalities in at least 10% of patients treated with CARVYKTI (N=188) and standard therapy (N=208) in CARTITUDE-4

Laboratory Abnormality	CARVYKTI (N=188) Grade 3 or 4 (%)	Standard Therapy (N=208) Grade 3 or 4 (%)
Lymphocyte count decreased	99	62
Neutrophil count decreased	95	88
White blood cell decreased	94	69
Platelet count decreased	47	20
Hemoglobin decreased	34	17

Laboratory abnormalities graded using NCI Common Terminology Criteria for Adverse Events version 5.0. Laboratory abnormalities are sorted by decreasing frequency in the Grade column.

Other clinically important Grade 3 or 4 laboratory abnormalities (based on laboratory data) that occurred in less than 10% of patients treated with CARVYKTI include gamma glutamyl transferase increased, fibrinogen decreased, aspartate aminotransferase increased, hypokalemia, alanine aminotransferase increased, hyponatremia, alkaline phosphatase increased, hypertriglyceridemia, hypomagnesemia, hypoalbuminemia, hypocalcemia, and blood bilirubin increased.

CARTITUDE-1

The safety data described in this section reflect the exposure of 97 adult patients with relapsed/refractory multiple myeloma in the CARTITUDE-1 study (USA cohort) to CARVYKTI and includes 17 patients (18%) with manufacturing failures either because they received CARVYKTI that did not meet product release specifications or there were insufficient data to confirm product release specifications for CARVYKTI. Patients received CARVYKTI across a dose range of 0.51 to 0.95×10⁶ CAR-positive viable T cells/kg body weight [see *Clinical Studies* (14) in Full Prescribing Information]. Patients with a history of CNS disease (such as seizure or cerebrovascular ischemia) or requiring ongoing treatment with chronic immunosuppression were excluded. The median duration of follow-up was 18 months. The median age of the study population was 61 years (range: 43 to 78 years); 36% were 65 years or older, and 59% were men. The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was 0 in 40%, 1 in 56%, and 2 in 4% of patients. Three of the patients treated with CARVYKTI had a creatinine clearance of <45 mL/min at baseline. For the details about the study population, see *Clinical Studies* (14) in Full Prescribing Information.

The most common (greater or equal to 10%) Grade 3 or higher nonlaboratory adverse reactions were infections-pathogen unspecified (19%), pneumonia (13%), hematologic malignancy (10%) and hypotension (10%).

The most common nonlaboratory adverse reactions (incidence greater than or equal to 20%) included pyrexia, CRS, hypogammaglobulinemia, hypotension, musculoskeletal pain, fatigue, infections of unspecified pathogen, cough, chills, diarrhea, nausea, encephalopathy, decreased appetite, upper respiratory tract infection, headache, tachycardia, dizziness, dyspnea, edema, viral infections, coagulopathy, constipation, and vomiting.

Serious adverse reactions occurred in 55% of patients. The most common non-laboratory (greater than or equal to 5%) serious adverse reactions included CRS (21%), sepsis (7%), encephalopathy (10%), and pneumonia (8%). Fatal adverse reactions occurred in 9% of patients.

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Table 3 summarizes the adverse reactions that occurred in at least 10% of patients treated with CARVYKTI.

Table 3: Adverse reactions observed in at least 10% of patients treated with CARVYKTI in CARTITUDE-1 (N=97)

System Organ Class (SOC) Preferred term	Any Grade (%)	Grade 3 or higher (%)
Blood and lymphatic system disorders	-	-
Coagulopathy ^a	22	2
Febrile Neutropenia	10	9
Cardiac disorders	-	-
Tachycardia*	27	1
Gastrointestinal disorders	-	-
Diarrhea ^b	33	1
Nausea	31	1
Constipation	22	0
Vomiting	20	0
General disorders and administrative site conditions	-	-
Pyrexia	96	5
Fatigue*	47	7
Chills	33	0
Edema ^c	23	0
Immune system disorders	-	-
Cytokine release syndrome*	95	5
Hypogammaglobulinemia ^d	93	2
Infections and infestations	-	-
Infections-pathogen unspecified*	41	19
Upper respiratory tract infection*	28	3
Viral infections*	23	7
Pneumonia*	14	13
Sepsis*	10	7
Metabolism and nutrition disorders	-	-
Decreased appetite	29	1
Musculoskeletal and connective tissue disorders	-	-
Musculoskeletal pain*	48	2
Nervous system disorders	-	-
Encephalopathy ^e	30	6
Headache	27	0
Dizziness*	23	1
Motor dysfunction ^f	16	3
Psychiatric disorders	-	-
Insomnia	13	0
Respiratory, thoracic and mediastinal disorders	-	-
Cough*	39	0
Dyspnea ^g	23	3
Nasal congestion	15	0
Hypoxia	12	4
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	-	-
Hematologic malignancy ^h	10	10
Vascular disorders	-	-
Hypotension*	51	10
Hypertension	19	6
Hemorrhage ⁱ	16	4

* Represents multiple related terms

^a Coagulopathy includes Activated partial thromboplastin time prolonged, Coagulopathy, Disseminated intravascular coagulation, Hypofibrinogenemia, International normalized ratio increased, and Prothrombin time prolonged.

