CAR T-Cell Therapy for Multiple Myeloma

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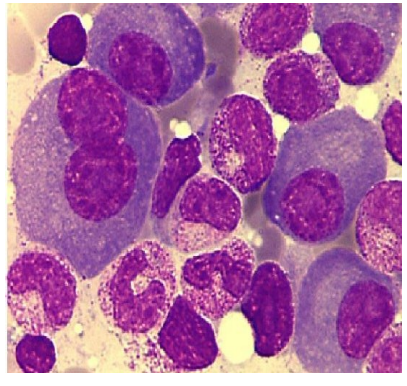
12/10/21



UT Southwestern
Harold C. Simmons
Comprehensive Cancer Center

NCI
Designated
Comprehensive
Cancer Center

Clinical Case

- 61 Female at Dx (age 70 now): Dx 7/2012 with Stage 3 Lambda Light Chain Myeloma (High risk double hit 17p deletion and add 1q)
- Progressed after at least 9 lines of therapy over the course of 6 years:

  7rh rib radiation 8/12 -> VRD 8/12-10/12 (CR) -> Auto SCT 11/12 -> obs x2 years -> Ixazomib trial 12/14-3/15 -> VRD 3/15-3/16 -> Dara/dex 4/16 -> Dara-CyBorD 5/16 -> Car/Pom/dex 5/16-3/17 -> hip radiation 3/17 -> Dara-CyBorD 4/17-7/17 -> solumedrol 8/17 -> 2nd Auto SCT 9/17 -> maint Dara/rev/dex 10/17-2/18 -> Dara-VRD 2/18-4/18 -> Progression with Lambda FLC in 500s
- Came from MN to UTSW Dallas 4/5/18, qualified for and enrolled on KarMMa trial (no slots in MN) -> Leukapheresis 4/12/18
- 1 cycle of “Bridging” therapy with Dara/Pom/Cytoxan/Dex 4/18 – 5/18
- LD chemo Flu/Cy x3 days 5/16-5/18/18 -> Day 0 Ide-Cel anti-BCMA CAR T-Cell infusion 5/21/18
- Admitted 2 weeks for monitoring and stayed in DFW for 2 months while not able to drive and needing to be close by medical center

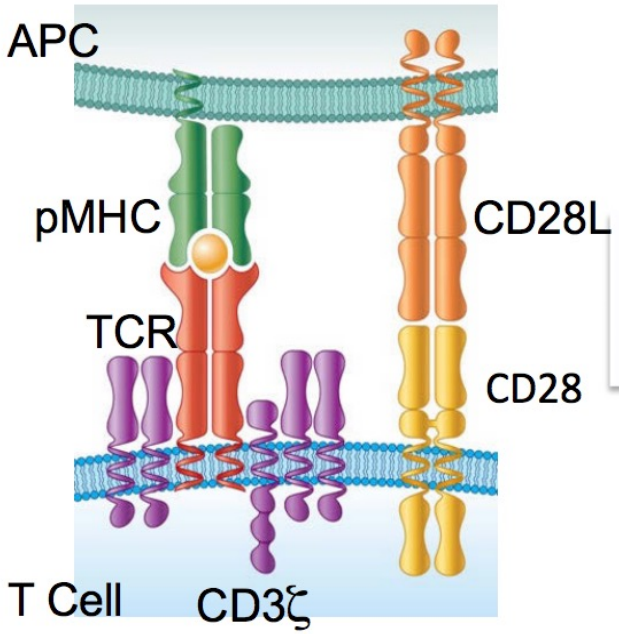
Clinical Case, cont'd

- She developed delayed grade 1 Cytokine Release Syndrome (CRS) day 14 and 15 so discharge delayed until day 18 but did not require Tocilizumab or steroids, resolved with Tylenol, No ICANS/NT
- Lambda FLC dropped from 580 mg/L on 5/14/18 to 370 on 5/28/21 to 138 on 6/4/18 (before fevers) to <2.31 mg/L on 6/11/18 (d21)
- M-spike was 0.06 pre-CAR-T and 0.03 at day 28 (VGPR) but undetectable in serum/urine IFE by 3 months Stringent CR at 3 months
- She remains in stringent CR at 42 months (3.5 year restaging still clear on 11/29/21 despite being OFF all therapy since 5/2018
- Ongoing IVIG replacement due to Hypogammaglobulinemia

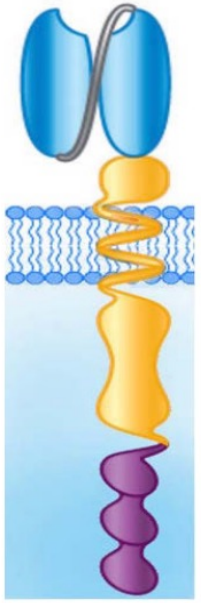
CAR Design: Critical Elements of T Cell Activation and Function in a Single Molecule

CAR T cells are genetically altered to express CAR on the cell surface.

T Cell Receptor



Chimeric Antigen Receptor



scFv: recognize tumor surface proteins

Costimulatory Signal 2:
CD28 or 4-1BB or OX40

Essential Signal 1:
CD3ζ

Activation Independent of MHC
Limited to cell surface proteins

Graeber, 2018: Immunotherapy and the Race to Cure Cancer

FDA Approved CAR-T Therapies
A New Era in Immunotherapy

- **Tisagenlecleucel** (Tisa-cel, Kymriah; Novartis)
- FDA Approved 8/17 for r/r ALL (up to 25 y/o) (2018 for r/r DLBCL)

- **Axicabtagene ciloleucel** (Axi-cel, Yescarta; Kite Pharma=Gilead)
- FDA Approved 10/17 for R/R DLBCL, r/r FL 3/21

- **Brexucabtagene autoleucel** (Brexu-cel, Tecartus; Kite = Gilead)
- FDA approved for Relapsed MCL 7/20, for adult ALL 10/21
- Uses same vector as axi-cel but w/ T-cell selection enrichment
- process to avoid circulating lymphoblasts

- **Lisocabtagene maraleucel** (Liso-cel, Breyanzi; BMS)
- FDA Approved 2/5/21 for relapsed DLBCL

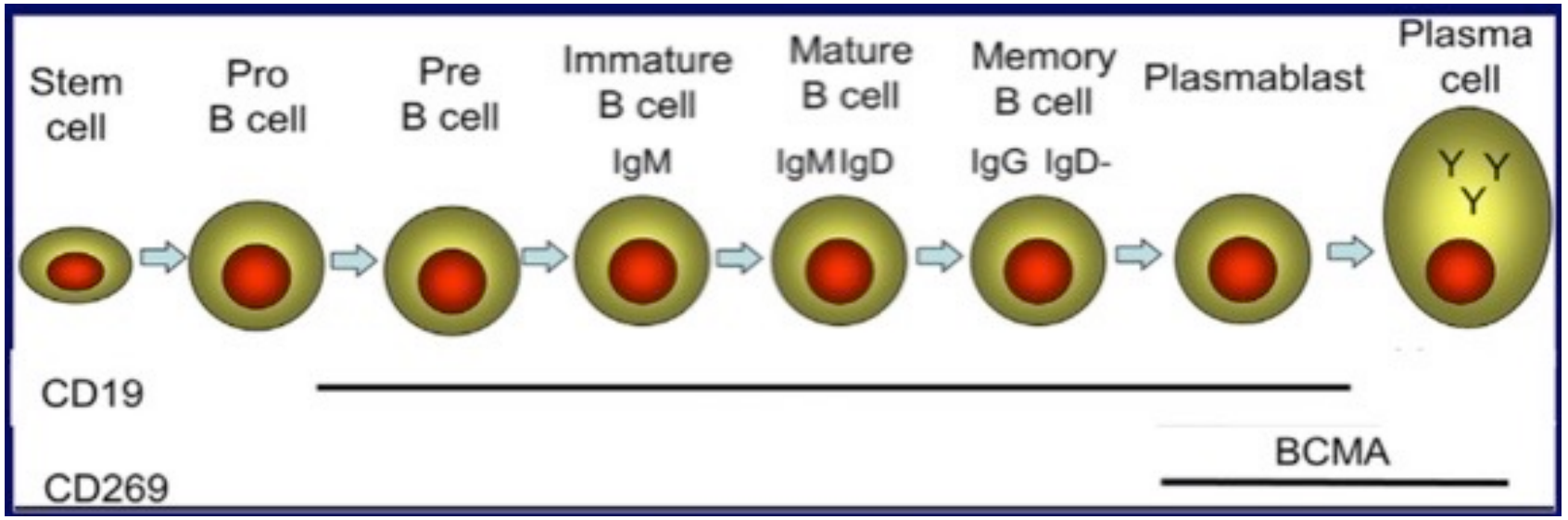
Idecabtagene vicleucel (Ide-cel, Abecma; BMS)
FDA approved for Rel/Ref Myeloma after 4 prior lines 3/26/21

