Fred Hutch Cancer Center

BCMA CAR-T in Multiple Myeloma: Current Practice and What's Next

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1 BCMA-targeted CAR-T

2 Overall schema

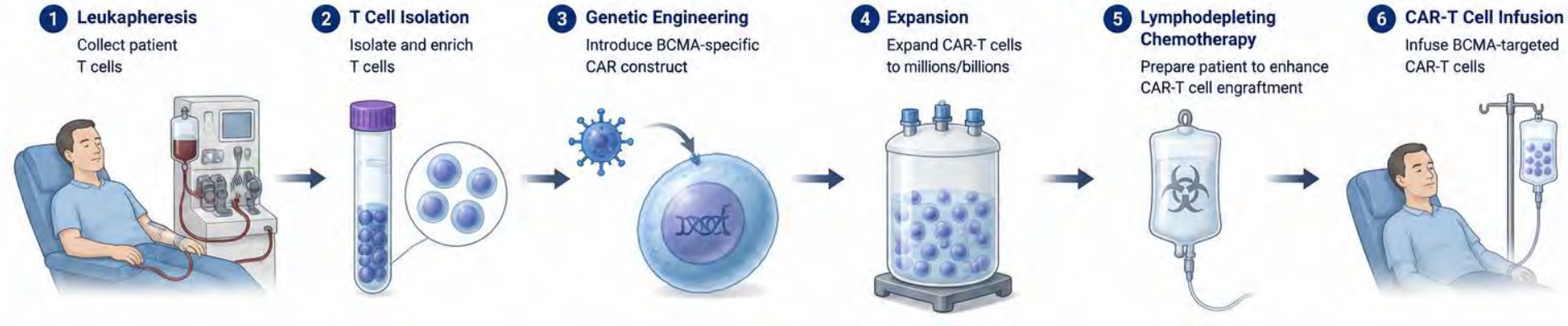
3 Toxicities and bridging

4 Our real-world experience

5 What's next?

BCMA-targeted CAR-T

BCMA-Targeted CAR-T Cell Therapy



BCMA-Targeted CAR-T Cell Therapy

1 Leukapheresis
Collect patient T cells

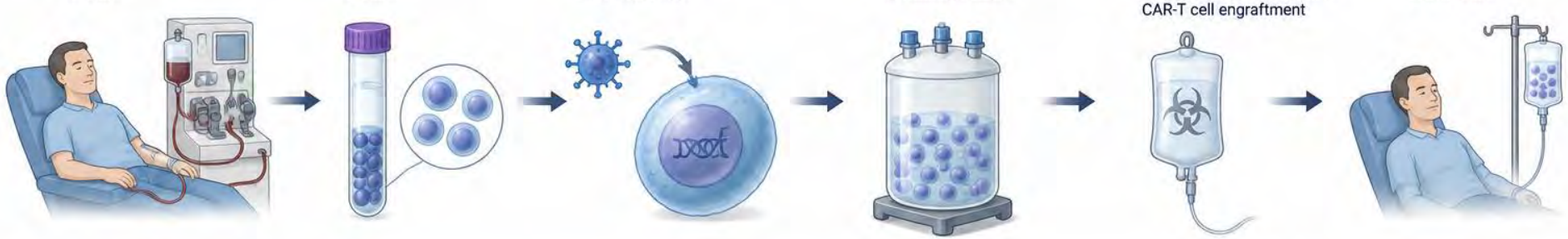
2 T Cell Isolation
Isolate and enrich T cells

3 Genetic Engineering
Introduce BCMA-specific CAR construct

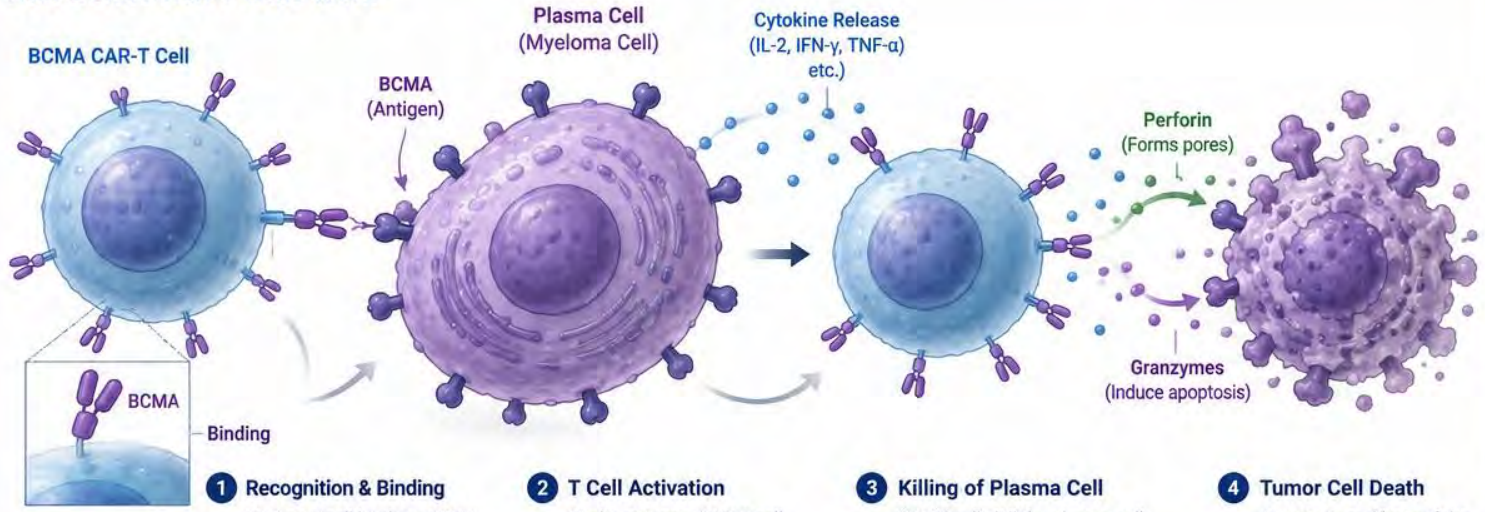
4 Expansion
Expand CAR-T cells to millions/billions

5 Lymphodepleting Chemotherapy
Prepare patient to enhance CAR-T cell engraftment

6 CAR-T Cell Infusion
Infuse BCMA-targeted CAR-T cells



How BCMA CAR-T Cells Work



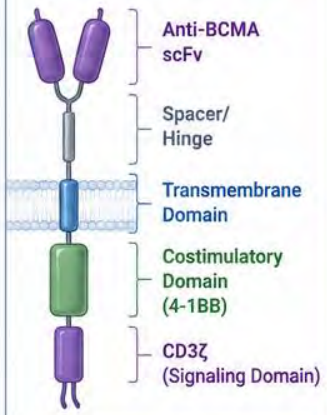
1 Recognition & Binding
CAR on T cell binds to BCMA on plasma cell

2 T Cell Activation
Binding triggers CAR-T cell activation and proliferation

3 Killing of Plasma Cell
CAR-T cells kill the plasma cell via multiple mechanisms

4 Tumor Cell Death
Apoptosis and lysis of the plasma cell

BCMA CAR Structure



The CAR combines antigen recognition with T cell activation to specifically target BCMA+ plasma cells.

Target: BCMA (B Cell Maturation Antigen) – highly expressed on malignant plasma cells in multiple myeloma, limited on normal tissues.

Goal: Eradicate myeloma cells and achieve deep, durable remission.

Key Clinical Evidence for BCMA-Directed CAR-T Therapy in Multiple Myeloma

Trial (Reference)	Design & Population	Intervention	Key Efficacy Results	Key Safety Results	Key Takeaway
CARTITUDE-1 ***Pivotal Phase 1b/2 Single-Arm Trial*** Berdeja JG, et al. *Lancet*. 2021;398:314–324. Jagannath S, et al. *J Clin Oncol*. 2025;43:2766–2771. THE LANCET JCO®	**Phase 1b/2, open-label, single-arm** • Relapsed/refractory MM (RRMM) • ≥3 prior lines of therapy • Triple-class exposed • N = 97 treated patients **Median follow-up: 61.3 months**	Ciltacabtagene autoleucel (cilta-cel) **Single infusion** (Target dose: 0.75 × 10^6 CAR+ T cells per kg)	• **Overall response rate: 97%** (95% CI, 91.2–99.4) • **Stringent complete response rate: 67%** • **Median duration of response: Not reached** **Median PFS 34.9 months** (95% CI, 22.2–NE) **Median OS 60.7 months** (95% CI, 41.9–NE) • **32/97 (33%) patients remain alive and progression-free ≥5 years after a single cilta-cel infusion (without maintenance)** • **100% MRD-negative (10^{-5}) and imaging-negative ≥5 years** (n = 12 serially assessed)	• Safety profile consistent with prior reports • No new safety signals with long-term follow-up • Cytokine release syndrome: 95% (grade ≥3: 4%) • ICANS: 21% (grade ≥3: 9%) • Manageable safety profile	**CARTITUDE-1 established that a single cilta-cel infusion produces deep and durable responses with long-term survival, with ~1/3 of patients remaining progression-free beyond 5 years.**

BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; cilta-cel = ciltacabtagene autoleucel; CI = confidence interval; ICANS = immune effector cell–associated neurotoxicity syndrome; IMiD = immunomodulatory drug; ITT = intention-to-treat; MM = multiple myeloma; MRD = minimal residual disease; NE = not estimable; OS = overall survival; PFS = progression-free survival; PVd = pomalidomide–bortezomib–dexamethasone; SOC = standard of care; TEAE = treatment-emergent adverse event.

