Zdravljenje s celicami CAR-T
&
Pregled kliničnih protokolov za zdravljenje s celicami CAR-T in vzpostavitev tovrstnega zdravljenja v slovenskem prostoru

prof. dr. Matjaž Sever dr., med.

&

prof. dr. Samo Zver, dr. med.

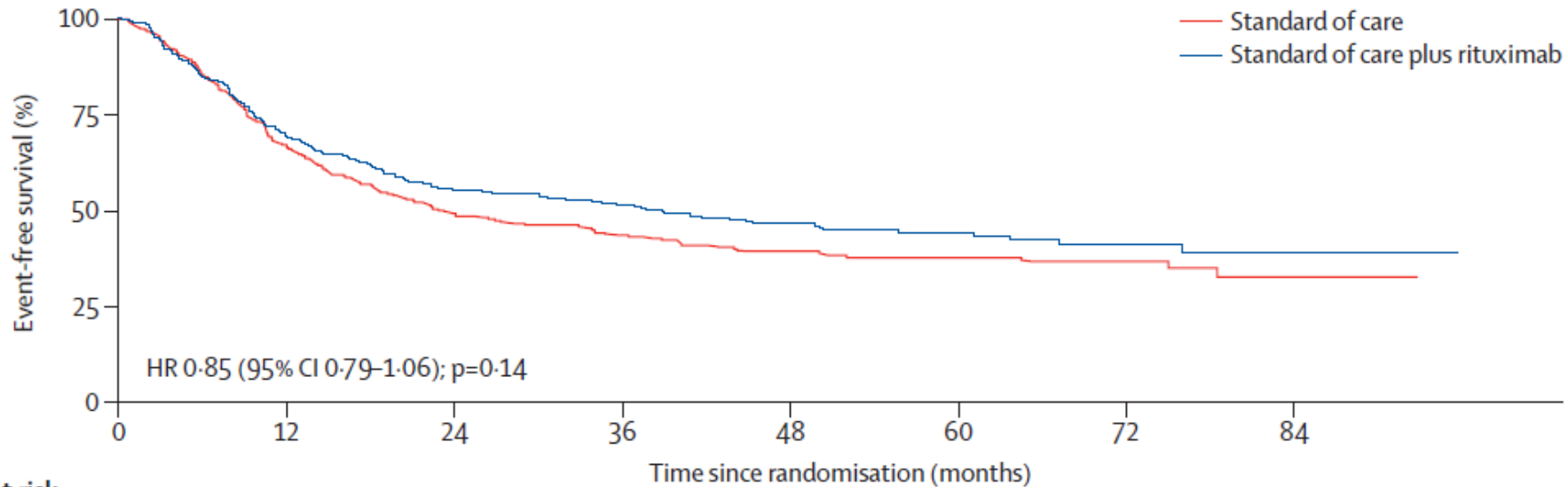
univerzitetni klinični center ljubljana
University Medical Centre Ljubljana

University *of Ljubljana*

AKUTNA LIMFOBLASTNA LEVKEMIJA

Addition of four doses of rituximab to standard induction chemotherapy in adult patients with precursor B-cell acute lymphoblastic leukaemia (UKALL14): a phase 3, multicentre, randomised controlled trial

David I Marks, Amy A Kirkwood*, Clare J Rowntree, Melanie Aguiar, Katharine E Bailey, Brendan Beaton, Paul Cahalin, Anna Z Castleton, Laura Clifton-Hadley, Mhairi Copland, Anthony H Goldstone, Richard Kelly, Emma Lawrie, SooWah Lee, Andrew K McMillan, Mary Frances McMullin, Tobias F Menne, Rachel J Mitchell, Anthony V Moorman, Bela Patel, Pip Patrick, Paul Smith, David Taussig, Deborah Yallop, Krisztina Zuborne Alapi, Adele K Fielding*

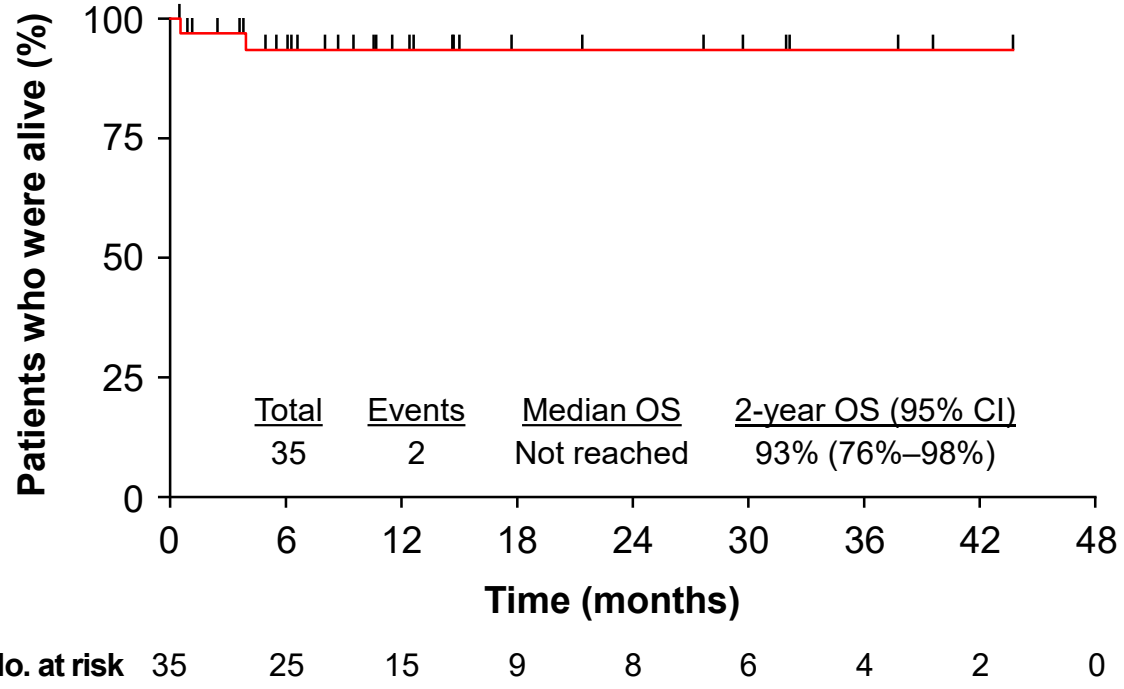


Number at risk (number censored)								
Standard of care	288 (0)	190 (4)	134 (10)	102 (28)	73 (48)	43 (75)	25 (92)	11 (104)
Standard of care plus rituximab	289 (0)	198 (2)	155 (6)	116 (35)	80 (61)	54 (83)	25 (109)	11 (122)

Lancet Haematol 2022; 9: e262–75

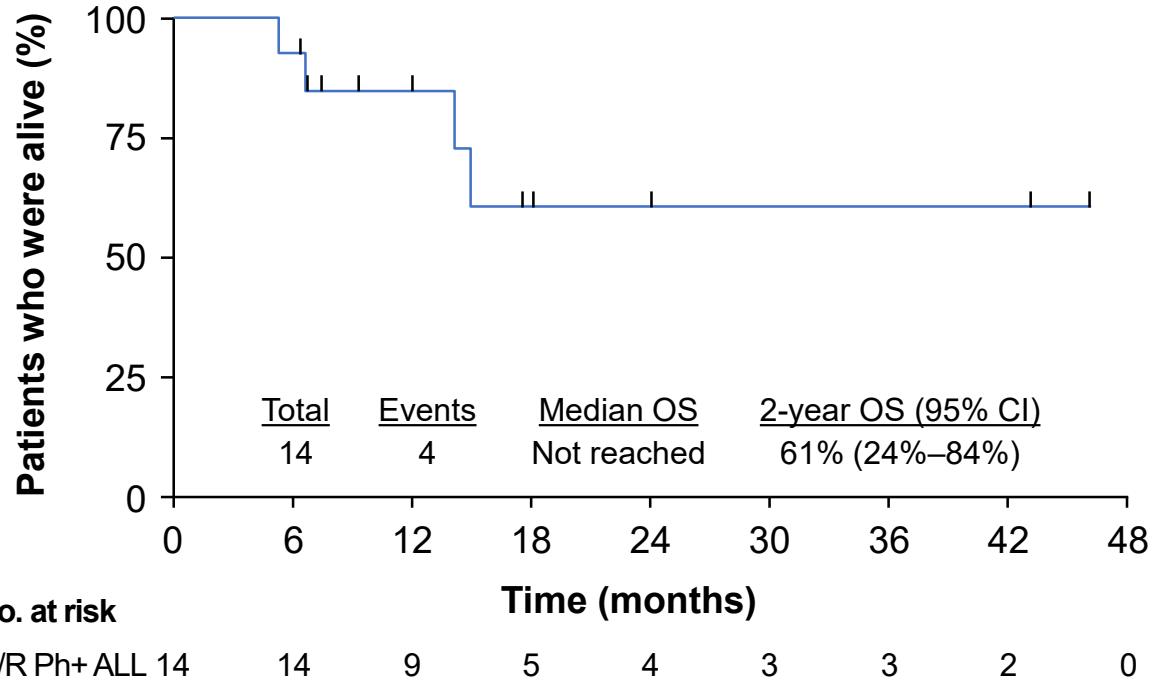
OS in Patients With ND or R/R Ph+ ALL After the Blinatumomab Plus Ponatinib Regimen

ND Ph+ ALL Cohort



No. at risk									
	35	25	15	9	8	6	4	2	0

R/R Ph+ ALL Cohort



No. at risk									
R/R Ph+ ALL	14	14	9	5	4	3	3	2	0

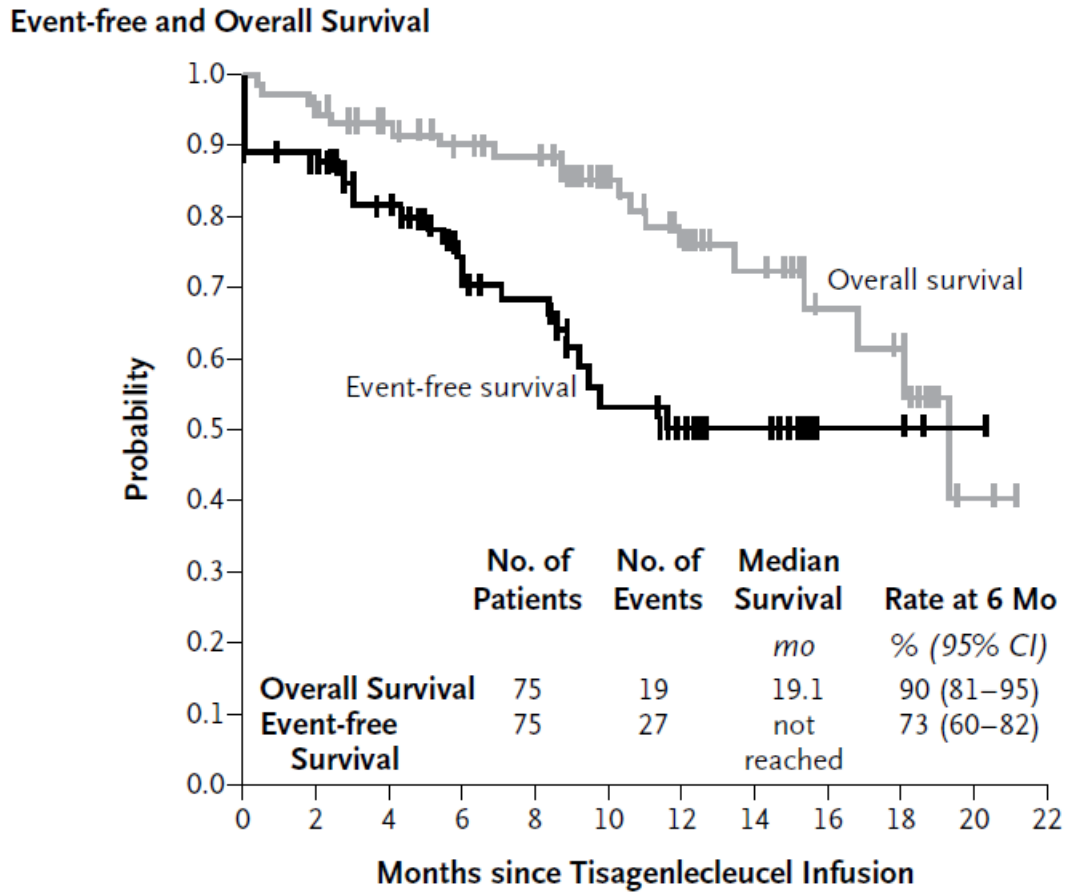
- Median follow-up was 11 months (range: 1 to 46+ months)
- The estimated 2-year OS and EFS rates were both 93% among ND patients and 61% and 42%, respectively, among the 13 responding R/R patients

ALL, acute lymphoblastic leukemia; CI, confidence interval; EFS, event-free survival; MDACC, Monroe Dunaway Anderson Cancer Center; ND, newly diagnosed; OS, overall survival; Ph+, Philadelphia chromosome positive; R/R, relapsed or refractory.

Short NJ, et al. Poster presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022; Chicago, IL.

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

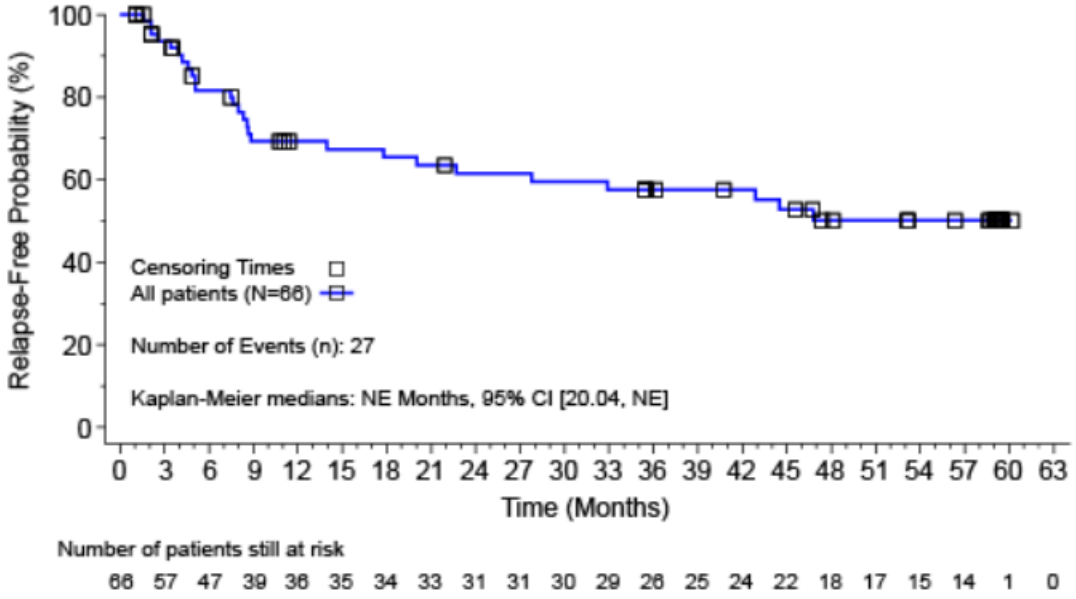
- Phase 2, single-cohort, 25-center, global study
- CD19+ relapsed or refractory B-cell ALL
- 75 patients received an infusion
- Overall remission rate within 3 months was 81%
- EFS and OS 50% and 76% at 12 months
- Persistence of tisagenlecleucel in the blood was observed for as long as 20 months
- CRS occurred in 77% of patients, 48% of whom received tocilizumab
- Neurologic events occurred in 40% of patients and were managed with supportive care



N Engl J Med 2018;378:439-48.

TISAGENLECLEUCEL IN PEDIATRIC AND YOUNG ADULT PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA (B-ALL): FINAL ANALYSES FROM THE ELIANA STUDY

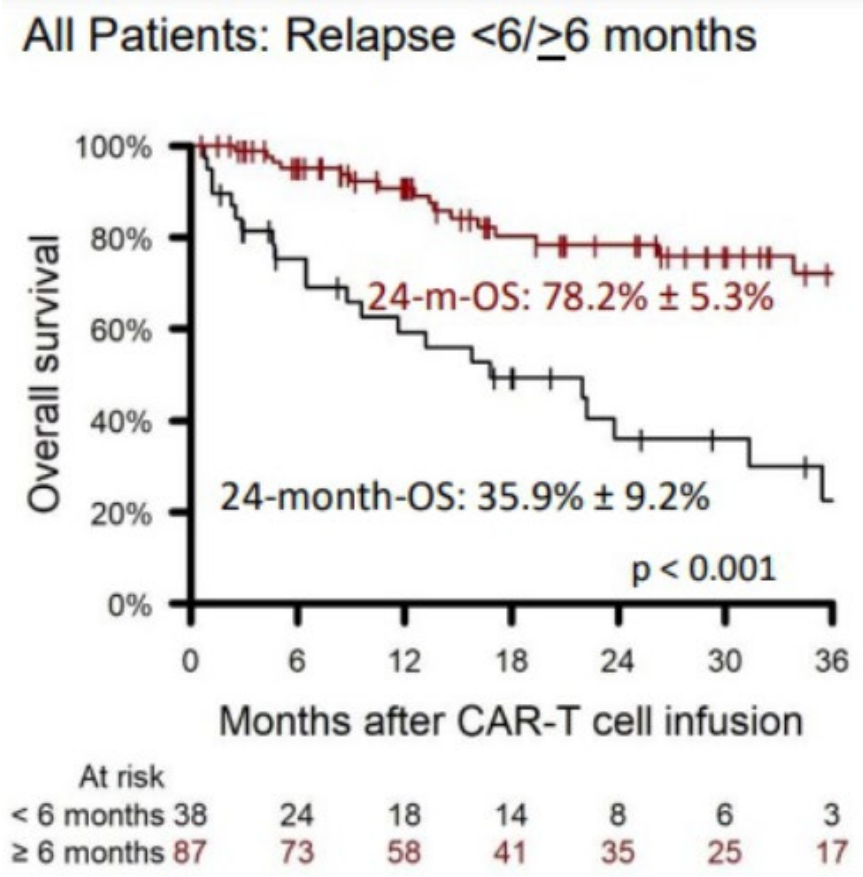
- 5y EFS and OS rates were 42% (95%CI, 29-54) and 55% (95% CI, 43-66), respectively
- No significant differences in any efficacy endpoint between pediatric (<18 y; n=65) and young adult (≥18 y; n=14) pts
- No new or unexpected AEs were reported during long-term follow-up
- Grade ≥3 AEs occurring >1 y post-infusion were infection (20%) and cytopenias (6%).
- Ten (14%) pts in remission experienced long-term cytopenias persisting for >1 y
- 82% of pts received IVIG any time post-infusion.



EHA 2022, S112

S111 TREATMENT OF POST-TRANSPLANT RELAPSE IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS WITH BCP ALL USING CD19-CAR-T: A EUROPEAN RETROSPECTIVE ANALYSIS OF REAL-WORLD DATA

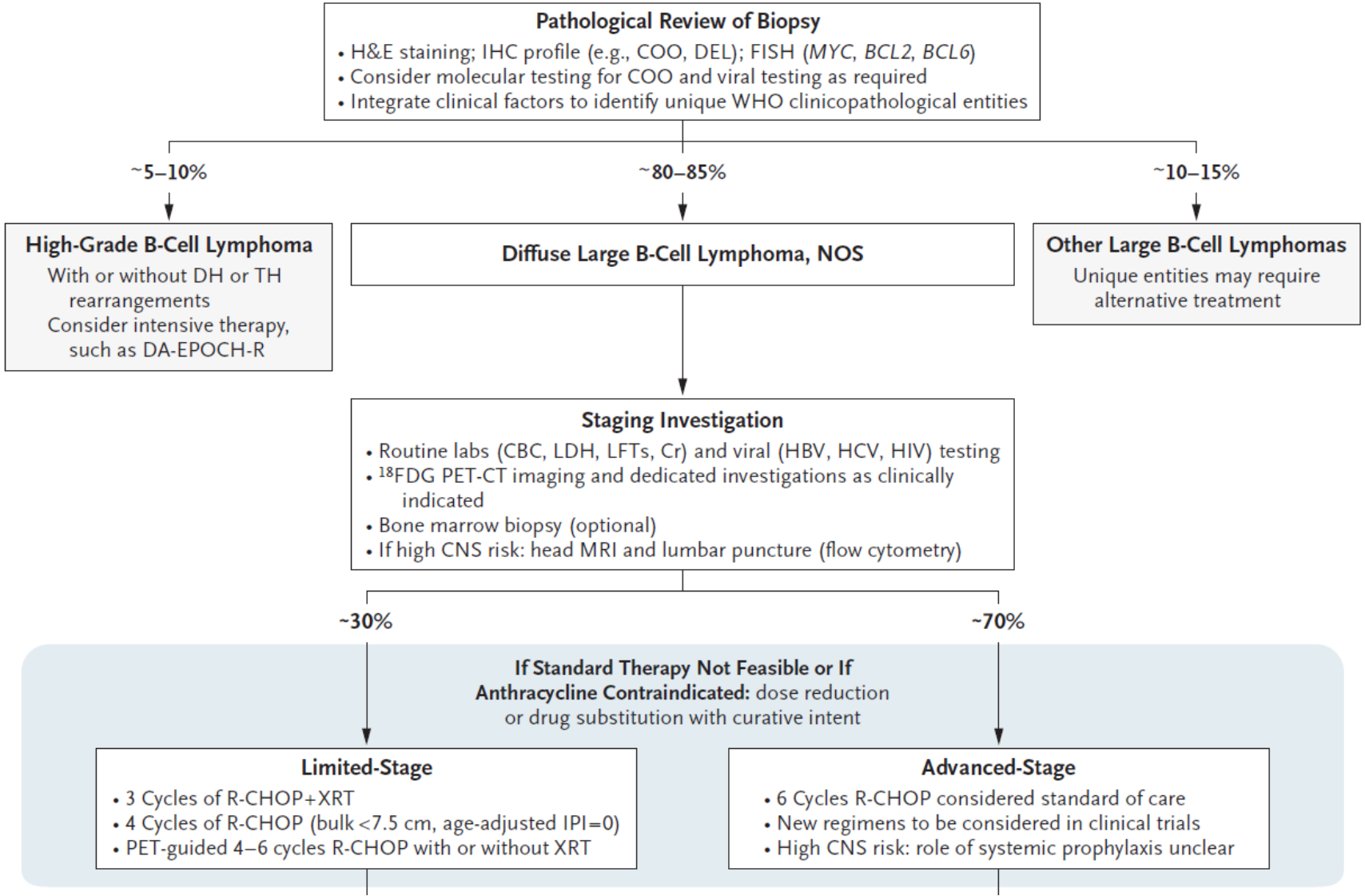
- In a retrospective study of 145 patients treated with Tisagenlecleucel (Tisa-cel) for post-SCT relapse, the 2-yr EFS was 44.3% and the 2-yr OS 64.0%.
- The post-SCT timing of relapse influenced outcome.
- The 2-yr EFS was 19.5% for early relapsed and 53.0% for late relapsed patients.
- Similarly, the 2-yr OS was 35.9% and 78.2% for early and late relapsed patients, respectively.
- Patients who relapsed >6 months from HSCT have an excellent prognosis with only a single Tisa-cel infusion and no further consolidation.
- These findings may become relevant for further clinical decision making.