^b Diarrhea includes Colitis and Diarrhea.

^c Edema includes Face edema, Generalized edema, Localized edema, Edema peripheral, Periorbital edema, Peripheral swelling, Pulmonary edema, and Scrotal edema.

^d Hypogammaglobulinemia includes subjects with adverse event of hypogammaglobulinemia and/or laboratory IgG levels that fell below 500 mg/dL following CARVYKTI infusion.

^e Encephalopathy includes Amnesia, Bradyphrenia, Confusional state, Depressed level of consciousness, Disturbance in attention, Encephalopathy, Immune effector cell-associated neurotoxicity syndrome, Lethargy, Memory impairment, Mental impairment, Mental status changes, Noninfective encephalitis, and Somnolence.

- ^f Motor dysfunction includes Motor dysfunction, Muscle spasms, Muscle tightness, Muscular weakness, and Myoclonus.
- ^g Dyspnea includes Acute respiratory failure, Dyspnea, Dyspnea exertional, Respiratory failure, and Tachypnea.
- ^h Hematologic malignancy includes Myelodysplastic syndrome and Acute myeloid leukemia.
- ⁱ Hemorrhage includes Conjunctival hemorrhage, Contusion, Ecchymosis, Epistaxis, Eye contusion, Hematochezia, Hemoptysis, Infusion site hematoma, Oral contusion, Petechiae, Post procedural hemorrhage, Pulmonary hemorrhage, Retinal hemorrhage, and Subdural hematoma.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with CARVYKTI include the following:

- **Cardiac disorders:** cardiac arrhythmias* (8%), chest pain* (7%)
- **Eye disorders:** diplopia (1%)
- **Gastrointestinal disorders:** dysphagia (1%)
- **Immune system disorders:** HLH (1%), hypersensitivity reaction (5%)
- **Infections and Infestations:** bacterial infections* (9%), urinary tract infection* (4.1%)
- **Injury, Poisoning and Procedural complications:** fall (3.1%)
- **Metabolism and Nutrition Disorders:** tumor lysis syndrome (1%)
- **Musculoskeletal and Connective tissue disorders:** posture abnormal (1%)
- **Nervous system disorders:** aphasia* (8%), ataxia* (8%), peripheral neuropathy* (7%), tremor (6%), parkinsonism (4.1%), micrographia (4.1%), dysgraphia (3.1%), reduced facial expression (3.1%), cranial nerve palsies (3.1%), bradykinesia (2.1%), paresis* (1%), cogwheel rigidity (1%), cerebrovascular accident (1%), seizure (1%), slow speech (1%), nystagmus (1%)
- **Psychiatric disorders:** delirium* (5%), depression* (4.1%), psychomotor retardation (1%)
- **Renal and urinary disorders:** renal failure* (7%)
- **Skin and subcutaneous tissues:** rash* (8%)
- **Vascular Disorders:** thrombosis* (5%)

* Represents multiple related terms

Laboratory Abnormalities

Table 4 presents the most common Grade 3 or 4 laboratory abnormalities based on laboratory data, occurring in at least 10% of patients.

Table 4: Grade 3 or 4 laboratory abnormalities in at least 10% of patients treated with CARVYKTI in CARTITUDE-1 (N=97)

Laboratory Abnormality	Grade 3 or 4 (%)
Lymphopenia	99
Neutropenia	98
White blood cell decreased	98
Anemia	72
Thrombocytopenia	63
Aspartate aminotransferase increased	21

Laboratory abnormalities graded using NCI Common Terminology Criteria for Adverse Events version 5.0. Laboratory abnormalities are sorted by decreasing frequency in the Grade column.

Other clinically important Grade 3 or 4 laboratory abnormalities (based on laboratory data) that occurred in less than 10% of patients treated with CARVYKTI include the following: fibrinogen decreased, hypoalbuminemia, alanine aminotransferase increased, hyponatremia, hypocalcemia, gamma glutamyl transferase increased, alkaline phosphatase increased, hypokalemia, blood bilirubin increased.