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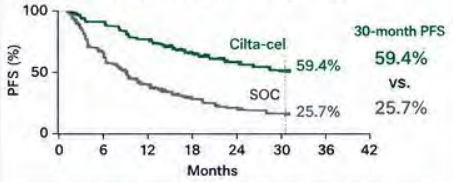
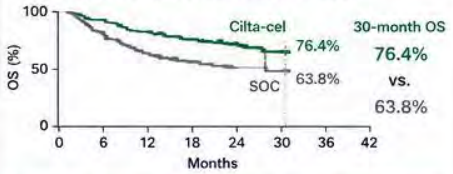
CARTITUDE-4 **Phase 3 Randomized Trial (Updated Analysis with OS Benefit)** San-Miguel J, et al. *N Engl J Med*. 2023;389:335–347. Einsele H, et al. *Lancet Oncol*. 2026;27:254–268. NEJM THE LANCET ONCOLOGY	**Phase 3, open-label, randomized (1:1)** • Lenalidomide-refractory MM • 1–3 prior lines of therapy • Includes a proteasome inhibitor and an immunomodulatory drug • N = 419 randomized 1:1 Cilta-cel (n = 208) Standard of care (n = 211) Median follow-up: 33.6 months (IQR, 20.3–35.0)	Ciltacabtagene autoleucel (cilta-cel) **Single infusion** (0.75 × 10^6 CAR+ T cells per kg) **vs.** **Physician's choice of standard of care:** • Pomalidomide–bortezomib–dexamethasone (PVd) or • Daratumumab–pomalidomide–dexamethasone (DPd)	Progression-free survival (ITT population) HR 0.29 (95% CI, 0.22–0.39); p < 0.0001  30-month PFS **59.4%** vs. 25.7% Overall survival (ITT population) HR 0.55 (95% CI, 0.39–0.79); p = 0.0009  30-month OS **76.4%** vs. 63.8% ★ First randomized trial in multiple myeloma to demonstrate an overall survival (OS) advantage with a BCMA CAR-T therapy.	• Grade ≥3 TEAEs: Cilta-cel 14% vs. SOC 37% • Grade 4 TEAEs: Cilta-cel 75% vs. SOC 56% • Serious TEAEs: 47% in each group • Deaths (safety population): 24% with cilta-cel vs. 33% with SOC • No new safety signals with longer follow-up	**CARTITUDE-4 demonstrated superior PFS and the first randomized overall survival benefit for cilta-cel versus standard therapy in lenalidomide-refractory MM after 1–3 prior lines.**

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Overall schema

Overall Treatment Schema: Cilta-cel (BCMA-Directed CAR-T)

1 Referral & Eligibility Assessment

Evaluate patient to confirm eligibility for cilta-cel.

- Disease status & measurable disease
- Prior therapies (1–3 prior lines; lenalidomide-refractory)
- Organ function & performance status (ECOG 0–1)
- Adequate marrow reserve
- Infection status
- Caregiver support & logistical readiness

Multidisciplinary evaluation and patient education

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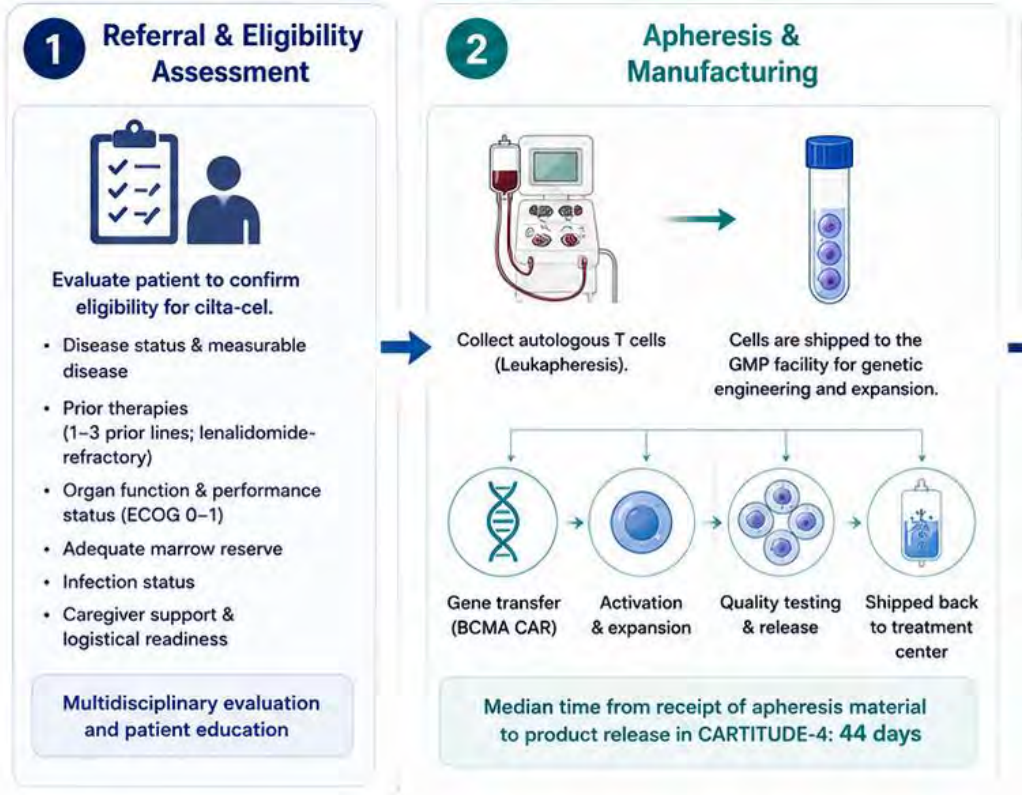

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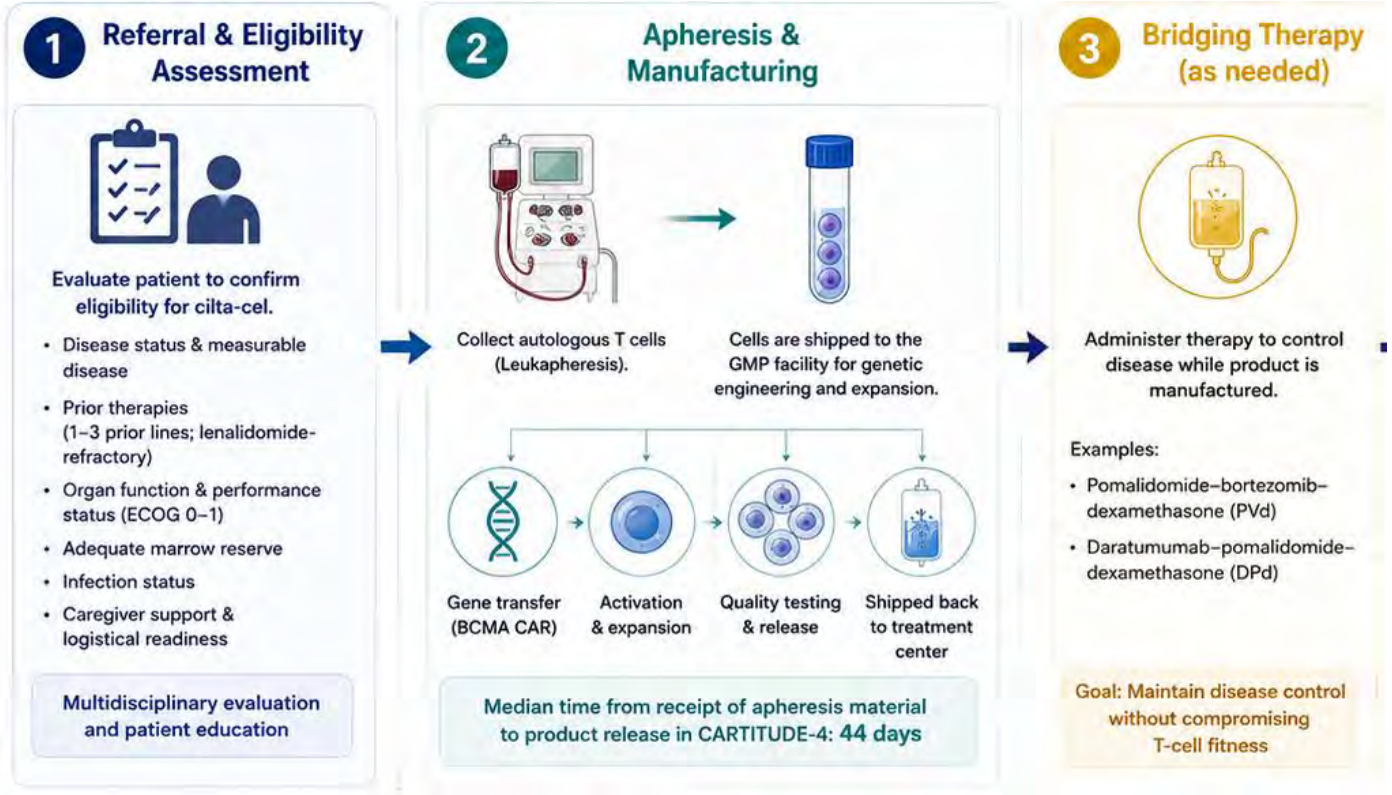

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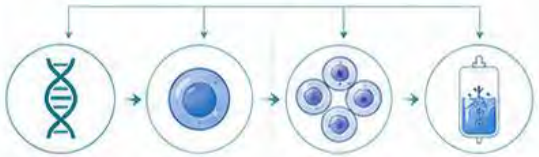
Multidisciplinary evaluation and patient education

2 Apheresis & Manufacturing

Collect autologous T cells (Leukapheresis).

Cells are shipped to the GMP facility for genetic engineering and expansion.



Median time from receipt of apheresis material to product release in CARTITUDE-4: **44 days**

3 Bridging Therapy (as needed)

Administer therapy to control disease while product is manufactured.

Examples:

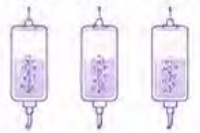
- Pomalidomide–bortezomib–dexamethasone (PVd)
- Daratumumab–pomalidomide–dexamethasone (DPd)

Goal: Maintain disease control without compromising T-cell fitness

4 Lymphodepletion & Cilta-cel Infusion

Lymphodepletion (Day −5 to −3)

Fludarabine 30 mg/m² IV + Cyclophosphamide 300 mg/m² IV daily for 3 days



Cilta-cel Infusion (Day 0)

5–7 days after the last day of lymphodepletion

Single infusion
0.75×10^6 CAR+ T cells/kg

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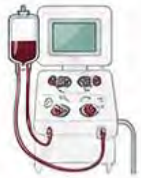

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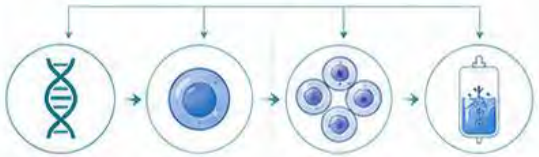

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5 Post-Infusion Monitoring

Patients are closely monitored inpatient (typically 7–14 days) and then as needed.

