ACC MED

SEZIONE DI EMATOLOGIA

CONVEGNO

GRANDANGOLO 2020 IN EMATOLOGIA

SELEZIONE E ANALISI RAGIONATA DEI PIÙ RECENTI DATI SCIENTIFICI

XI EDIZIONE

DIGITAL EVENT, 4-5-16-17 NOVEMBRE 2020

Highlights 2020 su CAR-T

Alice Di Rocco, Roma

Agenda

- Lymphoma :
  - Real world experience and predictive factors
  - Results from clinical trials
- New targets … beyond CD19
  - Leukemia/Lymphoma
  - Myeloma
- Future Challenges

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- **Lymphoma :**
  - **Real world experience and predictive factors**
  - Results from clinical trials
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  - Leukemia/Lymphoma
  - Myeloma
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Multicenter CD19 CAR-T cells trials in aggressive NHL

Study	ZUMA1 Axi-cel	JULIET Tisa-cel	TRANSCEND Liso-cel
Reference	**Locke et al. Lancet Oncol 2019**	**Schuster et al. NEJM 2019**	Abramson et al. Lancet 2020
CAR – T design	CD19/CD3ζ/CD28	CD19/CD3ζ/4-1BB	CD19/CD3ζ/4-1BB
Lymphoma subtypes	DLBCL / PMBCL / TFL	DLBCL / TFL	DLBCL / TFL / FL / Gr 3B
Treated / Enrolled	108/119 (91%)	111/165(67%)	268/342 (78%)
Bridging therapy	None	Allowed	Allowed
Best ORR rate	84%	52%	73%
Best CR rate	59%	40%	53%
F/U mo	27.1	14	18.8
PFS	2yr-PFS 72%	1yr-PFS 83%	1yr-PFS 44%
OS	2yr-PFS 50.5%	1yr-OS 49%	1yr-OS 58%
FDA/EMA	Approved	Approved	Waiting fo FDA approval (dec 2020?)

«Real world» experiences are consistent with pivotal trials

	France –Lyon Sesques P et al EHA2020	Germany _Munich Bucklein et al. EHA 2020	UK Kuhln et al. EHA 2020			US CIBMTR Jaglowski S et al ASH2019	US CAR T CELL CONSORTIUM Riedell R et al. TCT Meeting 2020	
	Overall (%)	Overall (%)	Overall (%)	Axi-cel (%)	Tisa-cel (%)	Tisa-cel (%)	Axi-cel (%)	Tisa-cel (%)
Patients infused, n	54	29	183	133	50	116	158	86
Age at infusion (median) range, yeras	59 (27-75)	60 (19-74)	58 (18-75)	56 (18-75)	61 (30-72)	65.11 (18.5-88.9)	59 (18-85)	67 (29-88)
Eastern Cooperative Oncology Group performance status								
0/1		59%	52%	51%	54%	81.4%	90%	95%
≥2	26%	41%	13%	14%	12%	4.3%		
Number of prior lines of antineoplastic therapy≥3	38%		39%	40%	42%	67.1%	73%	86%
Stem Cell Transplant								
Prior ASCT	28%	34%	14%	15%	10%	22.9%	26%	26%
Prior HCT	2%	10%	3%	3%	2%	5.7%	3%	0%

«Real world» experiences are consistent with pivotal trials

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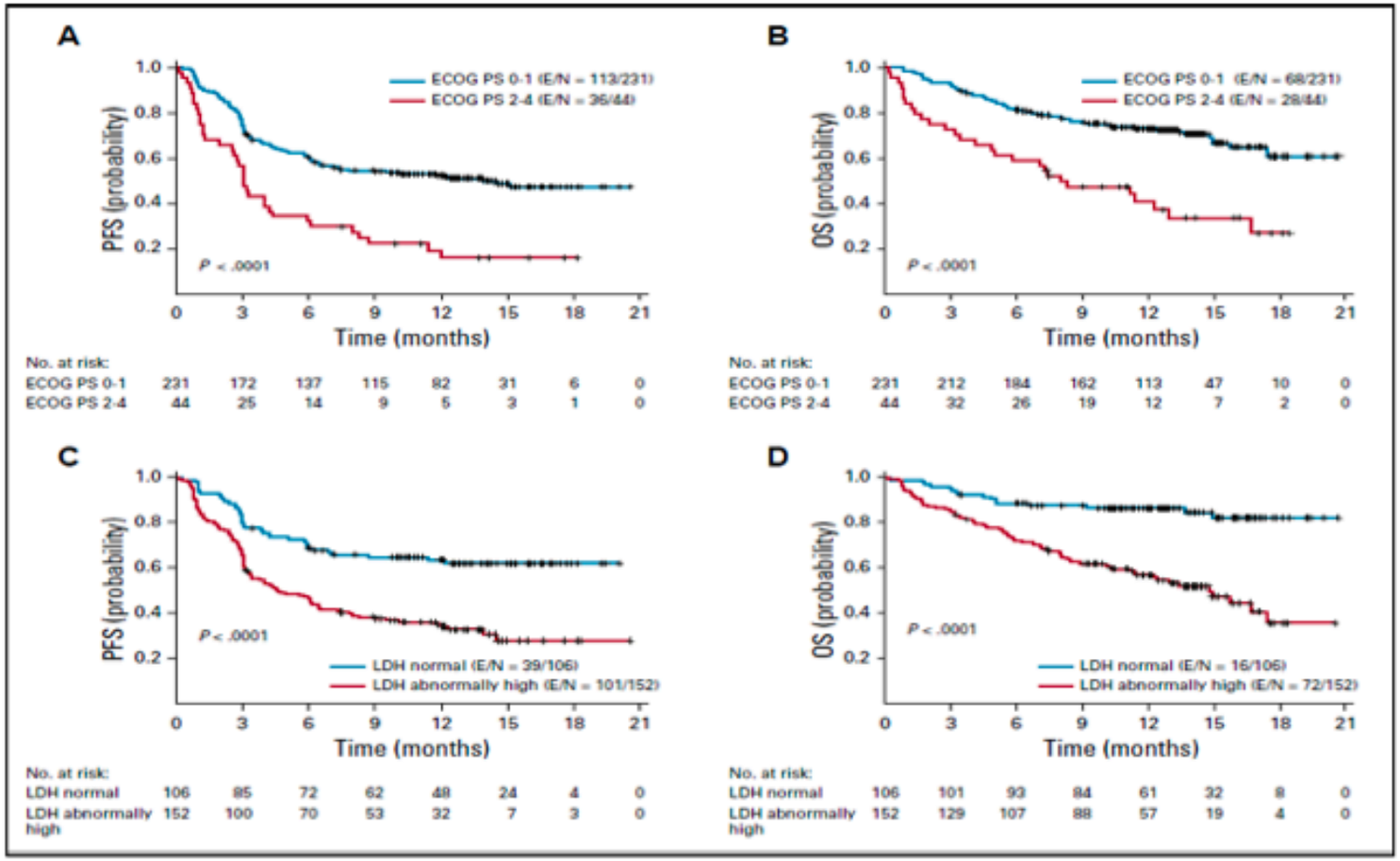
	Overall (%)	Overall (%)	Overall (%)	Axi-cel (%)	Tisa-cel (%)	Tisa-cel (%)	Axi-cel (%)	Tisa-cel (%)
Bridging Therapy	96%	79%	84.8%			//	61%	75%
EFFICACY								
ORR	35% (mo 3)	45% (mo 3)		45% (mo 3)	32% (mo 3)	58%	64% (mo 3)	51 % (mo 3)
CR	**32% (mo 3)**	**36% (mo 3)**		**30% (mo 3)**	**25% (mo 3)**	**38%**	**53% (mo 3)**	**42% (mo 3)**
SAFETY								
CRS ≥ 3	9%	10%		9%	6%	1%	8%	1%
ICANS ≥grade 3	11%	20%		19%	4%	5%	33%	0%
Tocilizumab	70%			73%	36%	20%	61%	15%
Steroid	37%			41%	22%	14%	53%	8%

Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium

CAR T-CELL Consortium

Effect	P	OR Estimate	Wald 95% CI
Grade ≥ 3 CRS			
ECOG PS 2-4	.001	5.3	2.0 to 14.3
Total bilirubin > 1.5 g/dL	.047	7.6	1.03 to 56.8
Grade ≥ 3 neurotoxicity			
Male	.09	1.6	0.9 to 2.8
Bulky disease ≥ 10 cm	.01	2.2	1.2 to 4.1
LVEF < 50%	.04	4.5	1.05 to 19.3
Platelets < 75,000/μL	.07	2.2	0.9 to 5.4
Best response of CR by 12 months			
Age > 60	.004	2.3	1.3 to 3.9
ECOG PS 0-1 *v* 2-4	.07	2.0	0.9 to 4.1
< 3 lines of therapy	.13	1.7	0.9 to 3.2
Prior ASCT	.07	1.8	0.96 to 3.3
LDH < ULN before conditioning	.007	2.2	1.2 to 4.0

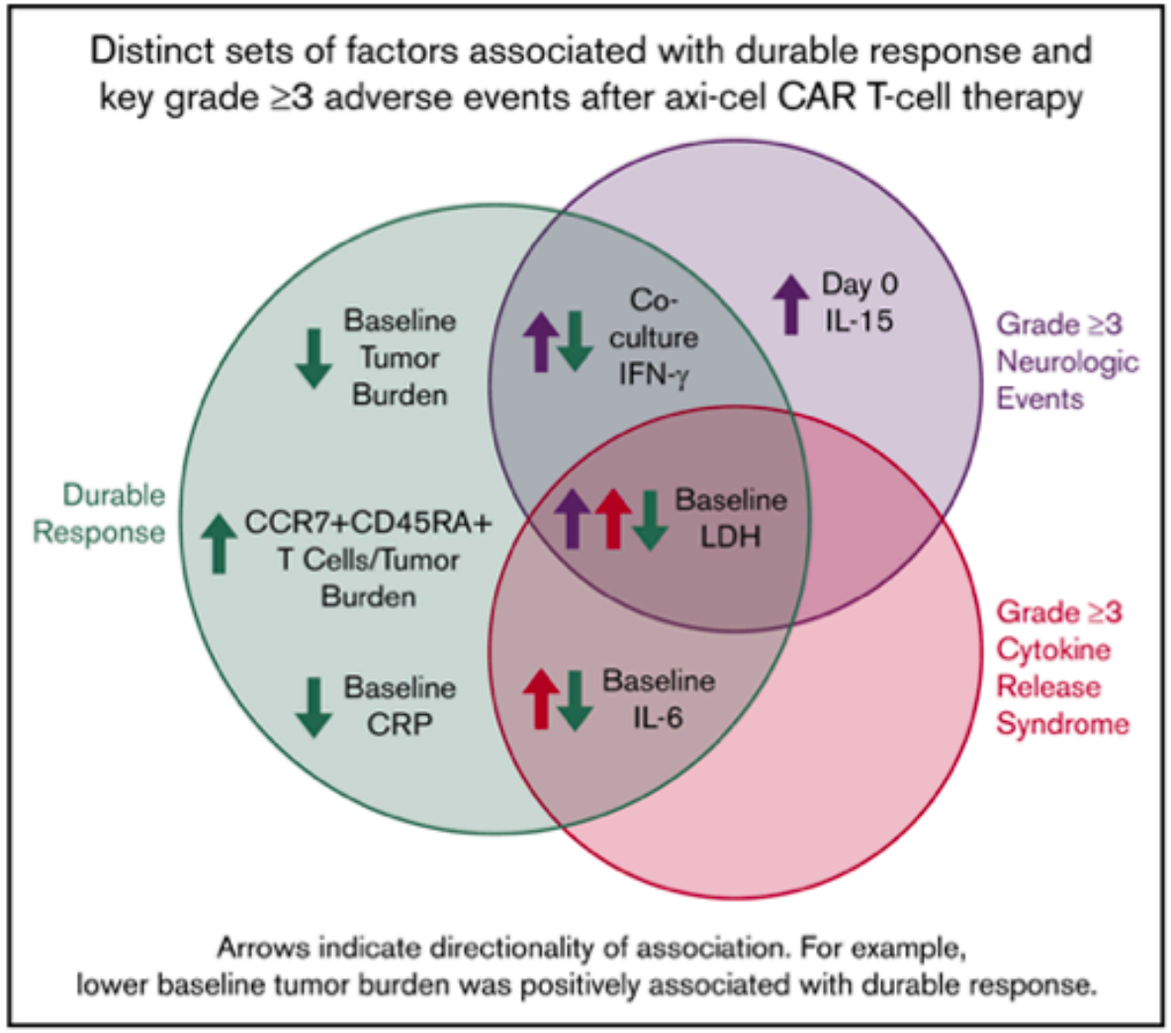


Nastoupil L et al, JCO 2020

blood advances

Tumor burden, inflammation, and product attributes determine outcomes of axicabtagene ciloleucel in large B-cell lymphoma

LOCKE et al 13 OCTOBER 2020 · VOLUME 4, NUMBER 19



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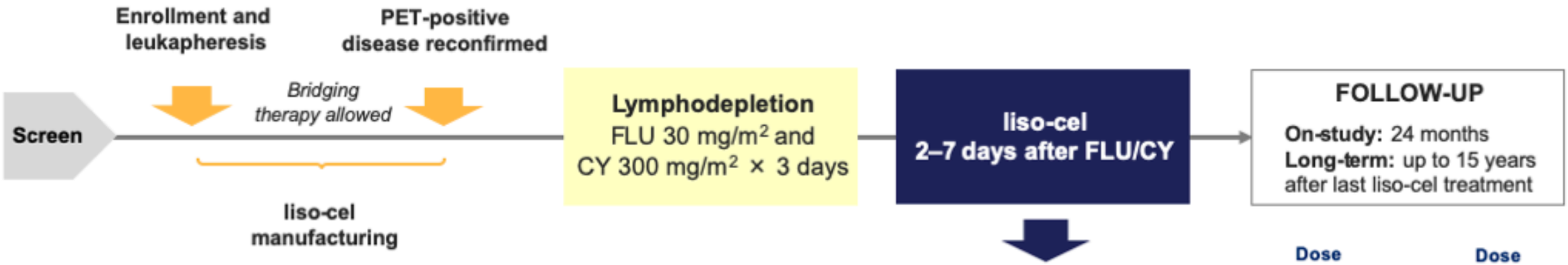
  - Real world experience
  - **Results from clinical trials**
- New targets … beyond CD19
  - Leukemia/Lymphoma
  - Myeloma
- Future Challenges