Postmarketing Experience

Because adverse events to marketed products are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure.

The following adverse events have been identified during postmarketing use of CARVYKTI.

Neoplasms: T cell malignancies including T-cell lymphoma of the gastrointestinal tract (including fatal cases).

Gastrointestinal disorders: immune effector cell-associated enterocolitis and gastrointestinal perforation (including fatal cases) [see **Warnings and Precautions**].

Immune System disorders: infusion related reactions.

Infections and infestations: John Cunningham (JC) virus progressive multifocal leukoencephalopathy (including fatal cases) [see **Warnings and Precautions**].

DRUG INTERACTIONS

HIV and the lentivirus used to make CARVYKTI have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests (NATs) may yield false-positive results in patients who have received CARVYKTI.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on the use of CARVYKTI in pregnant women. No reproductive and developmental toxicity studies in animals have been conducted with CARVYKTI to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known whether CARVYKTI has the potential to be transferred to the fetus and cause fetal toxicity. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia and hypogammaglobulinemia. Therefore, CARVYKTI is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised that there may be risks to the fetus. Pregnancy after CARVYKTI therapy should be discussed with the treating physician.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Lactation

Risk Summary

There is no information regarding the presence of CARVYKTI in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CARVYKTI and any potential adverse effects on the breastfed infant from CARVYKTI or from the underlying maternal condition.

Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy status for females of child-bearing age should be verified prior to starting treatment with CARVYKTI.

Contraception

There are insufficient data to provide a recommendation concerning duration of contraception following treatment with CARVYKTI.

In clinical trials, female patients of childbearing potential were advised to practice a highly effective method of contraception and male patients with partners of childbearing potential or whose partners were pregnant were instructed to use a barrier method of contraception, until one year after the patient has received CARVYKTI infusion.

See the prescribing information for lymphodepleting chemotherapy for information on the need for contraception in patients who receive the lymphodepleting chemotherapy.

Infertility

There are no data on the effect of CARVYKTI on fertility.

Pediatric Use

Safety and effectiveness of CARVYKTI in pediatric patients have not been established.

Geriatric Use

Of the 97 patients in CARTITUDE-1 that received CARVYKTI, 28% were 65 to 75 years of age, and 8% were 75 years of age or older. CARTITUDE-1 did not include sufficient numbers of patients aged 65 and older to determine whether the effectiveness differs compared with that of younger patients. In 62 patients less than 65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 19% (12/62) and 6% (4/62), respectively. Of the 35 patients ≥65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 37% (13/35) and 20% (7/35), respectively.

Of the 188 patients in CARTITUDE-4 that received CARVYKTI, 38% were 65 to 75 years of age, and 2% were 75 years of age or older. In 112 patients less than 65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 16% (18/112) and 3% (3/112) respectively. Of the 76 patients ≥65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 34% (26/76) and 7% (5/76) respectively.

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- 1 Lee DW, Santomaso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant* 2019; 25: 625-638.
- 2 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 5.0; 2017.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide). Inform patients of the risk of manufacturing failure [18%, (17/97 in the clinical study)]. In case of a manufacturing failure, a second manufacturing of CARVYKTI may be attempted. In addition, while the patient awaits the product, additional anticancer treatment (other than lymphodepletion) may be necessary and may increase the risk of adverse reactions during the pre-infusion period, which could delay or prevent the administration of CARVYKTI.

Advise patients that they will be monitored daily for the first 7 days following the infusion, and instruct patients to remain within proximity of a healthcare facility for at least 2 weeks following the infusion.

Prior to infusion, advise patients of the following risks and to seek immediate medical attention in the event of the following signs or symptoms:

Increased Early Mortality

Inform patients of the risk of early mortality. In a clinical study, treatment in the CARVYKTI arm was associated with a higher rate of death (14%) compared to the control arm (12%) in the first 10 months from randomization. This higher rate of death was observed before receiving CARVYKTI and after treatment with CARVYKTI. The reasons for death were progression of multiple myeloma and adverse events [see *Warnings and Precautions, Clinical Studies (14) in Full Prescribing Information*].

Cytokine Release Syndrome (CRS)

Signs or symptoms of CRS, including fever, chills, fatigue, headache, tachycardia, hypotension, hypoxia, dizziness/lightheadedness or organ toxicities [see *Warnings and Precautions, Adverse Reactions*].

