Request for New ICD-10-PCS Code for the Administration of Idecabtagene Vicleucel (Ide-cel)

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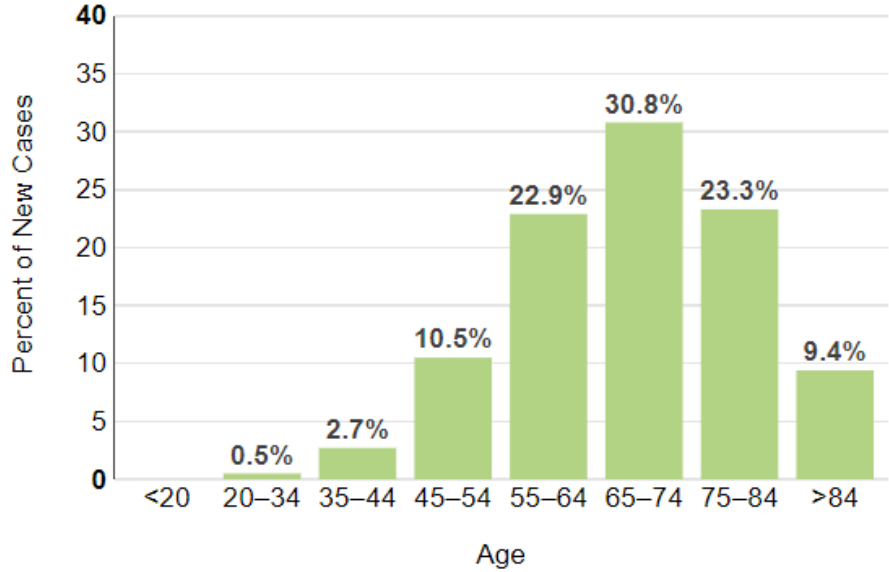
Multiple Myeloma - Introduction

- Multiple Myeloma (MM) is a cancer of plasma cells. A type of white blood cells that normally produce antibodies as part of the body's immune system
- More than 32,000 new cases are estimated in the US in 2020 and more than 12,500 deaths
- The median age of diagnosis is 69 years, affecting more males than females. 63.5% of new cases are in patients aged 65 years and older
- Clinical features include anemia, multiple bone fractures, renal failure, high calcium levels and frequent infections

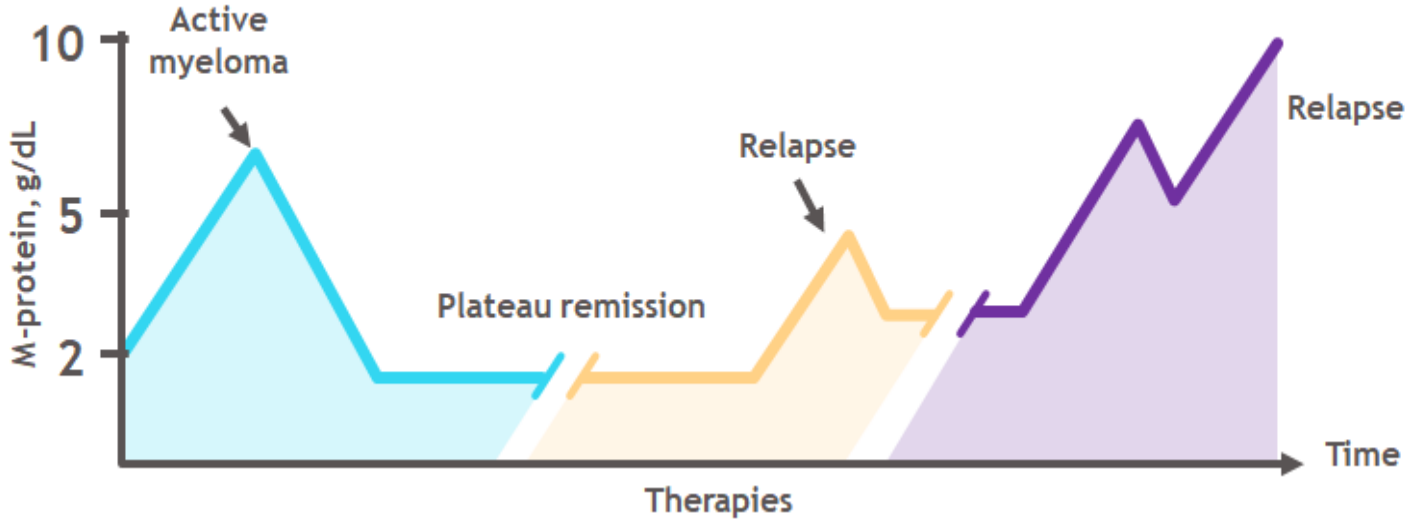
Percent of New Cases by Age Group: Myeloma



