22 February 2024
EMA/118923/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

CARVYKTI

International non-proprietary name: Ciltacabtagene autoleucel

Procedure No. EMEA/H/C/005095/II/0021

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

ADA anti-drug antibody

ADR adverse drug reaction

AE adverse event

AML acute myeloid leukemia

ASCT autologous stem cell transplantation

ASTCT American Society for Transplantation and Cellular Therapy AUC0-28d area under the concentration-time curve from time 0 to 28 days

BCMA B-cell maturation antigen

BLA Biologics License Application

CAR chimeric antigen receptor

CAR-T chimeric antigen receptor T (cells) CAT Committee for Advanced Therapies

CBR clinical benefit rate

CCDS Company Core Data Sheet

CCHMC Cincinnati Children's Hospital Medical Center

CCO clinical cutoff

CEAE cilta-cel-emergent adverse event

CHMP Committee for Medicinal Products for Human Use

CI confidence interval

CMA Conditional Marketing Authorization

Cmax maximum observed concentration

CMH Cochran Mantel Haenszel

CN cranial nerve

CPW constant piecewise weighted (log-rank test)

CR complete response

CSR clinical study report

DOR duration of response

DP drug product

DPd daratumumab, pomalidomide, and dexamethasone

DVRd daratumumab, bortezomib, lenalidomide, dexamethasone

ECLIA electrochemiluminescence immunoassay

ECOG Eastern Cooperative Oncology Group

EMA	European Medicines Agency
EOP2	end of Phase 2
ESMO	European Society for Medical Oncology
EU	European Union
FDA	(United States) Food and Drug Administration
FISH	fluorescence in situ hybridization
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
GHS	global health status
HR	hazard ratio
HRQol	health-related quality of life
ICANS	Immune Effector Cell-associated Neurotoxicity Syndrome
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IgG	immunoglobulin G
IHC	immunohistochemistry
IL	interleukin
IMiD	immunomodulatory agent
IMWG	International Myeloma Working Group
IND	Investigational New Drug Application
IRC	Independent Review Committee
ISS	International Staging System
ITT	intent-to-treat
IV	intravenous(ly)
Kd	carfilzomib and dexamethasone
LLOQ	lower quantifiable concentration
LS	least square
LV	lentivirus
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat

MNT movement and neurocognitive treatment-emergent adverse events

mPFS median PFS

MRD minimal residual disease

MSD Meso Scale Discovery

NCCN National Comprehensive Cancer Network

NCI-CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events

NDA New Drug Application

NE not estimable

NGF next generation flow cytometry

NGS next generation sequencing

NK natural killer

NMPA National Medical Products Administration

OR odds ratio

ORR overall response rate

OS overall survival

PASS Post-authorisation safety study

PBMC peripheral blood mononuclear cell

PD progressive disease

PFS progression-free survival

PFS2 PFS on next-line therapy

PI proteasome inhibitor

PK pharmacokinetics

PN peripheral neuropathy

PO per os

PR partial response

PRO patient reported outcome

PVd pomalidomide, bortezomib, and dexamethasone

qPCR quantitative polymerase chain reaction

RCL replication-competent lentivirus

RMP Risk Management Plan

RP2D recommended Phase 2 dose

RRMM relapsed or refractory multiple myeloma

R2R receipt to release

SAP	statistical analysis plan
SAWP	Scientific Advisory Working Party
sBLA	supplemental biologics license application
SC	subcutaneous(ly)
SCE	Summary of Clinical Efficacy
sCR	stringent complete response
SCS	Summary of Clinical Safety
SD	stable disease
SET	safety evaluation team
SmPC	Summary of Product Characteristics
SOC	system organ class
STORM	Selinexor Treatment of Refractory Myeloma
TEAE	treatment-emergent adverse event
tlast	time to last measurable concentration
TTR	time to response
t1/2	apparent terminal elimination half-life
ULN	upper limit of normal
US	United States of America
USPI	United States Prescribing Information
VGPR	very good partial response

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International NV submitted to the European Medicines Agency on 25 May 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 1 prior therapy, including an IMiD and a PI, have demonstrated disease progression on or after the last therapy and are refractory to lenalidomide for CARVYKTI, based on interim results from study MMY3002 listed as a specific obligation (SOB/006) in the Annex II. This is an ongoing, Phase 3, randomized, open-label, multicentre study to determine whether treatment with cilta-cel provides an efficacy benefit compared to standard therapy in participants with relapsed and lenalidomide-refractory multiple myeloma. As a consequence, sections 4.1, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to update Annex II of the PI. As part of the application the MAH is requesting a 1-year extension of the market protection.

The variation requested amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

CARVYKTI, was designated as an orphan medicinal product EU/3/20/2252 on 28 February 2020 in the following indication: Treatment of multiple myeloma.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0353/2019 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Protocol assistance

The MAH received Protocol Assistance from the CHMP on 19 September 2019 (EMA/CHMP/SAWP/492709/2019). The Protocol assistance pertained to clinical aspects of the dossier. Key design elements of Study 68284528MMY3002 were discussed. The choice of standard of care, physician's choice of either Kd or DPd at the time, was questioned and the need to guarantee the most efficacious treatment regimen for each patient in the standard of care arm emphasized. In response to this feedback, an EU advisory board was convened and recommended the use of triplets over Kd. While previous ESMO guidelines listed Kd as an acceptable option at first relapse following IMiD-based induction, based on available and approved regimens at the time, the recommendation from the EU KOLs was to use PVd as a second option as a standard therapy comparator. This opinion was also reflected in the updated ESMO guidelines, which omitted Kd as an option at first relapse in patients who received VRd induction. Therefore, standard therapies PVd and DPd, both triplets, were selected for the control arm in the final design of Study MMY3002.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CAT were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	25 May 2023
Start of procedure:	17 June 2023
CAT Rapporteur's preliminary assessment report circulated on	14 August 2023
PRAC Rapporteur's preliminary assessment report circulated on	18 August 2023
PRAC Rapporteur's updated assessment report circulated on	25 August 2023
PRAC RMP advice and assessment overview adopted by PRAC on	31 August 2023
CAT Rapporteur's updated assessment report circulated on	6 September 2023
Request for supplementary information adopted by the CAT on	8 September 2023
MAH's responses submitted on	6 October 2023
CAT Rapporteur's preliminary assessment report on the MAH's responses circulated on	15 November 2023
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	16 November 2023
PRAC RMP advice and assessment overview adopted by PRAC on	30 November 2023
CAT Rapporteur's updated assessment report on the MAH's responses circulated on	5 December 2023
2nd request for supplementary information adopted by the CAT on	8 December 2023
MAH's responses submitted on	16 January 2024

Timetable	Actual dates
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	29 January 2024
CAT Rapporteur's preliminary assessment report on the MAH's responses circulated on	02 February 2024
SAG meeting to address questions raised by the CAT/CHMP	6 February 2024
PRAC RMP advice and assessment overview adopted by PRAC on	8 February 2024
CAT Rapporteur's updated assessment report on the MAH's responses circulated on	12 February 2024
CAT Opinion adopted on	16 February 2024
CHMP Opinion adopted on	22 February 2024
The CAT/CHMP adopted a report on similarity of CARVYKTI with Imnovid, Ninlaro, Farydak, Kyprolis, Darzalex, Blenrep, Abecma, Talvey on	16/22 February 2024
The CAT/CHMP adopted a report on the novelty of the indication/significant clinical benefit for CARVYKTI in comparison with existing therapies on	16/22 February 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The extension of indication submitted concern the use of Carvykti in earlier line of Relapsed and refractory multiple myeloma treatment.

Therapeutic indication

CARVYKTI is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least one prior therapy, including an immunomodulatory agent and a proteasome inhibitor, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide.

Epidemiology

Worldwide, there were an estimated 80,000 deaths due to multiple myeloma and approximately 24,300 and 12,800 patients with this disease die annually in Europe and the United States, respectively.

Biologic features

Multiple Myeloma(MM) is characterized by the increased proliferation of malignant monoclonal plasma cells in the bone marrow, with the subsequent bone marrow failure due to replacement of normal bone marrow haematopoiesis, the over-production of monoclonal immunoglobulins (M-protein, either intact immunoglobulins and/or free light chains [FLC]) which could be detected in the serum or urine, and finally the presence of systemic symptoms named as CRAB (hyperCalcemia, Renal impairment, Anaemia and Bone lesions). Increased susceptibility to infections (immunoparesis) and neurological complications are also present (Palumbo 2011).

Based on karyotype, MM is classified as non-hyperdiploid and hyperdiploid, with the latter accounting for 50% to 60% of cases and characterized by trisomies in odd-numbered chromosomes. MM has a heterogeneous progression pathway, with multiple relapses over time, whereby several MM cell subclones coexist at baseline and compete for dominance over time, leading to the evolution of drug-resistance clones [Laubach, 2014].

Drug resistance to prior regimens in patients with relapsed/refractory (RR) MM is due to continuous changes in the disease biology, in which a higher proportion of malignant cells are expressing a more aggressive, highly proliferative phenotype over time (Anderson, 2008).

B-cell maturation antigen (BCMA) is predominantly expressed in B-lineage cells and selectively induced during plasma cell differentiation. In multiple myeloma cell lines and patient samples, BCMA is stably expressed specifically on the B cell lineage. The target antigen of the CAR is BCMA, which is expressed on malignant plasma cells.

Clinical presentation and diagnosis

Multiple myeloma, a malignant disorder of the plasma cells characterized by uncontrolled and progressive proliferation of a plasma cell clone, and accounts for approximately 10% of hematological malignancies (Rodriguez-Abreu 2007; Rajkumar 2011). The proliferation of the malignant clonal plasma cells leads to subsequent replacement of normal bone marrow hematopoietic precursors and overproduction of monoclonal paraproteins (M-proteins). Characteristic hallmarks of multiple myeloma include osteolytic lesions, anemia, increased susceptibility to infections, hypercalcemia, renal insufficiency or failure, and neurological complications (Palumbo 2011). Profound intratumoral heterogeneity is observed throughout the disease course but is especially problematic after multiple lines of treatment. The coexistence of different tumor subclones displaying different drug sensitivities contributes to both progression of disease and development of drug resistance (Barlogie 2014).

The criteria for diagnosis of MM as defined by the International Myeloma Working Group (IMWG), requires 10% clonal BM plasma cells or biopsy proven bony or extra-medullary plasmacytoma and evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, or biomarkers of malignancy (60% clonal BM plasma cells or involved/uninvolved serum-free light chain ratio >100 or > 1 focal lesion on magnetic resonance imaging studies).

The course of MM is characterized by a period of disease control after initial therapy followed by progression, typically with subsequently shorter periods of response and relapse with each successive therapy (Moreau, 2017). The treatment of MM has notably progressed with the availability of new drugs and its combinations, such way that survival of patients with newly diagnosed MM has increased from approximately 3 years in the years 1985 to 1998 (Kyle 2003) to 6 to 10 years (Moreau 2015) along the last 15 years. Despite the significant improvement in patients' survival over the past 20 years, only 10%-15% of patients achieve or exceed expected survival compared with the matched general population.

The estimated 5-year survival rate for patients with multiple myeloma is approximately 54% (Cancer.net 2020). With each successive relapse, symptoms return, quality of life worsens, and the chance and duration of response typically decreases. Therefore, there remains a significant and critical unmet need for new therapeutic options directed at alternative mechanisms of action that can better control the disease; provide deeper, more sustained responses; and yield better long-term outcomes including maintenance of HRQoL.

Despite advance in therapy, MM remains incurable. Although autologous stem cell transplant (ASCT) has extended survival in newly diagnosed MM, practically all patients eventually relapse, and with each successive relapse, the chance of response and duration of response typically decreases and ultimately the disease becomes refractory and results in cumulative end organ damage (e.g., renal, cytopenias, infections and bone complications).

Management

The treatment landscape for relapsed or refractory multiple myeloma (RRMM) has changed in recent years. Current treatment of MM includes glucocorticoids, chemotherapy, primarily alkylating agents, high dose chemotherapy followed by ASCT, proteasome inhibitors (PIs, such as bortezomib, carfilzomib and ixazomib), immunomodulatory agents (such as thalidomide, lenalidomide and pomalidomide), monoclonal antibodies ((mAbs), such as daratumumab, isatuximab and elotuzumab), the histone deacetylase inhibitor panobinostat, XPO1 inhibitors (selinexor) and antibody drug conjugates targeting BCMA (belantamab mafodotin-blmf). Furthermore, CAR-T cell products (ide-cel and ciltacabtagene autoleucel [cilta-cel]) are now available together with recently approved bispecific antibodies: teclistamab (CD3/BCMA) and talquetamab CD3/GPRC5D.

Common standard regimens include either a PI or an IMiD in combination with dexamethasone with or without a monoclonal antibody such as daratumumab. The triplet combination of bortezomib, lenalidomide, and dexamethasone (VRd) is a standard in many clinical treatment protocols (NCCN, ESMO).

The choice of therapy in the relapse setting depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse (i.e. clinical versus biochemical relapse; in the case of biochemical relapse, treatment can be delayed).

Despite multiple therapeutic options, multiple myeloma remains incurable. All patients eventually relapse and become refractory to existing treatments.

Study MMY3002 includes participants with PD after 1 to 3 prior lines of therapy for multiple myeloma including a PI and IMiD either individually or in combination. Participants were required to be refractory to lenalidomide for study entry. There are several approved triplet regimens for patients with multiple myeloma who have relapsed after 1 to 3 prior lines of therapy. However, these regimens have largely been tested in lenalidomide naïve or lenalidomide sensitive patients. Pivotal Phase 3 studies (ASPIRE, ELOQUENT-2, Tourmaline-MM1, POLLUX) excluded lenalidomide refractory patients because these studies randomized against lenalidomide plus dexamethasone control arms. Given that lenalidomide is now frequently administered in front-line maintenance, and relapsed/refractory settings, there are fewer options for patients with lenalidomide-refractory disease and there are no approved regimens specifically for this patient population. More recently, a number of studies evaluated combinations of a monoclonal antibody, with a PI or with pomalidomide. These studies included substantial proportions of lenalidomide-refractory patients: 93% in ICARIA (isatuximab, pomalidomide, dexamethasone), 80% in APOLLO (daratumumab, pomalidomide, dexamethasone), 70% in OPTIMISMM (bortezomib,

pomalidomide, and dexamethasone), 33% in CANDOR (carfilzomib, dexamethasone, and daratumumab), and 33% in IKEMA (isatuximab, carfilzomib, and dexamethasone). Among lenalidomide refractory patients treated with the triplet regimens in these studies, median PFS was 11.4 months for the ICARIA study, 9.9 months for the APOLLO study, and 9.5 months for the OPTIMISMM study, with longer median PFS noted for the CANDOR study (median 28.1 months) and the IKEMA study (median PFS for lenalidomide-refractory subgroup not reported), both of which used an anti CD38 monoclonal antibody in combination with carfilzomib and dexamethasone. The sustained response shown in these studies relies on ongoing therapy until progression of disease, potentially resulting in cumulative toxicity and significant treatment burden.

2.1.2. About the product

Ciltacabtagene autoleucel (cilta-cel) consists of autologous T cells genetically modified to express a chimeric antigen receptor (CAR) utilizing a lentiviral vector (LV). The target antigen of the CAR is BCMA, which is expressed on malignant plasma cells. The LV coding sequence is comprised of a human CD8 alpha signal peptide (CD8α SP), BCMA targeting single-domain antibodies (VHH1 and VHH2) designed to confer avidity, human CD8 alpha hinge and transmembrane domain (CD8α hinge+TM), human CD137 cytoplasmic domain (4-1BB), and a human CD3 zeta cytoplasmic domain (CD3ζ). The expression of the LV is driven/controlled by a human elongation factor 1 alpha promoter (hEF1α promoter).

In the EU, cilta-cel is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. Cilta-cel is to be administered in a single infusion at a target dose of 0.75×10^6 CAR-positive viable T cells/kg (range: 0.5 to 1.0×10^6 CAR-positive viable T cells/kg).

Janssen manufactures LV using 2 manufacturing processes for cilta-cel DP. The first process is an adherent culture LV manufacturing process. The LV produced is referred to as CCHMC LV. The second process in a suspension culture LV manufacturing process. The LV produced is referred to as Bern LV. Although the LV manufacturing processes differ, the Bern LV manufacturing process uses the same kanamycin plasmids as the CCHMC manufacturing process, and there is no change to the LV-Kan vector construct.

The comparability study demonstrated that the 2 LV results met the release acceptance criteria in place at the time of testing and that the results between the 2 LV manufacturing processes were highly similar.

In addition, Janssen has successfully manufactured CAR-T BCMA DP with either Bern LV or CCHMC LV, and these DP batches have been used in previously approved clinical trials. The results of a comprehensive formal comparability study (as well as a development study) demonstrated that DP manufactured using CCHMC LV and Bern LV are considered comparable. Therefore, Bern LV and CCHMC LV can be used interchangeably to manufacture CAR-T BCMA DP.

Both CCHMC LV and Bern LV were used during the conduct of Study MMY3002. Among the 196 subjects who received a cilta-cel infusion, 99 subjects received cilta-cel manufactured with Bern LV and 97 subjects received cilta-cel manufactured with CCHMC LV. In Study MMY2003, all 39 subjects received cilta-cel manufactured with CCHMC LV.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

CARVYKTI was granted eligibility to PRIME on 28.03.2019 in the following indication: Treatment of adult patients with relapsed or refractory multiple myeloma, whose prior regimens included a proteasome

inhibitor, an immunomodulatory agent and an anti-CD38 antibody and who had disease progression on the last regimen.

Ciltacabtagene autoleucel was designated as an orphan medicinal product EU/3/20/2252 on 28.02.2020 in the following condition: Treatment of multiple myeloma. The proposed expanded indication falls within the authorized orphan designation of "multiple myeloma" for cilta-cel. The MAH will submit the orphan maintenance report separately to the Committee for Orphan Medicinal Products in parallel to this variation application. Furthermore, an orphan similarity assessment (Module 1.7.1) is provided comparing cilta-cel to the current designated orphan medicinal products for multiple myeloma which have been granted an MA in the EU.

During the planning of the clinical development program of cilta-cel for the proposed indication, the MAH sought input and agreement from the CHMP SAWP regarding Study MMY3002 (EMA/CHMP/SAWP/492709/2019) as reported above.

2.1.4. General comments on compliance with GCP

No concerns were raised about compliance with GCP, related regulatory or ethical requirements, and a request for a GCP inspection has not been adopted.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application. This is considered acceptable by the CAT.

2.2.1. Ecotoxicity/environmental risk assessment

The environmental risk assessment of ciltacabtagene autoleucel is not affected by the proposed extension of indication.

The CHMP endorse the CAT conclusions on the non-clinical aspects as described above.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID/Protocol number	EudraCT number	Study Title	Participating Countries
68284528MMY2003	2018-004124-10	A Phase 2, Multicohort Open-Label Study of JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA in Subjects with Multiple Myeloma	Belgium, France, Germany, Israel, Netherlands, Saudi Arabia, Singapore, Spain
68284528MMY3002	2019-001413-16	A Phase 3 Randomized Study Comparing JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA, versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Subjects with Relapsed and Lenalidomide-Refractory Multiple Myeloma	Australia, Austria, Belgium, Canada, Denmark, France, Germany, Greece, Israel, Italy, Japan, Korea, Netherlands Poland, Spain, Sweden, UK

2.3.2. Pharmacokinetics

Table 1. Overview of Studies Contributing Information to the Summary of Clinical Pharmacology

Type of Study	Study ID	Population	Number of Subjects	Dose/Formulation
Phase 3, randomized, open-label, active-control study	68284528MMY3002	Subjects with relapsed and lenalidomide-refractory multiple myeloma	419 (total) Arm A: 209 Arm B: 196 (176 as study treatment and 20 as subsequent therapy)	Arm A: standard therapy (PVd or DPd) Arm B: PVd or DPd, followed by single infusion of cilta-cel target dose of 0.75×10^6 CAR-positive viable T cells/kg (range: 0.5×10^6 to 1.0×10^6 CAR-positive viable T cells/kg)
Phase 2, open-label, multicenter study	68284528MMY2003	Subjects with relapsed refractory multiple myeloma	Cohort A (initial group): 20 Cohort B: 19	Cohorts A and B: Single infusion of cilta-cel target dose of 0.75×10^6 CAR-positive viable T cells/kg (range: 0.5×10^6 to 1.0×10^6 CAR-positive viable T cells/kg)

CAR=chimeric antigen receptor; DPd=daratumumab, pomalidomide, and dexamethasone; ID=identifier; PVd=pomalidomide, bortezomib, and dexamethasone.
Number of subjects refers to those subjects who received at least 1 dose of study treatment on or before the clinical cut-off.

Traditional clinical pharmacology studies (absorption, distribution, metabolism, excretion, and drug-drug interaction) have not been conducted because cilta-cel is a genetically modified cell-based therapy. No dedicated drug-drug interaction studies were performed for cilta-cel. As cilta-cel is a single dose cell therapy treatment, no interactions with concomitant medications are expected.

Statistical methods

Values presented in the tables in this section represent arithmetic mean (SD); t_{max}, t_{last}, and t_{bql} values are presented as median (range).

All concentrations below the LLOQ or missing data were labeled as such in the database. Concentrations below the LLOQ were treated as zero in the summary statistics.

For calculation of the individual PK parameters, cilta-cel CAR transgene and $CD3^+CAR^+$ cell levels below the LLOQ were treated as zero wherever it occurred. When more than half (>50%) of the individual blood and bone marrow concentrations of cilta-cel transgene, blood and bone marrow concentrations of $CD3^+CAR^+$ cells, and serum concentrations of sBCMA for a given timepoint were below the LLOQ, the mean, minimum, and median were reported as BQL, while SD, %CV, and geometric mean were not reported. For graphical analysis, blood concentration values of cilta-cel CAR transgene, $CD3^+CAR^+$ cells, and serum concentrations values of sBCMA below LLOQ were treated as being zero for the linear plots and as missing for the semi-logarithmic plots.

For values presented in boxplots, the solid line in the box is the median. The boundaries of the box represent the 25^{th} and 75^{th} percentiles. The whiskers indicate the entire range of values. Any points beyond these values are outliers and are drawn individually.

Bioanalytical methods

The PK of cilta-cel is reported from results of flow cytometry and qPCR methods.

The flow cytometry method was used to determine the number of cells and cell phenotype of CAR lymphocytes present in blood and bone marrow samples from subjects treated with cilta-cel. The flow cytometry method was analytically validated and performed to analyze study samples. The method was validated according to industry standards at the respective organization. Study samples were collected and analyzed according to the protocol.

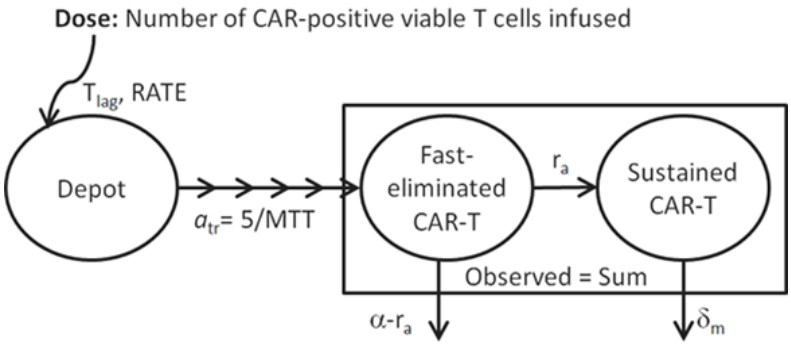
The qPCR analysis was developed and validated as 2 separate methods, one to specifically measure the cilta-cel CAR transgene and another for an endogenous reference gene. Both methods were validated for peripheral blood and bone marrow samples and used to report CAR-T transgene copy numbers per microgram of genomic DNA. The qPCR method was validated for the quantification of CAR T transgene copy numbers per microgram of genomic DNA.

The immunogenicity analyses for anti-cilta-cel antibodies were conducted for both studies MMY3002 and MMY2003 (Cohort A and Cohort B). This assay was validated according to applicable guidelines and with acceptance criteria as specified in the guidelines (EMA 2012; EMA 2008; FDA/CDER/CBER/2019) (Gupta 2011; Shankar 2008).

Population PK model

The base population PK model development was based on a previously developed model to describe the PK characteristics of cilta-cel after IV administration, using data from Study MMY2001. The model structure consisted of 2 compartments (with fast and slow decline rate from each compartment representing fast-eliminated and sustained CAR-T, respectively) and a chain of 4 transit compartments with lag time empirically representing the process from infused CAR-T to measurable CAR transgene systemic level (Figure 1). The model was parameterized in terms of apparent lag time for margination and appearance (T_{lag}), apparent mean transit time (MTT), apparent rapid decline rate (α), apparent transition rate from fast-eliminated to sustained CAR-T (r_a), and apparent gradual decline rate (δ_m). Nonlinear mixed-effects modeling software (NONMEM®, Version 7.4.0; ICON plc, Hanover, MD, USA), and the stochastic approximation, expectation, maximization, and importance sampling algorithms were used.

Figure 1. **Cilta-cel Pharmacokinetic Model**



α=apparent rapid decline rate; a_{tr}= rate constant for transition to the next transit compartment, defined as 5/MTT; δ_m=apparent gradual decline rate; CAR=chimeric antigen receptor; CAR-T=chimeric antigen receptor T cell; MTT=apparent mean transit time; r_a=apparent transition rate to longer-lived CAR-T; T_{lag}=apparent lag time for margination and appearance.

Dose of CAR-positive viable T cells (target dose 0.75×10^6 cells/kg) was infused into the depot compartment. A series of 4 transit compartments was used to characterize the initial appearance and proliferation of CAR-T. The CAR transgene level observation was defined as the sum of the fast-eliminated CAR-T and sustained CAR-T compartments.

The following steps briefly describe the covariate analysis for the population PK model:

- Graphical exploration was performed to investigate the influence on PK parameters of a list of potential baseline covariates. This led to a subset of covariates for further statistical significance testing. The baseline value in the covariate analysis was defined as the closest non-missing value before the cilta-cel infusion, with the exception of parameters associated with disease-related efficacy assessment for which the baseline value was defined as the non-missing value closest to the start of conditioning regimen and before cilta-cel infusion.
- Forward inclusion was applied for all physiologically plausible parameter-covariate relationships that had a significant correlation ($p<0.01$) in Step 1 (monovariate analysis). The parameter-covariate relationships that retained statistical significance ($p<0.01$; multivariate analysis) were then included into the population PK model as the full model.
- Starting from the full model, backward elimination was applied, and parameter-covariate relationships were removed from the model if they did not result in a statistically significant ($p<0.001$) increase of the objective function value. The resulting model was considered as the final model.

Study MMY3002

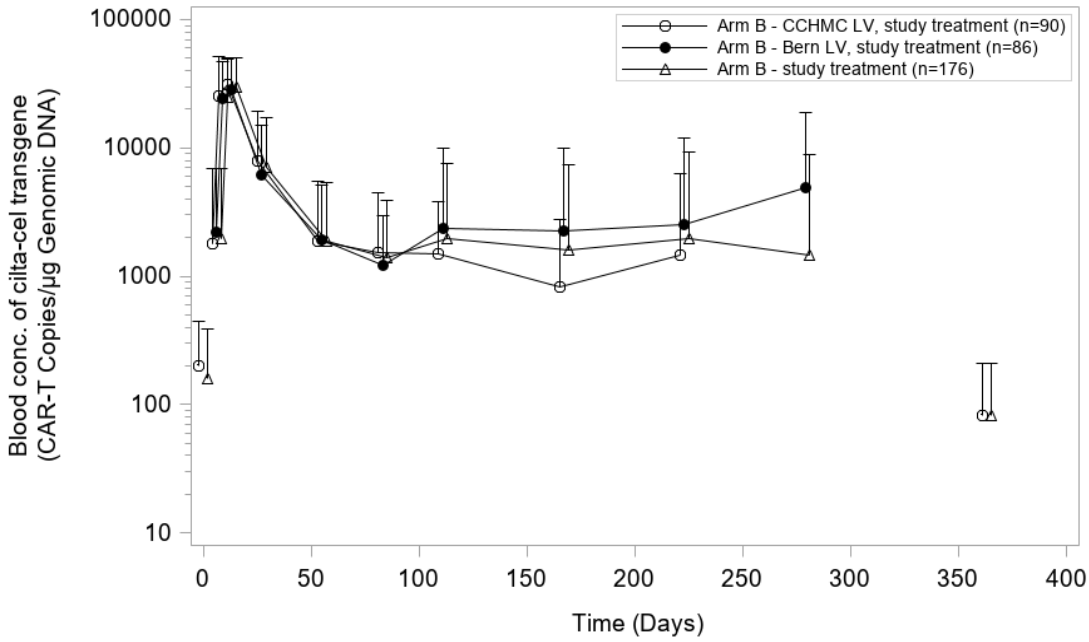
Among the 176 subjects who received cilta-cel as study treatment, 90 subjects received cilta-cel manufactured with CCHMC and 86 subjects received cilta-cel manufactured with Bern LV. PK assessments stratified by the 2 manufacturing processes of LV used were conducted. Subjects randomized to Arm A received PVd (21-day cycles) or DPd (28-day cycles) until confirmed progressive disease, death, intolerable toxicity, withdrawal of consent, or end of study. Subjects randomized to Arm B received a sequence of apheresis, bridging therapy with at least 1 cycle of PVd (21-day cycles) or DPd (28-day cycles), a conditioning regimen of cyclophosphamide and fludarabine, and cilta-cel infusion at the target dose of 0.75×10^6 CAR-positive viable T cells/kg at 5 to 7 days after the start of the

conditioning regimen. For the 176 subjects who received cilta-cel as study treatment, the median administered dose of cilta-cel was 0.706 × 10^6 CAR-positive viable T cells/kg (range: 0.39 × 10^6 to 1.07 × 10^6 cells/kg). The median duration of cilta-cel infusion was 15.0 minutes (range: 3 to 48 minutes).

PK of CAR Transgene Levels in Blood

At the time of the PK data cut-off, 175 of the 176 subjects who received cilta-cel as study treatment had appropriate samples for PK analysis. The mean plasma concentration-time profile of cilta-cel transgene after a single infusion of cilta-cel with the median administered dose of 0.71 x 10^6 CAR positive viable T cells/kg (range: 0.39 × 10^6 to 1.07 × 10^6 cells/kg) is presented in the figure below.

Figure 2. Semi-logarithmic Mean Blood Concentration-Time Profiles of Cilta-cel Transgene Levels After a Single Infusion of a Target Dose of 0.75 × 10^6 CAR-positive Viable T cells/kg in Subjects Who Received Cilta-cel as Study Treatment (MMY3002)



BQL=below quantifiable limit; CAR-T= chimeric antigen receptor T cells; CCHMC= Cincinnati Children's Hospital Medical Center; LV=lentivirus.

The interruptions in the concentration plots are due to more than 50% of the concentrations being BQL on certain timepoints. The error bars represent the standard deviation.

Cilta-cel transgene levels in blood were generally detectable on Day 7 or Day 10. The median t_{max} of CAR transgene levels in blood was 12.8 days (range: 7.8 to 222.8 days).

After the cell expansion, the persistence phase of the transgene levels was observed in the majority of subjects who received cilta-cel as study treatment. The overall mean (SD) $t_{1/2}$ was 21.8 (30.4) days. The overall median t_{last} and t_{bql} were 83.0 days (range: 12.9 to 630.9 days) and 100.5 days (range: 29.0 to 365.9 days), respectively (see table below).

Table 2. Pharmacokinetic Results of Cilta-cel Transgene Levels in Blood After a Single Infusion of a Target Dose of 0.75×10^6 CAR-positive Viable T Cells/kg in Subjects Who Received Cilta-cel as Study Treatment (MMY3002)

Pharmacokinetics of cilta-cel transgene (mean [SD], t_{max}, t_{last}, and t_{bql}: median [range])	Arm B CCHMC LV	Arm B Bern LV	Arm B
N	89 [a]	86 [b]	175 [c]
C_{max}, copies/µg genomic DNA	40219 (24399)	36228 (23825)	38258 (24133)
t_{max}, day	11.94 (7.92 – 222.83)	12.89 (7.80 – 162.00)	12.75 (7.80 – 222.83)
C_{last}, copies/µg genomic DNA	2140 (5960)	1352 (4770)	1752 (5407)
t_{last}, day	83.01 (12.86 – 630.89)	82.98 (13.83 – 334.97)	83.01 (12.86 – 630.89)
t_{bql}, day	92.06 (54.00 – 365.89)	110.93 (28.95 – 336.80)	100.48 (28.95 – 365.89)
$AUC_{0\text{-}28d}$, day × copies/µg genomic DNA	387902 (289905)	333548 (248695)	361038 (270918)
$AUC_{0\text{-}6m}$, day × copies/µg genomic DNA	783113 (677076)	667341 (789891)	723717 (736198)
$AUC_{0\text{-}last}$, day × copies/µg genomic DNA	601965 (597904)	603407 (1073821)	602674 (862607)
$t_{1/2}$, day	22.3 (35.2)	21.3 (25.7)	21.8 (30.4)

AUC=area under the analyte concentration-time curve; $AUC_{0\text{-}28d}$=AUC from time 0 to 28 days; $AUC_{0\text{-}6m}$=AUC from time 0 to 6 months; $AUC_{0\text{-}last}$=AUC from time 0 to the time of last measurable (non-BQL) concentration; BQL=below quantifiable limit; CAR=chimeric antigen receptor; CCHMC=Cincinnati Children's Hospital Medical Center; C_{last}=last measurable (non-BQL) concentration; C_{max}= maximum observed concentration; LV=lentivirus; N=maximum number of subjects with data; n=number of subjects with data for specific parameter; SD=standard deviation; t_{bql}=time of first BQL concentration after reaching C_{max}; $t_{1/2}$=apparent terminal half-life; tbql=time of first BQL concentration after reaching maximum observed analyte concentration; t_{last}=time of last measurable (non-BQL) concentration; t_{max}=time to reach maximum observed concentration.

[a] n=88 for $AUC_{0\text{-}28d}$, n=56 for $AUC_{0\text{-}6m}$, n=51 for t_{bql}, and n=24 for $t_{1/2}$.

[b] n=59 for $AUC_{0\text{-}6m}$, n=33 for t_{bql}, and n=25 for $t_{1/2}$.

[c] n=174 for $AUC_{0\text{-}28d}$, n=115 for $AUC_{0\text{-}6m}$, n=84 for t_{bql}, and n=49 for $t_{1/2}$.

High interindividual variability was observed for the cilta-cel transgene exposure including C_{max} and AUC.

No differences in PK characteristics were found between cilta-cel manufactured with CCHMC LV and manufactured with Bern LV (C_{max}, t_{max}, AUC, $t_{1/2}$, t_{last}, t_{bql}, data not shown).

PK of CD3+CAR+ Cell Counts in Blood

In general, mean $CD3^+CAR^+$ cells in blood samples were observed from Day 7 or 10 following a single cilta-cel administration. The median t_{max} of $CD3^+CAR^+$ cells was 12.9 days (range: 7.8 to 222.8 days).

After the cell expansion phase, the persistence phase was observed in the majority of subjects who received cilta-cel as study treatment. Overall mean (SD) $t_{1/2}$ was 18.9 (21.6) days. The median t_{last} and t_{bql} were 56.9 days (range: 12.9 to 630.9 days) and 83.9 days (range: 27.8 to 342.8 days), respectively.

High interindividual variability was observed for $CD3^+CAR^+$ cell exposure including C_{max} and AUC values.

PK characteristics of cilta-cel manufactured with Bern LV and manufactured with CCHMC LV were considered comparable based on the $CD3^+CAR^+$ cell PK data. Although subjects receiving Bern LV had a slightly higher mean exposure (C_{max}, $AUC_{0\text{-}28d}$, $AUC_{0\text{-}6m}$, and $AUC_{0\text{-}last}$) compared to subjects receiving CCHMC LV, the individual values of C_{max} and AUC overlapped (data not shown).

High interindividual variability was observed, however the profile of $CD3^+CAR^+$ cells in blood were concordant with CAR transgene levels in blood.

PK of CD3+CAR+ Cell Counts in Bone Marrow

Bone marrow samples were collected on Day 28 after the cilta-cel infusion. CD3+CAR+ cells were detectable in the bone marrow of subjects receiving cilta-cel manufactured with either CCHMC LV or Bern LV, indicating a distribution of cilta-cel from systemic circulation to the bone marrow. Interindividual variability was high with overlapping ranges for both LVs (data not shown).

Immunogenicity

Incidence of ADA

Table 3. Subject Sample Status and Titers of Antibodies to Cilta-cel in Serum After a Single Infusion

	Arm B
Subjects with appropriate samples[a]	176
Subjects positive for antibodies to cilta-cel[b,c]	37 (21.0%)
Peak titers	
• 1: 7	3
• 1: 14	5
• 1: 28	7
• 1: 56	10
• 1: 112	10
• 1: 448	1
• 1: 896	1
Subjects negative for antibodies to cilta-cel	139 (79.0%)
Median time (days) to first positive ADA sample (Min – Max)	111.89 (56.75 – 362.96)

ADA=anti-drug antibody; Max=maximum; Min=minimum.

[a] Subjects with appropriate samples had 1 or more samples of anti-cilta-cel antibody assessment obtained after their first study agent administration.

[b] Denominator is subjects with appropriate samples.

[c] Subjects positive for antibodies to cilta-cel are subjects who showed an increase in anti-cilta-cel antibody titers during the study.

No difference in the incidence of antibodies to cilta-cel was observed in subjects who received cilta-cel manufactured with CCHMC LV and subjects who received cilta-cel manufactured with Bern LV.

Impact of Immunogenicity on Cilta-cel PK in r/r Multiple Myeloma

Median cilta-cel transgene and $CD3^+CAR^+$ cell exposures (indicated by C_{max}, $AUC_{0\text{-}28d}$, and $AUC_{0\text{-}last}$) appeared to be lower for the ADA-positive subjects compared to the ADA-negative subjects. A similar trend was observed in subjects who received cilta-cel manufactured with CCHMC LV and subjects who received cilta-cel manufactured with Bern LV. However, given the high interindividual variability in PK and relatively smaller sample size of the ADA-positive group, there was no clear association between ADA status and cilta-cel exposure and persistence based on current data (data not shown).

Effect of Immunogenicity on Efficacy in Subjects with r/r Multiple Myeloma

In subjects who received cilta-cel as study treatment in Study MMY3002, the primary efficacy endpoint, PFS, was similar between ADA-positive and ADA-negative subjects. In addition, the presence of anti-cilta-cel antibodies had no apparent impact on the other efficacy endpoints including OS, DOR, ORR, CR or better, VGPR or better, and MRD negativity in subjects with r/r multiple myeloma (data not shown).

Effect of Immunogenicity on Safety in Subjects with r/r Multiple Myeloma

The presence of anti-cilta-cel antibodies had no apparent impact on the safety outcomes, including CRS, ICANS, other neurotoxicities, and SPM in subjects who received cilta-cel as study treatment in Study MMY3002. All CRS and ICANS AEs experienced by subjects positive for anti-cilta-cel antibodies were Grades 1 or 2 in severity (data not shown). However, the number of subjects who had experienced AEs and were positive for anti-cilta-cel antibodies was small, which limits a definitive conclusion regarding the impact of ADA on clinical safety.

Study MMY2003

Study MMY2003 is a Phase 2, multicohort, open-label, multicenter study to determine whether treatment with cilta-cel results in MRD negativity in adult subjects with multiple myeloma. The cohorts explore the safety and efficacy of cilta-cel in various multiple myeloma patient populations. In this submission, data are presented for Cohorts A and B:

Population of subjects identical to Study MMY3002

- Cohort A: Subjects with progressive disease after 1 to 3 prior lines of therapy (including a PI and an IMiD) and refractory to lenalidomide. Data from the protocol-specified primary analysis for the first 20 subjects enrolled into Cohort A of Study MMY2003 (clinical cut-off date of 08 October 2021) are presented and included in the population PK analysis. The median dose of cilta-cel administered was 0.656×10^6 cells/kg (range: 0.58×10^6 to 0.84×10^6 cells/kg). The median duration of cilta-cel infusion was 13.5 minutes (range: 5 to 35 minutes)

Population of subjects similar to Study MMY3002

- Cohort B: Subjects with 1 prior line of therapy including a PI and an IMiD and early relapse defined as disease progression $\leq$12 months after ASCT or $\leq$12 months after the start of front-line therapy for subjects who have not had ASCT. Data from the protocol-specified primary analysis for the 19 subjects who received a cilta-cel infusion in Cohort B of Study MMY2003 (clinical cut-off date of 01 June 2022) are presented and included in the population PK analysis. The median dose of cilta-cel administered was 0.696×10^6 cells/kg (range: 0.497×10^6 to 0.815×10^6 cells/kg). The median duration of cilta-cel infusion was 16.0 minutes (range: 6 to 36 minutes).

PK of CAR Transgene Levels in Blood

Cohort A:

After a single infusion of cilta-cel, mean CAR transgene levels in blood samples were below quantifiable limits (BQL) until Day 7 or 10, followed by cell expansion. The median t_{max} of CAR transgene levels in blood was 10.5 days (range: 8.7 to 42.9 days).

After the cell expansion, the persistence phase of the transgene levels was observed for all subjects. Mean (SD) $t_{1/2}$ was 38.3 (34.8) days. The median t_{last} and t_{bql} were 183.0 days (range: 21.0 to 331.9 days) and 153.5 days (range: 57.1 to 336.8 days), respectively.

Cohort B:

After a single infusion of cilta-cel mean CAR transgene levels in blood samples were BQL until Day 7 or 10. The median t_{max} of CAR transgene levels in blood was 13.1 days (range: 9.0 to 209.9 days).

After the cell expansion, the persistence phase of the transgene levels was observed for all subjects. Mean (SD) $t_{1/2}$ was 11.0 (5.8) days. The median t_{last} and t_{bql} were 97.0 days (range: 26.9 to 330.8 days) and 124.8 days (range: 41.0 to 221.8 days), respectively.

PK of Cilta-cel Transgene Levels in Bone Marrow

Cohort A:

After a single infusion of cilta-cel, bone marrow samples were collected for transgene level evaluation on Days 28, 56, and 184. The highest mean level of cilta-cel transgene levels in the bone marrow samples was reached on Day 28. Thereafter, levels of cilta-cel transgene in the bone marrow decreased over time. Like blood transgene levels, bone marrow transgene levels also declined over time and exhibited high interindividual variability.

Cohort B:

After a single infusion of cilta-cel, bone marrow samples were collected for transgene level evaluation on Days 28, 56, and 184. The highest mean level of cilta-cel transgene levels in the bone marrow samples was reached on Day 28. Thereafter, levels of cilta-cel transgene in the bone marrow decreased over time. By Day 184, mean concentrations had decreased further to BQL. Similar to blood transgene levels, bone marrow transgene levels also declined over time and exhibited high interindividual variability.

PK of Cellular CD3+CAR+ Cell Counts in Blood

Cohort A:

In general, $CD3^+CAR^+$ cells in blood samples were also observed from Day 7 or Day 10 onwards following single cilta-cel administration. The median t_{max} of $CD3^+CAR^+$ cells in blood was 12.8 days (range: 8.8 to 37.8 days).

After the cell expansion phase, the mean (SD) $t_{1/2}$ was 62.0 (51.6) days. The median t_{last} and t_{bql} were 277.0 days (range: 21.0 to 405.8 days) and 152.0 days (range: 57.1 to 272.9 days), respectively.

Cohort B:

In general, mean $CD3^+CAR^+$ cells in blood samples were also observed from Day 7 or 10 onwards following single cilta-cel administration. The median t_{max} of $CD3^+CAR^+$ cells in blood was 12.9 days.

After the cell expansion phase, the mean (SD) $t_{1/2}$ value of $CD3^+CAR^+$ cells in blood was 13.0 (8.2) days. The median t_{last} and t_{bql} were 76.8 days (range: 26.9 to 273.1 days) and 97.9 days (range: 34.1 to 295.9 days), respectively.

PK of CD3+CAR+ Cell Counts in Bone Marrow

Cohort A:

The highest mean concentrations of CD3+CAR+ cells in bone marrow were observed on Day 28. Thereafter, levels of CD3+CAR+ cells in bone marrow decreased.

Cohort B:

The highest mean concentrations of $CD3^+CAR^+$ cells in bone marrow were observed on Day 28. Thereafter, levels of $CD3^+$ CAR^+ cells in the bone marrow decreased over time. By Day 184, $CD3^+CAR^+$ cells in the bone marrow had decreased further to BQL.

Immunogenicity

Cohort A:

Impact of Immunogenicity on Cilta-cel PK in r/r Multiple Myeloma

The kinetics of expansion of cilta-cel was similar between subjects positive for ADA (5/20 subjects with appropriate samples) compared with subjects negative for ADA. There was no clear evidence to draw a conclusion on the association between ADA and cilta-cel persistence.