Neurologic Toxicities

Signs or symptoms associated with neurologic events, some of which occur days, weeks or months following the infusion including [see *Warnings and Precautions, Adverse Reactions*]:

ICANS: e.g., aphasia, encephalopathy, depressed level of consciousness, seizures, delirium, dysgraphia

Parkinsonism: e.g., tremor, micrographia, bradykinesia, rigidity, shuffling gait, stooped posture, masked facies, apathy, flat affect, lethargy, somnolence

Guillain Barré Syndrome: e.g., motor weakness and polyradiculoneuritis

Peripheral Neuropathy: e.g., peripheral motor and/or sensory nerve dysfunction

Cranial Nerve Palsies: e.g., facial paralysis, facial numbness

Prolonged and Recurrent Cytopenias

Signs or symptoms associated with bone marrow suppression including neutropenia, thrombocytopenia, anemia, or febrile neutropenia for several weeks or months. Signs or symptoms associated with bone marrow suppression may recur [see *Warnings and Precautions, Adverse Reactions*].

Infections

Signs or symptoms associated with infection [see *Warnings and Precautions, Adverse Reactions*].

Hypersensitivity Reactions

Signs or symptoms associated with hypersensitivity reactions including flushing, chest tightness, tachycardia, and difficulty breathing [see *Warnings and Precautions*].

Immune Effector Cell-associated Enterocolitis

Signs or symptoms including persistent and severe diarrhea, abdominal pain and weight loss, post-infusion. Signs or symptoms of gastrointestinal perforation [see *Warnings and Precautions*].

Secondary Malignancies

Secondary hematological malignancies, including myelodysplastic syndrome, acute myeloid leukemia, and T-cell malignancies (including in GI tract) have occurred [see *Boxed Warning, Warnings and Precautions, Adverse Reactions*].

Advise patients of the need to:

- Have periodic monitoring of blood counts before and after CARVYKTI infusion [see *Warnings and Precautions*].
- Contact Janssen Biotech, Inc. at 1-800-526-7736 if they are diagnosed with a secondary malignancy [see *Warnings and Precautions*].
- Avoid driving for at least 2 weeks [see *Warnings and Precautions*].
- Tell their physician about their treatment with CARVYKTI before receiving a live virus vaccine [see *Warnings and Precautions*].

Manufactured/Marketed by:

Janssen Biotech, Inc.

Horsham, PA 19044, USA

U.S. License Number 1864

Marketed by:

Legend Biotech

Somerset, NJ 08873, USA

For patent information: www.janssenpatents.com

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Treatment Sequencing Immunotherapies After BCMA Exposure

Immunotherapies, including CAR T-cells and bispecific antibodies, have revolutionized the treatment landscape for multiple myeloma and have demonstrated significant efficacy in patients with relapsed or refractory multiple myeloma; however, achieving durable remissions remains challenging, highlighting the need for optimized sequencing strategies.^{46,47} Due to complex therapeutic resistance mechanisms, deciphering the complex interplay between malignant plasma cells and their surrounding microenvironment is essential for optimizing treatment sequencing, preventing effector cell exhaustion, and designing next-generation therapeutic strategies to secure long-term, durable responses for patients.⁴⁶ Treatment sequencing has become more difficult as BCMA-directed CAR T-cell therapies, antibody-drug conjugates, and bispecific antibodies enter earlier lines of therapy. The primary challenge is that the most effective next therapy depends not only on prior drug classes, but also on the specific antigen targeted, the depth and duration of the prior response, the interval since treatment, the patient's immune reserve, and the urgency of disease control.

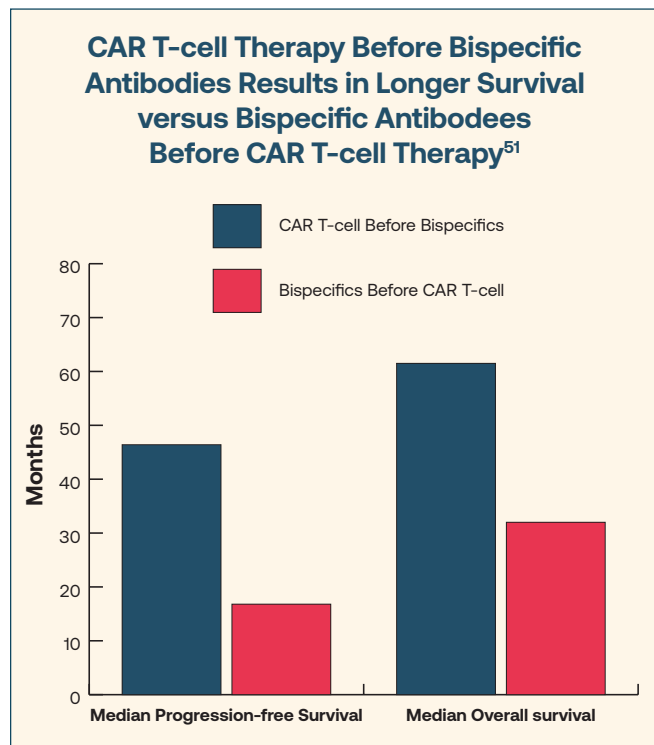
When both options are available, many experts favor collecting cells for CAR T-cell therapy before prolonged exposure to a T-cell redirecting bispecific antibody.^{4,19} Continuous bispecific therapy may contribute to T-cell exhaustion, infection, and immune suppression, and prior BCMA-directed treatment can affect the biology of subsequent BCMA therapy.^{4,19} This does not mean that CAR T-cell therapy cannot work after a bispecific antibody, but the probability and durability of response may depend on the type, duration, and timing of prior exposure.^{4,19}