CRS
Monitor for fever, hypotension, hypoxia (typically days 1–10)

Neurotoxicity (ICANS)
Monitor for confusion, aphasia, seizures, motor deficits

Infections
Monitor viral reactivation and bacterial/fungal infections

Cytopenias
Monitor neutropenia, anemia, thrombocytopenia

Delayed toxicities
Hypogammaglobulinemia, B-cell aplasia, secondary malignancies

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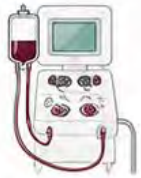

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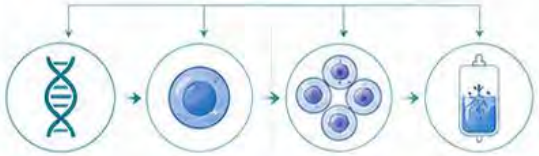

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Total time from apheresis to infusion: ~6–8 weeks (median ~44 days to product release in CARTITUDE-4)

Goal: Maximize efficacy while ensuring patient safety at every step.

Post-infusion monitoring focuses on:

- Frequent assessments inpatient (vitals, labs, neurologic exams)
- Management per guidelines (ASBMT, ASTCT, EBMT)
- Early intervention for CRS and neurotoxicity
- Supportive care (infection prophylaxis, transfusions, growth factors)
- Long-term follow-up for durability and late effects

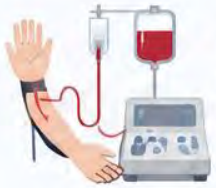
BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; ICANS = immune effector cell–associated neurotoxicity syndrome; GMP = good manufacturing practice; IV = intravenous; PVd = pomalidomide–bortezomib–dexamethasone; DPd = daratumumab–pomalidomide–dexamethasone.

What to Expect: Key Logistics of Your CAR-T Journey

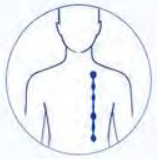
Apheresis, caregiver support, visit frequency, and the IMTX team are all key to a safe and successful experience.

1. APHERESIS

Takes 3–6 hours



Involves taking blood out and putting it back



Often requires a central line (i.e., large IV in the neck)

2. CAREGIVER SUPPORT

Need a 24/7 caregiver from lymphodepletion to discharge

Caregiver support is essential for monitoring, transportation, and peace of mind.

3. FREQUENCY / FLUIDITY OF VISITS

Daily visits (even on weekends/ holidays) post-CAR-T

Schedule is subject to change based on clinical status

Flexibility allows us to personalize your care every step of the way.

4. IMTX SERVICE IS A "WELL OILED MACHINE"

Very efficient and responsive

Our team works seamlessly together to deliver expert, coordinated care.

From apheresis through discharge, our goal is to make your CAR-T experience as **smooth, safe, and supportive** as possible.

Toxicities and bridging

Incidence of CRS and ICANS with Cilta-cel (CARTITUDE-1)

In CARTITUDE-1, cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) were common but predominantly low grade and manageable.

CYTOKINE RELEASE SYNDROME (CRS)

Any grade CRS

95%

92 of 97 patients

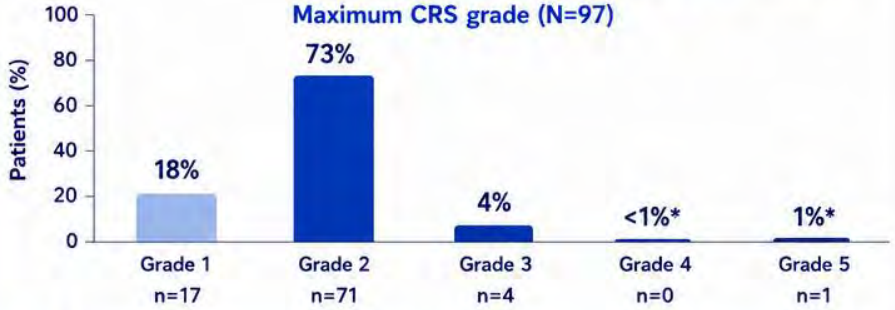
Median time to onset

7 days (IQR 5–8)

Median duration

4 days (IQR 3–6)

Maximum CRS grade (N=97)



Management

- 95% of CRS events occurred within the first 14 days
- CRS resolved in all except 1 patient (grade 5 CRS with HLH)

KEY TAKE-HOME MESSAGE

CRS occurred in most patients (95%) wad was predominantly low grade (91% grade 1–2); ICANS was less frequent (21%) and also predominantly low grade (20% grade 1–2).

CLINICAL TAKEAWAY

With early recognition and guideline-directed management, CRS and ICANS are typically transient and manageable.

CRS = cytokine release syndrome; ICANS = immune effector cell–associated neurotoxicity syndrome; HLH = haemophagocytic lymphohistiocytosis; IQR = interquartile range.

Source: Berdeja JG, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen–directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *Lancet*. 2021;398:314–324.

Safety population: Patients who received cilta-cel, N=97
Median follow-up: 12.4 months (IQR 10.6–15.2)

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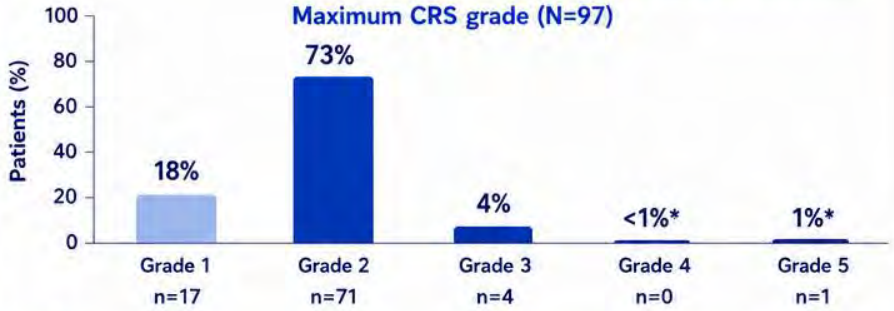

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IMMUNE EFFECTOR CELL–ASSOCIATED NEUROTOXICITY SYNDROME (ICANS)

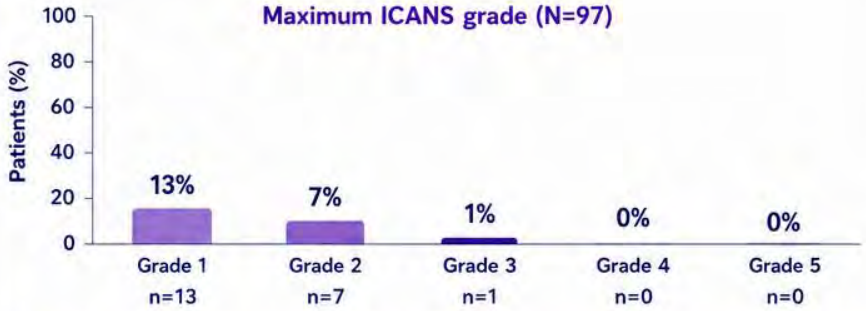
Any grade ICANS

21%

20 of 97 patients

Median time to onset

8 days (IQR 6–14)



Management

- 95% of ICANS events occurred within the first 21 days
- ICANS resolved in 19 of 20 patients (95%)

KEY TAKE-HOME MESSAGE

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BRIDGING THERAPY: CONTROL DISEASE, PREVENT ATTRITION, GET TO CARVYKTI® (CILTA-CEL)

Definition: Therapy given after apheresis and before lymphodepletion/infusion to control multiple myeloma while CARVYKTI is being manufactured (median 44 days in CARTITUDE-4).

1. MOST PATIENTS RECEIVE BRIDGING THERAPY

100%

of patients assigned to cilta-cel in CARTITUDE-4 received bridging therapy.

PHYSICIAN'S CHOICE OF REGIMEN

DPd	OR	PVd
Daratumumab–Pomalidomide–Dexamethasone		Pomalidomide–Bortezomib–Dexamethasone

Number of cycles based on clinical status and manufacturing time.

Goal: Maintain disease control without compromising T-cell fitness.

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2. BRIDGING MATTERS – ATTRITION CAN OCCUR BEFORE INFUSION

In CARTITUDE-4, 32 of 208 patients (15%) assigned to cilta-cel did NOT receive trial cilta-cel.

32/208 did not receive trial cilta-cel

Main reasons

- Disease progression during bridging therapy or lymphodepletion (majority)
- Clinical decline or other patient factors

The longer the wait, the higher the risk of progression and losing the opportunity for CARVYKTI infusion.

BRIDGING THERAPY: CONTROL DISEASE, PREVENT ATTRITION, GET TO CARVYKTI® (CILTA-CEL)

Definition: Therapy given after apheresis and before lymphodepletion/infusion to control multiple myeloma while CARVYKTI is being manufactured (median 44 days in CARTITUDE-4).

1. MOST PATIENTS RECEIVE BRIDGING THERAPY

100%

of patients assigned to cilta-cel in CARTITUDE-4 received bridging therapy.

PHYSICIAN'S CHOICE OF REGIMEN

DPd
Daratumumab–Pomalidomide–Dexamethasone

OR

PVd
Pomalidomide–Bortezomib–Dexamethasone

Number of cycles based on clinical status and manufacturing time.

Goal: Maintain disease control without compromising T-cell fitness.

2. BRIDGING MATTERS – ATTRITION CAN OCCUR BEFORE INFUSION

In CARTITUDE-4, 32 of 208 patients (15%) assigned to cilta-cel did NOT receive trial cilta-cel.

32/208
did not receive trial cilta-cel

Main reasons

- Disease progression during bridging therapy or lymphodepletion (majority)
- Clinical decline or other patient factors

The longer the wait, the higher the risk of progression and losing the opportunity for CARVYKTI infusion.

