IX CONGRESSO NAZIONALE
GIIMA

30 NOVEMBRE 2022
Aula San Raffaele
Ospedale San Raffaele - Milano

Giuseppe Gritti - Ospedale Papa Giovanni XXIII

Percorso terapeutico del paziente candidabile a CAR-T

Agenda

- Current indication of CAR-T cell therapy
- Fitting CAR T-Cell Therapy Into Current Treatment Paradigms
- Patient Journey in CAR T-Cell Therapy
- Current issue in managing CAR T-Cell candidates

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Current Commercial Indications for Lymphomas (US)

Product	Lymphoma Indications (FDA Approval Date)
Axicabtagene ciloleucel *(Yescarta)* ▪ Anti–CD19-CD28-CD3z construct ▪ Uses retroviral transduction	▪ **Adults with LBCL** either refractory to first-line chemoimmunotherapy or relapsed within 12 mo of first-line chemoimmunotherapy (April 1, 2022) ▪ **Adults with R/R LBCL** after ≥2 lines of systemic therapy, including DLBCL NOS, DLBCL arising from FL, primary mediastinal LBCL, high-grade B-cell lymphoma (October 18, 2017) ▪ **Adults with R/R FL** after ≥2 lines of systemic therapy (March 5, 2021)
Brexucabtagene autoleucel *(Tecartus)* ▪ Anti–CD19-CD28-CD3z construct ▪ Uses retroviral transduction	▪ **Adults with R/R MCL** (July 24, 2020)
Lisocabtagene maraleucel *(Breyanzi)* ▪ Anti–CD19-41BB-CD3z construct ▪ Uses lentiviral transduction	▪ **Adults with LBCL**, including DLBCL NOS, DLBCL arising from indolent lymphoma, high-grade B-cell lymphoma, primary mediastinal LBCL, and FL grade 3B, who have disease that is: • Either refractory to first-line chemoimmunotherapy or relapsed within 12 mo of first-line chemoimmunotherapy (June 24, 2022), *or* • Refractory to first-line chemoimmunotherapy or relapsed after first-line chemoimmunotherapy and ineligible for HSCT due to comorbidities or age (June 24, 2022), *or* • R/R after ≥2 lines of systemic therapy (February 5, 2021)
Tisagenlecleucel *(Kymriah)* ▪ Anti–CD19-41BB-CD3z construct ▪ Uses lentiviral transduction	▪ **Adults with R/R LBCL** after ≥2 lines of systemic therapy, including DLBCL NOS, high-grade B-cell lymphoma, and DLBCL arising from FL (May 1, 2018) ▪ **Adults with R/R FL** after ≥2 lines of systemic therapy (May 27, 2022)

Axicabtagene ciloleucel PI. Brexucabtagene autoleucel PI. Lisocabtagene maraleucel PI. Tisagenlecleucel PI.

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Pivotal Trials Leading to FDA Approval: Lymphomas

Outcome	Phase II ZUMA-1[1-3]	Phase II ZUMA-5[1,4-5]	Phase II JULIET[6-8]	Phase II ELARA[6,9-11]	Phase I TRANSCEND NHL 001[12-15]	Phase II ZUMA-2[16-18]
CAR T-cell product	Axi-cel (*Yescarta*)	Axi-cel (*Yescarta*)	Tisa-cel (*Kymriah*)	Tisa-cel (*Kymriah*)	Liso-cel (*Breyanzi*)	Brexu-cel (*Tecartus*)
Patient population	Adults with R/R LBCL	Adults with R/R FL	Adults with R/R LBCL post/ineligible for autoHSCT	Adults with R/R FL	Adults with R/R LBCL	Adults with R/R MCL
Pheresed/ treated, n	111/101	127/124	165/111	98/97	344/269	71/68
Bridging tx, %	Not permitted	4	92	44	59	37
ORR/CR, %	82/52	94/79	52/40	86.2/69.1	73/53	85/59
OS/PFS rate, %	1 yr: 59/44 5 yr: 42.6/--	2 yr: 81.2/63.4	1 yr: 49/-- 2 yr: 41.1/33.5	1 yr: --/67.0	1 yr: 58/44 2 yr: 50.5/40.6	1 yr: 83/61 2 yr: --/52.9