GPRC5D-directed therapy provides an important strategy after BCMA treatment. Talquetamab has demonstrated activity in heavily pretreated patients, including patients previously exposed to BCMA-directed therapy. Investigational FcRH5-directed antibodies and dual-target products may further expand options by reducing dependence on a single antigen and addressing antigen loss or downregulation.⁴⁸⁻⁵⁰ A retrospective multicenter study evaluated the safety and efficacy of BCMA-targeting bispecific antibodies following prior treatment with GPRC5D-targeting bispecific antibodies in 26 patients with relapsed or refractory multiple myeloma.⁴⁷ Over a median follow-up of 20.35 months, the overall response rate was 58%, with a median progression-free survival of 6.8 months and a median overall survival of 15.9 months. Responders demonstrated significantly longer

progression-free survival of 3.5 months compared with nonresponders (not reached). This study concluded that BCMA-targeting bispecific antibodies provide effective and well-tolerated treatment for patients who have progressed after treatment with GPRC5D-targeting bispecific antibodies, supporting the feasibility of this sequential approach.⁴⁷

A prior response to BCMA-directed therapy, a prolonged treatment-free interval, and evidence that BCMA remains expressed may support reuse in selected patients. In contrast, rapid progression during BCMA therapy or documented antigen loss may favor switching targets. Data support the use of CAR T-cell therapy before bispecific antibodies in patients receiving multiple lines of treatment (≥ 4 lines) to improve long-term patient outcomes.⁵¹ For instance, one study reported that CAR T-cell therapy before bispecific antibodies resulted in significantly longer survival versus bispecific antibodies before CAR T (median progression free survival, 46.4 months vs. 16.8 months; median overall survival, 61.5 months vs. 32.0 months).⁵¹

Because no single sequencing algorithm is supported by randomized comparative evidence, treatment decisions should remain individualized and ideally be made before clinical deterioration limits access to cellular therapy or a clinical trial.^{4,19}



Choice of BCMA-directed Therapy for Varied Patient Scenarios

Until high-level prospective evidence is generated in patients with first progression after upfront quadruplet therapy, the early use of a BCMA-directed therapy, such as CAR T-cell therapy or bispecific antibodies, should be considered at the earliest sign of relapse.¹⁴ Cilta-cel is favored given its closer alignment with the CARTITUDE-4 population.¹⁴ A subset of patients with multiple myeloma experiences early relapse without prior exposure to CD38-directed therapy.¹⁴ Although this scenario is becoming less common with increasing frontline use of CD38-based quadruplet combinations, it remains clinically important because these patients are eligible for all BCMA-directed treatments. In this setting, both cilta-cel and teclistamab-daratumumab (Tec-Dara) represent appropriate treatment options.¹⁴ In the management of frail patients with relapsed or refractory multiple myeloma, treatment selection should be driven by tolerability, infection risk, and logistical feasibility. Therefore, in frail patients, Tec-Dara is preferred, and ADC may be considered in those with advanced frailty or substantial logistical limitations.¹⁴ Patients progressing after frontline daratumumab-lenalidomide therapy represent a common clinical scenario, and in these patients CAR T-cell therapy with cilta-cel may represent an effective option, given its depth and durability of response in earlier-line settings, although a careful assessment of frailty and comorbidities is essential.¹⁴

The 2025 Bridging the Gaps Consensus Conference convened 16 multiple myeloma experts in the United States who reviewed data, debated controversies, and developed eleven consensus recommendations.⁵² One of the strongest consensus messages was that eligible patients should be referred for CAR T-cell evaluation

earlier in their disease course rather than waiting until very late-stage disease due to superior patient fitness earlier in treatment, manufacturing time, and better outcomes observed when CAR T is used after fewer prior therapies.⁵² The experts stressed that referral should occur before patients become too frail or refractory to benefit. They also recommended thoughtful sequencing relative to CAR T-cell therapy, with optimal sequencing between CAR T therapy and bispecific antibodies remaining uncertain.⁵²