3. HOW EFFECTIVE BRIDGING SUPPORTS SUCCESS

CONTROLS DISEASE
Limits tumor growth and reduces risk of progression while product is manufactured.

PRESERVES PATIENT STATUS
Maintains performance status, organ function, and marrow reserve.

PRESERVES T-CELL FITNESS
Avoids excessive chemotherapy exposure and treatment-related toxicity.

REDUCES ATTRITION
Improves the likelihood of reaching lymphodepletion and infusion.

MAXIMIZES OUTCOME POTENTIAL
Patients who get to infusion are more likely to benefit from the full potential of CARVYKTI.

KEY TAKE-HOME MESSAGE

Bridging therapy is not just "holding" therapy—it is a strategic intervention to get the patient to CARVYKTI.

Use the right regimen, for the right number of cycles, at the right time—based on the patient and manufacturing timeline.

BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; DPd = daratumumab–pomalidomide–dexamethasone; PVd = pomalidomide–bortezomib–dexamethasone.

Sources: San-Miguel J, et al. N Engl J Med 2023;389:335–47; Einsele H, et al. Lancet Oncol 2026;27:254–68).

WHY DISEASE STATE AT INFUSION MATTERS: SAFETY AND OUTCOMES

Key Concept: The disease burden and degree of disease control achieved during bridging therapy influence the risk of delayed neurotoxicity (DNT) after ciltacabtagene autoleucel (cilta-cel).

THE RATIONALE

Higher disease burden and **lack of disease control** may drive excessive immune activation and inflammation.

This heightened immune response is associated with a greater risk of **delayed neurotoxicity**, particularly Parkinsonism.

Therefore, disease state at infusion is not just an efficacy issue—it is a **safety issue**.

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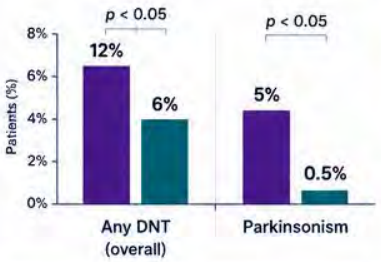
REAL-WORLD EVIDENCE: SIDANA et al. MULTICENTER ANALYSIS

761 standard-of-care cilta-cel patients at 15 US centers (May 2022 – December 2024)

1. LACK OF RESPONSE TO BRIDGING THERAPY IS ASSOCIATED WITH HIGHER DELAYED NEUROTOXICITY

Incidence of delayed neurotoxicity

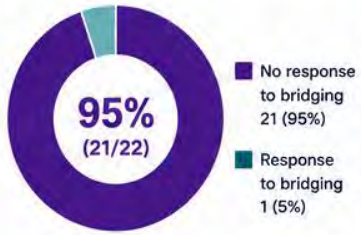
- No response to bridging (n=~509, 67%)*
- Response to bridging (≥ PR, n=~252, 33%)*



Parkinsonism was 10-fold higher when bridging did not achieve a response.

2. NEARLY ALL PARKINSONISM CASES HAD NO RESPONSE TO BRIDGING THERAPY

Among 22 patients who developed Parkinsonism



21 of 22 Parkinsonism cases (95%) occurred in patients who did NOT respond to bridging therapy.

3. HIGHER PEAK T-CELL EXPANSION IS ASSOCIATED WITH GREATER PARKINSONISM RISK

Risk of Parkinsonism by peak absolute lymphocyte count (ALC) in first month

Peak ALC Threshold (cells/µL)	Parkinsonism Risk
> 1,000	100% vs 57% $p < 0.001$
> 2,500	73% vs 19% $p < 0.001$
> 3,000	68% vs 14% $p < 0.001$

Absolute risk of Parkinsonism with peak ALC > 3,000/uL:

12% vs 1%

(p < 0.001)

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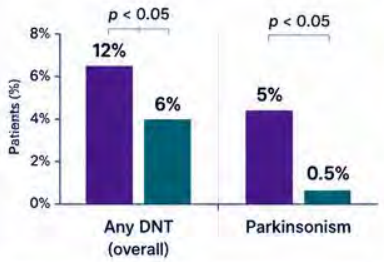

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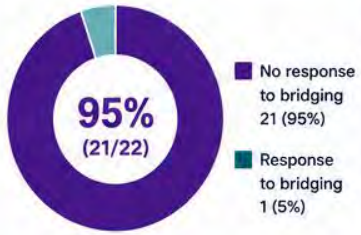

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THE IMPACT

Better disease control before infusion may **reduce the risk of** severe delayed neurotoxicity, especially Parkinsonism.

Optimizing disease state during bridging helps create a **safer** path to infusion.

Goal: Start lymphodepletion with the **lowest possible disease burden.**

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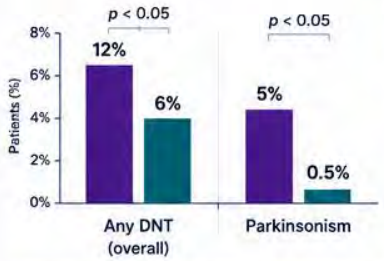

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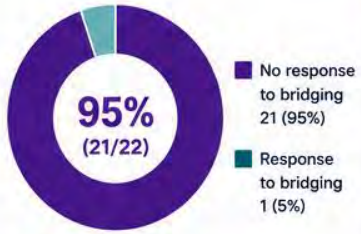

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Goal: Start lymphodepletion with the **lowest possible disease burden.**

KEY TAKE-HOME MESSAGE

Achieving the best possible disease control during bridging therapy is essential—not only to improve outcomes, but also to **minimize the risk of serious delayed neurotoxicity** after cilta-cel.

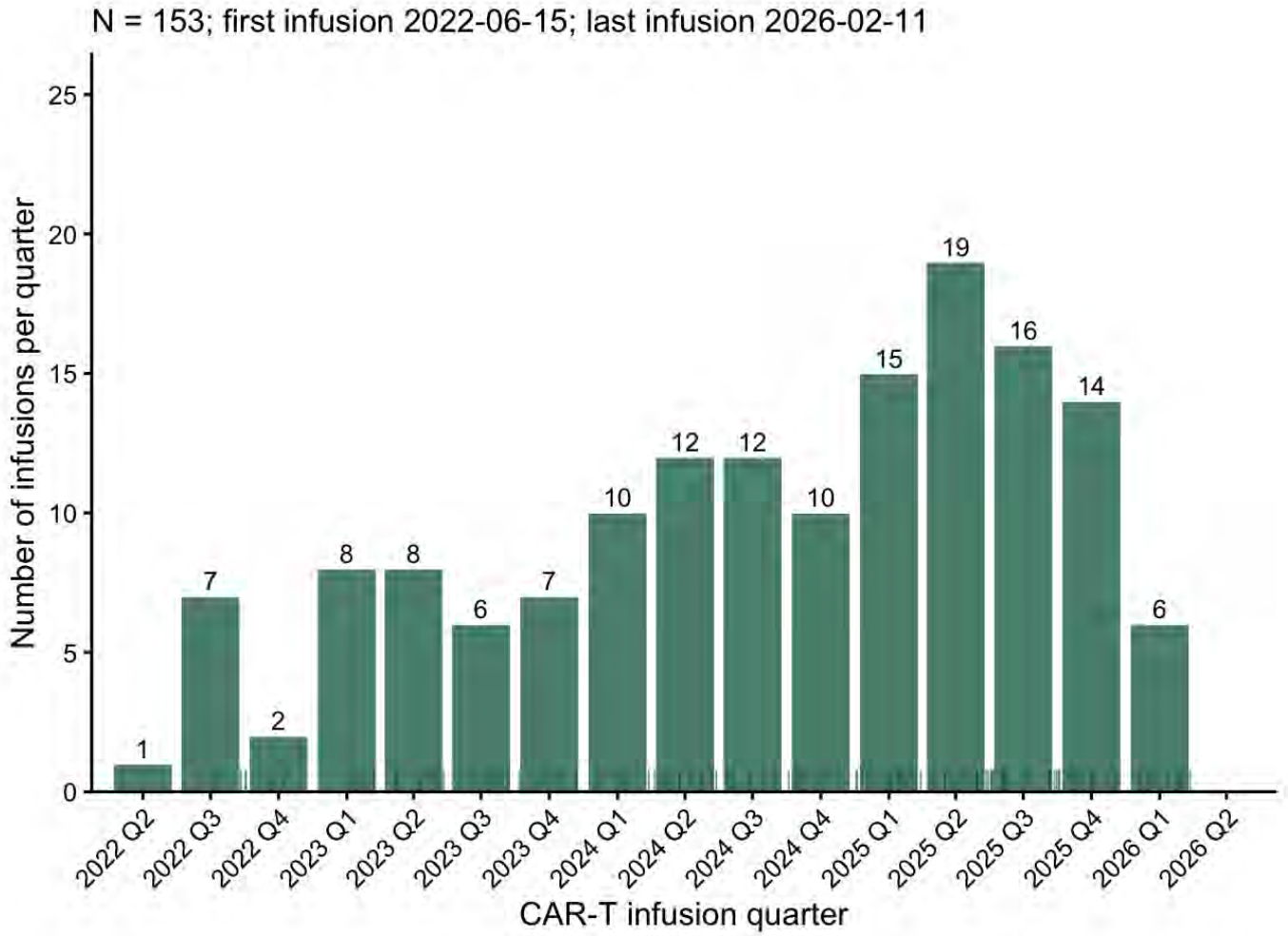
DNT = delayed neurotoxicity; PR = partial response; ALC = absolute lymphocyte count.

*Exact denominators not reported in abstract; percentages reflect reported proportions.

Sidana S, et al. Enhancing the safety of ciltacabtagene autoleucel in relapsed multiple myeloma (MM): Identification of potentially modifiable risk-factors associated with delayed neurotoxicity and non-relapse mortality. Blood 2025;146 (Supplement 1):1034–1035 (ASH Abstract 653A).