1. Axicabtagene ciloleucel PI. 2. Neelapu. NEJM. 2017;377:2531. 3. Jacobson. TCT 2022. Abstr 10. 4. Jacobson. Lancet Oncol. 2022;23:91. 5. Neelapu. EBMT 2022. Abstr OS08-01. 6. Tisagenlecleucel PI. 7. Schuster. NEJM. 2019;380:45. 8. Schuster. Leuk Lymphoma. 2022;63:845. 9. Fowler. Nat Med. 2022;28:325. 10. Thieblemont. TCT 2022. Abstr 74. 11. Schuster. ASCO 2021. Abstr 7508. 12. Lisocabtagene maraleucel PI. 13. Abramson. ASH 2019. Abstr 241. 14. Abramson. Lancet. 2020;396:839. 15. Abramson. EBMT 2022. Abstr OS08-07. 16. Brexucabtagene autoleucel PI. 17. Wang. NEJM. 2020;382:1331. 18. Wang. ASCO 2022. Abstr 7518.

Current Commercial Indications for Leukemia

Product	Leukemia Indications (FDA Approval Date)
Brexucabtagene autoleucel (*Tecartus*) ▪ Anti–CD19-CD28-CD3z construct ▪ Uses retroviral transduction	▪ **Adults with R/R B-cell precursor ALL** (October 1, 2021)
Tisagenlecleucel (*Kymriah*) ▪ Anti–CD19-41BB-CD3z construct ▪ Uses lentiviral transduction	▪ **Patients aged ≤25 yr with B-cell precursor ALL** that is refractory or in second or later relapse (August 30, 2017)

Brexucabtagene autoleucel PI. Tisagenlecleucel PI.

Slide credit: clinicaloptions.com

Pivotal Trials Leading to FDA Approval: Leukemia

Outcome	Phase II ELIANA[1-3]	Phase II ZUMA-3[4-6]
CAR T-cell product	Tisa-cel (*Kymriah*)	Brexu-cel (*Tecartus*)
Patient population	Children and young adults with R/R B-cell ALL	Adults with R/R B-cell ALL
Pheresed/treated, n	92/75	71/55
Bridging tx, %	87	93
ORR/CR, %	81/60	--/56
OS/PFS rate, %	1 yr: 76/-- 5 yr: 55/--	1 yr: 71/-- 2 yr: 56/--

- No head-to-head data presently for CAR T-cells vs SoC in adults with R/R B-cell ALL; however, pivotal trials reported longer median OS with CAR T-cells
  - Brexu-cel: 25.4 mo[6]; blinatumomab: 7.7 mo[7]; inotuzumab ozogamicin: 7.7 mo[8]; CT: 4.0-6.7 mo[7-8]

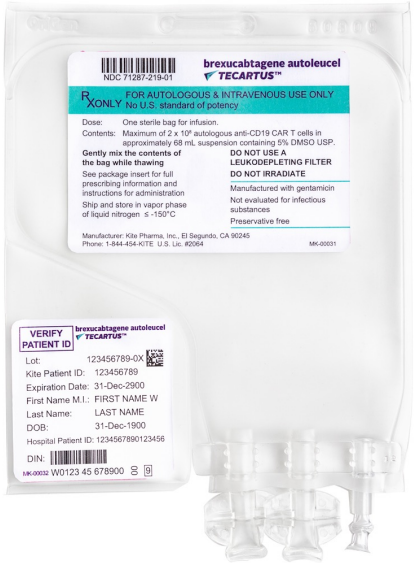
1. Tisagenlecleucel PI. 2. Maude. NEJM. 2018;378:439. 3. Rives. EHA 2022. Abstr S112. 4. Shah. Lancet. 2021;398:491.
5. Brexucabtagene autoleucel PI. 6. Shah. ASCO 2022. Abstr 7010. 7. Kantarjian. NEJM. 2017;376:836. 8. Kantarjian. NEJM. 2016;375:740.