All target CD19 except ide-cel (targets BCMA)

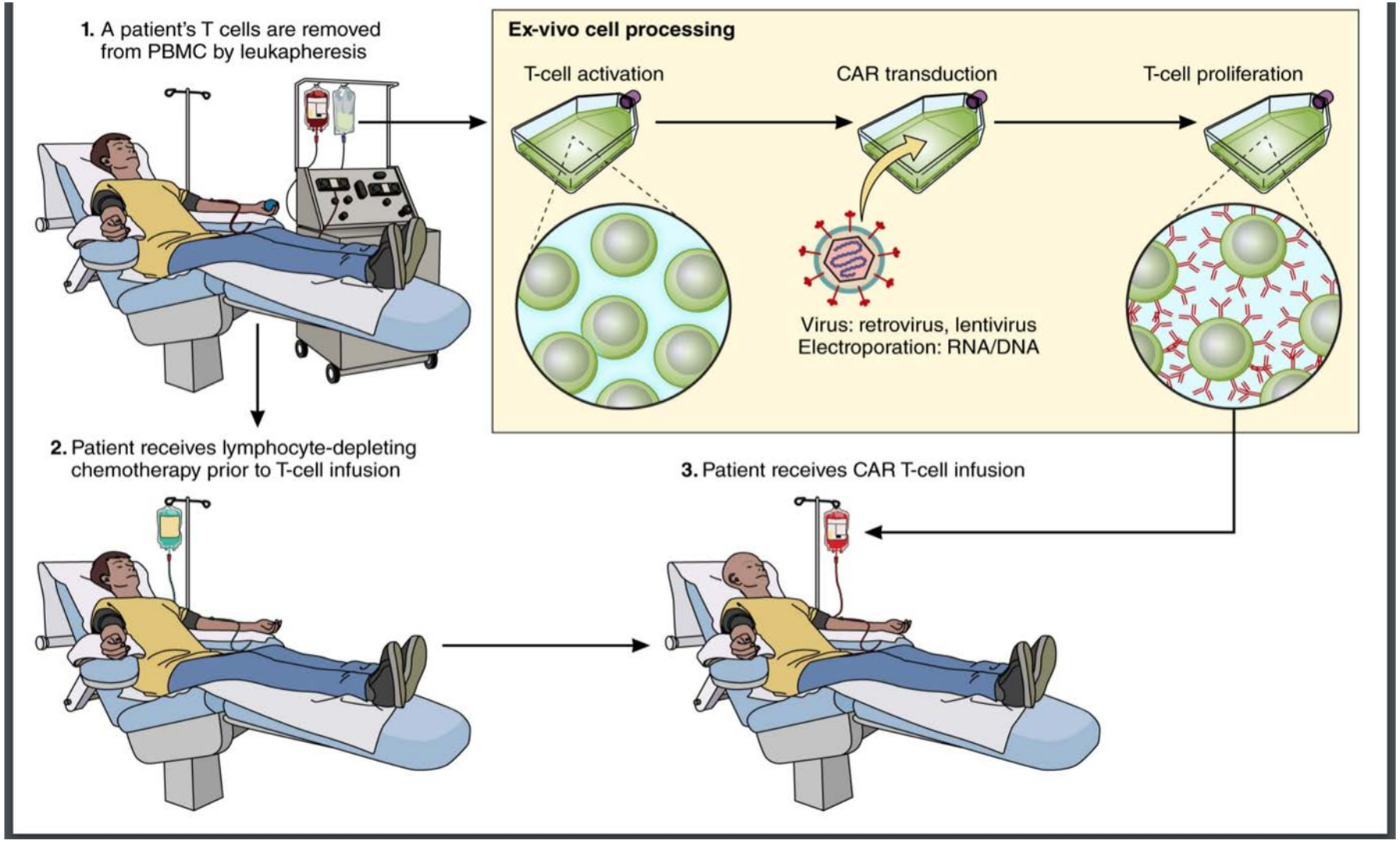
Borgert R, AJMC 2021

BCMA as a Target for Myeloma CAR T-Cell Therapy

- **BCMA:** B Cell Maturation Antigen
- Receptor expressed on Myeloma tumor cells, nonmalignant plasma cells, and some late stage mature B-cells
- Cell lineage specific so avoids off target toxicity



Overview of CAR T-Cell Process



McGuirk J. *et al*, Cytotherapy 2017; 19:1015-1024

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

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Drs. Munshi and Anderson contributed equally to this article.

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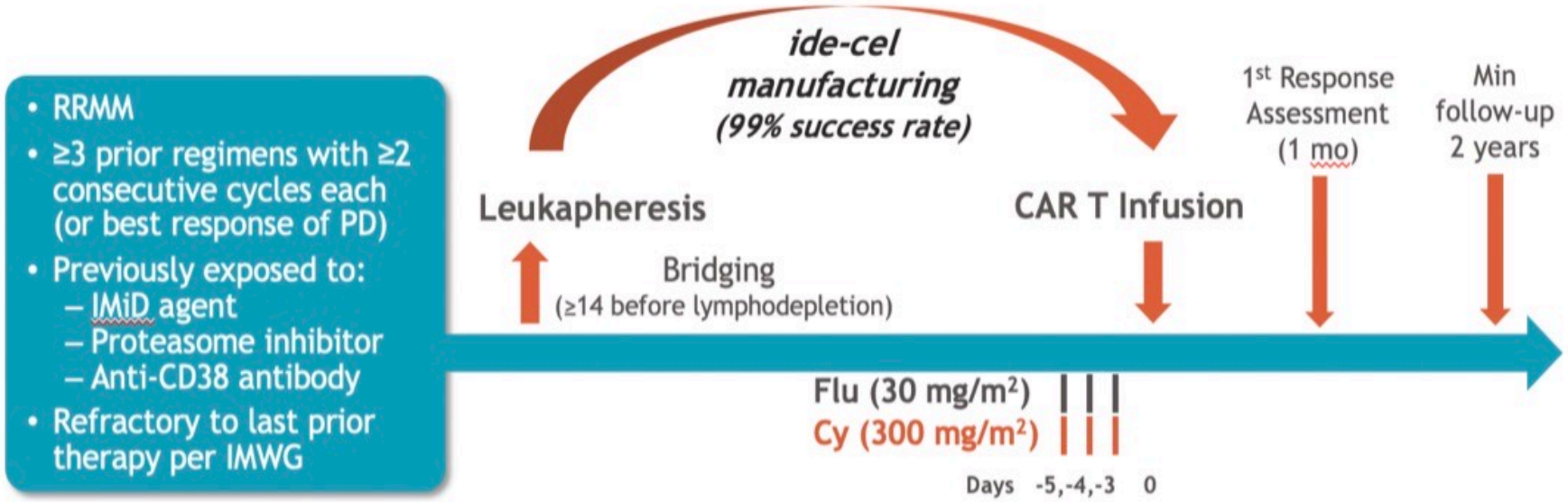
BCMA-Directed CAR-T Cells
Published 2/25/2021
FDA Approved 3/26/2021
ASCO Update 6/2021