TRANSCEND NHL 001 *trial: Liso-cel in multiply R/R aggressive B-NHL*



Patient Eligibility

- LBCL after ≥2 lines of therapy
  - DLBCL NOS (de novo)
  - DLBCL NOS (transformed from FL, CLL, MZL, or other)
  - HGBCL (double/triple hit)
  - PMBCL
  - FL3B
- Prior HSCT allowed (auto/allo)
- ECOG PS of 0–2
- Patients with secondary CNS lymphoma were eligible
- CrCl >30 mL/min/1.73 m²
- LVEF ≥40%
- No lower threshold for ALC, ANC, platelets, or hemoglobin

End Points

Primary

- Adverse events, ORR by IRC

Secondary

- CR rate by IRC, duration of response, PFS, OS, PK

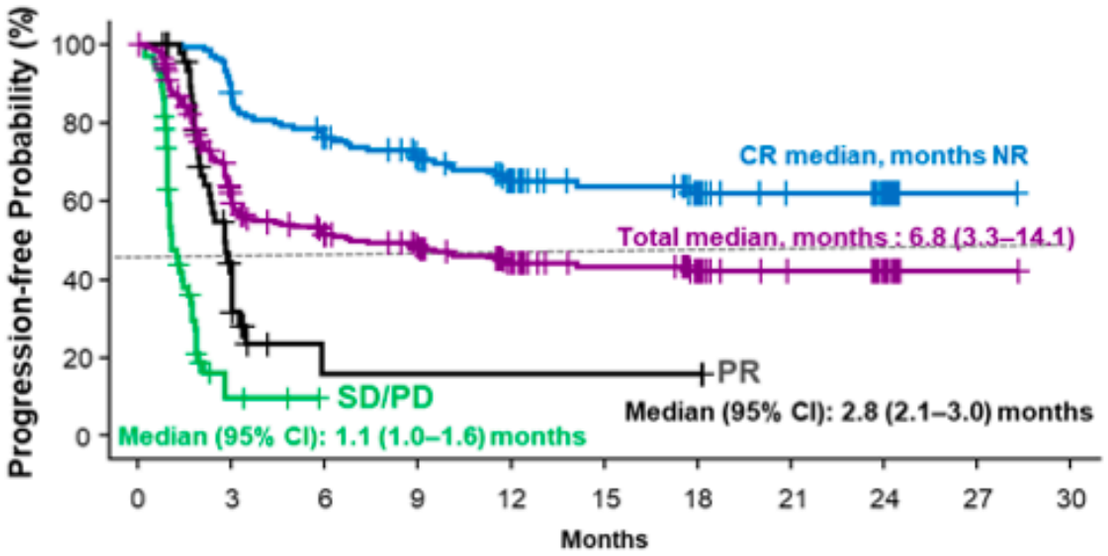
Abramson JS. et al. ASH 2019

TRANSCEND NHL 001 *trial: Liso-cel in multiply R/R aggressive B-NHL*

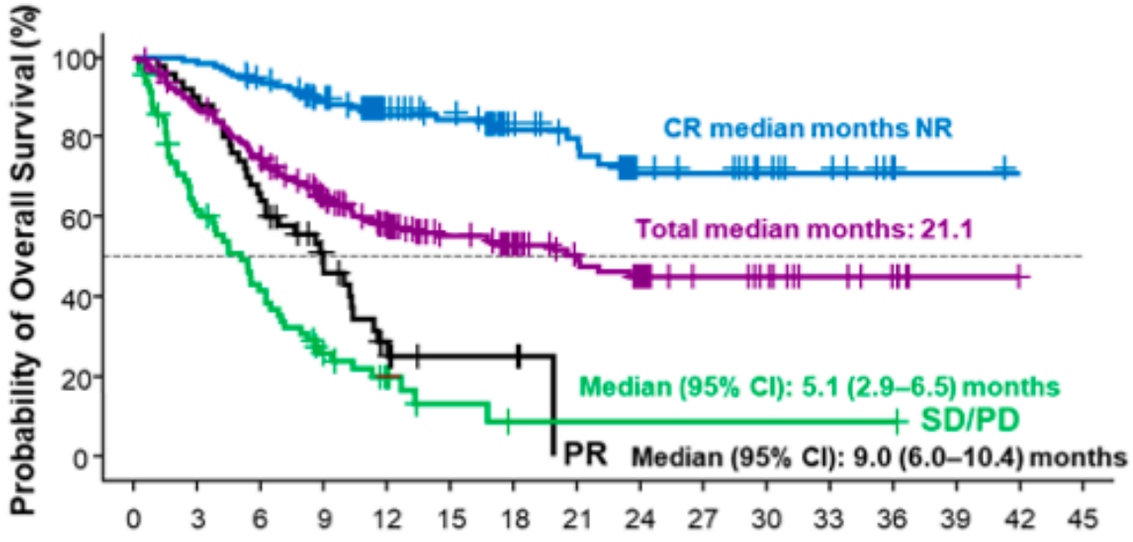
Characteristics	Patients (N= 269)
Age, median (range) years	63 (54-70)
Double-/triple hit lymphoma, n (%)	36 (13)
CNS involvement, n (%)	7 (3)
Median prior lines, n (range)	3 (2-4)
Prior HSCT, n (%)	94 (35)

Best response	Patients (N=256)
Best ORR, %	73
Best CR, %	53
12-months duration of response, %	55

PFS Median Follow-up (95% CI): 12.3 (12.0–17.5) Months



OS Median Follow-up (95% CI): 17.6 (13.5–18.0) Months



Abramson JS. et al. Lancet 2020

Multicenter CD19 CAR-T cells trials in aggressive NHL

Study/Sponsor	ZUMA1 Axi-cel	JULIET Tisa-cel	TRANSCEND Liso-cel
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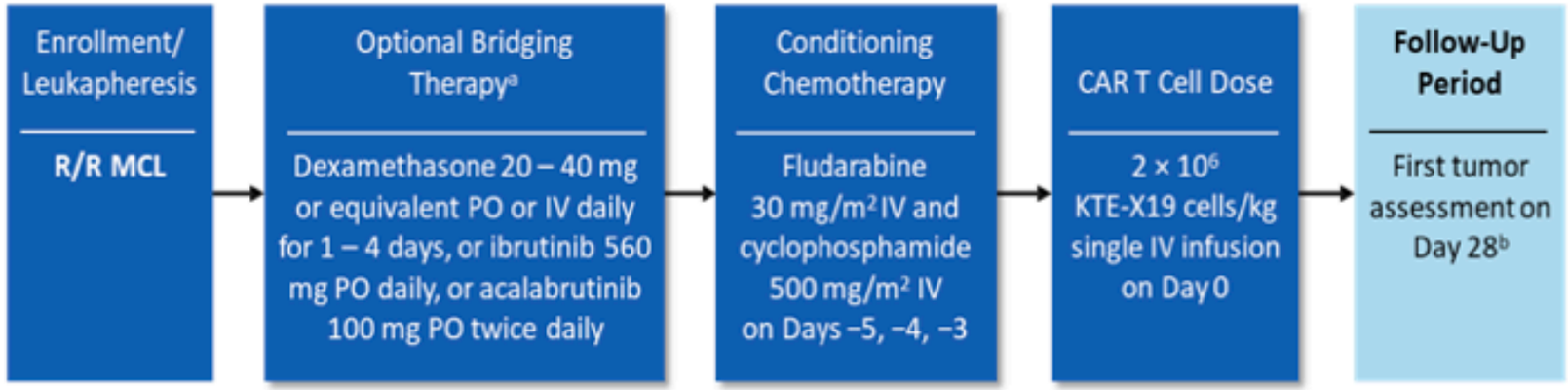
Toxicity of 3 Major CAR-T cell Products for R/R DLBCL