AXICABTAGENE CILOLEUCEL

- **KTE-C19, Axi-cel (Kite/Gilead)**
  - Indicated for the treatment of adult patients with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy
  - October 18, 2017: Approved by FDA
  - June 28, 2018: Approved by EMA

BREXUCABTAGENE AUTOLEUCEL

- **KTE-X19 (Kite/Gilead)**
  - Indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.
  - July 24, 2020: Approved by FDA
  - December 14, 2020: Approved by EMA



TISAGENLECLEUCEL

- **CTL019, Tisa-cel (Novartis)**
  - Indicated for the treatment of paediatric and young adult patients (up to 25 years of age) with B-cell ALL that is refractory or in second or later relapse, and in adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy
  - FDA Approval: August 30, 2017 (ALL) May 1, 2018 (DLBCL)
  - June 28, 2018: Approved by EMA

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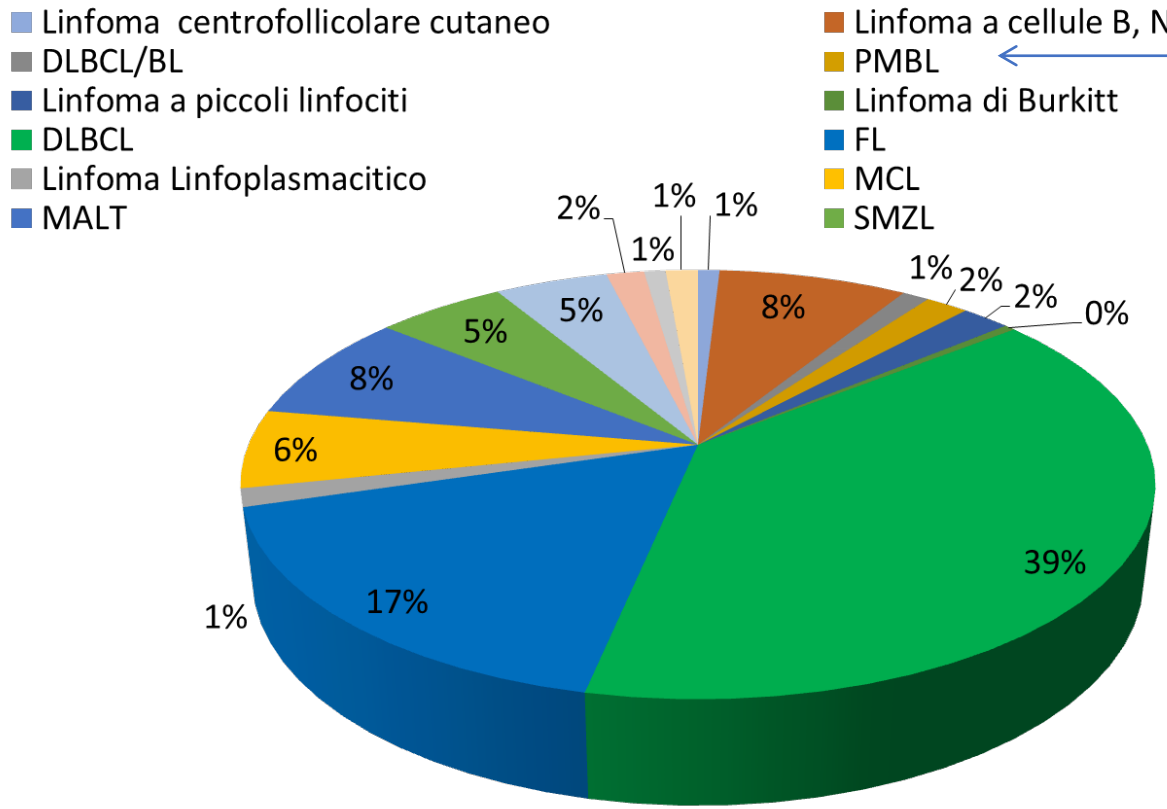
B-cell Lymphoma in Bergamo: Diagnosis in 2018-2019