HemaSphere | 2023;7(S3)

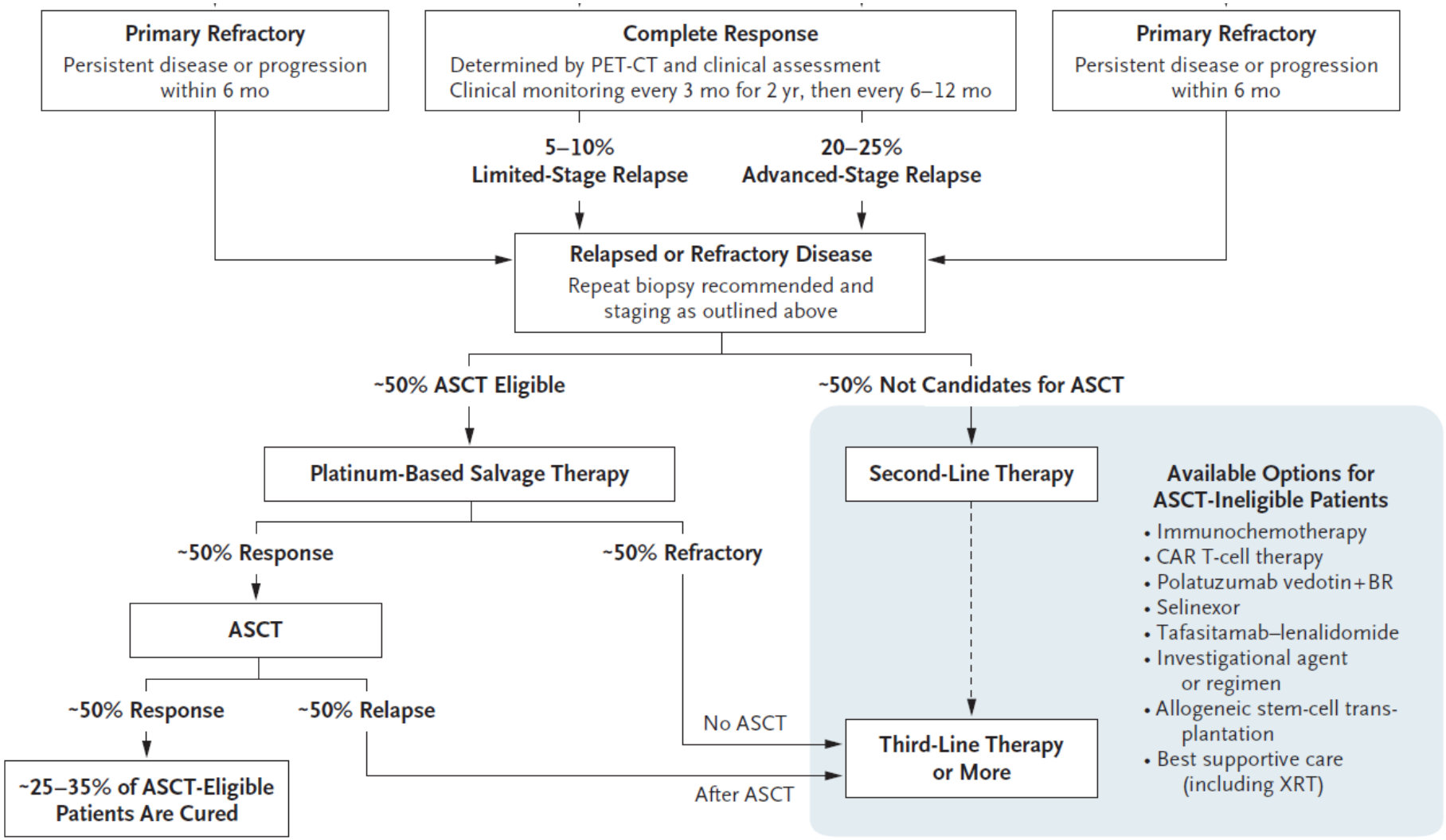
DIFUZNI VELIKOCELIČNI B-LIMFOM

DLBCL Management



N Engl J Med 2021;384:842-58.

DLBCL Management



N Engl J Med 2021;384:842-58.

CAR-T Approvals FDA/EMA

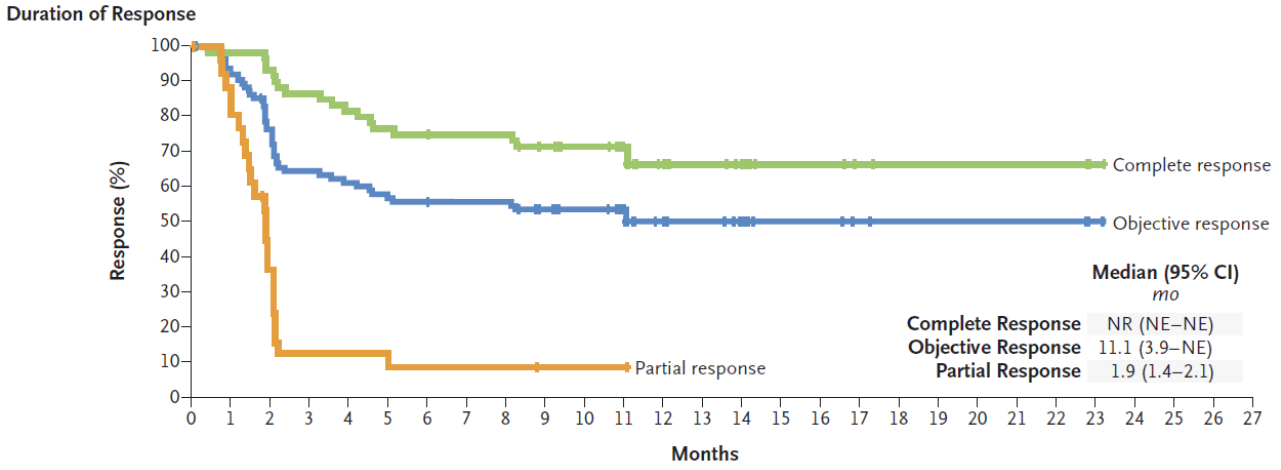
Commercial CAR T-cell therapy	Target	Indication	Date of EMA marketing authorization	Date of FDA marketing authorization
tisagenlecleucel/Kymriah®	CD19	Paediatric 3L+ ALL	September 2018 (EMA, 2021b)	August 2017 (FDA, 2021c)
		3L+ DLBCL	September 2018 (EMA, 2021b)	May 2018 (FDA, 2021c)
		3L+ HGBL	—	May 2018 (FDA, 2021c)
		3L+ DLBCL from FL	—	May 2018 (FDA, 2021c)
		3L+ FL	March 2022/positive CHMP opinion received (EMA, 2022c)	—
axicabtagene ciloleucel/Yescarta®	CD19	3L+ DLBCL	September 2018 (EMA, 2021d)	October 2017 (FDA, 2022c)
		2L+ DLBCL	—	April 2022 (FDA, 2022b)
		3L+ PMBCL	September 2018 (EMA, 2021d)	October 2017 (FDA, 2022c)
		3L+ HGBL	—	October 2017 (FDA, 2022c)
		3L+ DLBCL from FL	—	October 2017 (FDA, 2022c)
		4L+ FL (EMA) 3L+ FL (FDA)	April 2022/positive CHMP opinion received (EMA, 2022d)	April 2021 (FDA, 2022c)
brexucabtagene autoleucel/Tecartus®	CD19	3L+ MCL (EMA) 2L+ MCL (FDA)	December 2020 (EMA, 2021c)	July 2020 (FDA, 2021d)
		Adult 2L+ ALL	—	October 2021 (FDA, 2021d)
isocabtagene maraleucel/Breyanzi®	CD19	3L+ DLBCL	April 2022 (EMA, 2022a)	February 2021 (FDA, 2021b)
		3L+ PMBCL	April 2022 (EMA, 2022a)	February 2021 (FDA, 2021b)
		3L+ HGBL	—	February 2021 (FDA, 2021b)
		3L+ DLBCL from FL	—	February 2021 (FDA, 2021b)
		3L+ FL (grade 3B)	April 2022 (EMA, 2022a)	February 2021 (FDA, 2021b)
idecabtagene vicleucel/Abecma®	BCMA	4L+ MM (EMA) 5L+ MM (FDA)	August 2021 (EMA, 2021a)	March 2021 (FDA, 2021a)
ciltacabtagene autoleucel/Carvykti®	BCMA	4L+ MM (EMA) 5L+ MM (FDA)	March 2022/positive CHMP opinion received (EMA, 2022b)	February 2022 (FDA, 2022a)

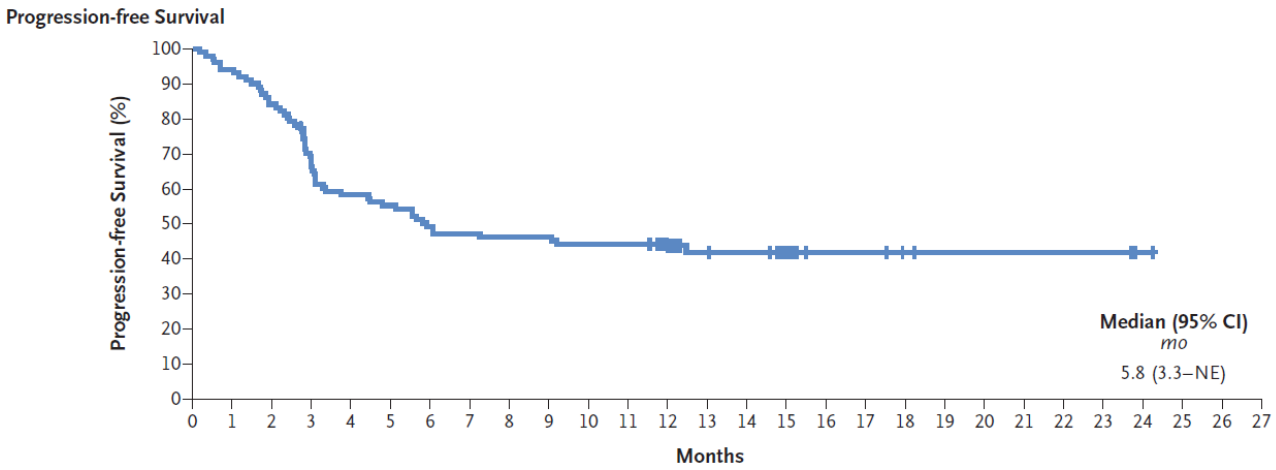
2L+, second or later-line systemic therapy; 3L+, third or later-line systemic therapy; 4L+, fourth or later-line systemic therapy; 5L+, fifth or later-line systemic therapy; CD19, B-lymphocyte antigen CD19 (Cluster of Differentiation 19); BCMA, B-cell maturation antigen; ALL, acute lymphoblastic leukaemia; DLBCL, diffuse large B-cell lymphoma; HGBL, high-grade B-ce lymphoma; FL, follicular lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma.

Front. Pharmacol. 13:915342.
doi: 10.3389/fphar.2022.915342

Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

- Multicenter, phase 2 trial
- 111 patients with diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma
- Refractory disease despite undergoing recommended prior therapy
- Objective response rate was 82%
- Complete response rate was 54%
- Overall rate of survival at 18 months was 52%
- Most common adverse events of grade 3 or higher:
  - neutropenia 78%, anemia 43%, thrombocytopenia 38%,
  - CRS 13%
  - neurologic events 28%

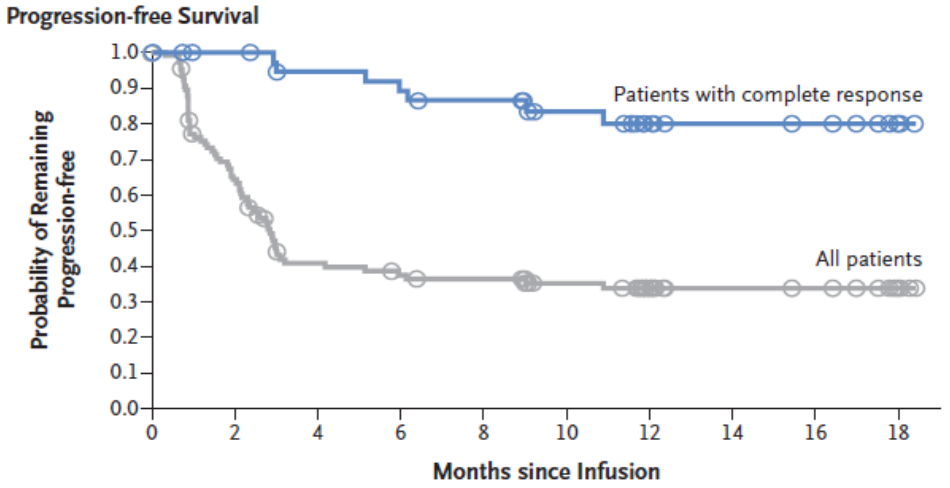


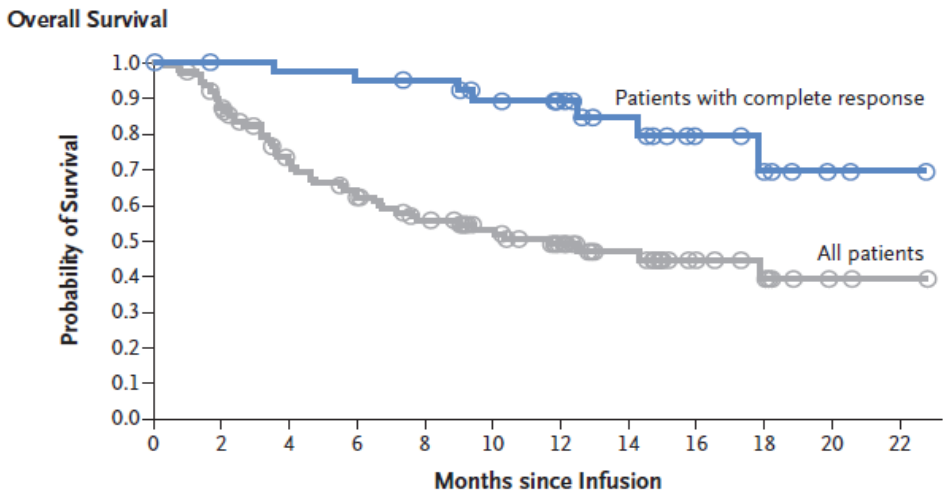


N Engl J Med 2017;377:2531-44.

Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma

- International, phase 2, pivotal study
- Relapsed or refractory diffuse large B-cell lymphoma, ineligible for or had disease progression after autologous hematopoietic stem-cell transplantation
- 93 patients received an infusion
- Best ORR was 52%
- 40% of the patients had CR, and 12% had PR
- At 12 months after the initial response, the rate of RFS was 65%
- Most common grade 3 or 4 adverse events:
  - cytokine release syndrome (22%),
  - neurologic events (12%),
  - cytopenias lasting more than 28 days (32%)
  - infections (20%),
  - febrile neutropenia (14%)

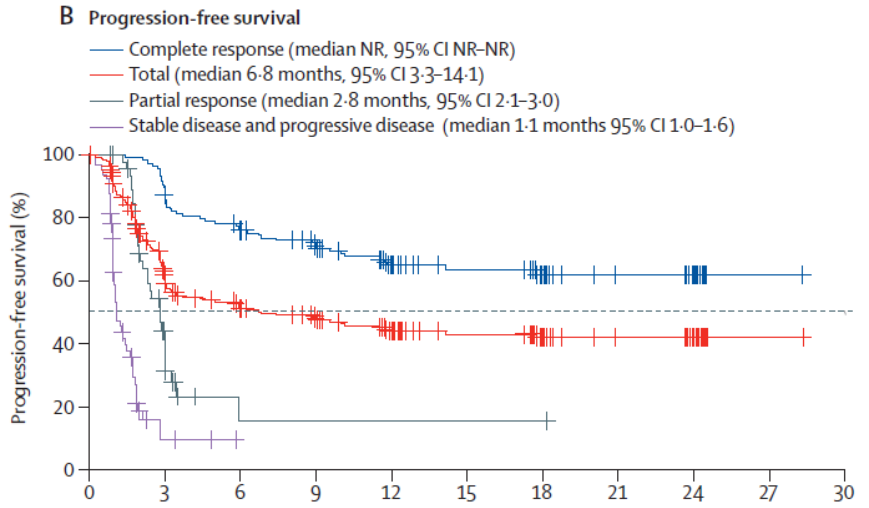


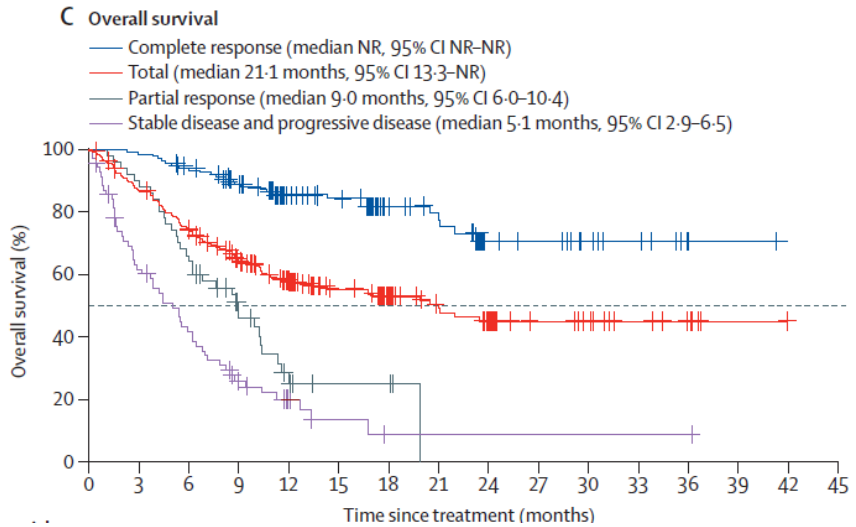


N Engl J Med 2019;380:45-56.

Lisocabtagene Maraleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

- Seamless design study at 14 cancer centres in the USA
- 269 pt with diffuse large B-cell lymphoma, double-hit or triple-hit lymphoma, transformed from any indolent lymphoma, primary mediastinal B-cell lymphoma, and follicular lymphoma grade 3B,
- Objective response rate was 73%
- Complete response rate was 53%
- Overall survival 18.8 months
- Most common adverse events of grade 3 or higher:
  - neutropenia 60%, anemia 37%, thrombocytopenia 72%,
  - CRS 42% (2%)
  - neurologic toxicity 30% (10%)





Lancet 2020; 396: 839–52

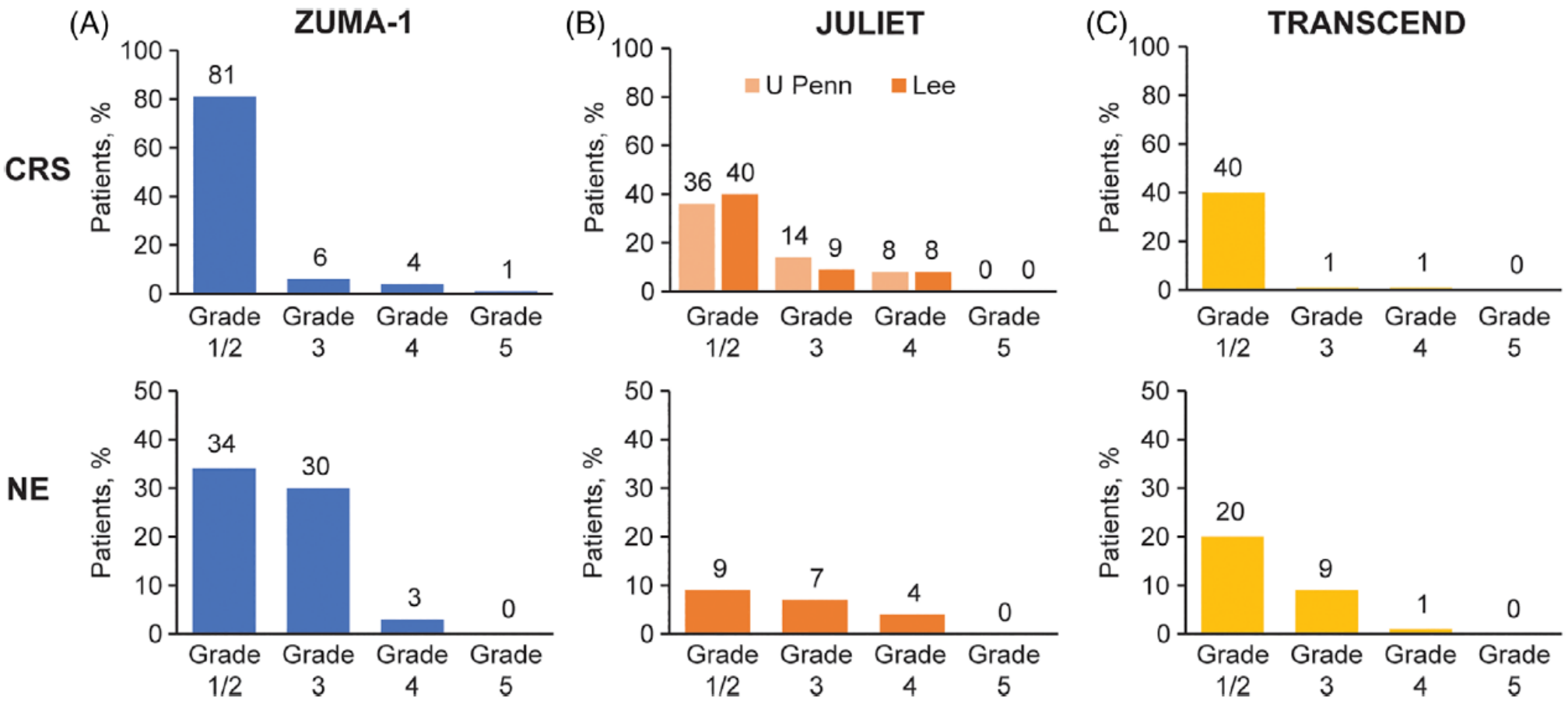
Observations from the JULIET, ZUMA-1, and TRANSCEND Trials

TABLE 3 Time-to-event outcomes of patients in CAR-T cell therapy clinical trials

	ZUMA-1[4] (N = 101)	JULIET[2,10,11] (N = 115)	TRANSCEND[6] (N = 256)
Median DOR, (95% CI)	NR (10.9-NE)	NR (10.0-NE)	NR (8.6-NR)
DOR at month 12, % (95% CI)	–	65 (49–78)	54.7 (46.7–62.0)
DOR at month 24, % (95% CI)	–	–	52.1 (43.6–49.8)
Median OS, months (95% CI)	NR (12.8-NE)[a]	11.1 (6.6–23.9)	21.1 (13.3-NR)
OS at month 12, % (95% CI)	59 (49–68)[5]	48.2 (38.6–57.1)	57.9 (51.3–63.8)
OS at month 24, % (95% CI)	50.5 (40.2–59.7)	40.0 (30.7–49.1)	44.9 (36.5–52.9)
Median PFS, months (95% CI)	5.9 (3.3–15.0)[a]	NR	6.8 (3.3–14.1)
PFS at month 12, % (95% CI)	44 (34–53)[5]	–[b]	44.1 (37.3–50.7)
PFS at month 24, % (95% CI)	–[c]	–	42.1 (35.0–48.9)
Follow-up, months	27.1	32.6	12.0–17.5[d]

Am J Hematol. 2021;96:1295–1312.