Cohort B:

Impact of Immunogenicity on Cilta-cel PK in r/r Multiple Myeloma

The kinetics of expansion of cilta-cel was similar between subjects positive for ADA (8/19 subjects with appropriate samples) compared with subjects negative for ADA. There was no clear evidence to draw a conclusion on the association between ADA and cilta-cel persistence.

Pharmacokinetics results across studies

Population PK Analysis

Objectives:

The objectives of the population PK analyses were:

- To update the previously developed population PK model to characterize the population PK of cilta-cel after IV infusion administration in subjects with r/r multiple myeloma.
- To assess the impact of potential covariates on the PK of cilta-cel.

Data:

The population PK analyses were based on data of adult subjects with r/r multiple myeloma from the following 2 studies:

- Study 68284528MMY3002 (CARTITUDE-4, hereafter referred to as MMY3002): PK cut-off date 29 August 2022
- Study 68284528MMY2003 (CARTITUDE-2, hereafter referred to as MMY2003):
    - Cohort A (subjects with lenalidomide-refractory multiple myeloma and 1 to 3 prior lines of therapy): PK cut-off date 08 October 2021
    - Cohort B (subjects with early relapse multiple myeloma after 1 line of prior therapy): PK cut-off date 01 June 2022

A total of 1,731 CAR transgene concentrations (1,276 concentrations in Study MMY3002 and 455 concentrations in Study MMY2003 Cohorts A and B) from 235 subjects (196 subjects in Study MMY3002 and 39 subjects in Study MMY2003 Cohorts A and B) were included in the population PK analysis. Subjects from both studies received cilta-cel intravenously as a single dose.

Results:

All parameter estimates had relative standard errors of <30%. Residual plots were approximately zero-centered and did not show major trends either at the population or at the individual level. Random

effects related to interindividual variability appeared to be approximately zero-centered and normally distributed.

Table 4. Parameter Estimates in Final Population Pharmacokinetic Model

Parameters [a]	Description	Estimate [a] (%RSE)	exp (Est) [b]	IIV variance	IIV %CV [c] (%RSE) [d]	Shrinkage [e] (%)
T_{lag} (days)	Lag time for margination and appearance	1.59 (1.38)	4.90	0.0224	15.1 (8.26)	20.7
MTT (days)	Mean transit time (to reparametrize a_{tr})	2.31 (2.34)	10.1	0.00967	9.86 (25.9)	58.2
α (1/day)	Rapid decline rate	5.31 (1.66)	202	0.704	101 (7.60)	19.8
r_a (1/day)	Rate constant for apparent transition	-4.70 (11.0)	0.00910	2.29	298 (17.6)	32.8
δ_m (1/day)	Gradual decline rate	-3.59 (7.38)	0.0276	1.50	187 (8.87)	22.1
Proportional residual error (%CV)		0.929 (3.54)	-	-	-	-

a_{tr}=rate constant for transition to the next transit compartment, defined as 5/MTT; %CV=percent coefficient of variation; exp(Est)=model parameter estimates; IIV=interindividual variability; RSE=relative standard error; SD=standard deviation; SE=standard error.

[a] Model parameters were estimated in natural log domain.

[b] Model parameters were converted to the normal scale.

[c] IIV %CV=100 × square root(exp(IIV variance)-1).

[d] RSE for IIV=(SE/variance estimate)/2.

[e] Shrinkage=1-SD(IIVposthoc)/square root(IIV variance).

[f] Residual error was parameterized for the log-transformed data as $\ln(C_{obs}) = \ln(C_{pred}) + \theta \times EPS(1)$, where θ is the standard deviation and EPS(1) is a normally distributed error with mean 0 and variance fixed to 1.

None of the covariates explored and tested in the population PK model had a statistically significant effect on CAR transgene systemic level. The model predicted individual CAR transgene systemic level C_{max} and $AUC_{0\text{-}28d}$ were also compared across different strata for covariates of interest (a subset of all tested covariates), respectively. None of the estimated geometric mean ratio CIs excluded the null value (i.e., geometric mean ratio of 1), except the C_{max} for non-white versus white subpopulations, the $AUC_{0\text{-}28d}$ for non-white versus white subpopulations and Asian versus non-Asian subpopulations. Because the upper limits of the geometric mean ratio 95% CIs between these subpopulations were close to 1 (from 0.986 to 0.998), the differences in C_{max} or $AUC_{0\text{-}28d}$ between the subpopulations were not considered as clinically relevant. Given the lack of evidence from the covariate analysis and the forest plots, the base model was still determined as the final model based on principle of parsimony.

Effect of Intrinsic Factors

Age, sex, body weight, and race/ethnicity had no impact on PK parameters. Population PK analysis confirmed that cilta-cel CAR transgene C_{max} and $AUC_{0\text{-}28d}$ in subjects with mild hepatic dysfunction (defined as total bilirubin ≤ ULN and AST > ULN, or ULN < total bilirubin ≤1.5 × ULN) (Patel 2004; National Cancer Institute 2020) were similar to subjects with normal hepatic function.

Renal Impairment

No dedicated renal impairment study was planned as cilta-cel is a genetically modified cell-based therapy and major changes in cilta-cel exposure are not anticipated in subjects with renal insufficiency. Population PK analysis showed that cilta-cel CAR transgene C_{max} and $AUC_{0\text{-}28d}$ in subjects with mild renal dysfunction (defined as 60 mL/min ≤ CRCL <90 mL/min) or moderate renal dysfunction (defined as 30 mL/min ≤ CRCL <60 mL/min) were similar to subjects with normal renal function (CRCL ≥90 mL/min).

Extrinsic Factors

Tocilizumab and Corticosteroids

Median CAR transgene C_{max} and $AUC_{0\text{-}28d}$ were higher among subjects who received tocilizumab or corticosteroids for CRS or ICANS management. Subjects treated with tocilizumab (n=112) had median C_{max} and $AUC_{0\text{-}28d}$ 68.6% and 83.2% higher, respectively, compared with subjects who did not receive tocilizumab (n=123). Subjects treated with corticosteroids (n=29) had median C_{max} and $AUC_{0\text{-}28d}$ 58.5% and 87.9% higher, respectively, compared with subjects who did not receive corticosteroids (n=206). For anakinra, due to quite limited subjects receiving this therapy (n=6), the comparison of PK exposure was not explored. The results related to tocilizumab and corticosteroids were consistent with those of Study MMY2001.

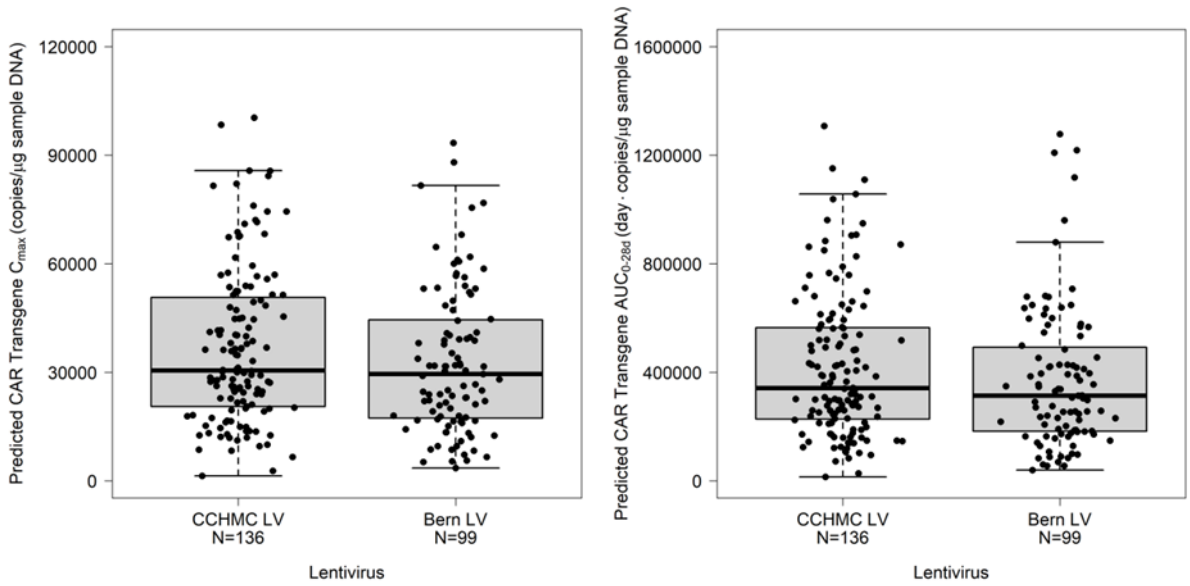
Manufactured Product Characteristics

There was no apparent relationships between CAR transgene exposure (C_{max} and $AUC_{0\text{-}28d}$) and manufactured product characteristics, including percent $CD4^+$ cells in cilta-cel DP, percent $CD8^+$ cells in cilta-cel DP, CD4/CD8 ratio in cilta-cel DP, transduction efficiency, CAR expression, percent CAR^+ naïve, percent CAR^+ effector, percent CAR^+ central memory, percent CAR^+ effector memory, percent CAR^- naïve, percent CAR^- effector, percent CAR^- central memory, percent CAR^- effector memory, percent $CD3^+$ cells, in vitro tumor kill assay, vector copy number, viable nucleated cells, and post-thaw viability (data not shown).

Lentiviral Vector Manufacturing Process

No PK (C_{max} or $AUC_{0\text{-}28d}$) difference was found in subjects receiving either CCHMC LV or Bern LV.

Figure 3. Relationship Between Predicted CAR Transgene Exposure (C_{max} and $AUC_{0\text{-}28d}$) and Lentivirus From Different Manufacturing Processes



CAR=chimeric antigen receptor; CCHMC=Cincinnati Children's Hospital Medical Center; LV=lentivirus; N=number of subjects; PPK=population pharmacokinetics.

$AUC_{0\text{-}28d}$ is area under the CAR transgene systemic level-time curve from the first dose to Day 28 predicted by the PPK final model. C_{max} is the maximum CAR transgene systemic level predicted by the PPK final model.

The N=136 subjects treated with cilta-cel manufactured using CCHMC LV included 97 subjects from Study MMY3002 and all 39 subjects from Study MMY2003 (Cohorts A and B). All N=99 subjects treated with cilta-cel manufactured using Bern LV were from Study MMY3002.

2.3.3. Pharmacodynamics

Table 5. Study MMY3002 Pharmacodynamic Sampling Schedule

Assessment	Sample Type	Sampling Timepoints
Soluble BCMA	Serum	Day 1 prior to the cilta-cel administration, Days 3, 7, 10, 14, 28, 56, 84, 112, then every 8 weeks up to 1 year, and at the time of progressive disease or at study completion for subjects without progressive disease.
Cytokine profiling	Serum	Before the first dose of conditioning therapy (≤7 days), Day 1 prior to the cilta-cel administration, Day 1 at 2 hours postdose, Days 3, 7, 10, 14, 21, 28, 56, 84, 112. Additional samples were also collected when CRS or CAR-T related neurotoxicity (eg, ICANS) (Grade ≥3) was observed or reported (at the time of onset, at any increase in grade of the CRS and at time of resolution), or as clinically indicated. If these additional sampling timepoints occurred on a day of a regularly scheduled sample collection, only 1 sample collection was required for that day.
MRD	Bone marrow	At time of suspected CR or sCR, at approximately 6, 12, 18, 24 months after administration of cilta-cel regardless of whether CR is achieved, and then yearly for subjects who achieved CR/sCR and remained in the study up to disease progression 24 months after administration of cilta-cel.
RCL	Whole blood	Day 1 prior to the cilta-cel administration, at approximately 3, 6, 12 months after administration, and then yearly for up to 15 years after administration.

BCMA=B-cell maturation antigen; CAR-T=chimeric antigen receptor T cell; CR=complete response; CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome; MRD=minimal residual disease; RCL=replication competent lentivirus; sCR=stringent CR.

Primary and secondary pharmacology

Pharmacodynamics of sBCMA in Serum

After a single infusion of cilta-cel, expansion of CAR-positive T cells coincided with decreases of serum sBCMA. All 176 subjects who received cilta-cel as study treatment showed similar kinetics of decline in sBCMA levels. Concentrations of sBCMA in serum slowly decreased as a function of time, with mean serum BCMA concentrations reaching nadir levels around the LLOQ value (ie, <0.25000 µg/L) at Day 56. At the time of data cut-off, sBCMA levels showed an increase from nadir (reversal) in some participants. In these participants, although sBCMA levels showed a trend of increase from nadir, levels were lower than baseline sBCMA (at pre-dose cilta-cel administration). (Data not shown)

Interindividual variability was also high for the serum concentration of sBCMA at baseline.

The declined sBCMA concentration-time profiles were comparable between subjects who received cilta-cel manufactured with CCHMC LV and subjects who received cilta-cel manufactured with Bern LV (data not shown).

Biomarkers – Cytokine Profiling

Across all subjects, levels of IL-6, IL-10, IFN-γ, and IL-2Ra increased post-infusion and peaked at Days 7 to 14. The serum levels of all cytokines generally returned to baseline levels within 2 to 3 months post-infusion. A positive association was observed between median IL-6, IL-10, IFN-γ, and IL-2Ra C_{max} and $AUC_{0\text{-}56d}$ and the worst grade of CRS experienced by the subjects.

MRD Negativity

At the time of the clinical data cut-off (29 August 2022), the MRD negativity rate (10^{-5}) as measured by NGS was approximately 4-fold higher for subjects in the cilta-cel arm (60.6% [126 of 208 subjects]) than for subjects in the PVd/DPd arm (15.6% [33 of 211 subjects]) in the intent-to-treat population (odds ratio=8.7; 95% CI: 5.42, 13.90; p<0.0001). Among the 176 subjects who received cilta-cel as study treatment, the overall MRD negativity rate (at the 10^{-5} threshold) was 71.6%.

Evaluable samples were defined as those that passed calibration or quality control and included sufficient cells for evaluation at the respective testing threshold. Considering only subjects with evaluable samples (cilta-cel, n=144; PVd/DPd, n=101), 126 (87.5%) and 33 (32.7%) subjects achieved MRD negativity, respectively.

RCL (replication-competent lentivirus)

At the time of the clinical data cut-off date, 58 and 80, 134, and 72 subjects had evaluable samples for RCL analysis pre-dose, and at 3, 6, and 12 months post cilta-cel infusion, respectively. Sample availability was lower at 3 months than 6 months post-infusion because of a lower compliance of RCL sample collection at 3 months post-infusion due to lack of robust protocol training. The issue was addressed and the compliance to RCL sample collection was improved from 54% (95 of 176) at 3 months to 85% (147 of 172) at 6 months and 93% (80 of 86) at 12 months post-infusion.

No positive samples for RCL had been detected in any subjects at any of the collection timepoints.

2.3.4. PK/PD modelling

Exposure-Response Relationships

Objectives:

The objectives of the E-R analyses were:

- To explore E-R relationship between cilta-cel exposure and efficacy endpoints, including PFS, OS, DOR, CR or better, ORR, VGPR or better, and overall MRD negativity rate.
- To explore E-R relationship between exposure and AEs, including CRS, CAR-T neurotoxicity, and any grade SPM.

Data and Methods: The E-R analyses were based on data from Study MMY3002 only (cut-off date for efficacy and safety 01 November 2022). The primary exposure metrics used for E-R analyses included CAR transgene systemic C_{max} and $AUC_{0\text{-}28d}$. Efficacy endpoints for E-R analysis included PFS, OS, DOR, CR or better, ORR, VGPR or better, and overall MRD negativity rate, and safety endpoints included CRS, CAR-T neurotoxicity (ICANS and other neurotoxicities), and SPM.

In Arm A of Study MMY3002 (control arm), 208 subjects received standard therapy (safety set). In Arm B, a total of 196 subjects received cilta-cel. Of these 196 subjects, 176 subjects received cilta-cel study treatment; these subjects were the focus of the E-R analyses. The remaining 20 subjects in Arm B had confirmed disease progression prior to cilta-cel exposure and received cilta-cel as subsequent therapy. The 208 subjects in the control group (Arm A) were included in the E-R analysis for efficacy only. The individual CAR transgene systemic levels as predicted from the final population PK model, including C_{max} and $AUC_{0\text{-}28d}$, were used as exposure metrics for the E-R analyses. The cilta-cel systemic exposure values (eg, C_{max} and $AUC_{0\text{-}28d}$) were set to 0 for the subjects from the control group.

The relationship between exposure metrics and the primary efficacy endpoint, PFS, was investigated through data visualization (eg, Kaplan-Meier plot). PFS was defined as time from the date of randomization to the date of first documented disease progression, as defined in the IMWG criteria analyzed by a validated computerized algorithm, or death due to any cause, whichever occurred first. Other efficacy endpoints, including OS, DOR, rate of CR or better, ORR (defined as the proportion of subjects who achieve a PR or better according to the IMWG criteria), VGPR or better, and overall MRD negativity rate were graphically explored.

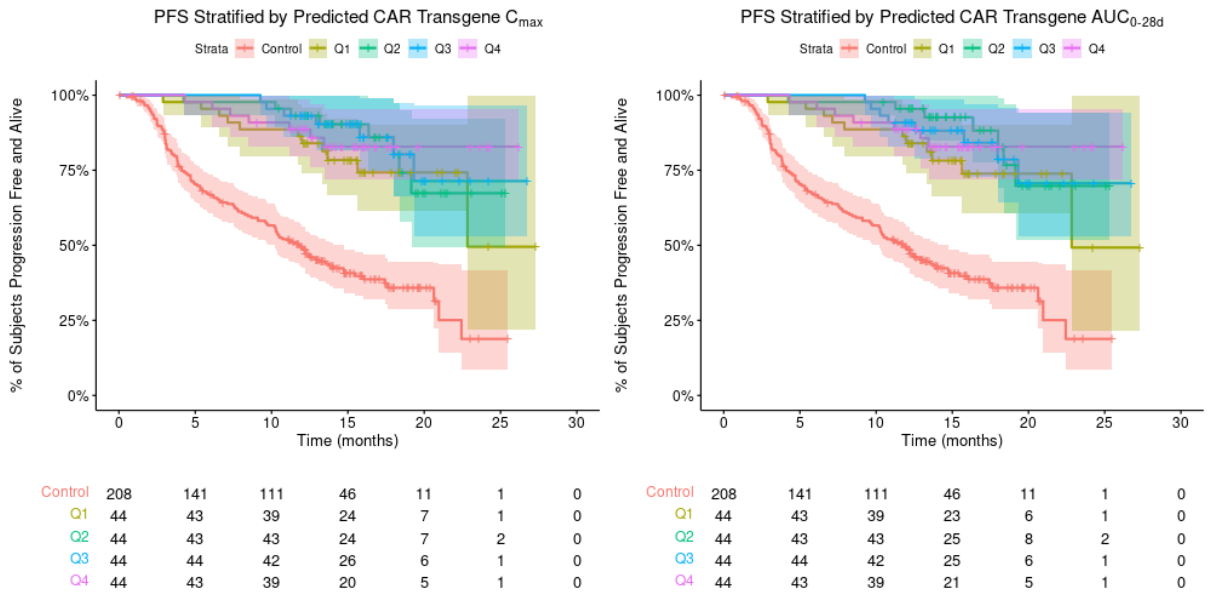
The E-R relationship for safety was explored between the predicted exposure metrics and the AEs of clinical interest, including CRS events, ICANS, other neurotoxicities, and any grade SPM, through statistics data visualization (eg, boxplot).

The E-R relationships for efficacy and safety using observed exposure metrics of CD3+CAR+ cell concentrations ($C_{max,flow}$ and $AUC_{0\text{-}28d,flow}$) were also graphically explored.

Exposure-efficacy Analysis

E-R relationships for the primary endpoint (PFS) and other time-to-event endpoints (OS and DOR) were evaluated according to 2 exposure metrics, CAR transgene C_{max} and $AUC_{0\text{-}28d}$, and presented in the figures below.

Figure 4. Kaplan-Meier Curves for PFS Stratified by Treatment Arm and Predicted CAR Transgene C_{max} and AUC_{0-28d} Quartiles



CAR=chimeric antigen receptor; N=number of subjects; PFS=progression-free survival; PPK=population pharmacokinetics; Q=quartile.

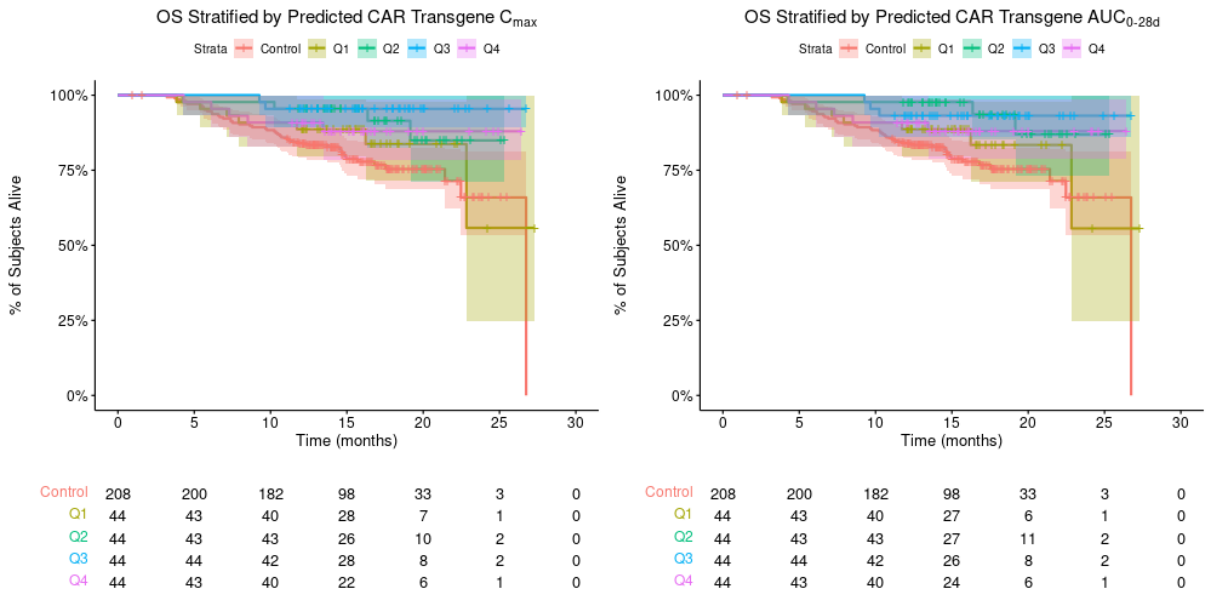
AUC_{0-28d} is area under the CAR transgene systemic level-time curve from the first dose to Day 28 predicted by the PPK final model. C_{max} is the maximum CAR transgene systemic level predicted by the PPK final model.

The quartiles for AUC_{0-28d} are: Q1 (27300 to 188000 day × copies/µg sample DNA), Q2 (188000 to 302000 day × copies/µg sample DNA), Q3 (302000 to 487000 day × copies/µg sample DNA), and Q4 (487000 to 1150000 day × copies/µg sample DNA).

The quartiles for C_{max} are: Q1 (2740 to 17900 copies/µg sample DNA), Q2 (17900 to 27900 copies/µg sample DNA), Q3 (27900 to 42300 copies/µg sample DNA), and Q4 (42300 to 100000 copies/µg sample DNA).

The N=208 of the control group are the subjects in Arm A of Study MMY3002, the N=44 per quartile are the 176 subjects from Arm B of Study MMY3002 who received cilta-cel as study treatment.

Figure 5. Kaplan-Meier Curves for OS Stratified by Treatment Arm and Predicted CAR Transgene C_{max} and $AUC_{0\text{-}28d}$ Quartiles



CAR=chimeric antigen receptor; N=number of subjects; OS=overall survival; PPK=population pharmacokinetics; Q=quartile.

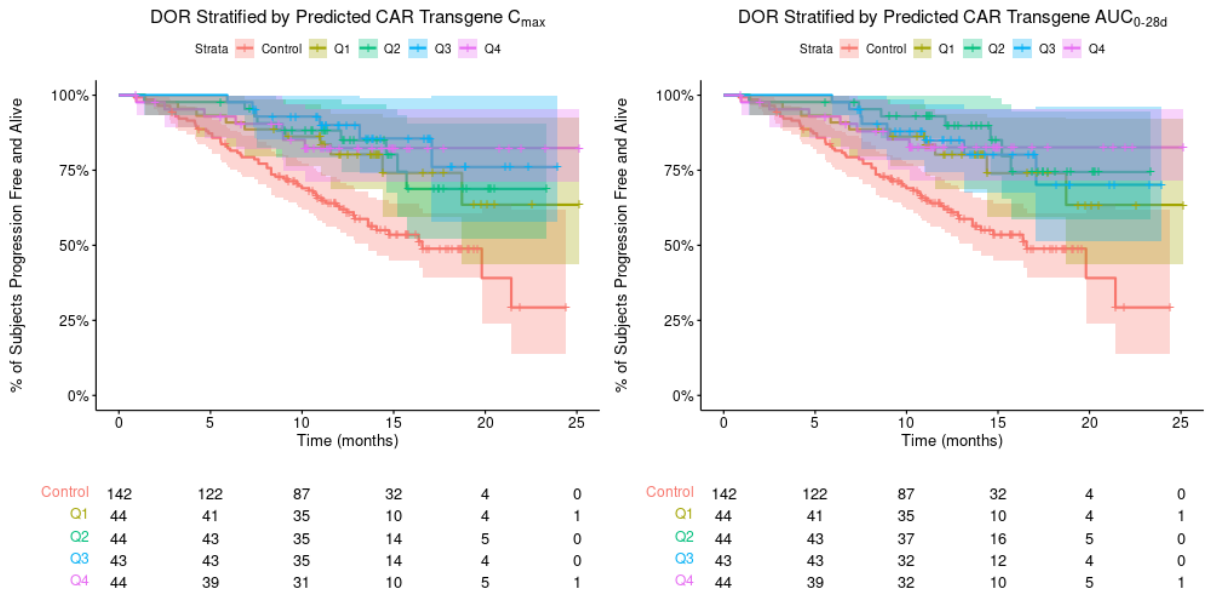
$AUC_{0\text{-}28d}$ is area under the CAR transgene systemic level-time curve from the first dose to Day 28 predicted by the PPK final model. C_{max} is the maximum CAR transgene systemic level predicted by the PPK final model.

The quartiles for $AUC_{0\text{-}28d}$ are: Q1 (27300 to 188000 day × copies/µg sample DNA), Q2 (188000 to 302000 day × copies/µg sample DNA), Q3 (302000 to 487000 day × copies/µg sample DNA), and Q4 (487000 to 1150000 day × copies/µg sample DNA).

The quartiles for C_{max} are: Q1 (2740 to 17900 copies/µg sample DNA), Q2 (17900 to 27900 copies/µg sample DNA), Q3 (27900 to 42300 copies/µg sample DNA), and Q4 (42300 to 100000 copies/µg sample DNA).

The N=208 of the control group are the subjects in Arm A of Study MMY3002, the N=44 per quartile are the 176 subjects from Arm B of Study MMY3002 who received cilta-cel as study treatment.

Figure 6. Kaplan-Meier Curves for DOR Stratified by Treatment Arm and Predicted CAR Transgene C_{max} and AUC_{0-28d} Quartiles



CAR=chimeric antigen receptor; DOR=duration of response; N=number of subjects; PPK=population pharmacokinetics; Q=quartile.

AUC_{0-28d} is area under the CAR transgene systemic level-time curve from the first dose to Day 28 predicted by the PPK final model. C_{max} is the maximum CAR transgene systemic level predicted by the PPK final model.

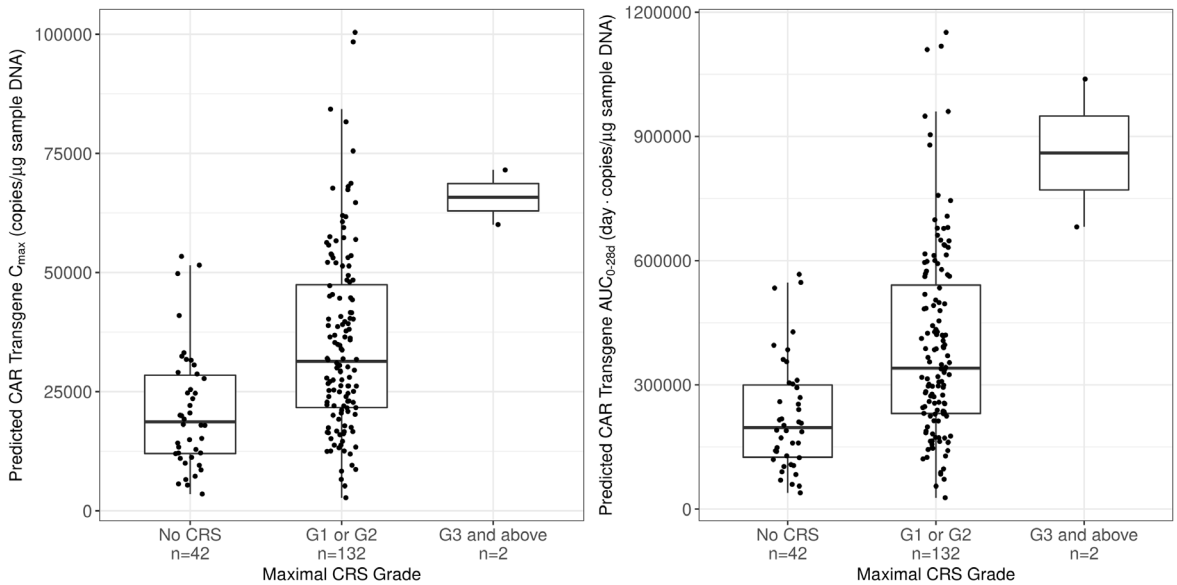
The quartiles for AUC_{0-28d} are: Q1 (39200 to 189000 day × copies/µg sample DNA), Q2 (189000 to 302000 day × copies/µg sample DNA), Q3 (302000 to 488000 day × copies/µg sample DNA), and Q4 (488000 to 1150000 day × copies/µg sample DNA).

The quartiles for C_{max} are: Q1 (3520 to 18000 copies/µg sample DNA), Q2 (18000 to 28000 copies/µg sample DNA), Q3 (28000 to 42900 copies/µg sample DNA), and Q4 (42900 to 100000 copies/µg sample DNA).

The control group are the subjects in Arm A of Study MMY3002, the N=44 per quartile are the 176 subjects from Arm B of Study MMY3002 who received cilta-cel as study treatment.

Exposure-safety Analysis

Figure 7. Comparison of Predicted CAR Transgene C_{max} and AUC_{0-28d} Between Subjects With Different Maximal CRS Grade

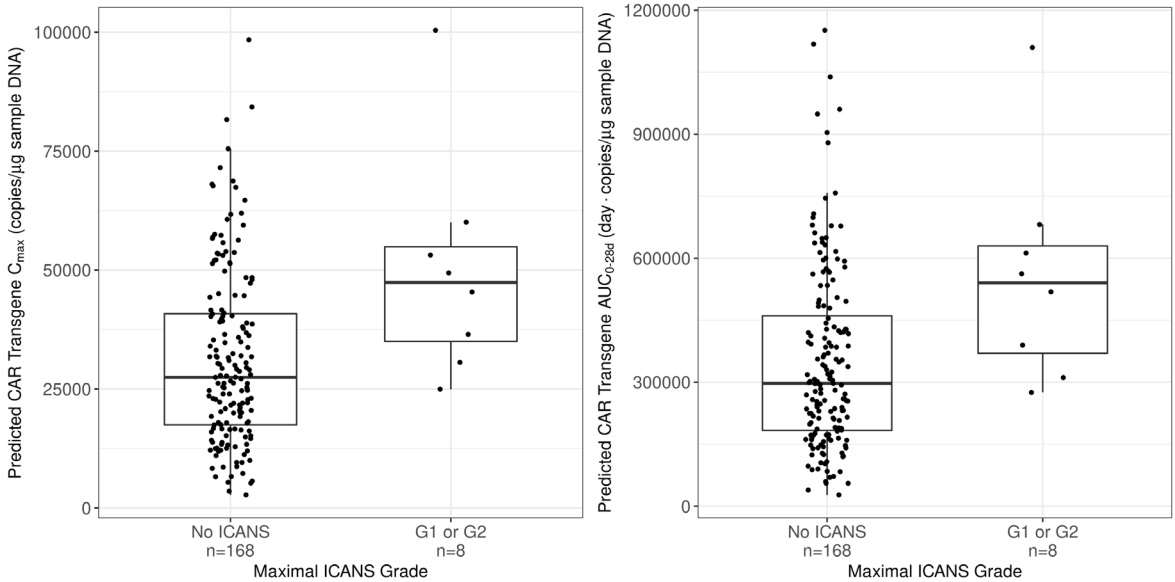


CAR=chimeric antigen receptor; CRS=cytokine release syndrome; G=adverse event grade; n=number of subjects; PPK=population pharmacokinetics.

Figure 7. Comparison of Predicted CAR Transgene C_{max} and AUC_{0-28d} Between Subjects With Different Maximal CRS Grade

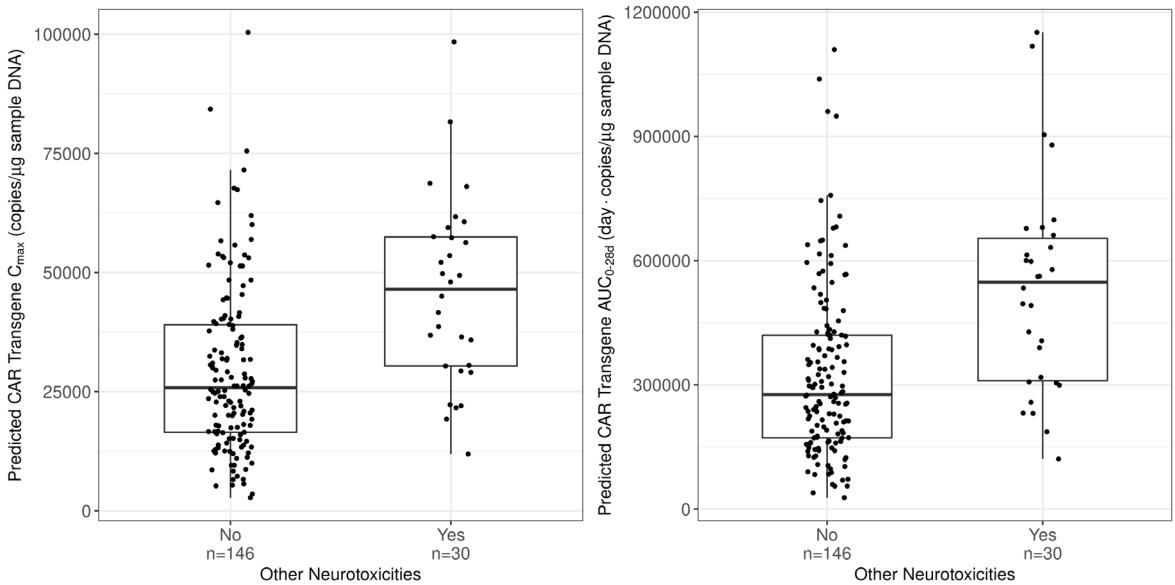
AUC_{0-28d} is area under the CAR transgene systemic level-time curve from the first dose to Day 28 predicted by the PPK final model. C_{max} is the maximum CAR transgene systemic level predicted by the PPK final model.
The n=176 subjects evaluated are the subjects from Arm B of Study MMY3002 who received cilta-cel as study treatment.

Figure 8. Comparison of Predicted CAR Transgene C_{max} and AUC_{0-28d} Between Subjects With Different Maximal ICANS Grade



CAR=chimeric antigen receptor; G=adverse event grade; ICANS=immune effector cell-associated neurotoxicity syndrome; n=number of subjects; PPK=population pharmacokinetics.
AUC_{0-28d} is area under the CAR transgene systemic level-time curve from the first dose to Day 28 predicted by the PPK final model.
C_{max} is the maximum CAR transgene systemic level predicted by the PPK final model.
The n=176 subjects evaluated are the subjects from Arm B of Study MMY3002 who received cilta-cel as study treatment.

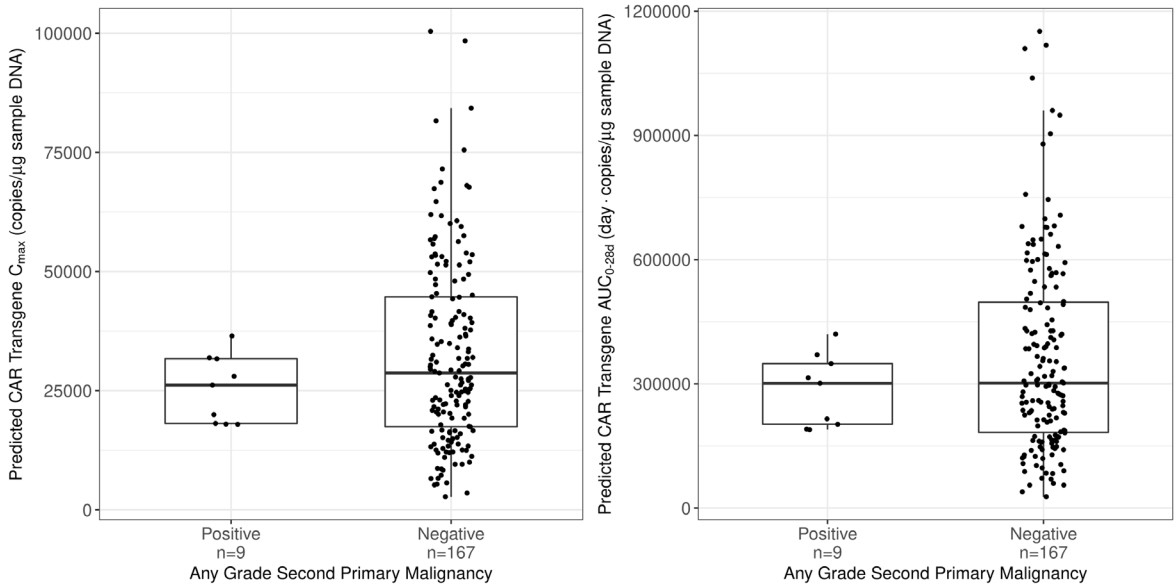
Figure 9. Comparison of Predicted CAR Transgene C_{max} and AUC_{0-28d} Between Subjects With and Without Other Neurotoxicities



CAR=chimeric antigen receptor; CAR-T=chimeric antigen receptor T cell; ICANS=immune effector cell-associated neurotoxicity syndrome; n=number of subjects; PPK=population pharmacokinetics.

$AUC_{0\text{-}28d}$ is area under the CAR transgene systemic level-time curve from the first dose to Day 28 predicted by the PPK final model.
C_{max} is the maximum CAR transgene systemic level predicted by the PPK final model.
Other neurotoxicities refer to other events of CAR-T neurotoxicity not defined as ICANS.
The n=176 subjects evaluated are the subjects from Arm B of Study MMY3002 who received cilta-cel as study treatment.

Figure 10. Comparison of Predicted CAR Transgene C_{max} and $AUC_{0\text{-}28d}$ Between Subjects With and Without Second Primary Malignancy



CAR=chimeric antigen receptor; n=number of subjects; PPK=population pharmacokinetics;.

$AUC_{0\text{-}28d}$ is the area under the CAR transgene systemic level-time curve from the first dose to Day 28 predicted by the PPK final model; C_{max} is the maximum CAR transgene systemic levels predicted by the PPK final model.

Justification of Dose and Dosing Regimen

The approved dose of 0.75×10^6 CAR-positive viable T cells/kg (range 0.5×10^6 to 1.0×10^6 CAR-positive viable T cells/kg) with a maximum total dose of 1.0×10^8 CAR-positive viable T cells of cilta-cel was established based on the totality of safety and efficacy data in previous clinical studies (both Phase 1b and 2 of Study MMY2001). In Study MMY3002, the single dose administration of the cilta-cel at the approved dose demonstrated sufficient exposure associated with efficacy, with a 12-month PFS rate of 89.7% in subjects who received cilta-cel as study treatment. The median PFS was not reached, and the 95% CI was not estimable as most data were censored at the data of the clinical cut-off. The ORR (PR or better) for subjects who received cilta-cel as study treatment was 99.4%.

CRS was found to be the most prevalent CAR-T related AE and was reported for 134 subjects (76.1%) who received cilta-cel as study treatment in Study MMY3002. Most subjects experienced Grade 1 or 2 CRS (Grade 1: 93 subjects [52.8%]; Grade 2: 39 subjects [22.2%]) when assessed using the American Society for Transplantation and Cellular Therapy consensus grading system. Two subjects (1.1%) experienced Grade 3 CRS, there were no Grade 4 or Grade 5 CRS events. All CRS events recovered or resolved after a median duration of 3.0 days.

Overall, 36 subjects (20.5%) who received cilta-cel as study treatment in Study MMY3002 experienced at least 1 treatment-emergent CAR T cell neurotoxicity event (ICANS and other neurotoxicities [including movement and neurocognitive TEAEs]). Five subjects (2.8%) experienced a Grade 3 or 4 event, there were no Grade 5 events. Eight subjects (4.5%) experienced ICANS; all ICANS were considered recovered or resolved after a median duration of 2 days.

2.3.5. Discussion on clinical pharmacology

PK

Overall, the bioanalytical methods are similar to those in the MAA procedure. These methods were adequately described and represent standard methods used in the field. The base population PK model development was based on a previously developed model to describe the PK characteristics of cilta-cel after IV administration. The E-R analyses was performed for both efficacy and safety endpoints.

No changes have been proposed to the approved posology, the dose is the same as for the initial indication: a single infusion of cilta-cel at the target dose of 0.75×10^6 CAR-positive viable T cells/kg.

In study MMY3002, PK measurements using both transgene and cellular levels were concordant, both being detectable in blood samples on Day 7 or Day 10 after administration. PK characteristics of cilta-cel manufactured with Bern LV and manufactured with CCHMC LV were considered comparable based on the CD3+CAR+ cell PK data. Still, subjects receiving Bern LV had a slightly higher mean exposure compared to subjects receiving CCHMC LV. CD3+CAR+ cells were detectable in the bone marrow of subjects receiving cilta-cel manufactured with either CCHMC LV or Bern LV, indicating a distribution of cilta-cel from systemic circulation to the bone marrow. Similar results have been observed in study MMY2003.

Among the 176 subjects, 37 subjects (21.0%) were observed to be positive for treatment-emergent anti-cilta-cel antibodies. The presence of anti-cilta-cel antibodies had no apparent impact on the efficacy endpoints or the safety outcomes. No difference in the incidence of antibodies to cilta-cel was observed between CCHMC LV and Bern LV from Study MMY3002. The presence of ADAs would only have a likely impact upon retreatment of patients with cilta-cel. Similar results have been observed in study MMY2003.

Based on the individual cilta-cel CAR transgene systemic levels in the current subject population, none of the strata of specific covariates (body weight, age, sex, race, renal function, hepatic function, type of myeloma, tumor burden, cytogenetic risk, serum sBCMA concentration, bone marrow percent plasma cells, tumor BCMA expression, ECOG score, ISS staging, time since multiple myeloma diagnosis, prior autologous transplantation) had a clinically meaningful difference in the cilta-cel CAR transgene C_{max} and $AUC_{0\text{-}28d}$. None of the estimated geometric mean ratio CIs excluded the null value (ie, geometric mean ratio of 1), except the C_{max} for non-white versus white subpopulations, the $AUC_{0\text{-}28d}$ for non-white versus white subpopulations and Asian versus non-Asian subpopulations. Individual outliers in the Asian subpopulation, which included only lower number of patients, may have influenced these findings.

No difference in PK parameters for the age groups could be identified. Cilta-cel is only indicated to treat adults. No investigations in children are required. Sex did not influence PK parameters. Body weight had no impact on PK parameters. Race/ethnicity does not influence PK characteristics. No hepatic accumulation/ elimination is expected, so dedicated studies were not carried out. Patients with inadequate hepatic/renal functions were excluded from the clinical trial. Mild hepatic/renal dysfunction had no negative impact on PK. These aspects are all indicated in the SmPC.

Median CAR transgene C_{max} and $AUC_{0\text{-}28d}$ were higher among subjects who received tocilizumab or corticosteroids for CRS or ICANS management.

No PK (C_{max} or $AUC_{0\text{-}28d}$) difference was found in subjects receiving either CCHMC LV or Bern LV.

