Inmunoterapia &Hemopatías

Tercera edición

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Recinte Modernista de Sant Pau, Barcelona.

Resultados actualizados de la terapia CAR-T. Mieloma múltiple.

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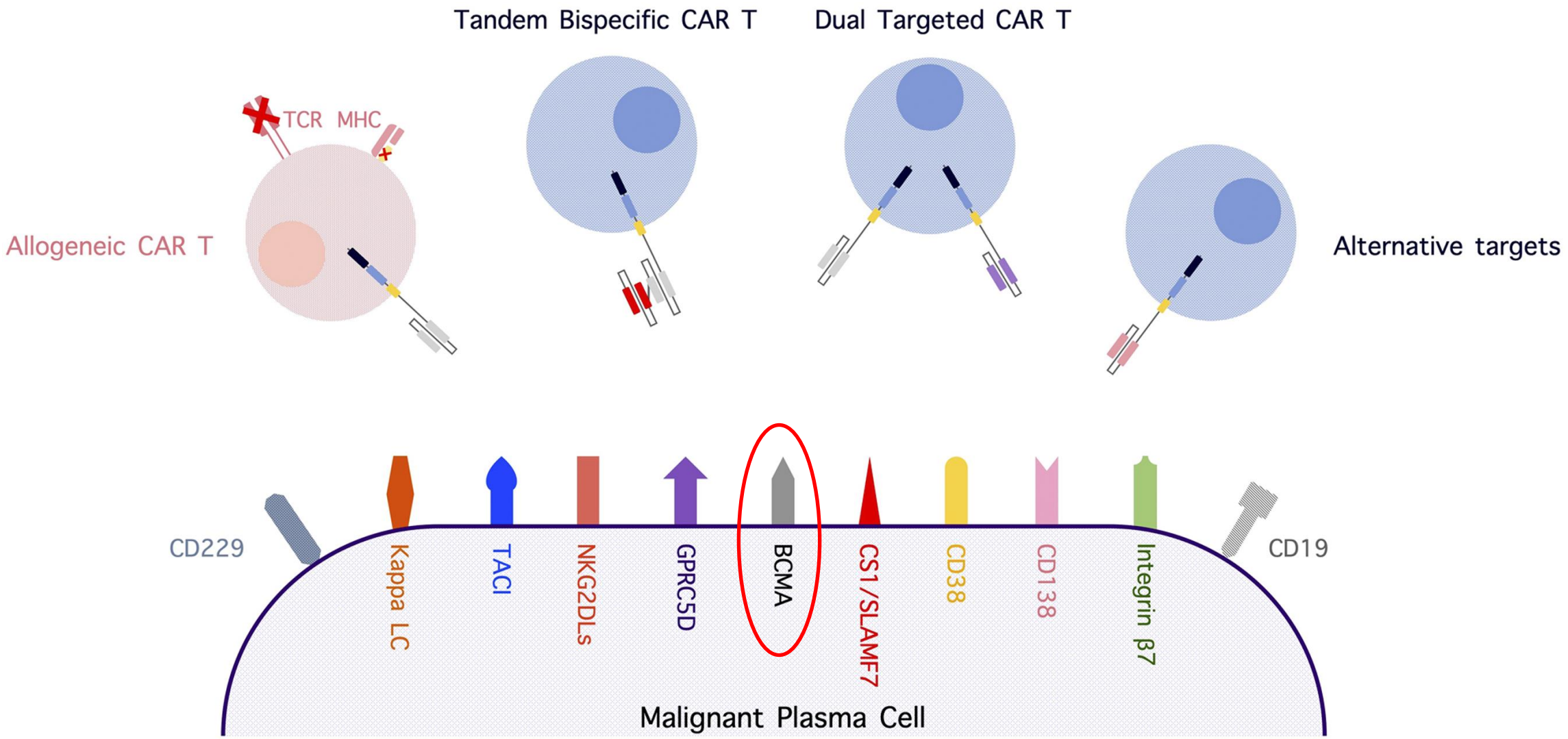
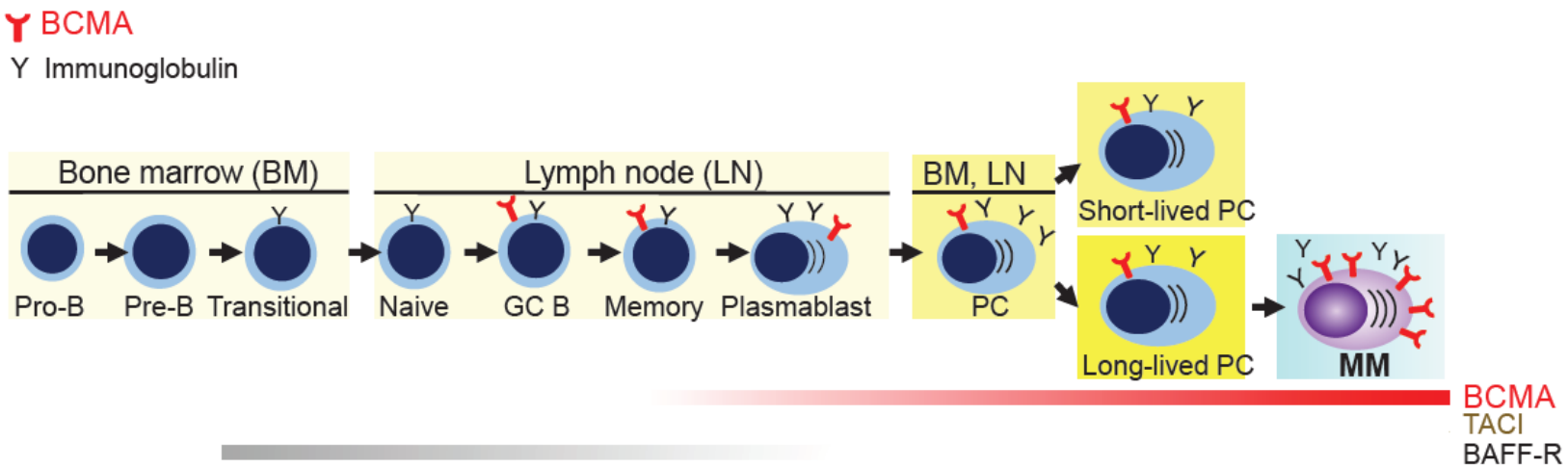
FLS SCIENCE FOSTERING LEARNING & SHARING

Future of CAR T cells in multiple myeloma



Kitsada Wudhikarn et al. Hematology Am Soc Hematol Educ Program, 2020.

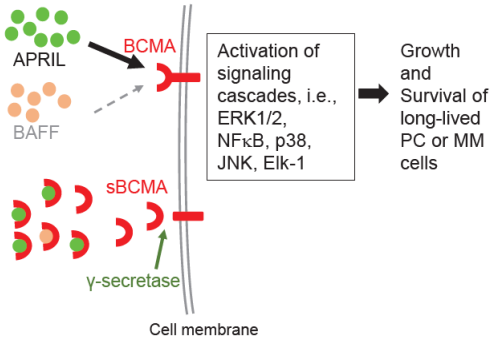
B-cell maturation antigen



BCMA is only induced in late memory B cells committed to the PC differentiation and is present on all PCs.

- **BCMA physiological functions**: Support survival of long-lived PCs, production of antibodies, class switch of immunoglobulin.
- **BCMA in MM:** Promote proliferation and survival, immunosuppressive BM microenvironment. Increased sBCMA level is associated with disease progression and poorer outcome.

APRIL and BAFF known ligands.



BCMA, BAFF-R and TACI regulate B cell proliferation, maturation, differentiation into PCs and survival.

γ-secretase can cleave BCMA. Soluble BCMA blocks APRIL and BAFF access to membrane receptors

Cho SF, et al. Front Immunol 2018;9:1821.