Phase II KarMMa study of Ide-Cel in Relapsed/Refractory Myeloma

KarMMa™



Endpoint

- **Primary**: ORR (null hypothesis ≤50%)

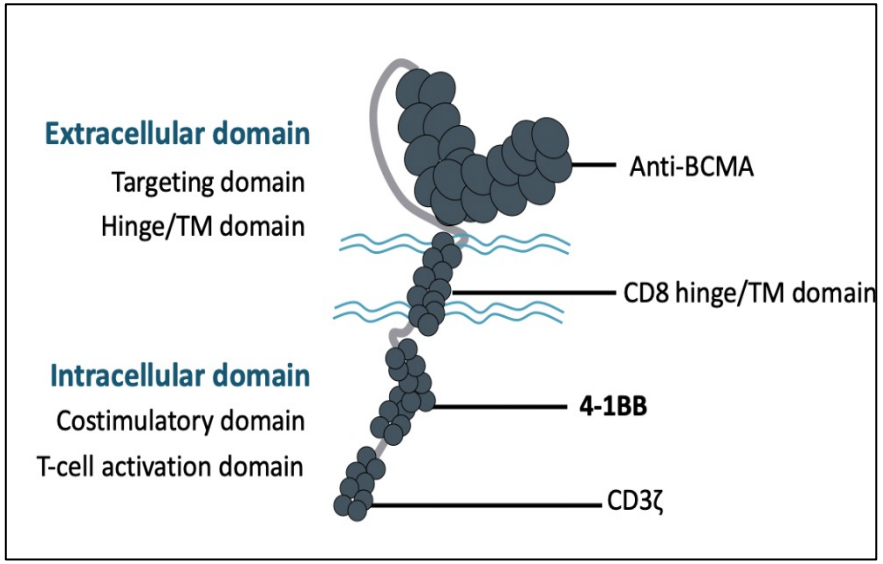
Median 6 Prior Lines of Rx

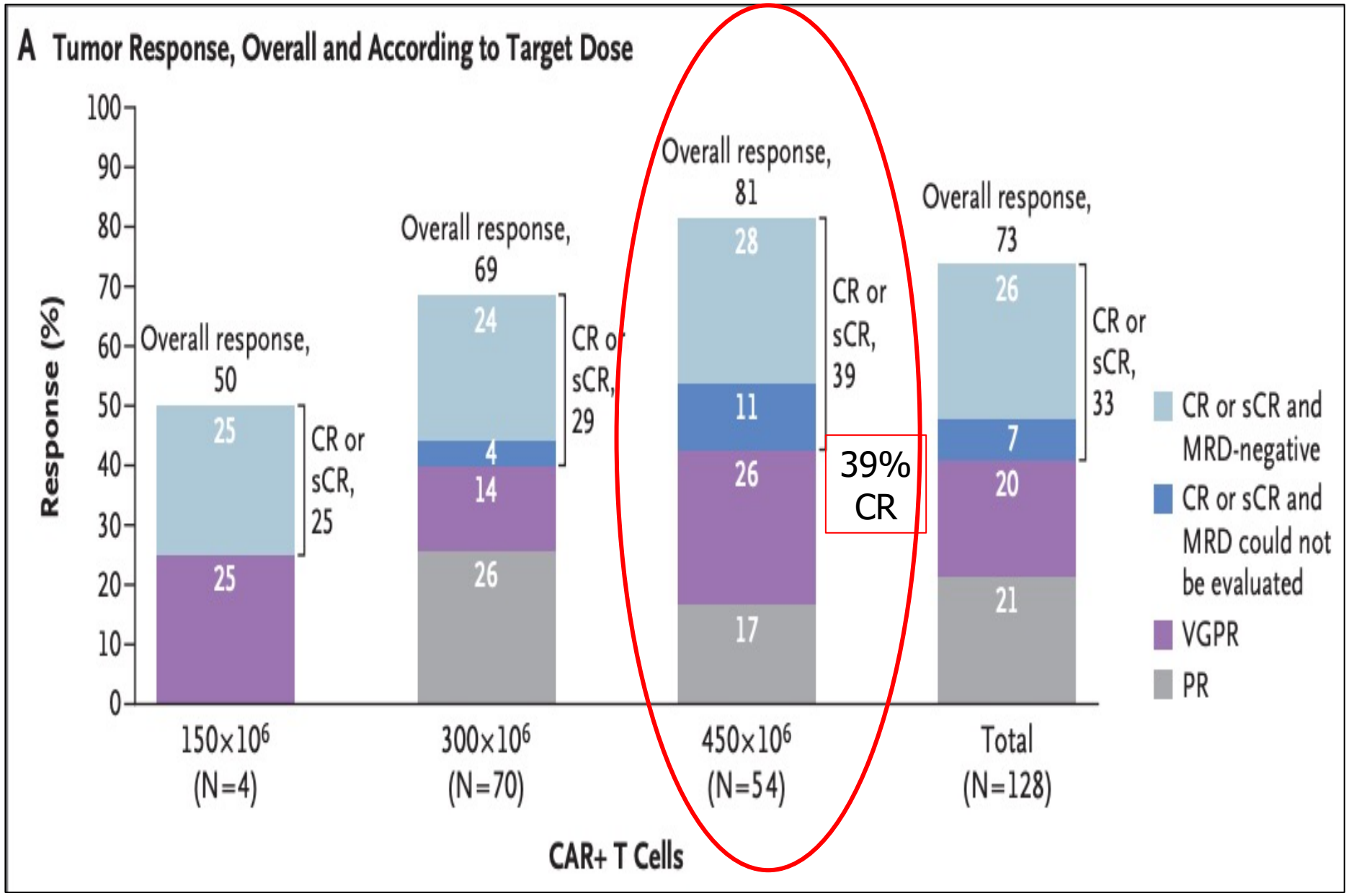
Expected response rate 25-30%, PFS 3-4 mo