PD

Expansion of CAR-positive T cells coincided with decreases of serum sBCMA. Concentrations of sBCMA in serum slowly decreased as a function of time, with mean serum BCMA concentrations reaching nadir levels at Day 56. At the time of data cut-off, sBCMA levels showed an increase from nadir (reversal) in some participants. In these participants, although sBCMA levels showed a trend of increase from nadir, levels were lower than baseline sBCMA (at pre-dose cilta-cel administration). This reversal of sBCMA

levels may be due to reproduction of normal BCMA+ plasma cells. The reversal of sBCMA levels seen in some participants may also have different causes than the reproduction of normal BCMA+ plasma cells, as suggested by the MAH. sBCMA elevations could also be induced by outgrowth of tumor cell clone(s) surviving after cilta-cel treatment, or the reproduction of normal BCMA+ plasma cells could be combined with the outgrowth of tumor cell clones. Indeed, as data provided by the MAH upon request indicate, in addition to reversal of sBCMA levels due to reproduction of normal BCMA+ plasma cells, reversal of sBCMA may also potentially be due to the relapse or a combination of relapse and reproduction of normal BCMA expressing plasma cells. This is based on a trend of patients without sBCMA reversal who had less progressive disease than patients with sBCMA reversal.

The declined sBCMA concentration-time profiles were comparable between subjects who received cilta-cel manufactured with CCHMC LV and subjects who received cilta-cel manufactured with Bern LV.

Cytokine expression increased post-infusion and peaked at Days 7 to 14. The serum levels of all cytokines generally returned to baseline levels within 2 to 3 months post-infusion. A positive association was observed between higher cytokine expression and the worst grade of CRS experienced by the subjects.

At the time of the clinical data cut-off, the MRD negativity rate (10^{-5}) was approximately 4-fold higher for subjects in the cilta-cel arm than for subjects in the PVd/DPd arm.

No positive samples for RCL had been detected in any subjects at any of the collection timepoints.

E-R relationships

The median PFS, OS, and DOR within the follow-up period were not reached for the subjects in Arm B who received cilta-cel as study treatment (n=176), while for the subjects in Arm A who received standard therapy (n=208), the median PFS was 11.8 months, median OS was 26.7 months, and median DOR was 16.6 months. Based on Kaplan-Meier curves for PFS, stratified by treatment arm and predicted CAR transgene C_{max} and $AUC_{0\text{-}28d}$, the subjects in Arm B who received cilta-cel as study treatment (n=176) had significantly longer PFS than the subjects in Arm A who received standard therapy (n=208). Within the subjects in Arm B who received cilta-cel as study treatment, no clear E-R relationship was observed for PFS. Similar results were observed for OS and DOR based on C_{max} and $AUC_{0\text{-}28d}$.

The ORR in subjects who received cilta-cel as study treatment in Arm B was 99.4% (175/176 subjects), while the ORR in Arm A was 68.3% (142/208 subjects). Within the subjects who received cilta-cel as study treatment in Arm B, no trends of E-R relationships were observed for ORR. CR or better, VGPR or better, and MRD negativity rate in subjects who received cilta-cel as study treatment in Arm B were also considerably higher than those in Arm A (CR or better: 86.4% versus 22.1%; VGPR or better: 96.0% versus 46.2%; MRD negativity rate: 71.6% versus 15.9%).[1] Within the subjects who received cilta-cel as study treatment in Arm B, the E-R relationship (both C_{max} and $AUC_{0\text{-}28d}$) showed slight trends of increased response for VGPR or better and of increased MRD negativity rate with increasing exposure. Both increases plateaued at quartile 2 and beyond, while the CIs of all quantiles were overlapped. For CR or better, no trends of E-R relationships were observed among quantiles of either C_{max} or $AUC_{0\text{-}28d}$.

The E-R relationships for efficacy based on the observed $CD3^{+}CAR^{+}$ cell exposure metrics ($C_{max,flow}$ and $AUC_{0\text{-}28d,flow}$) were concordant with those using the predicted CAR transgene exposure metrics.

The subjects with CRS had higher median CAR transgene systemic levels (C_{max} and $AUC_{0\text{-}28d}$) than those without CRS. However, due to the limited number of subjects with ≥ Grade 3 CRS (n=2), no conclusions could be drawn about the relationship between CAR transgene exposure and different grades of CRS. Although subjects with ICANS and other neurotoxicities had higher median CAR transgene systemic levels

[1] Because the 3 subjects in Arm A who did not receive standard therapy were excluded from the E-R analysis, the response rates in Arm A might be slightly different from those reported in the MMY3002 Clinical Study Report.

(C_{max} and $AUC_{0\text{-}28d}$) than those without ICANS and other neurotoxicities, the range of CAR transgene systemic exposure overlapped between subjects with and without ICANS and other neurotoxicities. Due to small sample sizes (no subjects with ≥ Grade 3 ICANS) and overlapped exposure range, no conclusions could be drawn about the relationship between CAR transgene exposure and ICANS and other neurotoxicities. In addition, no trends for differences in CAR transgene systemic exposure were observed between subjects with and without SPM.

The E-R relationships for safety based on the observed $CD3^+CAR^+$ cell exposure metrics ($C_{max,flow}$ and $AUC_{0\text{-}28d,flow}$) were concordant with those using the predicted CAR transgene exposure metrics. Together, the efficacy and safety data from Study MMY3002 and the absence of an apparent trend of the E R relationship between CAR transgene PK exposure and safety or efficacy suggest that cilta-cel at the dose of 0.75×10^6 CAR-positive viable T cells/kg (range 0.5×10^6 to 1×10^6 CAR positive viable T cells/kg) is efficacious and safe, providing therapeutic benefit in adult patients with r/r multiple myeloma who have received at least 1 prior line of therapy and are refractory to lenalidomide.

2.3.6. Conclusions on clinical pharmacology

The PK and PD data obtained in the MMY3002 study have been adequately described and the results are presented extensively throughout the documentation. These results correlate well to previous observations with cilta-cel and are in line with the current scientific knowledge for the pharmacology characteristics of CAR T cells.

Overall, the population PK and E-R analyses using data from Study MMY3002 (for population PK and E-R) and Study MMY2003 Cohorts A and B (for population PK) supported the selected target dose of 0.75×10^6 CAR-positive viable T cells/kg for the treatment of r/r multiple myeloma.

The CHMP endorse the CAT assessment regarding the conclusions on the Clinical pharmacology as described above.

2.4. Clinical efficacy

2.4.1. Main study

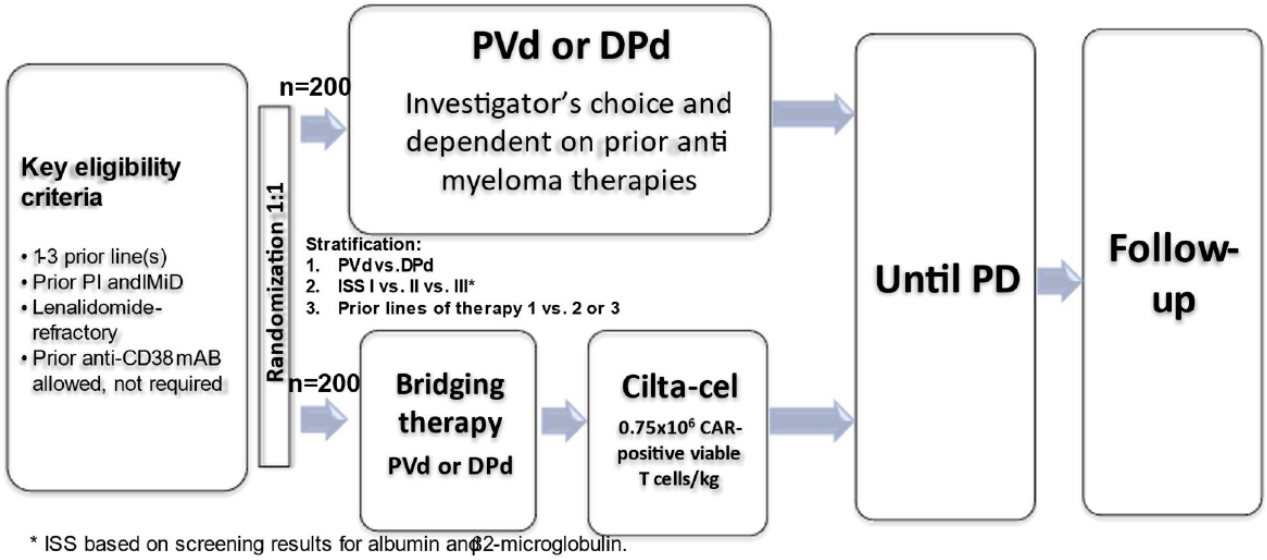
Title of Study

A Phase 3 Randomized Study Comparing JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA, versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Subjects with Relapsed and Lenalidomide-Refractory Multiple Myeloma.

Methods

Study design

Figure 11. Schematic Overview of the Study



Choice of Comparators for Study MMY3002

DPd is considered a clinically relevant comparator for Study MMY3002 based on its regulatory approval status and clinical use in the target population of patients with lenalidomide-refractory disease. The DPd regimen was evaluated in the Phase 3 APOLLO study (NCT03180736) which led to the approval of DPd in the European Union for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a PI and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a PI and have demonstrated disease progression on or after the last therapy. In the APOLLO study a total of 304 participants were randomized (151 DPd, 153 Pd) (Dimopoulos 2021). Participants had a median of 2 prior lines of therapy: 79.6% of participants were refractory to lenalidomide, 48.0% were refractory to a PI, and 42.4% were refractory to both. The median duration of treatment was 11.5 months with DPd. Results of the primary analysis demonstrated that the study met its primary endpoint of improved PFS, with a median PFS of 12.4 months, versus 6.9 months for participants treated with Pd. Among participants who were refractory to lenalidomide, a median PFS of 9.9 months (95% CI, 6.5–13.1) was reported for participants in the DPd arm and 6.5 months (95% CI, 4.7-8.9) in the Pd arm. Updated OS results showed that after a median (range) follow-up of 39.6 (0.1-56.9) months, median OS was longer in the DPd arm versus the Pd arm (median, 34.4 [95% CI, 23.7-40.3] months vs 23.7 [95% CI, 19.6-29.4] months, respectively; HR, 0.82; [95% CI, 0.61-1.11]; P=0.1989) (Dimopoulos 2022).

PVd was approved in the European Union for patients with relapsed or refractory multiple myeloma after one or more lines of therapy including lenalidomide, and it is a recommended treatment regimen in the NCCN treatment guidelines in the United States for patients whose multiple myeloma has relapsed after 2 or more therapies including an IMiD and a PI based on results from the Phase 3 OPTIMISMM study (Richardson 2019). Participants with relapsed or refractory multiple myeloma with 1 to 3 prior line(s) of therapy were randomized to either PVd (n=281) or bortezomib/dexamethasone (Vd) (n=278). Seventy percent of participants were lenalidomide-refractory. The ORR was 82% and 50% in the PVd and Vd cohorts, respectively. The median PFS in the entire population was 11.2 months in the PVd cohort versus 7.1 months in the Vd cohort. The median PFS was 9.5 months in lenalidomide-refractory participants in the PVd cohort (n=200) versus 5.6 months in the Vd cohort (n=191). Lenalidomide-refractory participants with only 1 prior line of therapy had a median PFS of 17.8 months on the PVd regimen versus

9.5 months on the Vd regimen. Based on these results, PVd was chosen as a comparator for Study MMY3002.

Study participants

Study MMY3002 main inclusion criteria:

- Have documented diagnosis of MM as defined by the criteria below:
    - Multiple myeloma diagnosis according to the IMWG diagnostic criteria.
    - Measurable disease at screening as defined by any of the following:
        - Serum monoclonal paraprotein (M-protein) level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or
        - Light chain MM without measurable M-protein in the serum or the urine: Serum free light chain ≥10 mg/dL and abnormal serum free light chain ratio.

Note: Local laboratory assessments may be used to establish measurable disease at Screening, with local laboratory result ≥125% of requirements. However, subjects must have laboratory studies for diseases assessment received by central laboratory prior to randomization. If central and local laboratory studies are performed on the same day, only the central laboratory results will be considered.

- Have received 1 to 3 prior lines of therapy including a PI and IMiD. Subject must have undergone at least 1 complete cycle of treatment for each line of therapy, unless PD was the best response to the line of therapy.

Note: induction with or without hematopoietic stem cell transplant, consolidation and maintenance therapy is considered a single line of therapy.

- Have documented evidence of PD by IMWG criteria based on investigator's determination on or within 6 months of their last regimen.
- Subjects with only 1 prior line of therapy must have progressed within 36 months of a stem cell transplant, or if not transplanted, then within 42 months of starting initial therapy.
- Be refractory to lenalidomide per IMWG consensus guidelines (Rajkumar 2011) (failure to achieve minimal response or progression on or within 60 days of completing lenalidomide therapy). Progression on or within 60 days of the last dose of lenalidomide given as maintenance will meet this criterion. For subjects with more than 1 prior line of therapy, there is no requirement to be lenalidomide refractory to the most recent line of prior therapy. However, subjects must be refractory to lenalidomide in at least one prior line.

Study MMY3002 main exclusion criteria:

- Prior treatment with CAR-T therapy directed at any target.
- Any previous therapy that is targeted to BCMA.
- Received either of the following:
    - An allogenic stem cell transplant within 6 months before apheresis. Subjects who received an allogeneic transplant must have stopped all immunosuppressive medications for 6 weeks without signs of graft-versus-host disease. Subjects with active graft-versus-host disease are excluded.
    - An autologous stem cell transplantation ≤12 weeks before apheresis.

- patients with known active or prior history of central nervous system involvement, clinical signs of meningeal involvement of multiple myeloma, a history of Parkinson's disease or other neurodegenerative disorder.

Treatments

Arm A

The median duration of study treatment for Arm A was 4.8 months (range: 0.5 to 19.9 months) for the 26 participants who received PVd and 11.8 months (range: 0.5 to 25.2 months) for the 182 participants who received DPd. The median number of treatment cycles started in Arm A was 12.0 (range: 1 to 28 cycles). Thirteen participants (6.3%) started 1 or 2 cycles of treatment, 58 participants (27.9%) started 3 to 6 cycles of treatment, and 137 participants (65.9%) started 7 or more cycles of treatment.

Table 6. Study Treatment Schedule for Standard Therapy (Arm A)

PVd[a] (21-day treatment cycles)
Cycles 1 to 8: Pomalidomide PO 4 mg on Days 1 to 14 Bortezomib SC 1.3 mg/m^2 on Days 1, 4, 8 and 11 Dexamethasone PO 20 mg/day on Days 1, 2, 4, 5, 8, 9, 11 and 12
Cycle 9 onwards: Pomalidomide PO 4 mg on Days 1-14 Bortezomib SC 1.3 mg/m^2 on Days 1 and 8 Dexamethasone PO 20 mg on Days 1, 2, 8, and 9
DPd[b] (28-day treatment cycles)
Cycles 1 and 2: Daratumumab SC 1800 mg (co-formulated with rHuPH20) weekly on Days 1, 8, 15, and 22 Pomalidomide PO 4 mg/day on Days 1 to 21 Dexamethasone PO/IV: 40 mg weekly on Days 1, 8, 15, and 22 or may be split with 20 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23. On days of daratumumab administration, dexamethasone must be given 1-3 hours prior to daratumumab.
Cycles 3 to 6: Daratumumab SC 1800 mg (co-formulated with rHuPH20) every 2 weeks on Days 1 and 15 Pomalidomide PO 4 mg/day on Days 1 to 21 Dexamethasone PO/IV: 40 mg weekly (may be split over 2 days). On days of daratumumab administration, dexamethasone must be given 1-3 hours prior to daratumumab.
Cycle 7 onwards: Daratumumab SC 1800 mg (co-formulated with rHuPH20) every 4 weeks on Day 1 Pomalidomide PO 4 mg/day on Days 1 to 21 Dexamethasone PO/IV: 40 mg weekly (may be split over 2 days). On days of daratumumab administration, dexamethasone must be given 1-3 hours prior to daratumumab.

DPd=daratumumab, pomalidomide, and dexamethasone; IV=intravenous; PO=oral; PVd=pomalidomide, bortezomib and dexamethasone; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous

[a] Participants >75 years of age who are receiving Cycles 1 to 8 of PVd should receive dexamethasone PO 10 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12. Participants >75 years of age who are receiving Cycle 9 onwards of PVd should receive dexamethasone PO 10 mg on Days 1, 2, 8, and 9.

[b] Participants >75 years of age who are receiving Cycle 1 of DPd should receive the entire dexamethasone PO/IV 20 mg weekly dose on Days 1, 8, 15, and 22. Starting with Cycle 2, dexamethasone may be split over 2 days: Day 1, 2, 8, 9, 15, 16, 22 and 23.

Cycle delays were reported for 138 participants (66.3%) in Arm A. The most common reason for cycle delay was AE for 115 participants (55.3%), including COVID-19 related AE in 18 participants (8.7%). Treatment modifications implemented for individual components of PVd/DPd in Arm A are summarized below.

Dexamethasone Treatment Modifications:

Treatment modifications for dexamethasone included dose delay, dose skip, and dose reduction. Dexamethasone dose delay was reported for 11 participants (5.3%), dose skip was reported for 139 participants (66.8%), and dose reduction was reported for 86 participants (41.3%).

Bortezomib Treatment Modifications:

Treatment modifications for bortezomib included dose delay, dose skip, dose reduction, and schedule change. Bortezomib dose delay was reported for 2 participants (7.7%), dose skip was reported for 20 participants (76.9%), and dose reduction was reported for 4 participants (15.4%). No bortezomib schedule changes were reported for participants in Arm A.

Daratumumab Treatment Modifications:

Treatment modifications for daratumumab included dose delay and dose skip. Daratumumab dose reduction was not allowed per protocol. Dose delay was reported for 20 participants (11.0%), and dose skip was reported for 117 participants (64.3%).

Pomalidomide Treatment Modifications:

Treatment modifications for pomalidomide included dose delay, dose skip, and dose reduction. No pomalidomide dose delay was reported for Arm A participants. Dose skip was reported for 151 participants (72.6%) and dose reduction was reported for 118 participants (56.7%).

Arm B

Table 7. Study Treatment Schedule for Cilta-cel (Arm B)

Drug Dose	Drug Schedule[a]
Either PVd OR DPd as bridging therapy:	
PVd	
Pomalidomide PO 4 mg/day	On Bridging Days 1-14
Bortezomib SC 1.3 mg/m^2	On Bridging Days 1, 4, 8, and 11
Dexamethasone PO 20 mg/day[b]	On Bridging Days 1, 2, 4, 5, 8, 9, 11, and 12
DPd	
Daratumumab SC 1800 mg (co-formulated with rHuPH20) weekly	On Bridging Days 1, 8, 15, and 22
Pomalidomide PO 4 mg/day	On Bridging Days 1 to 21
Dexamethasone PO or IV 40 mg weekly[c]	On Bridging Days 1, 8, 15 and 22 or may be split with 20 mg on Days 1, 2, 8, 9, 15, 16, 22 and 23
Followed by:	
Cyclophosphamide IV 300mg/m^2	Daily for 3 days on CAR-T Day -5, -4, -3 prior to cilta-cel infusion
Fludarabine[d] IV 30mg/m^2	Daily for 3 days on CAR-T Day -5, -4, -3 prior to cilta-cel infusion
Cilta-cel infusion 0.75 x 10^6 CAR-positive viable T cells/kg	Administered 5 to 7 days after the start of conditioning regimen

DPd=daratumumab, pomalidomide, and dexamethasone; IV=intravenous; PO=oral; PVd=pomalidomide, bortezomib, and dexamethasone; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous

[a] 1 cycle of PVd or DPd consists of 21 and 28 days, respectively. A second cycle of PVd or DPd bridging therapy may be administered if clinically warranted depending on when cilta-cel will be available. If more than two cycles of bridging therapy are indicated, daratumumab will be administered on Days 1 and 15.

[b] Participants >75 years of age receiving PVd should receive dexamethasone PO 10 mg on Bridging Cycle Days 1, 2, 4, 5, 8, 9, 11, and 12.

[c] Participants >75 years of age who are receiving DPd should receive the entire dexamethasone PO/IV 20 mg weekly dose on Bridging Days 1, 8, 15, and 22 for Cycle 1. If additional cycles are indicated, dexamethasone may be split over 2 days: Day 1, 2, 8, 9, 15, 16, 22 and 23.

[d] The dose of fludarabine should be reduced to 24 mg/m^2 for participants with an eGFR of 30 to 70 mL/min/1.73 m^2

All 208 participants (100.0%) randomized to Arm B received bridging therapy (PVd or DPd). Of these, 176 participants (85.6%) received the conditioning regimen of cyclophosphamide and fludarabine infusion followed by cilta-cel infusion as study treatment.

All 208 participants randomized to Arm B completed apheresis. One hundred and ninety-three participants (92.8%) underwent a single apheresis attempt, and 15 participants (7.2%) underwent 2 apheresis attempts. No participant required more than 2 apheresis attempts.

All 208 participants randomized to Arm B started at least 1 cycle of bridging therapy as required per protocol. Additional cycles of bridging therapy could be given based on a participant's clinical status and timing of availability of cilta-cel. The median number of bridging cycles started in Arm B was 2.0 (range: 1 to 6 cycles). One hundred and sixty-eight participants (80.8%) started 1-2 cycles of bridging therapy and 40 participants (19.2%) started 3-6 cycles of bridging therapy (3 cycles: 34 participants [16.3%], 4 cycles: 5 participants [2.4%], 6 cycles: 1 participant [0.5%]).

There were generally lower rates of modifications implemented for Arm B as compared with Arm A, consistent with the fact that fewer PVd/DPd treatment cycles were administered for participants in Arm B (median 2.0 cycles) relative to participants in Arm A (median 12.0 cycles).

Dexamethasone Treatment Modifications:

Treatment modifications for dexamethasone included dose delay, dose skip, and dose reduction. Dexamethasone dose delay was reported for 7 participants (3.4%), dose skip was reported for 97 participants (46.6%), and dose reduction was reported for 22 participants (10.6%).

Bortezomib Treatment Modifications:

Treatment modifications for bortezomib included dose delay, dose skip, dose reduction, and schedule change. Bortezomib dose delay was reported for 1 participant (3.8%), dose skip was reported for 14 participants (53.8%), and dose reduction was reported for 2 participants (7.7%). No bortezomib schedule changes were reported for participants in Arm B.

Daratumumab Treatment Modifications:

Treatment modifications for daratumumab included dose delay and dose skip. Daratumumab dose reduction was not allowed per protocol. Daratumumab dose delay was reported for 11 participants (6.0%), and dose skip was reported for 105 participants (57.7%).

Pomalidomide Treatment Modifications:

Treatment modifications for pomalidomide included dose delay, dose skip, and dose reduction. Pomalidomide dose delay was reported for 2 participants (1.0%), dose skip was reported for 106 participants (51.2%), and dose reduction was reported for 73 participants (35.3%).

Among the 208 participants in the ITT analysis set for Arm B, 154 participants (74.0%) had a decrease in tumour burden (defined as change in serum M-protein, urine M-protein, or difference between involved and uninvolved free light chain [dFLC]) between baseline and administration of the conditioning regimen. Among those participants who experienced a tumour burden decrease, 133 participants (63.9%) experienced a decrease of ≥50%. Eighteen participants (8.7%) who received bridging therapy experienced an increase in tumour burden. Twenty-three participants (11.1%) who received bridging therapy did not experience a change in tumour burden as a result of bridging therapy.

Arm B participants were to receive a conditioning regimen of IV cyclophosphamide 300 mg/m^2 and IV fludarabine 30 mg/m^2 daily for 3 days on CAR-T Day -5, -4, -3 prior to cilta-cel infusion. The median total dose of cyclophosphamide infusion was 891.6 mg/m^2 (range: 705 to 1490 mg/m^2). The median total dose of fludarabine infusion was 88.7 mg/m^2 (range: 58 to 96 mg/m^2).

Among the 176 Arm B participants who received cilta-cel as study treatment, cilta-cel infusion was interrupted for 2 participants (1.1%) due to AE. Cilta-cel infusion was delayed for 9 participants (5.1%), due to AE for 7 participants (4.0%) and due to other reason for 2 participants (1.1%).

Any cilta-cel batches that did not meet release specifications were released through the Exceptional Release process. Among Arm B participants who received cilta-cel as study treatment, 6 participants received infusions of cilta-cel product that did not meet all pre-specified release criteria. Release criteria not met were:

- 'CAR+ viable T-cells' below the specified range (release criterion: 0.5 - 1.0 x 10^6 CAR+ viable T cells/kg) for 2 participants;
- 'in vitro tumor killing' below the specified range (release criterion: ≥20%) for 1 participant;
- 'replication competent lentivirus' (release criterion: undetectable, or decrease of detected VSV-G and VSV-G is ≤9.47 x 10^5 copies/200 ng gDNA in post-harvest sample) for 1 participant;
- 'endotoxin' (release criterion: ≤1.95 EU/mL [1DP BAG]) for 1 participant; and
- 'transduction efficiency' above the specified range (release criterion: 0.05 vector copies/cell to 5.00 vector copies/cell) for 1 participant.

Cilta-cel drug products were manufactured at Janssen Pharmaceuticals Inc. (Raritan, New Jersey, US) between 06 August 2020 and 18 December 2021. To meet demand for LV, Janssen added a suspension culture LV manufacturing process at the Janssen Vaccines, Bern, Switzerland facility during the conduct

of Study MMY3002. The LV produced at this facility is referred to as Bern LV; LV produced at CCHMC using an adherent culture LV manufacturing process is referred to as CCHMC LV. Of the 176 Arm B participants who received cilta-cel as study treatment, 90 participants received cilta-cel manufactured with CCHMC LV and 86 participants received cilta-cel manufactured with Bern LV.

Objectives and endpoints

Objectives	Endpoints
Primary	
○ To compare the efficacy of cilta-cel with standard therapy, either PVd or DPd	○ PFS
Secondary	
○ To further compare the efficacy of cilta-cel with standard therapy, either PVd or DPd	○ Rate of CR/sCR ○ Overall MRD negative rate ○ Rate of MRD negativity in participants with CR/sCR at 12 months ±3 months ○ Rate of sustained MRD negative status ○ OS ○ ORR ○ PFS on next line of therapy (PFS2)
○ To assess the safety profile of cilta-cel	○ Incidence and severity of adverse events
○ To characterize the pharmacokinetics and pharmacodynamics of cilta-cel	○ Pharmacokinetic and pharmacodynamic markers including but not limited, to systemic cytokine concentrations, and markers of CAR-T cells, T cell expansion (proliferation), and persistence via monitoring CAR-T positive cell counts and CAR transgene level.
○ To assess the immunogenicity of cilta-cel	○ Presence of anti-cilta-cel antibodies
○ To evaluate the impact of cilta-cel treatment on the health-related quality of life of participants compared with standard therapy, either PVd or DPd	○ Time to worsening of symptoms using the MySIm-Q total symptom score ○ Change from baseline in health-related quality of life (HRQoL) subscale scores from the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q), EuroQol Five Dimension Questionnaire (EQ-5D-5L), Patient Global Impression of Severity (PGIS), and the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) items.
Exploratory	
○ To further characterize the pharmacodynamics of cilta-cel	○ Depletion of BCMA-expressing cells and circulating soluble BCMA levels
○ To determine whether replication competent lentivirus is present in participants who receive cilta-cel	○ Screen for presence of replication competent lentivirus
○ To characterize the impact of cilta-cel CAR-T process on medical resource utilization compared with standard therapy, either PVd or DPd	○ Number of participants with type and length of inpatient stay and overall medical encounters
○ To characterize potential early clinical, translational, and imaging markers for neurotoxicity (predictive markers)	○ Qualitative changes in handwriting assessment ○ T_{max}, C_{max}, and phenotypic analysis of CAR-T cells ○ Neuroimaging (CT/MRI/PET)

The primary efficacy endpoint of the study was PFS, defined as the time from the date of randomization to the date of first documented disease progression, as defined in the IMWG criteria, or death due to any cause, whichever occurs first. For participants who have not progressed and are alive, data was censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.

Sample size

419 subjects were randomised (211 SOC : 208 cilta-cel).

Randomisation

Central randomization was implemented in this study. Subjects were assigned randomly to 1 of the 2 arms based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization was balanced by using randomly permuted blocks.

Four hundred and nineteen participants were randomized in a 1:1 ratio to Arm A (standard therapy with PVd or DPd) or Arm B (cilta-cel) according to the planned stratification factors. Stratification factors included ISS at screening (I vs. II vs. III), investigator's choice of PVd vs. DPd, and number of prior lines of therapy (1 vs. 2 or 3).

Arm A (PVd or DPd)

Prior to screening, the investigator determined if the participant would be treated with investigator's choice of standard therapy, PVd or DPd, based on the participant's prior exposure to anti-myeloma therapies. After meeting eligibility criteria, participants randomized to Arm A were to start either PVd or DPd within 7 days after randomization.

Participants randomized to Arm A continued to receive PVd or DPd until confirmed progressive disease, death, intolerable toxicity, withdrawal of consent, or end of the study.

PVd was selected by the investigator for 28 participants (13.3%) and DPd was selected by the investigator for 183 participants (86.7%).

Arm B (Cilta-cel)

Eligible participants randomized to Arm B received a sequence of apheresis, performed 3 to 6 days after randomization; at least 1 cycle of bridging therapy with either PVd or DPd (determined by the investigator prior to screening and based on the participant's prior anti myeloma therapy), initiated no more than 7 days after randomization; a conditioning regimen of cyclophosphamide and fludarabine, administered daily for 3 days; and cilta-cel infusion administered with the target dose of 0.75×10^6 CAR-positive viable T cells/kg 5 to 7 days after the start of the conditioning regimen.

As bridging therapy, PVd was selected by the investigator for 26 participants (12.5%) and DPd was selected by the investigator for 182 participants (87.5%).

Blinding (masking)

Blinding was not applicable as this was an open-label study.

Statistical methods

The primary hypothesis was that cilta-cel will significantly improve PFS compared with standard therapy (PVd or DPd) in subjects who have previously received 1 to 3 prior line(s) of therapy, that included a PI and an IMiD, and who are refractory to lenalidomide. The sample size calculation was performed based on the assumption that cilta-cel can reduce the risk of progressive disease or death by 35%, ie, HR (cilta-cel

vs. standard therapy) of 0.65, which translated to a median PFS of 20 months for Arm B, assuming the median PFS for Arm A was 13 months. Approximately 400 participants (200/treatment arm) were to be randomized to observe a total of 250 PFS events to achieve approximately 90% power to detect this HR with a log-rank test (2-sided alpha of 0.05). The sample size calculation took into consideration an estimated annual dropout rate of 5% and 1 interim analysis for PFS, to be performed when approximately 188 PFS events, which is 75% of the total planned PFS events, were observed.

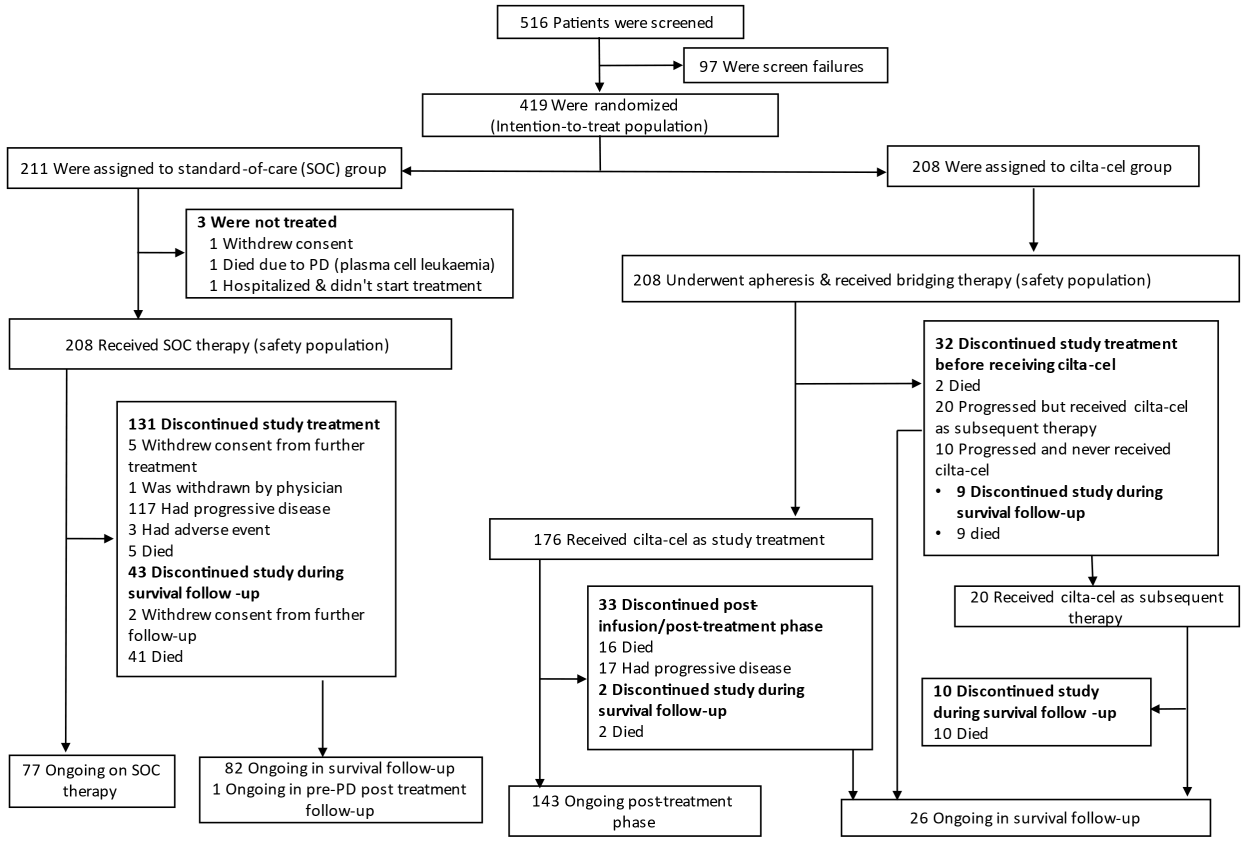
Analysis of PFS was based on the ITT analysis set. The Kaplan-Meier method was used to estimate the distribution of overall PFS for each treatment arm. Because participants in both arms were expected to receive approximately 2 cycles of the same therapy immediately after randomization, only PFS events that occurred more than 8 weeks post-randomization were included in the treatment comparison of overall PFS distribution between the 2 arms. The p-value from a stratified constant piecewise weighted (CPW) log-rank test is reported. HR (Arm B vs. Arm A) and its 95% CI were estimated based on a stratified Cox' s regression model, similarly, including only PFS events that occurred more than 8 weeks post-randomization, with treatment as the sole explanatory variable. Stratification factors used in the stratified analyses included investigator' s choice of PVd or DPd, ISS staging (I, II, III), and number of prior lines of therapy (1 vs. 2 or 3). If the primary endpoint PFS was statistically significant, the major secondary endpoints were sequentially tested for superiority utilizing a hierarchical procedure to control familywise Type I error rate at a 2-sided significance level of 0.05 (overall), in the following order: rate of CR/sCR, ORR, overall MRD negativity rate, OS, and time to worsening of symptoms in the MySIm-Q total symptom score. Comparison between the 2 treatment arms for rate of CR/sCR, ORR, overall MRD negativity rate, and other binary endpoints was conducted using the stratified CMH test. The stratified CMH estimate of odds ratio and its 95% CI and p-value for the difference in rates between treatment arms are reported.

An unweighted stratified log-rank test was used for the comparison of OS distribution between the 2 treatment arms and the Kaplan-Meier method was used to estimate OS distribution for each treatment arm. The treatment effect (HR) and its 2-sided 95% CI were estimated using a stratified Cox' s regression model with treatment as the sole explanatory variable. For time to worsening of symptoms in the MySIm-Q total symptom score, analysis methods were similar to those for OS. Time to worsening was defined as a worsening by the MID compared to baseline without subsequent improvement to a score above this level.

Results

Participant flow

Figure 12. Participant Study Disposition as of the Clinical Cutoff Date (01 November 2022); Study 68284528MMY3002



Recruitment

This study was conducted at 81 centres that enrolled participants in Europe (Belgium, Denmark, France, Germany, Greece, Italy, Netherlands, Poland, Spain, Sweden, and United Kingdom), North America (United States), and other regions (Australia, Israel, Japan, and Republic of Korea).

The first participant in the study was screened on 30 June 2020. The date of the last cilta-cel infusion was 15 March 2022. As of the 1 November 2022 cutoff date, the median duration of follow-up was 15.9 months. The study is ongoing.

Conduct of the study

Changes in the conduct of the study that were implemented by protocol amendment are described in the protocol.

Table 8. Overall Reasons for MMY3002 Global Protocol Amendments

Amendment # Date	Overall Reasons	Number of Participants Enrolled Under Each Amendment
Amendment 1 20 March 2020	The reason for the amendment was to add other neurotoxicities as a safety risk and implement additional monitoring and risk minimization measures for cilta-cel.	375
Amendment 2 02 July 2021	Reasons for the amendment were to provide guidance on study conduct during the COVID-19 pandemic (via a COVID-19-specific appendix); to enable increased patient access by allowing patients with a serum M-spike of 0.5 g/dL or greater to meet criteria for measurable disease; and to revise safety reporting requirements to allow extended data collection.	24
Amendment 3 14 June 2022	The reason for the amendment was to inform investigators that patients receiving cilta-cel are possibly at a higher risk of severe/fatal outcomes from COVID-19 infection compared with patients who are receiving standard of care therapy, and to provide additional guidance for prevention and mitigation. The reporting period for AEs and concomitant medications for the prevention or treatment of COVID-19 was extended. Additional guidance for HLH and additional clarifications were also incorporated.	0
Amendment 4 18 August 2022	The reason for the amendment was to change the number of PFS events required to trigger the interim analysis. Per health authority request, the interim analysis would take place after approximately 75% of the total PFS events had been observed.	0

Baseline data

Table 9. Summary of Demographics and Baseline Characteristics; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B	Total
Analysis set: intent-to-treat	211	208	419
Age, years			
N	211	208	419
Category, n (%)			
• < 65	131 (62.1%)	126 (60.6%)	257 (61.3%)
• 65 - 75	76 (36.0%)	78 (37.5%)	154 (36.8%)
• > 75	4 (1.9%)	4 (1.9%)	8 (1.9%)
• Mean (SD)	60.4 (9.09)	59.7 (10.09)	60.1 (9.60)
• Median	61.0	61.5	61.0
• Range	(35; 80)	(27; 78)	(27; 80)
• Interquartile range	(53.0; 68.0)	(52.0; 68.0)	(53.0; 68.0)
Sex			
N	211	208	419
• Female	87 (41.2%)	92 (44.2%)	179 (42.7%)
• Male	124 (58.8%)	116 (55.8%)	240 (57.3%)

Table 9. Summary of Demographics and Baseline Characteristics; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B	Total
Race			
N	211	208	419
• American Indian or Alaska Native	1 (0.5%)	1 (0.5%)	2 (0.5%)
• Asian	20 (9.5%)	16 (7.7%)	36 (8.6%)
• Black or African American	7 (3.3%)	6 (2.9%)	13 (3.1%)
• White	157 (74.4%)	157 (75.5%)	314 (74.9%)
• Not reported	26 (12.3%)	28 (13.5%)	54 (12.9%)
Ethnicity			
N	211	208	419
• Hispanic or Latino	10 (4.7%)	18 (8.7%)	28 (6.7%)
• Not Hispanic or Latino	165 (78.2%)	152 (73.1%)	317 (75.7%)
• Not reported	36 (17.1%)	38 (18.3%)	74 (17.7%)
Baseline ECOG score[a]			
N	211	208	419
• 0	121 (57.3%)	114 (54.8%)	235 (56.1%)
• 1	89 (42.2%)	93 (44.7%)	182 (43.4%)
• 2	1 (0.5%)	1 (0.5%)	2 (0.5%)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: ECOG=Eastern Cooperative Oncology Group
[a] The latest non-missing ECOG score on or prior to Apheresis/Cycle 1 Day 1 (C1D1) is used. All patients met the inclusion criteria of ECOG score of 0 or 1 prior to randomization.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.
Note: Baseline measurement is defined as the last non-missing measurement prior to the initiation of study treatment.

Table 10. Summary of Baseline Disease Characteristics; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B	Total
Analysis set: intent-to-treat	211	208	419
Type of myeloma by immunofixation, n (%)			
N	211	208	419
• IgG	108 (51.2%)	113 (54.3%)	221 (52.7%)

Table 10. Summary of Baseline Disease Characteristics; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B	Total
• IgA	37 (17.5%)	37 (17.8%)	74 (17.7%)
• IgM	1 (0.5%)	0	1 (0.2%)
• IgD	2 (0.9%)	2 (1.0%)	4 (1.0%)
• IgE	0	0	0
• Light chain	56 (26.5%)	47 (22.6%)	103 (24.6%)
• Kappa	27 (12.8%)	25 (12.0%)	52 (12.4%)
• Lambda	29 (13.7%)	22 (10.6%)	51 (12.2%)
• Biclonal	2 (0.9%)	1 (0.5%)	3 (0.7%)
• Negative immunofixation	5 (2.4%)	8 (3.8%)	13 (3.1%)
Type of measurable disease, n (%)			
N	211	208	419
• Serum only	111 (52.6%)	107 (51.4%)	218 (52.0%)
• Serum and urine	23 (10.9%)	24 (11.5%)	47 (11.2%)
• Urine only	28 (13.3%)	23 (11.1%)	51 (12.2%)
• Serum FLC only	49 (23.2%)	52 (25.0%)	101 (24.1%)
• Not evaluable	0	2 (1.0%)	2 (0.5%)
ISS staging at study baseline [a], n (%)			
N	211	208	419
• I	132 (62.6%)	136 (65.4%)	268 (64.0%)
• II	65 (30.8%)	60 (28.8%)	125 (29.8%)
• III	14 (6.6%)	12 (5.8%)	26 (6.2%)
Time from initial MM diagnosis to randomization, years			
N	211	208	419
• Mean (SD)	4.27 (3.195)	3.94 (2.862)	4.11 (3.035)
• Median	3.44	3.02	3.22
• Range	(0.4; 22.1)	(0.3; 18.1)	(0.3; 22.1)
• Interquartile range	(2.10; 5.69)	(1.98; 4.99)	(2.04; 5.38)
Cytogenetic risk [b]			
N	210	207	417

Table 10. Summary of Baseline Disease Characteristics; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B	Total
• Standard risk	70 (33.3%)	69 (33.3%)	139 (33.3%)
• High risk (any of the 4 markers abnormal)	132 (62.9%)	123 (59.4%)	255 (61.2%)
• del17p	43 (20.5%)	49 (23.7%)	92 (22.1%)
• t(4;14)	30 (14.3%)	30 (14.5%)	60 (14.4%)
• t(14;16)	7 (3.3%)	3 (1.4%)	10 (2.4%)
• gain/amp(1q)	107 (51.0%)	89 (43.0%)	196 (47.0%)
• At least 2 of the 4 markers abnormal	49 (23.3%)	43 (20.8%)	92 (22.1%)
• Excluding gain/amp(1q)	69 (32.9%)	73 (35.3%)	142 (34.1%)
• Unknown	8 (3.8%)	15 (7.2%)	23 (5.5%)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: FLC = free light chain; ISS = International Staging System; MM = multiple myeloma.
[a] ISS staging is derived based on serum β-2 microglobulin and albumin.
[b] Cytogenetic risk abnormalities are based on central fluorescence in situ hybridization (FISH) testing, or local FISH and karyotype testing if central FISH not available
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.
Note: The measurable disease for 2 subjects were evaluable at screening, but not at baseline.

Prior therapies

To be eligible for this study, participants must have received 1 to 3 prior lines of therapy including a PI and an IMiD. Additionally, participants must have been refractory to lenalidomide per IMWG consensus guidelines.