	Axicabtagene Ciloleucel	Tisagenlecleucel	Lisocabtagene Maraleucel
Construct	antiCD19-**CD28**-CD3z	antiCD19-**41BB**-CD3z	antiCD19-**41BB**-CD3z
n	101	111	269
Any CRS Median time to onset	93% 2 days	58% 3 days	42% 5 days
≥ Gr 3 CRS	11%	23%	2%
Any neurotoxicity	64%	21%	30%
≥ Gr 3 neurotoxicity	32%	12%	10%
Tocilizumab	43%	15%	20%
Steroid use	27%	11%	21%
	Locke, et al. Lancet Onc 2019	Schuster, et al. NEJM 2019	Abramson, et al. Lancet 2020

ZUMA-2: KTE-X19 for Patients With R/R MCL
Study Design

- KTE-X19 is a new anti-CD19 CAR T cell therapy containing a CD3z T cell activation domain and CD28 signaling domain
  - Manufacturing process removes circulating tumors cells
- Multicenter, single-arm, open-label phase II trial of KTE-X19 for adults with relapsed/refractory mantle cell lymphoma (N = 68 received agent)



Primary Endpoint
- ORR (IRRC-assessed per the Lugano classification[1])

Key Secondary Endpoints
- DOR
- PFS
- OS
- AEs
- ORR (Investigator-assessed per revised IWG criteria[2])
- EQ-5D
- Levels of CAR T cells in blood and cytokines in serum

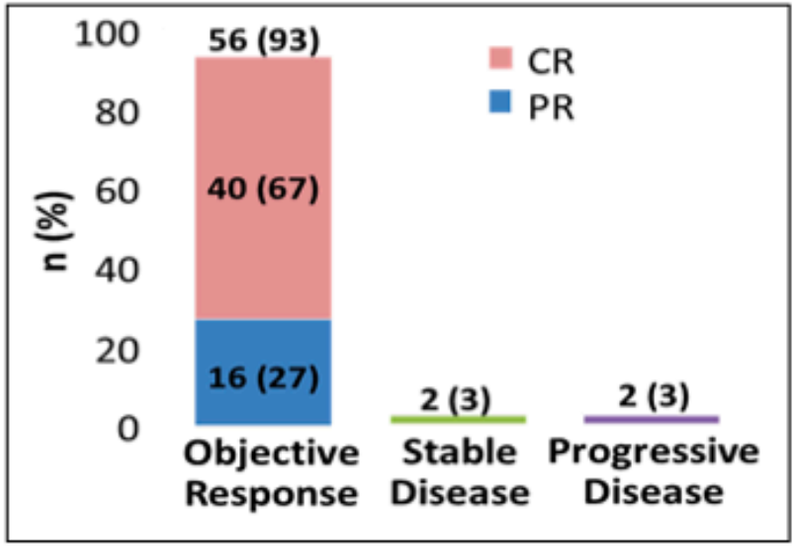
- **Inclusion criteria**
  - R/R MCL
  - 1-5 prior therapies including:
    - Antracycline- or bendamustine containing regimens
    - Anti-CD20 Ab therapy
    - Ibrutinb or acalabrutinib

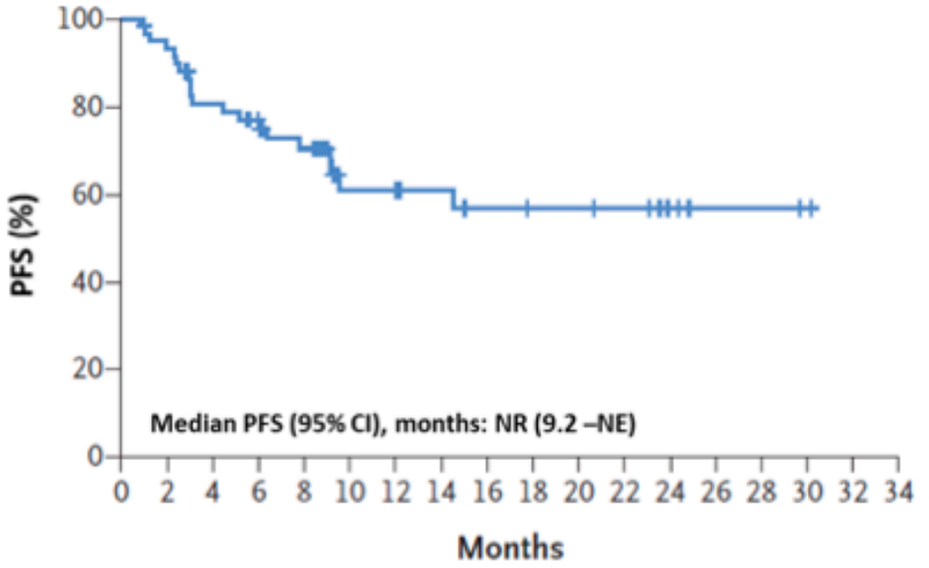
Wang, et al. ASH 2019.

KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

Wang. et al NEJM. 2020;382:1331.

Characteristics	n= 68
Age, median (range) years	65 (38-79)
Median no of prior treatments (range)	3 (1-5)
Prior BTKi, n (%)	68 (100)
BTKi refractory, n (%)	42 (62)
Prior ASCT, n (%)	29 (43)
Ki67% ≥ 30%, n/N (%)	40/49 (82%)
Blastoid variant, n (%)	21 (31%)