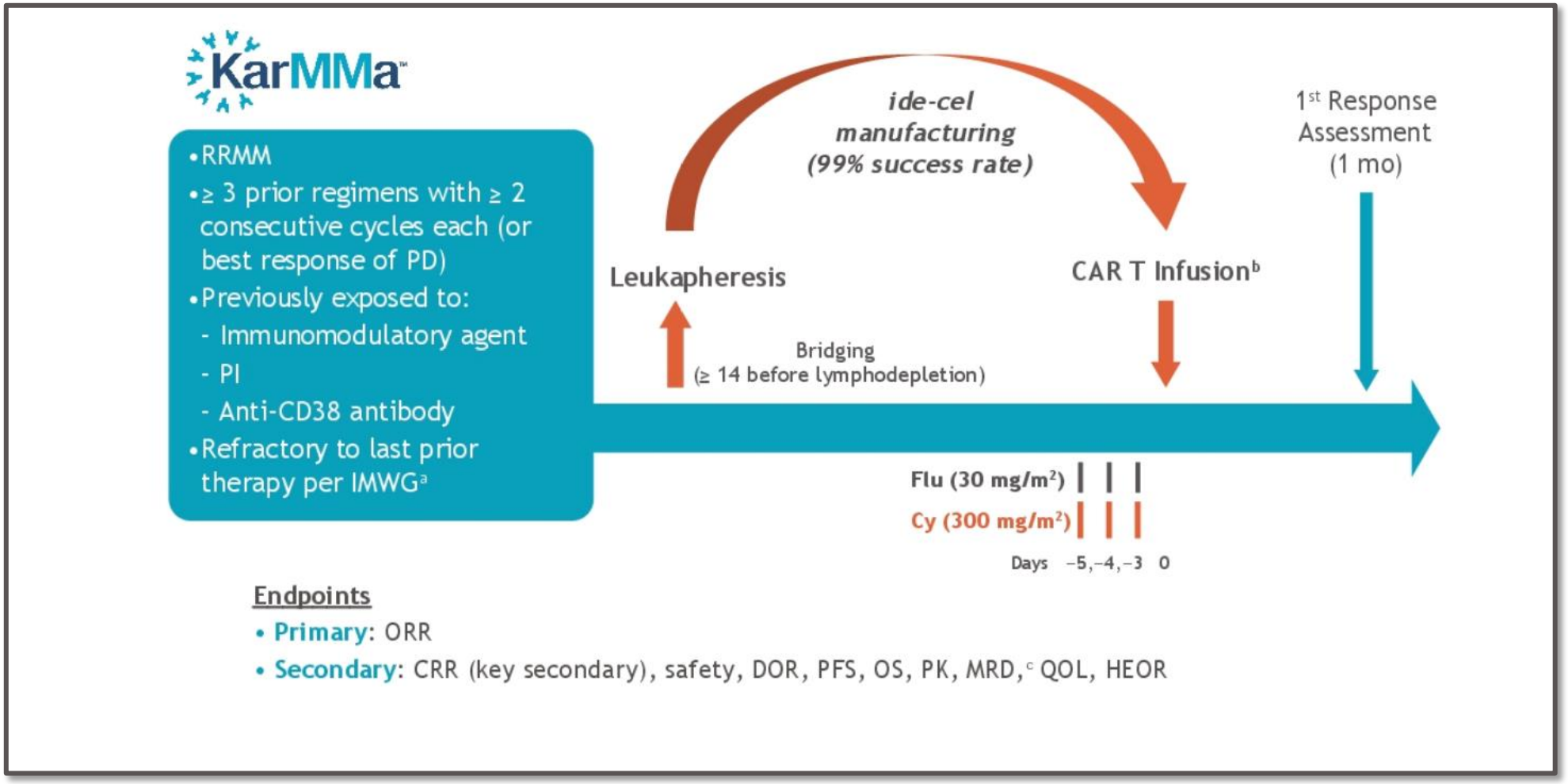
Gross, JA et al. Nature 2000;404:995-999.

Approved CAR-T cells against BCMA

- **Idecabtagene vicleucel (ide-cel).** **Ph II**
- **Ciltacabtagene autoleucel (cilta-cel).** **Ph I / Ph II**

Ide-cel. Phase 2 trial design

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



Munshi NC, et al. N Engl J Med. 2021 Feb 25;384(8):705-716.
Update Oriol A, et al. SEHH-SETH 2021. CO-068.

KarMMa trial. Baseline Characteristics of patients.

Characteristics	All ide-cel treated (N = 128)
Median age, years (range)	61 (33–78)
Male, %	59
ECOG PS (0/1/2), %	45/53/2
R-ISS Stage (I/II/III), %	11/70/16
High-risk cytogenetics, %	35
High tumor burden, %	51
Tumor BCMA expression (≥ 50%), %	85
Extramedullary disease, %	39
Median time since initial diagnosis, years (range)	6 (1–18)
Median number of prior anti myeloma regimens, n (range)	6 (3–16)
Prior ASCT (any/> 1), %	94/34
Any bridging therapies for MM, %	88
Refractory status, %	
Anti-CD38 mAb refractory	94
Triple refractory[e]	84
Penta refractory[f]	26

Heavily pre-treated highly refractory individuals

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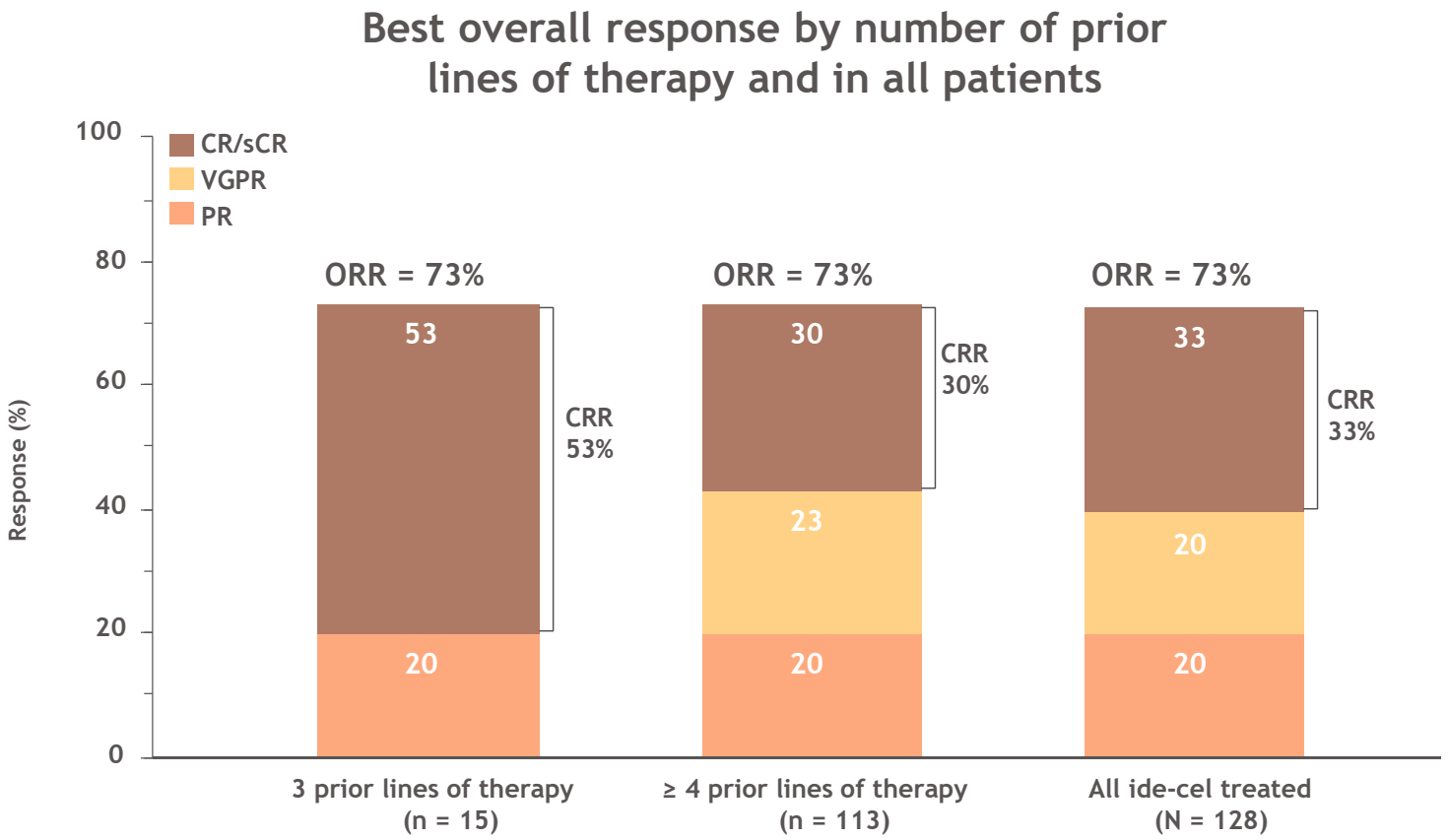
Update Oriol A, et al. SEHH-SETH 2021. CO-068.