Observations from the JULIET, ZUMA-1, and TRANSCEND Trials



Am J Hematol. 2021;96:1295–1312.

CAR-T Access in Italy

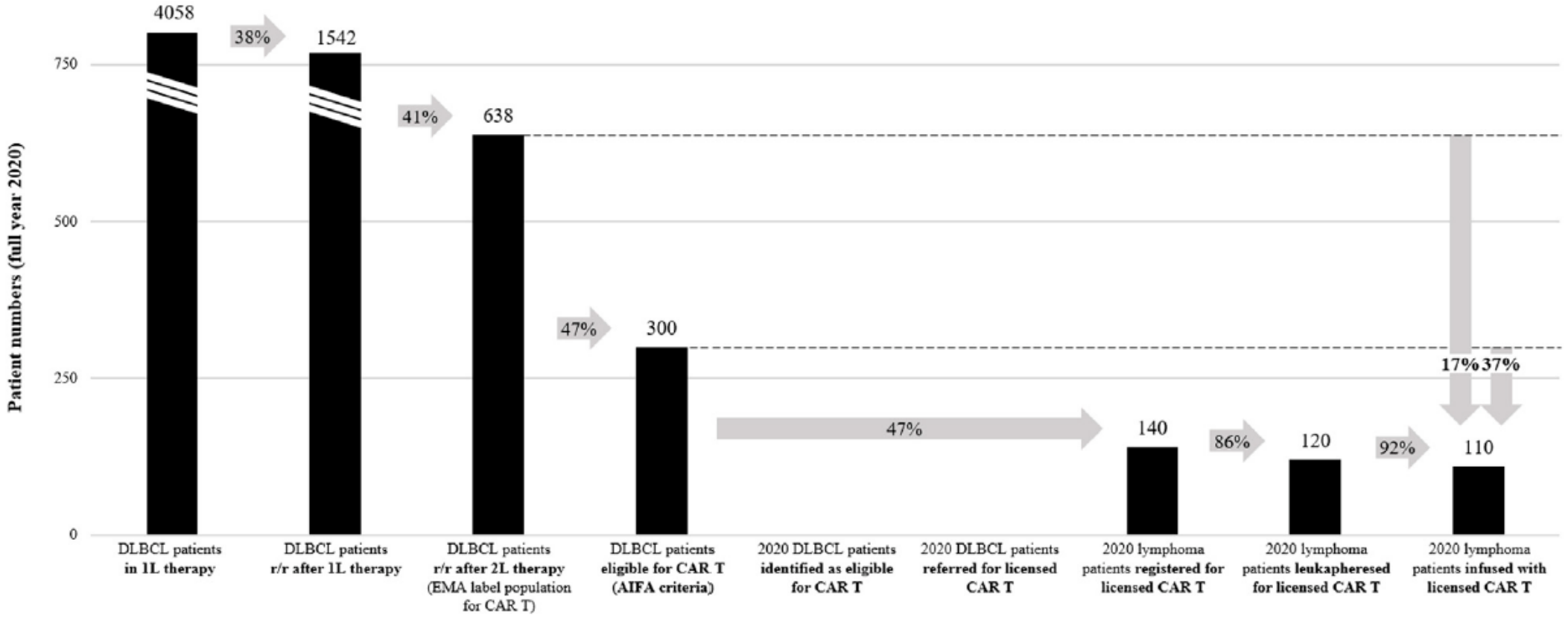


FIGURE 1 | 2020 DLBCL CAR T-cell therapy access analysis. Numbers in graph indicate the total patient numbers in Italy in 2020. Arrows indicate percentage of patients arriving at a specific step of the patient journey relative to a previous step. *See* **Supplementary Table S1** for calculations and references for the analysis. r/r, relapsed / refractory; 1L, first-line; 2L, second-line.

Front. Pharmacol. 13:915342.
doi: 10.3389/fphar.2022.915342

Transplant Ineligible and CAR-T Eligible Patients

Patient's characteristics in pivotal trials and real-life retrospective reports.

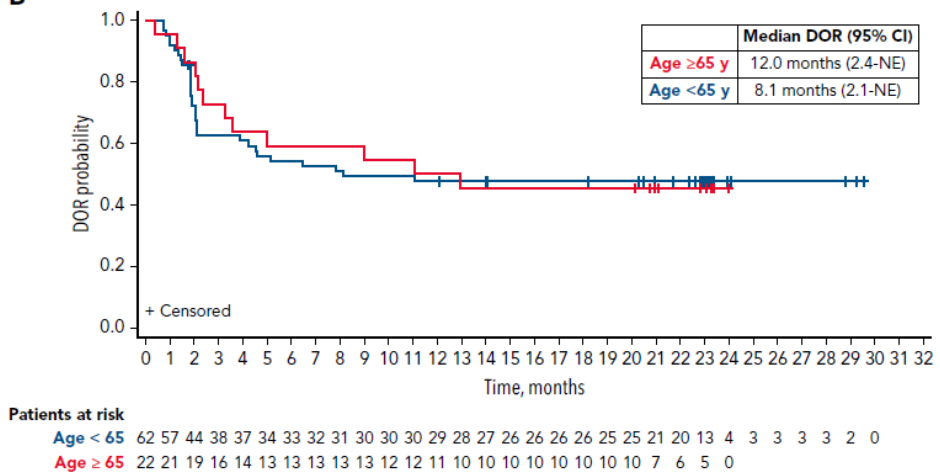
Study		Pivotal trials			Real-life retrospective reports				
		ZUMA-1 [4]	JULIET [5]	TRANSCEND NHL 001 [6]	Nastoupil JCO 2020 [43]	Jacobson JCO 2020 [44]	Pasquini Blood adv 2020 [46]	Landsburg ASH 2021 [47]	Locke ASH 2021 [45]
Product		Axi-cel	Tisa-cel	Liso-cel	Axi-cel	Axi-cel	Tisa-cel	Tisa-cel	Axi-cel
Patients	Enrolled	111	165	344	298	135	NA	NA	1500
	Manufacturing success	110 (99%)	153 (93%)	342 (99%)	298 (100%)	134 (99%)	NA	NA	NA
	Infused	101 (91%)	111 (67%)	269 (78%)	275	122	155	682	1500
	Eligible for clinical trial (%)	100%	100%	100%	57%	38%	NA	32%	49%
	Median age (range) - yr	58 (23–76)	56 (22–76)	63 (54–70)	60 (21–83)	62 (21–79)	65 (18–88)	66 (14–91)	62
	Age ≥60 yr	NA	NA	NA	154 (52%)	NA	NA	NA	NA
	Age ≥65 yr	24 (24%)	25 (23%)	112 (42%)	NA	NA	83 (54%)	377 (55%)	509 (38%)
	Age ≥75 yr	NA	NA	27 (10%)	NA	NA	27 (10%)	120 (18%)	NA
	Male sex	68 (67%)	72 (65%)	174 (65%)	192 (64%)	NA	91 (54%)	400 (59%)	872 (65%)
	ECOG-PS 0	42 (42%)	61 (55%)	110 (41%)	76 (26%)	36 (30%)	NA	NA	NA
	ECOG-PS 1	59 (58%)	50 (45%)	155 (58%)	164 (55%)	74 (61%)	NA	NA	NA
	ECOG-PS ≥ 2	0	0	4 (1%)	58 (19%)	12 (10%)	8 (5%)	137 (20%)	59 (4%)
	Prior ASCT	21 (21%)	54 (49%)	90 (33%)	98 (33%)	31 (25%)	40 (26%)	176 (26%)	359 (27%)
	Prior allo-SCT	0	0	9 (3%)	7 (2%)	4 (3%)	5 (3%)	11 (2%)	25 (2%)
	Renal disease[a]	0	0	51 (19%)	21 (7%)	NA	NA	NA	30 (2%)
	Cardiovascular disease[b]	0	0	13 (5%)	10 (3%)	2 (2%)	NA	NA	169 (13%)
Toxicity	Non-relapse mortality (%)	2%	0	3%	4.4%	6%	1.2%	NA	NA

European Journal of Cancer 175 (2022) 246–253

Outcomes of older patients in ZUMA-1, a pivotal study of axicabtagene ciloleucel in refractory large B-cell lymphoma

Sattva S. Neelapu,[1] Caron A. Jacobson,[2] Olalekan O. Oluwole,[3] Javier Munoz,[4] Abhinav Deol,[5] David B. Miklos,[6] Nancy L. Bartlett,[7,8] Ira Braunschweig,[9] Yizhou Jiang,[10] Jenny J. Kim,[10] Lianqing Zheng,[10] John M. Rossi,[10] and Frederick L. Locke[11]

B



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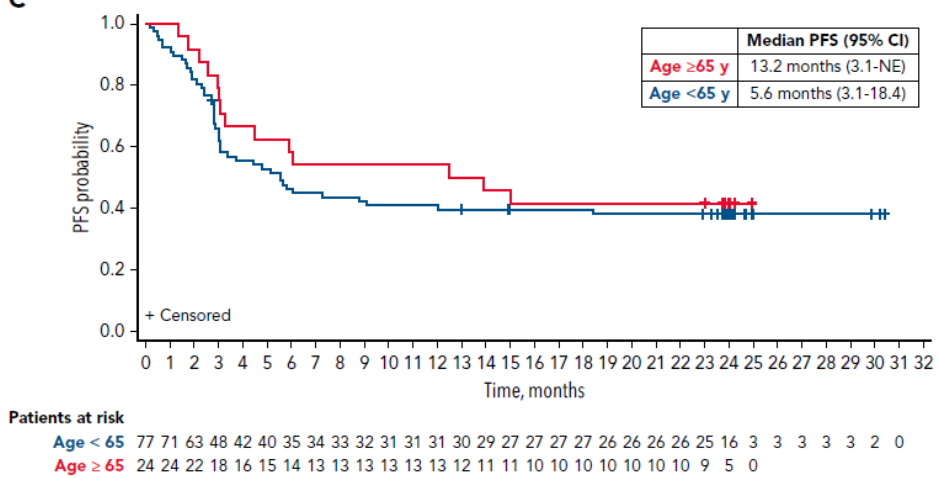


Transplant Ineligible and CAR-T Eligible Patients

ASCT-eligibility include:

- ECOG-PS 2 (or KPS >60%),
- left ventricular ejection fraction > 40-45%,
- diffusing capacity of the lung for carbon monoxide > 50-60%,
- creatinine clearance >50 mL/min,
- absence of liver cirrhosis.

CAR-T eligible (and not ASCT):

- Previous ASCT
- Poor mobilizers
- Chemo resistant disease
- Advanced age

Group		Double eligible	Single eligible	Ineligible
Transplant-eligible		+	-	-
CAR T-eligible		+	+	-
		Eligibility criteria		
Patient	Fitness	Fit	Not fit but not frail	Frail
	Age (years)	*≤65-70*	*>65-70*	-
	Performance status	*Good*	*Intermediate*	*Poor*
	Organ functions	*Good*	*Intermediate*	*Poor*
	Comorbidities	*Low*	*Intermediate*	*High*
Treatment	Prior ASCT	No	Yes	-
Graft	Stem cell collection	Successful	Failure	-
Tumor	Tumour response	Remission	Refractory	-

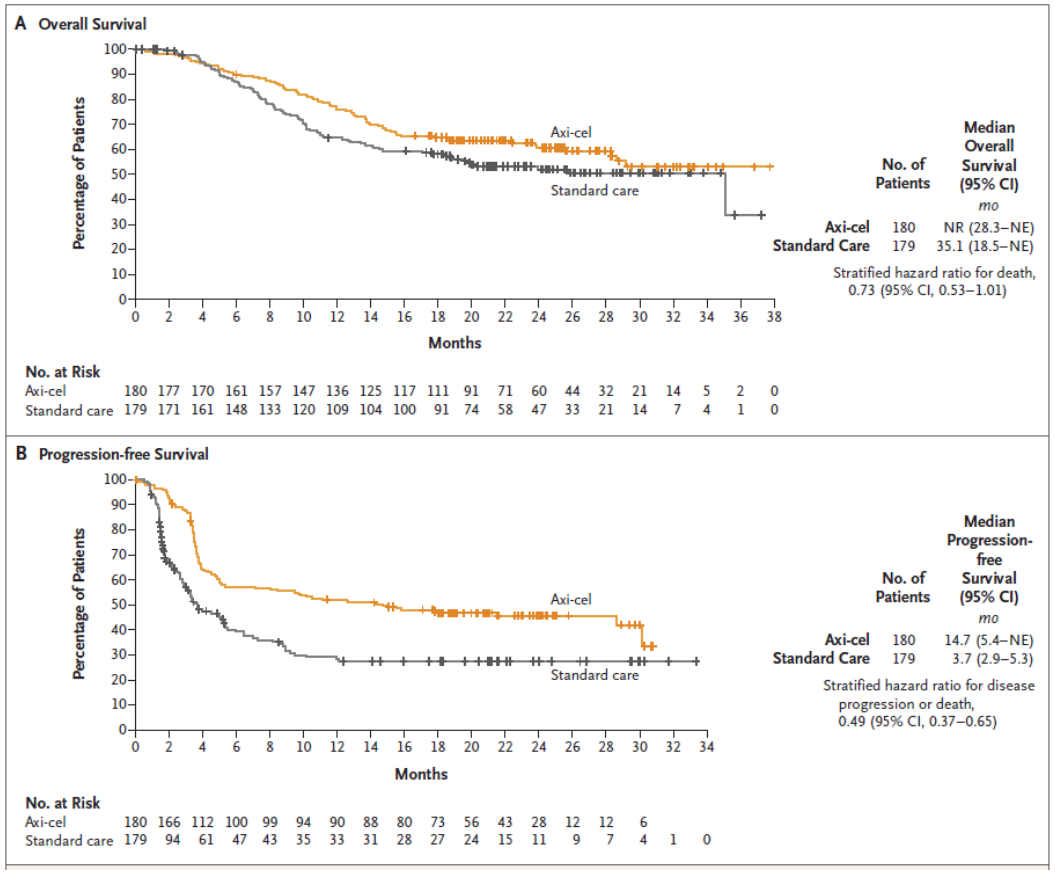
European Journal of Cancer 175 (2022) 246–253

ORIGINAL ARTICLE

Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma

F.L. Locke, D.B. Miklos, C.A. Jacobson, M.-A. Perales, M.-J. Kersten,

- International, phase 3 trial
- DLBCL, refractory to or had relapsed no more than 12 months after first-line chemoimmunotherapy
- Axi-cell vs chemo+AutoHSCT
- 359 patients, median follow-up of 24.9 months
- EFS 8.3 months in the axi-cel group and 2.0 months in the standard-care group
- Response occurred in 83% of the patients in the axi-cel group and in 50% of those in the standard-care group (with a complete response in 65% and 32%, respectively)
- AE of grade 3 or higher occurred in 91% of the patients who received axi-cel and in 83% of those who received standard care



N Engl J Med 2022;386:640-54.

CAR-T is superior to standard of care as second-line therapy for large B-cell lymphoma

	ZUMA-7 Locke et al.[15] 2021	BELINDA Bishop et al.[16] 2021	TRANSFORM Kamdar et al.[14] 2021
Autologous Anti-CD19 CAR	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
Co-stimulatory domain	CD28	4-1BB	4-1BB
T-cell selection	No	No	CD4:CD8
Inclusion criteria	RD and relapse <1 year	RD and relapse<1 year	RD and relapse <1 year
	LBCL	LBCL PMBL FL3B Hx of CNS	LBCL PMBL FL3B Sec. CNS lymphoma
Bridging chemotherapy	No (only steroids)	Allowed (switching allowed)	Allowed
Lymphodepletion	Flu 30/Cy500 mg/m^2 X3d	Flu 25/Cy250 mg/m^2 X3d	Flu 30/Cy300 mg/m^2 X3d
Cell dose	2×10^6 cell/kg	$0.6\text{-}6\times10^8$ cells Median 2.9×10^8	1×10^8 cells
SOC arm			
Salvage regimen	ICE DHAP GDP ESHAP	ICE DHAP GDP GEMOX	ICE DHAP GDP
Cycle number	2–3	2 (Switching allowed)	3

Br J Haematol. 2022;198:838–846.

CAR-T is superior to standard of care as second-line therapy for large B-cell lymphoma

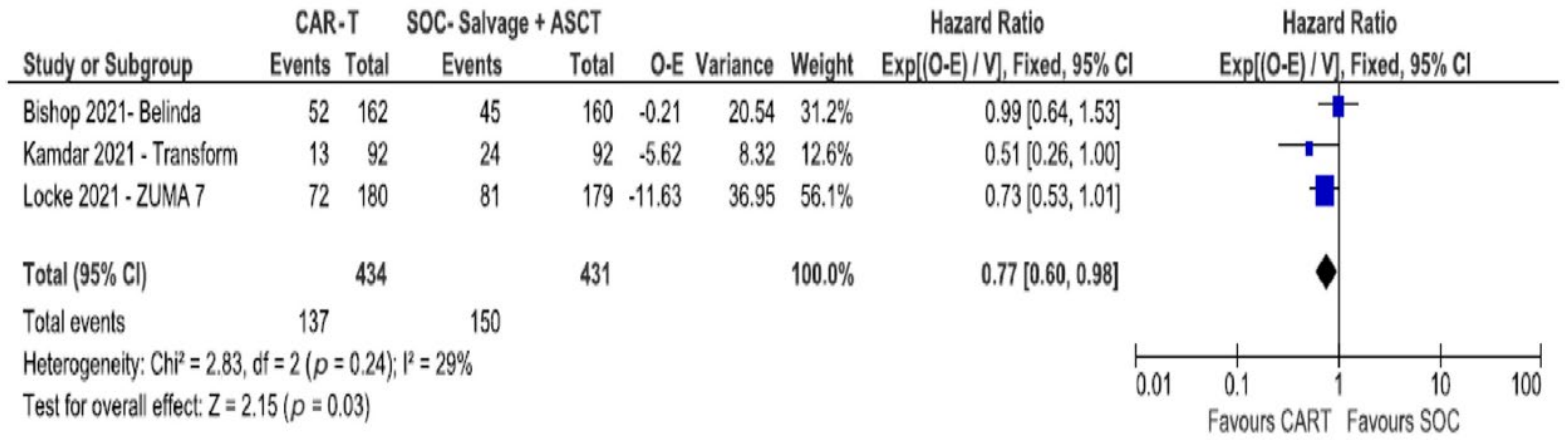


FIGURE 2 Overall survival

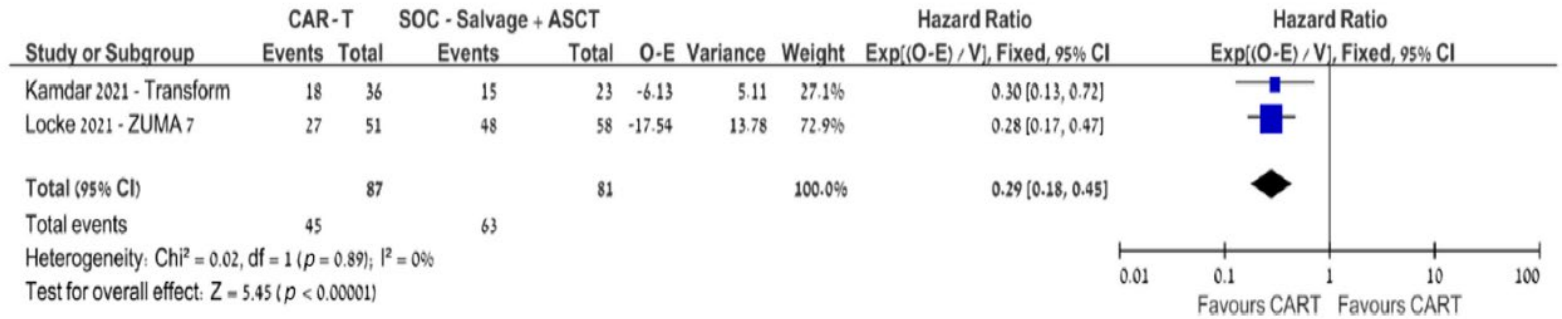


FIGURE 3 Event-free survival

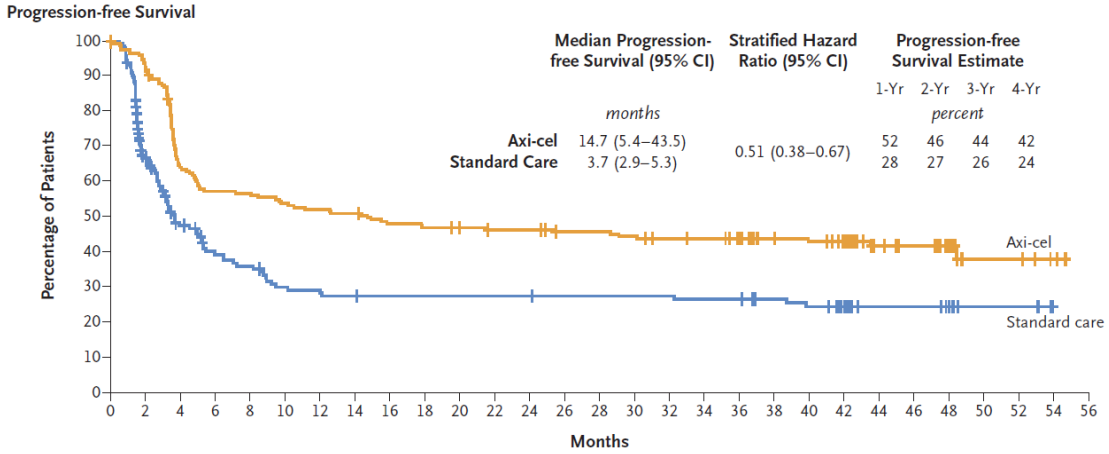
Br J Haematol. 2022;198:838–846.