Our real-world experience

Fred Hutch real-world data



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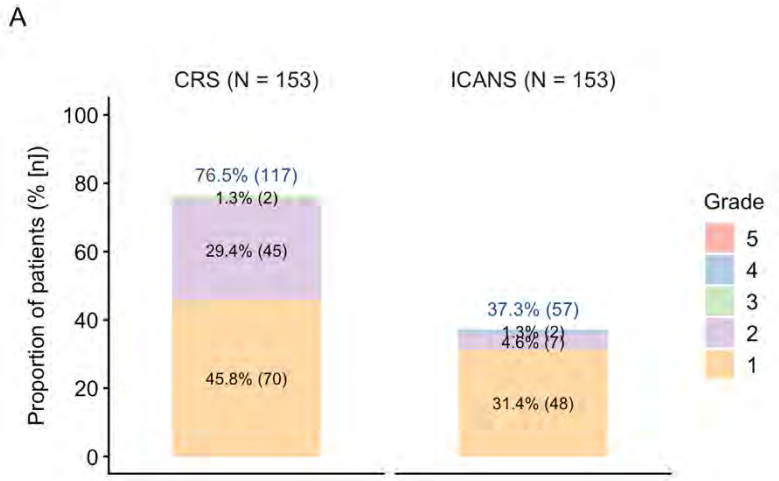

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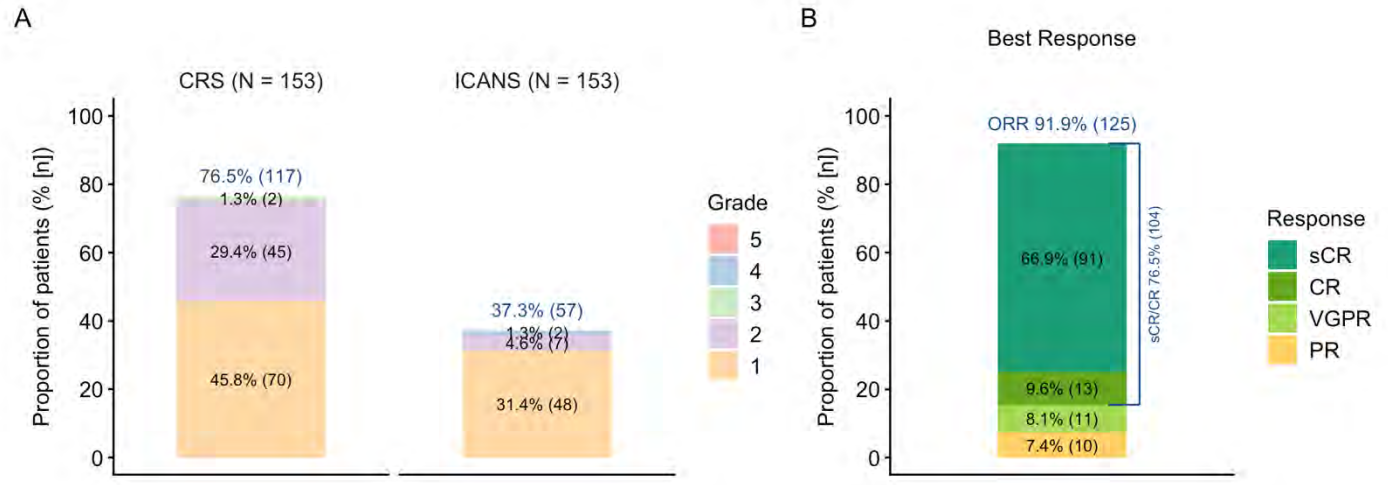

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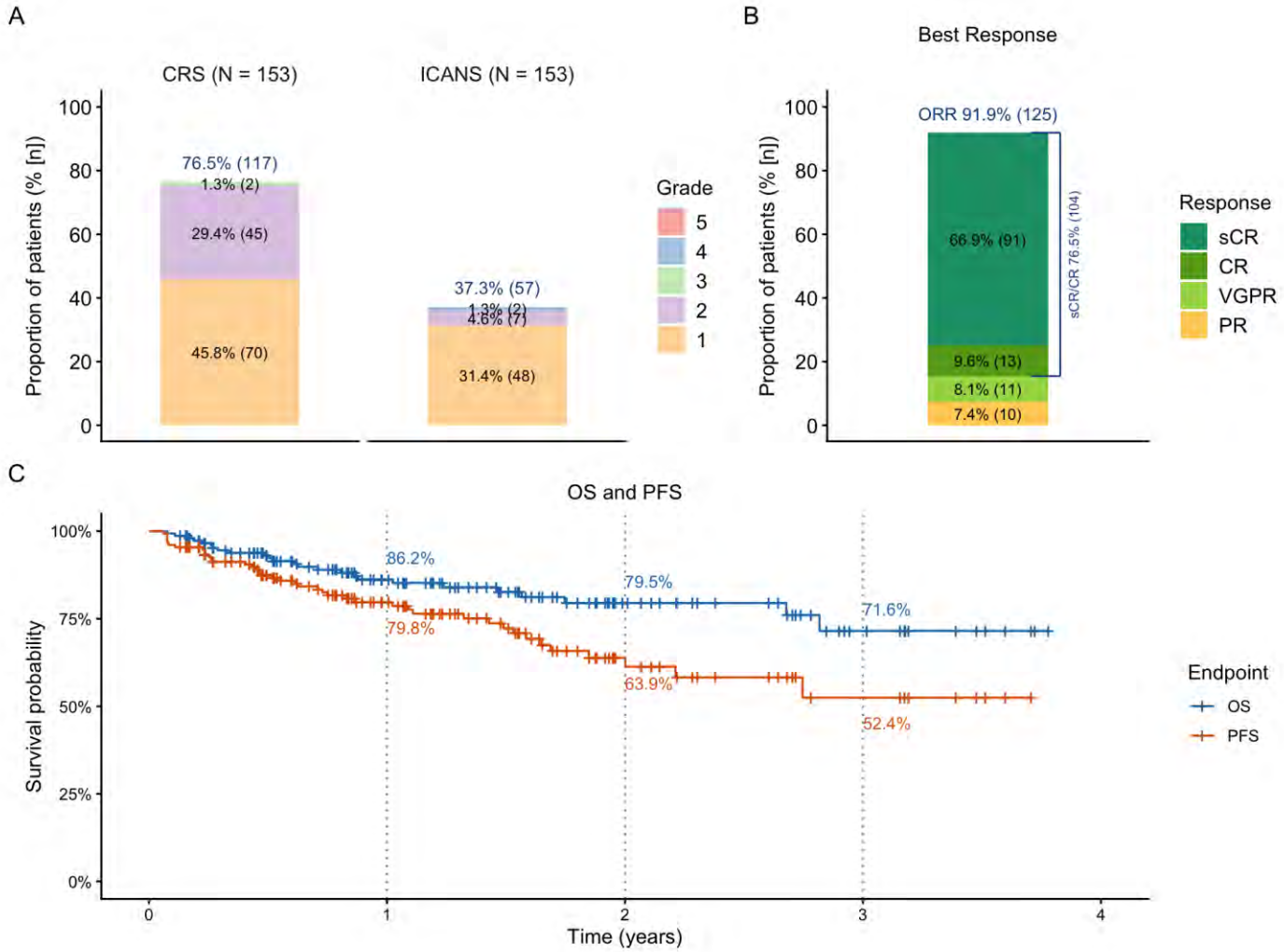

What’s next?

iMMagine-1: Anitocabtagene Autoleucel (Anito-cel) in RRMM

A Phase 2 Registrational Study of a Novel D-Domain Anti–BCMA CAR T-Cell Therapy

BACKGROUND

Anitocabtagene autoleucel (anito-cel) is an autologous anti–BCMA CAR T-cell therapy with a novel D-domain binder under development for patients with relapsed and/or refractory multiple myeloma (RRMM).

D-Domain attributes—small size, simple structure, and fast off-rate—facilitate high transduction efficiency, stable CAR expression, and decreased risk of tonic signaling.

In the Phase 1 trial (NCT04155749), at a median follow-up of 38.1 months:

- Median PFS was **30.2 months** for all pts
- Median PFS was **34.3 months** for pts achieving CR or better
- No delayed or non-ICANS neurotoxicities or IEC-associated enterocolitis have been observed

IRC = Independent Review Committee; IMWG = International Myeloma Working Group; MRD = minimal residual disease; CTCAE = Common Terminology Criteria for Adverse Events; CRS = cytokine release syndrome; ICANS = immune effector cell–associated neurotoxicity syndrome; ASTCT = American Society for Transplantation and Cellular Therapy.

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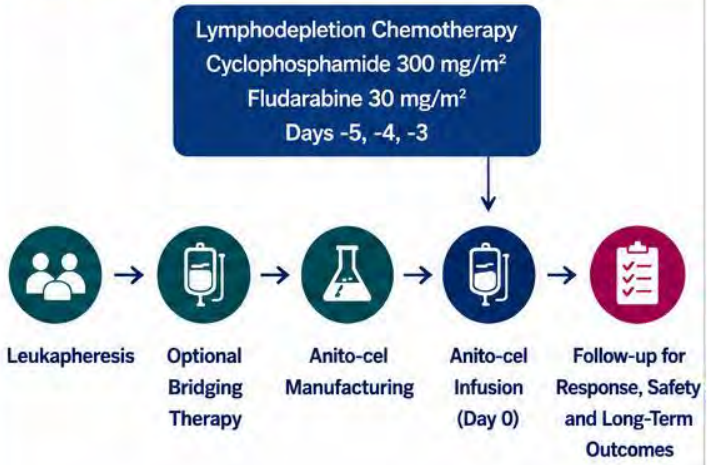
STUDY DESIGN (iMMagine-1 Phase 2)



- **Target dose:** 115 × 10^6 CAR+ T cells (single infusion)
- **Primary endpoint:** Overall response rate (ORR) by IRC per 2016 IMWG criteria
- **Assessments:** MRD by next-generation sequencing; toxicity per CTCAE v5.0; CRS and ICANS graded by ASTCT consensus criteria

IRC = Independent Review Committee; IMWG = International Myeloma Working Group; MRD = minimal residual disease; CTCAE = Common Terminology Criteria for Adverse Events; CRS = cytokine release syndrome; ICANS = immune effector cell–associated neurotoxicity syndrome; ASTCT = American Society for Transplantation and Cellular Therapy.