SEER program: https://seer.cancer.gov/statfacts/html/mulmy.html

Significant Unmet Need Remains in Multiple Myeloma

- Multiple myeloma is characterized by a remitting relapsing course
- Multiple relapses lead to low likelihood of deep response and poor durability
- Multiple myeloma remains incurable, and vast majority of patients succumb to the disease



		NDMM ASCT	NDMM No ASCT	R/R MM (2L-3L)	R/R MM (4L+)
CR/sCR	Induction	~35%	~15-47%	~30-42%	≤3%
	Post-ASCT	~50-60%			
PFS		~5.7 yr	~2-4+ yr	~1-3.5 yr	~4 mo

ASCT, autologous stem cell transplantation; CR, complete response; g/dL, grams per deciliter; NDMM, newly diagnosed multiple myeloma; R/R MM, relapsed refractory multiple myeloma; PFS, progression-free survival; sCR, stringent complete response; 2L, second-line; 3L, third-line; 4L+, fourth-line plus

1. Kumar SK . *Leukemia*. 2012;26:149-157; 2. Gandhi UH, et al. *Leukemia*. 2019;33(9):2266-2275; 3. Chari A, et al. *N Engl J Med*. 2019;381:727-738; 4. Lonial S, et al. *Lancet Oncol*. 2020;21(2):207-221.

Ide-cel Overview

The proposed indication for ide-cel is "For the treatment of adult patients with multiple myeloma who have received at least three prior therapies including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody"

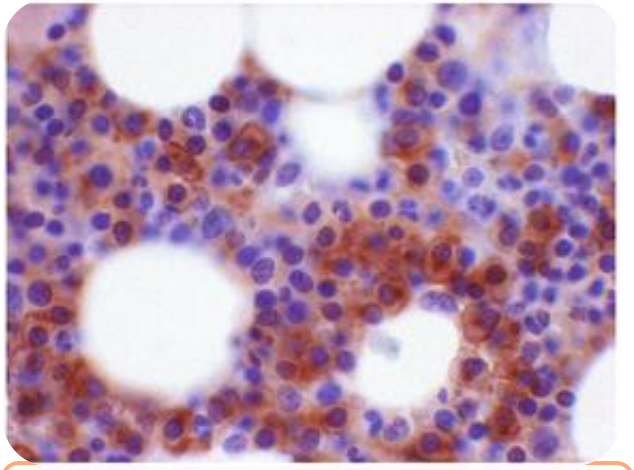
Food and Drug Administration (FDA) granted ide-cel Orphan Drug designation in May 2016

FDA granted Breakthrough Therapy designation in Nov 2017

Biologics License Application (BLA) submitted to FDA in July 2020

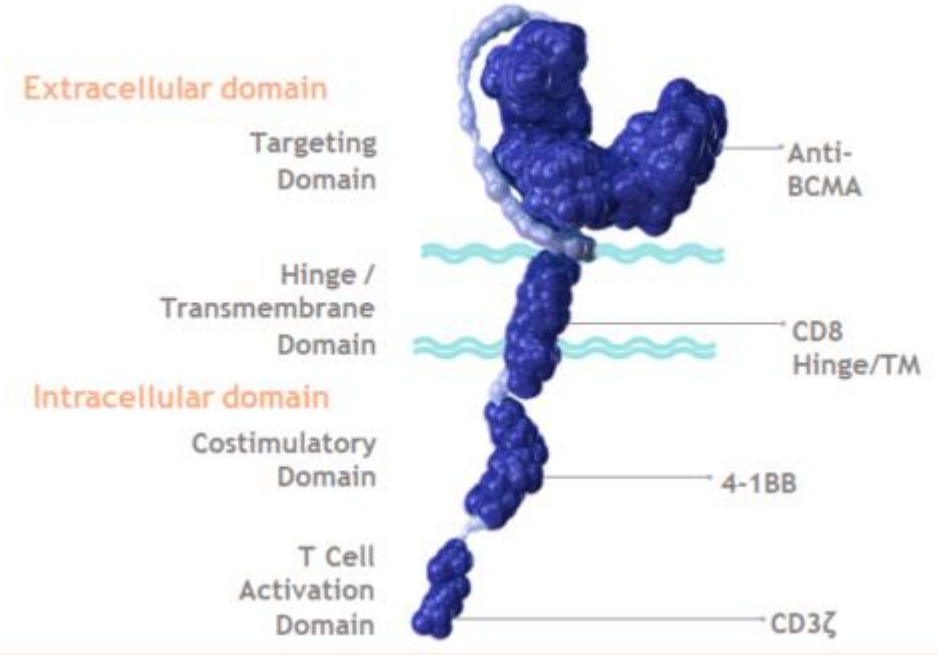
FDA approval is anticipated before July 1, 2021