Table 11. Summary of Prior Therapies for Multiple Myeloma; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B	Total
Analysis set: intent-to-treat	211	208	419
Number of lines of prior therapies for multiple myeloma			
N	211	208	419
Category, n (%)			
○ 1	68 (32.2%)	68 (32.7%)	136 (32.5%)
○ 2	87 (41.2%)	83 (39.9%)	170 (40.6%)
○ 3	56 (26.5%)	57 (27.4%)	113 (27.0%)
○ 2-3	143 (67.8%)	140 (67.3%)	283 (67.5%)

Table 11. Summary of Prior Therapies for Multiple Myeloma; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B	Total
○ Mean (SD)	1.9 (0.77)	1.9 (0.78)	1.9 (0.77)
○ Median	2.0	2.0	2.0
○ Range	(1; 3)	(1; 3)	(1; 3)
Prior transplantation	185 (87.7%)	171 (82.2%)	356 (85.0%)
Autologous	185 (87.7%)	171 (82.2%)	356 (85.0%)
○ 1 time	173 (82.0%)	157 (75.5%)	330 (78.8%)
○ 2 times	12 (5.7%)	14 (6.7%)	26 (6.2%)
Allogeneic	1 (0.5%)	3 (1.4%)	4 (1.0%)
Prior radiotherapy	54 (25.6%)	59 (28.4%)	113 (27.0%)
Prior PI	211 (100.0%)	208 (100.0%)	419 (100.0%)
○ Bortezomib	205 (97.2%)	203 (97.6%)	408 (97.4%)
○ Carfilzomib	66 (31.3%)	77 (37.0%)	143 (34.1%)
○ Ixazomib	21 (10.0%)	21 (10.1%)	42 (10.0%)
Prior IMiD	211 (100.0%)	208 (100.0%)	419 (100.0%)
○ Lenalidomide	211 (100.0%)	208 (100.0%)	419 (100.0%)
○ Pomalidomide	10 (4.7%)	8 (3.8%)	18 (4.3%)
○ Thalidomide	82 (38.9%)	100 (48.1%)	182 (43.4%)
Prior PI and Prior IMiD	211 (100.0%)	208 (100.0%)	419 (100.0%)
Prior corticosteroids	211 (100.0%)	206 (99.0%)	417 (99.5%)
○ Dexamethasone	211 (100.0%)	205 (98.6%)	416 (99.3%)
○ Prednisone	9 (4.3%)	12 (5.8%)	21 (5.0%)
Prior alkylating agents	194 (91.9%)	185 (88.9%)	379 (90.5%)
Prior anthracyclines	13 (6.2%)	22 (10.6%)	35 (8.4%)
Prior anti-CD38 antibodies	55 (26.1%)	53 (25.5%)	108 (25.8%)
○ Daratumumab	54 (25.6%)	51 (24.5%)	105 (25.1%)
○ Isatuximab	2 (0.9%)	2 (1.0%)	4 (1.0%)
Prior elotuzumab	6 (2.8%)	1 (0.5%)	7 (1.7%)
Prior PI+IMiD+ALKY	194 (91.9%)	185 (88.9%)	379 (90.5%)
Prior PI+IMiD+anti-CD38 antibodies	55 (26.1%)	53 (25.5%)	108 (25.8%)

Table 11. Summary of Prior Therapies for Multiple Myeloma; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B	Total
Prior PI+IMiD+anti-CD38 antibodies+ALKY	50 (23.7%)	46 (22.1%)	96 (22.9%)
Prior penta-exposed (at least 2 PIs + at least 2 IMiDs + 1 anti-CD38 antibodies)	10 (4.7%)	14 (6.7%)	24 (5.7%)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: ALKY=akylating agent; IMiD = Immunomodulatory agent; PI = proteasome inhibitor.
Note: Percentages calculated with the number of subjects in each treatment group as denominator.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

Table 12. Summary of Refractory Status to Prior Multiple Myeloma Therapy; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B	Total
Analysis set: intent-to-treat	211	208	419
Refractory at any point to prior therapy	211 (100.0%)	208 (100.0%)	419 (100.0%)
Refractory Status			
○ Any PI	96 (45.5%)	103 (49.5%)	199 (47.5%)
○ Any IMiD	211 (100.0%)	208 (100.0%)	419 (100.0%)
○ Any anti-CD38 antibody	46 (21.8%)	50 (24.0%)	96 (22.9%)
○ PI+IMiD	96 (45.5%)	103 (49.5%)	199 (47.5%)
○ PI+anti-CD38 antibody	33 (15.6%)	30 (14.4%)	63 (15.0%)
○ IMiD+anti-CD38 antibody	46 (21.8%)	50 (24.0%)	96 (22.9%)
○ PI+IMiD+anti-CD38 antibody	33 (15.6%)	30 (14.4%)	63 (15.0%)
○ At least 2 PIs + at least 2 IMiDs + 1 anti-CD38 antibody	1 (0.5%)	2 (1.0%)	3 (0.7%)
Refractory to last line of prior therapy	208 (98.6%)	205 (98.6%)	413 (98.6%)
Refractory to			
○ Bortezomib	48 (22.7%)	55 (26.4%)	103 (24.6%)
○ Carfilzomib	45 (21.3%)	51 (24.5%)	96 (22.9%)
○ Ixazomib	17 (8.1%)	15 (7.2%)	32 (7.6%)
○ Lenalidomide	211 (100.0%)	208 (100.0%)	419 (100.0%)

Table 12. Summary of Refractory Status to Prior Multiple Myeloma Therapy; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B	Total
○ Pomalidomide	9 (4.3%)	8 (3.8%)	17 (4.1%)
○ Thalidomide	11 (5.2%)	17 (8.2%)	28 (6.7%)
○ Daratumumab	45 (21.3%)	48 (23.1%)	93 (22.2%)
○ Isatuximab	2 (0.9%)	2 (1.0%)	4 (1.0%)
○ Elotuzumab	6 (2.8%)	1 (0.5%)	7 (1.7%)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: IMiD = Immunomodulatory agent; PI = proteasome inhibitor.
Note: Refractory to each medication refers to refractory to any medication-containing line.
Note: Percentages calculated with the number of subjects in each treatment group as denominator.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

Numbers analysed

In total, 419 participants were enrolled and randomized: 211 participants to Arm A and 208 participants to Arm B. The ITT analysis set (all participants randomized) was the primary analysis set for efficacy, and was also used for summaries of study populations, disposition, demographics, and baseline characteristics. One hundred and seventy-six participants received cilta-cel as study treatment.

Outcomes and estimation

Primary Endpoint: Progression-free Survival

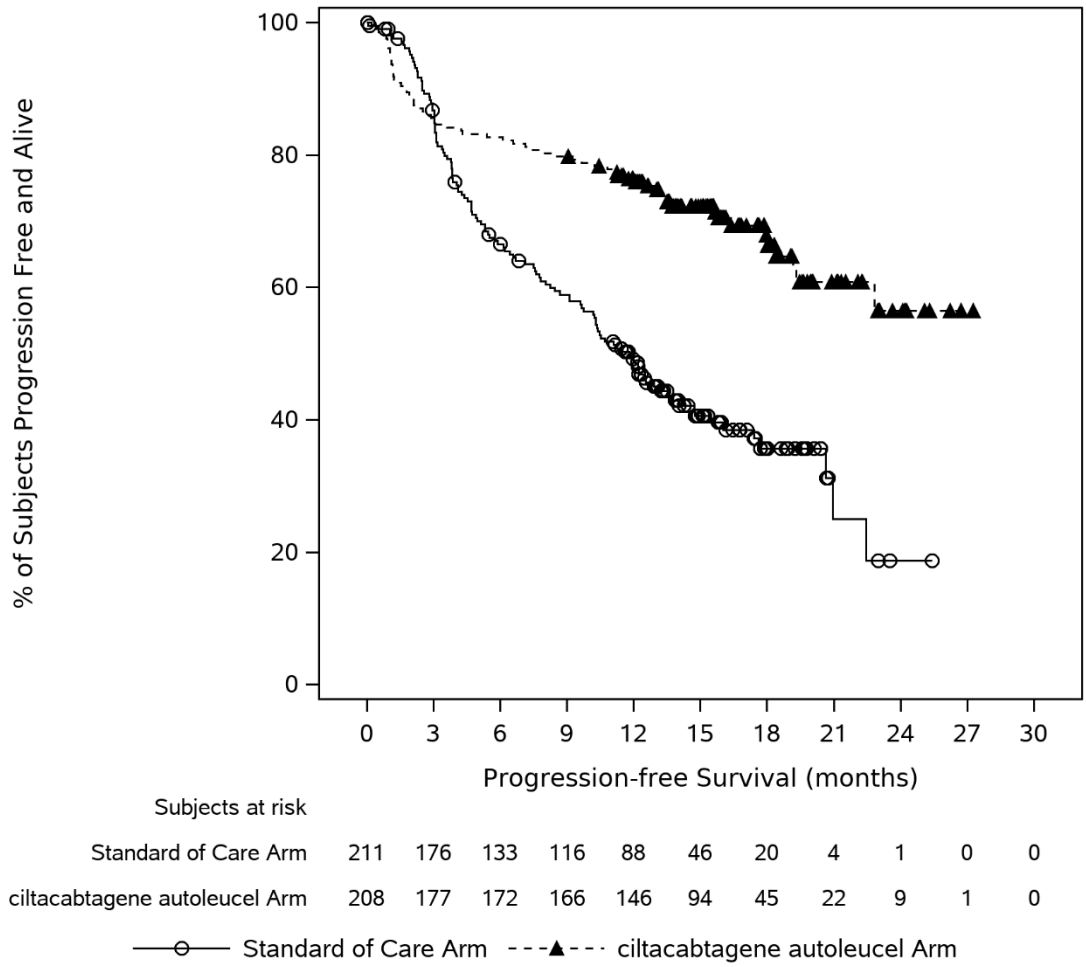
At a median follow-up of 15.9 months (data cut off 1 November 2022), a PFS event was reported for 57.8% of participants in Arm A and for 31.3% of participants in Arm B; median PFS was 11.8 months (95% CI: 9.7, 13.8) for Arm A and NE (95% CI: 22.8, NE) for Arm B. The HR was 0.26 (95% CI: 0.18, 0.38), with p-value of $<$0.0001 crossing the O'Brien-Fleming stopping boundary of 0.0191. The HR of 0.26 indicates a 74% reduction in the risk of death or progression for Arm B as compared with Arm A. The 12-month PFS rates were 48.6% for Arm A and 75.9% for Arm B.

Table 13. Summary of Progression-free Survival Based on Computerized Algorithm by Constant Piecewise Weighted (CPW) Log-rank Test; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B
Analysis set: intent-to-treat	211	208
Progression-free survival (PFS)		
○ Number of events (%)	122 (57.8%)	65 (31.3%)
○ Number of censored (%)	89 (42.2%)	143 (68.8%)
Kaplan-Meier estimate (months)		
○ 25% quantile (95% CI)	4.11 (3.38, 5.32)	12.91 (7.29, 17.97)
○ Median (95% CI)	11.79 (9.66, 13.77)	NE (22.83, NE)
○ 75% quantile (95% CI)	20.96 (20.63, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.26 (0.18, 0.38)
6-month PFS rate % (95% CI)	66.5 (59.5, 72.5)	82.7 (76.8, 87.2)
12-month PFS rate % (95% CI)	48.6 (41.5, 55.3)	75.9 (69.4, 81.1)
18-month PFS rate % (95% CI)	35.7 (28.0, 43.4)	67.8 (60.0, 74.5)
24-month PFS rate % (95% CI)	18.7 (6.8, 35.2)	56.4 (43.7, 67.3)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval; CPW=constant piecewise weighted.
[a] p-value is based on the CPW log-rank test (weight=0 in the log-rank statistic for the first 8 weeks post-randomization, and 1 afterwards) stratified with investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized.
[b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized, including only PFS events that occurred more than 8 weeks post-randomization. A hazard ratio <1 indicates an advantage for Arm B.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

Figure 13. Kaplan-Meier Plot for Progression-free Survival Based on Computerized Algorithm; Intent-to-Treat Analysis Set (Study 68284528MMY3002)



Key: Standard of Care Arm = PVd or DPd; ciltacabtagene autoleucel Arm = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd=pomalidomide-bortezomib-dexamethasone; DPd=daratumumab-pomalidomide-dexamethasone.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

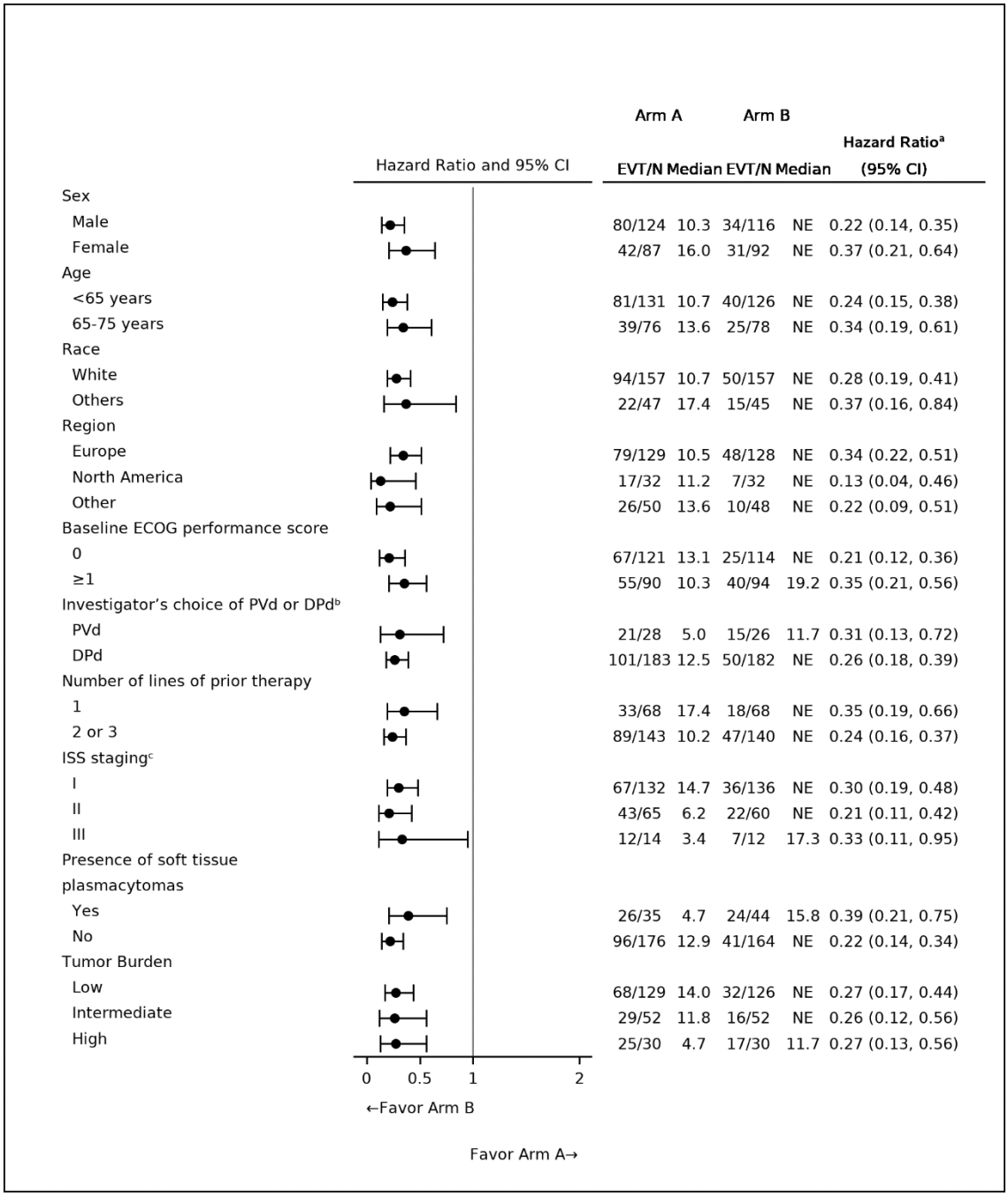
There were 19 additional PFS events (10 in Arm A and 9 in Arm B) reported between the 2 clinical cutoffs, 01 November 2022 and 17 April 2023, with 206 total cumulative PFS events.

Subgroup Analyses of Progression-free Survival

The treatment effect of Arm B over Arm A was consistent across all pre-specified subgroups, including the following key subgroups: participants with 1 prior line of therapy (HR=0.35 [95% CI: 0.19, 0.66]), ISS Stage III (HR=0.33 [95% CI: 0.11, 0.95]), high tumour burden (HR=0.27 [95% CI: 0.13, 0.56]), and high-risk cytogenetics (HR=0.25 [95% CI: 0.16, 0.38]).

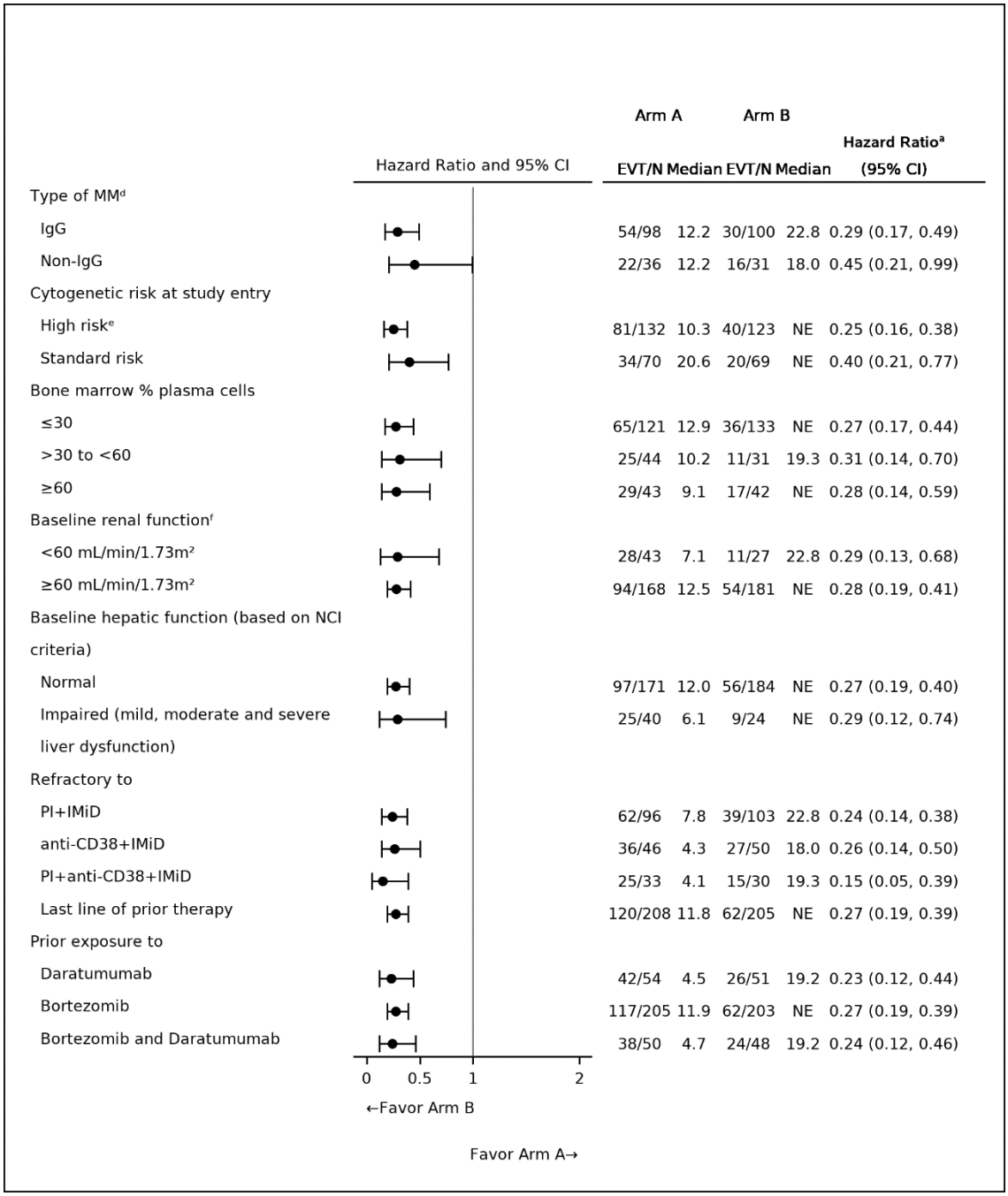
Subgroups with small sample size (fewer than 10 participants in either treatment arm) are suppressed as the estimations would be unreliable with wide CIs; these include age >75 years, African American race, unknown cytogenetic risk at study entry, penta-refractory status, and certain subgroups of prior exposure (pomalidomide, bortezomib and pomalidomide, and daratumumab and pomalidomide).

Figure 14. Forest Plot of Subgroup Analyses on Progression-free Survival Based on Computerized Algorithm Using Constant Piecewise Weighted (CPW) in Cox Model; Intent-to-Treat Analysis Set (Study 68284528MMY3002)



	Arm A		Arm B		Hazard Ratio[a]
	EVT/N	Median	EVT/N	Median	(95% CI)
Sex					
Male	80/124	10.3	34/116	NE	0.22 (0.14, 0.35)
Female	42/87	16.0	31/92	NE	0.37 (0.21, 0.64)
Age					
<65 years	81/131	10.7	40/126	NE	0.24 (0.15, 0.38)
65-75 years	39/76	13.6	25/78	NE	0.34 (0.19, 0.61)
Race					
White	94/157	10.7	50/157	NE	0.28 (0.19, 0.41)
Others	22/47	17.4	15/45	NE	0.37 (0.16, 0.84)
Region					
Europe	79/129	10.5	48/128	NE	0.34 (0.22, 0.51)
North America	17/32	11.2	7/32	NE	0.13 (0.04, 0.46)
Other	26/50	13.6	10/48	NE	0.22 (0.09, 0.51)
Baseline ECOG performance score					
0	67/121	13.1	25/114	NE	0.21 (0.12, 0.36)
≥1	55/90	10.3	40/94	19.2	0.35 (0.21, 0.56)
Investigator's choice of PVd or DPd[b]					
PVd	21/28	5.0	15/26	11.7	0.31 (0.13, 0.72)
DPd	101/183	12.5	50/182	NE	0.26 (0.18, 0.39)
Number of lines of prior therapy					
1	33/68	17.4	18/68	NE	0.35 (0.19, 0.66)
2 or 3	89/143	10.2	47/140	NE	0.24 (0.16, 0.37)
ISS staging[c]					
I	67/132	14.7	36/136	NE	0.30 (0.19, 0.48)
II	43/65	6.2	22/60	NE	0.21 (0.11, 0.42)
III	12/14	3.4	7/12	17.3	0.33 (0.11, 0.95)
Presence of soft tissue plasmacytomas					
Yes	26/35	4.7	24/44	15.8	0.39 (0.21, 0.75)
No	96/176	12.9	41/164	NE	0.22 (0.14, 0.34)
Tumor Burden					
Low	68/129	14.0	32/126	NE	0.27 (0.17, 0.44)
Intermediate	29/52	11.8	16/52	NE	0.26 (0.12, 0.56)
High	25/30	4.7	17/30	11.7	0.27 (0.13, 0.56)

Figure 14. Forest Plot of Subgroup Analyses on Progression-free Survival Based on Computerized Algorithm Using Constant Piecewise Weighted (CPW) in Cox Model; Intent-to-Treat Analysis Set (Study 68284528MMY3002)



	Arm A		Arm B		Hazard Ratio[a]
	EVT/N	Median	EVT/N	Median	(95% CI)
Type of MM[d]					
IgG	54/98	12.2	30/100	22.8	0.29 (0.17, 0.49)
Non-IgG	22/36	12.2	16/31	18.0	0.45 (0.21, 0.99)
Cytogenetic risk at study entry					
High risk[e]	81/132	10.3	40/123	NE	0.25 (0.16, 0.38)
Standard risk	34/70	20.6	20/69	NE	0.40 (0.21, 0.77)
Bone marrow % plasma cells					
≤30	65/121	12.9	36/133	NE	0.27 (0.17, 0.44)
>30 to <60	25/44	10.2	11/31	19.3	0.31 (0.14, 0.70)
≥60	29/43	9.1	17/42	NE	0.28 (0.14, 0.59)
Baseline renal function[f]					
<60 mL/min/1.73m²	28/43	7.1	11/27	22.8	0.29 (0.13, 0.68)
≥60 mL/min/1.73m²	94/168	12.5	54/181	NE	0.28 (0.19, 0.41)
Baseline hepatic function (based on NCI criteria)					
Normal	97/171	12.0	56/184	NE	0.27 (0.19, 0.40)
Impaired (mild, moderate and severe liver dysfunction)	25/40	6.1	9/24	NE	0.29 (0.12, 0.74)
Refractory to					
PI+IMiD	62/96	7.8	39/103	22.8	0.24 (0.14, 0.38)
anti-CD38+IMiD	36/46	4.3	27/50	18.0	0.26 (0.14, 0.50)
PI+anti-CD38+IMiD	25/33	4.1	15/30	19.3	0.15 (0.05, 0.39)
Last line of prior therapy	120/208	11.8	62/205	NE	0.27 (0.19, 0.39)
Prior exposure to					
Daratumumab	42/54	4.5	26/51	19.2	0.23 (0.12, 0.44)
Bortezomib	117/205	11.9	62/203	NE	0.27 (0.19, 0.39)
Bortezomib and Daratumumab	38/50	4.7	24/48	19.2	0.24 (0.12, 0.46)

Figure 14. Forest Plot of Subgroup Analyses on Progression-free Survival Based on Computerized Algorithm Using Constant Piecewise Weighted (CPW) in Cox Model; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval; CPW=constant piecewise weighted; EVT=event.
[a] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable, including only PFS events that occurred more than 8 weeks post-randomization. A hazard ratio <1 indicates an advantage for Arm B.
[b] Based on the IWRS randomization strata.
[c] ISS staging is derived based on serum β-2 microglobulin and albumin.
[d] Type of MM subgroup analysis is based on subjects with measurable disease in serum.
[e] High risk includes the subjects who are positive for any of del17p, t(14;16), t(4;14), or gain/amp(1q) by FISH testing.
[f] Based on the Modification of Diet in Renal Disease (MDRD) formula.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.
Note: The subgroup analysis for each parameter includes subjects with available data for that parameter.
Note: Baseline tumor burden is determined by the last non-missing measurement prior to the study treatment based on plasmacytosis, serum M-protein and serum free light chain. Please refer to SAP for the low/intermediate/high tumor burden classifications.
Note: Median of progression-free survival in months is displayed for each subgroup.
Note: The subgroups with less than 10 subjects in either treatment group are suppressed in this table.

Subgroup analyses for PFS based on computerized algorithm by number of lines of prior therapy (1 vs. 2 vs. 3) using CPW methodology in Cox proportional hazards model are presented for the ITT analysis set with the corresponding Kaplan-Meier plot. Twelve-month PFS rate was higher for Arm B than for Arm A for subgroups with 1 (77.7% [95% CI: 65.8, 85.9] for Arm B vs 58.5% [95% CI: 45.5, 69.4] for Arm A), with 2 (72.3% [95% CI: 61.3, 80.6] vs 50.2% [95% CI: 38.9, 60.4], respectively), and with 3 (78.9% [95% CI: 65.9, 87.4] vs 34.0% [95% CI: 21.7, 46.7], respectively) prior lines.

Table 14. Subgroup Analyses for Progression-free Survival Based on Computerized Algorithm by Number of Lines of Prior Therapy (1 vs. 2 vs. 3) Using Constant Piecewise Weighted (CPW) in Cox Model; Intent-to-treat analysis Set (Study 68284528MMY3002)

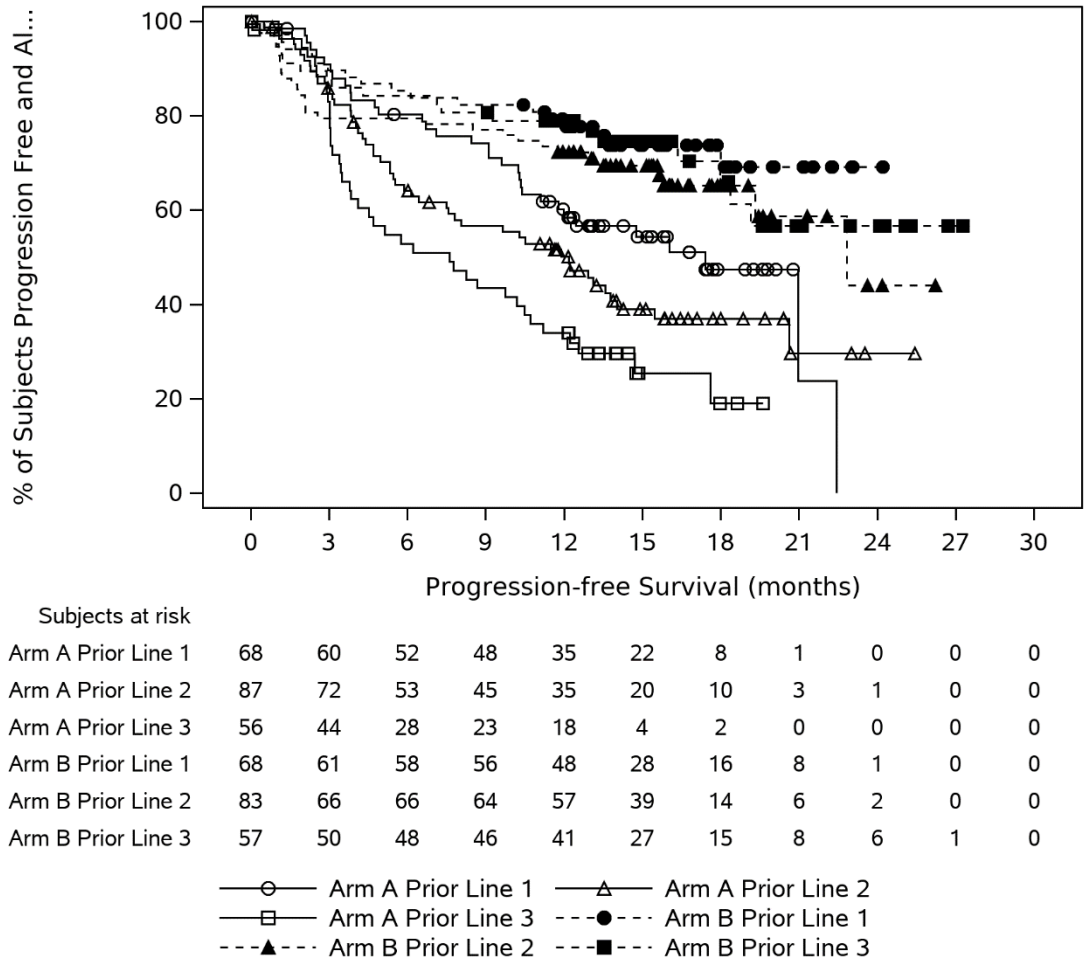
	Arm A	Arm B
Analysis set: intent-to-treat	211	208
Progression-free survival (PFS)		
Subjects with 1 line of prior therapy	68 (32.2%)	68 (32.7%)
○ Number of events (%)	33 (48.5%)	18 (26.5%)
○ Median PFS (95% CI) [a]	17.41 (11.10, NE)	NE (NE, NE)
○ 12-month PFS rate % (95% CI)	58.5 (45.5, 69.4)	77.7 (65.8, 85.9)
○ Hazard ratio (95% CI) [b]		0.36 (0.19, 0.68)
Subjects with 2 lines of prior therapy	87 (41.2%)	83 (39.9%)
○ Number of events (%)	50 (57.5%)	29 (34.9%)
○ Median PFS (95% CI) [a]	12.19 (7.49, 14.03)	22.83 (19.32, NE)
○ 12-month PFS rate % (95% CI)	50.2 (38.9, 60.4)	72.3 (61.3, 80.6)

Table 14. Subgroup Analyses for Progression-free Survival Based on Computerized Algorithm by Number of Lines of Prior Therapy (1 vs. 2 vs. 3) Using Constant Piecewise Weighted (CPW) in Cox Model; Intent-to-treat analysis Set (Study 68284528MMY3002)

	Arm A	Arm B
○ Hazard ratio (95% CI) [b]		0.25 (0.13, 0.46)
Subjects with 3 lines of prior therapy	56 (26.5%)	57 (27.4%)
○ Number of events (%)	39 (69.6%)	18 (31.6%)
○ Median PFS (95% CI) [a]	7.62 (3.78, 10.71)	NE (17.97, NE)
○ 12-month PFS rate % (95% CI)	34.0 (21.7, 46.7)	78.9 (65.9, 87.4)
○ Hazard ratio (95% CI) [b]		0.20 (0.10, 0.40)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval; CPW=constant piecewise weighted.
[a] Kaplan-Meier estimate
[b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized, including only PFS events that occurred more than 8 weeks post-randomization. A hazard ratio <1 indicates an advantage for Arm B.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.
Note: Percentages for subjects with number of lines of prior therapy are calculated with number of subjects in the intent-to-treat analysis set in each treatment group as denominator; Percentages for PFS events are calculated with the number of subjects in each prior line subgroup within each treatment group as denominator.

Figure 15. Kaplan-Meier Plot for Progression-free Survival Based on Computerized Algorithm by Number of Lines of Prior Therapy (1 vs. 2 vs. 3) and Treatment Group; Intent-to-treat analysis Set (Study 68284528MMY3002)



Subjects at risk											
Arm A Prior Line 1	68	60	52	48	35	22	8	1	0	0	0
Arm A Prior Line 2	87	72	53	45	35	20	10	3	1	0	0
Arm A Prior Line 3	56	44	28	23	18	4	2	0	0	0	0
Arm B Prior Line 1	68	61	58	56	48	28	16	8	1	0	0
Arm B Prior Line 2	83	66	66	64	57	39	14	6	2	0	0
Arm B Prior Line 3	57	50	48	46	41	27	15	8	6	1	0

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

12-month PFS rate was 88.6% (95% CI: 79.9%, 93.7%) for the subgroup <median value of total CAR-positive T cells infused as study treatment, and 90.7% (95% CI: 82.2%, 95.2%) for the subgroup ≥median value, indicating no difference in PFS according to whether participants were above or below the median value of 53.08×10^6.

12-month PFS rate was 89.0% (95% CI: 80.4%, 93.9%) for the subgroup <median value of cilta-cel dose administered as study treatment, and 90.5% (95% CI: 81.9%, 95.1%) for the subgroup ≥median value, indicating no difference in PFS according to whether participants were above or below the median value of 0.71×10^6 cells/kg.

For baseline tumour BCMA expression, 12-month PFS rate was 78.8% (95% CI: 68.4%, 86.1%) for participants <median value of 82%, and 70.6% (95% CI: 59.7%, 79.1%) for participants ≥median value.

For drug product release status, 12-month PFS rate was 89.3% (95% CI: 83.5%, 93.1%) for participants who received within-specification drug product as study treatment, and 100.0% (95% CI: 100.0%, 100.0%) for participants who received out-of-specification drug product as study treatment. It should be noted however that there were only 6 participants in the out-of-specification subgroup, of whom 2 participants had a PFS event.

12-month PFS rate was 87.8% (95% CI: 79.0%, 93.0%) for the CCHMC LV subgroup, and 91.6% (95% CI: 83.2%, 95.9%) for the Bern LV subgroup, indicating no difference in PFS according to whether participants received cilta-cel as study treatment manufactured with CCHMC LV or Bern LV.

Key secondary endpoint: Rate of Complete Response/Stringent Complete Response

The rate of CR or better (sCR + CR) by computerized algorithm was 21.8% (95% CI: 16.4%, 28.0%) for Arm A and 73.1% (95% CI: 66.5%, 79.0%) for Arm B; the stratified CMH estimate of odds ratio was 10.3 (95% CI: 6.5, 16.4; p<0.0001). In analysis of the 176 participants in Arm B who received cilta-cel infusion as study treatment, the rate of CR or better was 86.4% (95% CI: 80.4%, 91.1%).

Table 15. Summary of Overall Best Confirmed Response Based on Computerized Algorithm; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A		Arm B			
	n (%)	95% CI for %	n (%)	95% CI for %	Odds Ratio (95% CI)[a]	P-value[b]
Analysis set: intent-to-treat	211		208			
Response category						
○ Stringent complete response (sCR)	32 (15.2%)	(10.6%, 20.7%)	121 (58.2%)	(51.2%, 65.0%)		
○ Complete response (CR)	14 (6.6%)	(3.7%, 10.9%)	31 (14.9%)	(10.4%, 20.5%)		
○ Very good partial response (VGPR)	50 (23.7%)	(18.1%, 30.0%)	17 (8.2%)	(4.8%, 12.8%)		
○ Partial response (PR)	46 (21.8%)	(16.4%, 28.0%)	7 (3.4%)	(1.4%, 6.8%)		
○ Minimal response (MR)	11 (5.2%)	(2.6%, 9.1%)	1 (0.5%)	(0.0%, 2.6%)		
○ Stable disease (SD)	47 (22.3%)	(16.8%, 28.5%)	13 (6.3%)	(3.4%, 10.5%)		
○ Progressive disease (PD)	6 (2.8%)	(1.1%, 6.1%)	17 (8.2%)	(4.8%, 12.8%)		
○ Not evaluable (NE)	5 (2.4%)	(0.8%, 5.4%)	1 (0.5%)	(0.0%, 2.6%)		

Table 15. Summary of Overall Best Confirmed Response Based on Computerized Algorithm; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A		Arm B			
	n (%)	95% CI for %	n (%)	95% CI for %	Odds Ratio (95% CI)[a]	P-value[b]
○ Overall response (sCR + CR + VGPR + PR)	142 (67.3%)	(60.5%, 73.6%)	176 (84.6%)	(79.0%, 89.2%)	3.00 (1.81, 4.97)	<0.0001
○ Clinical benefit (Overall response + MR)	153 (72.5%)	(66.0%, 78.4%)	177 (85.1%)	(79.5%, 89.6%)	2.39 (1.42, 4.01)	0.0010
○ VGPR or better (sCR + CR + VGPR)	96 (45.5%)	(38.6%, 52.5%)	169 (81.3%)	(75.3%, 86.3%)	5.89 (3.70, 9.40)	<0.0001
○ CR or better (sCR + CR)	46 (21.8%)	(16.4%, 28.0%)	152 (73.1%)	(66.5%, 79.0%)	10.30 (6.48, 16.35)	<0.0001

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval.
[a] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. An odds ratio > 1 indicates an advantage for Arm B. The stratification factors are: Investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines of therapy (1 vs. 2 or 3) as randomized.
[b] P-value from the Cochran Mantel-Haenszel Chi-Squared test.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.
Note: Response was assessed by computerized algorithm, based on International Myeloma Working Group (IMWG) consensus criteria (Kumar 2016).
Note: Percentages are calculated with the number of subjects in each group as denominator.

Subgroup Analyses of CR or Better Rate

All pre-specified subgroup analyses of CR or better rate favoured Arm B, including key subgroups of 1 prior line of therapy (odds ratio=4.4 [95% CI: 2.1, 9.1]), ISS Stage III (odds ratio=26.0 [95% CI: 2.5, 275.8]), high tumour burden (odds ratio=9.0 [95% CI: 2.2, 36.2]) and high-risk cytogenetics (odds ratio=11.1 [95% CI: 6.2, 20.0]).

Subgroup analysis of CR or better rate based on computerized algorithm by number of lines of prior therapy (1 vs. 2 vs. 3) is provided for the ITT analysis set in Table below. Rate of CR or better was higher for Arm B than for Arm A for subgroups with 1 (Arm A: 35.3%; Arm B: 70.6%), with 2 (Arm A: 17.2%; Arm B: 74.7%), and with 3 (Arm A: 12.5%; Arm B: 73.7%) prior lines.

Table 16. Subgroup Analyses for Overall Response Rate and CR or Better Response Rate Based on Computerized Algorithm by Number of Lines of Prior Therapy (1 vs. 2 vs. 3); Intent-to-treat analysis Set (Study 68284528MMY3002)

	Arm A			Arm B			
	N[a]	n[b] (%)	95% CI for %	N[a]	n[b] (%)	95% CI for %	Odds Ratio (95% CI)[c]

Table 16. Subgroup Analyses for Overall Response Rate and CR or Better Response Rate Based on Computerized Algorithm by Number of Lines of Prior Therapy (1 vs. 2 vs. 3); Intent-to-treat analysis Set (Study 68284528MMY3002)

	Arm A			Arm B			
	N[a]	n[b] (%)	95% CI for %	N[a]	n[b] (%)	95% CI for %	Odds Ratio (95% CI)[c]
Analysis set: intent-to-treat	211			208			
Overall response by number of lines of prior therapy							
○ 1	68	54 (79.4%)	(67.9%, 88.3%)	68	61 (89.7%)	(79.9%, 95.8%)	2.26 (0.85, 6.01)
○ 2	87	59 (67.8%)	(56.9%, 77.4%)	83	66 (79.5%)	(69.2%, 87.6%)	1.84 (0.92, 3.70)
○ 3	56	29 (51.8%)	(38.0%, 65.3%)	57	49 (86.0%)	(74.2%, 93.7%)	5.70 (2.29, 14.21)
CR or better by number of lines of prior therapy							
○ 1	68	24 (35.3%)	(24.1%, 47.8%)	68	48 (70.6%)	(58.3%, 81.0%)	4.40 (2.14, 9.05)
○ 2	87	15 (17.2%)	(10.0%, 26.8%)	83	62 (74.7%)	(64.0%, 83.6%)	14.17 (6.73, 29.84)
○ 3	56	7 (12.5%)	(5.2%, 24.1%)	57	42 (73.7%)	(60.3%, 84.5%)	19.60 (7.30, 52.61)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval; CR=complete response
[a] N = number of subjects.
[b] n = number of subjects with response.
[c] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. An odds ratio > 1 indicates an advantage for Arm B.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.
Note: Response was assessed by computerized algorithm, based on International Myeloma Working Group (IMWG) consensus criteria (Kumar 2016).
Note: Overall response refers to PR or better response.
Note: Percentages are calculated with the number of subjects in each prior line subgroup within intent-to-treat analysis set as denominator.

Key secondary endpoint: Overall Response Rate

The ORR (sCR + CR + VGPR + PR) by computerized algorithm was 67.3% (95% CI: 60.5%, 73.6%) for Arm A and 84.6% (95% CI: 79.0%, 89.2%) for Arm B; the stratified CMH estimate of odds ratio was 3.0 (95% CI: 1.8, 5.0; p<0.0001).

In analysis of the 176 participants in Arm B who received cilta-cel infusion as study treatment, the ORR was 99.4% (95% CI: 96.9%, 100.0%)

Key secondary endpoint: Overall MRD Negativity Rate

The MRD negativity rate (10^{-5}) as measured by NGS was approximately 4-fold higher for participants in Arm B compared with participants in Arm A (Arm A: 15.6%, Arm B: 60.6%; odds ratio=8.7; 95% CI: 5.42, 13.90; p<0.0001).

Table 17. Summary of MRD Negativity Rate at 10^{-5} in Bone Marrow; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B
Analysis set: intent-to-treat	211	208
MRD negativity rate (10^{-5})	33 (15.6%)	126 (60.6%)
○ 95% CI[a]	(11.0%, 21.3%)	(53.6%, 67.3%)
○ Odds ratio with 95% CI[b]		8.68 (5.42, 13.90)
○ P-value[c]		<0.0001

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval, MRD = minimal residual disease.
[a] Exact 95% confidence interval.
[b] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are: Investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines of therapy (1 vs. 2 or 3) as randomized. An odds ratio > 1 indicates an advantage for Arm B.
[c] P-value from Fisher's exact test.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.
Note: MRD status result based on next-generation sequencing (NGS) and post-randomization assessment.
Note: Overall MRD negativity rate is defined as the proportion of subjects who have MRD negative status (at 10^{-5}) by bone marrow aspirate at any time after the date of randomization and prior to progressive disease (PD) or subsequent anti-myeloma therapy.

Evaluable samples are those that pass calibration and QC and include sufficient cells for evaluation at the respective testing threshold. Among participants with an evaluable sample (a clone identified at baseline and at least 1 post-baseline bone marrow sample), the MRD negativity rate at the 10^{-5} threshold was higher for Arm B (87.5%) as compared with Arm A (32.7%) (odds ratio [Arm B vs. Arm A] =14.1; 95% CI: 7.3, 27.2; p<0.0001).

Among participants in the ITT analysis set, summaries of MRD negativity rate at 10^{-5} in bone marrow within 3 months of achieving CR/sCR based on computerized algorithm are provided below (10.4% for Arm A vs. 51.4% for Arm B; odds ratio=9.5 [95% CI: 5.6, 16.1]; p<0.0001):

Table 18. Summary of MRD Negativity Rate at 10^{-5} in Bone Marrow with CR/sCR Based on Computerized Algorithm; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B
Analysis set: intent-to-treat	211	208
MRD negativity rate (10^{-5}) with CR/sCR	22 (10.4%)	107 (51.4%)
○ 95% CI[a]	(6.7%, 15.4%)	(44.4%, 58.4%)
○ Odds ratio with 95% CI[b]		9.49 (5.60, 16.06)
○ P-value[c]		<0.0001

Table 18. Summary of MRD Negativity Rate at 10^{-5} in Bone Marrow with CR/sCR Based on Computerized Algorithm; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval, MRD = minimal residual disease.
[a] Exact 95% confidence interval.
[b] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are: Investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines of therapy (1 vs. 2 or 3) as randomized. An odds ratio > 1 indicates an advantage for Arm B.
[c] P-value from Fisher's exact test.
Note: MRD status result based on next-generation sequencing (NGS) and post-randomization assessment.
Note: Overall MRD negativity rate is defined as the proportion of subjects who have MRD negative status (at 10^{-5}) by bone marrow aspirate after the date of randomization and prior to progressive disease (PD) or subsequent anti-myeloma therapy.
Note: MRD negativity with CR/sCR refers to MRD assessments (10^{-5} testing threshold) within 3 months of achieving CR/sCR until death / progression / subsequent therapy (exclusive).
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

Key secondary endpoint: Overall Survival

OS (data cut off 1 November 2022) was analyzed using an unweighted stratified log-rank test and is based on the ITT analysis set (Arm A: n=211; Arm B: n=208). As of the time of clinical cut off, 47 participants (22.3%) in Arm A and 39 participants (18.8%) in Arm B had died. Initial OS data suggested a trend towards improved survival in Arm B vs. Arm A (HR=0.78; 95% CI: 0.50, 1.20; p=0.2551); however, the OS data are yet to be mature to provide a reliable estimate for median OS. The estimated OS rates at 12 months were 83.6% (95% CI: 77.8%, 88.0%) for Arm A and 84.1% (95% CI: 78.4%, 88.4%) for Arm B.