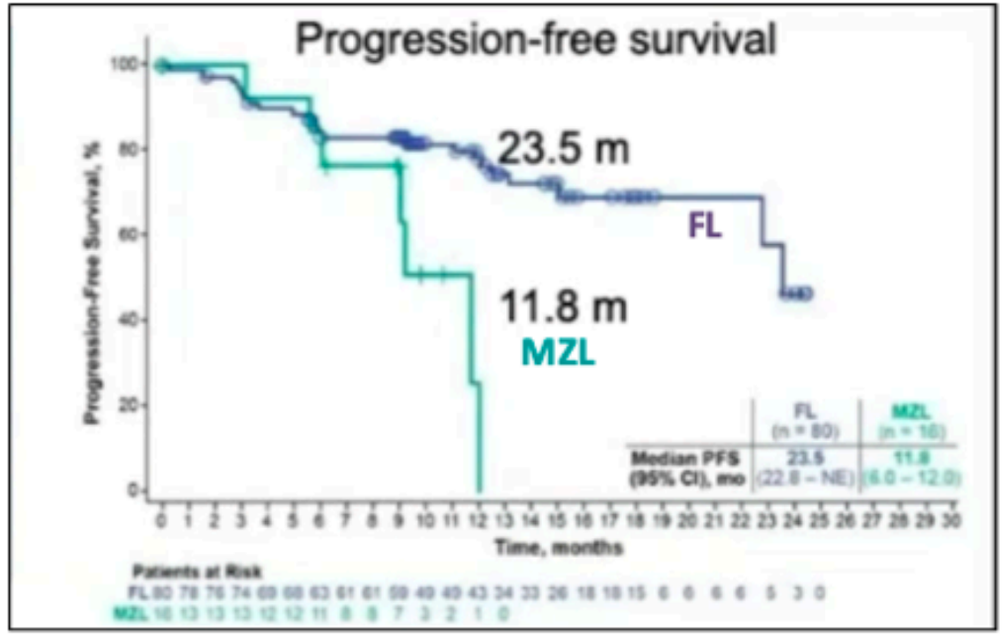


Toxicity	n= 68
Any-grade CRS, n (%)	65 (38-79)
Grade 3 or 4 CRS, n (%)	10(15)
Time to onset, median, days (range)	2 (1-13)
Any grade neurological toxicity, n (%)	43 (63)
Grade 3 or 4 neurological toxicity, n (%)	21 (31)
Time to onset, median, days (range)	7 (1-32

ZUMA-5 Study of Axi-cel in relapsed/refractory FL and MZL

- a Phase 2, multicenter study of axi-cel, an autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy, in patients with relapsed/refractory (R/R) iNHL

Characteristics	FL N = 80	MZL N = 14	All patients N= 94
Median Age (range)	62 (34-79)	67 (52-77)	63 (34-79)
FLIPI 3-5	38 (48%)	11(69%)	49 (51%)
High tumor burden (GELF)	40 (50%)	7(44%)	47 (49%)
Median prior tx, (range)	3 (2-9)	3 (2-8)	3(2-9)
Refractory	59 (74%)	11 (69%)	70(73%)
POD24	45(56%)	7(44%)	52(54%)



	All patients (n=96)	FL (n=80)	MZL (n=16)
ORR	94%	95%	86%
CR	79%	80%	71%
PR	13%	14%	6%

AEs of Special Interest (n=140)	
CRS	
Any grade	111 (79%)
Grade ≥ 3	11 (8%)
Neurological events	
Any grade	81 (58%)
Grade ≥ 3	24 (17%)

Jacobson C et al. ASCO 2020; EHA 2020.

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CD19-Negative Disease and Relapse Following CD19 CAR T-Cell Therapy for B-ALL

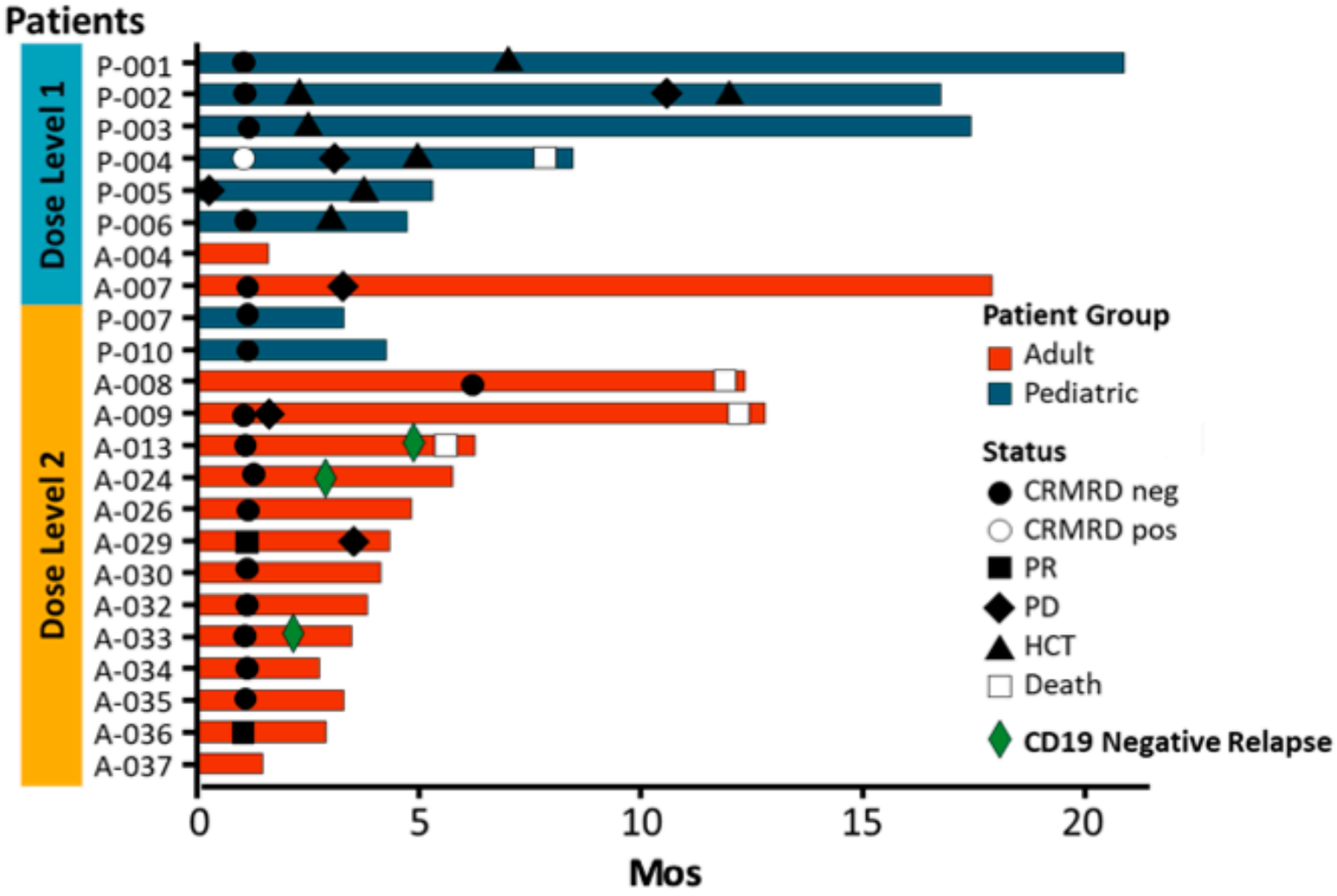
Trial	Phase	Population	CD19 CAR Construct	Relapse Rate, % (n/N)	CD19-Negative Relapse Rate, % (n/N)
Children's Hospital of Philadelphia	I	Pediatric	FMC63-4-1BB-ζ	36 (20/55)	24 (13/55)
ELIANA	II	Pediatric	FMC63-4-1BB-ζ	33 (20/61)	25 (15/61)
Seattle Children's	I	Pediatric	FMC63-CD28-ζ	45 (18/40)	18 (7/40)
NCI	I	Pediatric	FMC63-4-1BB-ζ	29 (8/28)	18 (5/28)
MSKCC	I	Adult	SJ25C1-CD28-ζ	57 (25/44)	9 (4/44)
FHCRC	I	Adult	FMC63-4-1BB-ζ	31 (9/29)	7 (2/29)

Treatment failure after CAR T-cell therapy

- Long-term outcomes confounded across trials by differing HCT use and other unique practices following CAR T-cell therapy
- True incidence of CD19+ and CD19- relapse unknown

Schultz. ASH 2019. Abstr 744.