Ide-cel: BCMA CAR T Cell Construct Design



Multiple Myeloma
cells expressing BCMA
(brown color is BCMA protein)

- BCMA- B cell maturation antigen
- Expression largely restricted to plasma cells and mature B cells
- Expressed universally on myeloma cells



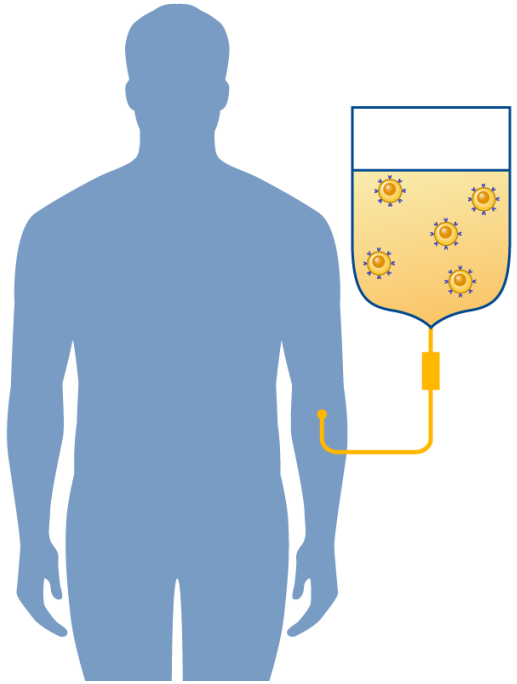
Key Facts

- Autologous T cells transduced with a lentiviral vector encoding CAR specific for human BCMA
- Targeting domain: anti-BCMA
- Costimulatory domain: 4-1BB
- T cell activation domain: CD3-zeta

BCMA, B-cell maturation antigen; MND, myeloproliferative sarcoma virus enhancer, negative control region deleted, dl587rev primer-binding site substituted; SP, signal peptide.
Raje N, et al: *J Clin Oncol*. 2018; 36(abstr 8007). Presented at the ASCO Annual Meeting. Chicago, IL; June 1-5, 2018.

Administration of Ide-cel

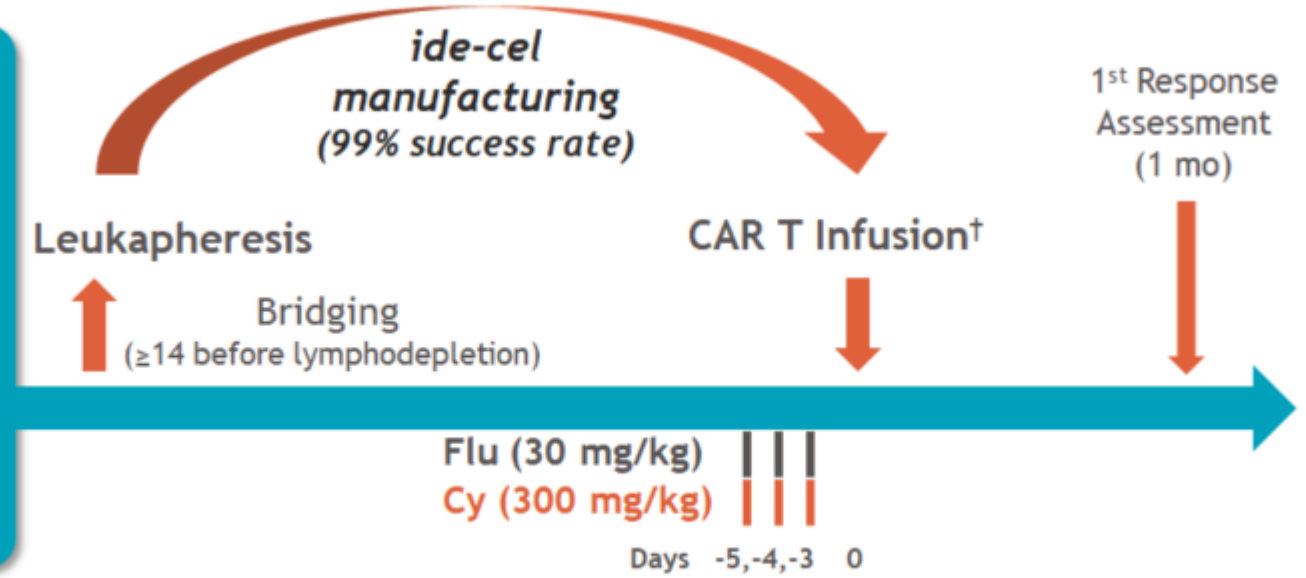
- Ide-cel is expected to be administered primarily in the hospital inpatient setting as a standalone procedure
- Ide-cel is given as a single treatment, administered through the central or peripheral vein
- Target dose is 450 x 10^6 CAR+ T cells, and ide-cel can be given within a dose range of 150 to 540 x 10^6 CAR+ T cells
  - ide-cel is provided in one or more infusion bags. Each infusion bag must be thawed individually and infused within 1 hour after start of thaw
  - the contents of the cryopreservation bag(s) are infused as quickly as tolerated by gravity flow
- Patients must be monitored at least daily for 7 days following ide-cel infusion at the certified healthcare facility for signs and symptoms of cytokine release syndrome (CRS) and neurologic toxicities (NT)*
- Patients should be instructed to remain within proximity of the qualified treatment center for at least 4 weeks following infusion