With the wide variety of available treatment regimens (including new combinations of approved therapies) and the need to tailor multiple myeloma treatment based on disease- and patient-centric factors, it can be challenging to select an appropriate treatment at first relapse.⁵³ This decision should also consider the effect of second-line therapy on future treatment options for eligible patients, particularly CAR T-cell therapy and other T-cell-engaging therapies (for example, bispecific antibodies).⁵³ Treatment selection should prioritize therapies with the greatest survival benefit to reduce risk of attrition with subsequent lines of therapy.⁵³ Key considerations include patient age, performance status, comorbidities, cytogenetics, prior drug exposure, and duration of response to initial therapy.⁵³ Furthermore, early referral before CAR T therapy is highly recommended to prepare for treatments received before apheresis (for example, holding therapy) as well as treatments received during CAR T manufacturing, between apheresis and CAR T infusion (for example, bridging therapy).⁵³ The timing of referral for CAR T-cell therapy is critical, as CAR T manufacturing may require 3 to 4 weeks or longer depending on product, during which time, disease progression may occur without effective bridging therapy.⁵³

Favored BCMA-directed Therapy for Clinical Scenarios Encountered in Early-relapse Multiple Myeloma¹⁴

Clinical Scenarios	Favored Treatment
First Progression After Upfront Quadruplet Therapy and Autologous Transplant	Cilta-cel
First or Second Progression in Anti-CD38 Naïve or Sensitive Patients	Cilta-cel or teclistamab combined with daratumumab (Tec-Dara)
Frail Patients with Relapsed or Refractory Multiple Myeloma	Tec-Dara or BCMA-directed antibody-drug conjugate (ADC)
Progression after frontline Daratumumab-Lenalidomide Therapy in Transplant Eligible Multiple Myeloma	ADC-based regimens or CAR T-cell therapy

Common and Rare Toxicities to Prevent Non-relapse Mortality and Preserve Quality of Remission

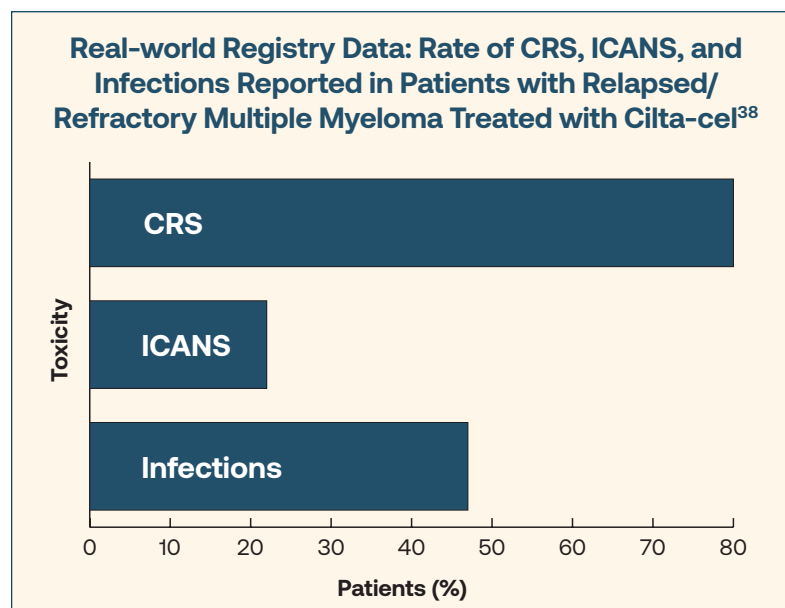
BCMA directed CAR T-cell therapy has emerged as an effective treatment for patients with relapsed or refractory multiple myeloma, demonstrating high response rates and durable remissions; however, its use is associated with toxicities, ranging from well characterized common events to rarer, less well described complications.^{54,55} As outcomes improve, toxicity management is expanding from short-term recognition of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), to long-term surveillance for infection, cytopenias, hypogammaglobulinemia, and delayed neurologic events. Therefore, the goal in multiple myeloma is not only to prevent treatment-related mortality but also to preserve the quality of the remission achieved.^{38,39,54}