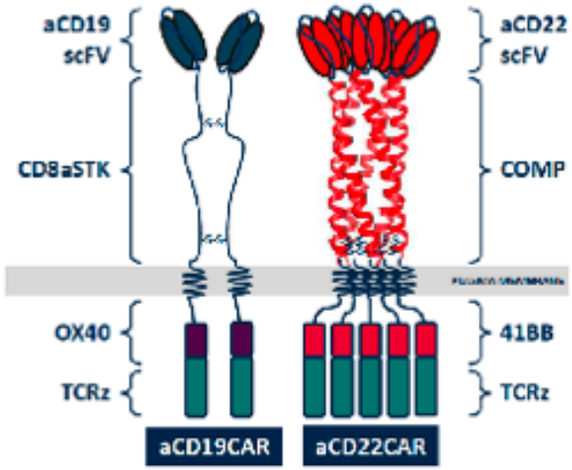
Phase I Study of CD19/CD22 CAR T-Cell Therapy for Patients With Relapsed/Refractory ALL



- Majority of pediatric patients underwent SCT after CAR T-cell therapy; all adult pts underwent surveillance
- Median f/u: 4 mos (range: 2-24)
  - OS: 62.3%
- Relapse rate: 33% (7/21)
  - CD19 negative relapse in 3/7 evaluable relapses

Schultz. ASH 2019. Abstr 744.

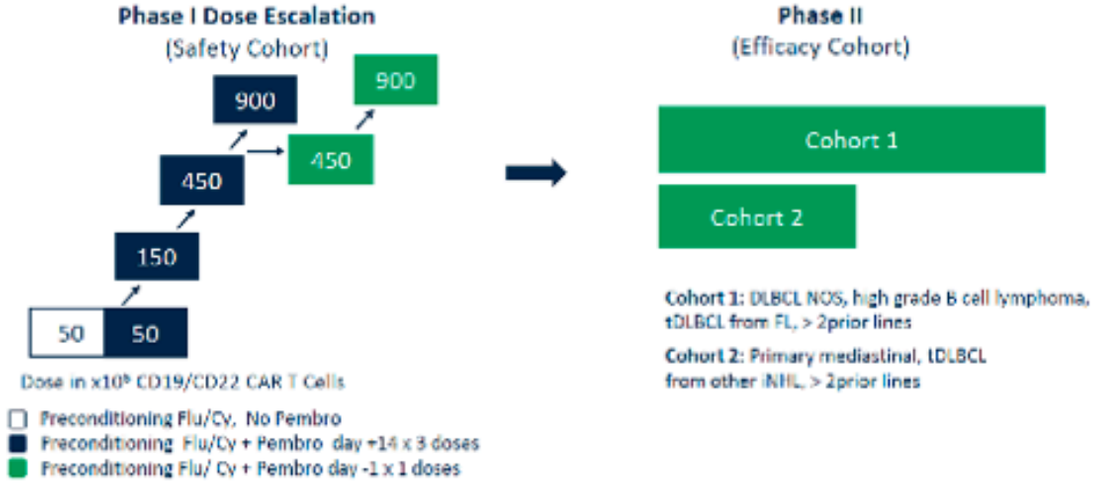
CD19/22 dual targeting CAR T cell therapy: AUTO3/Alexander Phase 1/2 Study in R/R DLBCL



- Dual antigen targeting
- Two indipendents CARs delivered in single retroviral vector
- Humanized binders
- OX40/41BB costimulatory domains designed to improve persistence
- Indipendently targets CD19 or CD22

Alexander Study Design

AUTO3-DB1, single-arm, open-label, multi-center, Phase 1/2 Study in r/r DLBCL



- **Inclusion criteria:**
  - Patients (≥ 18 years) with r/r DLBCL (NOS) or tDLBCLfrom FL;
  - > 2 prior lines
  - ECOG <2
- Patients received **AUTO3 alone, or with 3 doses of pembrolizumab** (pem) 200 mg q 3 wks starting on D14 (regimen A), or **with a single dose of pem** 200 mg on D-1 (regimen B)
- **Primary endpoint**: frequency of DLTs and grade 3-5 adverse events

Osborne W. ASCO 2020

CD19/22 dual targeting CAR T cell therapy: Alexander Phase 1/2 Study in R/R DLBCL

Preliminary Efficacy Results

	50 x 10^6 No Pem (n=4)	50 x 10^6 D14 Pem (n=3)	150 x 10^6 D14 Pem (n=4)	450 x 10^6 D14 Pem (n=4)	450 x 10^6 D-1 Pem (n=3)
CR	1	1	2	2	2
PR	1	1	0	1	NA
NE	0	1	0	0	0
CRR	**25%**	**33%**	**50%**	**50%**	**66%**

- 450 million : 5/7 (71%) and CR 4/7 (57%)
- All doses : 11/18 (61%) and **CR 8/18 (44%)**

Toxicity

- With primary infusion
  - 2 patients received Tocilizumab for CRS
  - 1 patient received steroids for NT

Adverse Events of Special Interest

	50 x10^6 AUTO3 no pem (n=4)	50 x10^6 AUTO3 D14 pem (n=3)	150 x10^6 AUTO3 D14 pem (n=4)	450 x10^6 AUTO3 D14 pem (n=4)	450 x10^6 AUTO3 D -1 pem (n=3)	Total (n=18)
All grades CRS*	1	0	2	2	2	7 (38.9%)
≥ G3 CRS	0	0[&]	0	0	0	0
All grades NT*	1	0	0	0	0	1 (5.6%)
≥ G3 NT	1	0	0	0	0	1 (5.6%)

Osborne W. ASCO 2020

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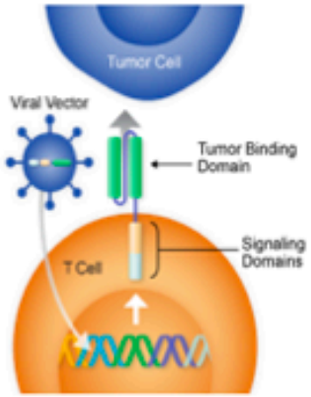
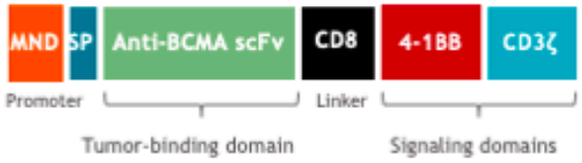
Phase 2 KarMMa Trial: Ide-cel (bb2121) in patients with R/R MM