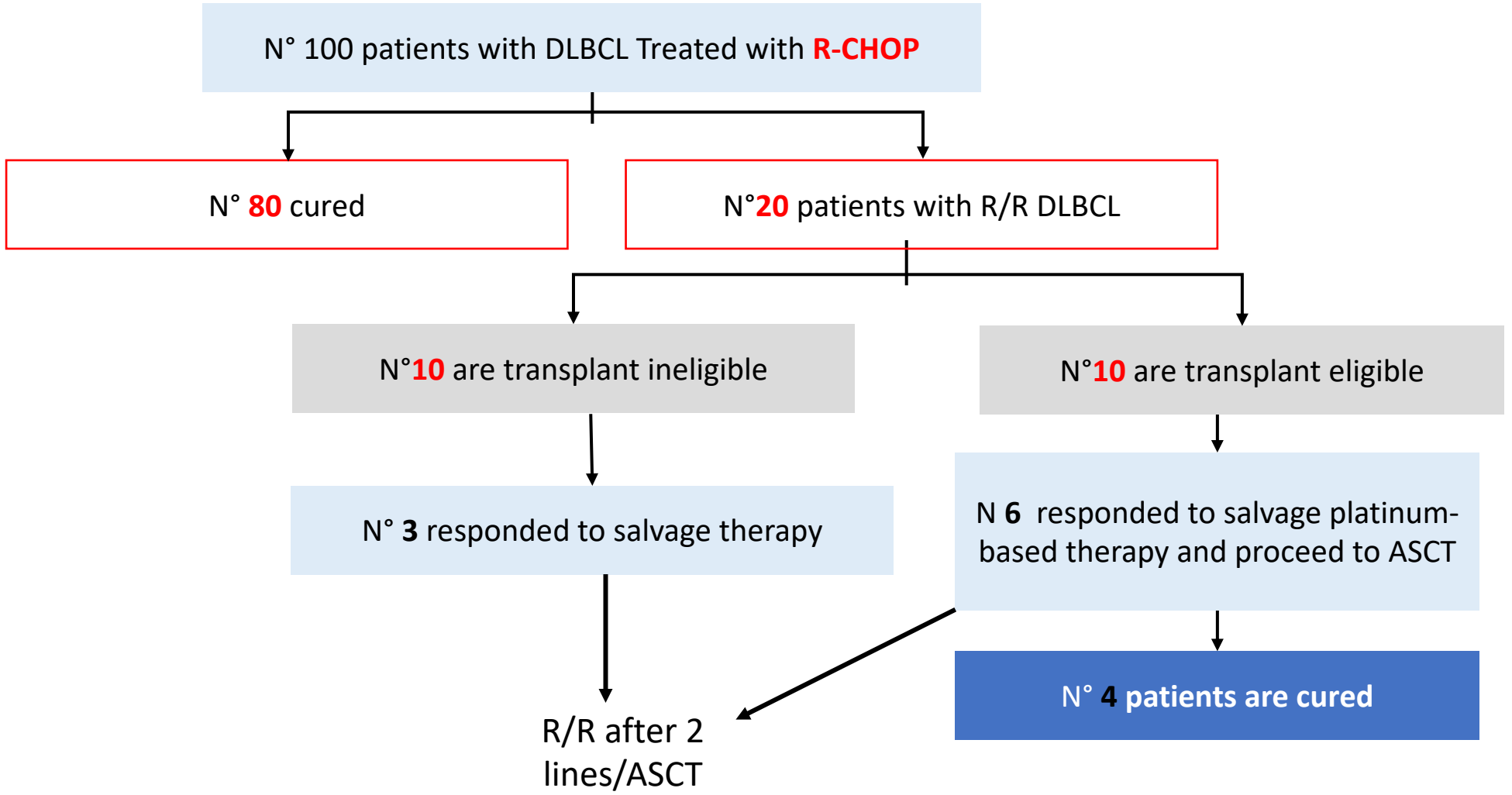
188 DLBCL



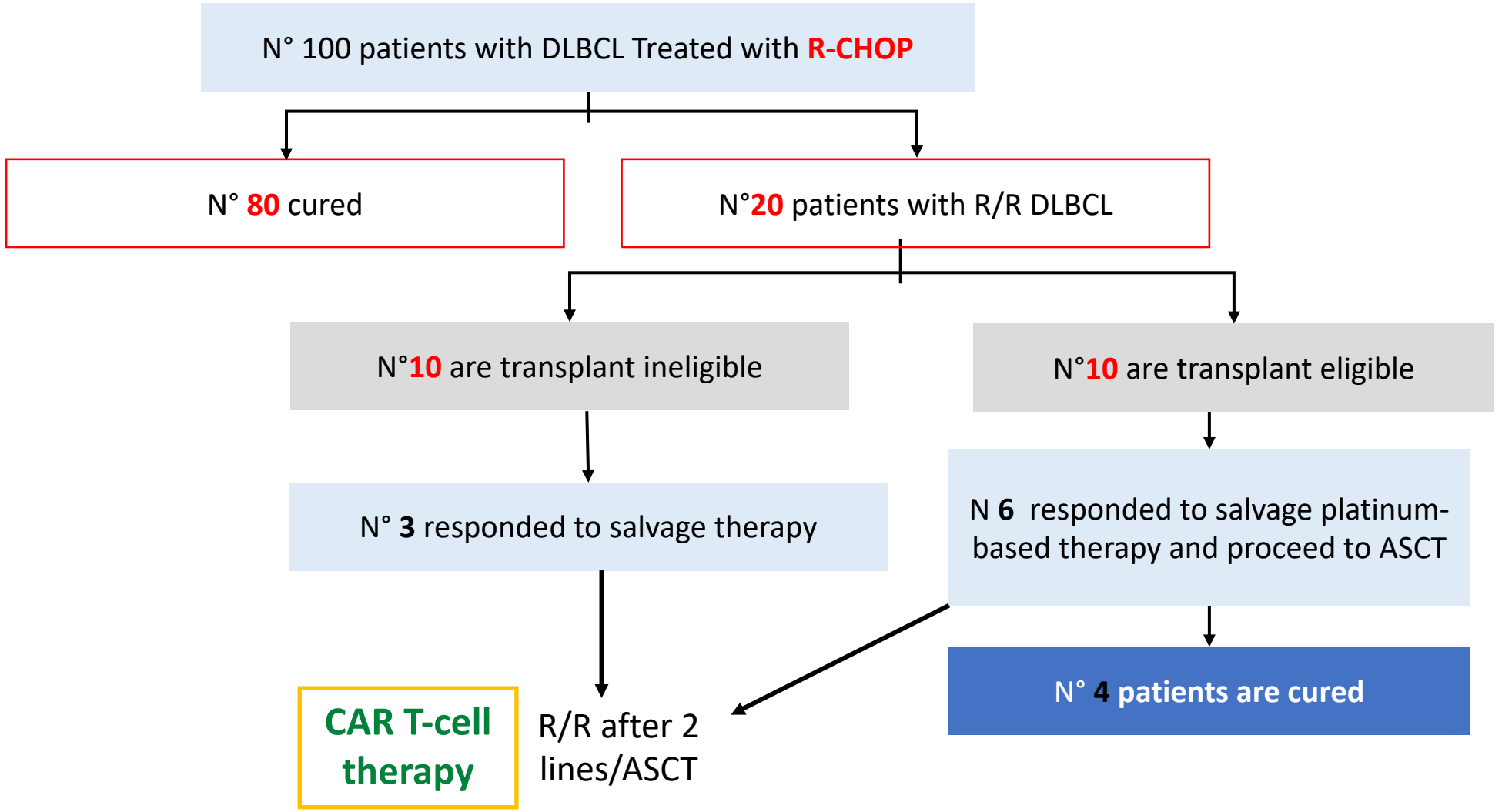