Based on other recently approved products in Triple class exposed MM

Munshi & Anderson et al, NEJM 2021

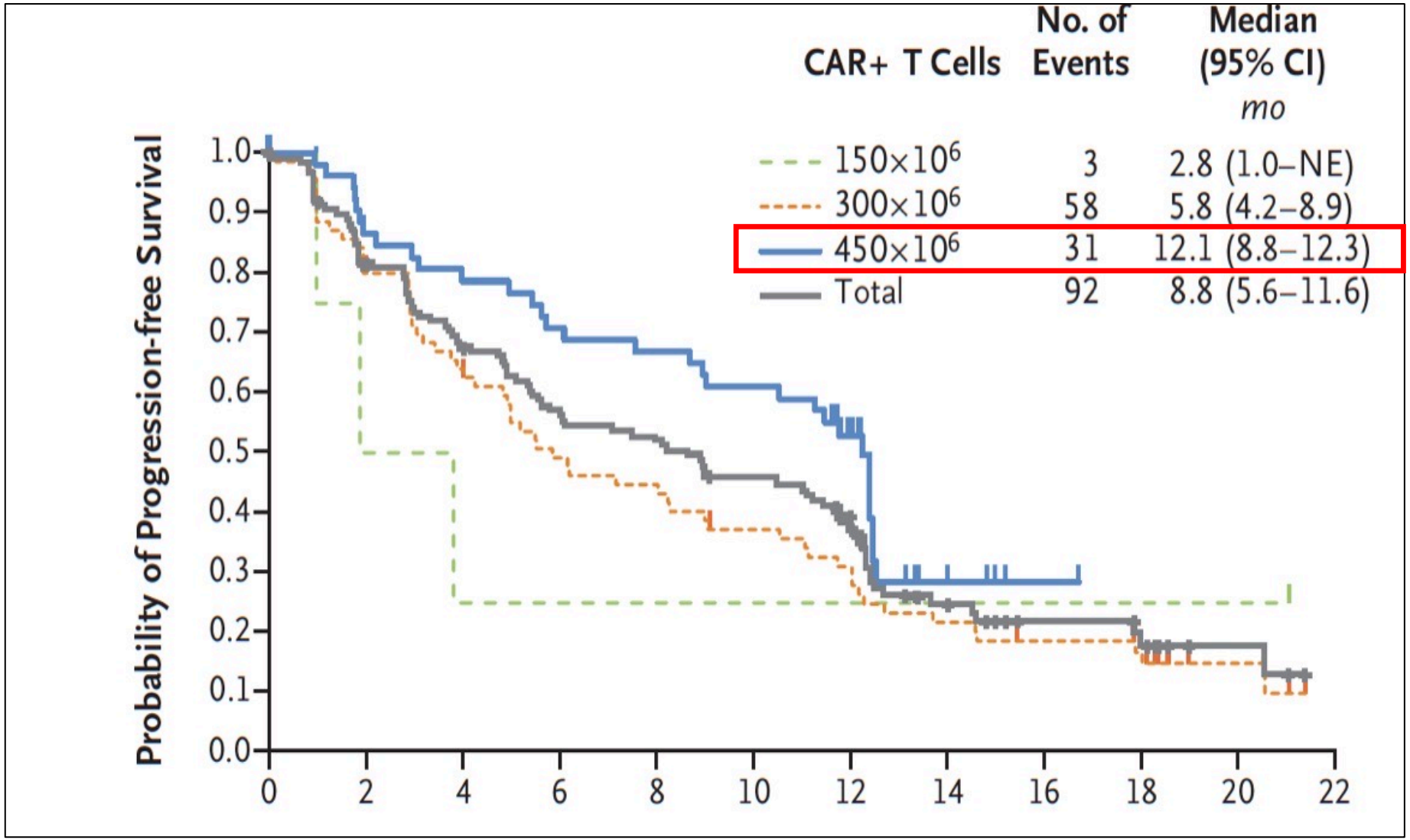
Anderson et al, ASCO 2021





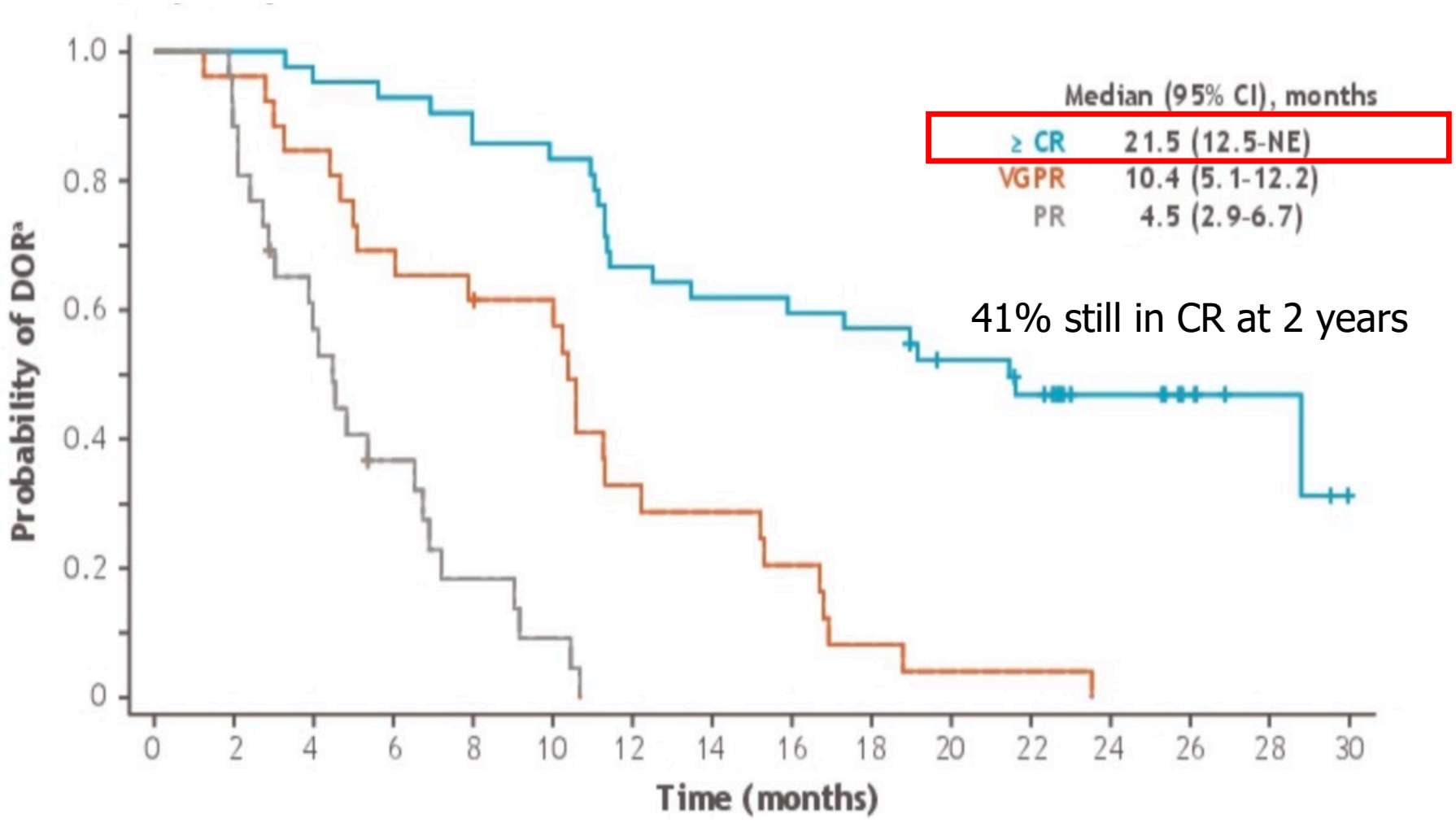
Munshi N & Anderson LD Jr et al, NEJM 2021

KarMMa Trial PFS According to Target Dose



Munshi and Anderson et al, NEJM 2021

KarMMa Trial DOR by Level of Response



Anderson LD Jr et al, ASCO 2021 and IMW 2021

Summary of KarMMa (Ide-Cel) Outcomes

- ORR 73%, 81% for $450x10^6$ target dose
- PFS 8.6 mo overall, 12.2 mo for $450x10^6$ target dose
- Median OS 24.8 mo (expected 9 mo in this population)
- Median OS >20 mo in several high-risk subgroups including age ≥65, EMD, and triple-refractory status
- Outcomes not affected by 3 vs 4+ lines of prior therapy
- Those in at least CR had PFS 20.2 mo and DOR 21.5 mo
- 84% CRS but mostly low grade and brief, only 5% grade 3-4 CRS, 1 fatality from CRS