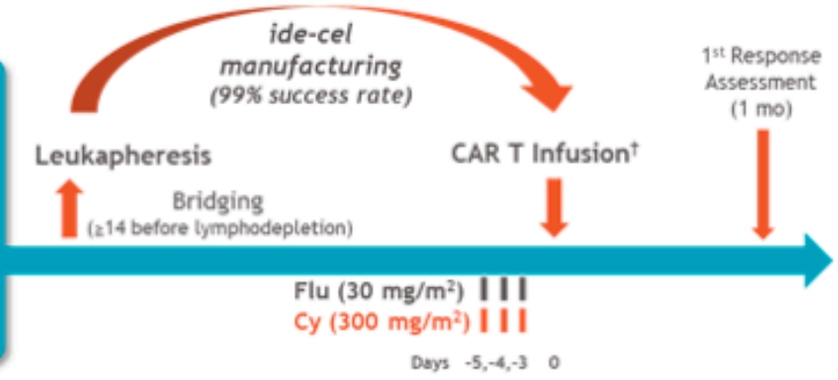
ide-cel CAR design

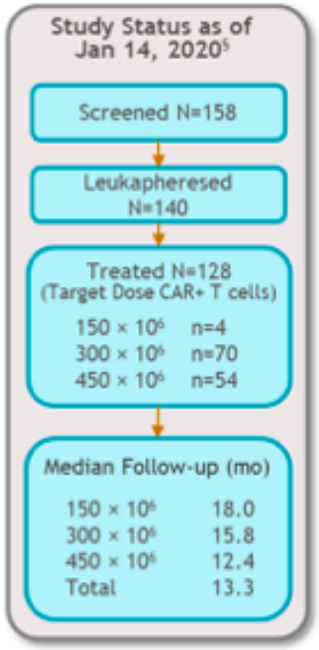


- Targeting domain: **anti-BCMA**
- Costimulatory domain: **4-1BB**
- T-cell activation domain: **CD3ζ**

- BCMA is expressed **specifically on PCs and myeloma cells**
  - **Higher** expression in myeloma cells than normal PCs
  - Key role in B-cell maturation and differentiation
  - **Promotes** myeloma **cell growth, chemoresistance** and **immunosuppression** in the BM microenvironment
- Expression of BCMA increases as the disease progresses from MGUS to advanced myeloma

- RRMM
- ≥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*





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

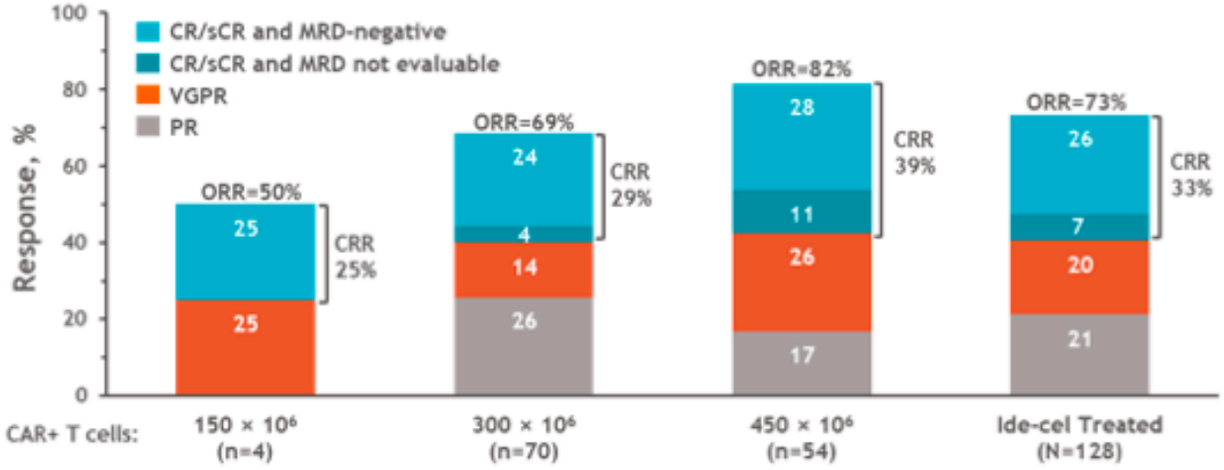
- Median Age : 61 (38-78)
- The majority of patients had **high tumor burden** and more than one third had **extramedullary disease** and high-risk **cytogenetics**
- Patients were **heavily pretreated**
- **All** were **refractory to their last line** per IMWG criteria
- Most were **refractory to all 3** major MM drug classes (IMiD agents, PIs, and anti-CD38 antibodies)

Endpoints

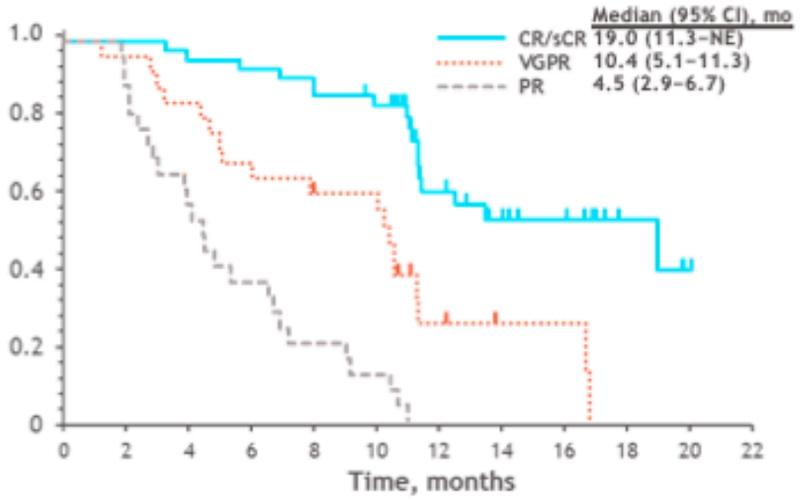
- **Primary:** ORR (null hypothesis ≤50%)
- **Secondary:** CRR (key secondary; null hypothesis ≤10%), Safety, DOR, PFS, OS, PK, MRD‡, QOL, HEOR
- **Exploratory:** Immunogenicity, BCMA expression/loss, cytokines, T cell immunophenotype, GEP in BM

San Miguel J. EHA 2020;

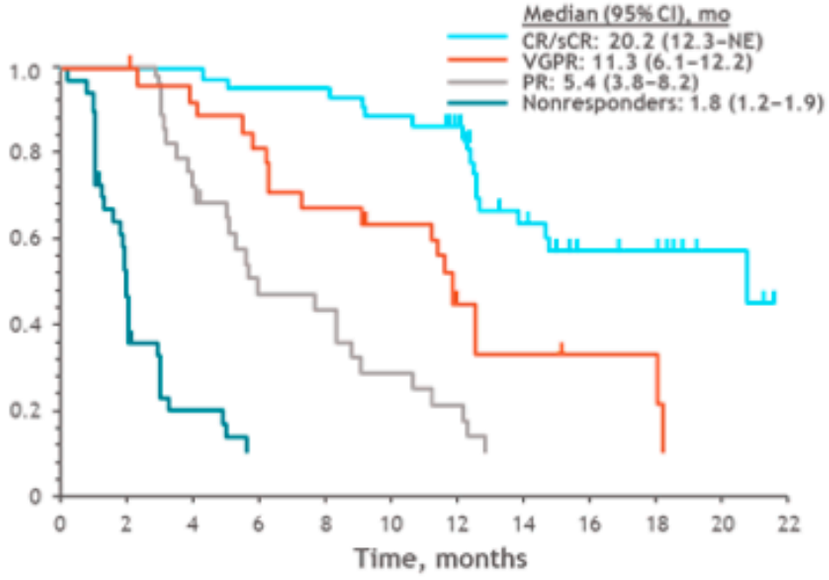
Phase 2 KarMMa Trial: Ide-cel (bb2121) in patients with R/R MM