Table 19. Summary of Overall Survival; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B
Analysis set: intent-to-treat	211	208
Overall survival (OS)		
○ Number of events (%)	47 (22.3%)	39 (18.8%)
○ Number of censored (%)	164 (77.7%)	169 (81.3%)
Kaplan-Meier estimate (months)		
○ 25% quantile (95% CI)	21.42 (14.62, NE)	22.83 (16.36, NE)
○ Median (95% CI)	26.74 (22.47, NE)	NE (NE, NE)
○ 75% quantile (95% CI)	26.74 (NE, NE)	NE (NE, NE)
P-value[a]		0.2551
Hazard ratio (95% CI)[b]		0.78 (0.50, 1.20)
6-month survival rate % (95% CI)	94.2 (90.1, 96.7)	91.3 (86.6, 94.5)
12-month survival rate % (95% CI)	83.6 (77.8, 88.0)	84.1 (78.4, 88.4)

Table 19. Summary of Overall Survival; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B
18-month survival rate % (95% CI)	75.1 (67.4, 81.2)	80.8 (74.2, 85.9)
24-month survival rate % (95% CI)	65.7 (50.0, 77.5)	73.6 (59.6, 83.4)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval.
[a] p-value is based on the log-rank test stratified with investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized.
[b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized. A hazard ratio <1 indicates an advantage for Arm B.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

Figure 16. Kaplan-Meier Plot for Overall Survival; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

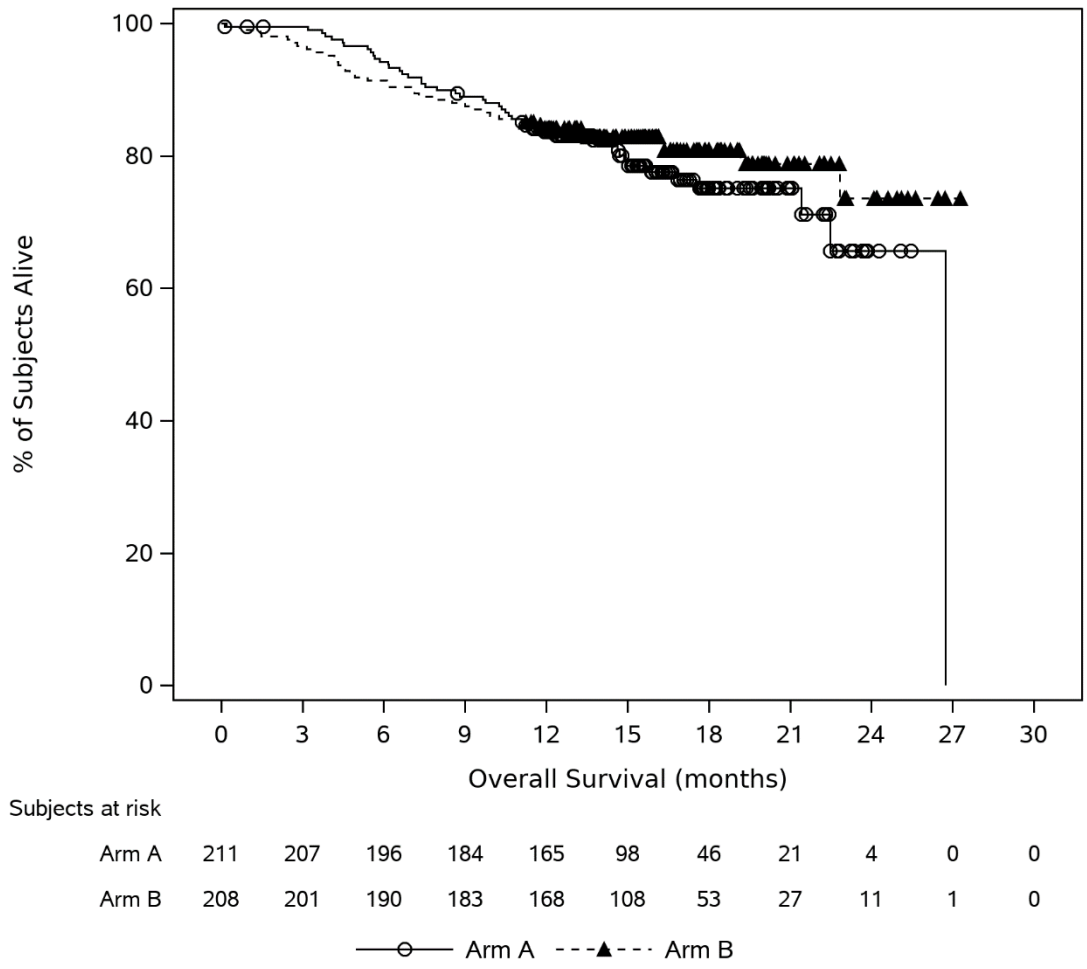


Figure 16. Kaplan-Meier Plot for Overall Survival; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd=pomalidomide-bortezomib-dexamethasone; DPd=daratumumab-pomalidomide-dexamethasone.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

Piecewise analysis of OS (by intervals of 0-≤3 months, >3-≤6 months, >6-≤9 months, >9-≤12 months, >12-≤24 months, and >24 months from randomization) indicated that the period of greatest imbalance between arms was for the period 0-≤3 months, in which 1 death (0.5%) was reported for Arm A vs. 7 deaths (3.4%) for Arm B. For all time periods thereafter, the rate of deaths was similar between arms or lower in Arm B. During the first 3 months from randomization, 1 Arm A participant died prior to starting study treatment and 7 participants died in Arm B. In Arm B, 6 of these 7 participants had not received cilta-cel (4 died due to disease progression, 1 due to AE, and 1 due to AE after subsequent therapy). One participant died of an AE after receiving cilta-cel as subsequent therapy.

The higher number of deaths in Arm B vs Arm A in the first 3 months after randomization is not related to cilta-cel. The deaths in the first 3 months were mainly due to disease progression and occurred before participants received cilta-cel. Thereafter, between 3 and 6 months, an equal number of deaths was observed on both arms. In Arm B, deaths during this period were primarily due to deaths in participants who progressed prior to receiving cilta-cel, COVID-19 in participants following cilta-cel, and participants who did not receive cilta-cel as study treatment and died after disease progression and subsequent therapy. From 6 months onwards, more deaths were consistently observed in Arm A compared with Arm B. Deaths on Arm B during this period included deaths due to COVID-19 pneumonia, and other infectious causes, in addition to disease progression in participants who received cilta-cel as subsequent therapy.

As the study was conducted during the COVID-19 pandemic period, COVID-19 deaths were observed (1 death in Arm A and 7 deaths in Arm B attributed to COVID-19 pneumonia).

Table 20. Piecewise Analysis of the Overall Survival; Intent-to-treat analysis Set (Study 68284528MMY3002)

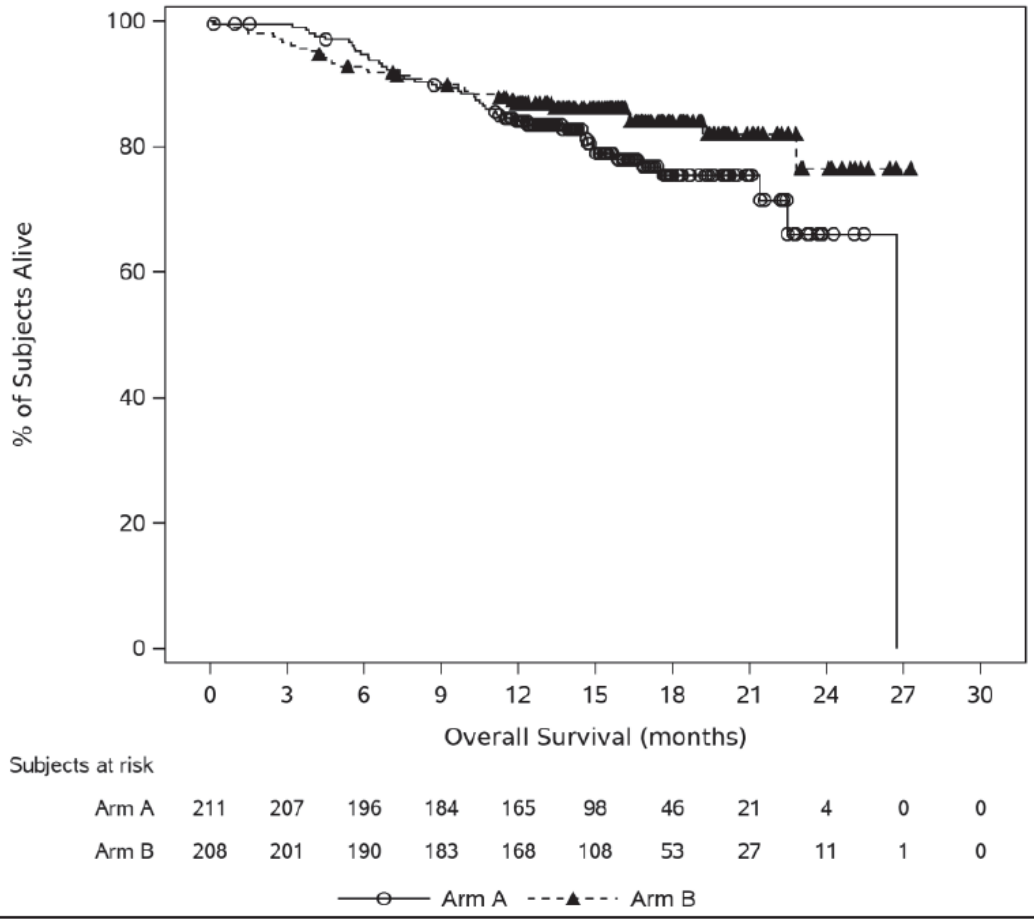
	Arm A	Arm B
Analysis set: intent-to-treat	211	208
Overall survival (OS)		
○ Number of events (%)	47 (22.3%)	39 (18.8%)
OS piecewise, since randomization		
0 - ≤ 3 months		
○ Number of events (%)	1 (0.5%)	7 (3.4%)
○ Hazard ratio (95% CI)		6.24 (0.75, 51.85)
> 3 - ≤ 6 months		
○ Number of events (%)	11 (5.2%)	11 (5.3%)
○ Hazard ratio (95% CI)		1.07 (0.46, 2.47)

Table 20. Piecewise Analysis of the Overall Survival; Intent-to-treat analysis Set (Study 68284528MMY3002)

	Arm A	Arm B
> 6 - ≤ 9 months		
○ Number of events (%)	11 (5.2%)	7 (3.4%)
○ Hazard ratio (95% CI)		0.65 (0.25, 1.68)
> 9 - ≤ 12 months		
○ Number of events (%)	11 (5.2%)	8 (3.8%)
○ Hazard ratio (95% CI)		0.72 (0.29, 1.78)
> 12 - ≤ 24 months		
○ Number of events (%)	12 (5.7%)	6 (2.9%)
○ Hazard ratio (95% CI)		0.34 (0.12, 0.99)
> 24 months		
○ Number of events (%)	1 (0.5%)	0
○ Hazard ratio (95% CI)		0.00 (0.00, NE)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval, NE=not estimable.
Note: Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized. A hazard ratio <1 indicates an advantage for Arm B.
Note: For each time interval, the events occurred after this interval are censored, the subjects who had the event or censored before this interval are excluded.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

Figure 17. Kaplan-Meier Plot for Overall Survival (Censored for Death due to COVID-19); Intent-to-treat Analysis Set (Study 68284528MMY3002)



Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: COVID-19= coronavirus disease 2019.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

At an updated clinical cutoff of 17 April 2023 (a safety regulatory requirement for the FDA), at a median follow up of 21.5 months, a total of 111 deaths had occurred among participants who received any part of study treatment (Safety analysis set): 66 deaths (31.7%) in Arm A and 45 deaths (21.6%) in Arm B. This reflects an increase of 20 deaths in Arm A and 6 deaths in Arm B since the 01 November 2022 clinical cutoff, including 2 deaths in participants who received cilta-cel as subsequent therapy.

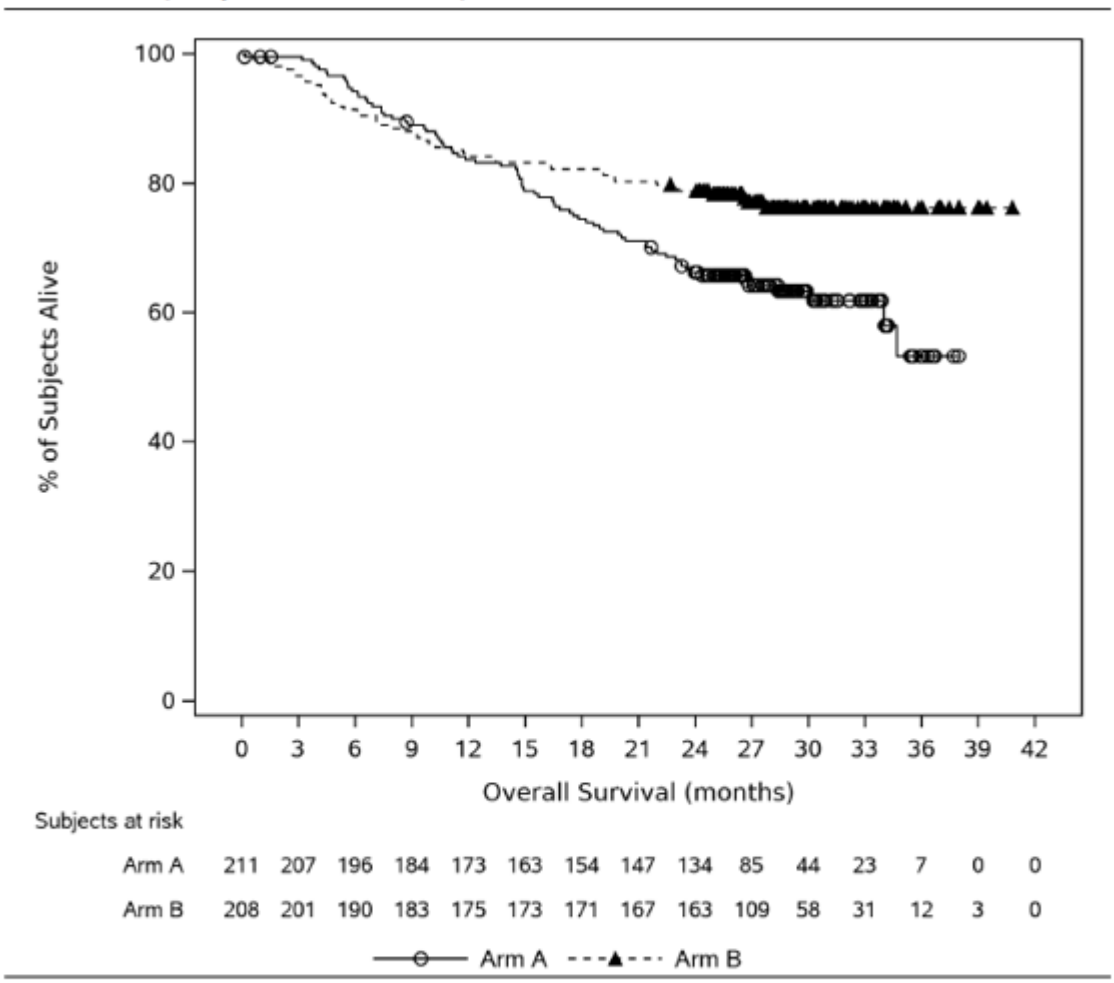
Further updated OS data were provided by the MAH following survival sweep analysis performed on 13 December 2023. The current analysis reflects 13 additional deaths (10 in Arm A; 3 in Arm B) since the clinical cutoff of 17 April 2023. Of note, to avoid any potential type I error inflation, statistical testing was not performed in this requested analysis. These data continue to demonstrate a favorable trend in OS that appears to be strengthening over time.

Table 21. Summary of Overall Survival; Intent-to-treat Analysis Set (study 68284528MMY3002)

	Arm A	Arm B
Analysis set: intent-to-treat	211	208
Overall survival (OS)		
Number of events (%)	77 (36.5%)	48 (23.1%)
Number of censored (%)	134 (63.5%)	160 (76.9%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	17.54 (14.69, 21.98)	NE (19.75, NE)
Median (95% CI)	NE (33.97, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
Hazard ratio (95% CI)[a]		0.57 (0.40, 0.83)
6-month survival rate % (95% CI)	94.2 (90.1, 96.7)	91.3 (86.6, 94.5)
12-month survival rate % (95% CI)	83.6 (77.9, 88.0)	84.1 (78.4, 88.4)
18-month survival rate % (95% CI)	74.4 (67.9, 79.8)	82.2 (76.3, 86.8)
24-month survival rate % (95% CI)	66.2 (59.3, 72.2)	78.8 (72.6, 83.8)
30-month survival rate % (95% CI)	63.3 (56.1, 69.6)	76.2 (69.6, 81.6)
36-month survival rate % (95% CI)	53.1 (39.6, 65.0)	76.2 (69.6, 81.6)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval.
[a] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized. A hazard ratio <1 indicates an advantage for Arm B.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.
Note: Clinical cut-off 13 December 2023 for survival sweep is used.

Figure 18. Kaplan-Meier Plot for Overall Survival; Intent-to-treat Analysis Set (study 68284528MMY3002)



Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd=pomalidomide-bortezomib-dexamethasone; DPd=daratumumab-pomalidomide-dexamethasone.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.
Note: Clinical cut-off 13 December 2023 for survival sweep is used.

Table 22. Summary of OS Events by Analysis Date

	1 November 2022 (Interim analysis)	17 April 2023 (120-Day Safety update)	13 December 2023 (Survival sweep)
Total deaths	86	112	125
Arm A	47	67	77
Arm B	39	45	48

Key secondary endpoint: Time to Worsening of Symptoms in the MySIm-Q Total Symptom Score

The MySIm-Q total symptom score measures the severity of pain, neuropathy, fatigue, digestive, and cognitive symptoms. Most participants (Arm A: 78.2%; Arm B: 85.6%) were censored as of the time of

clinical cutoff. The median time to a sustained worsening of multiple myeloma symptoms was longer for Arm B: median 18.9 months (95% CI: 16.8, NE) for Arm A and 23.7 months (95% CI: 22.1, NE) for Arm B (HR=0.42 [95% CI: 0.26, 0.68]).

Table 23. Time to Worsening in MySIm-Q Total Symptom Subscale; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B
Analysis set: intent-to-treat	211	208
Time to worsening in MySIm-Q total symptom score		
○ Number of events (%)	46 (21.8%)	30 (14.4%)
○ Number of censored (%)	165 (78.2%)	178 (85.6%)
Kaplan-Meier estimate (months)		
○ 25% quantile (95% CI)	9.20 (6.14, 11.79)	20.90 (16.69, NE)
○ Median (95% CI)	18.86 (16.76, NE)	23.66 (22.11, NE)
○ 75% quantile (95% CI)	NE (18.86, NE)	23.66 (22.57, NE)
P-value[a]		0.0003
Hazard ratio (95% CI)[b]		0.42 (0.26, 0.68)
6-month event-free rate % (95% CI)	84.5 (77.7, 89.3)	91.5 (86.2, 94.8)
12-month event-free rate % (95% CI)	65.6 (55.2, 74.2)	84.6 (77.7, 89.6)
18-month event-free rate % (95% CI)	51.9 (34.5, 66.8)	79.8 (69.6, 86.9)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval.
[a] p-value is based on the log-rank test stratified with investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized.
[b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with investigator's choice (PVd or DPd), ISS staging (I, II, III) and number of prior lines (1 vs. 2 or 3) as randomized. A hazard ratio <1 indicates an advantage for Arm B.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.
Note: Time to worsening is defined as the time from randomization to the first timepoint at which a decrease in score is at least half of a standard deviation from baseline values and without subsequent improvement to a score above this level, where standard deviation is calculated from the scores at baseline combining both treatment groups.
Note: Assessments after the start of subsequent therapy are excluded from the analysis.

Other endpoint: Rate of MRD Negativity in Participants with CR/sCR at 12 Months ± 3 Months

Fifteen participants (7.1%) in Arm A and 49 participants (23.6%) in Arm B achieved MRD-negative status at 10^{-5} and were in CR/sCR at 12 months ± 3 months as assessed by computerized algorithm; the odds ratio was 4.1 (95% CI: 2.2, 7.6).

Other endpoint: Rate of Sustained MRD-negative Status

At a median 15.9 months of follow-up, 2 participants (0.9%) in Arm A and 10 participants (4.8%) in Arm B achieved sustained (≥12 months) MRD-negativity at 10^{-5} in the bone marrow; these data were not yet mature. Using the ≥6 months definition, 8 participants (3.8%) in Arm A and 48 participants (23.1%) in

Arm B achieved sustained MRD-negativity at 10^{-5} in the bone marrow (odds ratio=7.6 [95% CI: 3.5, 16.6]).

Other endpoint: Progression-free Survival on Next Line of Therapy (PFS2)

A trend towards fewer PFS2 events by investigator assessment was observed in Arm B (45 participants, 21.6%) compared with Arm A (65 participants, 30.8%): HR=0.59 (95% CI: 0.40, 0.88).

Other endpoint: Duration of Response

DOR (1 November 2022) was calculated among responders (with a PR or better response) from the date of initial documentation of a response (PR or better) to the date of first documented evidence of disease progression based on the computerized algorithm, according to the IMWG response criteria, or death due to any cause, whichever occurred first. As most responders' DOR data (56.3% of participants in Arm A and 81.3% of participants in Arm B with PR or better) were censored as of the time of clinical cutoff, DOR data were not mature. Median DOR was 16.6 months (95% CI: 12.9, NE) for Arm A and NE (95% CI: NE, NE) for Arm B. 12-month event-free rates were 63.0% (95% CI: 54.2%, 70.6%) for Arm A and 84.7% (95% CI: 78.1%, 89.4%) for Arm B.

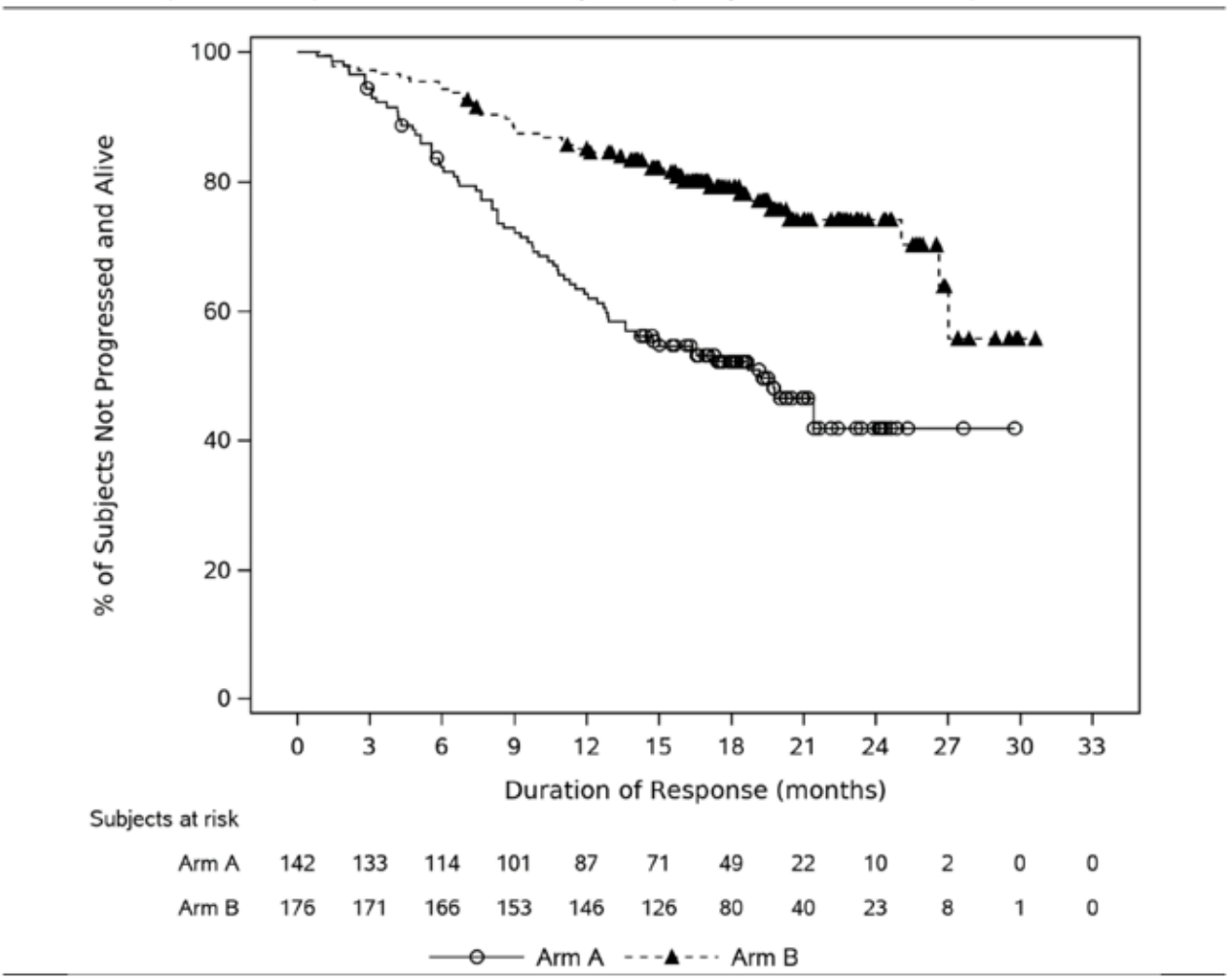
At the time of the 01 November 2022 clinical cut-off, the median follow-up was 15.9 months. At the time of the 17 April 2023 clinical cut off (a safety regulatory requirement for the FDA), the median follow-up was 21.5 months, corresponding to an additional 5.6 months. At the 17 April 2023 clinical cut-off, median duration of response (DOR) was 19.2 months (95% CI: 12.9, NE) for Arm A and NE (95% CI: 26.6 months, NE) for Arm B. The 18-month event-free rates were 52.1% (95% CI: 43.4%, 60.1%) for Arm A and 79.2% (95% CI: 72.2%, 84.6%) for Arm B.

Table 24. Summary of Duration of Response Based on Computerized Algorithm; Responders (PR or Better) in Intent-to-treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B
Analysis set: responders (PR or better) in intent-to-treat analysis set	142	176
Duration of response		
Number of events (%)	72 (50.7%)	42 (23.9%)
Number of censored (%)	70 (49.3%)	134 (76.1%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	8.31 (5.95, 10.38)	20.30 (15.21, 27.01)
Median (95% CI)	19.19 (12.91, NE)	NE (26.61, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
6-month event-free rate % (95% CI)	82.2 (74.9, 87.6)	94.3 (89.7, 96.9)
12-month event-free rate % (95% CI)	62.8 (54.2, 70.2)	85.1 (78.9, 89.6)
18-month event-free rate % (95% CI)	52.1 (43.4, 60.1)	79.2 (72.2, 84.6)
24-month event-free rate % (95% CI)	41.8 (31.5, 51.8)	74.2 (65.7, 80.9)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval; PR = partial response; NE = not estimable.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.
Note: Number of events refers to number of responders (PR or better) who developed disease progression or died.

Figure 19. Kaplan-Meier Plot for Duration of Response Based on Computerized Algorithm; Responders (PR or Better) in Intent-to-treat Analysis Set (Study 68284528MMY3002)



Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

Other endpoint: Time to Subsequent Anti-myeloma Treatment

With data censored for 45.5% of participants in Arm A and 77.9% of participants in Arm B, the median time to subsequent anti-myeloma treatment was 13.5 months (95% CI: 12.0, 17.1) for Arm A and NE (95% CI: NE, NE) for Arm B.

Other endpoint: Time to Disease Progression

With data censored for 44.1% of participants in Arm A and 76.9% of participants in Arm B, the median time to disease progression was 12.0 months (95% CI: 10.2, 14.7) for Arm A and NE (95% CI: NE, NE) for Arm B.

Ancillary analyses

Subgroup Analyses of CR or Better Rate

All pre-specified subgroup analyses of CR or better rate favoured Arm B, including key subgroups of 1 prior line of therapy (odds ratio=4.4 [95% CI: 2.1, 9.1]), ISS Stage III (odds ratio=26.0 [95% CI: 2.5, 275.8]), high tumour burden (odds ratio=9.0 [95% CI: 2.2, 36.2]) and high-risk cytogenetics (odds ratio=11.1 [95% CI: 6.2, 20.0]).

Subgroup analysis of CR or better rate based on computerized algorithm by number of lines of prior therapy (1 vs. 2 vs. 3) is provided for the ITT analysis set in Table below. Rate of CR or better was higher for Arm B than for Arm A for subgroups with 1 (Arm A: 35.3%; Arm B: 70.6%), with 2 (Arm A: 17.2%; Arm B: 74.7%), and with 3 (Arm A: 12.5%; Arm B: 73.7%) prior lines.

Table 25. Subgroup Analyses for Overall Response Rate and CR or Better Response Rate Based on Computerized Algorithm by Number of Lines of Prior Therapy (1 vs. 2 vs. 3); Intent-to-treat analysis Set (Study 68284528MMY3002)

	Arm A			Arm B			
	N[a]	n[b] (%)	95% CI for %	N[a]	n[b] (%)	95% CI for %	Odds Ratio (95% CI)[c]
Analysis set: intent-to-treat	211			208			
Overall response by number of lines of prior therapy							
○ 1	68	54 (79.4%)	(67.9%, 88.3%)	68	61 (89.7%)	(79.9%, 95.8%)	2.26 (0.85, 6.01)
○ 2	87	59 (67.8%)	(56.9%, 77.4%)	83	66 (79.5%)	(69.2%, 87.6%)	1.84 (0.92, 3.70)
○ 3	56	29 (51.8%)	(38.0%, 65.3%)	57	49 (86.0%)	(74.2%, 93.7%)	5.70 (2.29, 14.21)
CR or better by number of lines of prior therapy							
○ 1	68	24 (35.3%)	(24.1%, 47.8%)	68	48 (70.6%)	(58.3%, 81.0%)	4.40 (2.14, 9.05)
○ 2	87	15 (17.2%)	(10.0%, 26.8%)	83	62 (74.7%)	(64.0%, 83.6%)	14.17 (6.73, 29.84)
○ 3	56	7 (12.5%)	(5.2%, 24.1%)	57	42 (73.7%)	(60.3%, 84.5%)	19.60 (7.30, 52.61)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval; CR=complete response
[a] N = number of subjects.
[b] n = number of subjects with response.
[c] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. An odds ratio > 1 indicates an advantage for Arm B.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.
Note: Response was assessed by computerized algorithm, based on International Myeloma Working Group (IMWG) consensus criteria (Kumar 2016).
Note: Overall response refers to PR or better response.
Note: Percentages are calculated with the number of subjects in each prior line subgroup within intent-to-treat analysis set as denominator.

Table 25. Subgroup Analyses for Overall Response Rate and CR or Better Response Rate Based on Computerized Algorithm by Number of Lines of Prior Therapy (1 vs. 2 vs. 3); Intent-to-treat analysis Set (Study 68284528MMY3002)

	Arm A			Arm B			
	N[a]	n[b] (%)	95% CI for %	N[a]	n[b] (%)	95% CI for %	Odds Ratio (95% CI)[c]

Cytogenetic Risk

PFS

Patients with high-risk cytogenetics had longer PFS when treated with cilta-cel than patients with standard-risk cytogenetics when treated with standard of care.

In Arm A, 12-month PFS rates were 59.2% (95% CI: 46.7, 69.8) for standard-risk participants and 43.2% (95% CI: 34.3, 51.8) for high-risk participants, while in Arm B, these rates were 76.6% (95% CI: 64.7, 85.0) and 75.6% (95% CI: 66.9, 82.2), respectively.

Treatment benefit of cilta-cel over standard of care by PFS was consistently observed in both the high-risk and standard-risk cytogenetics participant subgroups with HR of 0.25 and 0.40, respectively. In Arm A, participants with high-risk cytogenetics had a median PFS of 10.3 months vs 20.6 months for participants with standard-risk cytogenetics. However, in Arm B, this difference between high-risk and standard-risk cytogenetics was overcome upon treatment with cilta-cel (12-month PFS rate of 75.6% and 76.6%, respectively).

Table 26. Summary of Progression-free Survival Based on Computerized Algorithm by Cytogenetic Risk Group at Baseline; Cytogenetic-evaluable/ Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A		Arm B	
	Cytogenetic Standard-Risk	Cytogenetic High-Risk	Cytogenetic Standard-Risk	Cytogenetic High-Risk
Analysis set: intent-to-treat/cytogenetic evaluable[a]	70	132	69	123
Progression-free survival				
○ Number of events (%)	34 (48.6%)	81 (61.4%)	20 (29.0%)	40 (32.5%)
○ Number of censored (%)	36 (51.4%)	51 (38.6%)	49 (71.0%)	83 (67.5%)
Kaplan-Meier estimate (months)				
○ 25% quantile (95% CI)	5.5 (2.6, 10.4)	4.1 (3.1, 5.1)	13.2 (3.0, NE)	12.6 (6.1, 18.0)

Table 26. Summary of Progression-free Survival Based on Computerized Algorithm by Cytogenetic Risk Group at Baseline; Cytogenetic-evaluable/ Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A		Arm B	
	Cytogenetic Standard-Risk	Cytogenetic High-Risk	Cytogenetic Standard-Risk	Cytogenetic High-Risk
○ Median (95% CI)	20.6 (11.2, NE)	10.3 (7.6, 12.5)	NE (NE, NE)	NE (18.4, NE)
○ 75% quantile (95% CI)	NE (20.6, NE)	21.0 (16.0, NE)	NE (NE, NE)	NE (NE, NE)
6-month progression-free survival rate % (95% CI)	72.5 (60.3, 81.5)	64.2 (55.2, 71.9)	84.1 (73.1, 90.8)	82.9 (75.0, 88.5)
12-month progression-free survival rate % (95% CI)	59.2 (46.7, 69.8)	43.2 (34.3, 51.8)	76.6 (64.7, 85.0)	75.6 (66.9, 82.2)
18-month progression-free survival rate % (95% CI)	50.1 (37.2, 61.6)	27.2 (17.3, 38.0)	67.0 (52.7, 77.9)	67.3 (56.7, 75.9)
24-month progression-free survival rate % (95% CI)	40.0 (20.5, 59.0	NE (NE, NE)	67.0 (52.7, 77.9)	55.6 (41.6, 67.5)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval; FISH= fluorescence in situ hybridization.
[a] Subjects who are in the intent to treat population and meet the following cytogenetic risk categories. Standard risk patients: subjects that are negative for all del17p, t(14;16), t(4;14), or gain/amp(1q) by FISH. High risk patients: subjects that are positive for any of del17p, t(14;16), t(4;14), or gain/amp(1q) by FISH.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

CR or Better Rate

In Arm A, CR or better rate based on computerized algorithm was 25.7% for participants with standard-risk cytogenetics at baseline versus 19.7% for participants with high-risk cytogenetics; in Arm B, CR or better rate based on computerized algorithm was 73.9% for participants with standard-risk cytogenetics at baseline versus 73.2% for participants with high-risk cytogenetics. Patients with high-risk cytogenetics had higher rates of deep response with cilta-cel than those treated with standard of care.

Table 27. Summary of CR or Better Rate Based on Computerized Algorithm by Cytogenetic Risk Group at Baseline; Cytogenetic-evaluable/ Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A		Arm B	
	Cytogenetic Standard-Risk	Cytogenetic High-Risk	Cytogenetic Standard-Risk	Cytogenetic High-Risk

Table 27. Summary of CR or Better Rate Based on Computerized Algorithm by Cytogenetic Risk Group at Baseline; Cytogenetic-evaluable/ Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A		Arm B	
	Cytogenetic Standard-Risk	Cytogenetic High-Risk	Cytogenetic Standard-Risk	Cytogenetic High-Risk
Analysis set: intent-to-treat/cytogenetic evaluable[a]	70	132	69	123
CR or Better Rate	18 (25.7%)	26 (19.7%)	51 (73.9%)	90 (73.2%)
95% CI of CR or better rate[b]	(16.0%, 37.6%)	(13.3%, 27.5%)	(61.9%, 83.7%)	(64.4%, 80.8%)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval; CR=complete response; FISH= fluorescence in situ hybridization.
[a] Subjects who are in the intent to treat population and meet the following cytogenetic risk categories. Standard risk patients: subjects that are negative for all del17p, t(14;16), t(4;14), or gain/amp(1q) by FISH. High risk patients: subjects that are positive for any of del17p, t(14;16), t(4;14), or gain/amp(1q) by FISH.
[b] Exact 95% confidence intervals are provided.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

ORR

In Arm A, ORR based on computerized algorithm was 71.4% for participants with standard-risk cytogenetics at baseline versus 65.9% for participants with high-risk cytogenetics; in Arm B, ORR based on computerized algorithm was 85.5% for participants with standard-risk cytogenetics at baseline versus 85.4% for participants with high-risk cytogenetics.

Table 28. Summary of Overall Response Rate Based on Computerized Algorithm by Cytogenetic Risk Group at Baseline; Cytogenetic-evaluable/ Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A		Arm B	
	Cytogenetic Standard-Risk	Cytogenetic High-Risk	Cytogenetic Standard-Risk	Cytogenetic High-Risk
Analysis set: intent-to-treat/cytogenetic evaluable[a]	70	132	69	123
Overall response (sCR + CR + VGPR + PR)	50 (71.4%)	87 (65.9%)	59 (85.5%)	105 (85.4%)
95% CI of ORR[b]	(59.4%, 81.6%)	(57.2%, 73.9%)	(75.0%, 92.8%)	(77.9%, 91.1%)

Table 28. Summary of Overall Response Rate Based on Computerized Algorithm by Cytogenetic Risk Group at Baseline; Cytogenetic-evaluable/ Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A		Arm B	
	Cytogenetic Standard-Risk	Cytogenetic High-Risk	Cytogenetic Standard-Risk	Cytogenetic High-Risk

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval; CR=complete response; FISH= fluorescence in situ hybridization; ORR=overall response rate; PR=partial response; sCR=stringent complete response; VGPR=very good partial response.
[a] Subjects who are in the intent to treat population and meet the following cytogenetic risk categories. Standard risk patients: subjects that are negative for all del17p, t(14;16), t(4;14), or gain/amp(1q) by FISH. High risk patients: subjects that are positive for any of del17p, t(14;16), t(4;14), or gain/amp(1q) by FISH.
[b] Exact 95% confidence intervals are provided.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

MRD Negativity

Patients with high-risk cytogenetics had higher rates of MRD negativity with cilta-cel than those treated with standard of care.

Table 29. Summary of MRD Negativity Rate at 10^{-5} in Bone Marrow by Cytogenetic Risk Group at Baseline; Cytogenetic-evaluable/ Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A		Arm B	
	Cytogenetic Standard-Risk	Cytogenetic High-Risk	Cytogenetic Standard-Risk	Cytogenetic High-Risk
Analysis set: intent-to-treat/cytogenetic evaluable[a]	70	132	69	123
Overall MRD Negativity Rate at 10^{-5} in Bone Marrow	13 (18.6%)	19 (14.4%)	34 (49.3%)	86 (69.9%)
95% CI of MRD Negativity Rate[b]	(10.3%, 29.7%)	(8.9%, 21.6%)	(37.0%, 61.6%)	(61.0%, 77.9%)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval; FISH= fluorescence in situ hybridization; MRD = minimal residual disease.
[a] Subjects who are in the intent to treat population and meet the following cytogenetic risk categories. Standard risk patients: subjects that are negative for all del17p, t(14;16), t(4;14), or gain/amp(1q) by FISH. High risk patients: subjects that are positive for any of del17p, t(14;16), t(4;14), or gain/amp(1q) by FISH.
[b] Exact 95% confidence intervals are provided.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

Table 30. Summary of MRD Negativity Rate at 10^{-5} in Bone Marrow by Cytogenetic High-Risk Marker at Baseline; Cytogenetic High-Risk/ Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A			Arm B		
	N[a]	n[b] (%)	95% CI for %	N[a]	n[b] (%)	95% CI for %
Analysis set: intent-to-treat/cytogenetic high risk[c]	132			123		
Overall MRD Negativity Rate at 10^{-5} in Bone Marrow						
○ t(4;14)	30 (22.7%)	4 (13.3%)	(3.8%, 30.7%)	30 (24.4%)	20 (66.7%)	(47.2%, 82.7%)
○ t(14;16)	7 (5.3%)	0	(NE, NE)	3 (2.4%)	2 (66.7%)	(9.4%, 99.2%)
○ del17p	43 (32.6%)	4 (9.3%)	(2.6%, 22.1%)	49 (39.8%)	32 (65.3%)	(50.4%, 78.3%)
○ gain/amp(1q)	107 (81.1%)	16 (15.0%)	(8.8%, 23.1%)	89 (72.4%)	63 (70.8%)	(60.2%, 79.9%)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval; FISH= fluorescence in situ hybridization; MRD = minimal residual disease.
[a] N = number of subjects.
[b] n = number of subjects with response.
[c] Subjects who are in the intent-to-treat population and meet the following cytogenetic risk category. High risk patients: subjects that are positive for any of del17p, t(14;16), t(4;14), or gain/amp(1q) by FISH.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.
Note: Response was assessed by computerized algorithm, based on International Myeloma Working Group (IMWG) consensus criteria (Kumar 2016).
Note: Percentages are calculated with the number of subjects in the intent-to-treat analysis set with cytogenetic high risk as denominator.

OS

As noted for the main OS analysis presented above, OS data for cytogenetic risk subgroups are not yet mature, and rates of OS events are similar for standard-risk and high-risk subgroups within each treatment arm.

There may be a trend towards OS benefit for patients with high-risk cytogenetics treated with cilta-cel than those treated with standard of care.

Table 31. Summary of Overall Survival by Cytogenetic Risk Group at Baseline; Cytogenetic-evaluable/ Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A		Arm B	
	Cytogenetic Standard-Risk	Cytogenetic High-Risk	Cytogenetic Standard-Risk	Cytogenetic High-Risk
Analysis set: intent-to-treat/cytogenetic evaluable[a]	70	132	69	123

Table 31. Summary of Overall Survival by Cytogenetic Risk Group at Baseline; Cytogenetic-evaluable/ Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A		Arm B	
	Cytogenetic Standard-Risk	Cytogenetic High-Risk	Cytogenetic Standard-Risk	Cytogenetic High-Risk
Overall survival				
○ Number of events (%)	14 (20.0%)	29 (22.0%)	13 (18.8%)	22 (17.9%)
○ Number of censored (%)	56 (80.0%)	103 (78.0%)	56 (81.2%)	101 (82.1%)
Kaplan-Meier estimate (months)				
○ 25% quantile (95% CI)	NE (10.5, NE)	21.4 (14.5, NE)	NE (7.1, NE)	NE (16.2, NE)
○ Median (95% CI)	NE (NE, NE)	26.7 (22.5, NE)	NE (NE, NE)	NE (NE, NE)
○ 75% quantile (95% CI)	NE (NE, NE)	26.7 (NE, NE)	NE (NE, NE)	NE (NE, NE)
6-month survival rate % (95% CI)	89.9 (79.9, 95.0)	96.9 (92.0, 98.8)	88.4 (78.2, 94.0)	93.5 (87.4, 96.7)
12-month survival rate % (95% CI)	82.6 (71.4, 89.7)	85.3 (78.0, 90.4)	82.6 (71.3, 89.7)	85.4 (77.8, 90.5)
18-month survival rate % (95% CI)	77.4 (64.0, 86.3)	75.1 (64.5, 83.0)	79.5 (66.6, 87.9)	81.4 (72.4, 87.7)
24-month survival rate % (95% CI)	77.4 (64.0, 86.3)	56.9 (30.4, 76.6)	79.5 (66.6, 87.9)	78.0 (66.3, 86.0)

Key: Arm A = PVd or DPd; Arm B = A sequence of apheresis, bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine), and cilta-cel infusion.
Key: PVd = pomalidomide-bortezomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone.
Key: CI = confidence interval; FISH= fluorescence in situ hybridization.
[a] Subjects who are in the intent to treat population and meet the following cytogenetic risk categories. Standard risk patients: subjects that are negative for all del17p, t(14;16), t(4;14) or gain/amp(1q) by FISH. High risk patients: subjects that are positive for any of del17p, t(14;16), t(4;14) or gain/amp(1q) by FISH.
Note: Intent-to-treat analysis set consists of subjects who were randomized in the study.