Response by Number of Prior Lines

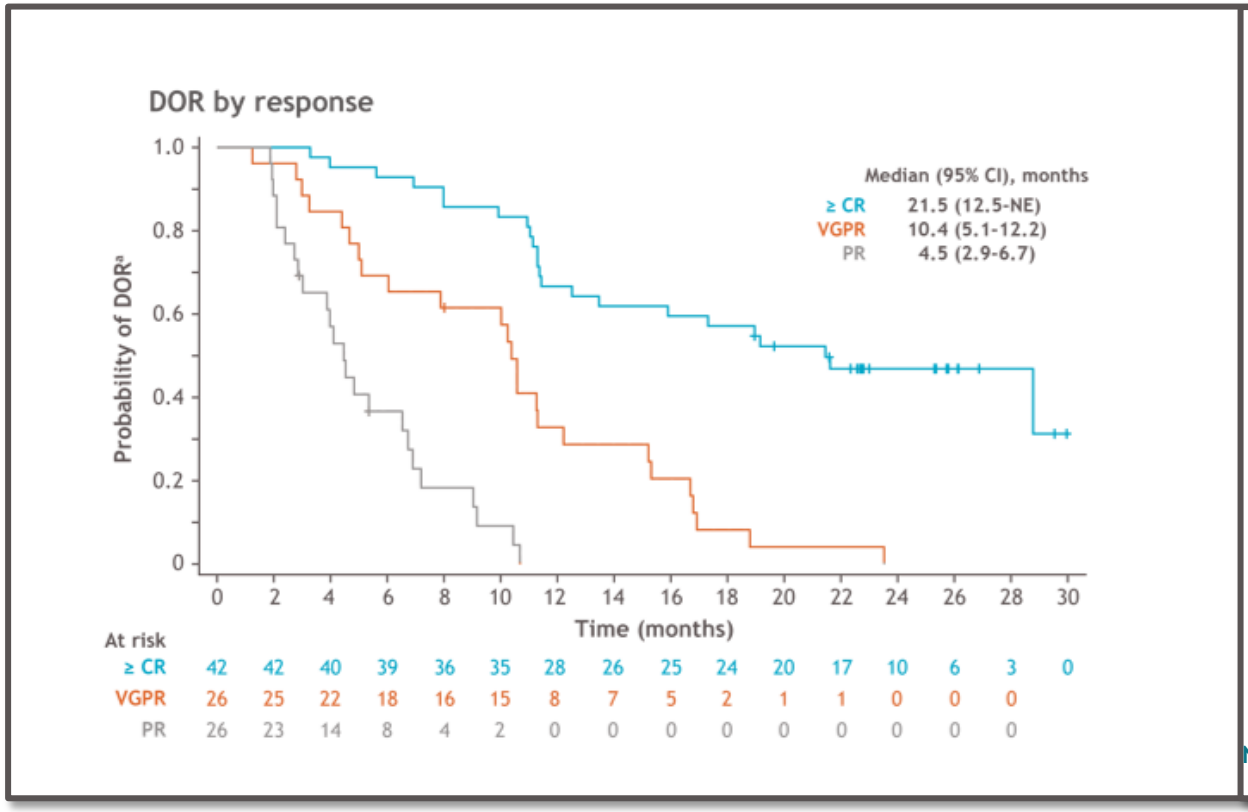
Data cut-off December 2020. Median follow-up 24.8 months (range, 1.7–33.6 months)

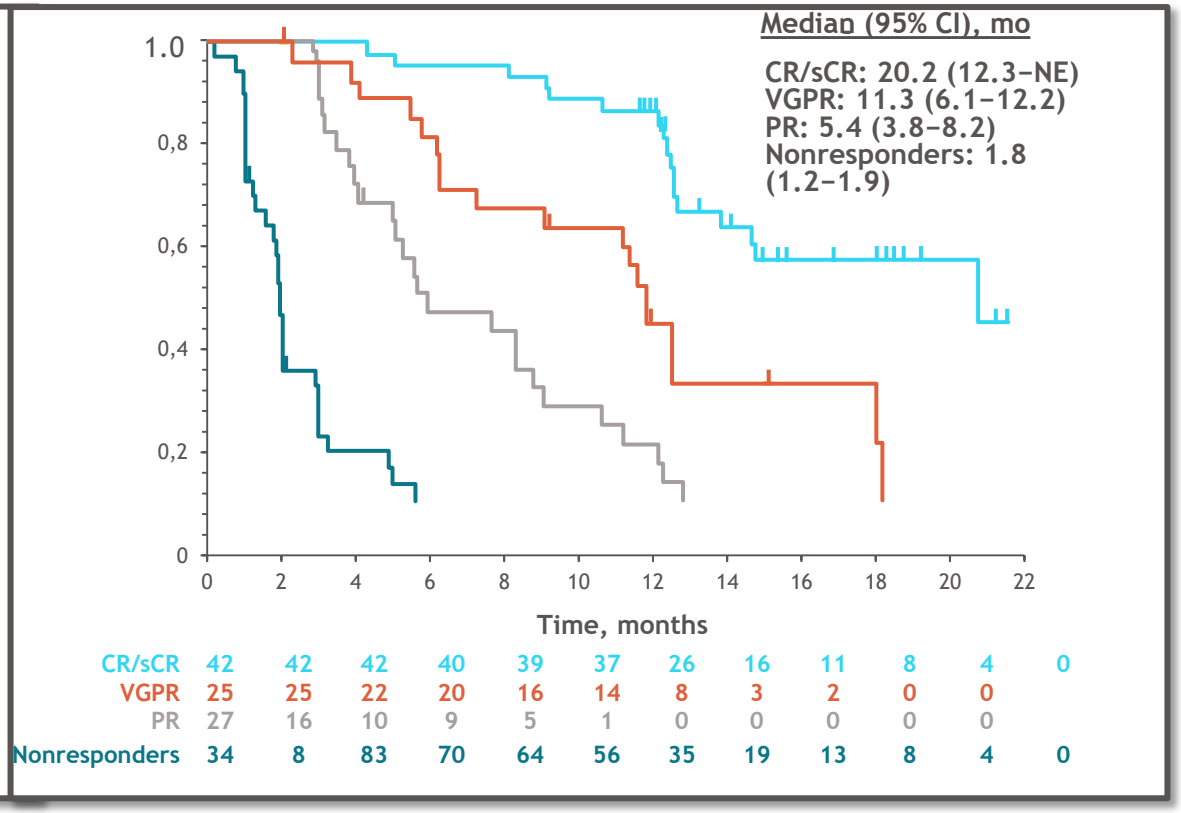


ORR was 73% and CRR 33% for the overall treated population

Munshi NC, et al. N Engl J Med. 2021 Feb 25;384(8):705-716.
Update Oriol A, et al. SEHH-SETH 2021. CO-068.