A comprehensive understanding of both common and rare toxicities is essential for timely recognition and management to prevent non-relapse mortality.⁵⁵ A recent registry data has indicated that CRS was seen in 80%, ICANS in 22%, and infections in 47% of patients receiving cilta-cel treatment for multiple myeloma.³⁸ In addition to frequently observed toxicities (i.e., CRS, ICANS, immune effector cell-associated hematotoxicity, and infections, less frequent adverse events have been reported (i.e, non-ICANS neurotoxicity, immune-mediated enterocolitis, hemophagocytic lymphohistiocytosis, and secondary malignancies).⁵⁵ The timing and severity of these toxicities is variable and may be influenced by the extent of CAR T-cell expansion and persistence, as well as individual patient factors.⁵⁵

CRS is a potentially life-threatening toxicity associated with CAR T-cell therapy, particularly in hematological malignancies.⁵⁶ As CAR T therapies are increasingly integrated into clinical practice, managing CRS effectively is critical to maximizing therapeutic benefit while minimizing harm.⁵⁶ CRS remains a major challenge, therefore early recognition, standardized grading, and targeted intervention will improve outcomes.

Cranial nerve palsies, movement disorders, Guillain-Barré syndrome, and other non-ICANS neurologic events have been reported after cilta-cel. A 2026 real-world cohort found low incidence of these events; most cranial nerve palsies improved, and the patient with Guillain-Barré syndrome experienced resolution. Higher peak absolute lymphocyte counts were observed in patients with neurologic events and may warrant further study as a monitoring biomarker.^{54,57}

A retrospective chart review study was conducted and found that cytomegalovirus is an underrecognized complication following CAR T-cell therapy.⁵⁸ Infection is one of the most important long-term risks of T-cell redirecting therapy. Prolonged cytopenias, hypogammaglobulinemia, impaired humoral immunity, and repeated exposure to corticosteroids or other immunosuppressive therapies can overlap. Current practice increasingly emphasizes antiviral and Pneumocystis prophylaxis, immunoglobulin monitoring and replacement when appropriate, vaccination planning, and early evaluation of fever or respiratory symptoms.^{38,59}



CAR T-cell therapies have demonstrated remarkable efficacy in relapsed or refractory multiple myeloma; however, emerging non-ICANS neurologic events—including cranial nerve palsy and immune effector cell-parkinsonism (also called movement and neurocognitive toxicity) warrant vigilance.⁶⁰ In clinical findings from the CARTITUDE trials, which included >300 patients, cranial nerve palsy occurred in 6.3% of patients, with a lower incidence in more heavily pretreated patients.⁶⁰ Median onset was day 22 post-infusion; most cases were low grade, and 90% recovered completely. Immune-effector cell-parkinsonism involves motor, cognitive, and personality changes; lower incidence was observed in less heavily pretreated patients. Median time to onset was 56 days postinfusion.⁶⁰

Current Studies in Multiple Myeloma: Clinical Trial Research Priorities

Emerging therapies for multiple myeloma have significantly improved patient outcomes extending survival and advancing treatment toward more targeted, effective, and less toxic approaches. An analysis of the therapeutic landscape of multiple myeloma was conducted by evaluating drug candidates in clinical trials from 2014 to 2024.⁶¹ Data were extracted from active and completed studies with results on newly diagnosed and refractory multiple myeloma, with 365 studies eligible for analysis.⁶¹ The results demonstrated a rise in multiple myeloma clinical trials that highlights a shift toward biologic therapies, particularly immunotherapies like CAR T. Phase I trials were the most common (n=182; 49.9%), and cell therapies were predominant (n=171; 46.8%), with CAR T products targeting BCMA (n=107), CD19 (n=16), and GPRC5D (n=12) emerging as the most studied in recent years. The number of active trials grew by approximately 4% per year, corresponding to an average increase of 26.5 studies each year. Several of the studies are researching how far cellular therapy and bispecific antibodies will move up into newly diagnosed disease and whether they can replace or complement established strategies such as autologous stem-cell transplantation. CARTITUDE-5 and CARTITUDE-6 are particularly important because they evaluate cilta-cel in newly diagnosed populations and address whether a cellular therapy approach can be integrated into initial treatment.



Current Cilta-cel Trials in Multiple Myeloma

Trial	Patient Population	Study Design	Key Question
CARTITUDE-5	Newly diagnosed multiple myeloma; transplant not planned initially	VRd followed by cilta-cel vs. VRd followed by Rd	Can CAR T-cell therapy improve outcomes in transplant-ineligible or transplant-deferred initial treatment?
CARTITUDE-6	Newly diagnosed, transplant-eligible multiple myeloma	DVRd followed by cilta-cel vs. DVRd followed by ASCT	Can cilta-cel replace ASCT in selected newly diagnosed patients?
CAR-PRISM	High-risk smoldering multiple myeloma	Single cilta-cel infusion	Can early cellular therapy produce sustained MRD-negative disease control before symptomatic multiple myeloma?
Earlier-line bispecific studies	Relapsed or refractory multiple myeloma after fewer prior lines of therapy	Bispecific antibody vs. active standard regimens or in combinations	Can off-the-shelf T-cell redirection deliver durable benefit with manageable cumulative infection risk?
Dual-target cellular therapy	Heavily pretreated or high-risk multiple myeloma	CAR T-cells targeting two antigens	Can multi-antigen targeting reduce antigen escape and extend remission?