Lentiviral Vector: Bern LV vs CCHMC LV

Of the 196 total Arm B participants who received cilta-cel, 97 participants received cilta-cel manufactured with CCHMC LV (including 90 participants who received cilta-cel as study treatment and 7 participants who received cilta-cel as subsequent therapy) and 99 participants received cilta-cel manufactured with Bern LV (including 86 participants who received cilta-cel as study treatment and 13 participants who received cilta-cel as subsequent therapy).

Comparable efficacy was observed regardless of LV (Bern vs CCHMC) used to manufacture the cilta-cel product:

PFS

The 12-month PFS rate was 87.8% (95% CI: 79.0%, 93.0%) for the CCHMC LV subgroup, and 91.6% (95% CI: 83.2%, 95.9%) for the Bern LV subgroup, indicating no difference in PFS according to whether participants received cilta-cel as study treatment manufactured with CCHMC LV or Bern LV.

CR or Better Rate

Rate of CR or better was higher for participants who received cilta-cel (as study treatment) manufactured with CCHMC LV vs. Bern LV (91.1% vs. 81.4%, respectively), though duration of follow-up was longer for the CCHMC LV subgroup (median 19.1 months) than for the Bern LV subgroup (median 13.7 months).

ORR

Arm B participants who received cilta-cel (as study treatment) manufactured with CCHMC LV vs. Bern LV: 98.9% vs. 100.0%, respectively.

MRD Negativity

Similar rates of MRD negativity were observed for Arm B participants who received cilta-cel (as study treatment) manufactured with CCHMC LV vs. Bern LV: 74.4% vs. 68.6%, respectively.

OS

The 12-month OS rate was 92.2% (95% CI: 84.4%, 96.2%) for the CCHMC LV subgroup, and 93.0% (95% CI: 85.1%, 96.8%) for the Bern LV subgroup, indicating no difference in OS according to whether participants received cilta-cel as study treatment manufactured with CCHMC LV or Bern LV.

Arm B Participants who Received Cilta-Cel as Subsequent Therapy

Twenty participants in Arm B had confirmed disease progression prior to cilta-cel infusion and received conditioning regimen and cilta-cel infusion as subsequent therapy with sponsor approval.

As any multiple myeloma therapy given after disease progression is considered subsequent therapy, adverse events and deaths that occurred after subsequent therapy with cilta-cel are not considered treatment-emergent. Separate analyses were performed for these 20 participants with early disease progression on bridging therapy.

Among the 20 Arm B participants, 6 participants (30%) received PVd and 14 participants (70%) received DPd as bridging therapy after randomization per investigator's choice. Seven participants (35%) received 1 additional subsequent therapy and 1 participant (5%) received 2 additional subsequent therapies after disease progression on bridging therapy and prior to lymphodepletion and cilta-cel infusion.

PFS data by computerized algorithm were censored for 8 participants (40%) who received cilta-cel as subsequent therapy. The 8 participants were alive and without disease progression as of the clinical cutoff.

Median PFS was 7.39 months (95% CI: 1.61, NE) since cilta-cel infusion. The 12-month PFS rate was 39.4% (95% CI: 18.6, 59.7).

Baseline is defined as last non-missing measurement prior to the start of conditioning regimen followed immediately by cilta-cel infusion. Based on computerized algorithm, CR or better rate was 40% (95% CI: 19.1%, 63.9%), and the ORR was 65% (95% CI: 40.8%, 84.6%) for Arm B participants who received cilta-cel as subsequent therapy.

At the time of clinical cutoff, 10 participants (50%) in Arm B who received cilta-cel as subsequent therapy had died. The median OS was 13.4 months (95% CI: 4.93, NE) and the 12-month OS rate was 54.5% (95% CI: 30.7, 73.2) since the time of randomization.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 32. Summary of Efficacy for trial MMY3002

Title: A Phase 3 Randomized Study Comparing JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA, versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Subjects with Relapsed and Lenalidomide-Refractory Multiple Myeloma		
Study identifier	CARTITUDE-4; 68284528MMY3002 (EudraCT number: 2019-001413-16)	
Design	Study MMY3002 is a Phase 3, randomized, open-label, multicenter study in participants with relapsed and lenalidomide-refractory multiple myeloma treated with 1 to 3 prior lines of therapy to determine whether treatment with cilta-cel would provide efficacy benefit compared to investigator's choice of PVd or DPd. Participants were randomized in a 1:1 ratio to Arm A (standard therapy with PVd or DPd) or Arm B (cilta-cel) according to the planned stratification factors. Stratification factors included ISS at screening (I vs. II vs. III), investigator's choice of PVd vs. DPd, and number of prior lines of therapy (1 vs. 2 or 3).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	30 June 2020 to 1 November 2022 (Date of last observation for last participant recorded as part of the database for the current analysis) not applicable not applicable
Hypothesis	Superiority: The primary hypothesis was that cilta-cel will significantly improve PFS compared with standard therapy (PVd or DPd) in subjects who have previously received 1 to 3 prior line(s) of therapy, that included a PI and an IMiD, and who are refractory to lenalidomide. It was assumed that cilta-cel can reduce the risk of progressive disease or death by 35%, ie, HR (cilta-cel vs. standard therapy) of 0.65, which translated to a median PFS of 20 months for Arm B, assuming the median PFS for Arm A was 13 months.	
Treatments groups	Arm A (SOCT)	PVd (pomalidomide-bortezomib-dexamethasone): 28 patients DPd (daratumumab-pomalidomide-dexamethasone): 183 patients Total number randomized: 211
	Arm B (Cilta-cel)	cilta-cel infusion administered with the target dose of 0.75 x 10^6 CAR-positive viable T cells/kg following conditioning regimen of IV cyclophosphamide 300 mg/m^2 and IV fludarabine 30 mg/m^2 daily for 3 days on CAR-T Day -5, -4, -3 prior to cilta-cel infusion. 208 patients randomized, 176 patients treated

Endpoints and definitions	Primary endpoint	PFS	Progression-free survival is defined as the time from the date of randomization to the date of first documented disease progression, as defined in the IMWG criteria, or death due to any cause, whichever occurs first. For subjects who have not progressed and are alive, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.
	Key secondary endpoints	CR/sCR	Complete response (CR)/sCR is defined as the proportion of subjects who achieve a CR or sCR response according to the IMWG criteria.
		Overall MRD negativity	Overall MRD negativity is defined as the proportion of subjects who achieve MRD negativity at any time after the date of randomization before initiation of subsequent therapy.
		OS	Overall survival is measured from the date of randomization to the date of the subject's death. If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive.
		ORR	Overall response rate (ORR) is defined as the proportion of subjects who achieve a PR or better according to the IMWG criteria. Response to treatment will be analyzed by a validated computerized algorithm.
		Time to worsening of symptoms	Time to worsening of symptoms is measured as the interval from the date of randomization to the start date of worsening in the MySIm-Q total symptom score. The criteria for worsening will be derived based on anchor-based methods using the PGIS for overall health. Death due to disease progression will be considered as worsening. Subjects who have not met the definition of worsening will be censored as of the last assessment date of the MySIm-Q.
	Other endpoints	Rate of MRD negativity in subjects with CR/sCR at 12 months $\pm$ 3 months	Defined as the proportion of subjects who achieve MRD-negative status and are in CR/sCR within time window.
		Rate of sustained MRD negativity	Defined as the proportion of subjects who achieve MRD negativity, confirmed minimum 1 year apart and without any examination showing MRD-positive status in between.
		Progression-free survival on next-line therapy (PFS2)	Defined as the time interval between the date of randomization and date of event, which is defined as progressive disease as assessed by investigator that starts after the next line of subsequent therapy, or death from any cause, whichever occurs first.
		Duration of Response	Time from the date of initial documentation of a response (PR or better) to the date of first documented evidence of disease progression
		Time to Subsequent Anti-myeloma Treatment	Time from randomization to the first day when subjects receive another antimyeloma treatment

		Time to Disease Progression	Time from randomization to disease progression
Database lock	15 December 2022		
Results and Analysis			
Analysis description	**Primary Analysis**		

	Arm A SOCT (PVd or DPd) (N = 211)	Arm B cilta-cel (N = 208)
Primary Endpoint		
Progression-free survival (PFS)		
Number of events (%)	122 (57.8%)	65 (31.3%)
Number of censored (%)	89 (42.2%)	143 (68.8%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	4.11 (3.38, 5.32)	12.91 (7.29, 17.97)
Median (95% CI)	11.79 (9.66, 13.77)	NE (22.83, NE)
75% quantile (95% CI)	20.96 (20.63, NE)	NE (NE, NE)
P-value[a] Hazard ratio (95% CI)[b]	<0.0001 0.26 (0.18, 0.38)	
6-month PFS rate % (95% CI)	66.5 (59.5, 72.5)	82.7 (76.8, 87.2)
12-month PFS rate % (95% CI)	48.6 (41.5, 55.3)	75.9 (69.4, 81.1)
18-month PFS rate % (95% CI)	35.7 (28.0, 43.4)	67.8 (60.0, 74.5)
24-month PFS rate % (95% CI)	18.7 (6.8, 35.2)	56.4 (43.7, 67.3)
Key Secondary Endpoints		
CR or better		
sCR + CR [n (%) (95% CI for %)]	46 (21.8%) (16.4%, 28.0%)	152 (73.1%) (66.5%, 79.0%)
sCR [n (%) (95% CI for %)]	32 (15.2%) (10.6%, 20.7%)	121 (58.2%) (51.2%, 65.0%)
CR [n (%) (95% CI for %)]	14 (6.6%) (3.7%, 10.9%)	31 (14.9%) (10.4%, 20.5%)
ORR		
sCR + CR + VGPR + PR [n (%) (95% CI for %)]	142 (67.3%) (60.5%, 73.6%)	176 (84.6%) (79.0%, 89.2%)
MRD negativity rate (10^{-5})		
n (%) (95% CI)	33 (15.6%) (11.0%, 21.3%)	126 (60.6%) (53.6%, 67.3%)
Overall survival (OS)		
Number of events (%)	47 (22.3%)	39 (18.8%)
Number of censored (%)	164 (77.7%)	169 (81.3%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	21.42 (14.62, NE)	22.83 (16.36, NE)
Median (95% CI)	26.74 (22.47, NE)	NE (NE, NE)
75% quantile (95% CI)	26.74 (NE, NE)	NE (NE, NE)

P-value[a] Hazard ratio (95% CI)[b]	0.2551* 0.78 (0.50, 1.20)	
6-month survival rate % (95% CI)	94.2 (90.1, 96.7)	91.3 (86.6, 94.5)
12-month survival rate % (95% CI)	83.6 (77.8, 88.0)	84.1 (78.4, 88.4)
18-month survival rate % (95% CI)	75.1 (67.4, 81.2)	80.8 (74.2, 85.9)
24-month survival rate % (95% CI)	65.7 (50.0, 77.5)	73.6 (59.6, 83.4)
Time to worsening in MySIm-Q total symptom score		
Number of events (%)	46 (21.8%)	30 (14.4%)
Number of censored (%)	165 (78.2%)	178 (85.6%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	9.20 (6.14, 11.79)	20.90 (16.69, NE)
Median (95% CI)	18.86 (16.76, NE)	23.66 (22.11, NE)
75% quantile (95% CI)	NE (18.86, NE)	23.66 (22.57, NE)
P-value[a] Hazard ratio (95% CI)[b]	0.0003 0.42 (0.26, 0.68)	
6-month event-free rate % (95% CI)	84.5 (77.7, 89.3)	91.5 (86.2, 94.8)
12-month event-free rate % (95% CI)	65.6 (55.2, 74.2)	84.6 (77.7, 89.6)
18-month event-free rate % (95% CI)	51.9 (34.5, 66.8)	79.8 (69.6, 86.9)
Other Endpoints		
Rate of MRD negativity (10^{-5}) with CR/sCR at 12+/-3 months		
n (%) (95% CI)	15 (7.1%) (4.0%, 11.5%)	49 (23.6%) (18.0%, 29.9%)
Sustained MRD-negative status **		
n (%)	2 (0.9%)	10 (4.8%)
Progression-free survival on next line of therapy		
n (%)	65 (30.8%)	45 (21.6%)
Duration of response in responders (Arm A: 142, Arm B: 176)		
Number of events (%)	62 (43.7%)	33 (18.8%)
Number of censored (%)	80 (56.3%)	143 (81.3%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	8.31 (5.95, 10.61)	17.08 (14.39, NE)
Median (95% CI)	16.56 (12.88, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (19.81, NE)	NE (NE, NE)
6-month event-free rate % (95% CI)	82.2 (74.9, 87.6)	94.3 (89.6, 96.9)
12-month event-free rate % (95% CI)	63.0 (54.2, 70.6)	84.7 (78.1, 89.4)
18-month event-free rate % (95% CI)	48.9 (38.0, 58.8)	74.3 (63.9, 82.0)
24-month event-free rate % (95% CI)	29.3 (10.5, 51.3)	71.3 (59.5, 80.2)
Time to subsequent anti-myeloma treatment		
months (95% CI)	13.5 (12.0, 17.1)	NE (NE, NE)
Time to disease progression		
months (95% CI)	12.0 (10.2, 14.7)	NE (NE, NE)

Notes	*- OS was not statistically significant, but shows a tendency for benefit in the cilta-cel arm ** - data not yet mature.	
Analysis description	**The following sensitivity and subgroup analyses were performed (amongst others):** PFS: unweighted stratified log-rank test. HR=0.40 (95%-CI: 0.29, 0.55), p<0.0001 PFS: CPW unstratified log-rank test. HR=0.27 (95%-CI: 0.19, 0.39), p<0.0001 PFS: based on investigator assessed disease progression, by CPW. HR=0.25 (95%-CI: 0.18, 0.37), p<0.0001 PFS: Subgroup analyses for baseline hepatic function, refractory status, prior exposure to different treatment lines, region, sex, age group, and baseline ECOG (all consistent with overall analysis) ORR: based on investigator assessment, and different subgroup analyses (all consistent with overall analysis) OS: CPW unstratified log-rank test. HR=0.82 (95%-CI: 0.54, 1.26), p<0.0001 OS: different subgroup analyses (mostly consistent with main analysis, however not significant)	

Supportive study

Study 68284528MMY2003, a Phase 2, Multicohort Open-Label Study of JNJ-68284528, a Chimeric Antigen Receptor T cell (CAR-T) Therapy Directed Against BCMA in Subjects with Multiple Myeloma.

This was an open-label, uncontrolled study. Cohort A enrolled 40 subjects (initially 20 subjects: LV CCHMC; expanded cohort A 20 subjects: LV Bern). 26 subjects provided informed consent, whereof 20 received the conditioning regimen followed by cilta-cel at the targeted dose (mITT and All-treated Analysis Sets).

ORR by computerized algorithm was 95.0% (95% CI: 75.1% - 99.9%). Stringent CR and CR were achieved by 75.0% (95% CI: 50.9%-91.3%) and 10.0% (95% CI: 1.2%-31.7%) of subjects, respectively; 95.0% (95% CI: 71.5%-99.9%) subjects achieved VGPR or better.

Median PFS was not yet reached, 12-month PFS rate was 75% (95%-CI: 50.0%, 88.7%).

Median OS was not yet reached, 12-month OS rate was 95% (95%-CI: 69.5%, 99.3%).

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The study is a randomised clinical trial and its design is acceptable. A total of 419 patients were randomized 1:1 into two arms of the study. Arm A was the standard of care treatment arm, where patients were treated with PVd or DPd. In Arm B patients underwent apheresis, received bridging therapy (same as in Arm A), were subjected to lymphodepleting chemotherapy and then received cilta-cel. No crossover of patients from Arm A to Arm B occurred. The patients are fairly distributed and well-balanced in the two treatment arms, similar distributions across age, sex race ethnicity and ECOG score were included in the trial. No major discrepancies were seen in the subgroups of disease characteristics, the

patients are distributed in similar numbers across both arms of the study. Regarding prior lines of therapy, patients are similarly distributed along the subgroups in the two arms. Only one third of the patients in both arms received one line of prior therapy.

As for the choice of the control arm and bridging therapy, in general, the choice of treatment scheme for multiple myeloma depends on prior drug exposure and the subsequent response. Options to treat lenalidomide refractory patients include DPd and PVd, according to the refractory status to bortezomib or daratumumab, therefore, the choice of the two combinations are reflecting current standard of care for the selected patient population, and their use as comparators/bridging therapy is considered appropriate.

The inclusion and exclusion criteria are acceptable and are adequately summarized in the SmPC.

The dose of cilta-cel is the same as in the initial approval. Bridging therapy in Arm B was allowed and included the same combination schemes as in the control Arm A of the study. This is an appropriate choice of bridging therapy. A standard cyclophosphamide/fludarabine lymphodepletion chemotherapy regimen was administered. This is considered acceptable.

During the study, the lentiviral vector for cilta-cel was produced at two manufacturing sites. Of the 176 Arm B participants who received cilta-cel as study treatment, 90 participants received cilta-cel manufactured with CCHMC LV and 86 participants received cilta-cel manufactured with Bern LV. For all PK/PD and clinical efficacy data, results are compared for the two product versions.

The primary and secondary endpoints are acceptable and in line with the current EMA Guideline "Evaluation of anticancer medicinal products in man". Importantly, CR/sCR and MRD negativity were also reported as secondary endpoints. This is highly endorsed because these are the main measures to investigate the depth of the therapeutic success in Multiple Myeloma.

The sample size, randomization and stratification design are appropriate to address the formulated study hypothesis.

The primary hypothesis was that Carvykti significantly improves PFS compared with standard therapy (PVd or DPd) in subjects who have previously received 1 to 3 prior lines of therapy, that included a PI and an IMiD, and who are refractory to lenalidomide. The sample size calculation was performed based on the assumption that cilta-cel can reduce the risk of progressive disease or death by 35%, ie, HR (cilta-cel vs. standard therapy) of 0.65, which translated to a median PFS of 20 months for Arm B, assuming the median PFS for Arm A was 13 months.

Initially, a regular log-rank test was planned for evaluation of the primary endpoint. However, as both arms received 2 cycles of same bridging therapy (approx. 8 weeks), primary analysis of the PFS endpoint utilized a constant piecewise weighted (CPW) log-rank test (with stratification factors from randomisation), where the weight was 0 for the first 8 weeks post-randomization, and 1 afterwards. The statistical methods are acceptable.

Efficacy data and additional analyses

As of clinical cutoff date of 01 November 2022, the study is ongoing, with a number of participants still ongoing follow-up or SOC therapy.

208 subjects were randomized to Arm B. 32 patients discontinued before receiving cilta-cel. From these 11 died without receiving cilta-cel, 10 died following cilta-cel therapy (totalling 21 deaths). 176 subjects received cilta-cel as a study treatment. From 176 patients 17 discontinued because they had progressive disease post-infusion, and 16 subjects died. Additionally, 2 subjects died during follow-up, totalling 18 deaths. In total, 39 patients died in this study arm.

For the primary endpoint, a statistically significant difference in PFS favouring cilta-cel was demonstrated. At a median follow-up of 15.9 months (data cut off 1 November 2022), a PFS event was reported for 57.8% of participants in Arm A and for 31.3% of participants in Arm B; median PFS was 11.8 months (95% CI: 9.7, 13.8) for Arm A and NE (95% CI: 22.8, NE) for Arm B. The HR was 0.26 (95% CI: 0.18, 0.38). The HR of 0.26 indicates a 74% reduction in the risk of death or progression for Arm B as compared with Arm A. The 12-month PFS rates were 48.6% for Arm A and 75.9% for Arm B. The follow-up is rather short (Arm A: median 15.9 months, range 0.1-26.7; Arm B: median 16.0 months, range 0.2-27.3). Of the 176 patients who received CARVYKTI as study treatment, the median progression free survival (PFS) was not estimable (95% CI: not estimable, not estimable) with a 12month PFS rate of 89.7%.

The treatment effect of Arm B over Arm A was consistent across all pre-specified subgroups, including the following key subgroups: participants with 1 prior line of therapy (HR=0.35 [95% CI: 0.19, 0.66]), ISS Stage III (HR=0.33 [95% CI: 0.11, 0.95]), high tumour burden (HR=0.27 [95% CI: 0.13, 0.56]), and high-risk cytogenetics (HR=0.25 [95% CI: 0.16, 0.38]).

Interestingly, the 2 Kaplan-Meier curves crossed at around 3 months after randomization, by which time 27 and 31 PFS events had occurred in Arm A and Arm B, respectively. It is unknown at this stage what caused this early imbalance in PFS events. The time from first apheresis to cilta-cel infusion was a median of 79 days; the impact of cilta-cel on PFS becomes apparent after the first 3 months. The conclusion of the MAH that the imbalance in PFS events may have been due to random variability or the higher relative dose intensity of study treatment in Arm A compared with bridging therapy on Arm B during the first 3 cycles of treatment is not providing a satisfactory explanation of the finding on crossing curves. In the first 8 weeks, 22 PFS events were observed on Arm B compared with 8 on Arm A. During this period, both arms were receiving the same treatment (PVd/DPd as bridging therapy on Arm B and as standard therapy on Arm A). All 22 events on Arm B occurred prior to cilta-cel infusion, all patients had progressive disease. This is surprising given the fact that no major differences were described for the two arms. Crossing survival curves is generally a result of the survival times having greater variance in one treatment group than another (Trials. 2011; 12(Suppl 1): A137.). Additional subgroup analysis carried out by the MAH did not identify any subgroups that could have an additional risk for worst outcome in the Arm B.

Additional analyses have been provided as requested in which the applicant concluded that other than lower relative dose intensity of pomalidomide, no other baseline or early post-baseline covariate imbalance has been identified. Lower doses of pomalidomide administered during bridging cycles to participants in Arm B, compared to the doses of pomalidomide administered during this period to participants in Arm A, may have played a role in the higher number of early PFS events in Arm B. Nevertheless, this relationship is also valid for the other patients in both groups who did not have an early PFS event (95.5% Arm A vs 81.3% Arm B). In the subgroup of Arm B patients with a PFS event within 8 weeks after randomization, relative dose proportion of pomalidomide was 71.4%, but in Arm A this was 69%. This similar value would imply a similar number of early PFS events in both arms of the study, but this is not the case (7 in arm A vs. 22 in Arm B). Additionally, 56.7% of subjects in Arm A and 35.3% of subjects in the cilta-cel arm received reduced pomalidomide. Therefore it is less likely that pomalidomide dose may have not contributed to the crossing curves in the KM plots. Moreover, similar relationships can be seen for bortezomib dose intensity as well.

The only important difference between the patients in the two arms is found in the number of lytic bone lesions, where patients in Arm B had relatively higher numbers as compared to patients in Arm A. However, this aspect should not have an influence on PFS events.

At this stage it can only be concluded, that despite a probably well-balanced distribution of the presented subgroups in both arms of the study, there is a likelihood of an unidentified patient subgroup, which may be prone to have an elevated early risk of PFS events, thus less likely to benefit from the therapeutic

approach involving the CAR-T cells. A relevant warning is added to the SmPC to address this uncertainty also in line with the SAG suggestions (See also Additional expert consultation in this section).

It is well known that in general CAR-T cells require a median expression of 2,000-3,000 target molecules/cell in order to achieve adequate clinical responses. It is well known from the CD19 targeting CAR-T cell literature that low antigen expression has a negative influence on efficacy and outcomes of CAR-T cell therapy (Nat Med. 2021 Aug;27(8):1419-1431). Additionally, heterogeneously expressed BCMA at the intra-tumor level can lead to preferential targeting of cells with high BCMA while sparing those with low/zero BCMA expression (Blood Cancer J. 2021 Apr 29;11(4):84). Further analysis of BCMA expression intensity indicated that there were no differences in 12-month PFS rate, ORR, or CR or better rate according to whether participants' BCMA expression intensity was above or below the median value. All patients were BCMA expressor in the trial, and no low expressors with an inferior outcome could be identified.

The sCR/CR, ORR and MRD negativity rate (10^{-5}) data look compelling. There is a clear advantage of cilta-cel treatment over SOC for these measures.

Initial OS data suggested a trend towards improved survival in Arm B vs. Arm A (HR=0.78; 95% CI: 0.50, 1.20; p=0.2551). The KM plot for OS also shows crossing curves. There is no difference between the curves until about 1.5 months into the study period, then there is a better outcome for the SOC Arm A until about months 11-12, from which time point then there is an OS advantage for the Arm B patients. Censoring for COVID-19 related deaths does not radically influence the shape of the curves.

Crossing survival curves is generally a result of the survival times having greater variance in one treatment group than another (Trials. 2011; 12(Suppl 1): A137.). There seems to be a well-balanced distribution of subgroups in both arms of the study. The higher number of deaths in Arm B vs Arm A in the first 3 months after randomization is not related to cilta-cel. The deaths in the first 3 months were mainly due to disease progression and occurred before participants received cilta-cel. This aspect is again unexpected, as the two arms were well balanced. As for PFS, additional analysis did not identify any underlying subgroup, which could be linked to the higher number of OS events in Arm B. The cause of death was mainly PD in the patients in Arm B, and died before being treated with cilta-cel. There are no obvious underlying differences to link this finding to bridging therapy or patient characteristics.

Updated OS data were provided by the MAH following survival sweep analysis performed on 13 December 2023. The current analysis reflects 13 additional deaths (10 in Arm A; 3 in Arm B) since the clinical cutoff of 17 April 2023. Of note, to avoid any potential type I error inflation, statistical testing was not performed in this requested analysis. The number of events was 77 (36.5%) in Arm A and 48 (23.1%) in Arm B, respectively. The 36-months survival rate was 53.1% (95% CI: 39.6. 65.0) for the SOC arm and 76.2 (95% CI: 69.6, 81.6) for the cilta-cel arm. These data continue to demonstrate a favourable trend in OS that appears to be strengthening over time. These OS data are supportive of the clinical benefit in combination with the unambiguous PFS data and the other clinically meaningful endpoints such as rate of CR/sCR, ORR, and overall MRD negativity rate when compared to standard of care.

The time to worsening of symptoms in the MySIm-Q Total Symptom Score was longer for Arm B; however, the results should be interpreted with caution due to open-label design of the study.

Further, other endpoints (PFS2, DOR, rate of MRD negativity rate, Time to Subsequent Anti-myeloma Treatment and Time to Disease Progression) keeping in consideration the statistical uncertainties were all in favour of the treatment arm.

Overall, the efficacy profile (PFS, ORR, CR or better, MRD-negativity rate, OS) for cilta-cel manufactured with CCHMC LV and Bern LV was comparable and consistent with the efficacy profile demonstrated in the CARTITUDE-1 (68284528MMY2001) pivotal study and study MMY2003.

Final data from the pivotal study (MMY3002) submitted in support of this extension of indication, even though no more object of the SOB as the data submitted provide comprehensive evidence for a full marketing authorisation, are recommended to be submitted post approval when final (REC in the letter of recommendations).

Additional expert consultation

On February 6th, 2024 a SAG oncology has been organised to answer the following questions to which the relevant position of the experts is provided:

1. *Given the overall effect on PFS, an unexplained possible early detrimental effect for PFS as well as OS and immaturity of OS data overall, does the SAG consider that the available data support that a clinically relevant benefit has been demonstrated in the target population?*

The SAG agreed that overall a benefit has been demonstrated in terms of PFS, the primary endpoint, and ORR. The results were statistically and clinically convincing. The benefit was clear in the claimed indication and corroborated by a consistent effect across subgroups and in terms of health-related quality of life (HRQoL). The benefit was also clear from a patient perspective, especially considering the observed treatment-free interval following CAR-T therapy compared to other treatments and the benefit in HRQoL. A slight but not significant improvement in OS in favour of cilta-cel (Carvykti) has been observed.

Early deaths were observed for some patients applying the bridging strategies in the MMY3002 Phase 3, randomized trial. These events may be associated with high-risk patients with worse prognosis for OS. However, it is expected that bridging therapies according to current standards, including adapting the strategy according to prognosis, might be able to reduce the risk of early death.

Further data (e.g., observational) should be collected to confirm the benefit of optimising bridging therapy to avoid early deaths in high-risk patients.

2. *Please discuss for which patients with r/r multiple myeloma, matching study inclusion criteria, cilta-cel would be an appropriate treatment option. Please also consider if there are identifiable subpopulations where cilta-cel should be avoided.*

The early deaths observed were not associated with cilta-cel (Carvykti) but appeared to be related to suboptimal bridging strategies and failure to undergo CAR-T cell infusion.

Poor prognostic factors for progression may also increase the risk of early death and this needs to be managed through more effective bridging therapy rather than patient exclusion. In any case, the choice of prognostic factors is not clear and risk classifications are evolving.

If patients have clinically rapidly progressive disease, the aim of treatment should be controlling the disease so that CAR-T therapy becomes a possibility. If patients are not expected to be able to access infusion in due time, then CAR-T therapy should be avoided until this becomes feasible and/or patients should be referred to alternative therapeutic options. However, *a priori* exclusion of high-risk patients should be avoided. Information on high-risk patients prone to rapid progression of disease due to specific clinical abnormalities should be reflected as a warning in the SmPC (section 4.4).

2.4.3. Conclusions on the clinical efficacy

CARTITUDE-4 demonstrated superior efficacy of cilta-cel in adult patients with relapsed and refractory multiple myeloma, who have received at least 1 prior therapy, including an immunomodulatory agent and a proteasome inhibitor, have demonstrated disease progression on the last therapy and are refractory to lenalidomide. The chosen SOC arm is in line with the current clinical practice, and, as such, acceptable.

Patients in the cilta-cel arm received bridging therapy with the same therapeutic schemes as in the control arm.

In the KM plots crossing curves are presented for both PFS and OS. Crossing survival curves are generally a result of the survival times having greater variance in one treatment group than another. The subgroup analysis presented by the MAH indicates a well-balanced distribution for a variety of subgroups between the two arms. The early PFS and OS events within 8 weeks after randomization in Arm B occurred before treatment with cilta-cel. There are no obvious differences in the treatment provided to patients during bridging therapy and the treatment in Arm A. No further subgroups could be identified so far, which could have an inferior outcome following treatment with the CAR-T cells. All in all, therefore, the updated OS data provided by the MAH following survival sweep analysis performed on 13 December 2023 are supportive of the clinical benefit in combination with the unambiguous PFS data and the other clinically meaningful endpoints such as rate of CR/sCR, ORR, and overall MRD negativity rate when compared to standard of care.

The efficacy profile for cilta-cel manufactured with CCHMC LV and Bern LV was comparable.
Furthermore, efficacy data received provide satisfactory reassurance on the comprehensiveness of the dossier to allow switch from conditional marketing authorisation to full, considering the Specific obligation fulfilled. The company has committed to provide final study data for study MMY3002 as recommendation post approval.

The following measures are considered necessary to address issues related to efficacy:

- The company commits to provide post approval as recommendation the final study report for MMY3002 when available.

The CHMP endorse the CAT conclusion on clinical efficacy as described above.

2.5. Clinical safety

Introduction

The safety data set for this Type II variation for expansion of therapeutic indication submitted is based upon n=416 subjects as of DCO 01 November 2022, who received any study treatment in the pivotal Study MMY3002 (CARTITUDE-4). Supporting studies are Studies MMY2003 (CARTITUDE-2) and MMY2001 (CARTITUDE-1).

Description of the clinical trials

Studies MMY3002 and MMY2003 have been described under the clinical efficacy section.

CARTITUDE-1 (MMY2001), is a Phase 1b-2, open-label, multicenter study that enrolled heavily pretreated and highly refractory patients with multiple myeloma. The end-of-study analysis includes data from the 97 participants in the main cohort at 2 years after the last participant received their initial dose of cilta-cel (clinical cutoff date: 11 January 2022).

The supporting studies are used for presentation of a pooled analysis (MMY2001; MMY2003 Cohorts A, B, C, D, E; and MMY3002) for adverse drug reactions (ADRs) in n=396 MM subjects treated with cilta-cel, which is considered an acceptable approach.

Patient exposure

Pivotal Study MMY3002

Arm B (Cilta-cel): n=208 subjects. All subjects were leukapheresed and received bridging therapy. N=176/208 participants (84.6%) underwent treatment with cilta-cel (as treated population). N=32/208 (15.4%) discontinued before receiving cilta-cel due to several reasons (see table below), n=20/32 (62.5%) received cilta-cel as subsequent therapy, and n=10/20 (50%) had died during follow-up.

Bridging therapy

Drug Dose	Drug Schedule
Either PVd OR DPd as bridging therapy:	
PVd	
Pomalidomide PO 4 mg/day	On Bridging Days 1-14
Bortezomib SC 1.3 mg/m2	On Bridging Days 1, 4, 8, and 11
Dexamethasone PO 20 mg/day	On Bridging Days 1, 2, 4, 5, 8, 9, 11, and 12
DPd	
Daratumumab SC 1800 mg (co-formulated with rHuPH20) weekly	On Bridging Days 1, 8, 15, and 22
Pomalidomide PO 4 mg/day	On Bridging Days 1 to 21
Dexamethasone PO or IV 40 mg weekly	On Bridging Days 1, 8, 15 and 22 or may be split with 20 mg on Days 1, 2, 8, 9, 15, 16, 22 and 23
Followed by:	
Cyclophosphamide IV 300mg/m2	Daily for 3 days on CAR-T Day -5, -4, -3 prior to cilta-cel infusion
Fludarabine IV 30mg/m2	Daily for 3 days on CAR-T Day -5, -4, -3 prior to cilta-cel infusion
Cilta-cel infusion 0.75 x 10^6 CAR-positive viable T cells/kg	Administered 5 to 7 days after the start of conditioning regimen

The median number of bridging cycles in Arm B was 2.0 (range: 1 to 6 cycles). N=168 participants (80.8%) started 1-2 cycles of bridging therapy, and n=40 participants (19.2%) started 3-6 cycles of bridging therapy (3 cycles: 34 participants [16.3%], 4 cycles: 5 participants [2.4%], and 6 cycles: 1 participant [0.5%]). Median relative dose intensity: 87.5% for bortezomib, 85.7% for pomalidomide, 87.5% for dexamethasone, and 83.3% overall for daratumumab.

Conditioning regimen: Cyclophosphamide and fludarabine

Participants in Arm B were to receive a conditioning regimen of IV cyclophosphamide 300 mg/m^2 and IV fludarabine 30 mg/m^2 daily for 3 days on Day -5, -4, -3 prior to cilta-cel infusion.

Table 33. Summary of Conditioning Regimen Infusions; Safety Analysis Set, Arm B

	Arm B
Analysis set: safety, Arm B, subjects who received cilta-cel	176
Total dose of cyclophosphamide infusion (mg/m^2)	
• N	176
• Mean (SD)	884.1 (60.51)
• Median	891.6
• Range	(705; 1490)
Total dose of fludarabine infusion (mg/m^2)	
• N	176
• Mean (SD)	85.4 (7.22)
• Median	88.7
• Range	(58; 96)

Cilta-cel Infusion

Table 34. Summary of Cilta-cel Infusion; Safety Analysis Set, Arm B, Subjects Who Received Cilta-cel as Study Treatment (Study 68284528MMY3002);

	Arm B
Analysis set: safety, arm B, subjects who received cilta-cel	176
Time from apheresis to cilta-cel infusion (days)	
• N	176
• Mean (SD)	78.6 (21.47)
• Median	77.5
• Range	(45; 246)
• Interquartile range	(64.0; 85.0)
Time from first apheresis to cilta-cel infusion (days)	
• N	176

Table 34. Summary of Cilta-cel Infusion; Safety Analysis Set, Arm B, Subjects Who Received Cilta-cel as Study Treatment (Study 68284528MMY3002);

	Arm B
• Mean (SD)	83.0 (25.96)
• Median	79.0
• Range	(45; 246)
• Interquartile range	(68.0; 90.0)
Receipt-to-release (R2R)[a] (days)	
• N	176
• Mean (SD)	45.7 (14.72)
• Median	44.0
• Range	(25; 127)
• Interquartile range	(35.0; 52.0)
Duration of cilta-cel infusion (minutes)	
• N	176
• Mean (SD)	16.8 (9.14)
• Median	15.0
• Range	(3; 48)
• Interquartile range	(10.0; 21.5)
Total volume infused (mL)	
• N	176
• Mean (SD)	58.6 (18.07)
• Median	70.0
• Range	(30; 70)
• Interquartile range	(30.0; 70.0)
Total CAR-positive viable T cells infused (x10E6 cells)	
• N	176
• Mean (SD)	55.360 (15.9564)
• Median	53.080
• Range	(22.68; 106.50)
• Interquartile range	(43.450; 65.495)

Table 34. Summary of Cilta-cel Infusion; Safety Analysis Set, Arm B, Subjects Who Received Cilta-cel as Study Treatment (Study 68284528MMY3002);

	Arm B
Cilta-cel dose formulated (x10E6 cells/kg)	
• N	176
• Mean (SD)	0.699 (0.1138)
• Median	0.700
• Range	(0.40; 1.00)
• Interquartile range	(0.600; 0.800)
Cilta-cel dose administered (x10E6 cells/kg)	
• N	176
• Mean (SD)	0.705 (0.1163)
• Median	0.706
• Range	(0.39; 1.07)
• Interquartile range	(0.618; 0.778)

[a]Receipt to release (R2R) is calculated from the day after the receipt of leukapheresis material at the manufacturing facility up to, and inclusive of, the day on which the CAR-T product is released for shipment to the clinical trial site.

Administration of cilta-cel out of specification (OOS) batches: N=6 participants (3.4%), based upon Investigator and Sponsor decision. Release criteria not met were:

- 'CAR+ viable T-cells' below the specified range (release criterion: 0.5 - 1.0 x 10^6 CAR+ viable T cells/kg) for 2 participants;
- 'in vitro tumor killing' below the specified range (release criterion: ≥20%) for 1 participant;
- 'replication competent lentivirus' (release criterion: undetectable, or decrease of detected VSV-G and VSV-G is ≤9.47 x 10^5 copies/200 ng genomic DNA in post-harvest sample) for 1 participant;
- 'endotoxin' (release criterion: ≤1.95 EU/mL [1DP BAG]) for 1 participant; and
- 'transduction efficiency' above the specified range (release criterion: 0.05 vector copies/cell to 5.00 vector copies/cell) for 1 participant.

Arm A (**SOC therapy regimens):** N=211 subjects were randomized and n=208 treated with PVd or DPd. PVd was selected for 28 participants (13.3%) and DPd for 183 participants (86.7%) by the investigators. As of data cutoff date, n=131 (63%) discontinued due to several reasons (see table below) and n=77 (37%) remained on study treatment. The median duration of study treatment was 4.8 months (range: 0.5 to 19.9 months) for participants who received PVd and 11.8 months (range: 0.5 to 25.2 months) for the participants who received DPd. The median number of treatment cycles started was 12.0 (range: 1 to 28 cycles). The majority of participants (n=127; 61.1%) received at least 9 cycles of treatment.

Study Treatment Schedule Arm A

PVd (21-day treatment cycles)
Cycles 1 to 8: • Pomalidomide PO 4 mg on Days 1 to 14 • Bortezomib SC 1.3 mg/m2 on Days 1, 4, 8 and 11 • Dexamethasone PO 20 mg/day on Days 1, 2, 4, 5, 8, 9, 11 and 12
Cycle 9 onwards: • Pomalidomide PO 4 mg on Days 1-14 Bortezomib SC 1.3 mg/m2 on Days 1 and 8 • Dexamethasone PO 20 mg on Days 1, 2, 8, and 9
DPd (28-day treatment cycles)
Cycles 1 and 2: • Daratumumab SC 1800 mg (co-formulated with rHuPH20) weekly on Days 1, 8, 15, and 22 • Pomalidomide PO 4 mg/day on Days 1 to 21 • Dexamethasone PO/IV: 40 mg weekly on Days 1, 8, 15, and 22 or may be split with 20 mg on Days 1, 2, 8, 9, 15, 16, 22, and 23. On days of daratumumab administration, dexamethasone must be given 1-3 hours prior to daratumumab.
Cycles 3 to 6: • Daratumumab SC 1800 mg (co-formulated with rHuPH20) every 2 weeks on Days 1 and 15 • Pomalidomide PO 4 mg/day on Days 1 to 21 • Dexamethasone PO/IV: 40 mg weekly (may be split over 2 days). On days of daratumumab administration, dexamethasone must be given 1-3 hours prior to daratumumab.
Cycle 7 onwards: • Daratumumab SC 1800 mg (co-formulated with rHuPH20) every 4 weeks on Day 1 • Pomalidomide PO 4 mg/day on Days 1 to 21 • Dexamethasone PO/IV: 40 mg weekly (may be split over 2 days). On days of daratumumab administration, dexamethasone must be given 1-3 hours prior to daratumumab.

Median relative dose intensity of the SOC study drugs (ratio of total dose actually received to total dose planned):

- 91.7% for bortezomib,
- 77.6% for pomalidomide,
- 82.3% for dexamethasone, and
- 95.7% overall for daratumumab (87.5% in Cycles 1-2, and 100.0% in Cycles 3-6 and Cycles 7+).