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Lymphodepletion Chemotherapy
Cyclophosphamide 300 mg/m²
Fludarabine 30 mg/m²
Days -5, -4, -3

Leukapheresis → Optional Bridging Therapy → Anito-cel Manufacturing → Anito-cel Infusion (Day 0) → Follow-up for Response, Safety and Long-Term Outcomes

- **Target dose:** 115 × 10^6 CAR+ T cells (single infusion)
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WHO, WHAT, WHY

WHO

Patients who had received ≥3 lines of therapy including:

- CD38-targeted therapy (Daratumumab/Darzalex or Isatuximab/Sarclisa)
- IMiD (Revlimid/Lenalidomide or Pomalyst/pomalidomide)
- Proteasome Inhibitor (Velcade/bortezomib or Kyprolis/carfilzomib)

- "Fit" = Spent more than ½ day out of the bed AND can carry out light activity
- Had measurable disease

WHAT

Anito-cel

WHY

- Responses get better over time
- Great responses
- With minimal toxicity

IRC = Independent Review Committee; IMWG = International Myeloma Working Group; MRD = minimal residual disease; CTCAE = Common Terminology Criteria for Adverse Events; CRS = cytokine release syndrome; ICANS = immune effector cell–associated neurotoxicity syndrome; ASTCT = American Society for Transplantation and Cellular Therapy.

iMMagine-1 Phase 2 Results (Data Cut-off: May 1, 2025)

117 patients infused with anito-cel under the final manufacturing process; median follow-up 12.6 months

PATIENTS (N=117)

Median age:
64 years (range, 38–78)

Race:
76% White, 15% Black or African American, 9% Asian or Other

Median time from MM diagnosis:
7.2 years (range, 1.0–23.1)

Median prior LoT:
3 (range, 3–8);
51% received only 3 prior LoT

- **All pts (100%) refractory to last LoT**
- **Triple-class refractory: 86%**
- **Penta-drug refractory: 40%**
- **Extramedullary disease: 15%**
- **High-risk cytogenetics: 38%**
- **Outpatient infusion: 9% (n=10)**

AE = adverse event; CAR = chimeric antigen receptor; CRS = cytokine release syndrome;
ICANS = immune effector cell–associated neurotoxicity syndrome; IEC = immune effector cell;
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EFFICACY (Investigator-Assessed)

ORR (IMWG)	CR/sCR Rate	MRD Negativity (10^{-5})	MRD Negativity (10^{-6}) achieved in
97% (114/117)	68% (79/117)	93% (70/75 evaluable)	78% (53/68)

TIME TO RESPONSE

First response:
1.0 month
(range, 0.9–13.4)

Best response:
4.8 months
(range, 1.0–14.1)

TIME TO MRD NEGATIVITY (10^{-5})

Median:
1.0 month
(range, 0.9–6.4)

DURABILITY (Kaplan-Meier Milestone Estimates)

12-MONTH PFS	18-MONTH PFS	12-MONTH OS	18-MONTH OS
79%	66%	95%	90%

Median PFS: Not reached

Median OS: Not reached

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SAFETY (Investigator-Assessed)

MOST COMMON GRADE 3/4 TEAES

Neutropenia	77 (66%)
Anemia	28 (24%)
Thrombocytopenia	28 (24%)
Grade 3/4 Infections	11 (9%)

CYTOKINE RELEASE SYNDROME (CRS)

Any Grade CRS:
85% (100/117)

No CRS:
15% (17/117)

Grade	n (%)
Grade 1	82 (70%)
Grade 2	17 (15%)
Grade 3	0 (0%)
Grade 4	0 (0%)
Grade 5	1 (1%)

Median onset:
4 days
(range, 1–17)

Median duration:
2 days
(range, 1–9)

IMMUNE EFFECTOR CELL–ASSOCIATED NEUROTOXICITY SYNDROME (ICANS)

Any Grade ICANS:
8% (9/117)

No ICANS:
92% (108/117)

Grade	n (%)
Grade 1	4 (3%)
Grade 2	4 (3%)
Grade 3	1 (1%)
Grade 4	0 (0%)
Grade 5	0 (0%)

ADDITIONAL SAFETY FINDINGS

- No delayed or non-ICANS neurotoxicities:
  - No Parkinsonism
  - No cranial nerve palsies
  - No Guillain-Barré syndrome
- No IEC-associated enterocolitis
- No secondary primary malignancies of T-cell origin

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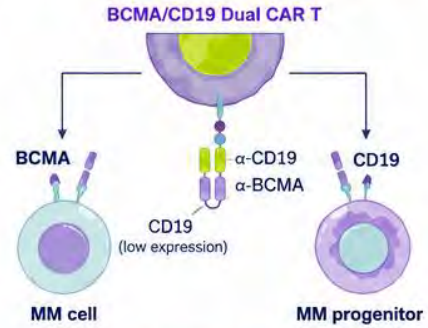
AZD0120: A Novel BCMA/CD19 Dual CAR-T

A Next-Generation, Rapidly Manufactured, Dual-Targeting CAR T-Cell Therapy for Relapsed/Refractory Multiple Myeloma

BACKGROUND

AZD0120 is an autologous BCMA/CD19 dual-targeting CAR T-cell therapy being developed for patients with relapsed/ refractory multiple myeloma (RRMM).

Dual targeting to address antigen heterogeneity and enhance depth and durability of response.



Next-Generation Manufacturing

Faster to Patients
Manufactured in
<3 days

Better T Cells
Younger, fitter
naive T cells

Safety profile enabling outpatient administration and monitoring

Making cell therapy available to more patients

AZD0120 is designed to deliver the potential benefits of **dual-targeted** CAR T-cell therapy with the convenience and accessibility of **rapid manufacturing**, aiming to bring effective cell therapy to **more patients** with RRMM.

[a] Prior exposure to BCMA-directed therapy permitted per protocol.

Abbreviations: Ab, antibody; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CD19, cluster of differentiation 19; DL, dose level; Flu, fludarabine; Cy, cyclophosphamide; IMiD, immunomodulatory drug; LOT, line of therapy; MM, multiple myeloma; PI, proteasome inhibitor; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma.

Source: Richards S, Gaballa M, Gregory T, et al. Safety and efficacy of AZD0120, a BCMA/CD19 dual-targeting CAR T-cell therapy, in relapsed/refractory multiple myeloma: Preliminary Results from the DURGA-1 Phase 1b/2 study. Abstract #269.

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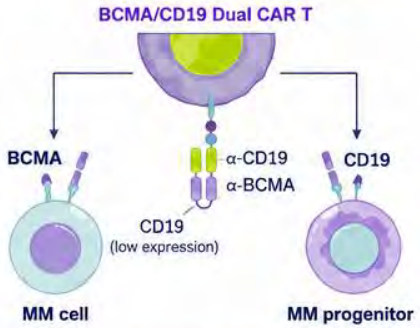


Next-Generation Manufacturing

Faster to Patients
Manufactured in
<3 days

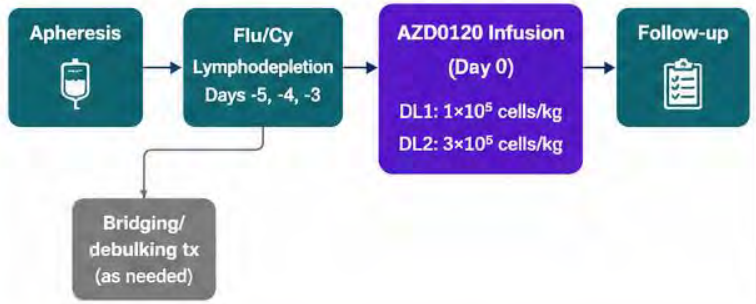
Better T Cells
Younger, fitter naive T cells

Safety profile enabling outpatient administration and monitoring

Making cell therapy available to more patients

STUDY DESIGN (DURGA-1 Phase 1b/2)

Study Schema



Key Inclusion Criteria

- ≥3 prior lines of therapy (exposure to PI, IMiD, and anti-CD38 Ab required)
- Documented evidence of progressive disease (PD) with most recent LOT
- Prior exposure to BCMA-directed therapy permitted[a]

Phase 1b Primary Objectives

- Safety/tolerability
- **RP2D determination**

AZD0120 is designed to deliver the potential benefits of dual-targeted CAR T-cell therapy with the convenience and accessibility of rapid manufacturing, aiming to bring effective cell therapy to more patients with RRMM.

[a] Prior exposure to BCMA-directed therapy permitted per protocol.

Abbreviations: Ab, antibody; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CD19, cluster of differentiation 19; DL, dose level; Flu, fludarabine; Cy, cyclophosphamide; IMiD, immunomodulatory drug; LOT, line of therapy; MM, multiple myeloma; PI, proteasome inhibitor; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma.

Source: Richards S, Gaballa M, Gregory T, et al. Safety and efficacy of AZD0120, a BCMA/CD19 dual-targeting CAR T-cell therapy, in relapsed/refractory multiple myeloma: Preliminary Results from the DURGA-1 Phase 1b/2 study. Abstract #269.

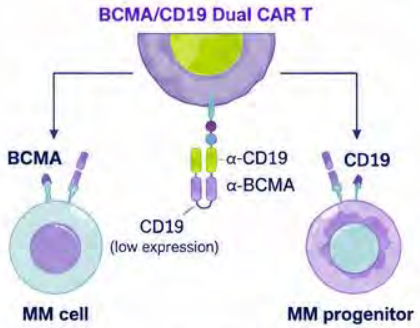
AZD0120: A Novel BCMA/CD19 Dual CAR-T

A Next-Generation, Rapidly Manufactured, Dual-Targeting CAR T-Cell Therapy for Relapsed/Refractory Multiple Myeloma

BACKGROUND

AZD0120 is an autologous BCMA/CD19 dual-targeting CAR T-cell therapy being developed for patients with relapsed/ refractory multiple myeloma (RRMM).

Dual targeting to address antigen heterogeneity and enhance depth and durability of response.