- Neurotoxicity all grades only 18%, only 4% grade 3-4

Anderson LD Jr, et al. ASCO 2021

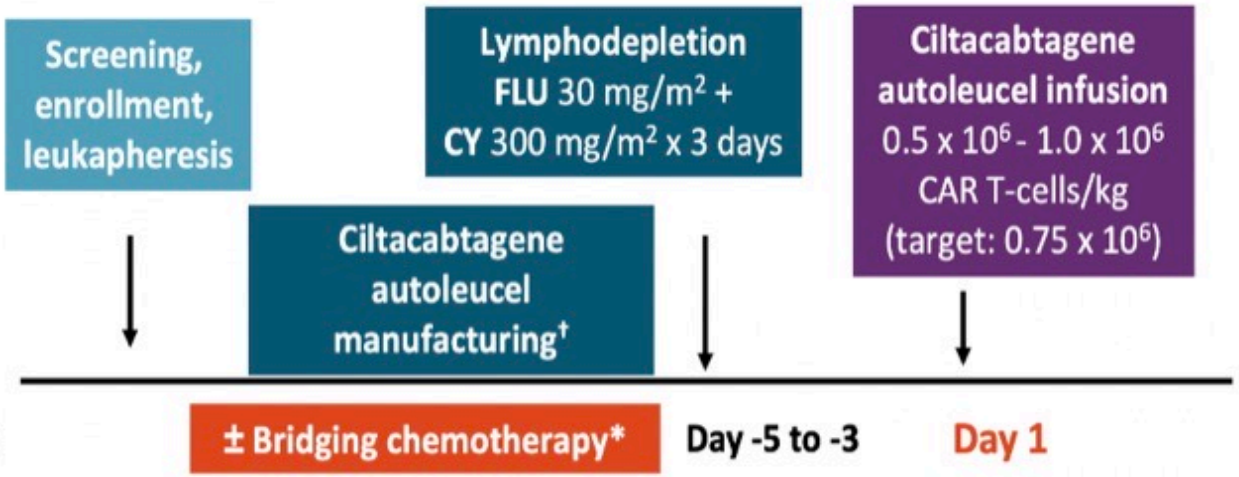
Idecabtagene vicleucel (Ide-cel)
FDA APPROVED 3/26/2021

- First CAR T-cell therapy approved for Multiple Myeloma
- Approved for Relapsed or Refractory Myeloma after at least 4 Prior Lines of Therapy including an IMiD, a PI, and an anti-CD38 mAb
- Requires REMS program, and pt must live within 2 hrs of CAR-T center for 1 mo and no driving for 2 mo
- Limited to tertiary BMT & Cell Therapy centers
- Due to production limitations most cancer centers are currently only allowed 1 to 3 collection slots per month
- Now trials are exploring earlier lines of therapy in KarMMa 2, 3, 4
- Testing culture with PI3k inhibitor to enrich memory T cells (bb21217)

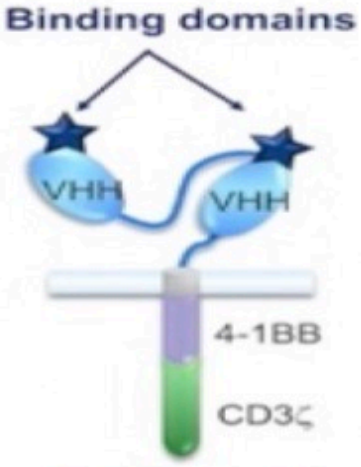
CARTITUDE-1 Phase Ib/II Study of Ciltacabtagene Autoleucel: BCMA-Directed CAR T-Cells in R/R MM

- Phase Ib/II trial conducted in the United States

Patients with R/R MM
ECOG PS ≤ 1; ≥ 3 prior therapies including PI, IMiD, and anti-CD38 therapy, or double refractory to PI and IMiD
(N = 113)



*73 patients received bridging therapy with previously used agents to maintain
†0 patients d/c due to manufacturing failure.

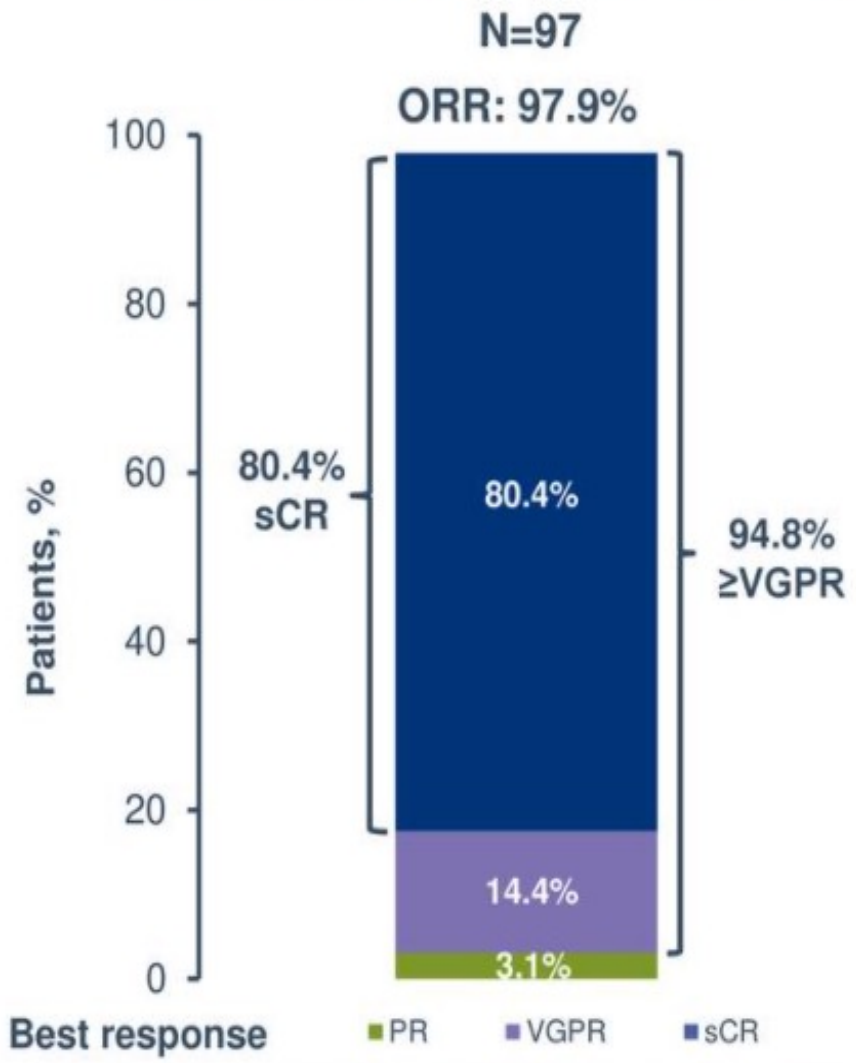


(Cilta-Cel)

- Of 113 patients enrolled, 97 received ciltacabtagene autoleucel; phase Ib (n = 29); phase II (n = 68); median administered dose: 0.71 x 106 (0.51–0.95 x 106) CAR+ viable T-cells/kg
- Primary endpoints: safety and RP2D (phase Ib), efficacy (phase II)