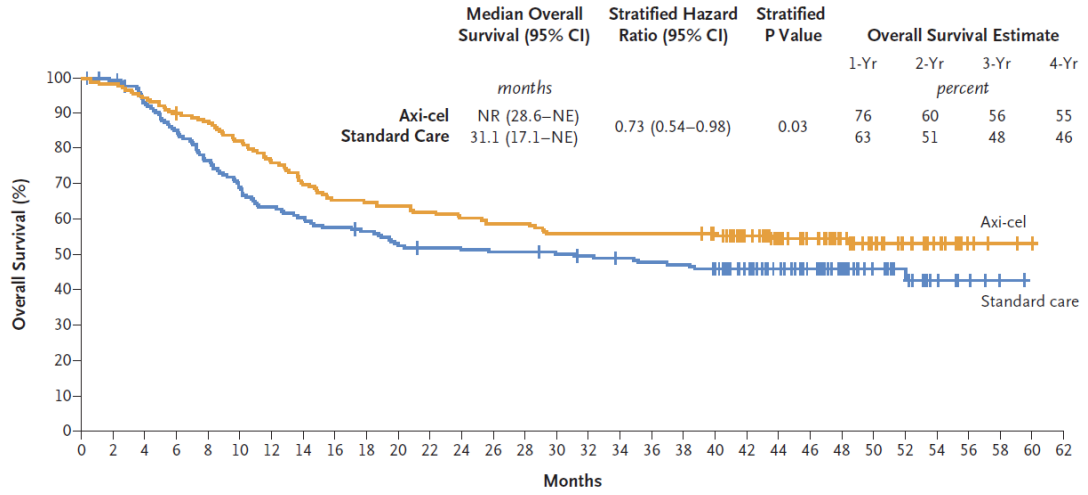
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma

- In a phase 3 trial, patients with early relapsed or refractory large B-cell lymphoma who received axicabtagene ciloleucel (axi-cel) as second-line treatment had significantly longer event-free survival than those who received standard care.
- At a median follow-up of 47.2 months, the median overall survival was not reached in the axi-cel group and was 31.1 months in the standard-care group.
- The median investigator-assessed progression-free survival was 14.7 months in the axi-cel group and 3.7 months in the standard-care group, with estimated 4-year percentages of 41.8% and 24.4%



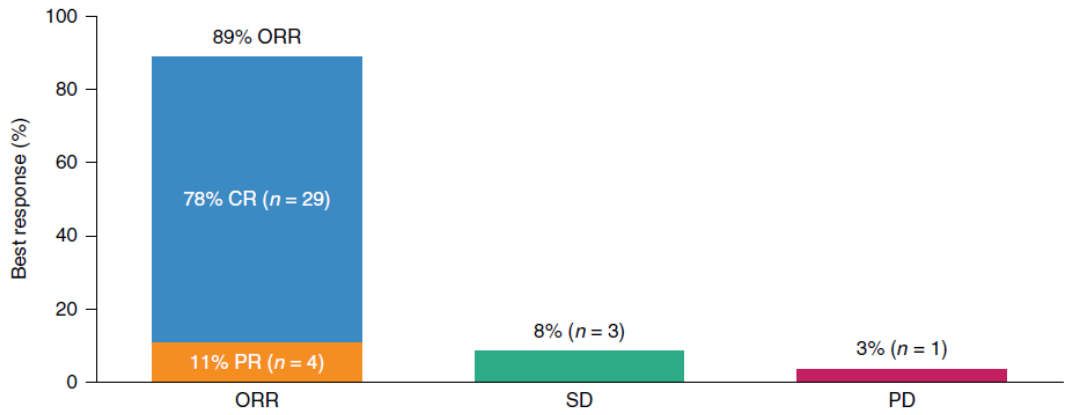


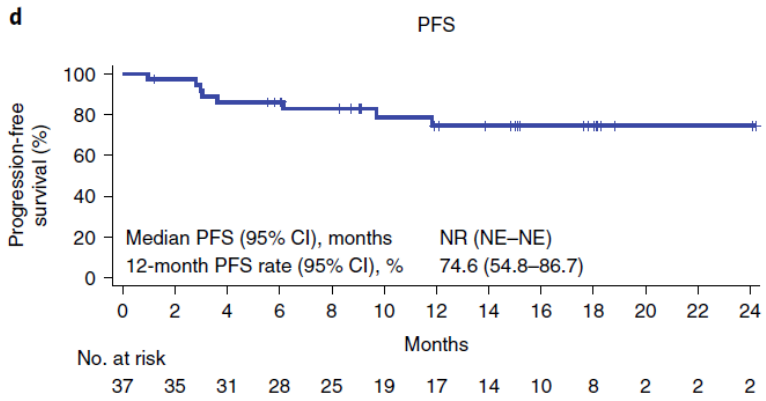
DOI: 10.1056/NEJMoa2301665

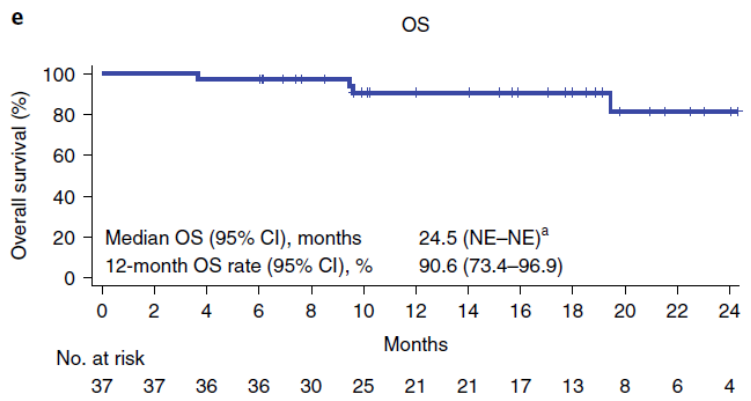
Axicabtagene ciloleucel as first-line therapy in high-risk large B-cell lymphoma: the phase 2 ZUMA-12 trial

Sattva S. Neelapu[1]✉, Michael Dickinson[2], Javier Munoz[3], Matthew L. Ulrickson[3],

- Phase 2, multicenter, single-arm ZUMA-12 study
- 40 patients with high-risk LBCL, median follow-up, 15.9 months
- 78% CRR (95% confidence interval (CI), 62–90) and 89% ORR (95% CI, 75–97)
- 73% of patients remained in objective response
- Grade ≥3 cytokine release syndrome (CRS) and neurologic events occurred in three patients (8%) and nine patients (23%), respectively

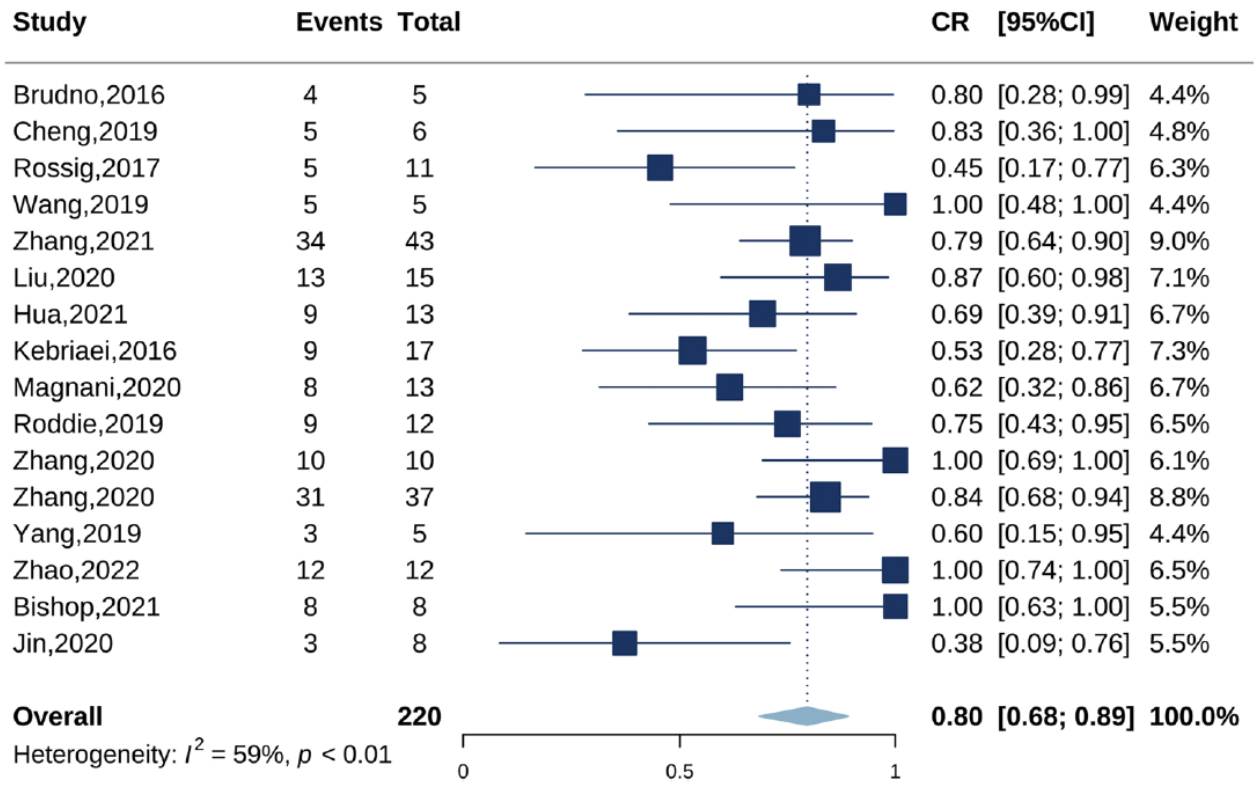






Donor-derived and off-the-shelf allogeneic anti-CD19 CAR T-cell therapy for R/R ALL and NHL

- Potential for extensive clinical applications
- Donor derived CAR-Ts:
  - ALL patients had a complete remission (CR) rate of 80% and a 1-year overall survival rate of 51%
  - GvHD rate was 4%, CRS was 69%, and ICANS was 8%
- Off-the-shelf CAR-Ts:
  - CR rate for ALL was 70%, and for NHL, it was 52%
  - GvHD incidence 0%



Critical Reviews in Oncology / Hematology 179 (2022) 103807

Donor-derived and off-the-shelf allogeneic anti-CD19 CAR T-cell therapy for R/R ALL and NHL

Outcomes of the included off-the-shelf CAR T-cell studies and pooled results.

Study	N	CR (%)	ORR (%)	GvHD (%)	Severe CRS (%)	Severe ICANS (%)
ALL						
(Benjamin et al., 2020)	21/21	14 (67)	14 (67)	2 (10)	3 (14)	0 (0)
(Shah et al., 2021)	5/5	4 (80)	4 (80)	0 (0)	0 (0)	0 (0)
Pooled results	**26/26**	**70 %**	**70 %**	**5 %**	**9 %**	**NA**
(95 % CI)		**(49–88)**	**(49–88)**	**(0–20)**	**(0–25)**	
I^2	**NA**	**0 %**	**0 %**	**0 %**	**0 %**	**NA**
NHL						
(Lekakis et al., 2021)	12/9	6 (50)	6 (50)	0 (0)	0 (0)	0 (0)
(Neelapu et al., 2021)	36/46	18 (50)	27 (75)	0 (0)	1 (2)	0 (0)
(Shah et al., 2021)	13/16	8 (62)	11 (85)	0 (0)	0 (0)	1 (6)
Pooled results	**61/71**	**52 %**	**72 %**	**0 %**	**0 %**	**0 %**
(95 % CI)		**(39–65)**	**(55–87)**	**(0–5)**	**(0–5)**	**(0–6)**
I^2	**NA**	**0 %**	**43 %**	**0 %**	**0 %**	**19 %**

N, number of patients evaluable for efficacy/ safety outcomes. CR, complete remission. ORR, objective response rate. GvHD, graft versus-host disease. CRS, cytokine release syndrome. ICANS, immune effector cell-associated neurotoxicity syndrome. NA, not available.

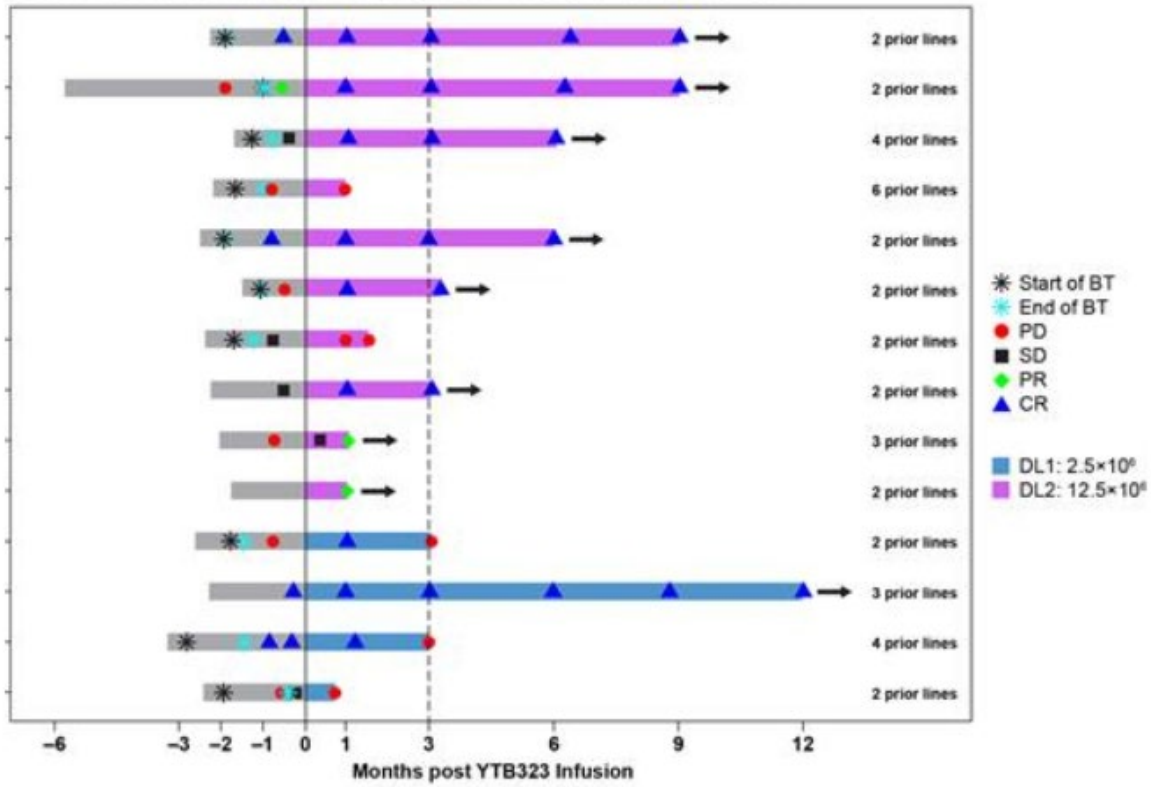
* Severe CRS/ICANS are defined as CRS/ICANS $\geq$ Grade 3.

Critical Reviews in Oncology / Hematology 179 (2022) 103807

A First-in-Human Study of YTB323, a Novel, Autologous CD19-Directed CAR-T Cell Therapy Manufactured Using the Novel T-Charge ™ platform, for the Treatment of Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma

- YTB323 is an autologous CD19-directed CAR-T cell therapy utilizing the FMC63 domain for CD19 recognition and 4-1BB costimulatory domain
- Ex vivo culture time to about 24 hours and takes <2 d to manufacture the final product - the T-Charge ™ platform
- Phase I, multicenter, dose-escalation study (NCT03960840)
- 15 pts with r/r DLBCL, median age 65 years, 60% received 2 prior lines

Figure. YTB323 infusions at DL1 and DL2 in patients with DLBCL



Arrow denotes ongoing efficacy assessments; gray bars represent screening assessments.
BT, bridging therapy; CR, complete response; DL, dose level; PD, progression of disease; PR, partial response; SD, stable disease.

Blood (2021) 138 (Supplement 1): 740.

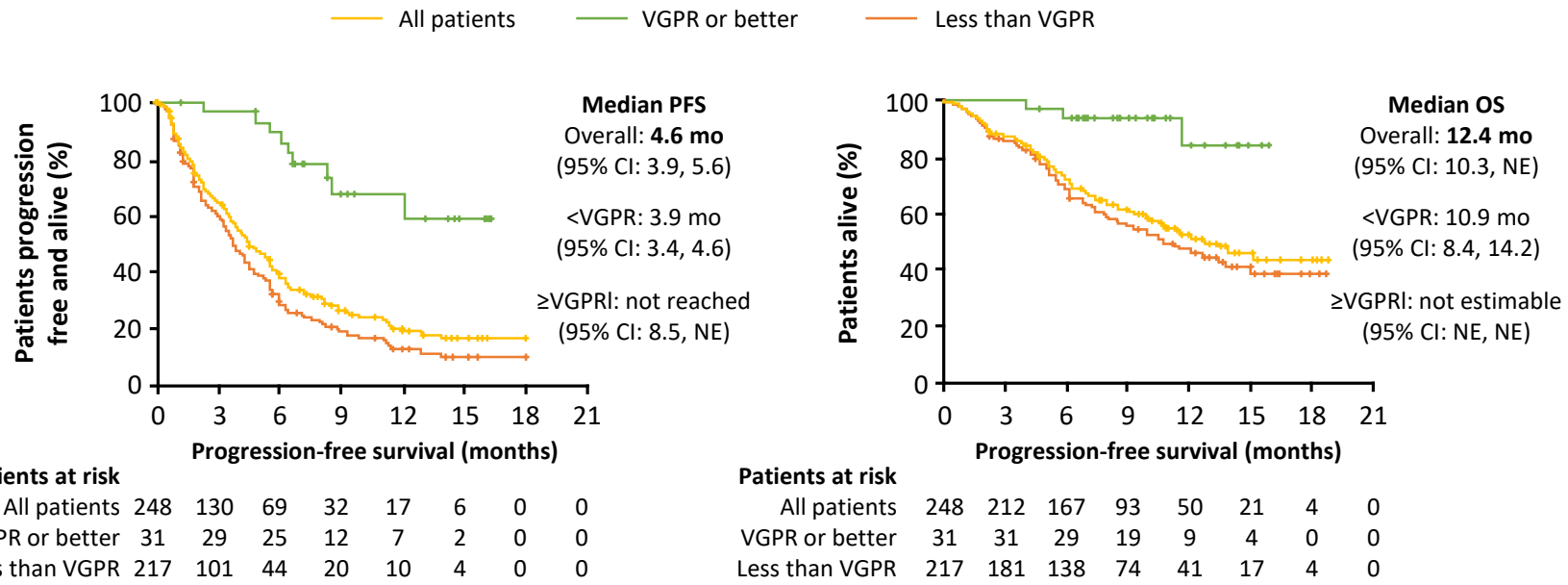
DISEMINIRANI PLAZMOCITOM

Response rates, PFS and OS[1]

Response to SOC treatment

	N=248
ORR[a], %	29.8
Best response, %	
sCR	0
CR	0.4
VGPR	12.1
PR	17.3
Minimal response	5.2
Stable disease	31.0
Progressive disease	18.5
Not evaluable	15.3
Median DOR, months (95% CI)	7.4 (4.7-12.5)

PFS and OS by VGPR status



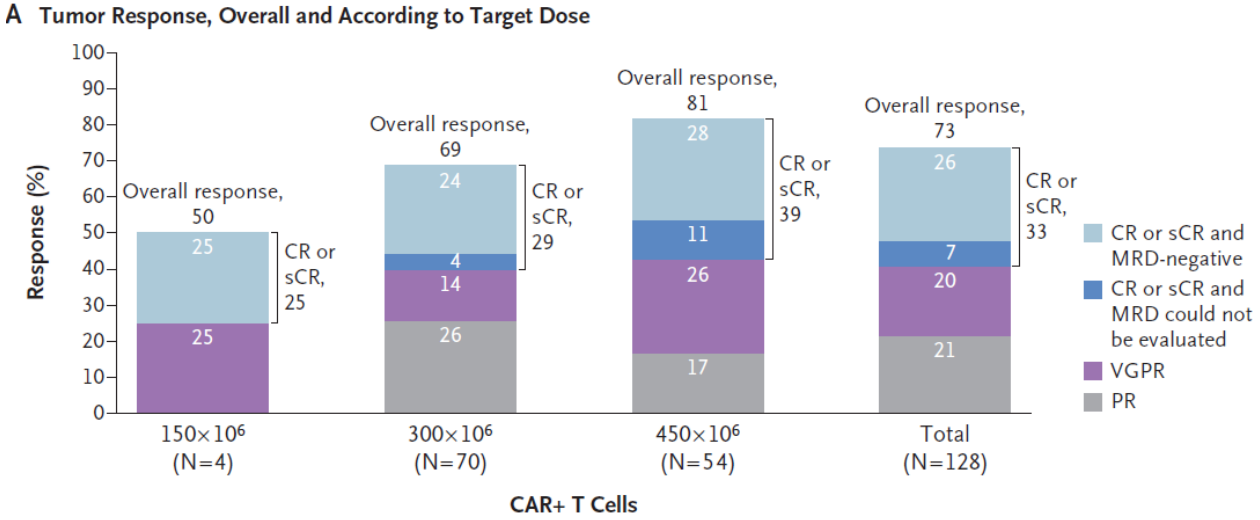
- Only 12.5% of patients achieved ≥VGPR and 0.4% of patients achieved ≥CR, and many patients had rapid disease progression
- Patients who did not reach VGPR had shorter PFS and OS than those who achieved ≥VGPR

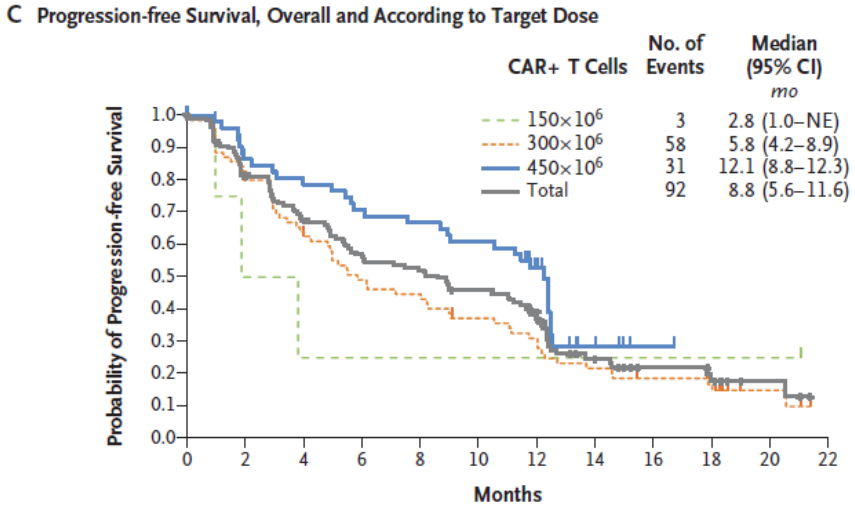
Real-life SOC treatment in heavily pre-treated, triple-class exposed patients with RRMM results in poor outcomes

[a]Response review committee assessed.
NE, not estimable.
1. Moreau P et al. 2021 ASH Annual Meeting. Poster 3057.

Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

- Phase 2 study in relapsed and refractory myeloma
- At least three previous regimens including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody were enrolled
- Patients received ide-cel target doses of 150 × 106 to 450 × 10^6 CAR-positive (CAR+) T cells
- 128 received ide-cel
- 73% had a response, 33% had a complete response or better
- Median PFS was 8.8 months
- Side effects:
  - neutropenia 91%,
  - anemia 70%,
  - thrombocytopenia 63%,
  - CRS 84%
  - neurotoxic effects 18%

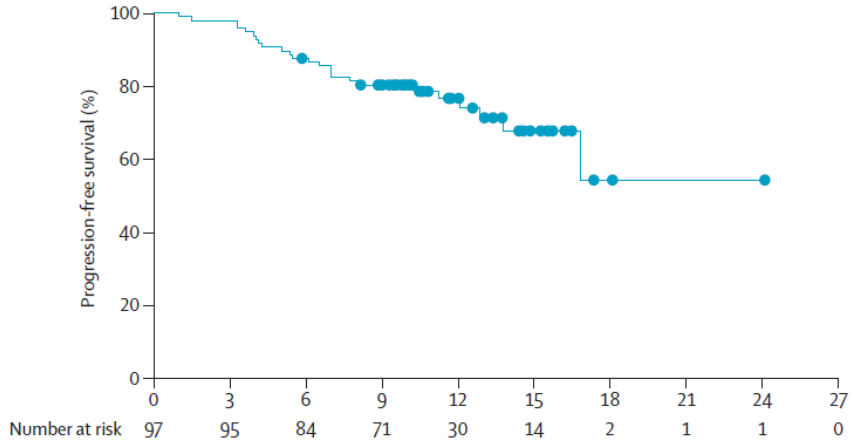


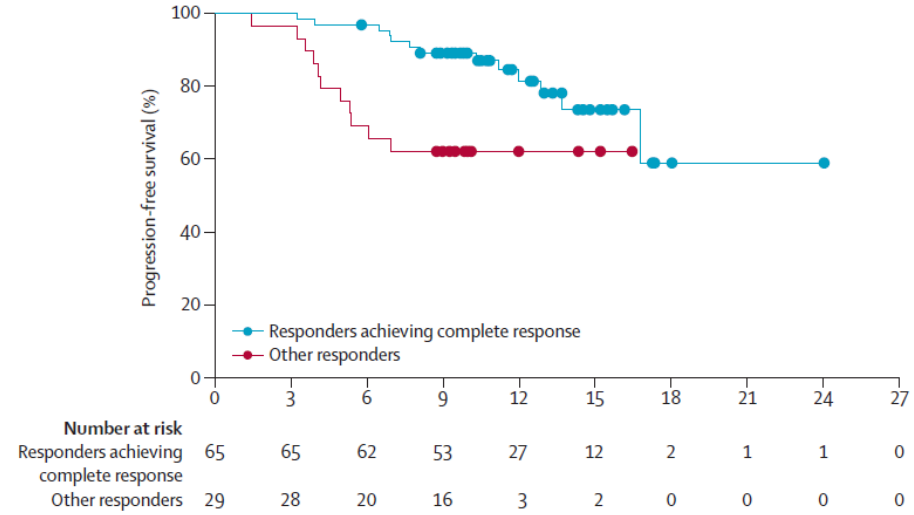


N Engl J Med 2021;384:705-16.

Ciltacabtagene autoleucel in patients with relapsed or refractory multiple myeloma - CARTITUDE-1

- Ciltacabtagene autoleucel – open-label, multicentric, phase 1/2 study
- Patients received 3 or more previous lines of therapy or were double-refractory
- 97 patients, median follow-up 12.4 months
- 97% ORR, 67% CR, PFS 77% at 12 months
- CRS 95% (grade 3/4 in 4%), neurotoxicity 21% (grade ¾ in 9%)





Lancet 2021; 398: 314–24

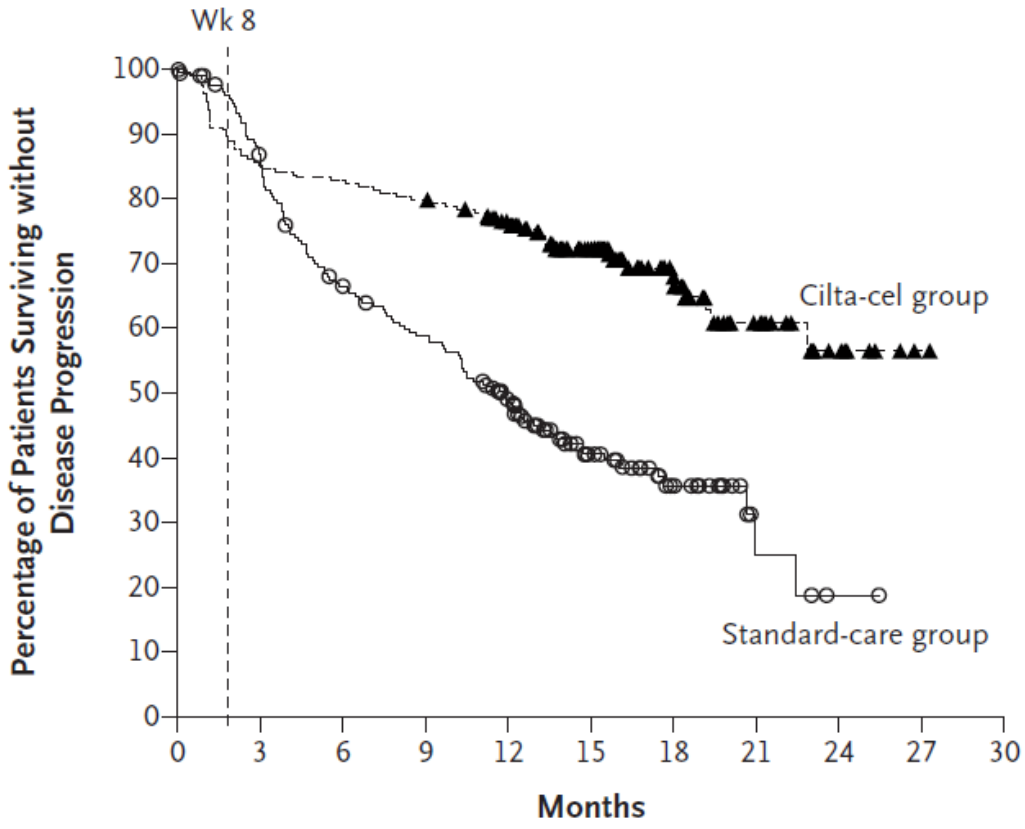
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma

- In a phase 3 trial of 419 patients with lenalidomide-refractory multiple myeloma, cilta-cel resulted in a lower risk of disease progression or death than standard care.
- At a median follow-up of 15.9 months, the median PFS was not reached in the cilta-cel group and was 11.8 months in the standard-care group.
- PFS at 12 months was 75.9% in the cilta-cel group and 48.6% in the standard-care group.
- More patients in the cilta-cel group had an overall response, a complete response or better, and an absence of minimal residual disease.

Variable	Cilta-cel (N=208)	Standard Care (N=211)
Complete response or better	152 (73.1)	46 (21.8)
Very good partial response or better	169 (81.2)	96 (45.5)
12-month duration of response — % (95% CI)	84.7 (78.1–89.4)	63.0 (54.2–70.6)
Median time to first response (range) — mo	2.1 (0.9–11.1)	1.2 (0.6–10.7)
Median time to best response (range) — mo	6.4 (1.1–18.6)	3.1 (0.8–20.6)



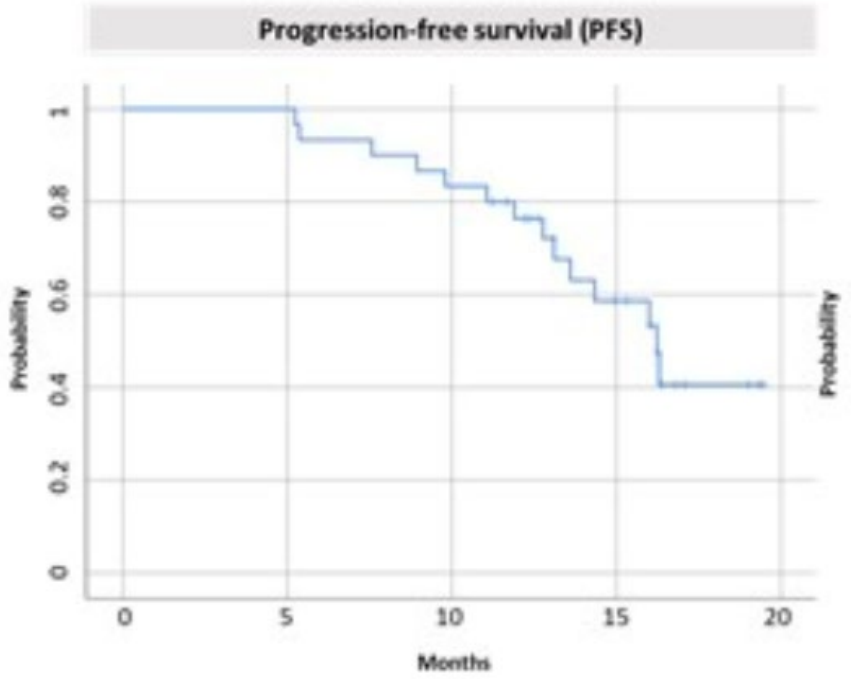
EFFICACY AND SAFETY OF ARI0002H, AN ACADEMIC BCMA-DIRECTED CAR-T CELL THERAPY WITH FRACTIONATED INITIAL THERAPY AND BOOSTER DOSE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

- ARI0002h is a lentiviral autologous CAR T-cell product with a 4-1BB co-stimulatory domain and a humanized single chain variable fragment targeting BCMA
- ≥2 prior regimens, including a proteasome inhibitor, an immunomodulatory drug and an anti-CD38 antibody
- Refractory to the last line
- $3x10^6$/kg CAR+ cells and was administered in a fractionated manner (10%/30%/60%), with at least 24h between infusions.
- Second dose of $3x10^6$ CAR+ cells/kg was planned at least 4 months after the first dose

EHA 2022, S103

EFFICACY AND SAFETY OF ARI0002H, AN ACADEMIC BCMA-DIRECTED CAR-T CELL THERAPY WITH FRACTIONATED INITIAL THERAPY AND BOOSTER DOSE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

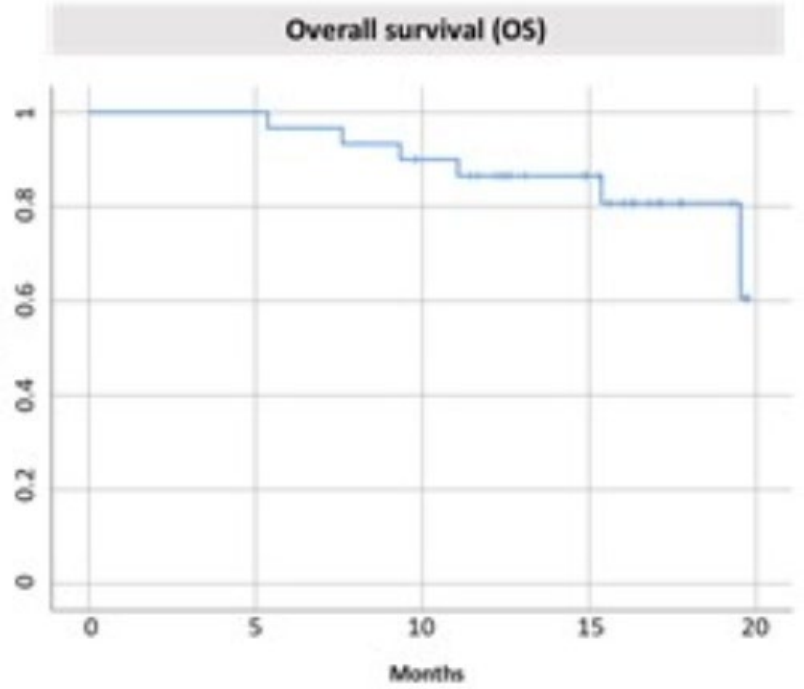
- 35 pts (median age 61 years)
- Median CAR-T cell production time was 11 days (range 9-14) with a 100% manufacture success
- Median follow-up was 16 months.
- ORR of 30 evaluable pts was 100%, sCR and VGPR rate of 90%
- 26 MRD-evaluable pts at day +100, 92% were MRD-negative
- 53% of patients were alive and without progression at 16 months
- 16-month OS rate was 80%
- Median time after first infusion was 4 months and 38% received a second lymphodepletion regimen. No relevant toxicities after second infusions were reported



EHA 2022, S103

EFFICACY AND SAFETY OF ARI0002H, AN ACADEMIC BCMA-DIRECTED CAR-T CELL THERAPY WITH FRACTIONATED INITIAL THERAPY AND BOOSTER DOSE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

- CRS (87%; grade [gr] 3/4 0%; gr 1 73%),
- neutropenia (97%; gr 3/4 100%),
- anemia (85%; gr 3/4 43%),
- thrombocytopenia (79%; gr 3/4 70%)
- No CAR-T cell-related neurotoxicity cases were reported.
- Tocilizumab and corticosteroids were administered in 76% (mainly for persistent grade 1 CRS) and 12% of pts, respectively.

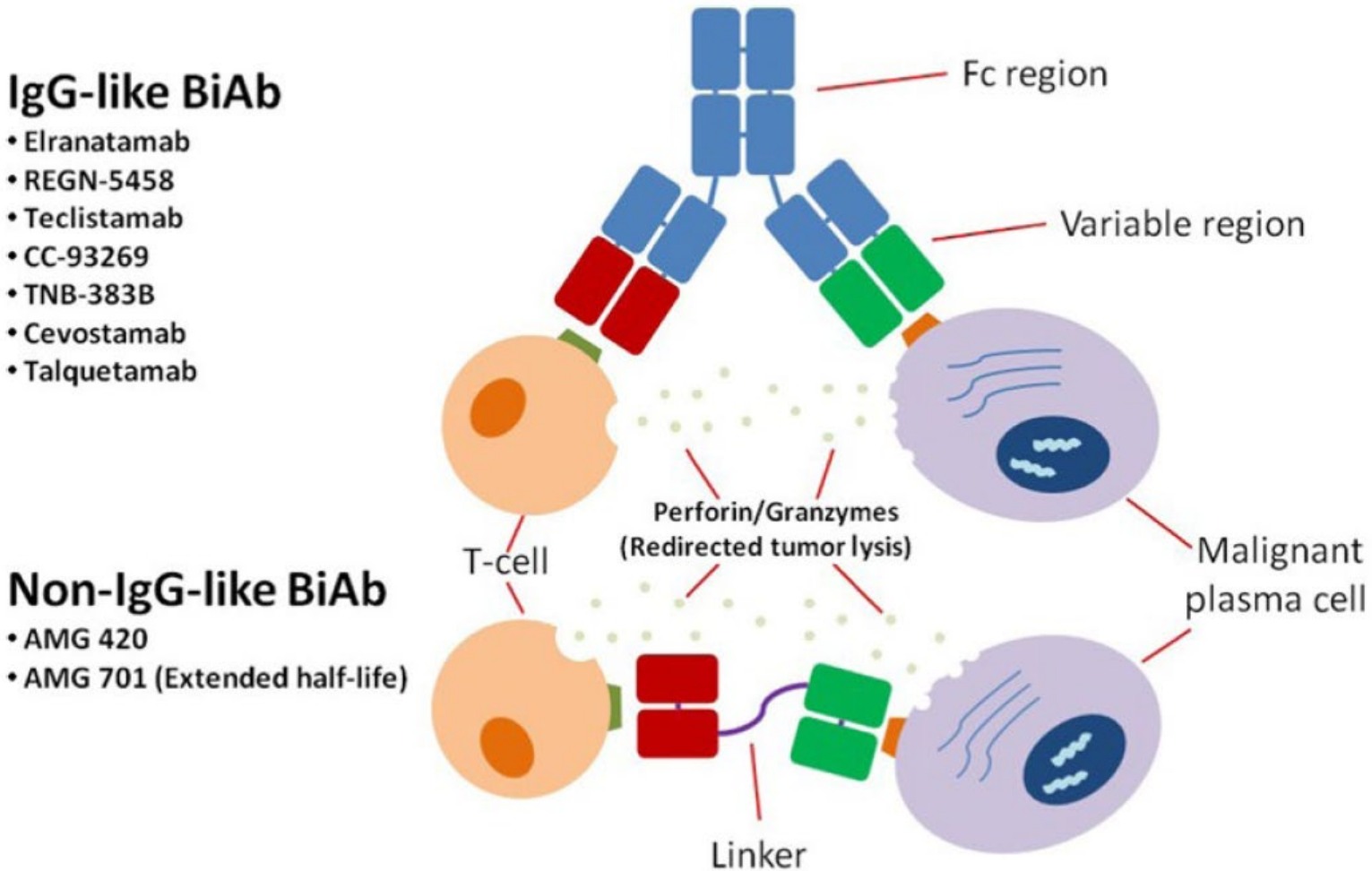


EHA 2022, S103

	BB21217 CRB-402 (n = 72)	CT053 LUMMICAR (n = 18)	CT103A FUMANBA-1 (n = 79)	C-CAR088 (n = 23)	P-BCMA-101 PRIME (n = 53)	ALLO-715 Universal (n = 43)	ARI-002h (n = 30)	BMS-986354 (n = 65)	MCARH109 (n = 19)	BMS-95266 (n = 33)
Phase	1	1b/2	1/2	1	1/2	1	1	1	1	1
Follow-up (months), median (range)	23 (9-46)	6 (2-11)	25.3 (4.1-36.7)	6.2 (0.7-16.1)	NA	10.2	17.5 (5-23)	9 (1-16)	10.1	3.1
Target/ costimulation	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	BCMA/4-1BB	GPRC5d/ 4-1BB	GPRC5d/ 4-1BB
scFv	Mouse	Human	Human	Human	Mouse	Human	Human	Human	Human	Human
Specificity	Autologous	Autologous	Autologous	Autologous	Autologous	Allogeneic	Autologous	Autologous	Autologous	Autologous
CAR-T-cell dose	150-450 × 10^6	1.5-3.0 × 10^8	1.0 × 10^6/kg	1.0-6.0 × 10^6/kg	51-1,178 × 10^6	40-480 × 10^6	3 × 10^6/kg	10-80 × 10^6	25-450 × 10^6	25-450 × 10^6
Population										
Age, years, median (range)	62 (33-76)	62 (36-78)	56 (39 - 70)	60 (45-74)	60 (42-74)	64 (46-77)	61 (53-65)	63 (43-75)	60 (38-76)	63 (48-80)
Previous lines, median (range)	6 (3-17)	5 (3-11)	5 (3 - 13)	4 (2-12)	8 (2-18)	5 (3-11)	4 (3-5)	5 (3-13)	6 (4-14)	4 (3-13)
Triple-class refractory, No. (%)	50 (69)	85	13 (16.5)	NR	60	90.7	67	90.8	16 (94)	NR
Penta-refractory, No. (%)	NR	50	NR	NR	NR	42	23	47.7	NR	NR
Efficacy										
ORR, No. (%)	69	94	75 (94.9)	22 (95.7)	50-75	55.8	100	95.1	71	89.5
CR, No. (%)	36	27.8	58.2	43.5	NR	≥VGPR: 34.9	67	39.3	6 (35)	47.4
PFS (months), median (95% CI)	12.8 (7.3 to 18.6)	NR	25.3 (3.0 to NE)	6 PFS: 65.1%	NR	NR	NR (53% at 18)	NR	NR	NR
CRS										
All grade, No. (%)	54 (75)	15/18 (83.3)	72 (92.4)	21 (91.3)	17%	24 (55.8)	80%	53 (81.5)	15 (88)	21 (63.6)
Grade 3-4, No. (%)	3 (2 grade 5)	0 (0)	2 (2.5)	1 (4.3)	0%	1 (2.3)	0 (0)	1 (1.5)	1 (6)	2 (6.1)
Onset (days), median (range)	2 (1-20)	2 (DLO) and 1 (DL1)	6 (1-12)	6 (1-11)	NR	7	7 (4.5-8)	4 (1-8)	NR	3 (1-9)
Duration (days), median (range)	4	4 (DLO) and 3 (DL1)	5 (1-30)	5 (2-9)	NR	4	2 (1-14)	2 (2-9)	NR	4 (1-11)
Tocilizumab/steroids %/%	53/17	≈30/20	20/34.7	26/9	7/6	23.3/14	63/15	≈70/30-57	53/24	45.5/24.2
ICANS										
All grade, No. (%)	11 (15)	2 (DLO) and 1 (DL1)	1 (1.3)	1 (4.3)	4	6 (14)	0	6 (9.2)	1 (6)[a]	2 (6.1)
Grade 3-4, No. (%)	3 (4)	1 patient	0	0 (0)	4	0 (0)	0	1 (1.5)	1 (6)	

Antibodies and bispecifics for multiple myeloma: effective effector therapy

Christopher Cipkar, Christine Chen, and Suzanne Trudel



DOI 10.1182/hematology.2022000334

Bispecific antibodies in MM

	Teclistamab[1] (n=165)	AMG701[2] (n=85)	REGN5458[3] (n=49)	TNB-383B[4] (n=58)	CC-93269[5] (n=30)	Elranatamab[6] (n=30)	Talquetamab[7] (n=82)	Cevostamab[8] (n=53)
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	GPRC5D	FcRH5
Administration	SC, QW	IV, QW	IV, QW then Q2W	IV, Q3W	IV, QW then Q2W	SC, QW	SC, QW/Q2W 405/800 µg/kg	IV, Q3W
Median prior LoT	5 (2-14)	6 (2-25)	5 (2-17)	6 (3-15)	5 (3-13)	8 (3-15)	6 (2-17)/5 (2-17)	6 (2-15)
Triple refractory	77.6%	62%	100%	64%	67%	87%	76%/77%	72%
CRS, G≥3	72%, 0.6%	64%, 9%	38%, 0%	69%, 3%	77%, 3%	73%, 0%	76%, 1%/79%, 0	76%, 2%
Neurotoxicity, G≥3	14.5%, 0.6%	NR	12%, 0	NR	NR	NR	NR	28%, 0
ORR	63%	26%	51%	50.7%	89% at 6-10 mg	83% at RP2D	70%/64%	53%
CR	CR 7%	17% ≥VGPR	43% ≥VGPR	43% ≥CR	44% at 6-10 mg	30%	7%/11.4%	18%
MRD – (10^{-5})	44 out of 54	6 out of 7	4 out of 10	NR	12 out of 13	3 patients	NR	6 out of 7