ASCT, autologous stem cell transplant; DVRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone; Rd, lenalidomide and dexamethasone.

NOVEL TARGETS IN MULTIPLE MYELOMA

BCMA remains the most clinically validated immune target in multiple myeloma, but reliance on one antigen creates predictable resistance pressures. Myeloma cells can reduce target density, lose antigen expression, or persist in microenvironments that limit immune-cell access. New targets and multi-antigen approaches are intended to preserve T-cell redirection while reducing the opportunity for antigen escape.

G Protein-coupled Receptor Class C Group 5 Member D (GPRC5D)

GPRC5D is highly expressed on malignant plasma cells and has limited expression in most normal tissues, although expression in keratinized structures contributes to characteristic toxicities involving taste, skin, and nails. Talquetamab established GPRC5D as a clinically actionable target and offers an off-the-shelf option after BCMA exposure. Current research

is evaluating earlier use, fixed-duration treatment, and combinations designed to deepen response without unacceptable cumulative toxicity.^{48,62} In the first real-world study to assess the efficacy of talquetamab (n=151;

median follow-up=12.7 months), the overall response rate was 67.6%, median progression-free survival was 7 months, and 12-month overall survival was 65%.⁶² This study shows that talquetamab efficacy is maintained in a heavily pretreated real-world population with high prior BCMA exposure and notable comorbidity burden.

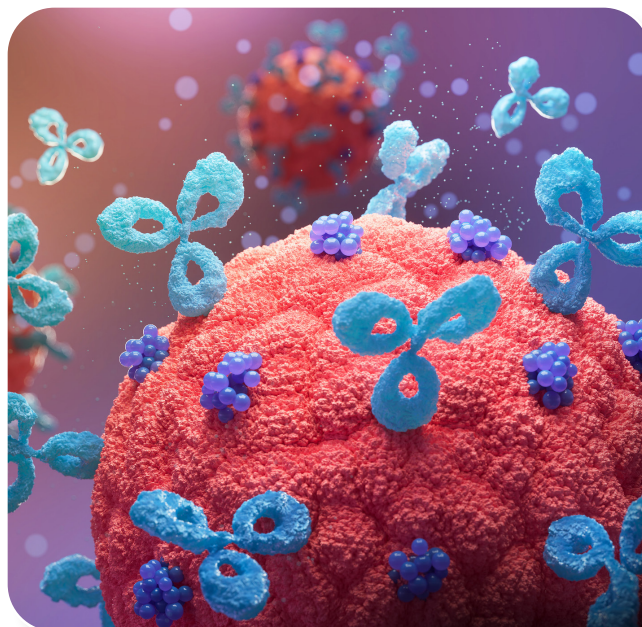
Fc Receptor-like 5 (FcRH5)

FcRH5 is expressed across the B-cell lineage and is retained on many myeloma cells. FcRH5-directed approaches remain investigational but are of interest for patients whose disease has progressed after BCMA- or GPRC5D-directed therapy. Their eventual role will depend on response durability, infection burden, and feasibility of sequencing with established agents.^{21,49}

Dual-target CAR T-cell Therapies and Trispecific Antibodies

Dual-target CAR T-cell products and trispecific antibodies are designed to engage more than one tumor antigen or provide additional immune co-stimulation. In principle, these strategies may reduce antigen-negative relapse and improve immune synapse formation. However, broader immune engagement may also increase cytokine-mediated toxicity or accelerate T-cell dysfunction. Early-phase studies will need to demonstrate that improved disease control outweighs added complexity.⁵⁰

The next generation of studies should compare active immunotherapies directly, define evidence-based sequencing after BCMA exposure, and test fixed-duration strategies that preserve efficacy while reducing immune suppression. Long-term follow-up must include secondary malignancies, delayed neurologic effects, immune reconstitution, quality of life, caregiver burden, and healthcare resource utilization.^{4,5,38}



The next generation of studies should compare active immunotherapies directly, define evidence-based sequencing after BCMA exposure, and test fixed-duration strategies that preserve efficacy while reducing immune suppression.

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