Participants' Disposition (Arm A and Arm B)

Table 35. Summary of Subject Study Disposition; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B	Total
Analysis set: intent-to-treat	211	208	419
Subjects randomized but not treated	3 (1.4%)	0	3 (0.7%)
Subjects treated	208 (98.6%)	208 (100.0%)	416 (99.3%)
Subjects who discontinued from study treatment	131 (63.0%)	32 (15.4%)	163 (39.2%)
• Adverse event	3 (1.4%)	0	3 (0.7%)
• Death	5 (2.4%)	2 (1.0%)	7 (1.7%)
• Progressive disease	117 (56.3%)	30 (14.4%)	147 (35.3%)
• Lost to follow-up	0	0	0
• Manufacturing failure	0	0	0
• Failure to meet pre-treatment criteria	0	0	0
• Physician decision	1 (0.5%)	0	1 (0.2%)
• Pregnancy	0	0	0
• Protocol deviation	0	0	0
• Non-compliance with study drug	0	0	0
• Site terminated by sponsor	0	0	0
• Subject refused further study treatment	5 (2.4%)	0	5 (1.2%)
• Other	0	0	0
Subjects who discontinued from the study	51 (24.2%)	39 (18.8%)	90 (21.5%)
• Death	47 (22.3%)	39 (18.8%)	86 (20.5%)
• Lost to follow-up	0	0	0
• Site terminated by sponsor	0	0	0
• Study terminated by sponsor	0	0	0
• Withdrawal by subject	4 (1.9%)	0	4 (1.0%)
Subjects who are still on study	160 (75.8%)	169 (81.3%)	329 (78.5%)
• On study treatment (Arm A) or post-infusion follow-up (Arm B)	77 (36.5%)	0	77 (18.4%)
• On post-treatment follow-up	1 (0.5%)	143 (68.8%)	144 (34.4%)
• On survival follow-up	82 (38.9%)	26 (12.5%)	108 (25.8%)

Participants' Demographics (Arm A and Arm B)

Table 36. Demographics and Baseline Characteristics; Intent-to-Treat Analysis Set (Study 68284528MMY3002)

	Arm A	Arm B	Total
Analysis set: intent-to-treat	211	208	419
Age, years			
N	211	208	419
Category, n (%)			
< 65	131 (62.1%)	126 (60.6%)	257 (61.3%)
65 - 75	76 (36.0%)	78 (37.5%)	154 (36.8%)
> 75	4 (1.9%)	4 (1.9%)	8 (1.9%)
Mean (SD)	60.4 (9.09)	59.7 (10.09)	60.1 (9.60)
Median	61.0	61.5	61.0
Range	(35; 80)	(27; 78)	(27; 80)
Interquartile range	(53.0; 68.0)	(52.0; 68.0)	(53.0; 68.0)
Sex			
N	211	208	419
Female	87 (41.2%)	92 (44.2%)	179 (42.7%)
Male	124 (58.8%)	116 (55.8%)	240 (57.3%)
Race			
N	211	208	419
American Indian or Alaska Native	1 (0.5%)	1 (0.5%)	2 (0.5%)
Asian	20 (9.5%)	16 (7.7%)	36 (8.6%)
Black or African American	7 (3.3%)	6 (2.9%)	13 (3.1%)
White	157 (74.4%)	157 (75.5%)	314 (74.9%)
Not reported	26 (12.3%)	28 (13.5%)	54 (12.9%)
Ethnicity			
N	211	208	419
Hispanic or Latino	10 (4.7%)	18 (8.7%)	28 (6.7%)
Not Hispanic or Latino	165 (78.2%)	152 (73.1%)	317 (75.7%)
Not reported	36 (17.1%)	38 (18.3%)	74 (17.7%)
Weight, kg			
N	211	208	419
Mean (SD)	76.64 (15.322)	78.45 (18.496)	77.54 (16.976)
Median	77.10	79.00	78.00
Range	(42.8; 118.1)	(40.4; 147.3)	(40.4; 147.3)
Interquartile range	(65.90; 87.00)	(63.75; 88.90)	(65.30; 88.40)
Height, cm			
N	211	208	419
Mean (SD)	168.60 (10.095)	168.52 (10.431)	168.56 (10.251)
Median	168.00	168.00	168.00
Range	(143.0; 196.0)	(142.0; 193.0)	(142.0; 196.0)
Interquartile range	(162.00; 177.00)	(161.00; 176.00)	(161.00; 176.00)
Body surface area (BSA), m^2			
N	211	208	419
Mean (SD)	1.89 (0.225)	1.91 (0.259)	1.90 (0.242)
Median	1.88	1.92	1.90
Range	(1.3; 2.4)	(1.3; 2.5)	(1.3; 2.5)
Interquartile range	(1.73; 2.05)	(1.69; 2.09)	(1.72; 2.08)
Baseline ECOG score			
N	211	208	419
0	121 (57.3%)	114 (54.8%)	235 (56.1%)
1	89 (42.2%)	93 (44.7%)	182 (43.4%)
2	1 (0.5%)	1 (0.5%)	2 (0.5%)

Type of myeloma by immunofixation, n (%)			
N	211	208	419
IgG	108 (51.2%)	113 (54.3%)	221 (52.7%)
IgA	37 (17.5%)	37 (17.8%)	74 (17.7%)
IgM	1 (0.5%)	0	1 (0.2%)
IgD	2 (0.9%)	2 (1.0%)	4 (1.0%)
IgE	0	0	0
Light chain	56 (26.5%)	47 (22.6%)	103 (24.6%)
Kappa	27 (12.8%)	25 (12.0%)	52 (12.4%)
Lambda	29 (13.7%)	22 (10.6%)	51 (12.2%)
Biclonal	2 (0.9%)	1 (0.5%)	3 (0.7%)
Negative immunofixation	5 (2.4%)	8 (3.8%)	13 (3.1%)
Type of measurable disease, n (%)			
N	211	208	419
Serum only	111 (52.6%)	107 (51.4%)	218 (52.0%)
Serum and urine	23 (10.9%)	24 (11.5%)	47 (11.2%)
Urine only	28 (13.3%)	23 (11.1%)	51 (12.2%)
Serum FLC only	49 (23.2%)	52 (25.0%)	101 (24.1%)
Not evaluable	0	2 (1.0%)	2 (0.5%)
ISS staging at study baseline, n (%)			
N	211	208	419
I	132 (62.6%)	136 (65.4%)	268 (64.0%)
II	65 (30.8%)	60 (28.8%)	125 (29.8%)
III	14 (6.6%)	12 (5.8%)	26 (6.2%)
Time from initial MM diagnosis to randomization, years			
N	211	208	419
Mean (SD)	4.27 (3.195)	3.94 (2.862)	4.11 (3.035)
Median	3.44	3.02	3.22
Range	(0.4; 22.1)	(0.3; 18.1)	(0.3; 22.1)
Interquartile range	(2.10; 5.69)	(1.98; 4.99)	(2.04; 5.38)
Number of lytic bone lesions			
N	211	208	419
None	64 (30.3%)	41 (19.7%)	105 (25.1%)
1-3	35 (16.6%)	46 (22.1%)	81 (19.3%)
4-10	41 (19.4%)	33 (15.9%)	74 (17.7%)
More than 10	71 (33.6%)	88 (42.3%)	159 (37.9%)
Presence of soft tissue plasmacytomas			
N	211	208	419
Yes	35 (16.6%)	44 (21.2%)	79 (18.9%)
No	176 (83.4%)	164 (78.8%)	340 (81.1%)
Presence of evaluable bone marrow assessment			
N	211	208	419
Yes	208 (98.6%)	206 (99.0%)	414 (98.8%)
No	3 (1.4%)	2 (1.0%)	5 (1.2%)

% Plasma cells, bone marrow biopsy or aspirate			
N	208	206	414
⩽30	121 (58.2%)	133 (64.6%)	254 (61.4%)
>30-<60	44 (21.2%)	31 (15.0%)	75 (18.1%)
⩾60	43 (20.7%)	42 (20.4%)	85 (20.5%)
Cytogenetic risk			
N	210	207	417
Standard risk	70 (33.3%)	69 (33.3%)	139 (33.3%)
High risk (any of the 4 markers abnormal)	132 (62.9%)	123 (59.4%)	255 (61.2%)
del17p	43 (20.5%)	49 (23.7%)	92 (22.1%)
t(4;14)	30 (14.3%)	30 (14.5%)	60 (14.4%)
t(14;16)	7 (3.3%)	3 (1.4%)	10 (2.4%)
gain/amp(1q)	107 (51.0%)	89 (43.0%)	196 (47.0%)
At least 2 of the 4 markers abnormal	49 (23.3%)	43 (20.8%)	92 (22.1%)
Excluding gain/amp(1q)	69 (32.9%)	73 (35.3%)	142 (34.1%)
Unknown	8 (3.8%)	15 (7.2%)	23 (5.5%)

Trial Protocol Deviations

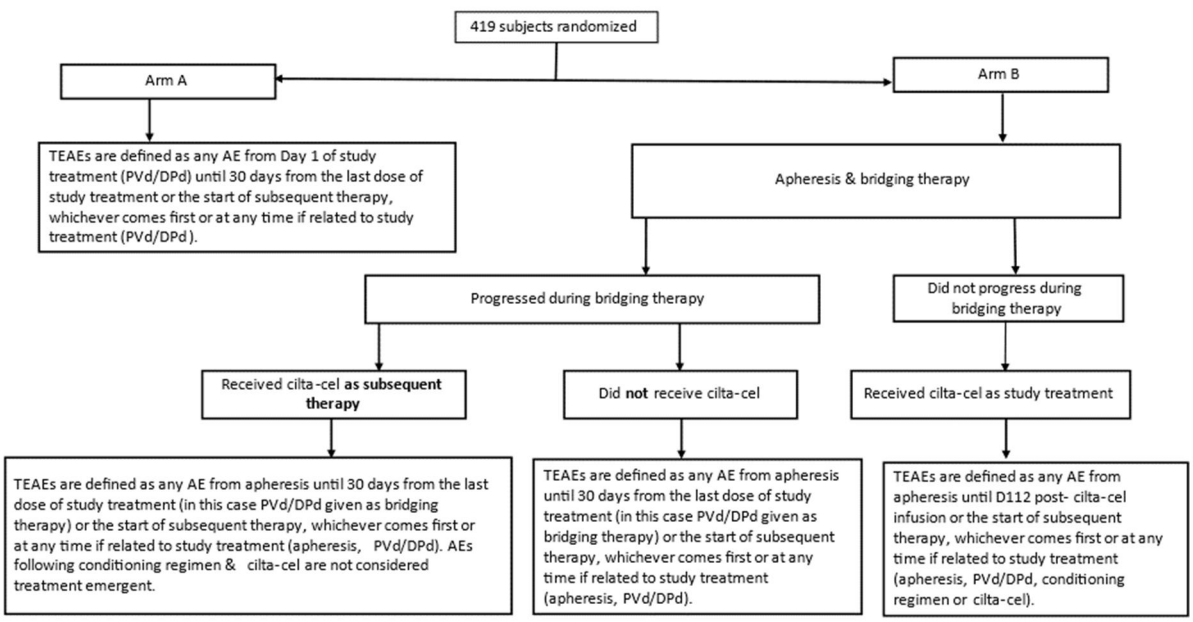
Table 37. Summary of Subjects with Major Protocol Deviations; Intent-to-Treat Analysis Set (Study MMY3002)

	Arm A	Arm B	Total
Analysis set: intent-to-treat	211	208	419
Subjects with major protocol deviation	8 (3.8%)	12 (5.8%)	20 (4.8%)
Type of major protocol deviation			
Entered but did not satisfy criteria	1 (0.5%)	0	1 (0.2%)
Received a disallowed concomitant treatment	1 (0.5%)	1 (0.5%)	2 (0.5%)
Received wrong treatment or incorrect dose	4 (1.9%)	5 (2.4%)	9 (2.1%)
Other	2 (0.9%)	7 (3.4%)	9 (2.1%)

Adverse events

Definition of TEAEs is summarised in Figure 20.

Figure 20. Definitions of TEAEs in Study



Results

Table 38. ADRS (>=10%) in MM patients treated with Cilta-cel in Study MMY3002; (n=176)

System Organ Class	Adverse Reaction	Incidence (%)		
		All Grades	Grade 3-4	Grade 5
Infections and infestations	Upper respiratory tract infection	46 (26.1%)	2 (1.1%)	0
	Viral infection	43 (24.4%)	8 (4.5%)	0
	Bacterial infection	25 (14.2%)	10 (5.7%)	0
	Pneumonia	24 (13.6%)	7 (4.0%)	8 (4.5%)
Immune system disorders	Cytokine release syndrome	134 (76.1%)	2 (1.1%)	0
	Hypogammaglobulinaemia	86 (48.9%)	15 (8.5%)	0
Metabolism and nutrition disorders	Decreased appetite	19 (10.8%)	1 (0.6%)	0
Nervous system disorders	Headache	44 (25.0%)	0	0
Vascular disorders	Hypotension	36 (20.5%)	4 (2.3%)	0
Respiratory, thoracic and mediastinal disorders	Cough	28 (15.9%)	0	0
	Hypoxia	18 (10.2%)	4 (2.3%)	0
Gastrointestinal disorders	Diarrhea	49 (27.8%)	6 (3.4%)	0
	Nausea	35 (19.9%)	0	0
	Constipation	18 (10.2%)	0	0
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	61 (34.7%)	3 (1.7%)	0
General disorders and administration site conditions	Pyrexia	136 (77.3%)	10 (5.7%)	0
	Fatigue	52 (29.5%)	4 (2.3%)	0
	Edema	21 (11.9%)	1 (0.6%)	0
	Pain	19 (10.8%)	2 (1.1%)	0

Table 39. Overall Summary TEAEs; SAS (Study 68284528MMY3002)

Analysis set: safety	Arm A 208	Arm B 208
Any TEAE	208 (100.0%)	208 (100.0%)
At least one related	204 (98.1%)	204 (98.1%)
At least one related to cilta-cel	0	171 (82.2%)
Any serious TEAE	81 (38.9%)	92 (44.2%)
At least one related	46 (22.1%)	61 (29.3%)
At least one related to cilta-cel	0	44 (21.2%)
Maximum severity of any TEAE		
Grade 1	0	1 (0.5%)
Grade 2	12 (5.8%)	6 (2.9%)
Grade 3	73 (35.1%)	31 (14.9%)
Grade 4	117 (56.3%)	157 (75.5%)
Grade 5	6 (2.9%)	13 (6.3%)
TEAE leading to discontinuation of cilta-cel	0	0
At least one related to cilta-cel	0	0
TEAE leading to discontinuation of Daratumumab	6 (2.9%)	1 (0.5%)
At least one related to Daratumumab	1 (0.5%)	0
TEAE leading to discontinuation of Bortezomib	1 (0.5%)	0
At least one related to Bortezomib	1 (0.5%)	0
TEAE leading to discontinuation of Pomalidomide	9 (4.3%)	5 (2.4%)
At least one related to Pomalidomide	4 (1.9%)	4 (1.9%)
TEAE leading to discontinuation of Dexamethasone	27 (13.0%)	2 (1.0%)
At least one related to Dexamethasone	21 (10.1%)	0

Table 39. Overall Summary TEAEs; SAS (Study 68284528MMY3002)

	Arm A	Arm B
TEAE leading to discontinuation of Cyclophosphamide	0	1 (0.5%)
At least one related to Cyclophosphamide	0	1 (0.5%)
TEAE leading to discontinuation of Fludarabine	0	1 (0.5%)
At least one related to Fludarabine	0	1 (0.5%)
TEAE with outcome death	6 (2.9%)	13 (6.3%)
At least one related to cilta-cel	0	4 (1.9%)

Table 40. Number of Subjects With G3/G4 TEAEs Frequency of at Least 5% by SOC/PT; SAS (Study 68284528MMY3002)

	Arm A	Arm B
Analysis set: safety	208	208
Total number of subjects with Grade 3 or 4 TEAE	196 (94.2%)	201 (96.6%)
MedDRA system organ class/preferred term		
Blood and lymphatic system disorders	179 (86.1%)	196 (94.2%)
Neutropenia	171 (82.2%)	187 (89.9%)
Thrombocytopenia	39 (18.8%)	86 (41.3%)
Anaemia	30 (14.4%)	74 (35.6%)
Lymphopenia	25 (12.0%)	43 (20.7%)
Leukopenia	10 (4.8%)	25 (12.0%)
Febrile neutropenia	8 (3.8%)	11 (5.3%)
Immune system disorders	1 (0.5%)	19 (9.1%)
Hypogammaglobulinaemia	1 (0.5%)	15 (7.2%)

Serious adverse event/deaths/other significant events

Table 41. TEAEs by SOC, PT, and Toxicity Grade of 3 or 4; SAS (Study 68284528MMY3002)

	Arm A		Arm B	
	Total	Grade 3 or 4	Total	Grade 3 or 4
Analysis set: safety	208		208	
Total number of subjects with serious TEAE	81 (38.9%)	70 (33.7%)	92 (44.2%)	67 (32.2%)
MedDRA system organ class/preferred term				
Infections and infestations	51 (24.5%)	47 (22.6%)	50 (24.0%)	40 (19.2%)
COVID-19 pneumonia	9 (4.3%)	9 (4.3%)	12 (5.8%)	10 (4.8%)
Pneumonia	9 (4.3%)	7 (3.4%)	6 (2.9%)	5 (2.4%)
Blood and lymphatic system disorders	9 (4.3%)	9 (4.3%)	15 (7.2%)	14 (6.7%)
Febrile neutropenia	5 (2.4%)	5 (2.4%)	5 (2.4%)	5 (2.4%)
Anaemia	1 (0.5%)	1 (0.5%)	4 (1.9%)	3 (1.4%)
Neutropenia	1 (0.5%)	1 (0.5%)	4 (1.9%)	4 (1.9%)

Table 41. TEAEs by SOC, PT, and Toxicity Grade of 3 or 4; SAS (Study 68284528MMY3002)

	Arm A		Arm B	
	Total	Grade 3 or 4	Total	Grade 3 or 4
Cytopenia	0	0	1 (0.5%)	1 (0.5%)
Immune thrombocytopenia	0	0	1 (0.5%)	1 (0.5%)
Lymphocytosis	0	0	1 (0.5%)	1 (0.5%)
Thrombocytopenia	0	0	1 (0.5%)	1 (0.5%)
Nervous system disorders	3 (1.4%)	2 (1.0%)	14 (6.7%)	5 (2.4%)
Facial paralysis	1 (0.5%)	0	9 (4.3%)	1 (0.5%)
Facial paresis	0	0	1 (0.5%)	0
IIIrd nerve paralysis	0	0	1 (0.5%)	1 (0.5%)
Immune effector cell-associated neurotoxicity syndrome	0	0	1 (0.5%)	0
Parkinsonism	0	0	1 (0.5%)	0
Polyneuropathy	0	0	1 (0.5%)	1 (0.5%)
Spinal cord compression	0	0	1 (0.5%)	1 (0.5%)
Subdural hygroma	0	0	1 (0.5%)	1 (0.5%)
Trigeminal palsy	0	0	1 (0.5%)	1 (0.5%)
General disorders and administration site conditions	7 (3.4%)	2 (1.0%)	8 (3.8%)	1 (0.5%)
Pyrexia	5 (2.4%)	2 (1.0%)	4 (1.9%)	0
Immune system disorders	1 (0.5%)	0	7 (3.4%)	1 (0.5%)
Cytokine release syndrome	1 (0.5%)	0	7 (3.4%)	1 (0.5%)
Metabolism and nutrition disorders	3 (1.4%)	1 (0.5%)	7 (3.4%)	4 (1.9%)
Hypercalcaemia	2 (1.0%)	1 (0.5%)	5 (2.4%)	3 (1.4%)
Gastrointestinal disorders	3 (1.4%)	2 (1.0%)	6 (2.9%)	5 (2.4%)
Diarrhoea	0	0	5 (2.4%)	4 (1.9%)

Table 42. Summary of Deaths and Primary Cause of Death; SAS (Study 68284528MMY3002)

	Arm A	Arm B
Analysis set: safety	208	208
Total number of subjects who died during study	46 (22.1%)	39 (18.8%)
Primary cause of death		
Treatment-emergent adverse event	5 (2.4%)	10 (4.8%)
Progressive disease	30 (14.4%)	14 (6.7%)
Other	11 (5.3%)	15 (7.2%)
Total number of subjects who died within 30 days of the study treatment start	0	2 (1.0%)
Primary cause of death		
Treatment-emergent adverse event	0	1 (0.5%)
Progressive disease	0	1 (0.5%)
Other	0	0
Total number of subjects who died >30 days and within 3 months of the study treatment start	0	6 (2.9%)
Primary cause of death		
Treatment-emergent adverse event	0	0
Progressive disease	0	4 (1.9%)
Other	0	2 (1.0%)
Total number of subjects who died at >3 – 6 months of the study treatment start	12 (5.8%)	12 (5.8%)
Primary cause of death		
Treatment-emergent adverse event	3 (1.4%)	4 (1.9%)
Progressive disease	6 (2.9%)	3 (1.4%)
Other	3 (1.4%)	5 (2.4%)

Table 42. Summary of Deaths and Primary Cause of Death; SAS (Study 68284528MMY3002)

	Arm A	Arm B
Total number of subjects who died at >6 – 9 months of the study treatment start	10 (4.8%)	6 (2.9%)
Primary cause of death		
Treatment-emergent adverse event	1 (0.5%)	2 (1.0%)
Progressive disease	7 (3.4%)	1 (0.5%)
Other	2 (1.0%)	3 (1.4%)
Total number of subjects who died at >9 – 12 months of the study treatment start	11 (5.3%)	7 (3.4%)
Primary cause of death		
Treatment-emergent adverse event	1 (0.5%)	1 (0.5%)
Progressive disease	9 (4.3%)	3 (1.4%)
Other	1 (0.5%)	3 (1.4%)
Total number of subjects who died at >12 – 24 months of the study treatment start	12 (5.8%)	6 (2.9%)
Primary cause of death		
Treatment-emergent adverse event	0	2 (1.0%)
Progressive disease	7 (3.4%)	2 (1.0%)
Other	5 (2.4%)	2 (1.0%)
Total number of subjects who died at >24 – 36 months of the study treatment start	1 (0.5%)	0
Primary cause of death		
Treatment-emergent adverse event	0	0
Progressive disease	1 (0.5%)	0
Other	0	0

Table 43. Summary of Treatment-emergent Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) in participants treated with Cilta-cel; Arm B; n=176 (Study 68284528MMY3002)

Number of subjects with ICANS	8 (4.5%)
Maximum toxicity grade	
Grade 1	6 (3.4%)
Grade 2	2 (1.1%)
Grade 3	0
Grade 4	0
Grade 5	0
Number of subjects with ICANS	8 (4.5%)
With concurrent CRS	6 (3.4%)
Without concurrent CRS	2 (1.1%)
Time from initial infusion of cilta-cel to first onset of ICANS (days)	
N	8
Mean (SD)	9.6 (2.56)
Median	9.5
Range	(6; 15)
Interquartile range	(8.5; 10.0)
Duration of ICANS (days)	
N	8
Mean (SD)	2.1 (1.64)
Median	2.0
Range	(1; 6)
Interquartile range	(1.0; 2.0)

Number of subjects with supportive measures to treat ICANS	4 (2.3%)
IL-6 signaling pathway modulators	2 (1.1%)
IL-6 receptor antagonist (Tocilizumab)	2 (1.1%)
Corticosteroid	4 (2.3%)
Dexamethasone	4 (2.3%)
Methylprednisolone	1 (0.6%)
Outcome of ICANS	
Recovered or resolved	8 (4.5%)

Development of second primary malignancies

Table 44. Summary of Second Primary Malignancies During Study; Safety Analysis Set (Study MMY3002)

	Arm A	Arm B
Analysis set: safety	208	208
Subjects with second primary malignancies	14 (6.7%)	9 (4.3%)
Type		
Preferred term		
Cutaneous/non-invasive malignancies	10 (4.8%)	5 (2.4%)
Basal cell carcinoma	7 (3.4%)	2 (1.0%)
Bowen's disease	2 (1.0%)	0
Lip squamous cell carcinoma	1 (0.5%)	0
Malignant melanoma	0	1 (0.5%)
Malignant melanoma in situ	0	1 (0.5%)
Squamous cell carcinoma of skin	4 (1.9%)	2 (1.0%)
Hematologic malignancies	0	3 (1.4%)
Acute myeloid leukaemia	0	1 (0.5%)
Myelodysplastic syndrome	0	1 (0.5%)
Peripheral T-cell lymphoma unspecified	0	1 (0.5%)
Non-cutaneous/invasive malignancies	4 (1.9%)	1 (0.5%)
Angiosarcoma	0	1 (0.5%)
Invasive lobular breast carcinoma	1 (0.5%)	0
Pleomorphic malignant fibrous histiocytoma	1 (0.5%)	0
Renal cell carcinoma	1 (0.5%)	0
Tonsil cancer	1 (0.5%)	0

Laboratory findings

Table 45. Laboratory Abnormalities following treatment with Cilta-cel Study MMY3002(N=176)

Laboratory Abnormality	Any Grade (%)	Grade 3 or 4 (%)
Anemia	176 (100.0%)	52 (29.5%)
Lymphopenia	176 (100.0%)	174 (98.9%)
White blood cell decreased	176 (100.0%)	166 (94.3%)
Neutropenia	175 (99.4%)	167 (94.9%)
Thrombocytopenia	168 (95.5%)	78 (44.3%)

Table 45. Laboratory Abnormalities following treatment with Cilta-cel Study MMY3002(N=176)

Laboratory Abnormality	Any Grade (%)	Grade 3 or 4 (%)
Fibrinogen decreased	15 (8.5%)	12 (6.8%)
Hypoalbuminemia	112 (63.6%)	0
Alanine aminotransferase increased	95 (54.0%)	7 (4.0%)
Aspartate aminotransferase increased	86 (48.9%)	6 (3.4%)
Gamma Glutamyl Transferase increased	83 (47.2%)	12 (6.8%)
Hypocalcemia	80 (45.5%)	1 (0.6%)
Hypokalemia	73 (41.5%)	9 (5.1%)
Hypomagnesemia	69 (39.2%)	4 (2.3%)
Alkaline phosphatase increased	66 (37.5%)	6 (3.4%)
Hyponatremia	54 (30.7%)	5 (2.8%)
Hypertriglyceridaemia	40 (22.7%)	5 (2.8%)
Blood bilirubin increased	23 (13.1%)	1 (0.6%)

Note: Lab assessments following cilta-cel infusion until the start of subsequent therapy are included in the analysis.

Haematology

G3 or G4 Cytopenia TEAEs were reported for 93.8% of participants in Arm B and 86.1% in Arm A. Among the 176 participants in Arm B who received cilta-cel as study treatment, most Grade 3 or 4 cytopenias had onset and recovery to Grade 2 or better within 60 days following cilta-cel infusion. For Arm B, neutrophils, platelets had returned to baseline levels through Day 84 and for lymphocytes through Day 112.

Chemistry and coagulation

The changes in values for AST, ALT, C-reactive protein, ferritin and coagulation parameters reported from baseline over the time can be considered expected. In the majority, the values had recovered to baseline levels during the observation period.

Vital Signs

According to listings submitted there seem to be no clinically meaningful differences between Arm A and Arm B with respect to the assessment of vital signs, echocardiogram and MUGA scan during the study.

Adverse drug reaction in the polled analysis

Table 46. Adverse Drug Reactions – Pooled analysis [Study MMY2001, MMY2003 (cohorts, A, B, C, D and E) and Study MMY3002]; N=396

System Organ Class	Frequency	Adverse Reaction	Incidence n(%)		
			All Grades	Grade 3-4	Grade 5
Infections and infestations	Very common	Upper respiratory tract infection	117 (29.5%)	8 (2.0%)	0
		Viral infection	67 (16.9%)	14 (3.5%)	0
		Bacterial infection	53 (13.4%)	19 (4.8%)	2 (0.5%)
		Pneumonia	47 (11.9%)	25 (6.3%)	10 (2.5%)

	Common	Sepsis	35 (8.8%)	23 (5.8%)	5 (1.3%)
		Gastroenteritis[6]	22 (5.6%)	4 (1.0%)	0
		Urinary tract infection	20 (5.1%)	5 (1.3%)	0
		Fungal infection	12 (3.0%)	1 (0.3%)	0
Blood and lymphatic system disorders	Very common	Neutropenia	352 (88.9%)	349 (88.1%)	0
		Thrombocytopenia	239 (60.4%)	175 (44.2%)	0
		Anemia	237 (59.8%)	173 (43.7%)	0
		Lymphopenia	135 (34.1%)	129 (32.6%)	0
		Leukopenia	130 (32.8%)	127 (32.1%)	0
		Coagulopathy	48 (12.1%)	11 (2.8%)	0
	Common	Febrile neutropenia	31 (7.8%)	30 (7.6%)	0
		Lymphocytosis	11 (2.8%)	4 (1.0%)	0
Immune system disorders	Very common	Cytokine release syndrome	330 (83.3%)	14 (3.5%)	1 (0.3%)
		Hypogammaglobulinaemia	116 (29.3%)	18 (4.5%)	0
	Common	Haemophagocytic lymphohistiocytosis	10 (2.5%)	5 (1.3%)	1 (0.3%)
Metabolism and nutrition disorders	Very common	Hypophosphataemia	67 (16.9%)	17 (4.3%)	0
		Hypokalaemia	66 (16.7%)	9 (2.3%)	0
		Hypocalcaemia	62 (15.7%)	10 (2.5%)	0
		Decreased appetite	61 (15.4%)	5 (1.3%)	0

		Hypomagnesaemia	46 (11.6%)	1 (0.3%)	0
		Hypoalbuminaemia	44 (11.1%)	1 (0.3%)	0
	Common	Hyperferritinemia	39 (9.8%)	7 (1.8%)	0
		Hyponatraemia	39 (9.8%)	7 (1.8%)	0
Psychiatric disorders	Common	Delirium	13 (3.3%)	1 (0.3%)	0
		Personality changes	10 (2.5%)	2 (0.5%)	0
Nervous system disorders	Very common	Headache	97 (24.5%)	0	0
		Dizziness	51 (12.9%)	3 (0.8%)	0
		Motor dysfunction	50 (12.6%)	9 (2.3%)	0
		Immune effector cell-associated neurotoxicity syndrome	45 (11.4%)	7 (1.8%)	1 (0.3%)
		Sleep disorder	40 (10.1%)	4 (1.0%)	0
	Common	Encephalopathy	39 (9.8%)	7 (1.8%)	1 (0.3%)
		Cranial nerve palsies	27 (6.8%)	4 (1.0%)	0
		Neuropathy peripheral	27 (6.8%)	5 (1.3%)	0
		Tremor	20 (5.1%)	1 (0.3%)	0
		Aphasia	18 (4.5%)	1 (0.3%)	0
		Ataxia	16 (4.0%)	1 (0.3%)	0
	Uncommon	Neurotoxicity	3 (0.8%)	2 (0.5%)	1 (0.3%)
		Paresis[25]	3 (0.8%)	1 (0.3%)	0
		Guillain-Barre syndrome	1 (0.3%)	1 (0.3%)	0

Cardiac disorders	Very common	Tachycardia	52 (13.1%)	3 (0.8%)	0
	Common	Cardiac arrhythmias	16 (4.0%)	6 (1.5%)	0
Vascular disorders	Very common	Hypotension	132 (33.3%)	22 (5.6%)	0
		Hypertension	44 (11.1%)	16 (4.0%)	0
	Common	Hemorrhage	39 (9.8%)	6 (1.5%)	3 (0.8%)
		Thrombosis	16 (4.0%)	2 (0.5%)	0
	Uncommon	Capillary leak syndrome	2 (0.5%)	0	0
Respiratory, thoracic and mediastinal disorders	Very common	Cough	81 (20.5%)	0	0
		Dyspnea	57 (14.4%)	10 (2.5%)	1 (0.3%)
		Hypoxia	51 (12.9%)	15 (3.8%)	0
Gastrointestinal disorders	Very common	Diarrhea	121 (30.6%)	10 (2.5%)	0
		Nausea	92 (23.2%)	1 (0.3%)	0
		Constipation	58 (14.6%)	0	0
		Vomiting	46 (11.6%)	0	0
	Common	Abdominal pain	33 (8.3%)	0	0
Hepatobiliary disorders	Common	Hyperbilirubinemia	13 (3.3%)	5 (1.3%)	0
Skin and subcutaneous tissue disorders	Common	Rash	34 (8.6%)	0	0
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain	152 (38.4%)	11 (2.8%)	0
Renal and urinary disorders	Common	Renal failure	25 (6.3%)	14 (3.5%)	0

General disorders and administration site conditions	Very common	Pyrexia	331 (83.6%)	25 (6.3%)	0
		Fatigue	138 (34.8%)	16 (4.0%)	0
		Edema	63 (15.9%)	5 (1.3%)	0
		Chills	56 (14.1%)	0	0
		Pain	43 (10.9%)	5 (1.3%)	0
Investigations	Very common	Transaminase elevation	100 (25.3%)	43 (10.9%)	0
	Common	Gamma-glutamyltransferase increased	39 (9.8%)	22 (5.6%)	0
		Blood alkaline phosphatase increased	33 (8.3%)	11 (2.8%)	0
		C-reactive protein increased	28 (7.1%)	5 (1.3%)	0

Post marketing experience

The cumulative search of the GMS global safety database from 28 February 2022 through 31 January 2023 retrieved a total of 146 cases. Of these, 5 cases were excluded for the following reasons: multiple unidentifiable patients (4 cases) and 1 duplicate case. The remaining 141 cases were further analysed.

Table 47. Cumulative Post-marketing Patient Exposure to Cilta-cel (01 March 2022 through 31 January 2023)

Product	Number of Patients Receiving Apheresis	Number of Patients Receiving Cilta-cel
Cilta-cel	495	475

Table 48. Case and Event Characteristics of Cilta-cel Post-marketing Cases (N=141 Cases; N=290 Events)

Case Characteristics		Number of Cases (N=141) n (%)
Patient Sex	Female	44 (31.2)
	Male	55 (39.0)
	NR	42 (29.8)
Patient Age (Years)[a]	18 to 35	0
Mean: 63.5	36 to 50	10 (7.1)
Median: 64	51 to 64	29 (20.6)

Range: 41-77	≥65	38 (27.0)
	Adult	3 (2.1)
	Elderly	2 (1.4)
	NR	59 (41.8)
Source	Spontaneous[b]	65 (46.1)
	Solicited[c]	19 (13.5)
	Clinical study[d]	57 (40.4)
Indication (MedDRA PT)	Plasma cell myeloma[e]	95 (67.4)
	Plasma cell myeloma refractory	8 (5.7)
	Leukaemia recurrent[e]	1 (0.7)
	NR	37 (26.2)
Case Characteristics		Number of Cases (N=141) n (%)
Country/Territory of Origin	United States	133 (94.3)
	France	5 (3.6)
	Austria	1 (0.7)
	China, PRC[f]	1 (0.7)
	Romania[f]	1 (0.7)
Event Characteristics		Number of Events (N=290) n (%)
Seriousness[g]	Serious	171 (59.0)
	Nonserious	119 (41.0)
Outcome[g]	Not resolved	55 (19.0)
	Resolved	61 (21.0)
	Resolving	27 (9.3)
	Fatal[g]	17 (5.9)
	NR	128 (44.1)

Key: n= Number; NR= Not Reported; PRC=People's Republic of China; MedDRA=Medical Dictionary of Regulatory Activities; PT=Preferred Term.

a: Cases where age was not reported, age group has been presented. Of note, one case reporting an age of 700 years was captured as unknown.

b: Including 1 case sourced from the literature.

c: Including cases from 68284528MMY4004 (1 case [0.7%]), 68284528MMY4007 (1 case [0.7%]) and other multiple myeloma portfolio marketing programs (17 cases [12.1%]).

d: Including cases from studies 68284528MMY2005 (40 cases [28.4%]), 68284528MMY4006 (16 cases [11.3%]) and 68284528MMY4012 (1 case [0.7%]); Trial 68284528MMY2005 is a post-authorization trial that includes patients receiving a cilta-cel commercial drug product not meeting all the pre-specified commercial release criteria; this is considered an interventional trial.

e: Plasma cell myeloma includes cases reported as plasma cell disorder. The reported term for the MedDRA PT of Leukaemia recurrent was "Plasma cell leukemia relapsed/refractory". NR includes cases reported as disease progression.

f: Of note, the case from China is a spontaneous report from the literature and the spontaneous case from Romania, provided very limited information such as the country of origin for the administration of the cilta-cel infusion, precluding an assessment.

g: A single case may report more than 1 event.

h: Excluding 2 cases reporting the MedDRA PT of Disease progression with a fatal outcome and 1 case with a cause of death (MedDRA PT) of Plasma cell myeloma recurrent.

Table 49. Frequency Distribution of the MedDRA PTs Reported More Than Once by MedDRA SOC in Descending Order and Seriousness for Cilta-cel Post-marketing Cases (N=141 Cases; N=290 events)

MedDRA SOC	MedDRA PTs (>1 Event)	Seriousness Number of Events		Total Number of Events (N=290) n (%)
		Nonserious n=119 n (%)	Serious n=171 n (%)	
General Disorders and Administration Site Conditions		*25(8.6)*	*31 (10.7)*	*56 (19.3)*
	Pyrexia	7 (2.4)	5 (1.7)	12 (4.1)
	Disease progression	0	12 (4.1)	12 (4.1)

	Therapeutic product effect incomplete	5 (1.7)	2 (0.7)	7 (2.4)
	Drug ineffective	1 (0.3)	4 (1.4)	5 (1.7)
	Fatigue	5 (1.7)	0	5 (1.7)
	Death	0	3 (1.0)	3 (1.0)
	Adverse event	2 (0.7)	0	2 (0.7)
	Asthenia	1 (0.3)	1 (0.3)	2 (0.7)
	Multiple organ dysfunction	0	2 (0.7)	2 (0.7)
Immune System Disorders		*1 (0.3)*	*42 (14.5)*	*43 (14.8)*
	Cytokine release syndrome	1 (0.3)	36 (12.4)	37 (12.8)
	Haemophagocytic lymphohistiocytosis	0	6 (2.1)	6 (2.1)
Nervous System Disorders		*4 (1.4)*	*37 (12.8)*	*41 (14.1)*
	Immune effector cell-associated neurotoxicity syndrome	1 (0.3)	11 (3.8)	12 (4.1)
	Neurotoxicity	0	6 (2.1)	6 (2.1)
	Bell's palsy	0	3 (1.0)	3 (1.0)
	Loss of consciousness	0	2 (0.7)	2 (0.7)
Investigations		*19 (6.6)*	*5(1.7)*	*24 (8.3)*
	Aspartate aminotransferase increased	4 (1.4)	0	4 (1.4)
	Alanine aminotransferase abnormal	3 (1.0)	0	3 (1.0)
	Platelet count decreased	2 (0.7)	1 (0.3)	3 (1.0)
	Alanine aminotransferase increased	2 (0.7)	0	2 (0.7)
	Full blood count abnormal	2 (0.7)	0	2 (0.7)
Infections and Infestations		*3 (1.0)*	*20 (6.9)*	*23 (7.9)*
	COVID-19	3 (1.0)	2 (0.7)	5 (1.7)
	Sepsis	0	4 (1.4)	4 (1.4)
	Septic shock	0	4 (1.4)	4 (1.4)
Product Issues		*16 (5.5)*	*2 (0.7)*	*18 (6.2)*
	Product label issue	5 (1.7)	0	5 (1.7)
	Product packaging issue	3 (1.0)	0	3 (1.0)
	Physical product label issue	2 (0.7)	0	2 (0.7)
Injury, Poisoning and Procedural Complications		*13 (4.5)*	*4 (1.4)*	*17(5.9)*
	Product dose omission issue	2 (0.7)	1 (0.3)	3 (1.0)
	Off -label use	3 (1.0)	0	3 (1.0)
	Medication error	2 (0.7)	0	2 (0.7)
	Infusion related reaction	1 (0.3)	1 (0.3)	2 (0.7)
Respiratory, Thoracic and Mediastinal Disorders		*5(1.7)*	*6 (2.1)*	*11 (3.8)*
	Dyspnoea	1 (0.3)	1 (0.3)	2 (0.7)
	Respiratory failure	0	2 (0.7)	2 (0.7)
Musculoskeletal and Connective Tissue Disorders		*7 (2.4)*	*2 (0.7)*	*9 (3.1)*
	Arthralgia	4 (1.4)	1 (0.3)	5 (1.7)
	Myalgia	2 (0.7)	0	2 (0.7)
Vascular Disorders		*6 (2.1)*	*3 (1.0)*	*9 (3.1)*

	Hypotension	4 (1.4)	1 (0.3)	5 (1.7)
Blood and Lymphatic System Disorders		*4 (1.4)*	*3 (1.0)*	*7(2.4)*
	Febrile neutropenia Neutropenia	0 1 (0.3)	2 (0.7) 1 (0.3)	2 (0.7) 2 (0.7)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)		*0*	*5(1.7)*	*5(1.7)*
	Plasma cell myeloma	0	4 (1.4)	4 (1.4)
Renal and Urinary Disorders		*1 (0.3)*	*3 (1.0)*	*4 (1.4)*
	Acute kidney injury	0	3 (1.0)	3 (1.0)
Metabolism and Nutrition Disorders		*2 (0.7)*	*0*	*2 (0.7)*
	Decreased appetite	2 (0.7)	0	2 (0.7)
GRAND TOTAL		119 (41.0)	171 (59.0)	290 (100.0)

Table 50. Frequency Distribution of MedDRA PTs Reporting a Fatal Outcome in Cilta-cel Post-marketing Cases (n=14 Cases; n=17 Events)

MedDRA SOC	MedDRA PT	Total Number of Events (N=290) n (%)
Infections and Infestations		*6 (2.1)*
	Septic shock Adenovirus infection Septic embolus COVID-19 Sepsis	2 (0.7) 1 (0.3) 1 (0.3) 1 (0.3) 1 (0.3)
General Disorders and Administration Site Conditions		*5(1.7)*
	Death Multiple organ dysfunction syndrome	3 (1.0) 2 (0.7)
Immune System Disorder		*2 (0.7)*
	Cytokine release syndrome Haemophagocytic lymphohistiocytosis	1 (0.3) 1 (0.3)
Nervous System Disorders		*2 (0.7)*
	Immune effector cell-associated neurotoxicity syndrome Cerebral haemorrhage	1 (0.3) 1 (0.3)
Cardiac Disorders		*1 (0.3)*
	Cardiac arrest	1 (0.3)
Respiratory, Thoracic and Mediastinal Disorders		*1 (0.3)*
	Respiratory failure	1 (0.3)
GRAND TOTAL		17 (5.9)

Table 51. Number of Post-marketing Cases and Estimated Patient Exposure for Adverse Events of Interest and Fatal Cases in Patients Treated With Cilta-cel

Adverse Event of Interest	Total Number of Cases & Estimated Patient Exposure (475 Patients) n (RR%)

CRS (Including HLH)	38 (8.0)
CRS	37 (7.8)
HLH	6 (1.3)
Neurologic Toxicities (Including ICANS and Other Neurotoxicities)	27 (5.7)
ICANS	12 (2.5)
Prolonged or Recurrent Cytopenia (Excluding Anemia)	1 (0.2)
Serious Infections	15 (3.2)
Hypogammaglobulinemia	0
Second Primary Malignancy	1 (0.2)
Fatal Cases	14 (3.0)

Table 52. Frequency Distribution of MedDRA PTs of Interest by Seriousness in Cilta-cel Post-marketing Cases Reporting Events of Neurologic Toxicities (including ICANS and Other Neurotoxicities) (n=27 Cases; n=32 Events)

MedDRA PTs Category	Number of Events n (%)		Total Number of Events (n=32) n (%)
	Serious (n=28) n (%)	Nonserious (n=4) n (%)	
Cranial Palsies	*5(15.6)*	*0*	*5(15.6)*
Bell's palsy	3 (9.4)	0	3 (9.4)
Cranial nerve paralysis	1 (3.1)	0	1 (3.1)
Facial paresis	1 (3.1)	0	1 (3.1)
ICANS	*11 (34.4)*	*1 (3.1)*	*12 (37.5)*
Immune effector cell-associated neurotoxicity syndrome	11 (34.4)	1 (3.1)	12 (37.5)
Movement and Neurocognitive Toxicity	*2 (6.3)*	*1 (3.1)*	*3 (9.4)*
Encephalopathy	1 (3.1)	0	1 (3.1)
Flat affect	0	1 (3.1)	1 (3.1)
Parkinsonism	1 (3.1)	0	1 (3.1)
Other Neurotoxicities	*11 (34.4)*	*2 (6.3)*	*13 (40.6)*
Neurotoxicity	6 (18.8)	0	6 (18.8)
Amnesia	1 (3.1)	0	1 (3.1)
Confusional state	0	1 (3.1)	1 (3.1)
Depressed level of consciousness	1 (3.1)	0	1 (3.1)
Loss of consciousness	2(6.3)	0	2(6.3)
Tremor	0	1 (3.1)	1 (3.1)
Unresponsive to stimuli	1 (3.1)	0	1 (3.1)
Guillain-Barre syndrome	*0*	*0*	*0*
Peripheral Neuropathy	*0*	*0*	*0*
TOTAL	28 (87.5)	4 (12.5)	32 (100.0)

2.5.1. Discussion on clinical safety

In study MMY3002 demographics and diseases characteristics between the participants in both treatment arms A and B can be considered balanced, cytogenic high-risk factors such as del(17p) or t(4;14) included. The majority of participants in both treatment arms had ECOG 0 or ECOG 1, only 1 subject in each arm had ECOG 2. Figures for tumour BCMA expression ≥50% were n=142 (67.8%) and n=138 (65.4%) for Arm B and A, respectively. During the randomization period (8 weeks) disease progression or death occurred in n=8 subjects in Arm A and n=22 in Arm B.

Identified differences between both treatment arms:

- PVd/DPd treatment regimen (used as both bridging therapy in Arm B and in Arm A): The doses of pomalidomide and bortezomib as bridging therapy in Arm B were approx. 14% lower compared to them in the SOC treatment regimens in Arm A.

- Major protocol deviations: The total number of subjects with major deviations in both arms, is considered not meaningful (20/419; 4.8%). However, the number of major trial protocol deviations was higher in Arm B (n=12; 5.8%) than in Arm A (n=8; 3.8%);

The methods for the assessment of the cilta-cel safety profile are generally supported; they are considered suitable for a comparison of events between both treatment arms in Study MMY3002. The assessment of AEs was made according to NCI-CTCAE V5, except for CRS and ICANS (graded by ASTCT consensus grading system). Second primary malignancies were considered adverse events of special interest (AESI) in both treatment arms.

All participants in both treatment arms experienced at least one TEAE any grade, and the majority of TEAEs occurred was reported as related to any component of the treatment regimen in both arms. The most important commonly reported TEAEs any grade included CRS, pancytopenia (neutropenia, anemia, thrombocytopenia, lymphopenia), hypogammaglobulinemia, gastrointestinal disorder, headache, fatigue and Covid-19 infection. For Arm A, 38.9% of the participants experienced serious TEAEs, and for Arm B 44.2% (serious TEAEs related to any part of study treatment: 22.1% and 29.3%, respectively). G3 or G4 TEAEs were reported for 91.3% and 90.4% of participants in Arm A and Arm B, respectively. N=6 participants (2.9%) in Arm A and n=13 participants (6.3%) in Arm B experienced a TEAE with an outcome of death.

As of DCO date 1 November 2022, there were n=85 deaths in Study MMY3002: Arm A: n=46 (22.1%), Arm B: n=39 (18.8%) including 11 participants who had not received cilta-cel.. Among the subjects in Arm B (n=176), n=18 (10.2%) died after receiving cilta-cel infusion, 9 patients between 31 and 180 days and 9 patients in the period more than 180 days after infusion. TEAE as primary cause of death was reported for n=5 subjects in Arm A and n=10 (4.8%). These were for Arm A: COVID-19 pneumonia, progressive multifocal leukoencephalopathy, respiratory tract infection, septic shock, and pulmonary embolism; and for Arm B: n=1 due to respiratory failure prior to cilta-cel infusion, n=7 due to COVID-19 pneumonia, n=1 due to pneumonia, and n=1 due to neutropenic sepsis. For 4 participants in Arm B, the TEAE reported as primary cause of death was considered as related to cilta-cel (COVID-19 pneumonia for 3 participants and neutropenic sepsis for 1 participant.

For 11 participants in Arm A (5.3%) and 15 in Arm B (7.2%) cases of death were considered not treatment emergent. In Arm B, 2 subjects died prior to cilta-cel infusion, and 7 death cases were reported more than 112 days after infusion of cilta-cel. 6 cases of death were reported in subjects, who received cilta-cel as subsequent therapy.