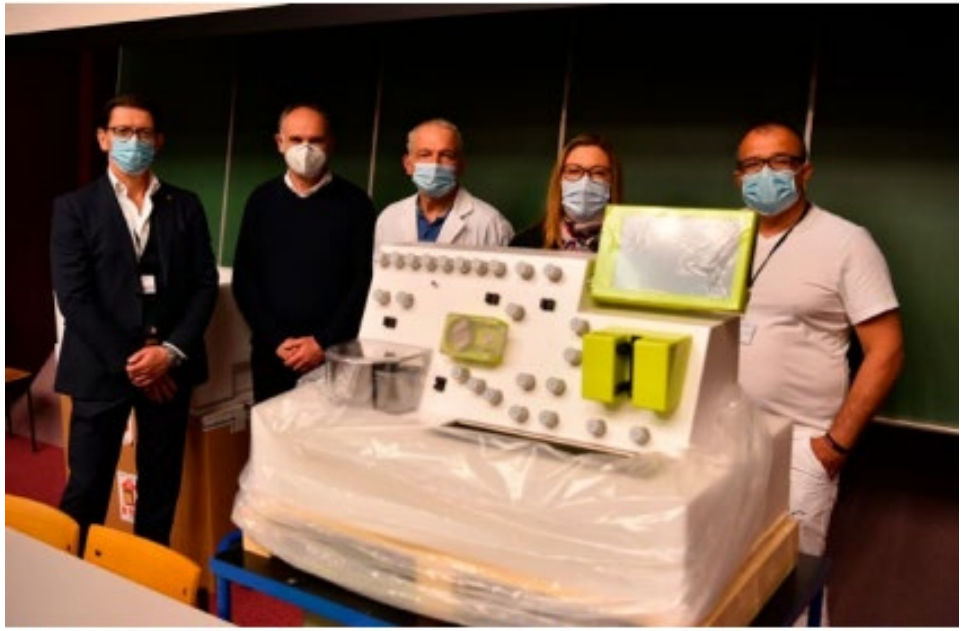
*There are no head-to-head comparisons of these data and naïve comparison should be conducted with caution

BCMA, B-cell maturation antigen; CR, complete response; CRS, cytokine release syndrome; IV, intravenous; LoT, lines of treatment; NR, not reported; RP2D, recommended phase 2 dose; SC, subcutaneous; MRD, minimal residual disease; NT, neurotoxicity; ORR, overall response rate; QW, weekly, Q2W/Q3W, every 2/3 weeks; VGPR, very good partial response

[1]Nooka A et al. ASCO 2022;abstract 8007; [2]Harrison S et al. ASH 2020;abstract 181; [3] Zonder J, et al. COMy 2022;abstract only; [4]Kumar S et al. ASH 2021;abstract 900; [5]Costa L et al. ASH 2019;abstract 143; [6]Bahlis N et al. ASCO 2021;abstract 8006; [7]Minnema M et al. ASCO 2022;abstract 8015; [8]Cohen A et al. ASH 2020;abstract 292

Klinično preskušanje v praksi - vzpostavitev zdravljenja s CAR-T celično terapijo

Od ideje do izvedbe



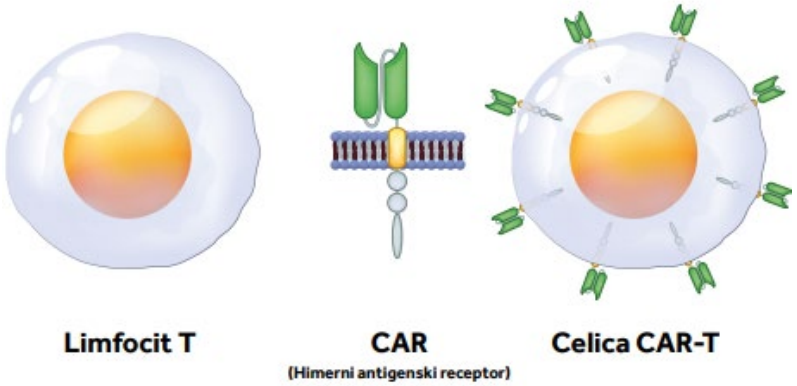
Jože Golobič, prof. dr. Roman Jerala, prof. dr. Alojz Ihan, Kristina Modic in prof. dr. Samo Zver ob predaji doniranih naprav CAR-T Kliničnemu oddelku za hematologijo UKC Ljubljana.
Ljubljana, 21. maj 2021

SEVER, Matjaž: ABC o celični terapiji CAR-T : vodnik za bolnike
Ljubljana : Slovensko združenje bolnikov z limfomom in levkemijo, L&L, 2021

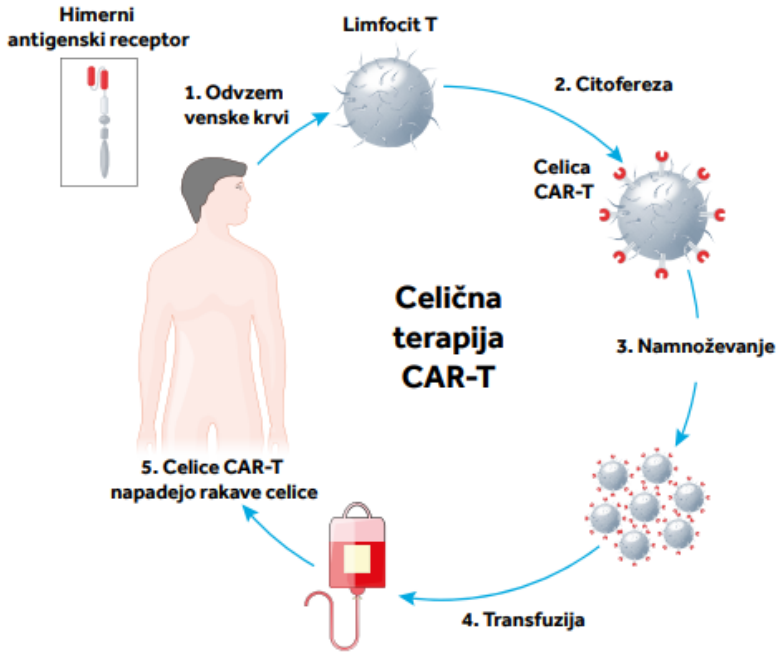

LIVE
Podelitev nagrade
DRŽAVLJAN EVROPE 2021
Kristina Modic in prof. dr. Samo Zver
5. november ob 11:00

CAR-T

Himerni antigenski receptor



Postopek zdravljenja



SEVER, Matjaž: ABC o celični terapiji CAR-T : vodnik za bolnike
Ljubljana : Slovensko združenje bolnikov z limfomom in levkemijo, L&L, 2021

Celična terapija z vidika zakonodaje

Zdravila za napredno zdravljenje

(*ATMPs- advanced therapy medicinal products*)

Evropska regulativa, ki naslavlja področje ATMPs
Uredba št. 1394/2007

Klinična preskušanja ATMPs v EU
Uredba št. 536/2014
Uredba o izvajanju uredbe (EU)

Klinično preskušanje

Phase I/II Study of UMCF-LJU anti-CD19 Chimeric Antigen Receptor T Cells In Adults with CD19 Positive Acute Lymphoblastic Leukemia

Protocol Number: < Number>

National Clinical Trial (NCT) Identified Number: <Number, if available>
Principal Investigator: < Principal investigator>
<IND/IDE> Sponsor: <Sponsor name, if applicable> Version Number: v.<x.x>
<Day Month Year>

STUDY AGENTS:

Investigational Product(s) Name: anti-CD19 CAR T cells	IND #: <IND number >
Other Agent(s): Fludarabine, Cyclophosphamide	

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

Miltenyi Biotec

Poslovni model podjetja, ki izdeluje vektor:

- Uporaba vektorja izven indikacij, ki so odobrene znotraj države
- Klinično preskušanje na pobudo raziskovalca (IIT)

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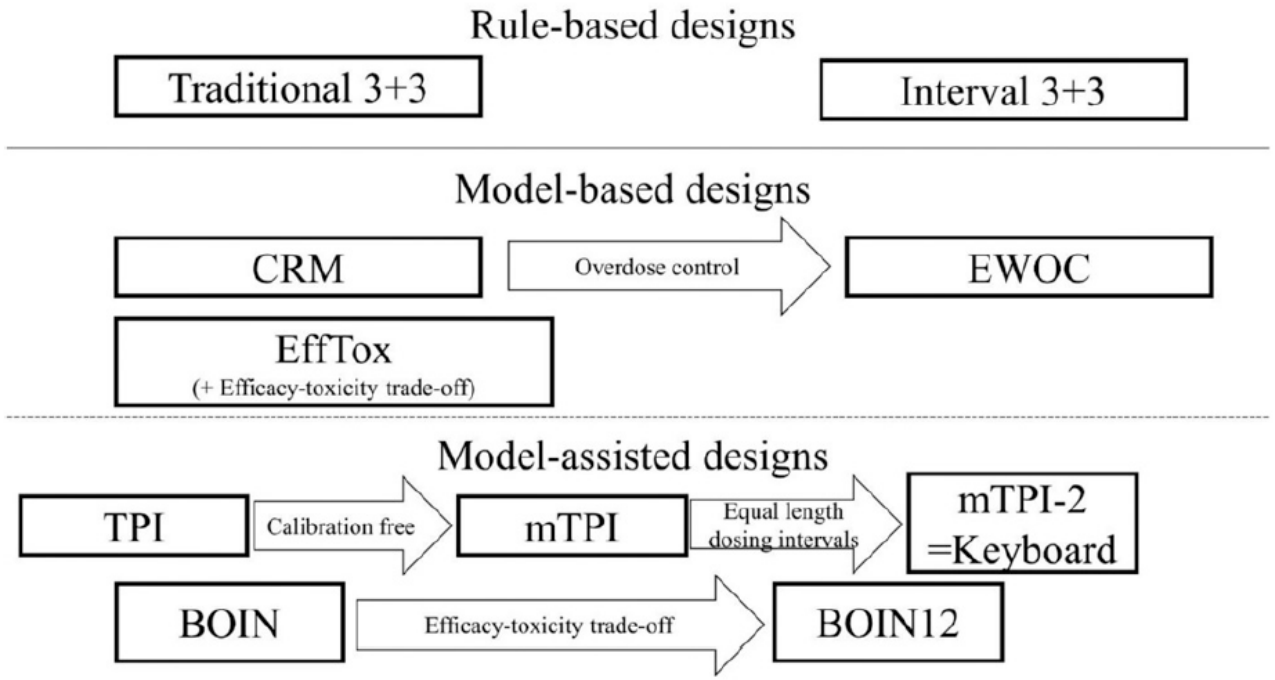
DEVELOPMENTAL THERAPEUTICS—MOLECULARLY TARGETED AGENTS AND TUMOR BIOLOGY

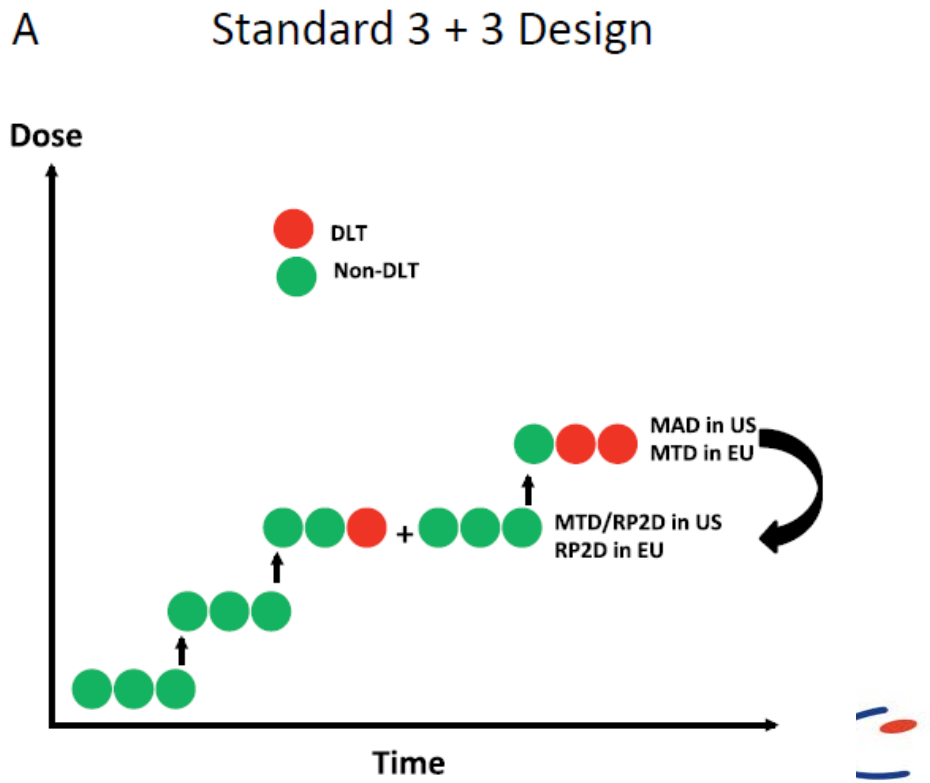
Moving Beyond 3+3: The Future of Clinical Trial Design

Razelle Kurzrock, MD[1]; Chia-Chi Lin, MD, PhD[2]; Tsung-Che Wu, MD[2]; Brian P. Hobbs, PhD[3]; Roberto Carmagnani Pestana, MD[4]; and David S. Hong, MD[5]

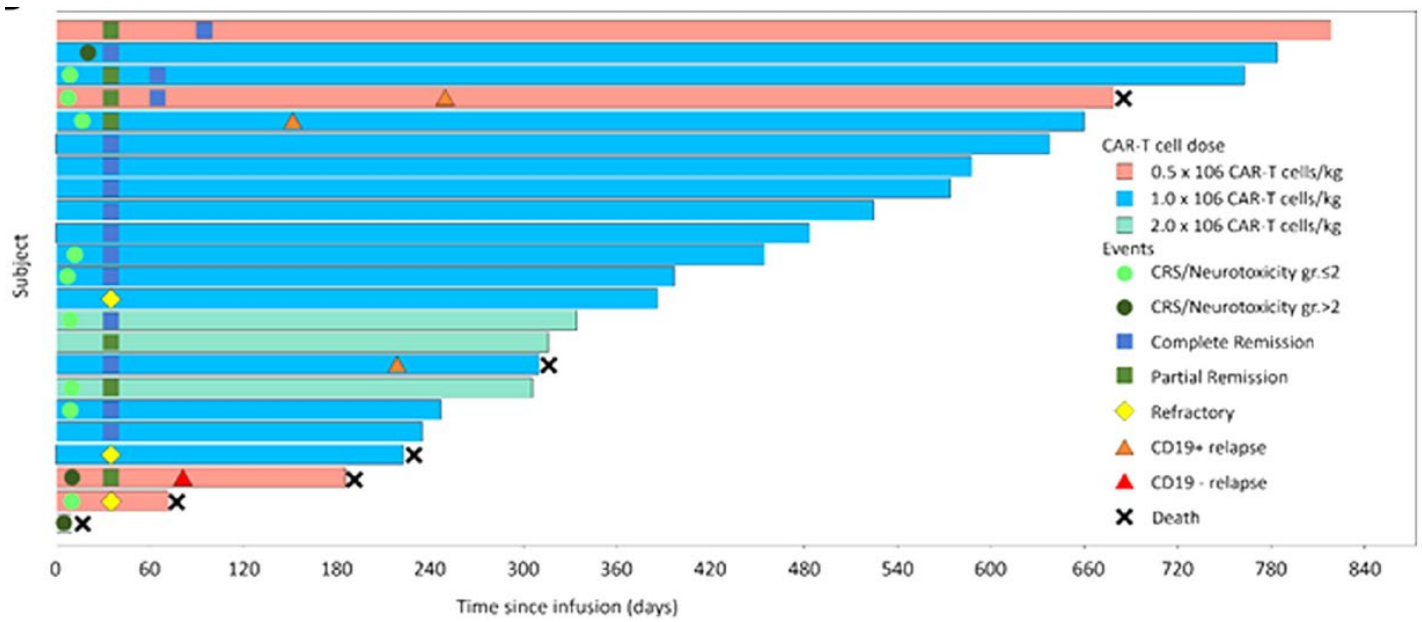
Phase 1 Trial Design: Is 3 + 3 the Best?

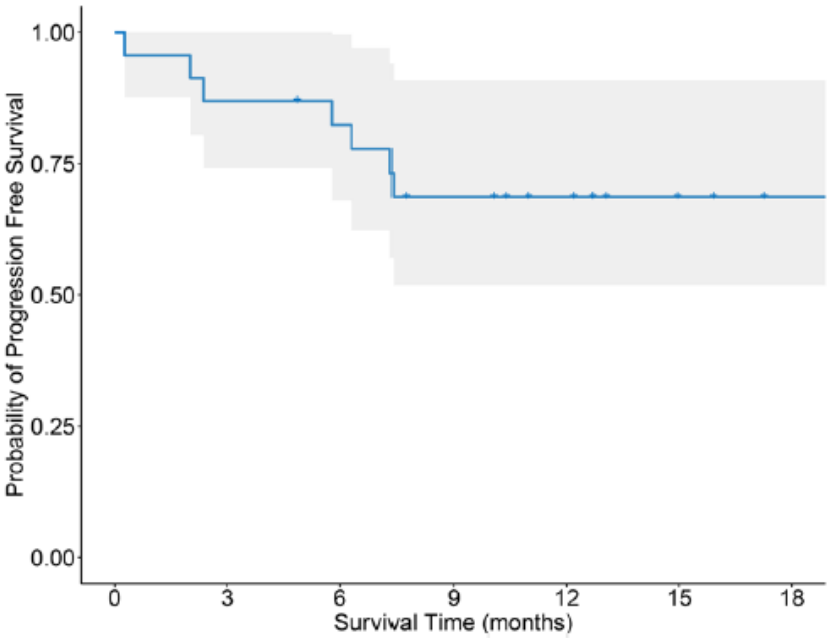
Aaron R. Hansen, MBBS, Donna M. Graham, MBBCh, Gregory R. Pond, PhD, and Lillian L. Siu, MD





Multiple site place-of-care manufactured anti-CD19 CAR-T cells induce high remission rates in B-cell malignancy patients





Raziskave v teku (vektor proizvajalca Miltenyi)

	Indication	Intervention	Estimated enrollment	Phase
NCT03321123	MB-CART19.1 in Patients With R/R ALL	MB-CART19.1	10	II
NCT04544592	UCD19 Car-T in Treatment of Pediatric B-ALL and B-NHL	**CD19CAR**-CD3Zeta-4-1BB-Expressing Autologous T-Lymphocyte Cells	50	I/II
NCT04787263	CD19-CAR_Lenti T Cells in Pediatric Patients Affected by Relapsed/Refractory CD19+ ALL and DLBCL or PML	**CD19-CAR**_Lenti T cell	32	I/II
NCT04943016	**CD19 CAR** T Cells in Children and Adults With Relapsed or Refractory **CD19** Positive B Cell Malignancies	CD19 Chimeric Antigen Receptor (CAR) T Cells	12	I
NCT03853616	MB-CART19.1 r/r CD19+ B-cell Malignancies (BCM)	CD19 Chimeric Antigen Receptor (CAR)	48	I/II
NCT05281809	Local Manufacture of CAR T-Cell Products for the Treatment of B-Cell Lymphoma and B-Acute Lymphoblastic Leukemia	Chimeric Antigen Receptor (CAR) T-Cell Product (Autologous)	30	II
NCT04792489	DALY 2.0 USA/ MB-CART2019.1 for DLBCL	MB-CART2019.1; Chimeric antigen receptor (CAR) T cell therapy	65	II
NCT03870945	Safety of MB-CART2019.1 in Lymphoma Patients (MB-CART2019.1 Lymphoma / DALY 1)	MB-CART2019.1	12	I/II
NCT05094206	CAR20.19.22 T-cells in Relapsed, Refractory B-cell Malignancies	**CAR**20.19.22	36	I

Vir: https://clinicaltrials.gov/ct2/show/record/NCT04943016?term=Miltenyi+CD19+CAR&draw=2&rank=4

Raziskave CAR-T po izbranih boleznih (zajeti samo največji sklopi bolezni):

~ 1146 raziskav na temo CAR-T;

Evropa ~ 101

Preglednica: raziskave po izbranih boleznih, večina jih poteka na področju hematoloških oblik raka.