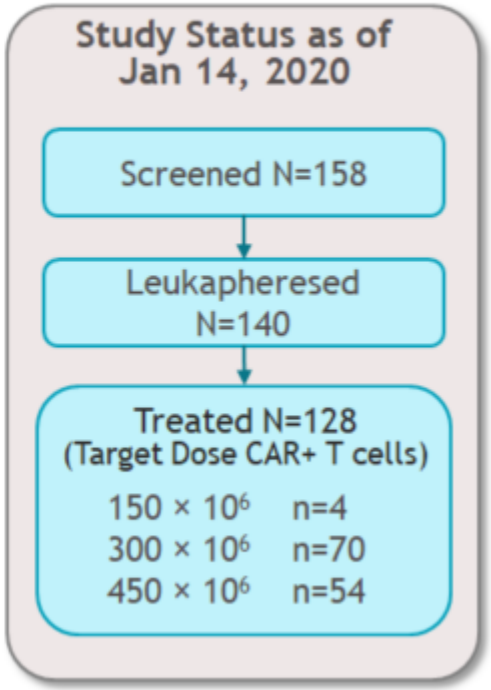


*Specific requirements regarding patient monitoring are pending FDA approval

Phase II Pivotal KarMMa Study

- RRMM
- Median age (61); Range (33-78)
- ≥3 prior regimens with ≥2 consecutive cycles each (or best response of PD)
- Previously exposed to:
  - IMiD agent
  - Proteasome inhibitor
  - Anti-CD38 antibody
- Refractory to last prior therapy per IMWG*