Best response and duration of response (DoR)





Median DoR 10.9 months among all ide-cel-treated patients, median DoR was 21.5 months in patients achieving CR/sCR

Median PFS 20.2 months for patients achieving CR

Data cut-off December 2020. Median follow-up 24.8 months (range, 1.7–33.6 months)

Munshi NC, et al. N Engl J Med. 2021 Feb 25;384(8):705-716.
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Dose – response relationship.

	Dose, × 10^6 CAR T+ cells				Total ide-cel treated (N = 128)
	150 (n = 4)	300 (n = 70)	450 (n = 54)	300-450 (n = 124)	
ORR, n (%)	2 (50)	48 (69)	44 (81)	92 (74)	94 (73)
CR/sCR, n (%)	1 (25)	20 (29)	21 (39)	41 (33)	42 (33)
Median DOR, months	-	9,9	11,3	10,9	10,9
Median DFS, months	-	5,8	12,2	8,8	8,6
Median OS, months	-	20,4	24,8	24,8	24,8

- Median follow-up 24,8 months (1,7–33,6).
- Median time to response 1 month (0,5–8,8); time to CR 2,8 months (1,0–15,8).

300 to 450 x10^6 recommended dose

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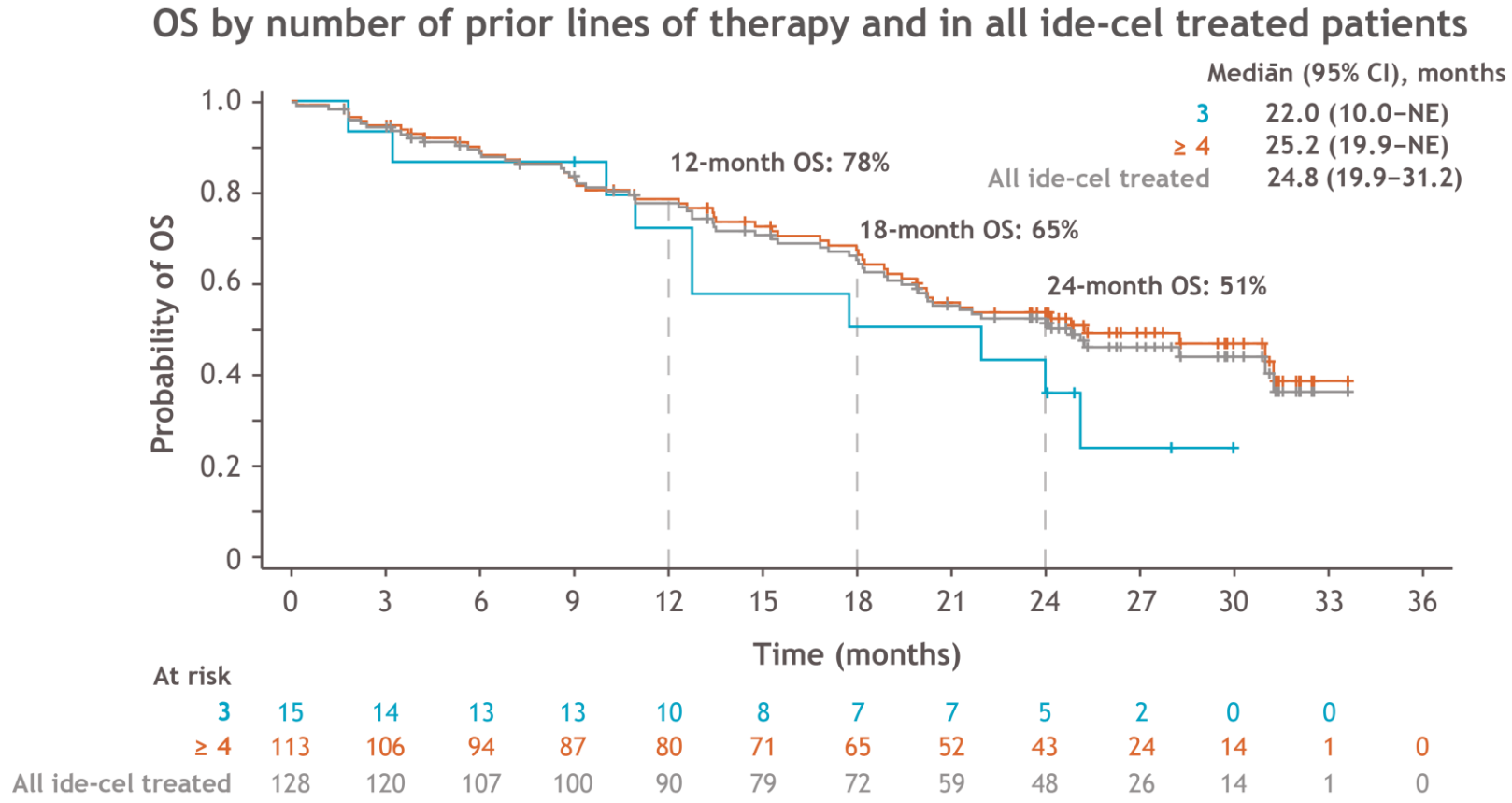
Munshi NC, et al. N Engl J Med. 2021 Feb 25;384(8):705-716.
Oriol A, et al. SEHH-SETH 2021. CO-068.

Overall survival



Median OS 24.8 months among all ide-cel-treated patients;

Median OS 22.0 months and 25.2 months in patients who received 3 and ≥ 4 prior lines of therapy, respectively.

Munshi NC, et al. N Engl J Med. 2021 Feb 25;384(8):705-716.
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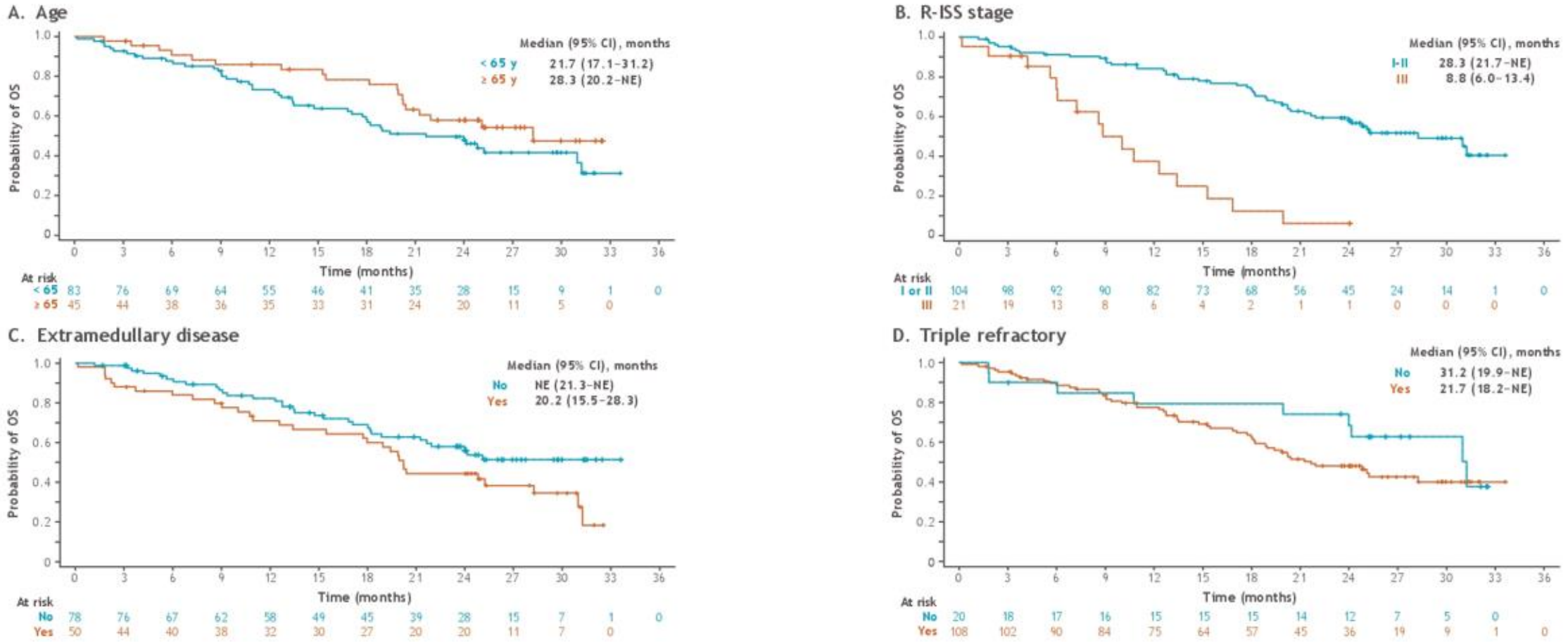
Overall survival in high risk populations

Figure 6. Overall survival in high-risk patient subgroups



Munshi NC, et al. N Engl J Med. 2021 Feb 25;384(8):705-716.
Update Oriol A, et al. SEHH-SETH 2021. CO-068.