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Faster to Patients
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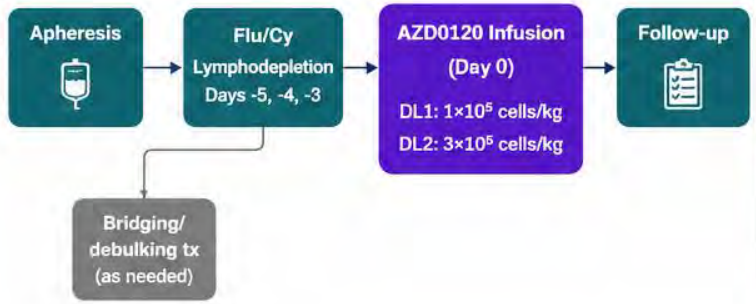

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- Documented evidence of progressive disease (PD) with most recent LOT
- Prior exposure to BCMA-directed therapy permitted[a]

Phase 1b Primary Objectives

- Safety/tolerability
- **RP2D determination**

WHO, WHAT, WHY

WHO

Patients with relapsed/refractory multiple myeloma who had received ≥3 lines of therapy including:

- CD38-targeted therapy (Daratumumab/Darzalex or Isatuximab/Sarclisa)
- IMID (Revlimid/Lenalidomide or Pomalyst/ pomalidomide)
- Proteasome Inhibitor (Velcade/bortezomib or Kyprolis/carfilzomib)

- "Fit" = Spent more than ½ day out of the bed AND can carry out light activity
- Had measurable disease

WHAT

AZD0120
BCMA/CD19 dual-targeting CAR T-cell therapy

WHY

- Dual targeting to overcome antigen heterogeneity and target myeloma cells and progenitors
- Faster time to patients with next-generation manufacturing (<3 days)
- Better T cells (younger, fitter naive T cells)
- Safety profile enabling outpatient administration and monitoring
- Designed to improve depth and durability of response with minimal toxicity

AZD0120 is designed to deliver the potential benefits of **dual-targeted** CAR T-cell therapy with the convenience and accessibility of **rapid manufacturing**, aiming to bring effective cell therapy to **more patients** with RRMM.

[a] Prior exposure to BCMA-directed therapy permitted per protocol.

Abbreviations: Ab, antibody; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CD19, cluster of differentiation 19; DL, dose level; Flu, fludarabine; Cy, cyclophosphamide; IMiD, immunomodulatory drug; LOT, line of therapy; MM, multiple myeloma; PI, proteasome inhibitor; RP2D, recommended phase 2 dose; RRMM, relapsed/refractory multiple myeloma.

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GC012F/AZD0120: Responses and Prior PFS/OS Results in Newly Diagnosed Multiple Myeloma (NDMM)

Combined Results from Two Phase 1 NDMM Trials (NCT04935580, NCT05840107)

CURRENT NDMM EFFICACY (Pooled Analysis)

Best Overall Response
(N = 30)

- **97%** sCR/CR (n = 29)
- **3%** VGPR/PR (n = 1)

100% MRD negativity
(10^{-6} sensitivity)
All patients across all dose levels

Median time to first response
28 days

Median time to best response
68 days

Patients (N = 30)
- Median age: 64 years (range, 43–78); 27% ≥70 years
- 63% male; 83% R-ISS stage II/III; 48% high-risk cytogenetics†
- 57% had plasmacytomas (3 with soft tissue involvement)
- 97% received 2 cycles of RVd prior to infusion

GC012F/AZD0120 produced universal responses, universal MRD negativity, and durable disease control through long-term follow-up in newly diagnosed MM.

★ Historical data from: Du J, Qiang W, Lu J, et al. A dual targeting BCMA and CD19 fastcar-t (GC012F/AZD0120) as first-line therapy for newly diagnosed multiple myeloma. ASH Annual Meeting. Abstract #258.

† High risk defined as presence of del(17p), amp(1q21), t(4;14), t(14;16).

Data cutoff (current pooled analysis): June 3, 2025.

Abbreviations: CR, complete response; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; sCR, stringent complete response; VGPR, very good partial response.

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- 97% received 2 cycles of RVd prior to infusion

RESPONSES DEEPEN OVER TIME

92%
MRD negative at Month 12

81.5%
Sustained MRD negativity >12 months (22/27 pts)

Responses continue to deepen after infusion, with durable MRD negativity over time.

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PRIOR LONG-TERM FOLLOW-UP*

Long-term outcomes from the prior Chinese Phase 1 NDMM studies of GC012F/AZD0120 (Du et al., ASH Abstract #258).

Outcome	Result
Median follow-up	30 months
Median PFS	Not reached
30-month PFS rate	**88%** (95% CI 67–96)
Median OS	Not reached
30-month OS rate	**92%** (95% CI 71–98)

Key observations from prior study
- No difference in PFS or OS between high-risk and non-high-risk cytogenetics
- Shorter PFS and OS observed only in patients with soft tissue plasmacytomas
- No patients died within 12 months of infusion in prior study

These data are historical results from a prior study and not from the current pooled analysis.

GC012F/AZD0120 produced universal responses, universal MRD negativity, and durable disease control through long-term follow-up in newly diagnosed MM.

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Arlocabtagene Autoleucel (Arlo-cel): GPRC5D-Targeted CAR T-Cell Therapy in Heavily Pretreated Relapsed/Refractory Multiple Myeloma

Phase 1, Dose-Escalation/Expansion Study (NCT04674813)

BACKGROUND

- Patients with relapsed/refractory multiple myeloma (RRMM) have limited treatment options.
- Arlo-cel (BMS-986393) is an autologous CAR T-cell therapy targeting G protein–coupled receptor class C group 5 member D (GPRC5D).
- This phase 1 study evaluated the safety, tolerability, and efficacy of arlo-cel in heavily pretreated RRMM patients.

ARLO-CEL TARGET

Arlo-cel (CAR T cell)

GPRC5D on myeloma cell

One-time intravenous infusion of arlo-cel (autologous)

Arlo-cel demonstrated deep and durable responses with a manageable safety profile in heavily pretreated RRMM patients.

Reference: Bal S, Htut M, Nadeem O, Anderson LD Jr, Gregory T, Kocoglu M, Rossi AC, Martin TG, Egan DN, Costa LJ, Hu H, Chen J, Li S, Kelly LM, Sarkis N, Ziyad S, Jordahl K, Kao WM, Keeding AJ, Burgess MR, Berdeja JG. Arlocabtagene autoleucel-a GPRC5D-targeted CAR T-cell therapy in heavily pretreated relapsed/refractory multiple myeloma. *Blood*. 2026 Jun 2:blood.2025030750. doi: 10.1182/blood.2025030750. Epub ahead of print. PMID: 42233419.

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ARLO-CEL TARGET

Arlo-cel (CAR T cell) → GPRC5D on myeloma cell

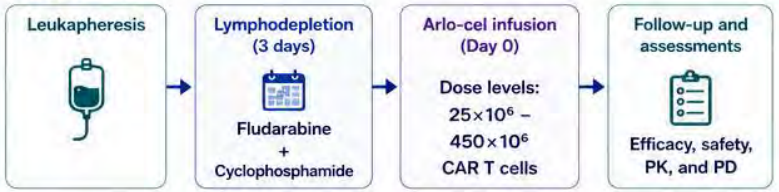
One-time intravenous infusion of arlo-cel (autologous)

STUDY DESIGN

Key inclusion criteria

- Adult patients with RRMM
- ≥3 prior antimyeloma regimens including an IMID, a proteasome inhibitor, and an anti-CD38 antibody

Study schema



Primary endpoints

- Safety
- Maximum tolerated dose (MTD)

Secondary endpoints

- Overall response rate (ORR)
- Progression-free survival (PFS)
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STUDY DESIGN

Key inclusion criteria
- Adult patients with RRMM
- ≥3 prior antimyeloma regimens including an IMID, a proteasome inhibitor, and an anti-CD38 antibody

Study schema

Leukapheresis → Lymphodepletion (3 days): Fludarabine + Cyclophosphamide → Arlo-cel infusion (Day 0): Dose levels: 25×10^6 – 450×10^6 CAR T cells → Follow-up and assessments: Efficacy, safety, PK, and PD

Primary endpoints
- Safety
- Maximum tolerated dose (MTD)

Secondary endpoints
- Overall response rate (ORR)
- Progression-free survival (PFS)
- Overall survival (OS)

PATIENT CHARACTERISTICS (N = 84)

- Median age: 64 years (range, 43–78)
- 27% aged ≥70 years
- 19 (63%) male
- Median prior regimens: 5
- 25 (83%) R-ISS stage II/III
- High-risk cytogenetics*: 14/29 (48%)
- 49% previously received BCMA-targeted therapy
  - 38% received BCMA-targeted CAR T-cell therapy
- 17 (57%) had plasmacytomas
  - 3 had soft tissue plasmacytomas
- 29 (97%) received 2 cycles of RVd induction therapy prior to arlo-cel

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IMID, immunomodulatory drug; R-ISS, Revised International Staging System; RVd, lenalidomide, bortezomib, and dexamethasone.

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IMID, immunomodulatory drug; R-ISS, Revised International Staging System; RVd, lenalidomide, bortezomib, and dexamethasone.

SAFETY SUMMARY

Cytokine release syndrome (CRS) 82% (69/84)	• All grade 1–2 (Grade 1: 61%, n=51; Grade 2: 21%, n=18) • No grade ≥3 CRS • Median onset: 8 days (range, 6–18) • Median duration: 2 days (range, 1–8) • Treated with tocilizumab: 3 pts (1 dose); tocilizumab + corticosteroids: 1 pt
Immune effector cell–associated neurotoxicity syndrome (ICANS) 10% (8/84)	• No ICANS of any grade ≥3
On-target/off-tumor events (transient, mostly grade 1–2)	• Skin: 30% • Nail: 19% • Oral: 32% • Most resolved without intervention

1 death due to CRS at the highest dose level.

MTD was not reached.

Arlo-cel demonstrated deep and durable responses with a manageable safety profile in heavily pretreated RRMM patients.

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- This phase 1 study evaluated the safety, tolerability, and efficacy of arlo-cel in heavily pretreated RRMM patients.