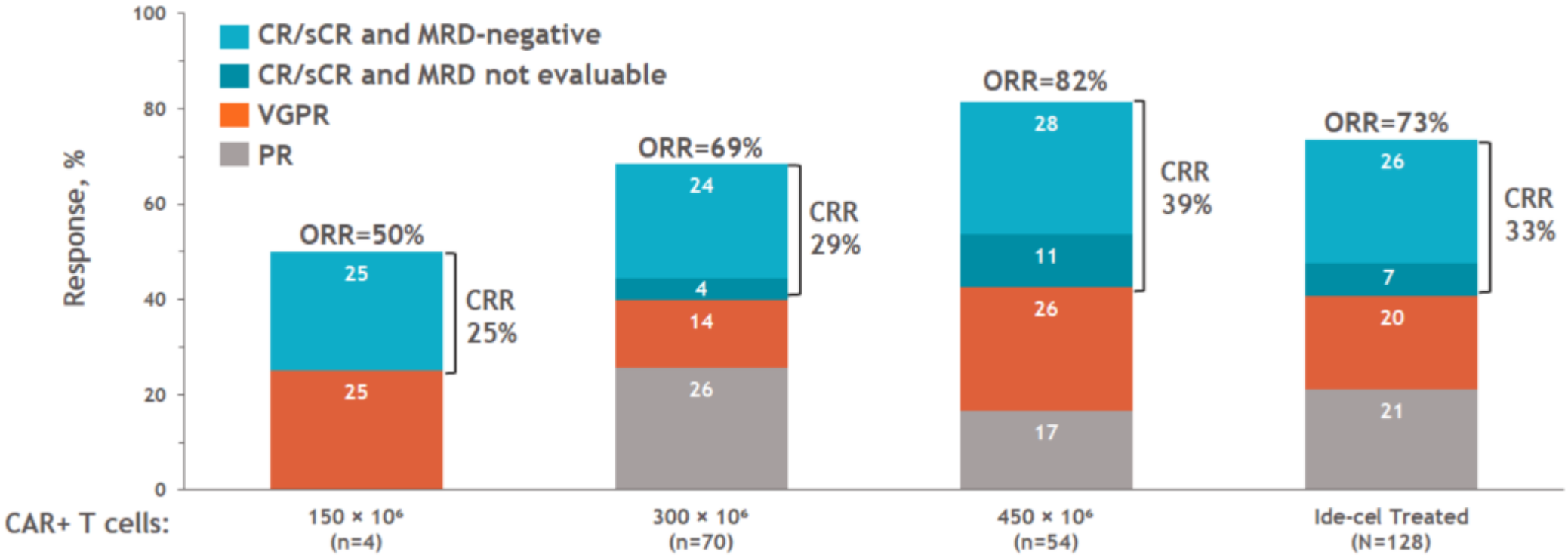
Endpoints

- **Primary**: ORR (null hypothesis ≤50%)
- **Secondary**: CRR (key secondary; null hypothesis ≤10%), Safety, DOR, PFS, OS, PK, MRD‡, QOL, HEOR
- **Exploratory**: Immunogenicity, BCMA expression/loss, cytokines, T cell immunophenotype, GEP in BM

EudraCT: 2017-002245-29
ClinicalTrials.gov: NCT03361748

CRR, complete response ratio; Cy, cyclophosphamide; DOR, duration of response; Flu, fludarabine; GEP in BM, gene expression profile in bone marrow; HEOR, health economics and outcomes research; IMiD, immunomodulatory imide drugs; IMWG, International Myeloma Working Group; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; QOL, quality of life.
*Defined as documented disease progression during or within 60 d from last dose of prior antimyeloma regimen. †Patients were required to be hospitalized for 14 d post-infusion. Ide-cel retreatment was allowed at disease progression for best response of at least stable disease. ‡By next-generation sequencing.

Best Overall Response



- *ORR of 73% (95% CI, 65.8–81.1; P<0.0001*)*
- *CRR (CR/sCR) of 33% (95% CI, 24.7–40.9; P<0.0001)*

- Clinically meaningful efficacy (ORR) observed across subgroups including patients over the age of 65
- Median time to first response of 1.0 mo (range, 0.5–8.8); median time to CR of 2.8 mo (range, 1.0–11.8)
- Median follow-up of 13.3 mo across target dose levels

Data cutoff: 14 Jan 2020. MRD-negative defined as $<10^{-5}$ nucleated cells by next generation sequencing. Only MRD values within 3 mo of achieving CR/sCR until progression/death (exclusive) were considered.
Values may not add up due to rounding.
CR/sCR, complete response/stringent CR; CRR, CR rate; MRD, minimal residual disease; ORR, overall response rate (≥PR); PR, partial response; VGPR, very good PR. **P* value at the primary data cutoff with same ORR and 95% CI.

Incidence and Management of CRS and Neurotoxicity

Target Dose, × 10^6 CAR+ T cells	150 (n=4)	300 (n=70)	450 (n=54)	Ide-cel Treated (N=128)
≥1 CRS event, n (%)	2 (50)	53 (76)	52 (96)	107 (84)
Max. grade (Lee Criteria)*				
1/2	2 (50)	49 (70)	49 (91)	100 (78)
3	0	2 (3)	3 (6)	5 (4)
4	0	1 (1)	0	1 (<1)
5	0	1 (1)	0	1 (<1)
Median onset, d (range)	7 (2–12)	2 (1–12)	1 (1–10)	1 (1–12)
Median duration, d (range)	5 (3–7)	4 (2–28)	7 (1–63)	5 (1–63)
Tocilizumab, n (%)	1 (25)	30 (43)	36 (67)	67 (52)
Corticosteroids, n (%)	0	7 (10)	12 (22)	19 (15)

- CRS frequency increased with dose, but mostly low grade
- ≤6% grade 3 or higher CRS events at all target doses, including one grade 5 event

Data cutoff: 14 Jan 2020. Siltuximab was used to manage CRS in 1 patient who was treated with 300 x 10^6 CAR+ T cells. Anakinra was used to manage CRS in 1 patient who was treated with 300 x 10^6 CAR+ T cells.
*CRS graded according to Lee criteria [Lee et al., *Blood* 2014;10;124(2):188-195].
CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable; NCI, National Cancer Institute.