Ide-cel safety profile

CRS and NT	All ide-cel treated (N = 128)
≥ 1 CRS event, n (%)	107 (84)
Maximum grade (Lee criteria), n (%)[a] 1/2 3 4 5	 100 (78) 5 (4) 1 (< 1) 1 (< 1)
Median onset, days (range)	1 (1–12)
Median duration, days (range)	5 (1–63)
≥1 NT event, n (%)	23 (18)
Maximum grade (CTCAE), n (%)[b] 1 2 3	 11 (9) 7 (5) 5 (4)
Median onset, days (range)	2 (1–10)
Median duration, days (range)	3 (1–26)

Neurotoxicity reported in 23 (18%) patients.
Most low grade, occurred early and with a short duration

AESI, n (%)	All ide-cel treated (N = 128)	
	Any grade	Grade 3-4
Hematologic		
Neutropenia	117 (91)	114 (89)
Anemia	90 (70)	78 (61)
Thrombocytopenia	82 (64)	67 (52)
Leukopenia	54 (42)	50 (39)
Lymphopenia	36 (28)	35 (27)
Non-hematologic		
Infections	90 (70)	34 (27)
SPM	9 (7)	3 (2)
HLH/MAS	4 (3)	2 (2)

Median time to recovery of grade ≥ 3 neutropenia and thrombocytopenia 2 months

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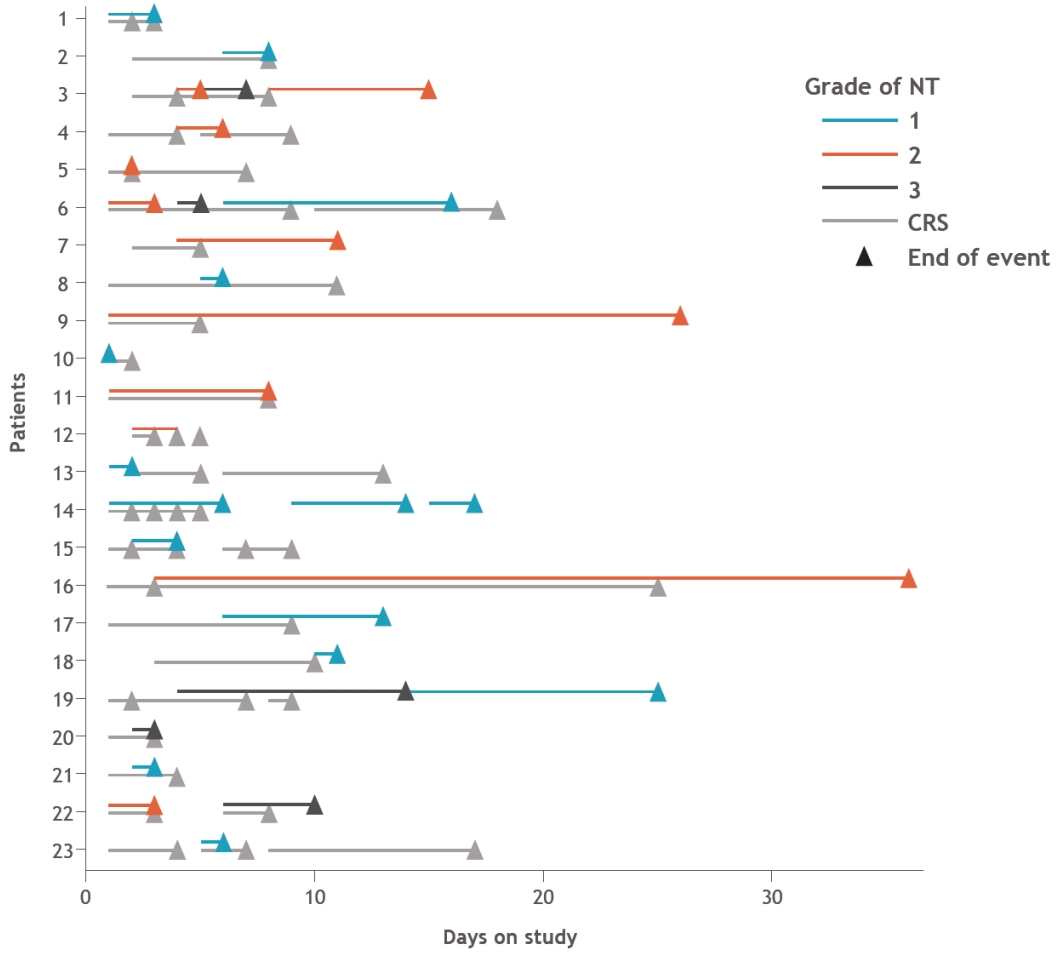
Update Oriol A, et al. SEHH-SETH 2021. CO-068.

Ide-cel related neurotoxicity

Association of onset and duration of CRS with grade of neurotoxicity



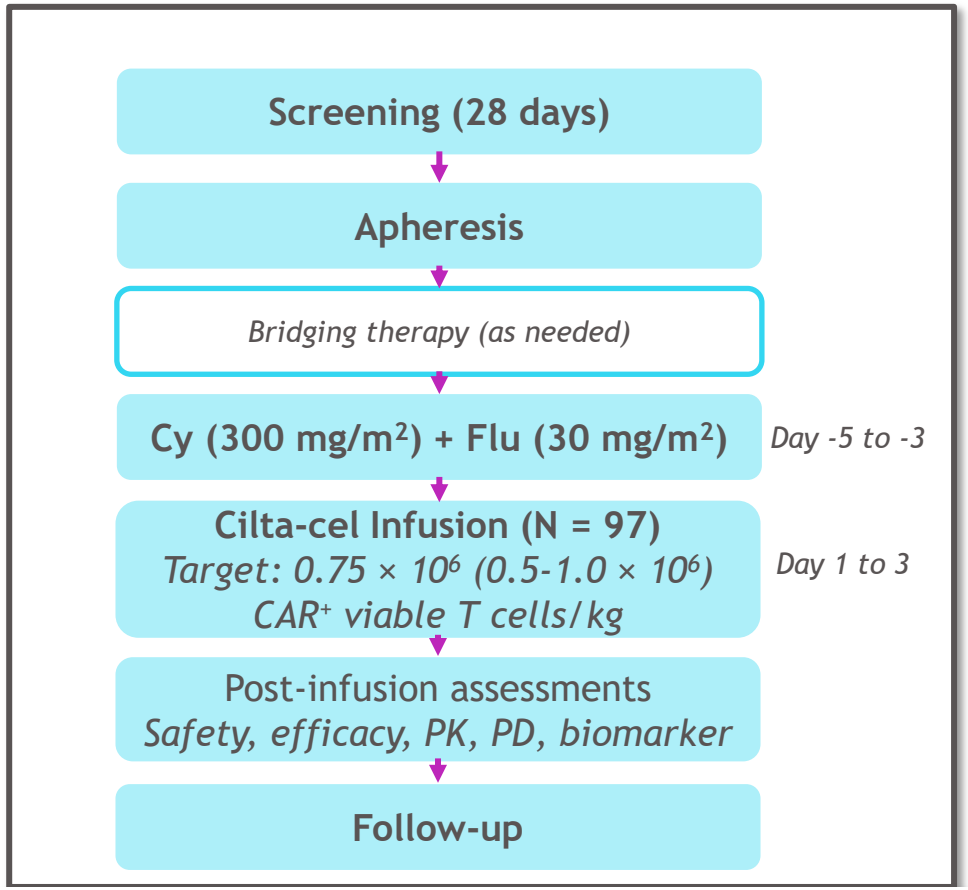
Neurotoxicity	Grade 1 (n = 11)	Grade 2 (n = 7)	Grade 3 (n = 5)
Median time to onset, days (range)	2 (1-10)	2 (1-4)	2 (1-4)
Median duration, days (range)	2.5 (1-9)	5.5 (1-26)	8.5 (2-22)
Events by duration, %			
1-5 days	75	43	50
6-10 days	25	29	0
> 10 days	0	14	50
Ongoing at FU-end	0	14	0
Tocilizumab, %	9	0	40
Steroids, %	18	57	80
Anakinra, %	0	0	20