Adverse events of special interest Arm B

CRS

In Arm B (cilta-cel as study treatment), 134 participants (76.1%) experienced CRS: 93 participants [52.8%]) had G1 CRS; Grade 2 CRS was reported for 39 participants (22.2%). Two participants (1.1%) experienced Grade 3 CRS. No participants experienced Grade 4 or 5 CRS events.

CAR-T cell neurotoxicity

Events were documented for 36 participants (20.5%), including 5 participants (2.8%) with Grade 3 or 4 events. No participants experienced a Grade 5 event.

ICANS

For participants in Arm B, ICANS events were reported for 8 subjects (4.5%): Grade 1 (6 participants [3.4%]), Grade 2 ICANS (2 participants [1.1%]). The median time from initial cilta-cel infusion to first onset of ICANS was 9.5 days (range: 6 to 15 days), and the median duration of ICANS was 2.0 days (range: 1 to 6 days). All events of ICANS were considered as recovered or resolved. Six participants (3.4%) had ICANS concurrent with CRS. Treatment for ICANS or symptoms of ICANS was administered to 4 participants (2.3%), most commonly dexamethasone (4 participants [2.3%]).

Other Neurotoxicities

Movement disorders and Parkinsonism: Among 176 Arm B participants who received cilta-cel as study treatment, 1 participant experienced Movement and Neurocognitive (MNT) AEs. Specific events (all of Grade 1 toxicity, with onset on Day 85 post cilta-cel infusion) were balance disorder, bradykinesia, extrapyramidal disorder, gait disturbance, micrographia, parkinsonism, psychomotor retardation, and reduced facial expression All events were reported as not resolved as of the time of clinical cutoff.

Regarding the risk of development of parkinsonism after cilta-cel, the introduced early detection measures and treatment recommendations lead to a reduction in the occurrence of parkinsonism. However, the MAH's reported finding of an association between CD4+CAR+ to CD8+CAR+ T-cell-ratio (albeit weak in the presented results) after cilta-cel administration and the occurrence of cranial nerve palsies in patients may be of future clinical importance, particularly in view of the fact that a number of cases of parkinsonism is reported unresolved, and available medicinal products for treatment of Parkinson Disease (PD) turned out to be non-effective in cilta-cel related parkinsonism. Taking the post-marketing figures, 5 events of serious cranial palsies, a known clinical symptom of parkinsonism, have been reported for 32 identified events (16%) with unknown outcome. According to literature data base, T-cell related dopaminergic neurotoxicity is associated with CD8+and CD4+ T cells, reported in both PD animal models and PD human brains postmortal. Currently, the potential contribution of cilta-cel (and BCMA targeting CAR T cells in general) to PD related pro-inflammatory pathways and processes, leading to neuronal cell death, cannot be ruled out. All cases of (symptoms of) parkinsonism occurred in the clinical trials are adequately reflected in the SmPC, recommendations for early detection measures included.

Cranial nerve palsy: Among the 176 Arm B participants, 16 participants (9.1%) had an event of cranial nerve palsy, including 14 participants (8.0%) with Grade 2 events and 2 participants (1.1%) with Grade 3 events.

Peripheral Neuropathy: Among 176 Arm B participants, 13 (7.4%) had an event of peripheral neuropathy, including 6 participants (3.4%) with Grade 1 events, 6 participants (3.4%) with Grade 2 events, and 1 participant (0.6%) with Grade 3 events. 5/13 (38%) participants had peripheral neuropathy that was flagged as CAR-T cell neurotoxicity by the investigator.

Second Primary Malignancies (SPM)

For Arm A, 14 (6.7%) cases were reported, 10 in the category cutaneous/non-invasive; no case of hematologic malignancies. For Arm B, 9 (4.3%) cases were reported, 5 cases in the category cutaneous/non-invasive; 3 cases of hematologic malignancies or 1 case of acute myeloid leukaemia. The MAH provided an assessment of the 1 case of peripheral T-cell Lymphoma unspecified. The MAH's conclusion in the case of the identified CAR positive T-cell lymphoma indicating the malignant potential of the pre-existing clone prior to cilta-cel administration being responsible for the development of the CAR positive T-cell lymphoma could be accepted. Further investigations with regard to the finding of lentivirus integration at a predominant integration site at the 3' untranslated region (3' UTR) of gene PBX2 are ongoing and will be presented in the next PSUR and in the ongoing signal procedure. The finding of SPM, T-cell malignancies in particular in context with BCMA- and CD19-directed autologous CAR T cell immunotherapies in general is currently considered a clinically important identified risk to be followed. As

investigations are ongoing for all reported cases, the MAH committed to provide available results with the next PSUR. Relevant signal procedure is also ongoing for t-cell malignancies in the class of product. The risk for development of secondary malignancies in patients with RRMM is known, and up to now, the reported cases of T-cell lymphoma after treatment with Carvykti are rather low. However, if a relationship to the treatment with Carvykti cannot be ruled out currently, this information will be adequately addressed in the SmPC sections 4.4 and 4.8 during the PSUR or the signal procedure.

ADRs (adverse drug reactions) of cilta-cel

For the assessment of ADRs, the MAH provided a pooled analysis for Studies MMY3002 (n=196), MMY2003 (n=94), and MMY2001 (n=106), including participants from the main cohorts (n=97) and an additional cohort (n=9)). The most common ADRs (≥20% of participants) of any severity were CRS (83.3%), pyrexia (83.6%), pancytopenia (thrombocytopenia, anemia, lymphopenia, leukopenia), hypogammaglobulinemia (29.3%), hypotension (33.3%), gastrointestinal disorders (diarrhea 30.6%; nausea 23.2%), musculoskeletal pain (38%) upper respiratory tract infection (29.5%), musculoskeletal pain (38.4%) and fatigue (35%). . Since blood lactate dehydrogenase increase had an overall incidence rate of less than 10% and no severe forms have been reported, the MAH concluded to no longer include this abnormality as ADR, which can be accepted. From the pooled analysis the following new ADRs were identified: sleep disorders (10.1%), gastroenteritis (5.6%), urinary tract infection (5.1%), fungal infection (3%), lymphocytosis (2.8%), and capillary leak syndrome (0.5%), which is also considered acceptable. Additionally, cranial nerve palsies (6.8%) were separated out from under a previous group term of paresis (0.8%). The relevant changes to the SmPC have been implemented.

2.5.2. Conclusions on clinical safety

No new critical short- and/or mid-term safety issues were identified in the clinical trials, submitted to support the proposed extension of indication. Given the different safety profile of components of the (combined) SOC treatment regimens used in the randomized phase III Study MMY2003, in principle, the safety profile of cilta-cel can be considered comparable. The higher incidence rate of TEAEs G3/G4/G5 in the cilta-cel arm can be explained by the adverse events of neurotoxicity and CRS, attributed to cilta-cel alone. The higher frequency of cytopenia ≥ G3 (93.8% Arm B vs 86.1% Arm A) and hypogammaglobulinemia (90.9% Arm B vs 71.6% Arm A) ≥ G3 in the cilta-cel arm compared to the components of the SOC treatment arm is known. With regard to cytokine profiling, results submitted are more or less in line with known positive associations between $AUC_{0\text{-}56d}$ and IL6, IL-10, IL2Ra and IFNg.

Overall, the Applicant provided a thorough and comprehensive safety report of cilta-cel in the postmarketing setting, including stratified analysis by patient demographics (sex, age) and case characteristics (e. g, seriousness, indication, events of interest, and outcome), and including a summary of the fatal cases (Attachment 1). The estimated cumulative exposure to cilta-cel postmarketing is n=475 patients. N=290 events were reported in n=141 cases, about three-fifths as serious (59%). Among the 141 post-marketing cases/events, n= 14 were fatal (10%) with the following 17 fatal MedDRA PTs: multiple organ dysfunction syndrome and septic shock; adenovirus infection; cardiac arrest, cerebral haemorrhage; COVID-19; CRS; haemophagocytic lymphohistiocytosis; ICANS; respiratory failure; sepsis and septic embolus. For event outcome, when known (56%; 162/290), more events were resolved (21%; 61/290), followed by not resolved (19%; 55/290) and resolving (9%; 27/290).

In general, the majority of the events reported – fatal cases included – can be considered consistent with the known safety profile of cilta-cel and potential complications arising from CRS, HLH, ICANS, and cytopenia.

The CHMP endorse the CAT conclusion on clinical safety as described above.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version (4.3) with this application.

The CAT received the following PRAC Advice on the submitted Risk Management Plan:

Changes were made in the latest version of the RMP as part of this variation procedure. Mostly, figures were updated to reflect the newly available information with the completion of study 3002. As well study MMY3002 has been removed from the RMP as it is not considered anymore a specific obligation for the product due to the approvable switch from Conditional Marketing Authorization to a full MA not subject to specific obligations as result of this assessment. This is endorsed by the PRAC.

In conclusion the PRAC considered that the risk management plan version 4.3 is acceptable.

The CAT and CHMP endorsed this advice without changes.

The CAT and CHMP endorsed the Risk Management Plan version 4.3 with the following content:

Safety concerns

Important Identified Risks	Cytokine release syndrome (including HLH)
	Neurologic toxicities (including ICANS and other neurotoxicities)
	Prolonged or recurrent cytopenia (excluding anemia)
	Serious infections
	Hypogammaglobulinemia
Important Potential Risks	Second primary malignancy
	Decrease in cell viability due to inappropriate handling or preparation of the product
	Tumor lysis syndrome
	Aggravation of Graft versus Host Disease
	Generation of replication competent lentivirus
Missing Information	Long-term safety
	Impact on pregnancy and lactation
	Use in patients with pre-existing autoimmune disease
	Use in patients with pre-existing neurodegenerative disorders
	Use in patients with active CNS involvement by malignancy
	Use in patients with chronic controlled HIV and HBV/HCV infection

Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel Planned	Primary: To collect long-term follow-up data on delayed adverse events after administration of ciltacabtagene autoleucel, and to characterize and understand the long-term safety profile of ciltacabtagene autoleucel. Secondary: To collect additional long-term data on RCL, ciltacabtagene autoleucel persistence, efficacy, and OS. This study will include subjects who received ciltacabtagene autoleucel in company sponsored clinical trials. Consented subjects will be enrolled in this study once the individual study is completed and will be followed up for 15 years after their last dose of ciltacabtagene autoleucel.	Neurologic toxicities (including ICANS and other neurotoxicities) Prolonged or recurrent cytopenia (excluding anemia) Serious infections Hypogammaglobulinemia Second primary malignancy Aggravation of GvHD Generation of RCL Long-term safety Impact on pregnancy and lactation Use in patients with chronic controlled HIV and HBV/HCV infection	Protocol submission FPI Interim report Final report	Q2 2022 Q1 2022 (US) CSRs every 3 years from study start (ie, Q4 2025 and every 3 years thereafter) and routine PBRER and DSUR reporting Jun 2043
68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Planned	Primary: To evaluate the short- and long-term safety and risk of subsequent malignancy of ciltacabtagene autoleucel in adult patients with multiple myeloma. Secondary: To evaluate the effectiveness of ciltacabtagene autoleucel in adult	CRS (including HLH) Neurologic toxicities (including ICANS and other neurotoxicities) Prolonged or recurrent cytopenia (excluding anemia) Serious infections Hypogammaglobulinemia Second primary malignancy	Draft Protocol Final Protocol FPI Interim report	Feb 2022 Jul 2022 Q2 2022 Q3 2023 and annually thereafter and routine PBRER and DSUR reporting

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	patients with multiple myeloma. This study will include data from patients receiving ciltacabtagene autoleucel in the commercial setting, using data from patients consecutively enrolled in a registry as applicable. Other data sources may also include analysis from tumor samples or adverse events spontaneously reported to the MAH, where available.	TLS Aggravation of GvHD Generation of RCL Long-term safety Impact on pregnancy and lactation Use in patients with pre-existing autoimmune disease Use in patients with pre-existing neurodegenerative disorders Use in patients with active CNS involvement by malignancy Use in patients with chronic controlled HIV and HBV/HCV infection	Final report	Q4 2042
68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene autoleucel Planned	Primary: to evaluate the short- and long-term safety and risk of subsequent malignancy of ciltacabtagene autoleucel in adult patients with multiple myeloma. Secondary: To evaluate the effectiveness of ciltacabtagene autoleucel in adult patients with multiple myeloma.	CRS (including HLH) Neurologic toxicities (including ICANS and other neurotoxicities) Prolonged or recurrent cytopenia (excluding anemia) Hypogammaglobulinemia Serious infections TLS Aggravation of GvHD Generation of RCL Second primary malignancy Long-term safety Impact on pregnancy and lactation Use in patients with pre-existing autoimmune disease	Draft Protocol	Feb 2022
			Final Protocol	Jul 2022
			FPI	Q1 2024
			Interim report	Q3 2025 and annually thereafter and routine PBRER and DSUR reporting
			Final report	Q4 2042

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
		Use in patients with pre-existing neurodegenerative disorders Use in patients with active CNS involvement by malignancy Use in patients with chronic controlled HIV and HBV/HCV infection		
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Category 3 - Required additional pharmacovigilance activities				
Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training Planned	Survey to measure the effectiveness of the HCP Educational Program and the Product Handling Training: Guide for Health Care Professionals, an additional risk minimization measure to advise and increase awareness of the risks of CRS (including HLH) and neurologic toxicity (including ICANS and other neurotoxicities) and how to minimize these. To measure information on awareness of the HCP of the existence of the Patient Alert Card, as well as the intention and time of providing it to the patients. Product Handling Training, an additional risk minimization measure intended to increase awareness of the potential risk of decrease in cell viability due to inappropriate handling or preparation of the product.	CRS (including HLH) Neurologic toxicity (including ICANS and other neurotoxicities) Decrease in cell viability due to inappropriate handling or preparation of the product	Protocol submission Initiation of survey (wave 1) Initiation of survey (wave 2) Reports	3 months after EC decision within 18 months of availability of the approved educational materials in selected countries: Q4 2024 within 3 years of availability of the approved educational materials in selected countries: Q2 2026 24 months and 3.5 years after availability of the approved educational materials. Updates will also be reported in the PBRER and PSUR.

Risk minimisation measures

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures
CRS (including HLH)	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 6.6 • PL Section 2 • PL Section 3 • PL section 4 • Requirement to have tocilizumab (or suitable alternative measures if not available and listed in the EMA shortage catalogue) and emergency equipment available prior to infusion and during the recovery period is included in SmPC Sections 4.2, 4.4, and 6.6. • Recommendation for monitoring patients daily for signs and symptoms of CRS for 14 days after dosing and periodically for an addition 2 weeks are included in SmPC Section 4.4. • Recommendation for patients to remain within the proximity of a qualified clinical facility for at least 4 weeks following infusion is provided in SmPC Section 4.4 and in PL Section 3. • Recommendation to counsel patients to seek immediate medical attention if signs and symptoms of CRS occur, and recommendation to evaluate the patient for hospitalization and institute treatment at the first sign of CRS is provided in SmPC Section 4.4. • Recommendation to delay ciltacabtagene autoleucel infusion for patients with unresolved serious adverse reactions from preceding lymphodepleting or bridging chemotherapies (including cardiac toxicity and pulmonary toxicity), rapid disease progression, or clinically significant active infection is provided in SmPC Section 4.4. • Recommendations for the treatment of ongoing infections (which may increase the risk of a fatal CRS event) and recommendation to delay ciltacabtagene autoleucel infusion until any infections are resolved, are provided in SmPC Section 4.4. • Recommendation for potential early use of tocilizumab in patients with high tumor burden or early or persistent fever is provided in SmPC Section 4.4. • Recommendations for evaluation, treatment, and management of CRS are provided in SmPC Section 4.4. • Recommendations for treating high grade CRS that remains severe following use of tocilizumab and corticosteroids are provided in SmPC Section 4.4. • Recommendation to avoid the use of myeloid growth factors (particularly

Safety Concern	Risk Minimization Measures
	GM-CSF) during CRS is provided in SmPC Section 4.4. • Recommendation to evaluate for HLH in patients with severe or unresponsive CRS, and a warning that patients who develop HLH may have an increased risk of severe bleeding, is provided in SmPC Section 4.4. • Recommendation for reducing baseline burden of disease with bridging therapy prior to infusion in patients with high tumor burden in SmPC Section 4.4. • Recommendations on treatment for concurrent CRS and neurologic toxicity, including the use of corticosteroids, tocilizumab, and anti-seizure medication, is provided in SmPC Section 4.4. • Information regarding the incidence of CRS and the specific signs and symptoms seen in clinical trials is provided in SmPC Section 4.8. • Patients should inform their doctor or nurse immediately if CRS symptoms occur, as described in PL Section 2, and should seek medical help as described in PL Section 4. • Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** • Controlled Distribution Program and Availability of Tocilizumab • HCP Educational Program • Patient Educational Program
Neurologic toxicities (including ICANS and other neurotoxicities)	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to consider reducing baseline disease burden with bridging therapy prior to infusion in patients with high tumor burden is included in SmPC Section 4.4. • Recommendation for monitoring patients daily for signs and symptoms of neurologic events for 14 days after dosing and periodically for an addition 2 weeks are included in SmPC Section 4.4. • Recommendations on monitoring patients for signs and symptoms of ICANS for 4 weeks after infusion and thereafter for other neurotoxicity are included in SmPC Section 4.4. • Recommendation to continue to monitor patients for signs and symptoms of neurologic toxicity after recovery from CRS and/or ICANS is provided in SmPC Section 4.4. • Recommendation to counsel patients on the signs and symptoms of neurologic

Safety Concern	Risk Minimization Measures
	toxicities and to seek immediate medical attention if signs and symptoms occur is provided in SmPC Section 4.4. ● Recommendations on treating patients with symptoms of neurotoxicity, including intensive care supportive therapy (including steroids) for severe of life-threatening cases, are included in SmPC Section 4.4. ● SmPC Section 4.4 provides information on a subset of patients with a cluster of movement and neurocognitive adverse reactions that progressed in some to an inability to work or care for oneself. These events were associated with 2 or more factors at baseline such as higher tumor burden, prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence. Patients should be monitored for these symptoms and managed with supportive care measures. ● Instruction that patients should be monitored for GBS and treatment with intravenous immunoglobulin (IVIG) and plasmapheresis should be considered is included in SmPC Section 4.4. ● Instruction that patients should be monitored for signs and symptoms of peripheral neuropathies and cranial nerve palsies, and that management with short-course systemic corticosteroids should be considered, is included in SmPC Section 4.4. ● Instructions for treatment of neurotoxicities with early and aggressive supportive care (including steroids) in patients presenting with higher grade CRS or any grade ICANS is included in SmPC Section 4.4. ● Recommendations on treatment for concurrent CRS and neurologic toxicity, including the use of corticosteroids, tocilizumab, and anti-seizure medication, is provided in SmPC Section 4.4. ● Recommendation to refrain from driving and engaging in hazardous occupations or activities in the 8 weeks following infusion is provided in SmPC Section 4.7. ● Information regarding the incidence of neurologic toxicities (including ICANS and other neurotoxicities) and the specific symptoms seen in clinical trials is provided in SmPC Section 4.8. ● Patients should inform their doctor or nurse immediately if symptoms of ICANS or other neurotoxicities occur, as described in PL Section 2, and should seek medical help for ICANS as described in PL Section 4. ● Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** ● Controlled Distribution Program and Availability of Tocilizumab ● HCP Educational Program ● Patient Educational Program
Prolonged or recurrent cytopenia (excluding anemia)	**Routine risk minimization measures:** ● SmPC Section 4.4 ● SmPC Section 4.8

Safety Concern	Risk Minimization Measures
	• PL Section 2 • PL Section 4 • Recommendation to monitor blood counts prior to and after ciltacabtagene autoleucel infusion is provided in SmPC Section 4.4. • Recommendation to consider supportive care with transfusions for treatment of thrombocytopenia is provided in SmPC Section 4.4. • Recommendation to avoid the use of myeloid growth factors (particularly GM-CSF) during CRS is provided in SmPC Section 4.4. • Information regarding the incidence of prolonged or recurrent cytopenia (excluding anemia) is provided in SmPC Section 4.8. • Patients should inform their doctor right away if they have any symptoms of prolonged or recurrent cytopenia, as described in PL Sections 2 and 4. • Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** • None
Serious infections	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to delay lymphodepletion therapy if a patient has clinically significant active infection is provided in Section 4.2. • Recommendation that infection prophylaxis should follow local guidelines, and that infections are known to complicate the course and management of concurrent CRS, are provided in SmPC Section 4.4. • Recommendation to delay ciltacabtagene autoleucel infusion until any clinically significant active infection or inflammatory disorder is resolved is provided in SmPC Section 4.4. • Recommendation that patients should be counselled on the importance of prevention measures for COVID-19, as patients treated with ciltacabtagene autoleucel may be at increased risk of severe/fatal COVID-19 infections, is provided in SmPC Section 4.4. • Recommendation on monitoring patients for signs and symptoms of infection is provided in SmPC Section 4.4. • Recommendations for the management and treatment of febrile neutropenia are included in SmPC Section 4.4. • Recommendation to screen for HBV, HCV, and HIV prior to collection of cells for manufacturing is included in SmPC Section 4.4. • Recommendation to monitor immunoglobulin levels after treatment and treat

Safety Concern	Risk Minimization Measures
	according to standard guidelines, including administration of immunoglobulin replacement, antibiotic prophylaxis and monitoring for infection is included in SmPC Section 4.4. ● Information regarding the incidence of serious infections is provided in SmPC Section 4.8. ● Ciltacabtagene autoleucel may increase the risk of life-threatening infections that may lead to death. Patients should tell their doctor right away if they have any signs or symptoms of infection, as described in PL Sections 2 and 4. ● Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** ● None
Hypogamma-globulinemia	**Routine risk minimization measures:** ● SmPC Section 4.4 ● SmPC Section 4.6 ● SmPC Section 4.8 ● Recommendation that immunoglobulin levels should be monitored after treatment with ciltacabtagene autoleucel, IVIG should be administered for IgG <400 mg/dL, and patients should be managed according to standard guidelines, including antibiotic or antiviral prophylaxis and monitoring for infection, is described in SmPC Section 4.4. ● Recommendation that assessment of immunoglobulin levels in newborns of mothers treated with ciltacabtagene autoleucel should be considered is provided in SmPC Section 4.6. ● Information regarding the incidence of hypogammaglobulinemia infections is provided in SmPC Section 4.8. ● Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** ● None
Second primary malignancy	**Routine risk minimization measures:** ● SmPC Section 4.4 ● Recommendation for life-long monitoring of patients for secondary malignancies is provided in SmPC Section 4.4. ● Recommendation to contact the MAH for instructions on collecting patient samples for testing is provided in SmPC Section 4.4. ● Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** ● None
Decrease in cell viability	**Routine risk minimization measures:**

Safety Concern	Risk Minimization Measures
due to inappropriate handling or preparation of the product	• SmPC Section 4.2 • SmPC Section 6.3 • SmPC Section 6.4 • SmPC Section 6.6 • Instructions for preparation of ciltacabtagene autoleucel, including thawing, are provided in SmPC Section 4.2. • Shelf life and special precautions for storage of ciltacabtagene autoleucel are provided in SmPC Sections 6.3 and 6.4. • Special precautions for disposal and other handling are provided in SmPC Section 6.6. **Additional risk minimization measures:** Product Handling Training
TLS	**Routine risk minimization measures:** • Use restricted to physicians experienced in the treatment of hematological cancer **Additional risk minimization measures:** • None
Aggravation of GvHD	**Routine risk minimization measures:** • SmPC Section 4.4 • PL Section 2 • Instruction that ciltacabtagene autoleucel infusion should be delayed if a patient has active GvHD is provided in SmPC Section 4.4. • Instruction for patients to tell their doctor prior to infusion of ciltacabtagene autoleucel if they have signs or symptoms of GvHD in provided in PL Section 2. • Use restricted to physicians experienced in the treatment of hematological cancer **Additional risk minimization measures:** • None
Generation of RCL	**Routine risk minimization measures:** • Use restricted to physicians experienced in the treatment of hematological cancer **Additional risk minimization measures:** • None
Long-term safety	**Routine risk minimization measures:** • None **Additional risk minimization measures:** • None

Safety Concern	Risk Minimization Measures
Impact on pregnancy and lactation	**Routine risk minimization measures:** ● SmPC Section 4.6 ● PL Section 2 ● Recommendations that pregnancy status for females of childbearing age should be verified prior to starting treatment is provide in SmPC Section 4.6. ● Recommendation on the need for effective contraception in patients who receive the lymphodepleting chemotherapy according to the corresponding prescribing information is provided in SmPC Section 4.6. ● Recommendation to advise pregnant or breastfeeding women that there may be risks to the fetus or the breast-fed infant is provided in SmPC Section 4.6. ● Recommendation that for any pregnant woman who receives ciltacabtagene autoleucel, assessment of immunoglobulin levels in newborns of mothers should be considered is provided in SmPC Section 4.6. ● Patients should notify their doctor immediately if they are pregnant or think they may be pregnant following treatment with ciltacabtagene autoleucel, as described in PL Section 2. ● Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** ● None
Use in patients with pre-existing autoimmune disease	**Routine risk minimization measures:** ● Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** ● None
Use in patients with pre-existing neurodegenerative disorders	**Routine risk minimization measures:** ● SmPC Section 4.4 ● PL Section 2 ● A warning indicating that patients with significant CNS disease are likely to be more vulnerable to the consequences of adverse reactions observed with ciltacabtagene autoleucel and may require special attention is provided in SmPC Section 4.4. ● Patients should tell their doctor before treatment with ciltacabtagene autoleucel if they have current or past nervous system disorders, as described in PL Section 2. ● Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** ● None
Use in patients with active CNS involvement by	**Routine risk minimization measures:**

Safety Concern	Risk Minimization Measures
malignancy	• Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** • None
Use in patients with chronic controlled HIV and HBV/HCV infection	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • Instructions for screening of HBV, HCV, and HIV are included in SmPC Sections 4.2 and 4.4. • Use restricted to physicians experienced in the treatment of hematological cancers **Additional risk minimization measures:** • None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes are made to the Opinion Annex II conditions as detailed in the recommendations section to delete the remaining SOB as it has been considered fulfilled by this extension of indication procedure.

Changes were also made to the annex IIIA to bring it in line with the current ATMP QRD template.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

Full user testing was already performed on the package leaflet developed for CARVYKTI for the initial Marketing Authorisation Application. As a result of a recommendation a further full user testing was performed under procedure EMEA/H/C/005095/N/0013 and the compliance of the package leaflet of CARVYKTI with the EU requirements was confirmed.

With the currently proposed indication extension, only minimal changes have been introduced to the package leaflet and the proposed changes reflect language and a format that is consistent with that in the currently approved leaflet. The use of lay language for additional symptoms and side effects is consistent with the current approved leaflet. New terms (sleep disorders, gastroenteritis, urinary tract infection, fungal infection, lymphocytosis, and capillary leak syndrome) have been added, which are not associated with new warnings or precautions and do not affect the overall benefit/risk profile of CARVYKTI.

Therefore, a further user consultation is not deemed necessary in the course of the current variation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The present variation application concerns the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 1 prior therapy, including an immunomodulatory agent and a proteasome inhibitor, have demonstrated disease progression on the last therapy and are refractory to lenalidomide.

3.1.2. Available therapies and unmet medical need

There are several approved triplet regimens for patients with multiple myeloma who have relapsed after 1 to 3 prior lines of therapy. However, these regimens have largely been tested in lenalidomide naïve or lenalidomide sensitive patients. Given that lenalidomide is now frequently administered in front-line maintenance, and relapsed/refractory settings, there are fewer options for patients with lenalidomide-refractory disease and there are no approved regimens specifically for this patient population. More recently, a number of studies evaluated combinations of a monoclonal antibody, with a PI or with pomalidomide. These studies included substantial proportions of lenalidomide-refractory patients: 93% in ICARIA (isatuximab, pomalidomide, dexamethasone), 80% in APOLLO (daratumumab, pomalidomide, dexamethasone), 70% in OPTIMISMM (bortezomib, pomalidomide, and dexamethasone), 33% in CANDOR (carfilzomib, dexamethasone, and daratumumab), and 33% in IKEMA (isatuximab, carfilzomib, and dexamethasone). Among lenalidomide-refractory patients treated with the triplet regimens in these studies, median PFS was 11.4 months for the ICARIA study, 9.9 months for the APOLLO study, and 9.5 months for the OPTIMISMM study, with longer median PFS noted for the CANDOR study (median 28.1 months) and the IKEMA study (median PFS for lenalidomide-refractory subgroup not reported), both of which used an anti-CD38 monoclonal antibody in combination with carfilzomib and dexamethasone. The sustained response shown in these studies relies on ongoing therapy until progression of disease, potentially resulting in cumulative toxicity and significant treatment burden.

3.1.3. Main clinical studies

The results supporting the indication extension of cilta-cel to MM in an earlier treatment line were obtained from Study MMY3002. Study MMY3002 is a Phase 3, randomized, open-label, multicentre study in participants with relapsed and lenalidomide-refractory multiple myeloma treated with 1 to 3 prior lines of therapy to determine whether treatment with cilta-cel would provide efficacy benefit compared to investigator's choice of PVd or DPd.

The planned total sample size was approximately 400 participants (200 participants per arm). Four hundred and nineteen participants were randomized in a 1:1 ratio to Arm A (standard therapy with PVd or DPd) or Arm B (cilta-cel) according to the planned stratification factors.

The primary hypothesis was that cilta-cel will significantly improve PFS compared with standard therapy (PVd or DPd) in subjects who have previously received 1 to 3 prior line(s) of therapy, that included a PI and an IMiD, and who are refractory to lenalidomide. It was assumed that cilta-cel can reduce the risk of progressive disease or death by 35%, ie, HR (cilta-cel vs. standard therapy) of 0.65, which translated to a median PFS of 20 months for Arm B, assuming the median PFS for Arm A was 13 months.

3.2. Favourable effects

At a median follow-up of 15.9 months (data Cut off 1 November 2022), a PFS event was reported for 57.8% of participants in Arm A and for 31.3% of participants in Arm B; median PFS was 11.8 months (95% CI: 9.7, 13.8) for Arm A and NE (95% CI: 22.8, NE) for Arm B. The HR was 0.26 (95% CI: 0.18, 0.38), with p-value of 0.0001 crossing the O'Brien-Fleming stopping boundary of 0.0191. The HR of 0.26 indicates a 74% reduction in the risk of death or progression for Arm B as compared with Arm A. The 12-month PFS rates were 48.6% for Arm A and 75.9% for Arm B.

The treatment effect of Arm B over Arm A was consistent across all pre-specified subgroups, including the following key subgroups: participants with 1 prior line of therapy (HR=0.35 [95% CI: 0.19, 0.66]), ISS Stage III (HR=0.33 [95% CI: 0.11, 0.95]), high tumour burden (HR=0.27 [95% CI: 0.13, 0.56]), and high-risk cytogenetics (HR=0.25 [95% CI: 0.16, 0.38]).

The rate of CR or better (sCR + CR) by computerized algorithm was 21.8% (95% CI: 16.4%, 28.0%) for Arm A and 73.1% (95% CI: 66.5%, 79.0%) for Arm B; the stratified CMH estimate of odds ratio was 10.3 (95% CI: 6.5, 16.4; p<0.0001). In analysis of the 176 participants in Arm B who received cilta-cel infusion as study treatment, the rate of CR or better was 86.4% (95% CI: 80.4%, 91.1%).

All pre specified subgroup analyses of CR or better rate favoured Arm B, including key subgroups of 1 prior line of therapy (odds ratio=4.4 [95% CI: 2.1, 9.1]), ISS Stage III (odds ratio=26.0 [95% CI: 2.5, 275.8]), high tumour burden (odds ratio=9.0 [95% CI: 2.2, 36.2]) and high risk cytogenetics (odds ratio=11.1 [95% CI: 6.2, 20.0]).

Rate of CR or better was higher for Arm B than for Arm A for subgroups with 1 (Arm A: 35.3%; Arm B: 70.6%), with 2 (Arm A: 17.2%; Arm B: 74.7%), and with 3 (Arm A: 12.5%; Arm B: 73.7%) prior lines.

The ORR (sCR + CR + VGPR + PR) by computerized algorithm was 67.3% (95% CI: 60.5%, 73.6%) for Arm A and 84.6% (95% CI: 79.0%, 89.2%) for Arm B; the stratified CMH estimate of odds ratio was 3.0 (95% CI: 1.8, 5.0; p<0.0001). In analysis of the 176 participants in Arm B who received cilta-cel infusion as study treatment, the ORR was 99.4% (95% CI: 96.9%, 100.0%).

The MRD negativity rate (10^{-5}) as measured by NGS was approximately 4-fold higher for participants in Arm B compared with participants in Arm A (Arm A: 15.6%, Arm B: 60.6%; odds ratio=8.7; 95% CI: 5.42, 13.90; p<0.0001).

Initial OS data suggested a trend towards improved survival in Arm B vs. Arm A (HR=0.78; 95% CI: 0.50, 1.20; p=0.2551). Updated OS data were provided by the MAH following survival sweep analysis performed on 13 December 2023. The number of events was 77 (36.5%) in Arm A and 48 (23.1%) in Arm B, respectively. The 36-months survival rate was 53.1% (95% CI: 39.6. 65.0) for the SOC arm and 76.2 (95% CI: 69.6, 81.6) for the cilta-cel arm.

As most responders' DOR data (56.3% of participants in Arm A and 81.3% of participants in Arm B with PR or better) were censored as of the time of clinical cutoff, DOR data were not mature. Median DOR was 16.6 months (95% CI: 12.9, NE) for Arm A and NE (95% CI: NE, NE) for Arm B. 12-month event-free rates were 63.0% (95% CI: 54.2%, 70.6%) for Arm A and 84.7% (95% CI: 78.1%, 89.4%) for Arm B.

3.3. Uncertainties and limitations about favourable effects

The present variation application concerns the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 1 prior therapy, However, there is a limited number of patients with 1 prior line of therapy in the study: only one third of patients (68 patients in each arm). Nevertheless, the sCR/CR/ORR data in this subgroup are considered compelling.

In the KM plots crossing curves are presented for both PFS and OS. Crossing survival curves are generally a result of the survival times having greater variance in one treatment group than another. The subgroup analysis presented by the MAH indicates a well-balanced distribution for a variety of subgroups between the two arms. The early PFS and OS events within 8 weeks after randomization in Arm B occurred before treatment with cilta-cel. There are no obvious differences in the treatment provided to patients during bridging therapy and the treatment in Arm A. No further subgroups could be identified who could have an inferior outcome following treatment with the CAR-T cells.

The initial OS data were still immature, however, the updated OS following survival sweep analysis performed on 13 December 2023 demonstrate a favourable trend in OS that appears to be strengthening over time. These OS data are supportive of the clinical benefit in combination with the unambiguous PFS data and the other clinically meaningful endpoints such as rate of CR/sCR, ORR, and overall MRD negativity rate when compared to standard of care.

3.4. Unfavourable effects

The unfavourable effects of cilta-cel as a BCMA targeted CAR T cell product are mostly known. The safety profile is characterised by high incidence of cytopenias, diarrhoea, fatigue, by immune system disorders including hypogammaglobulinemia, CRS and ICANS. Furthermore, movement disorders/parkinsonism are clearly related to treatment. Cranial nerve palsies have also been observed with a rather high incidence (9%). Overall, they were diagnosed and treated according to recommendations and guidelines as outlined in the SmPC, and have been manageable in the course of the trial(s). Compared to standard therapy there is a shift to more severe TEAE with the majority of TEAE reaching grade 4.

Second primary malignancies (SPM) have occurred in both treatment arms with similar frequency. Based on the product class, malignancies involving blood derived cells are of particular interest. The development of SPM after Carvykti, in particular T-cell malignancy is considered an important identified risk.

3.5. Uncertainties and limitations about unfavourable effects

Cases of symptoms of Parkinsonism after treatment with Carvykti were reported. The fact that they did not respond to therapy with dopamine-agonists may indicate that these movement disorders do not share the same pathophysiology with Parkinson Disease.. All cases of (symptoms of) parkinsonism occurred in the clinical trials are adequately reflected in the SmPC and recommendations for early detection measures included.

T-Cell Malignancies, as reported for Carvykti in the current pivotal study, have been reported with a higher frequency in several CAR-T cell products and this have triggered a signal procedure to investigate the relevance of these cases. The cases included in this assessment report are being therefore analysed in the relevant signal procedure and relevant regulatory action will be defined upon finalisation of it after the closure of the ongoing signal.

3.6. Effects Table

Table 53. Effects Table for cilta-cel: (Efficacy and safety: MMY3002, CARTITUDE-4; DCO: 01 November 2022);

Effect	Short description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References

Effect	Short description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS	time from randomization to disease progression or death.	months (95% CI)	NE (22.8, NE)	11.8 months (9.7, 13.8)	HR (95% CI)= 0.26 (0.18, 0.38) Crossing KM plot curves, initial advantage of SOCT, from month 3 on advantage for cilta-cel	
sCR	stringent complete response	n (%)	121 (58.2%)	32 (15.2%)		
sCR + CR	sCR + complete response	n (%)	152 (73.1%)	46 (21.8%)		
ORR	best overall response of PR or better	n (%)	176 (84.6%)	142 (67.3%)		
MRD negativity	MRD negativity rate (10^{-5})	n (%)	126 (60.6%)	33 (15.6%)		
Unfavourable Effects						
Serious TEAEs G3/G4		N (%)	67/208 (32.2) Arm B	70/208 (33.7) Arm A		
TEAE G5 as (Fatal)		N (%)	13/208 (6.3) Arm B	6 /208 (2.9) Arm A		
Number of subj. with TEAE as primary death cause		N (%)	10/208 (4.8) Arm B	5/208 (2.4) Arm A		
Second prim. T-cell malignancies		N (%)	1/208 (1.4)	0	CAR pos. T-cell lymphoma in a subject with no relevant medical history	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The strength of the findings is given by the fact that the proposed new indication is based on a randomized trial comparing cilta-cel versus SOCT in adult subjects with relapsed and refractory multiple myeloma.

PFS was used as the primary endpoint in this trial and is accepted as a clinically relevant endpoint that demonstrated benefit to the patient per se. The observed effect size is convincing and considered relevant. Further support for the observed treatment effect is given by most secondary endpoints which

consistently favour the experimental arm. Furthermore, subgroup analyses (prior therapy, cytogenetic risk) also show a consistent effect.

Updated OS following survival sweep analysis performed on 13 December 2023 demonstrate a favourable trend in OS that appears to be strengthening over time. These OS data are supportive of the clinical benefit in combination with the unambiguous PFS data and the other clinically meaningful endpoints such as rate of CR/sCR, ORR, and overall MRD negativity rate when compared to standard of care.

CRS, neurotoxicity, haematological side effects (cytopenia, hypogammaglobulinemia) and its consequences such as the risk of severe infections are of high patient relevance. The higher incidence of severe AE with the experimental treatment is notable and considered of clinical relevance. The majority of AE are treatable, a possible exception being the observed neurological disorders, identified as (symptoms of) parkinsonism. However, it is expected that once the acute phase of treatment with a CAR-T cell has passed, the AE frequency is lower, thus providing additional benefit to the patient.

3.7.2. Balance of benefits and risks

The demonstrated benefit outweighs the observed unfavourable effects.

3.7.3. Additional considerations on the benefit-risk balance

Currently Carvykti is approved under a Conditional Marketing Authorisation (CMA). Based on this submission the MAH applies for the conversion to a standard marketing authorisation. This is agreed after consideration of the data provided. Indeed, considering all efficacy and safety data and the latest updates in OS data presented for this extension of indication, it can be concluded that comprehensive clinical data has been provided to confirm efficacy and safety of cilta-cel in the approved indication. The remaining Specific Obligation (SOB) can therefore be considered fulfilled. Therefore, the switch to a marketing authorisation in accordance with Article 14-a(8) of Regulation (EC) No 726/2004 (‘marketing authorisation not subject to specific obligations’) is justified. Final study report for the study MMY3002 is now requested as recommendation post approval to be provided when available.

With the data on clinical comparability of the two lentiviral vector manufacturing processes from the Study MMY3002 the MAH also demonstrated comparability in terms of efficacy and safety of the two manufacturing processes which closes also the relevant recommendation to provide further data on the clinical effect of such process differences.

3.8. Conclusions

The overall B/R of Carvykti is positive for the applied extension of indication.

The CHMP endorse the CAT conclusion on Benefit Risk balance as described above.

4. Recommendations

Outcome

Based on the draft CHMP opinion adopted by the CAT and the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least 1 prior therapy, including an IMiD and a PI, have demonstrated disease progression on the last therapy and are refractory to lenalidomide for CARVYKTI, based on interim results from study MMY3002 listed as a specific obligation (SOB/006) in the Annex II. This is an ongoing, Phase 3, randomized, open-label, multicentre study to determine whether treatment with cilta-cel provides an efficacy benefit compared to standard therapy in participants with relapsed and lenalidomide-refractory multiple myeloma. As a consequence, sections 4.1, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The SOB is considered fulfilled and therefore deleted from Annex II. Version 4.3 of the RMP has also been submitted. In addition, the MAH took the opportunity to update Annex II of the PI. As part of the application the MAH is requesting a 1-year extension of the market protection.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

The following obligation has been fulfilled, and therefore it is recommended that is deleted from the Annex II:

Description	Due date
In order to confirm the efficacy and safety of CARVYKTI in adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy, the MAH should submit the results of the Phase 3 study CARTITUDE-4 (MMY3002).	December 2026

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Controlled distribution program and availability of tocilizumab

To minimise the risks of CRS (including HLH) and neurotoxicity (including ICANS and other neurotoxicity) associated with the treatment of CARVYKTI the MAH will ensure that centres that dispense CARVYKTI are qualified in accordance with the agreed controlled distribution program by:

- ensuring immediate, on-site access to one dose of tocilizumab per patient prior to CARVYKTI infusion. The treatment centre must have access to an additional dose of tocilizumab within 8 hours of each previous dose. In the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, the MAH will ensure that suitable alternative measures to treat CRS instead of tocilizumab are available on-site.

CARVYKTI will only be supplied to centres that are qualified and only if the Healthcare professional (HCP) involved in the treatment of a patient has completed the HCP educational program.

Educational program: Prior to the launch of CARVYKTI in each Member State the MAH must agree the content and format of the educational materials with the National Competent Authority.

HCP educational program

The MAH shall ensure that in each Member State where CARVYKTI is marketed, all HCPs who are expected to prescribe, dispense, and administer CARVYKTI shall be provided with guidance:

- to increase awareness of CRS (including HLH) and neurotoxicity (including ICANS and other neurotoxicity) and its appropriate monitoring, prevention, and management, including the importance of on-site availability of tocilizumab before treating a patient.
- to facilitate patient counseling relevant information.
- on reporting these serious adverse reactions associated with CARVYKTI.
- before treating a patient, to ensure that tocilizumab for each patient is available on site; in the exceptional case where tocilizumab is not available due to a shortage that is listed in the European Medicines Agency shortage catalogue, ensure that suitable alternative measures to treat CRS are available on site.

Medicinal product handling training

The MAH shall ensure that all HCPs and other personnel involved in the transport, storage, thawing, preparation, or handling of CARVYKTI shall be provided training:

- to increase awareness of the important potential risk of decrease in cell viability due to inappropriate handling or preparation of the medicinal product.
- to provide guidance on precautions to take before handling or administering CARVYKTI (i.e., how to check the medicinal product prior to administration, how to thaw, and how to administer).

Patient educational program

To inform and explain to patients:

- the risks of CRS (including HLH) and neurotoxicity (including ICANS and other neurotoxicity) associated with CARVYKTI and increase awareness of symptoms requiring immediate medical attention.
- the need to carry the patient alert card at all times and share it with any HCP providing care (including emergency) so the HCP can contact the CAR-T treating HCP.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to further characterise the long-term safety and efficacy of CARVYKTI within the indicated relapsed and refractory multiple myeloma population, the MAH shall submit the results of the long-term follow-up study for participants previously treated with ciltacabtagene autoleucel.	June 2043
In order to further characterise the long-term safety of CARVYKTI within the indicated relapsed and refractory multiple myeloma population, the MAH shall conduct and submit the results of an observational post-authorisation safety study based on a registry.	December 2042
In order to further characterise the long-term safety of CARVYKTI within the indicated relapsed and refractory multiple myeloma population, the MAH shall conduct and submit the results of an observational post-authorisation safety study based on patient's data primarily from the EU region.	December 2042

Similarity with authorised orphan medicinal products

The CAT by consensus is of the opinion that Carvykti is not similar to Imnovid, Ninlaro, Farydak, Kyprolis, Darzalex, Blenrep, Abecma, Talvey within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

The CHMP endorse the CAT conclusion on the similarity with authorised orphan medicinal products.

Additional market protection

Furthermore, the CAT reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

The CHMP endorse the CAT conclusion on the Additional market protection.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Carvykti-H-C-5095-II-0021'