Limfomi (vsi)	555
ALL	219
DP	162
KLL	94
DVCBL	108
Tumorji CŽS	51
FL	66
AML	57
LPC	41
Tumorji jeter	43
Ca pankreasa	42
Ca dojke	30
Ca želodca	33
Ca kolona/rektuma	18
Tu pljuč	35
HB	19
Glioblastom	27
Sarkomi	23
Tu glave/vratu	18
Ca ledvic	17
Melanom	12

Vir: https://clinicaltrials.gov/ct2/results?term=car-t&Search=Clear&age_v=&gndr=&type=&rslt= (dostopano: 29.11.2022)

Potreba za izdelavo CAR-T na akademski ravni

Omejitve proizvajalcev CAR-T

- *Visoka cena (vpliva na dostopnost do zdravljenja v posameznih državah)*
- *Čas proizvodnje je daljši*
- *Majhna kapaciteta izdelave*
- *Nabor indikacije ožji*

Akademska raven

- *Nižji stroški*
- *Krajši proizvodni čas*
- *Širši nabor indikacij*

Vir: Bremer E. Point of Care CAR-T cell based therapy. Cellular therapy center Groningen. NL. Povzeto EBMT maj 2023 (Pariz)

Potreba za izdelavo CAR-T na akademski ravni za naš prostor - cena ni edina prednost

	CAR-T celična terapija- Registrirana zdravila, ki delujejo proti antigenu CD19 (komercialni CAR-T pripravki)	CAR-T celična terapija- raziskovalno pripravljeni pripravki	DOPRINOS lastne izdelave
	V Sloveniji razvrščen 1 produkt (tisagenlecleucel) (2/3 indikacij); v EU 3 produkti; FDA 4	Lentivirusni vektor anti-CD 19 CAR - SF	
INDIKACIJE	za tisagenlecleucel B-ALL do 25 let, DVCLB	- B ALL (ne glede na starost) - difuzni velikocelični limfom B (DVCLB) -primarni mediastinalni limfom B - limfom plaščnih celic,…	DA- širši doseg indikacij
ČAS OD ODVZEMA CELIC DO APLIKACIJE ZDRAVILA	Mediana 41-52 dni	12 -14 dni	Hitrejša izdelava pomeni boljšo dostopnost do zdravljenja; zmanjša potrebo premostitvenega zdravljenja v času izdelave produkta in verjetnost ponovnega zagona
POT IZDELAVE	V tujini- decentralizirano	V Sloveniji	
CENA PRODUKTA	265.000 € (cbz, maj 2023)	41.000 € brez vektorja 70.000 € z vektorjem + obračunan kader (skupno odstopanje +/- 5.000)	
CELOTEN POSTOPEK ZDRAVLJENJA/ OBRAVNAVA Bolnika	Je primerljiva, ob dejstvu, da gre za primerljivo učinkovitost in varnost		

VIR: Povzeto po Vlogi za Zdravstveni svet , marec 2022

CAR-T zdravljenje v Sloveniji

Kymriah (tisagenlecleucel)	2020 (20.02.2020)	2021	2022	2023
KOH (odrasla populacija)	1	2	4 (+1 produkt *out of specification*)	2
KOOHO (pediatrična populacija)	1	0	1	1
SKUPAJ/leto	2	2	5	3
SKUPAJ vsi kumulativno	2	4	9	**9+3**

Proces zdravljenja s CAR-T celično terapijo

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University Medical Centre Ljubljana

Klinični oddelek za hematologijo

1 . Izbor za CAR-T (komercialni, akademski)

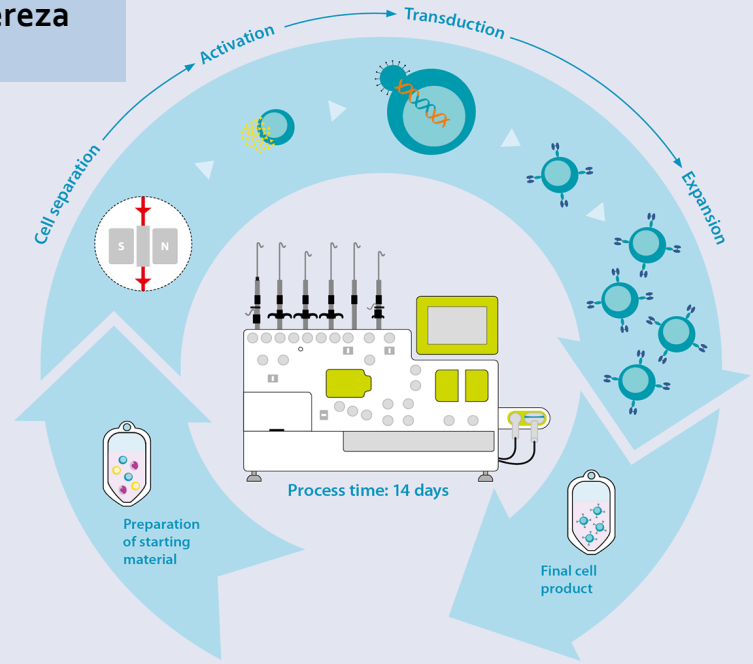
Veljaven postopek napotitve pacientov na transplantacijo KMC

Zavod Republike Slovenije za transfuzijsko medicino
Blood Transfusion Centre of Slovenia

2. Afereza

University of Ljubljana | Faculty of Medicine
INSTITUTE OF MICROBIOLOGY AND IMMUNOLOGY

3. Proizvodnja in sproščanje pripravka



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Klinični oddelek za hematologijo

4. Zdravljenje s CAR-T celično terapijo in sledenje (SOP, Klinična pot)

univerzitetni klinični center ljubljana
University Medical Centre Ljubljana

Pogoji za izvedbo KP

Proizvodni del

- postavitev čiste sobe razreda D (ISO8) in laboratorija za kontrolo kakovosti
- pridobitev dovoljenja za izdelavo zdravila, GMP potrdilo (JAZMP)
- prijava zaprtega sistema za delo z GSO 2.VR, delo z GSO 2. VR (MOPE)

Klinični del

- kvalificirana zdravstvena ustanova
- multidisciplinaren tim
- enota intenzivne terapije
- odobritev študije (JAZMP in KME)
- prijava zaprtega sistema za delo z GSO 2. VR, delo z GSO 2. VR, namerno sproščanje (MOPE)

Vir: Front. Pharmacol. 13:915342.
doi: 10.3389/fphar.2022.915342

Dokumentacija od A - Ž

- **Klinični protokol**
- Brošura za raziskovalca
- Privolitev/Informacije za bolnike
- e- CRF elektronski Case Report Form
- SMP – Site Management Plan
- CMP – Clinical Monitoring Plan
- IDSMB Charter
- DMP – Data Management Plan
- SMP – Safety Management Plan
- MMP – Medical Monitoring Plan
- Pharmacy Manual
- Laboratory Manual
- CCG – CRF completion guidelines
- eCRF sample
- PD report – Protocol Deviation Report
- Training Matrix
- Certifikati dobaviteljev (vseh zunanjih sodelavcev/ustanov)
- Na GSO vezana dokumentacija

1. Izbor pacienta

univerzitetni klinični center ljubljana
University Medical Centre Ljubljana

Klinični oddelek za hematologijo

Indikacija → hematološki konzilij → razgovor s pacientom in podpis informiranega pristanka

Redna praksa

Informiran pristanek in informacije za pacienta:

- pridobivanje vhodnega materiala (afereza)
- zdravljenje s povečanim tveganjem

Klinična študija

Informiran pristanek in informacije za pacienta:

- pridobivanje vhodnega materiala (afereza)
- sodelovanje v klinični študiji

2. Afereza

Zavod Republike Slovenije za transfuzijsko medicino
Blood Transfusion Centre of Slovenia

Izpolnitev kriterijev za zbiranje → afereza → obdelava afereznega produkta

Redna praksa

Obdelava celic:

- ločevanje celic, koncentriranje
- zamrzovanje

Klinična študija

Obdelava celic:

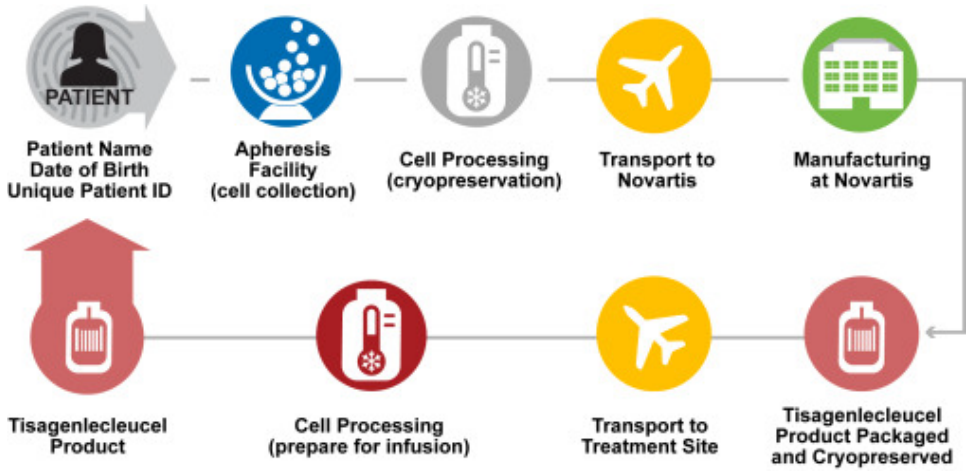
- ločevanje celic, koncentriranje
- ni zamrzovanja!

3. Proizvodnja

University of Ljubljana | Faculty of Medicine
INSTITUTE OF MICROBIOLOGY AND IMMUNOLOGY

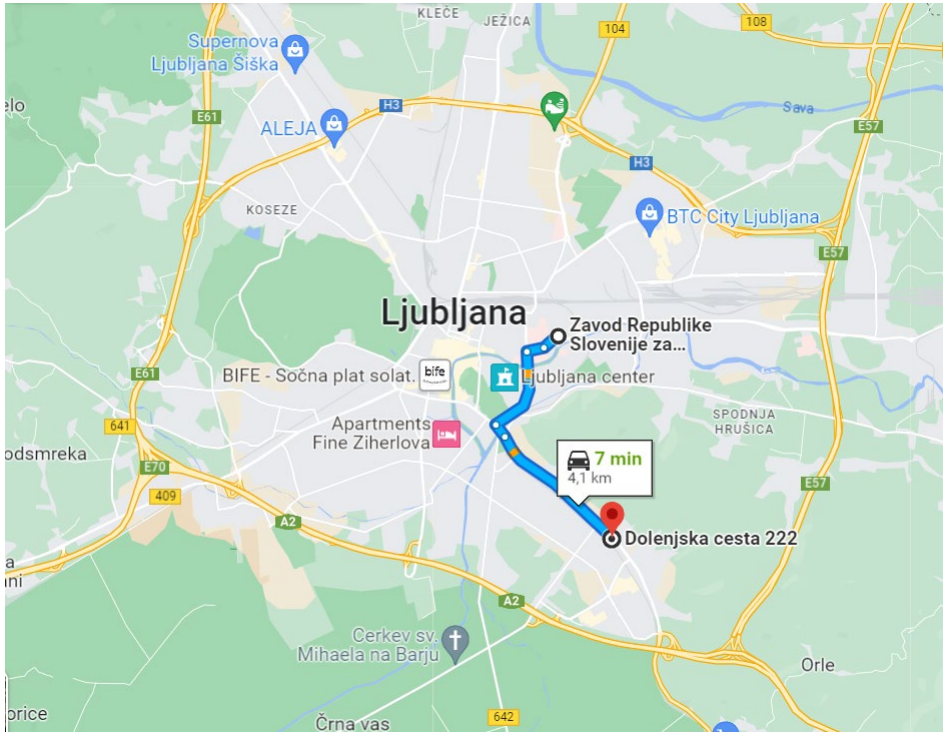
Redna praksa

Proizvodni center v tujini



Klinična študija

Proizvodni center v Ljubljani



4. Zdravljenje

univerzitetni klinični center ljubljana
University Medical Centre Ljubljana

Klinični oddelek za hematologijo

Redna praksa

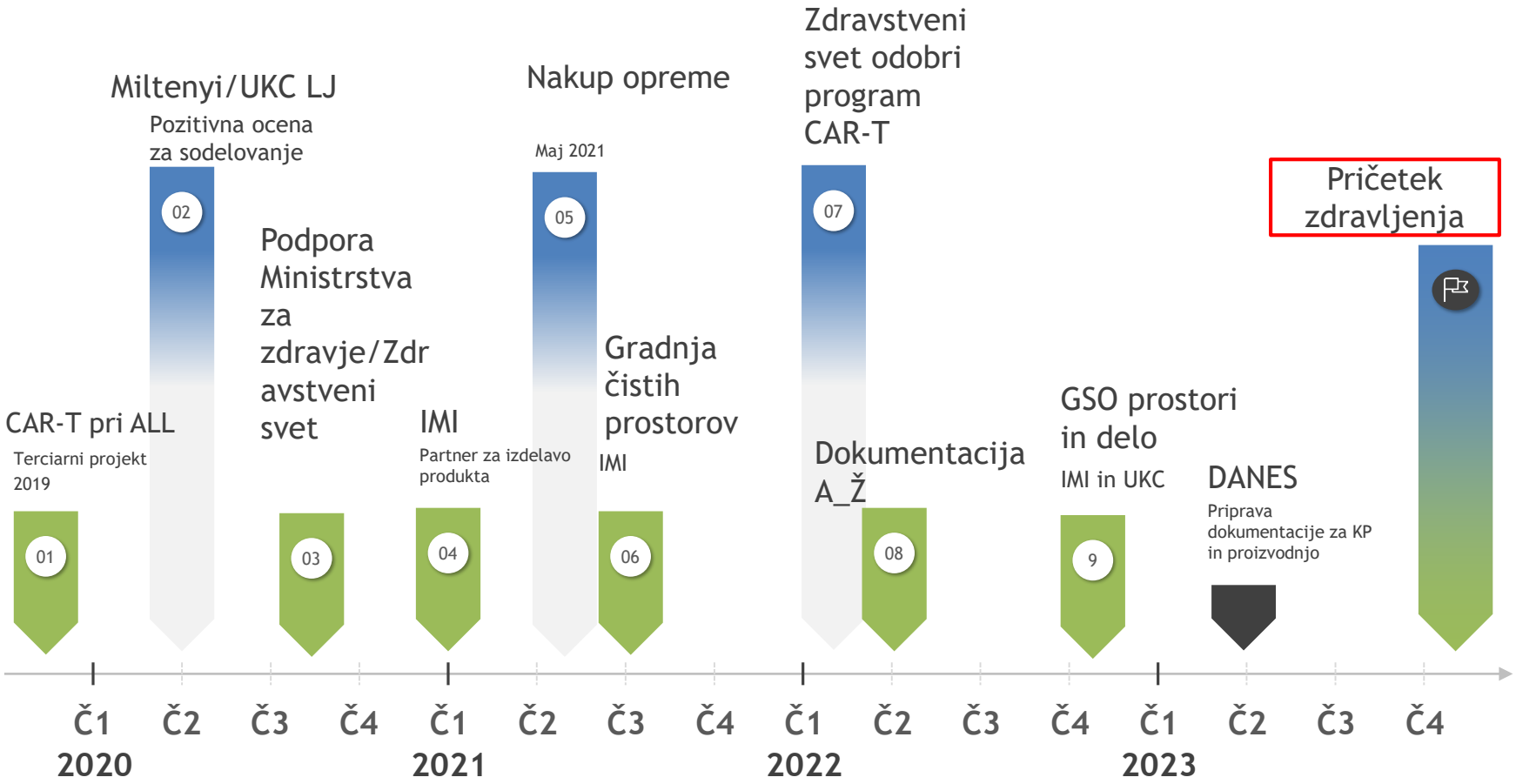
- EBMT/JACIE/EHA smernice
- SOP 0534 Zdravljenje s CAR-T celično terapijo

Klinična študija

- dodatni pogoji zaradi GSO

(prostor, varnostna oprema, ravnanje z odpadki)

Časovni potek projekta



Obdobja Č1: jan-marec; Č2:april-junij; Č3:julij-sept, Č4:okt-december; IMI –Inštitut za mikorbiologijo in imunologijo, Medicinska fakulteta, Univerza LJ

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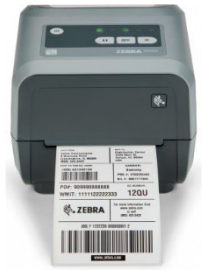
Vrednotenje projekta s kadrovskega vidika

- V okviru nove dejavnosti CAR-T celičnega zdravljenja se odobri dodatnih 27 kadrov (za potrebe laboratorija in kliničnega oddelka s predvideno širitvijo dejavnosti v sklopu CAR-T):
- Specializiranem hematološki laboratorij se predvidi 13 novo zaposlenih
- Klinika za hematologijo 14

Od ideje do izvedbe



Phase I/II Study of UMCF-LJU anti-CD19 Chimeric Antigen Receptor T Cells In Adults with CD19 Positive Acute Lymphoblastic Leukemia

Protocol Number: < Number>

National Clinical Trial (NCT) Identified Number: <Number, if available>
Principal Investigator: < Principal investigator>
<IND/IDE> Sponsor: <Sponsor name, if applicable> Version Number: v.<x.x>
<Day Month Year>

STUDY AGENTS:

Investigational Product(s) Name: anti-CD19 CAR T cells	IND #: <IND number >
Other Agent(s): Fludarabine, Cyclophosphamide	

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

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Projekti za prihodnost

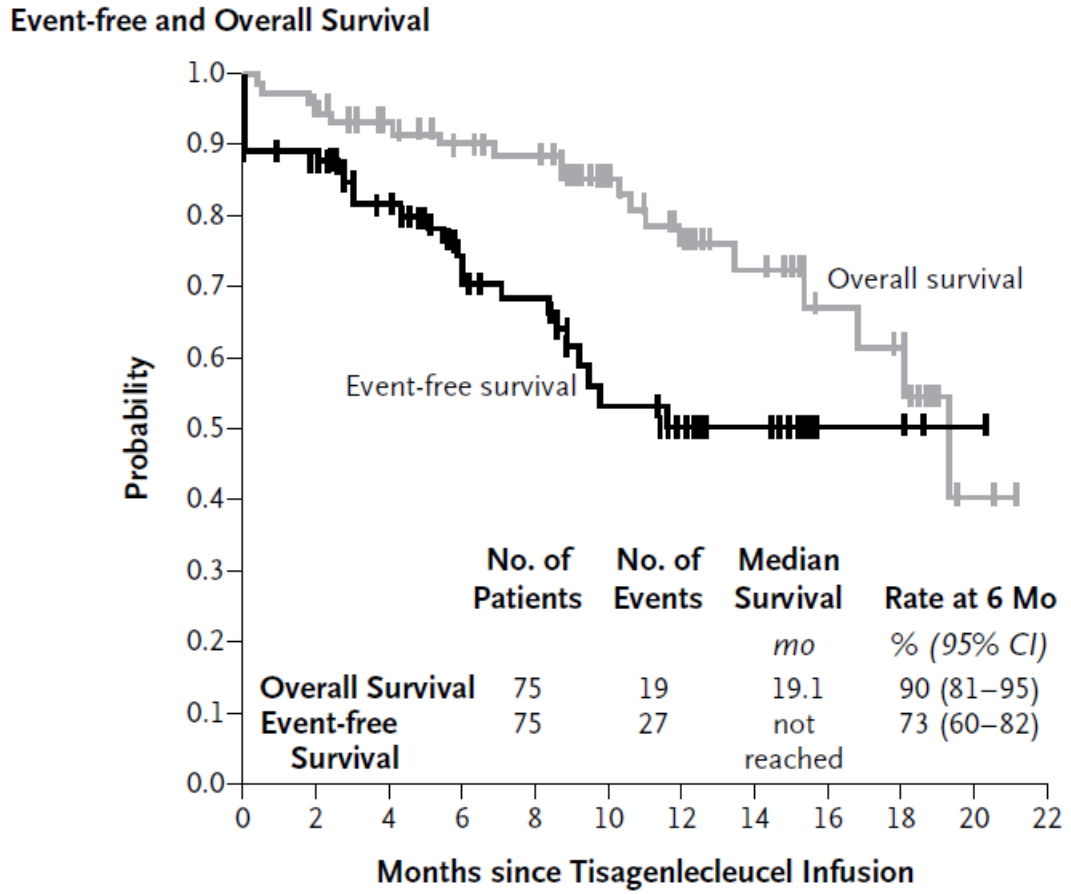
- Izdelava lastnega vektorja in CAR-T (za diseminirani plazmocitom Kemijski inštitut)
- Izvedba aferez KOH/LAB
- Kriobanka
- Možnosti izdelave oz zamrzovanja produkta (IMI)

idecabtagene vicleucel/Abecma	BCMA	DP
ciltacabtagene autoleucel/Carvykti	BCMA	DP

Thank You

Tisagenlecleucel in zdravljenje otrok in mladih odraslih z akutno limfoblastno levkemijo

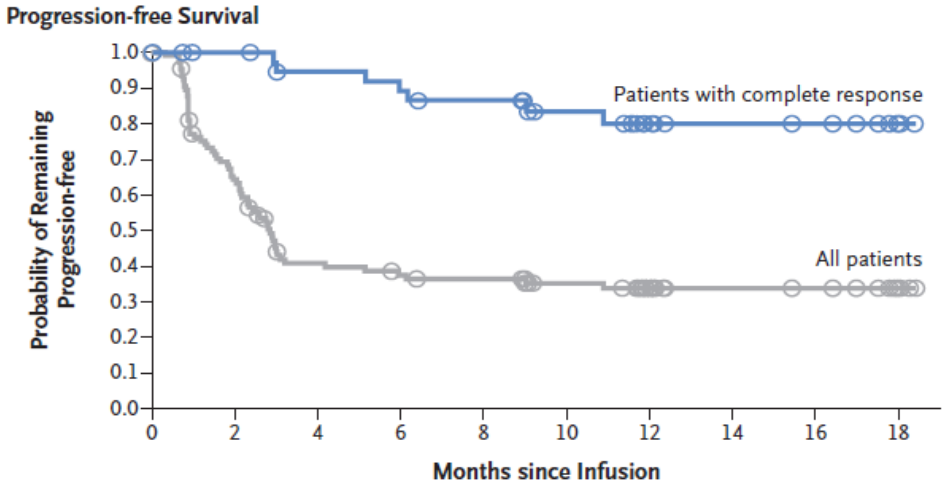
- Svetovna raziskava faze 2, 25 centrov
- CD19+ B ALL, ob ponovitvi ali neodzivnosti na zdravljenje
- 75 bolnikov je prejelo CAR-T celično terapijo
- Celokupen delež remisij po 3 mesecih je znašal 81%
- Po 12 mesecih sta znašala čas do napredovanja bolezni 50% in celokupno preživetje76%
- Vztrajanje CAR-T celic v krvi je bilo beleženo tudi do 20 mesecev
- Sindrom citokinskega sproščanja se je pojavil pri 77% bolnikov, od the je 48% bolnikov potrebovalo zdravljenje s tocilizumabom
- Nevrološke sopojave so sledili pr 40% bolnikov, uspešno je bilo podporno zdravljenje

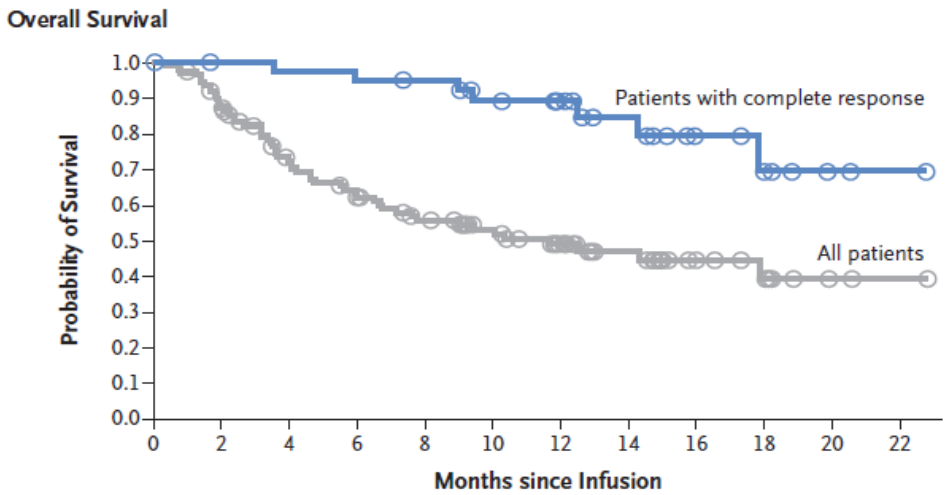


N Engl J Med 2018;378:439-48.