Usmani SZ et al, ASCO 2021. Berdeja JG et al, Lancet 2021

CARTITUDE-1: Overall Response Rate

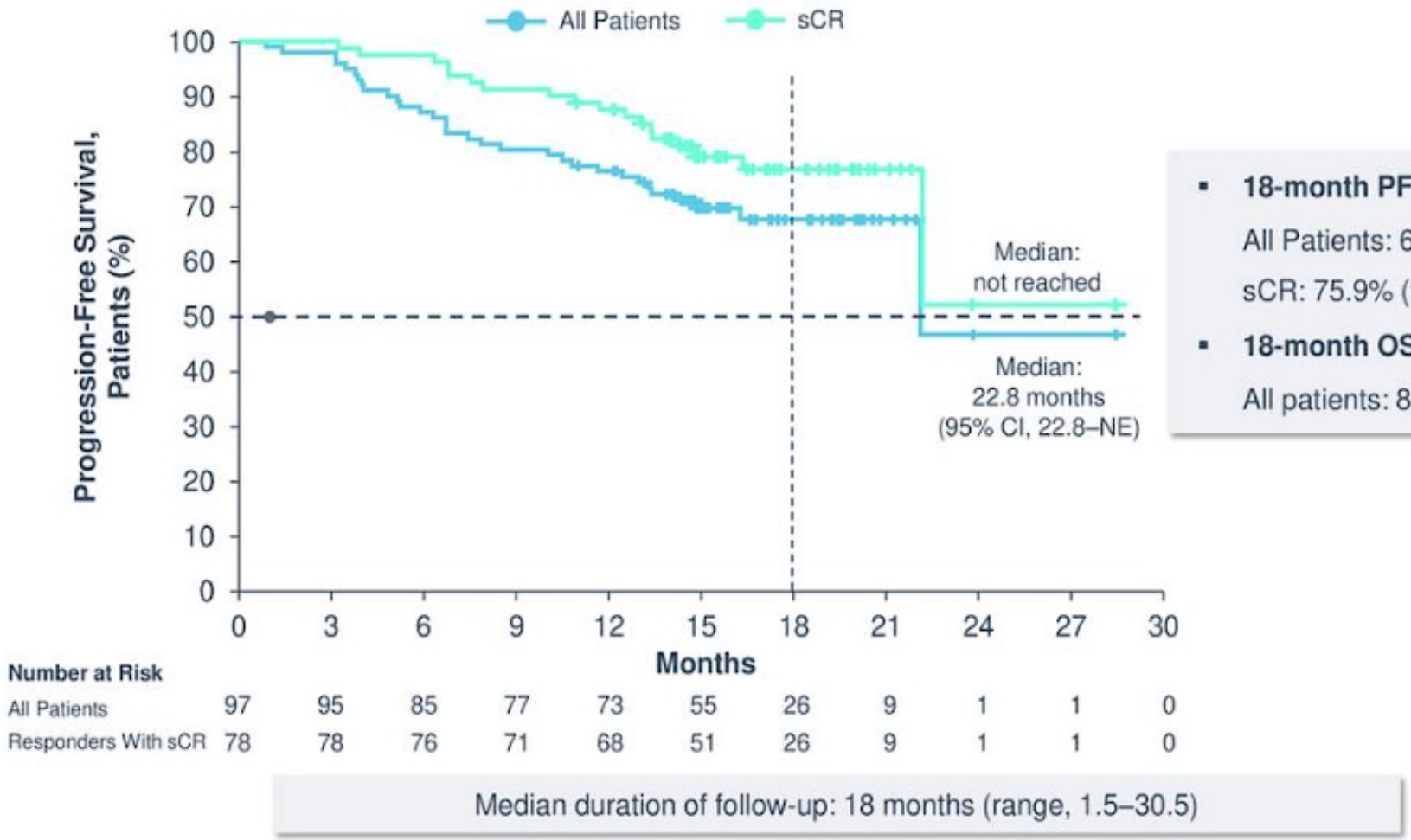


With longer follow-up, responses deepened with increasing rate of sCR

- Median time to first response: 1 month (range, 0.9–10.7)
- Median duration of response: 21.8 months (95% CI, 21.8–NE); not reached in patients with sCR
- Response rates were comparable (range, 95–100%) across different subgroups (eg, number of prior lines of therapy, refractoriness, extramedullary plasmacytomas, and cytogenetic risk)[a]
- 91.8% of 61 evaluable patients were MRD negative[b]
  - Median time to MRD 10^{-5} negativity: 1 month (range, 0.8–7.7)

Usmani SZ et al, ASCO 2021. Berdeja JG et al, Lancet 2021

CARTITUDE-1: Progression Free Survival



- **18-month PFS:**
  All Patients: 66.0% (95% CI, 54.9–75.0)
  sCR: 75.9% (95% CI, 63.6–84.5)
- **18-month OS:**
  All patients: 80.9% (95% CI, 71.4–87.6)

Median duration of follow-up: 18 months (range, 1.5–30.5)

Usmani SZ et al, ASCO 2021

CARTITUDE-1: Safety

- CRS
  - 94.6% of patients experienced low-grade CRS (n=92)
  - Median time to onset of 7 days (range, 1-12)
  - Median duration of 4 days (range, 1-97)[b] and resolved in 91 (98.9%) patients within 14 days of onset
- Neurotoxicity
  - 20.6% of patients experienced neurotoxicity in total with overlap between ICANS and Other Neurotoxicities (Grade ≥3: 10.3%)
    - ICANS observed in 16.5% (Grade ≥3: 2.1%)
    - Other Neurotoxicities[c] observed in 12.4% (Grade ≥3: 9.3%)
- 6 treatment-related deaths as assessed by the investigator[d]

5 Movement and/or Neurocognitive/ Parkinsonian
7 Nerve Palsy or motor neuropathy

To be Reviewed by FDA by end of Feb 2022

Usmani SZ et al, ASCO 2021. Berdeja JG et al, Lancet 2021

CARTITUDE Program: Safety

Successful new patient management strategies have been implemented in the CARTITUDE program to prevent and reduce the incidence of neurotoxicity[1-3]

Movement and Neurocognitive TEAEs[a]

- Occurred in 5 of 97 patients in CARTITUDE-1

Risk factors (2 or more)

- High tumour burden[b]
- Grade ≥2 CRS
- ICANS
- High CAR T-cell expansion and persistence

Patient Management Strategies

- Enhanced bridging therapy to reduce tumour burden
- Early and aggressive treatment of CRS and ICANS
- Handwriting assessments and extended monitoring

CARTITUDE Program Level

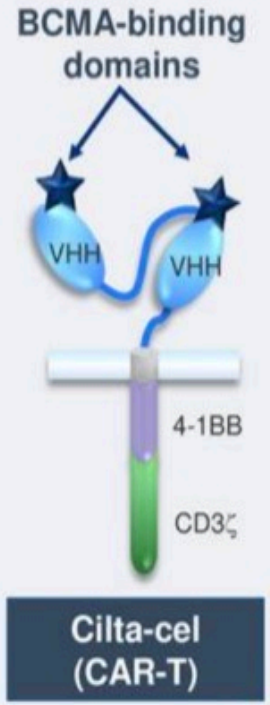
>100 additional patients have been dosed[c]

- Patient management strategies to prevent or reduce these AEs have been successfully implemented in new and ongoing cilta-cel studies
- This is reliant on effective implementation of these patient management strategies

Usmani SZ et al, ASCO 2021

CARTITUDE-2: Multicohort Study
Cohort A: 1 – 3 prior lines, lenalidomide refractory RRMM