ARLO-CEL TARGET

One-time intravenous infusion of arlo-cel (autologous)

STUDY DESIGN

Key inclusion criteria
- Adult patients with RRMM
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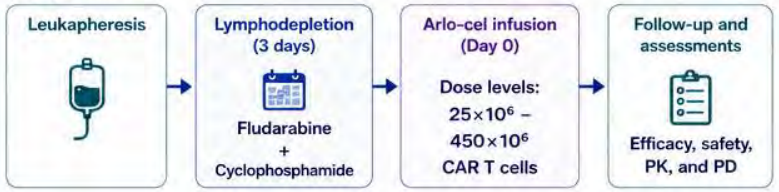

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- No ICANS of any grade ≥3

On-target/off-tumor events (transient, mostly grade 1–2)
- Skin: 30%
- Nail: 19%
- Oral: 32%
- Most resolved without intervention

1 death due to CRS at the highest dose level.

MTD was not reached.

EFFICACY RESULTS (Data cutoff: 23Aug2024)

Response (N = 84)

- Median duration of response: 18.0 months
- Median PFS: 18.3 months (95% CI, 11.8–21.9) (N = 79)
- 1-year OS rate: 90% (N = 84)

Depth of Response – MRD Negativity
(Assessed by Euroflow, sensitivity 10^{-6})

- 100% of all treated patients across all dose levels achieved MRD negativity (10^{-6})
- 81.5% (22/27) sustained MRD negativity >12 months

Prior Long-Term Outcomes*
(from Prior Chinese Phase 1 NDMM Studies)

Progression-Free Survival (PFS)	Overall Survival (OS)
Median PFS: Not reached	Median OS: Not reached
30-month PFS rate: 88% (95% CI, 67–96)	30-month OS rate: 92% (95% CI, 71–98)

These are historical results from a prior study and not from the current pooled analysis.

Arlo-cel demonstrated deep and durable responses with a manageable safety profile in heavily pretreated RRMM patients.

Reference: Bal S, Htut M, Nadeem O, Anderson LD Jr, Gregory T, Kocoglu M, Rossi AC, Martin TG, Egan DN, Costa LJ, Hu H, Chen J, Li S, Kelly LM, Sarkis N, Ziyad S, Jordahl K, Kao WM, Keeding AJ, Burgess MR, Berdeja JG. Arlocabtagene autoleucel-a GPRC5D-targeted CAR T-cell therapy in heavily pretreated relapsed/refractory multiple myeloma. *Blood*. 2026 Jun 2:blood.2025030750. doi: 10.1182/blood.2025030750. Epub ahead of print. PMID: 42233419.

Data cutoff: 23Aug2024.

CARTITUDE-6: Phase 3 Trial of Cilta-cel vs Autologous Stem Cell Transplant in Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM)

Randomized, Open-Label, Multicenter Study (NCT05257083)

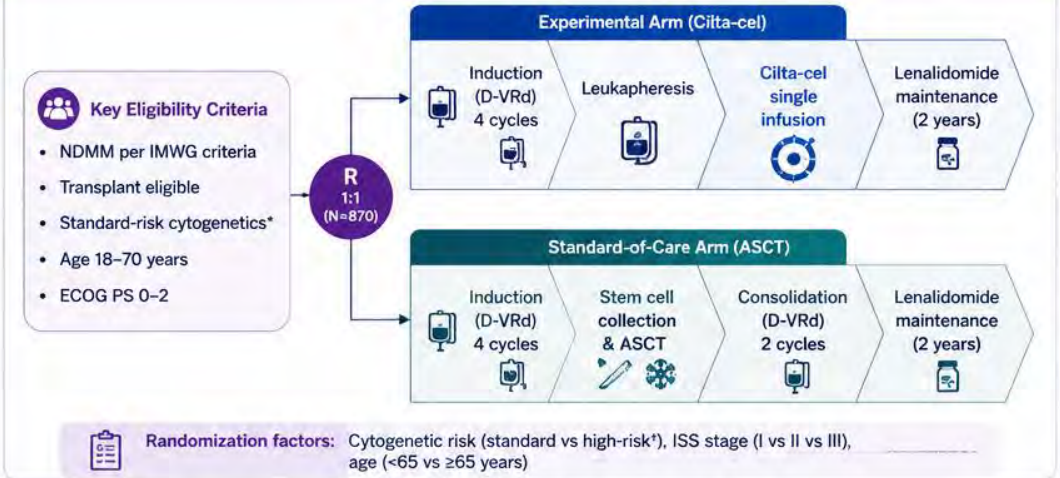
STUDY OVERVIEW

Aim: To determine whether earlier use of cilta-cel can improve outcomes compared with the current standard of care (ASCT) in transplant-eligible NDMM patients.

Cilta-cel (cilta-cabtagene autoleucel) is a BCMA-targeted CAR T-cell therapy designed to deliver deep and durable responses.

This study tests a cell therapy–based approach versus the current standard paradigm using autologous stem cell transplant (ASCT).

STUDY DESIGN



STUDY INFORMATION

- Phase 3, randomized, open-label, multicenter
- ~870 patients (1:1 randomization)
- Estimated enrollment completed in 2024
- Planned follow-up: 5 years
- Sites: ~150 centers worldwide

* Standard-risk defined as absence of del(17p), t(4;14) and t(14;16).
† High-risk defined as presence of del(17p), t(4;14) and/or (114;16).

ASCT = autologous stem cell transplant; BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; D-VRd = daratumumab, bortezomib, lenalidomide, dexamethasone; ECOG PS = Eastern Cooperative Oncology Group performance status; IMWG = International Myeloma Working Group; IRC = independent review committee; ISS = International Staging System; MRD = minimal residual disease.

ClinicalTrials.gov. NCT0527083. Accessed May 2025.

Study sponsored by: Janssen Research & Development, LLC and Legend Biotech USA, Inc.

CARTITUDE-6: Phase 3 Trial of Cilta-cel vs Autologous Stem Cell Transplant in Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM)

Randomized, Open-Label, Multicenter Study (NCT05257083)

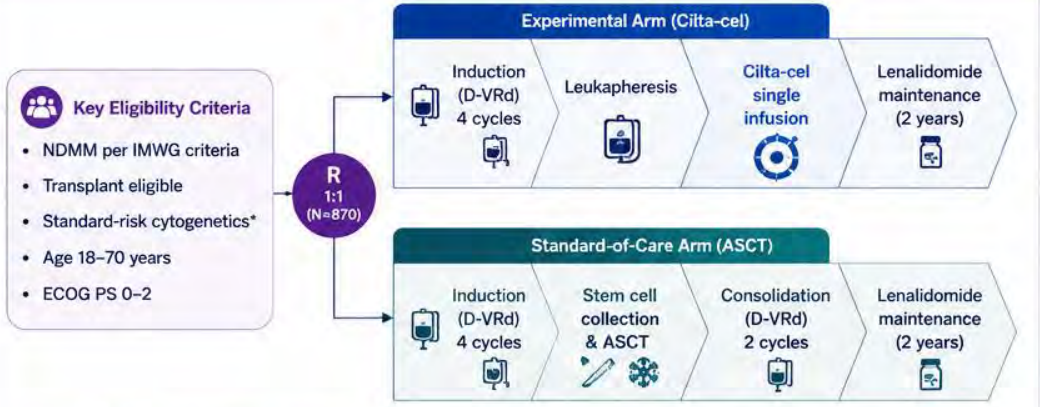
STUDY OVERVIEW

Aim: To determine whether earlier use of cilta-cel can improve outcomes compared with the current standard of care (ASCT) in transplant-eligible NDMM patients.

Cilta-cel (cilta-cabtagene autoleucel) is a BCMA-targeted CAR T-cell therapy designed to deliver deep and durable responses.

This study tests a cell therapy–based approach versus the current standard paradigm using autologous stem cell transplant (ASCT).

STUDY DESIGN



Randomization factors: Cytogenetic risk (standard vs high-risk†), ISS stage (I vs II vs III), age (<65 vs ≥65 years)

STUDY INFORMATION

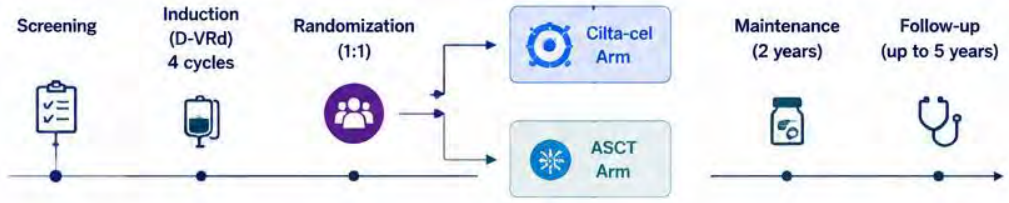
- Phase 3, randomized, open-label, multicenter
- ~870 patients (1:1 randomization)
- Estimated enrollment completed in 2024
- Planned follow-up: 5 years
- Sites: ~150 centers worldwide

ENDPOINTS

Primary Endpoint
- Progression-free survival (PFS) by independent review committee (IRC)

Key Secondary Endpoints
- MRD negativity rate (10^{-5})
- Complete response (CR) rate
- Overall survival (OS)
- Duration of response (DoR)
- Safety and tolerability
- Quality of life (QoL)

STUDY SCHEMA



Key question: Can frontline BCMA CAR T-cell therapy (cilta-cel) replace upfront ASCT and improve progression-free survival in transplant-eligible NDMM?

KEY TAKEAWAY

CARTITUDE-6 is the first phase 3 trial to evaluate earlier use of BCMA-targeted CAR T-cell therapy in transplant-eligible NDMM patients compared with the current standard of care using ASCT.

* Standard-risk defined as absence of del(17p), t(4;14) and t(14;16).
† High-risk defined as presence of del(17p), t(4;14) and/or (114;16).

ASCT = autologous stem cell transplant; BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; D-VRd = daratumumab, bortezomib, lenalidomide, dexamethasone; ECOG PS = Eastern Cooperative Oncology Group performance status; IMWG = International Myeloma Working Group; IRC = independent review committee; ISS = International Staging System; MRD = minimal residual disease.

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Fred Hutch Cancer Center

Thank you!

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