Neurotoxicity or neurotoxicity treatment did not impact efficacy

Munshi NC, et al. N Engl J Med. 2021 Feb 25;384(8):705-716.
Update Oriol A, et al. SEHH-SETH 2021. CO-068.

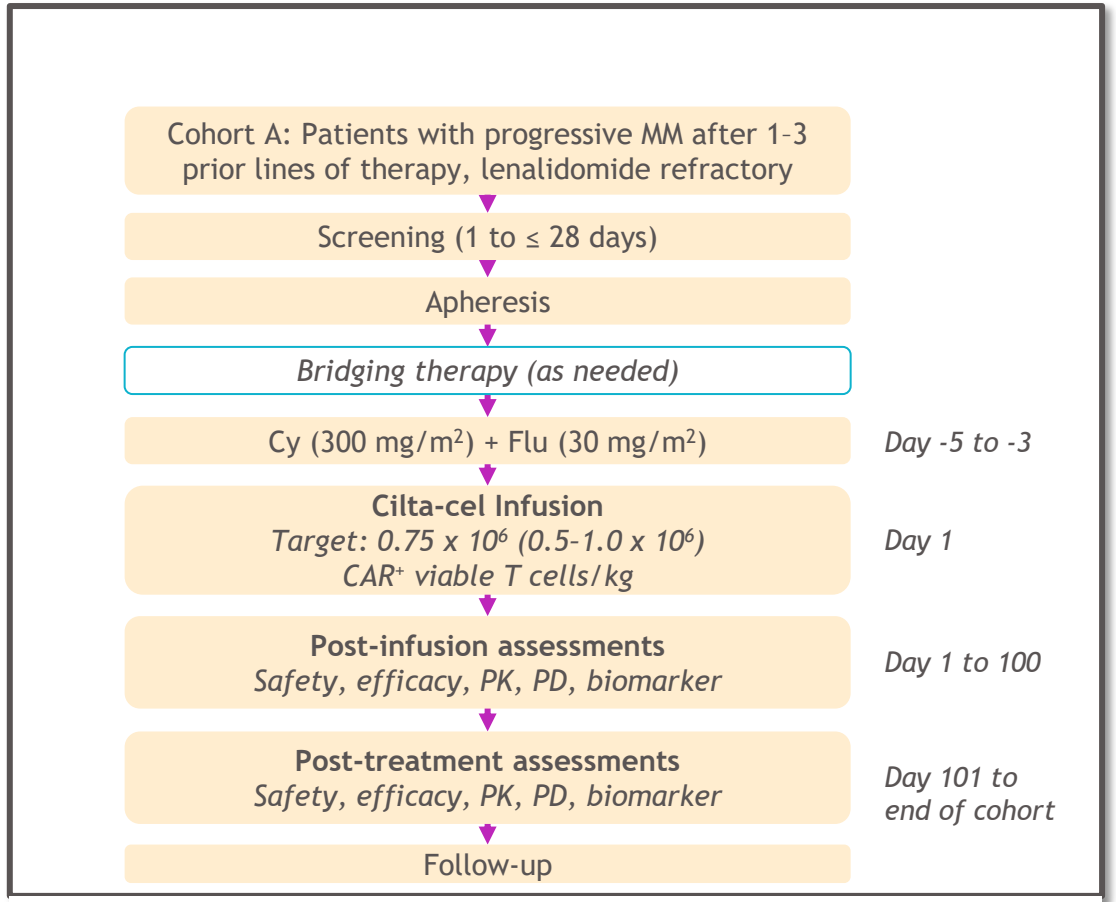
Ciltacabtagene autoleucel phase 1b/2 study design

CARTITUDE-1 Phase 1b/2 Study Design



Primary objectives:
Phase 1b: Cilta-cel safety and confirm recommended phase 2 dose
Phase 2: Evaluate cilta-cel efficacy

CARTITUDE-2 Phase 2 Study Design



Primary endpoint: MRD 10-5 negativity
Secondary endpoints: ORR, DoR, Time and duration of MRD negativity
Incidence and severity of AEs

Berdeja JG, et al. Lancet 2021;398(10297):314-324.
Usmani S, et al. ASCO 2021

CARTITUDE-1 Baseline Characteristics

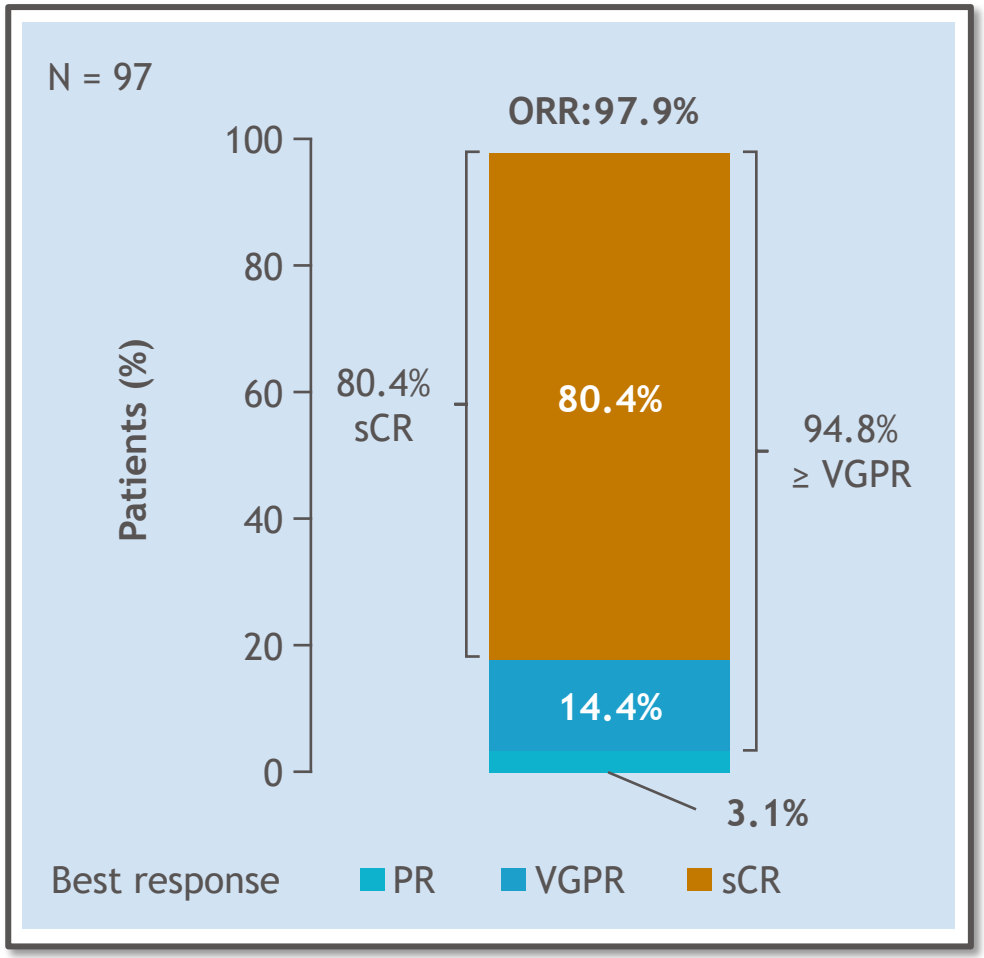
Characteristic	N = 97
Age, median (range) years	61.0 (43-78)
Male, n (%)	57 (58.8)
Black/African American, n (%)	17 (17.5)
All plasmacytomas,[a] n (%)	19 (19.6)
Extramedullary plasmacytomas, n (%)	13 (13.4)
Bone-based plasmacytomas, n (%)	6 (6.2)
Bone marrow plasma cells > 60%, n (%)	21 (21.9)
Years since diagnosis, median (range)	5.9 (1.6-18.2)
High-risk cytogenetic profile, n (%)	23 (23.7)
del17p	19 (19.6)
t(14;16)	2 (2.1)
t(4;14)	3 (3.1)
Tumor BCMA expression > 50%, n (%)	57 (91.9)