DOR by Best Response



PFS by Best Response



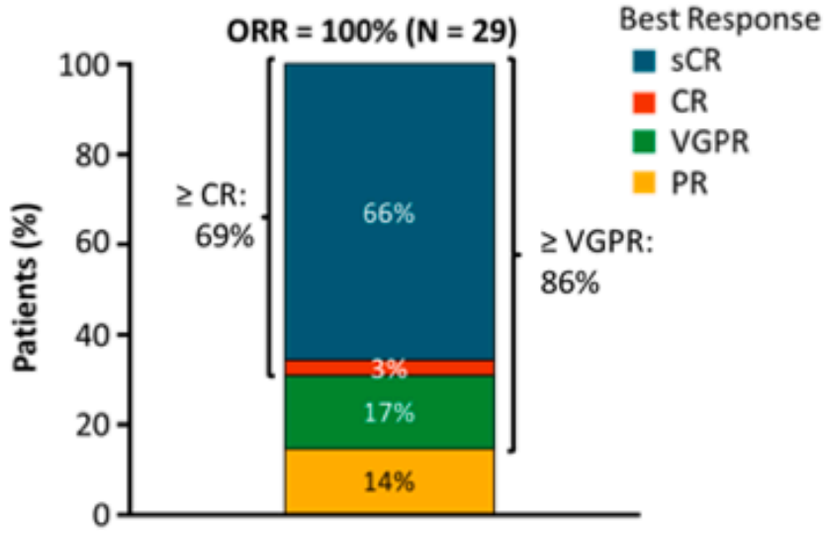
- Ide-cel demonstrated frequent, deep and durable responses in heavily pretreated, highly refractory MM patients in the pivotal KarMMa trial
- Efficacy was highest at the target dose of 450 × 10^6 CAR+ T cells
  - ORR of 82% including 39% CRR; median DOR and PFS of 11.3 mo and 12.1 mo, respectively
- Ide-cel was tolerable across the dose range
  - The frequency of grade ≥3 CRS or investigator-identified NT ≤6% at target dose of 450 × 10^6 CAR+ T cells

San Miguel J. EHA 2020;

Phase IB/II CARTITUDE: JNJ-4528 in patients with R/R MM

- JNJ-68284528 (JNJ-4528) is a chimeric antigen receptor T (CAR-T) cell therapy containing 2 BCMA-targeting single-domain antibodies.
- Patients were heavily pretreated
- 97% refractory to their last line per IMWG criteria
- 76% penta-exposed, 86% triple-refractory, 31% penta-refractory

Characteristic	All Patients (N = 29)
Median age, yrs (range)	60 (50-75)
Female, n (%)	15 (52)
≥ 1 extramedullary plasmacytomas, n (%)	4 (14)
≥ 60% bone marrow plasma cells, n (%)	7 (24)
Median time from diagnosis, yrs (range)	6 (2-16)
Any high-risk cytogenetics*, n (%) ▪ del(17p) ▪ t(14;16) ▪ t(4;14)	7 (25) 4 (14) 2 (7) 1 (4)
Median no. prior lines of therapy, n (range)	5 (3-18)
Prior bridging therapy, n (%)	24 (83)



- Median Follow up = 11.5 mo (3-17)
- 22/29 patients alive and progression-free
- 3 deaths: 1 from CRS, 1 AML (treatment unrelated), and 1 PD
- 9-mo PFS rate= 86% (95% CI, 67-95)

Madduri et al. ASH 2019; Berdeja JG et al. ASCO 2020.

Agenda

- Lymphoma :
  - Real world experience and predictive factors
  - Results from clinical trials
- New targets … beyond CD19
  - Leukemia/Lymphoma
  - Myeloma
- **Future Challenges**

Notable Studies from 2020

Abstract/ NCT No.	Title	Key Findings
Siddiqi T. et al. ASH2019, abst 4075	CD19-Targeting CAR-T Cell Therapy in CNS Lymphoma	▪ Ongoing City of Hope CAR-T cell phase 1 trial targeting CD19 in patients with primary and secondary CNS lymphoma (N= 7) ▪ ORR 57%, CR 14%; No patients experienced any severe CRS or neurologic toxicity.
Newman et al. ASCO2020,abst 10511	CD19-targeted chimeric antigen receptor (CAR) T-cells in CNS relapsed acute lymphoblastic leukemia (ALL)	▪ Multitrial analysis of efficacy of CD19-targeting CAR T-cells in children/young adults with R/R CNS B-ALL (N = 65) ▪ Similar CR rates for CNS- vs CNS+; low CNS relapse rate
Wang et al. EHA2020; abst S115	First-in-human clinical trial of the autologous CD7-CART for relapsed/refractory acute lymphoblastic leukemia/lymphoma	▪ Phase I study of CD7-targeting CAR T-cells for R/R T-ALL/LBL (N = 5) ▪ Cells manufactured; efficacy noted in small population
Liu et al. EHA2020;abst S149	First-in-human CLL1-CD33 compound CAR (CCAR) T Cell therapy in relapsed and refractory acute myeloid leukemia	▪ To evaluate the toxicity and efficacy of the CLL1-CD33 cCAR in the treatment of R/R AML (N=9) ▪ 7/9 MRD negative; high efficacy and manageable toxicity in R/R AML patients
Neelapu SS et al ASCO2020	First-in-human data of ALLO-501 and ALLO-647 in relapsed/refractory large B-cell or follicular lymphoma (R/R LBCL/FL): ALPHA study	▪ An open-label, Phase 1 trial (NCT03939026) in adults with R/R LBCL/FL who have received ≥ 2 prior lines of therapy; prior anti-CD19 cell therapy is allowed (N=12) ▪ ORR: 78%; 3 CR. No CRS / NT AE grade > 3.

Take home messages

- **The real life results** demonstrate that the **overall efficacy of commercial products is comparable** to what is observed on the pivotal trials and that the **toxicity was slightly lower**, despite that many patients would not have met eligibility criteria for clinical trial because of comorbidities.

- The reported improved safety profile of **liso-cel** with comparable efficacy to other FDA approved products is of great interest and likely will allow for outpatient administration of this product.

- Results of ZUMA-2 study using **KTE-X19** demonstrate high durable responses with manageable toxicities in R/R MCL patients with previously limited options **(FDA approval on Jul.2020) .**

- **Novel constructs** addressed topics such as targeting resistance mechanism, decreasing production time and increasing CAR T persistence.

- **In R/R MM, anti-BCMA CAR-T cells** demonstrated high efficacy overcoming all conventional drug-related resistance mechanisms. Ide-cel and other CAR-T cell products are on their way to approval.