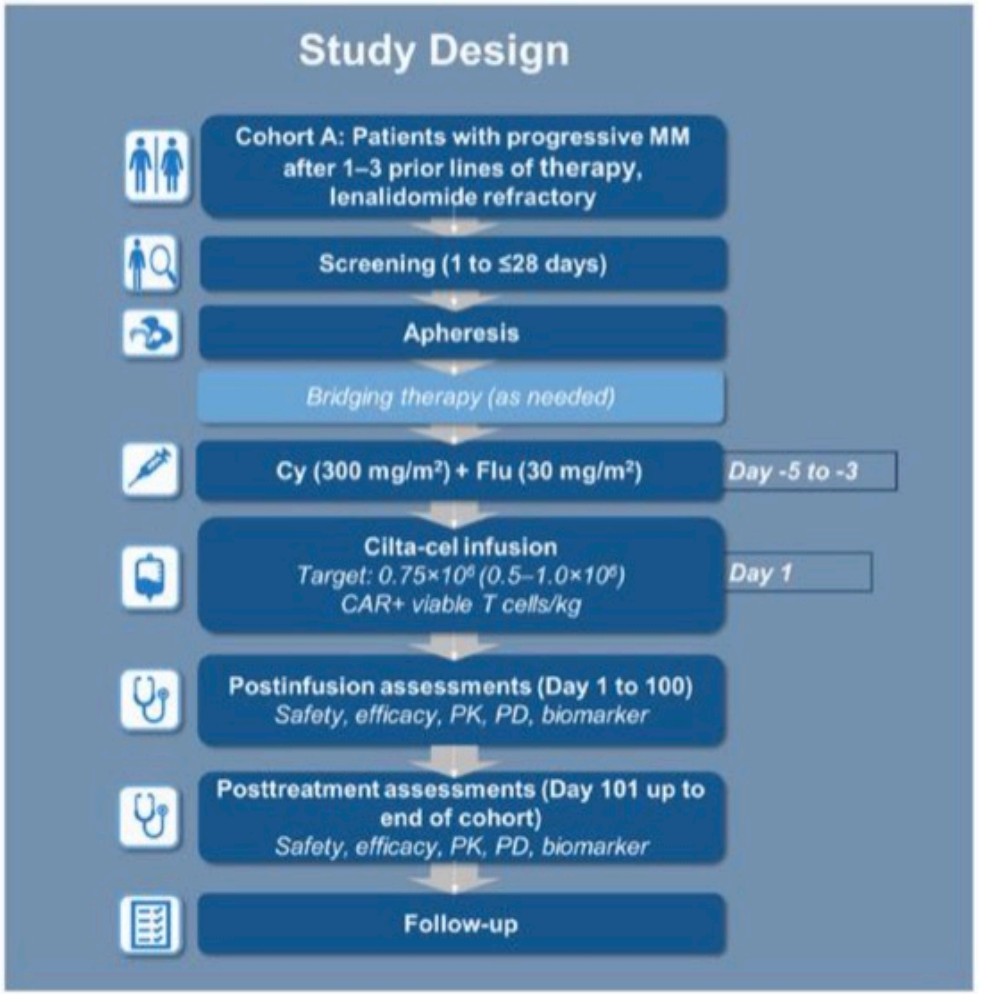
- CARTITUDE-2 is a phase 2, multicohort, open-label study assessing the efficacy and safety of cilta-cel in patients with multiple myeloma in various clinical settings



Cohort A:
- Cohort A patients had progressive MM after 1–3 prior lines of therapy, and were refractory to lenalidomide
- Despite advances continued unmet need with mPFS of 9.9 months (DPd)[1]

Primary objective
- Minimal residual disease (MRD) 10^{-5} negativity

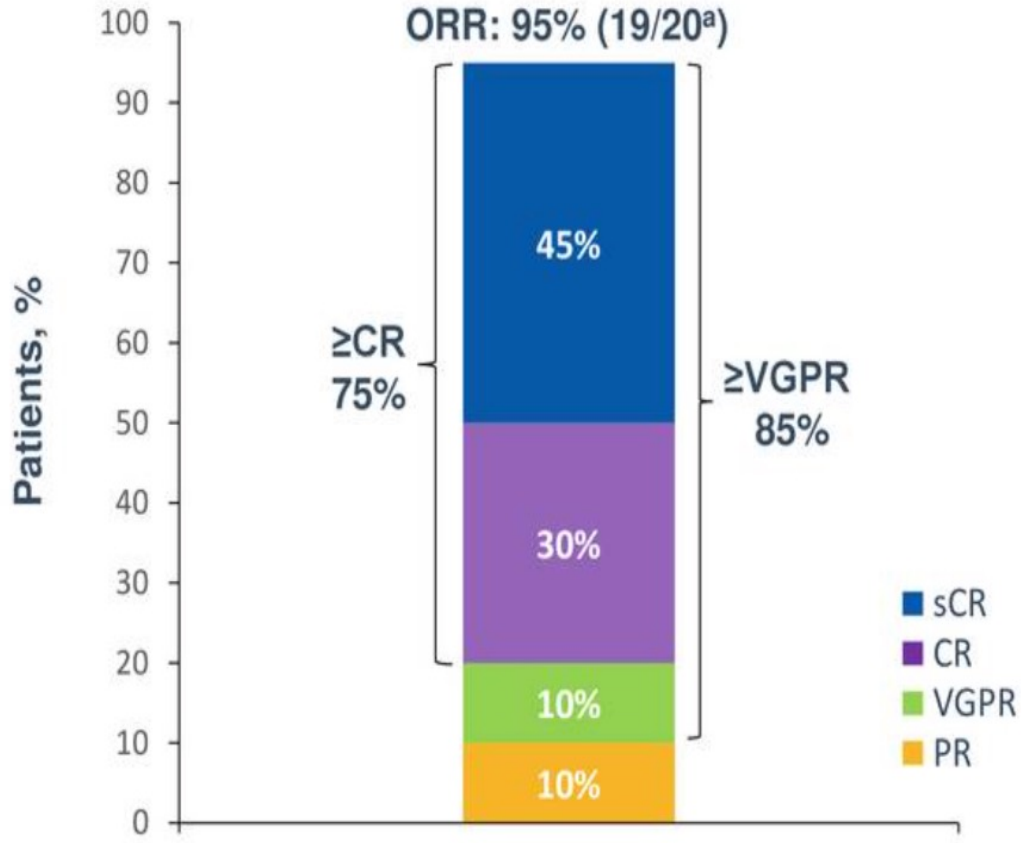
Secondary objective
- ORR, duration of response, time and duration of MRD negativity, and incidence and severity of adverse events



Agha ME et al, ASCO 2021

CARTITUDE-2: Phase 2 Multi-Cohort Study

- Cohort A included 20 patients who had progressive MM after 1–3 prior lines of therapy and were refractory to lenalidomide
- Median prior lines of therapy: 2 (range, 1-3); 1 patient treated in an outpatient setting



- No progression of disease at median follow-up of 5.8 months (range 2.5-9.8)
- All patients (n=4) with MRD-evaluable[b] samples at the 10^{-5} threshold were MRD negative at data cut-off
- The safety profile was manageable
  - CRS occurred in 85% (n=17); mostly grades 1/2; median time to CRS onset was 7 days (range, 5–9)
  - Neurotoxicities occurred in 20% (n=4) of patients; no grade ≥3; no incidence of movement and neurocognitive TEAEs
  - 1 death occurred 100 days after infusion due to COVID-19 (assessed as tx related by the investigator)