Characteristic	
Prior lines of therapy, median (range)	6.0 (3-18)
Prior lines of therapy, n (%)	
3	17 (17.5)
4	16 (16.5)
> 5	64 (66.0)
Previous stem cell transplantation, n (%)	
Autologous	87 (89.7)
Allogeneic	8 (8.2)
Triple-class exposed,[c] n (%)	97 (100)
Penta-drug exposed,[d] n (%)	81 (83.5)
Triple-class refractory[c]	85 (87.6)
Penta-drug refractory[d]	41 (42.3)
Refractory status, n (%)	
Carfilzomib	63 (64.9)
Pomalidomide	81 (83.5)
Anti-CD38 antibody	96 (99.0)
Refractory to last line of therapy, n (%)	96 (99.0)

Median administered dose: 0.71 x 10^6 (0.51–0.95 x 10^6) CAR^+ viable T cells/kg

Berdeja JG, et al. Lancet 2021;398(10297):314-324.
Usmani S, et al. ASCO 2021

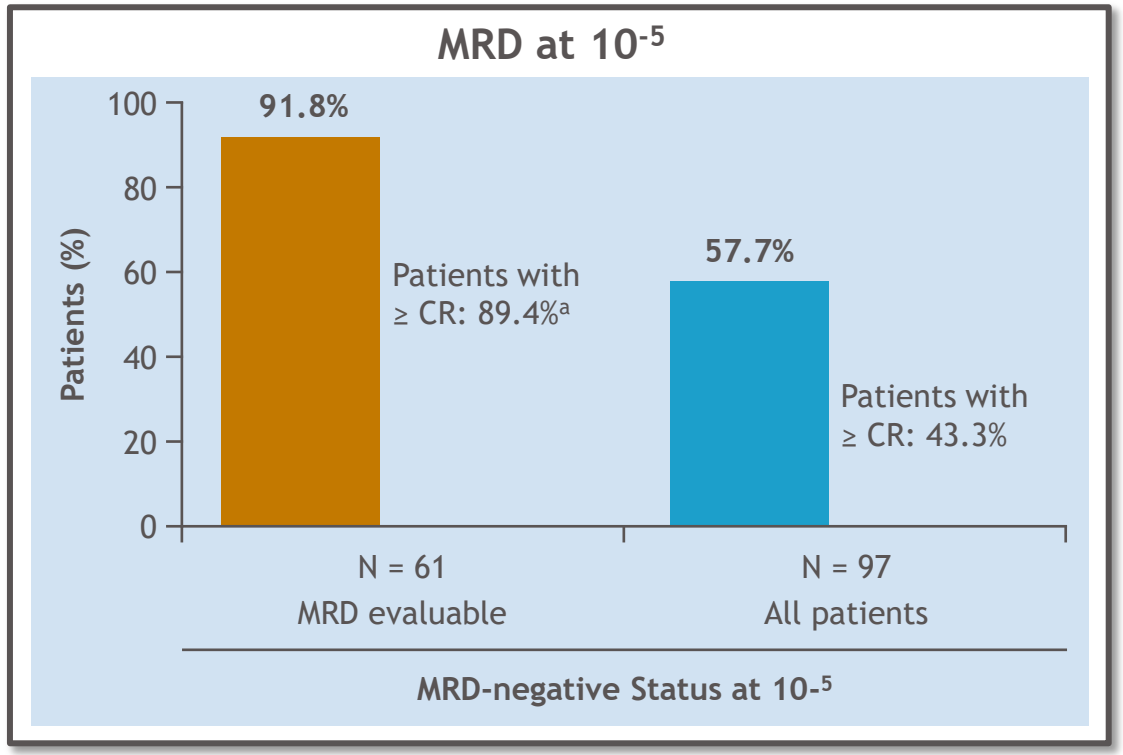
CARTITUDE-1: Overall response rate



ORR 97.9% with 80.4% achieving sCR;
response rates comparable across subgroups

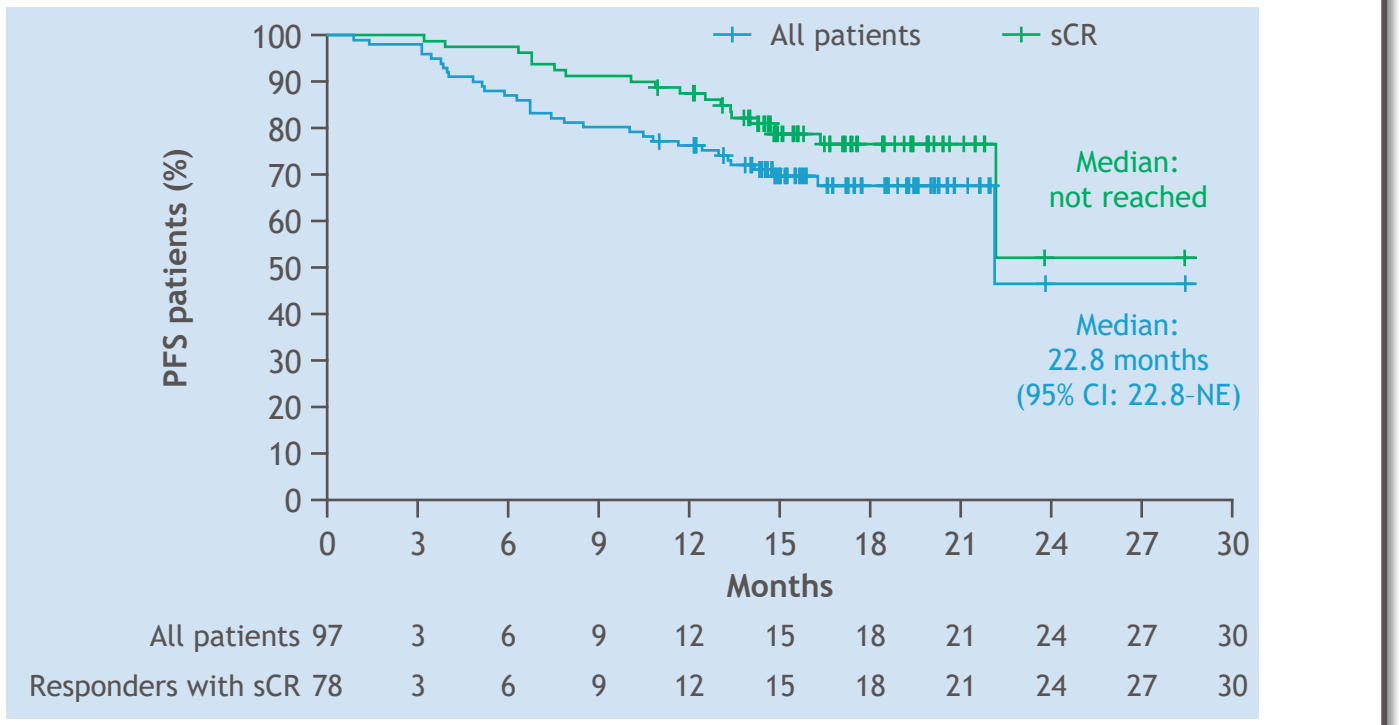
Median time to first response 1 month (range: 0.9–10.7)