Target Dose, × 10^6 CAR+ T cells	150 (n=4)	300 (n=70)	450 (n=54)	Ide-cel Treated (N=128)
≥1 NT event, n (%)	0	12 (17)	11 (20)	23 (18)
Max. grade (CTCAE)*				
1	0	7 (10)	5 (9)	12 (9)
2	0	4 (6)	3 (6)	7 (5)
3	0	1 (1)	3 (6)	4 (3)
Median onset, d (range)	NA	3 (1–10)	2 (1–5)	2 (1–10)
Median duration, d (range)	NA	3 (2–26)	5 (1–22)	3 (1–26)
Tocilizumab, n (%)	NA	0	3 (6)	3 (2)
Corticosteroids, n (%)	NA	2 (3)	8 (15)	10 (8)

- NT mostly low grade and was similar across target doses
- Incidence of grade 3 NT events was uncommon (≤6%) at all target doses; no grade 4 or 5 events
- NT managed with corticosteroids was infrequent (≤15%) at all target doses

Data cutoff: 14 Jan 2020. CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable; NCI, National Cancer Institute; NT, neurotoxicity (investigator-identified).
*Investigator-identified NT events were graded according to the NCI CTCAE v4.03.

Most Common Adverse Events

AE,* n (%)	Ide-cel Treated (N=128)	
	Any Grade	Grade ≥3
Hematologic		
Neutropenia	117 (91)	114 (89)
Anemia	89 (70)	77 (60)
Thrombocytopenia	81 (63)	67 (52)
Leukopenia	54 (42)	50 (39)
Lymphopenia	35 (27)	34 (27)
Gastrointestinal		
Diarrhea	45 (35)	2 (2)
Nausea	37 (29)	0
Other		
Hypokalemia	45 (35)	3 (2)
Fatigue	43 (34)	2 (2)
Hypophosphatemia	38 (30)	20 (16)
Hypocalcemia	34 (27)	10 (8)
Pyrexia	32 (25)	3 (2)
Hypomagnesemia	30 (23)	0
Decreased appetite	27 (21)	1 (<1)
Headache	27 (21)	1 (<1)
Hypogammaglobulinemia	27 (21)	1 (<1)
Cough	26 (20)	0
CRS†	107 (84)	7 (5)

- Cytopenias were common; not dose related
- Median time to recovery of grade ≥3 neutropenia and thrombocytopenia was 2 mo (95% CI, 1.9–2.1) and 3 mo (95% CI, 2.1–5.5), respectively
- Delayed recovery (>1 mo) of grade ≥3 neutropenia in 41% of patients and thrombocytopenia in 48%‡
- Infections (including bacterial, viral, fungal) were common (69%); not dose-related
- 5 deaths (4%) within 8 wk of ide-cel infusion
  - 2 following MM progression
  - 3 from AEs (CRS, aspergillus pneumonia, GI hemorrhage)
- 1 additional death from AE (CMV pneumonia) within 6 mo, in the absence of MM progression

Data cutoff: 14 Jan 2020. AE, adverse event; CMV, cytomegalovirus; CRS, cytokine release syndrome; GI, gastrointestinal.
*Events reported in 20% or more patients. †Clustered term including the preferred term; uniformly graded per Lee DW, et al. Includes 2 patient with grade 5 CRS event was observed. ‡Includes patients with grade 3/4 cytopenia at 1 mo post-infusion.

Conclusion

MM remains incurable, and most patients eventually relapse and require several lines of therapy. With each line of therapy, patients become increasingly resistant to treatment

Ide-cel is a BCMA directed CAR T cell therapy. CAR T cells expressing the anti-BCMA02 CAR construct can recognize MM cells and mount an immune response against them leading to cell death

Ide-cel has shown deep and durable responses in R/R MM patients with a predictable safety profile

There is currently no unique ICD-10-PCS code to describe the administration of ide-cel; BMS requests that unique ICD-10-PCS codes be created

Thank you

Bristol Myers Squibb™