Agha ME et al, ASCO 2021

Cohen et al ASH 2021 abstract now shows
1 grade 2 facial paralysis but no Parkinsonian
Now All responses VGPR or better in 19/20

A Phase 1b/2 Study of Fully Human B-cell Maturation Antigen-Specific CAR T Cells (CT053) in Patients with Relapsed and/or Refractory Multiple Myeloma (RRMM) Results from LUMMICAR STUDY 2

- CARSGEN FULLY HUMANIZED BCMA CAR RECEPTOR
- Designed to prevent recognition of murine epitopes by Ab or T cells

- 20 patients with RRMM treated with 1.5-3.0×10^8 CT053 T cells
  - 14 patients received 1.5-1.8×10^8 CT053 T cells (DL0)
  - 6 patients received 2.5-3.0×10^8 CT053 T cells (DL1)

- CT053 was well tolerated with acceptable safety profiles
  - No CRS ≥ grade 3 occurred
  - One grade 3 neurotoxicity occurred at DL0 and resolved with steroids

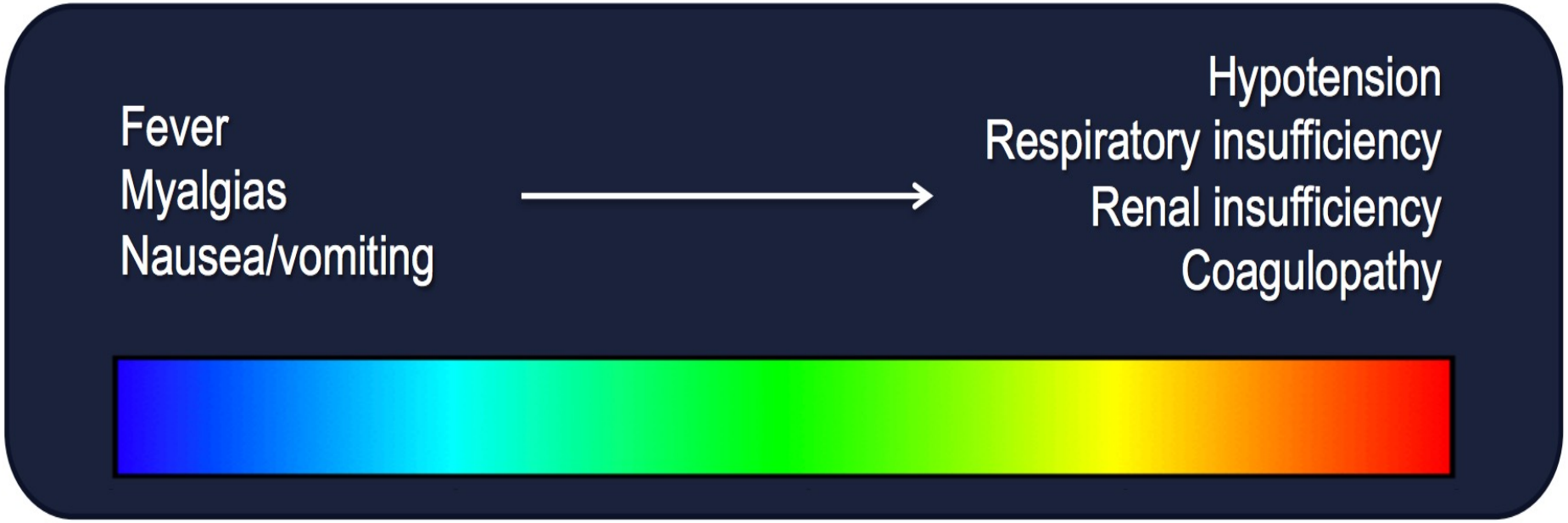
- 94% ORR in 18 patients with at least 8 weeks efficacy assessment
- Early and deepened responses observed in patients with heavy tumor burden
- Phase 2 Recently launched

Kumar et al, ASH 2020

Cytokine Release Syndrome (CRS)

CRS is related to T-cell expansion and may be necessary for efficacy

- Symptoms typically occur 1-14 days after CAR T- cell infusion in ALL



- Inflammatory response from IL-6 and other cytokine production
- The more CAR-T triggering the more cytokine release (increases w/ dz burden)
- Low grade treated with symptom management (anti-pyretics)
- Higher grade or refractory treated with Tocilizumab +/- steroids

Neurotoxicity (ICANS) with CAR T-cell Therapy

- **CRES** = Cytokine Related Encephalopathy Syndrome
- **ICANS** = Immune effector Cell Associated Neurologic Syndrome
- Symptoms and signs: somnolence, encephalopathy, global aphasia, seizures, confusion, delirium, tremors, paralysis of limbs, incontinence.
- Onset of neurotoxicity may be biphasic:
  - 1st phase (Days 0-5) – symptoms may appear with other CRS
  - 2nd phase (After day 5) – starts after CRS s/s have subsided
  - Neurotoxicity such as seizures may occur later even in 3rd or 4th week
- Neurotoxicity typically lasts 2-4 days, but may vary in duration from hours to few weeks. Its generally reversible
- Corticosteroids treatment of choice in managing neurotoxicity
- Tocilizumab might reverse neurological toxicity during 1st phase only
- Seizure prophy with Keppra if high risk product or if ICANS symptoms.
- Cilta-cel with risk of delayed Parkinsonian movement disorder, motor neuropathy, and CN palsies

Biol Blood Marrow Transplant 25 (2019) 625–638

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Guideline

Simplified Grading scales for CRS and Neurotoxicity (ICANS)

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells

Daniel W. Lee[1,#], Bianca D. Santomasso[2,#], Frederick L. Locke[3], Armin Ghobadi[4], Cameron J. Turtle[5], Jennifer N. Brudno[6], Marcela V. Maus[7], Jae H. Park[8], Elena Mead[9], Steven Pavletic[6], William Y. Go[10], Lamis Eldjerou[11], Rebecca A. Gardner[12], Noelle Frey[13], Kevin J. Curran[14], Karl Peggs[15], Marcelo Pasquini[16], John F. DiPersio[4], Marcel R.M. van den Brink[8], Krishna V. Komanduri[17], Stephan A. Grupp[18,*], Sattva S. Neelapu[19,**]

Myeloma CAR T-Cell Therapy Product Summary and Future Directions

	Idecabtagene vicleucel (Ide-Cel)(BMS)	Ciltacabtagene autoleucel (Cilta-Cel)(Janssen)
Pivotal trial	Phase II KARMMa (N = 128)	Phase Ib/II CARTITUDE-1 (N = 97)
Prior therapy	≥ 3 prior lines	≥ 3 prior lines
Median (range)	6 lines (3–16)	6 lines (4-8)
CAR T-cell dose	150–450 x 10^6 cells	Median: 0.75 x 10^6 cells/kg
Grade ≥ 3 CRS	5%	4%
Grade ≥ 3 NT	3%	9% (+ some non-CNS NT)
ORR	73% (81% at target dose)	97%
CR	33% (39% at target dose)	67% (80% sCR at update)
PFS	Median PFS: 8.8 mo (12.2 mo)	12-mo PFS: 77%, 18 mo 65%
OS	Median 24.8 mo	18-mo OS 81%
FDA	Approved 3/2021	To be Reviewed 2/2022

- Several other products are being tested and appear very promising:
- Orva-cel, bb21217, Allo-715, CT053, pBCMA-101, et al, but no FDA date
- Now looking at non-BCMA targets like GPRC5D and combination targets

Munshi and Anderson et al NEJM 2021; Berdeja et al. *Lancet.* 2021; Usmani et al ASCO 2021