Median time to best response 2.6 months (range: 0.9–15.2)



Berdeja JG, et al. Lancet 2021;398(10297):314-324.
Usmani S, et al. ASCO 2021

CARTITUDE-1 Progression-free survival



18-month PFS
All patients: 66 % (95% CI: 54.9–75.0)
sCR: 76 % (95% CI: 63.6–84.5)

18-month OS
All patients: 81 % (95% CI: 71.4–87.6)

Short follow-up

Best outcome for patients achieving a CR

Berdeja JG, et al. Lancet 2021;398(10297):314-324.
Usmani S, et al. ASCO 2021

CARTITUDE-1 Safety profile

AEs	N = 97 Any grade	Grade 3/4
Hematologic AEs > 25%, n (%)		
Neutropenia	93 (95.9)	92 (94.8)
Anemia	79 (81.4)	66 (68.0)
Thrombocytopenia	77 (79.4)	58 (59.8)
Leukopenia	60 (61.9)	59 (60.8)
Lymphopenia	51 (52.6)	48 (49.5)
Non-hematologic AEs > 25%, n (%)		
Metabolism and nutrition disorders		
Hypocalcemia	31 (32.0)	3 (3.1)
Hypophosphatemia	30 (30.9)	7 (7.2)
Decreased appetite	28 (28.9)	1 (1.0)
Hypoalbuminemia	27 (27.8)	1 (1.0)
Gastrointestinal		
Diarrhea	29 (29.9)	1 (1.0)
Nausea	27 (27.8)	1 (1.0)
Other		
Fatigue	36 (37.1)	5 (5.2)
Cough	34 (35.1)	0
AST increased	28 (28.9)	5 (5.2)
ALT increased	24 (24.7)	3 (3.1)

CRS	N = 97
Patients with a CRS event, n (%)	92 (94.8)
Time to onset, median (range) days	7 (1-12)
Duration, median (range) days	4 (1-97)

Later CRS appearance

Neurotoxicity	N = 97
Total CAR T cell neurotoxicities, n (%)	
Any grade	20 (20.6)
Grade > 3	10 (10.3)
ICANS, n (%)	
Any grade	16 (16.5)
Grade > 3	2 (2.1)
Late neurotoxicity, n (%)	
Any grade	12 (12.4)
Grade > 3	9 (9.3)

Successful strategies implemented to prevent and reduce the incidence of neurotoxicity

Berdeja JG, et al. Lancet 2021;398(10297):314-324.
Usmani S, et al. ASCO 2021

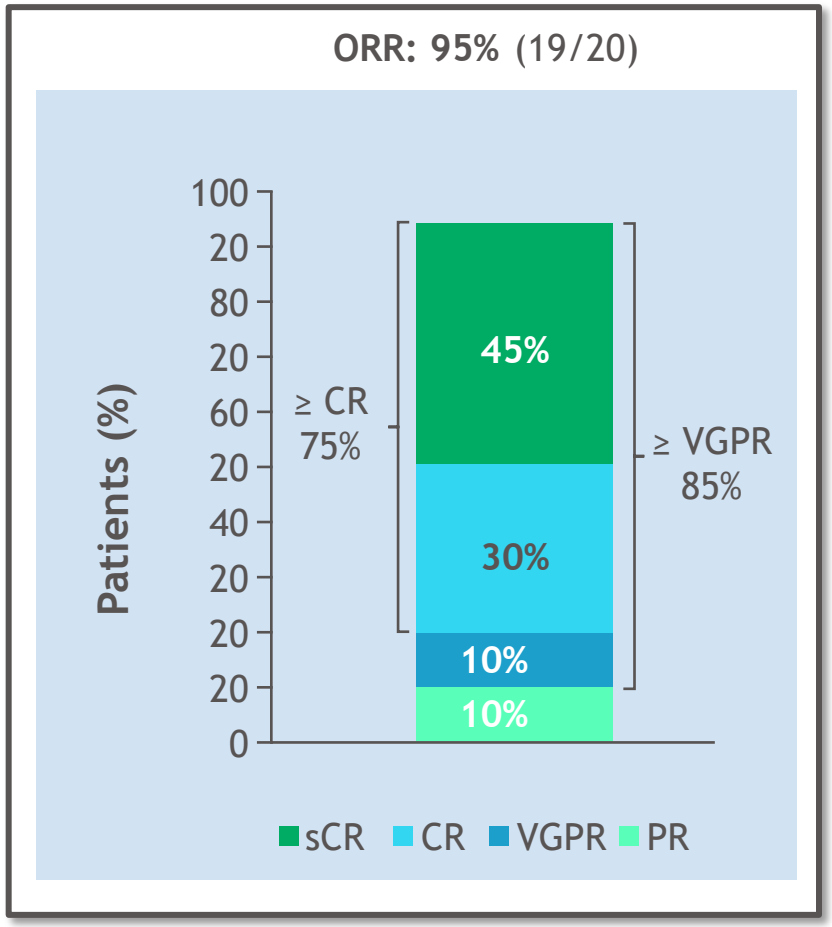
CARTITUDE-2: Baseline characteristics of patients

Characteristics	N = 20
Years since diagnosis, median (range)	3.5 (0.7-8.0)
Prior lines of therapy, median (range)	2 (1-3)
Previous autologous stem cell transplantation, n (%)	17 (85)
Triple-class exposed, n (%)	13 (65)
Triple-class refractory, n (%)	8 (40)
Penta-drug exposed, n (%)	4 (20)
Penta-drug refractory, n (%)	1 (5)
Refractory status, n (%)	
Bortezomib	8 (40)
Carfilzomib	2 (10)
Pomalidomide	7 (35)
Daratumumab	12 (60)
Refractory to last line of therapy, n (%)	19 (95)

Jan/21 data cut-off, median follow-up 5.8 months.

All patients exposed to PI, IMiD, and dex, 95% to alkylating agents, 65% to daratumumab

CARTITUDE-2: Response rates



Median time to first response	1 month
Median time to best response	1.9 months

ORR 95%, 75% achieving ≥ CR and 45% sCR

Patients (n = 4) MRD-evaluable at 10^{-5} threshold were MRD negative

Agha M, et al. ASCO. 2021; Oral Presentation 8013.

CARTITUDE-2: Safety profile

Neurologic toxicity in cilta-cel-treated patients

Neurotoxicity	N = 20	
	Grade 1/2	Grade 3/4
ICANs, n (%)	3 (15)	0
Other neurotoxicities, n (%)	1 (5)	0

Management strategies: effective bridging therapy.

ICANs

- Median time to onset of symptoms 8 days (range: 7–11).
- Median duration was 2 days (range: 1–2)
- Supportive measures (steroids) effective. Resolved 3/3

Late onset neurotoxicity

- Grade 2 isolated facial paralysis on Day 29 (N=1)
- Treated with dex for 29 days , recovered after 51 days.
- No movement or neurocognitive TEAEs observed.

Agha M, et al. ASCO. 2021; Oral Presentation 8013; 2. Einsele H, et al. ASCO. 2021; Oral Presentation 8028.

Conclusions

Two CAR-T products approved / on approval process to treat relapsed/refractory multiple mieloma.

- **Efficacy**
  - High response rate, mostly, deep responses, apparently durable in a relevant proportion of patients.
  - Similar efficacy in patients with high-risk features. No impact of previous refractory status.
- **Manageable toxicity**
  - Predictable CRS and neurotoxicity.
  - Hematological toxicity.
  - Concern about long term immunosuppression.
- **Applicability**
  - Need to manage bridging therapy
  - Apparently aplicable to elderly and frail patients.

- **Next steps**
  - Earlier use: high-risk patients from first line, early relapse after firs line therapy
  - As consolidation or maintenance strategy.
  - In combination with other therapies.

Thank you for your attention

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