Tisagenlecleucel in zdravljenje odraslih bolnikov z difuznim velikoceličnim B limfomom

- Mednarodna raziskava faze 2
- Vključili so bolnike z rezistentno obliko bolezni oz. ponovitvijo bolezni po avtologni PKMC oz. neprimernih za zdravljenje z avtologno PKMC
- 93 bolnikov je v raziskavi prejelo CAR-T
- Celokupni odgovor je znašal 52%
- 40% bolnikov je doseglo popoln odgovor, 12% pa delen odgovor
- Po začetnem odgovoru in 12 mesecih spremljenja je bilo preživetje brez napredovanja bolezni 65%
- Najpogostejši sopojavi stopnje 3 in 4 so bili:
  - Sindrom citokinskega sproščanja (22%),
  - Nevrološki zapleti (12%),
  - Citopenije daljše od 28 dni (32%)
  - Okužbe (20%),
  - Febrilna nevtropenija (14%)

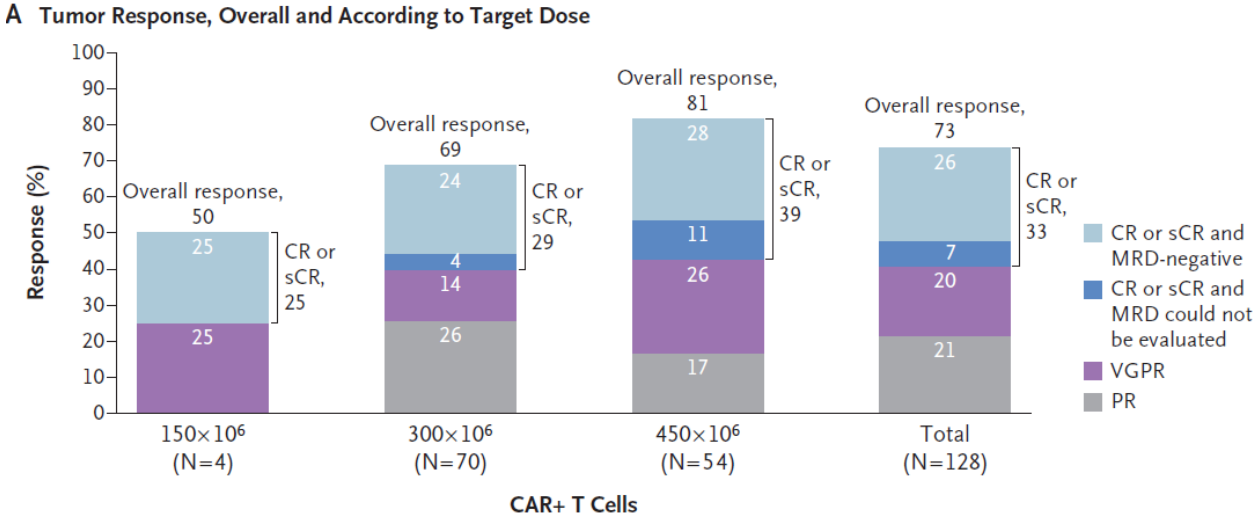


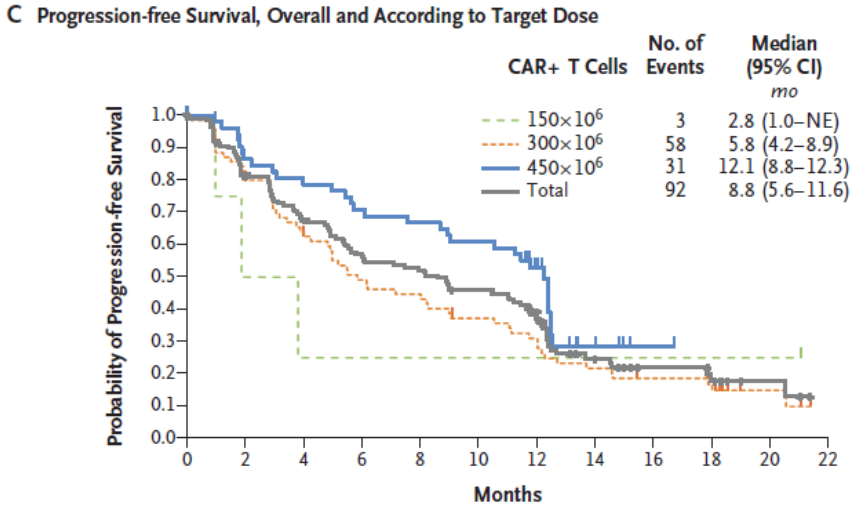


N Engl J Med 2019;380:45-56.

Idecabtagene vicleucel pri zdravljenju R/R diseminiranega plazmocitoma

- Raziskava faze 2
- Bolniki so prejeli vsaj tri rede zdravljenja vključujoč inhibitor proteasomov, imunomodulator in anti-CD38 protitelo
- Bolniki so prejeli odmerek ide-cel 150 × 10^6 do 450 × 10^6 CAR-T celic
- Zdravili so 128 bolnikov
- 73% bolnikov je imelo odgovor na zdravljenje, 33% popoln odgovor
- Mediana PFS je znašala 8.8 meseca
- Sopojavi CAR-T:
  - nevtropenija 91%,
  - anemija 70%,
  - trombocitopenija 63%,
  - CRS 84%,
  - nevrotoksičnost 18%

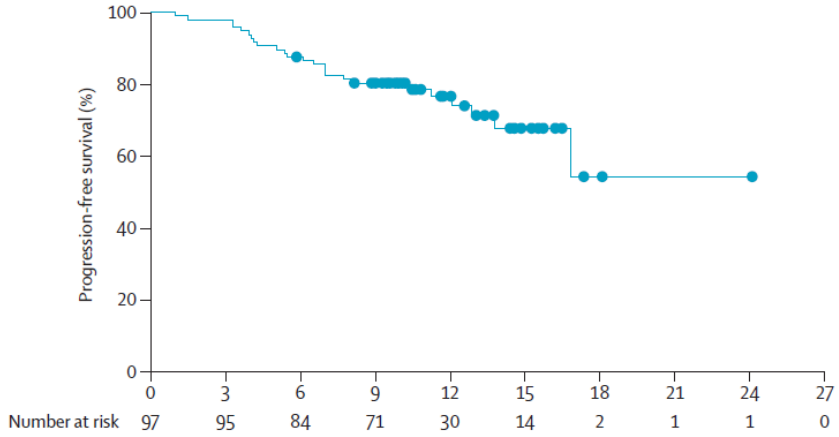


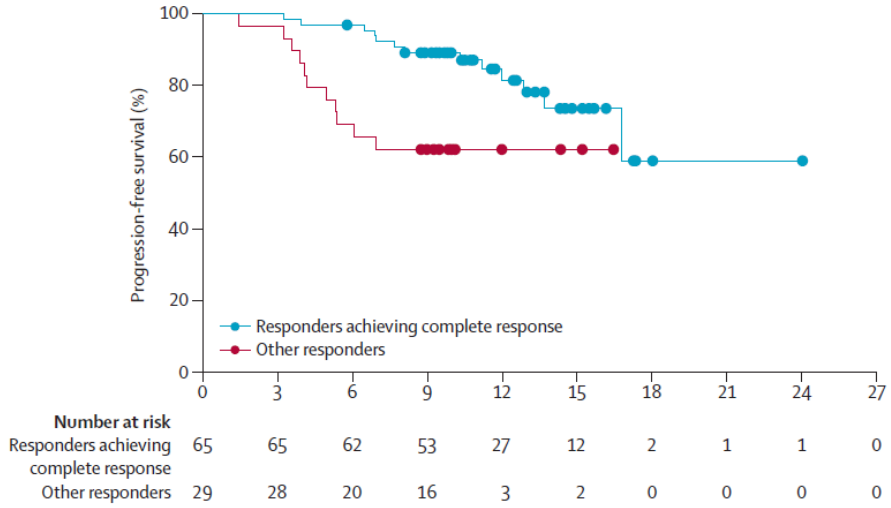


N Engl J Med 2021;384:705-16.

CAR-T celična terapija za DP: cilta-cel

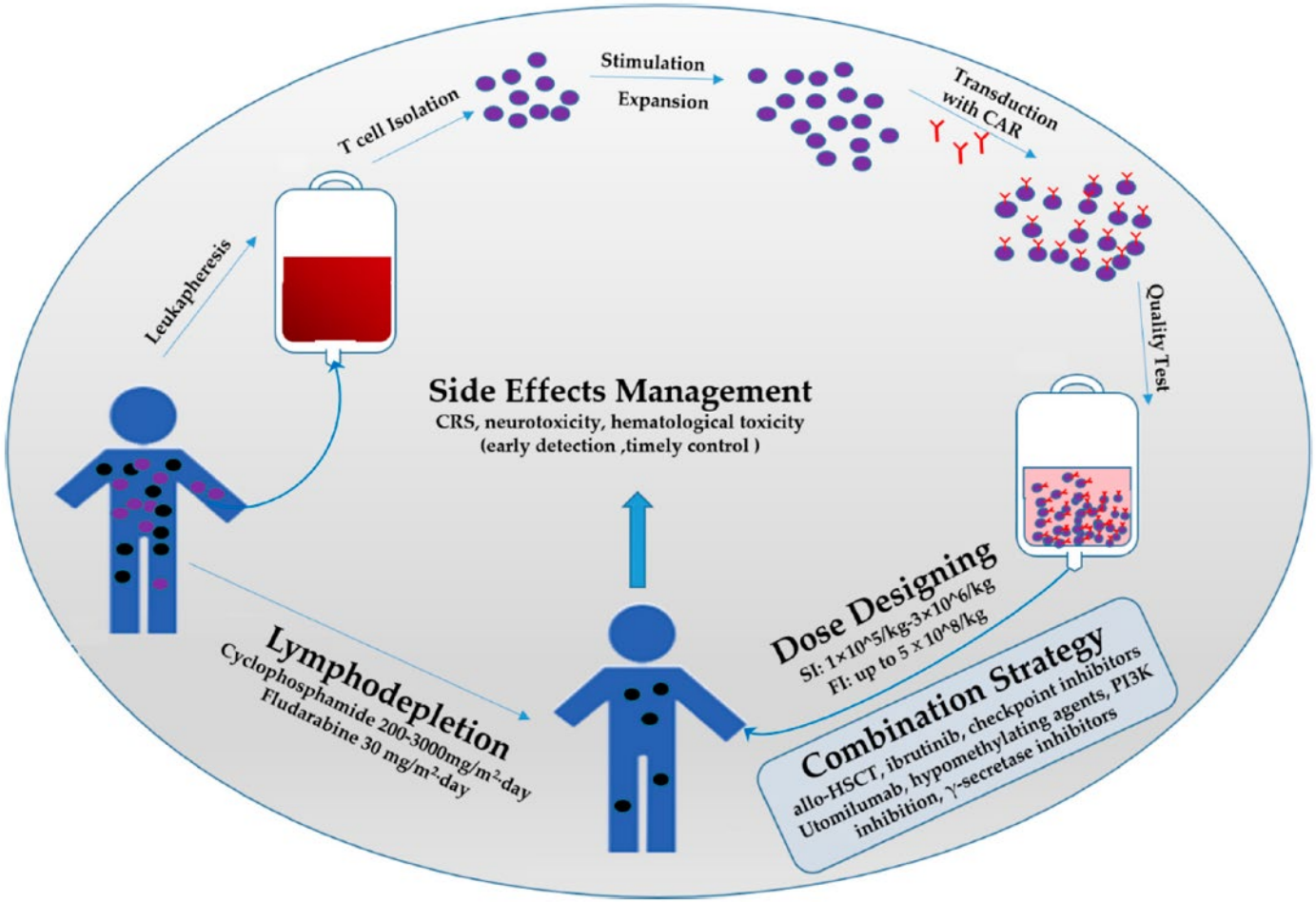
- Ciltacabtagene autoleucel – odprta, multicentrična raziskava faze 1/2,
- Vključeni bolniki z vsaj tremi predhodnimi terapijami in rezistenco na proteasome in imunomodulatorno terapijo,
- 97 bolnikov, mediana spremljanja 12,4 meseca,
- 97% celokupen odgovor, 67% popoln odgovor, PFS 77% po 12 mesecih
- CRS 95% (gradus 3/4 pri 4%), nevrotoksičnost 21% (g 3/4 9%)





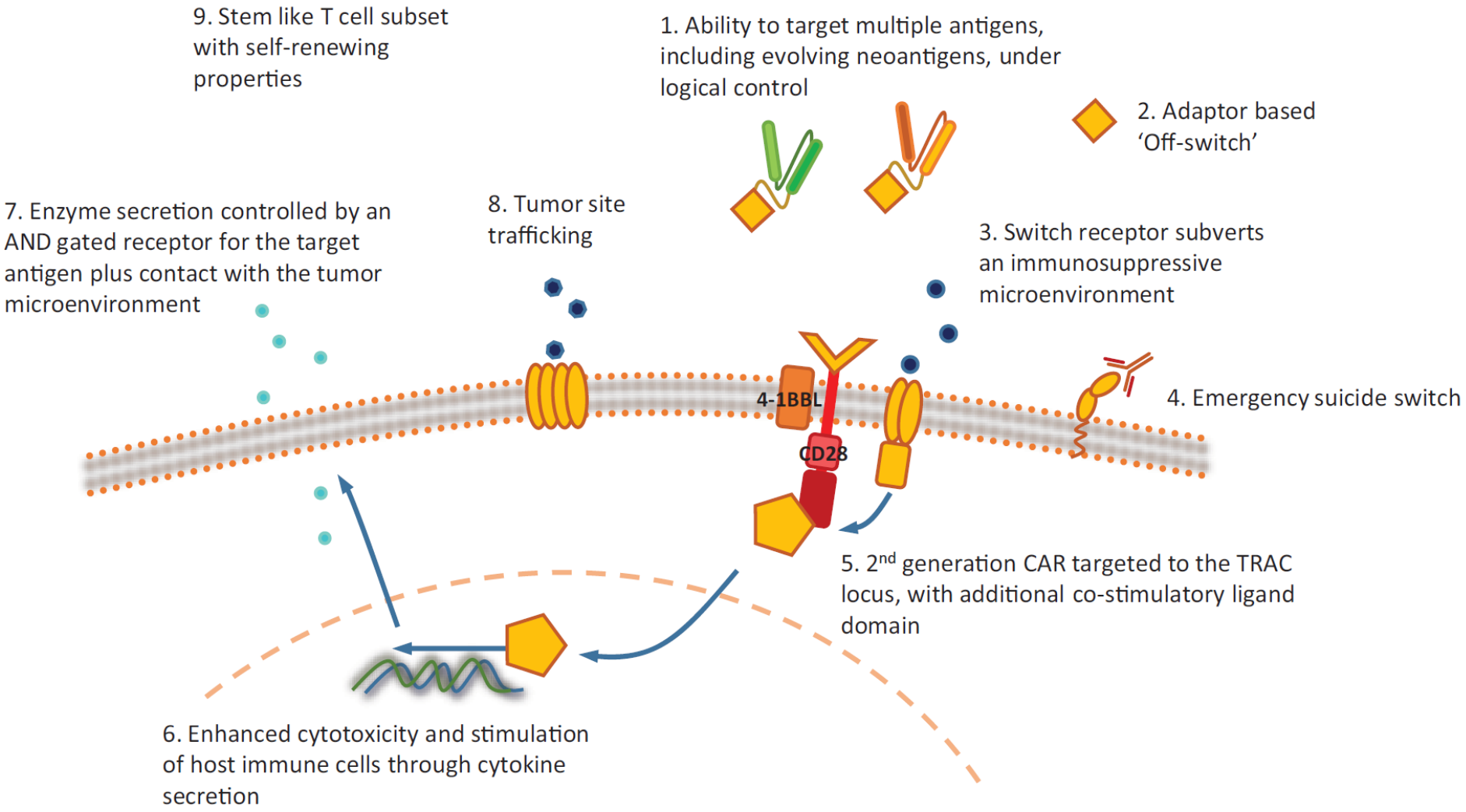
Lancet 2021; 398: 314–24

Clinical Strategies for Enhancing the Efficacy of CAR T-Cell Therapy for Hematological Malignancies

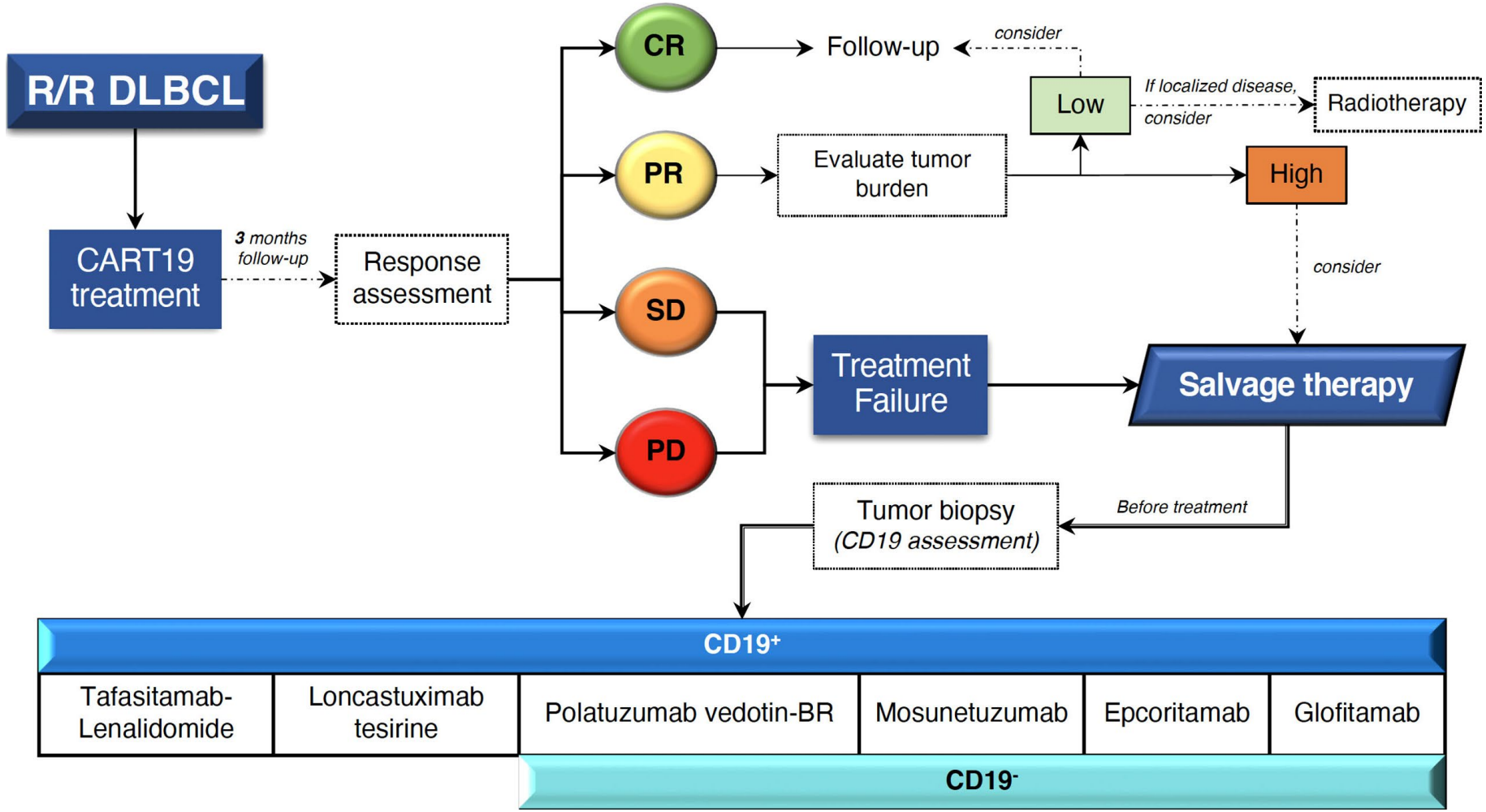


Cancers **2022**, *14*, 4452

Idealised CAR-T



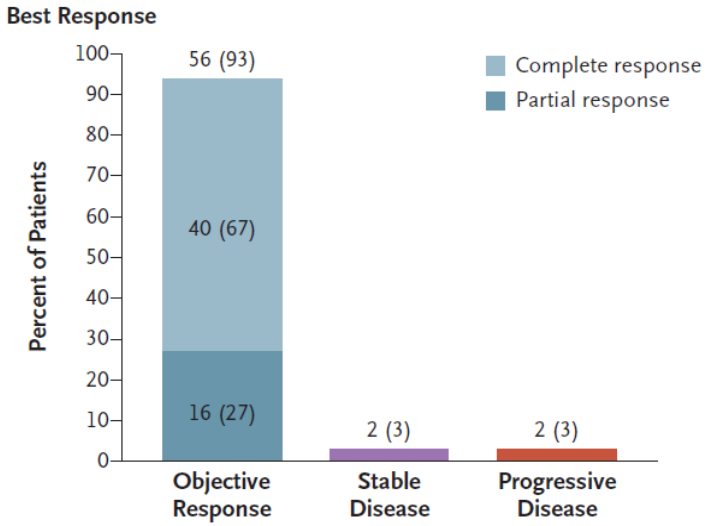
Management for Patients with R/R DLBCL Who Fail CART19 Treatment

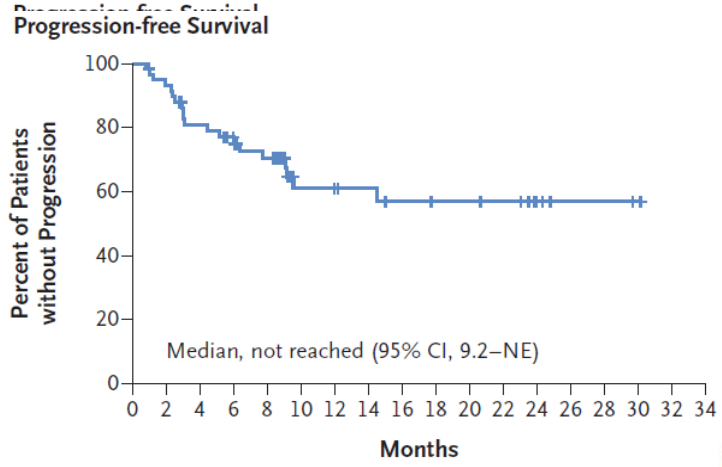


Front. Immunol. 13:904497.
doi: 10.3389/fimmu.2022.904497

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

- Multicenter, phase 2 trial
- Relapsed or was refractory after the receipt of up to five previous therapies
- 74 patients were enrolled
- 93% had an objective response
- 67% had a complete response
- At 12 months, the estimated PFS and OS were 61% and 83%,
- Adverse events of grade 3 or higher:
  - cytopenias 94%
  - infections 32%
  - CRS 15%
  - Neurologic events 31%





N Engl J Med 2020;382:1331-42.