9 PMBCL

N=484

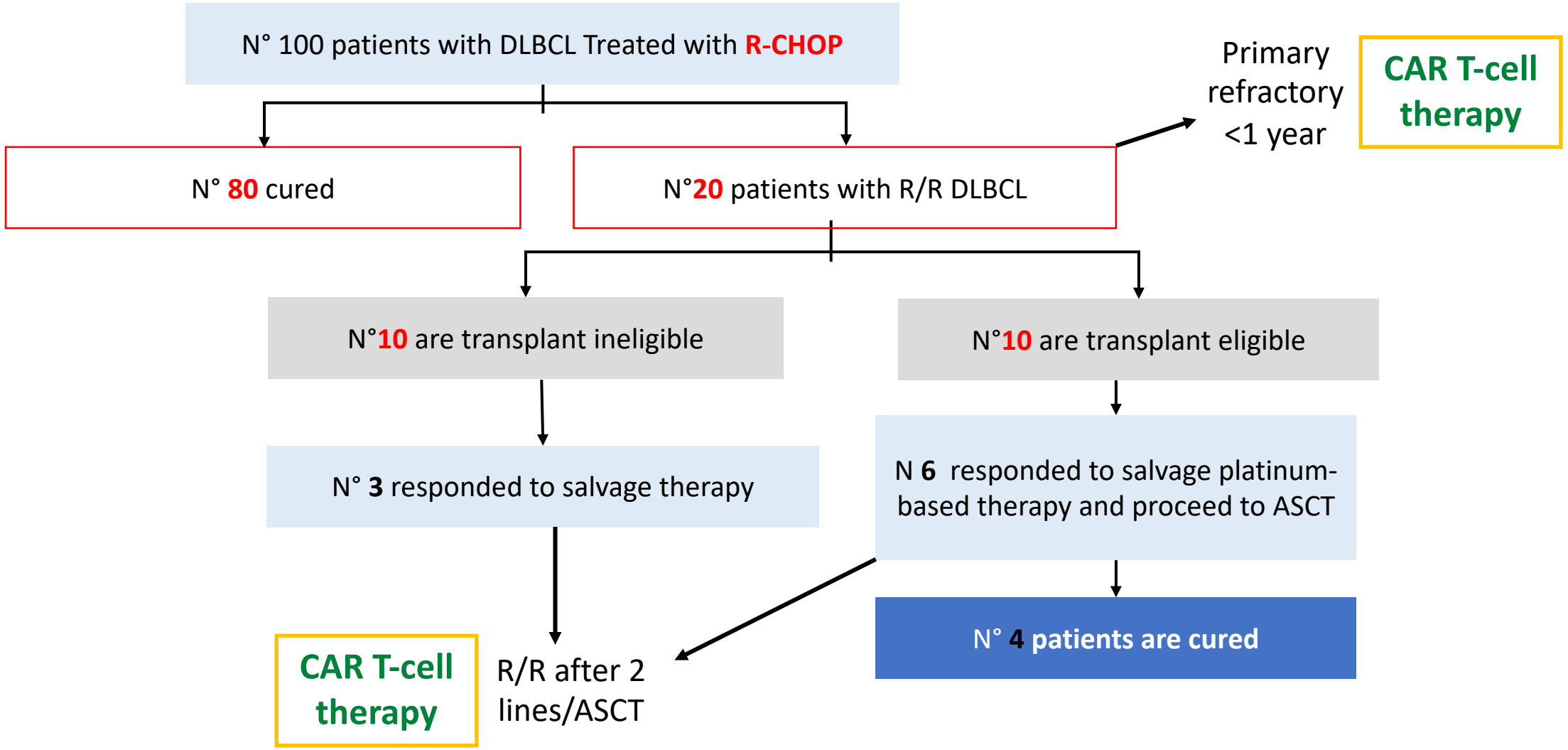
Diffuse Large B-cell Lymphoma



Diffuse Large B-cell Lymphoma



Diffuse Large B-cell Lymphoma



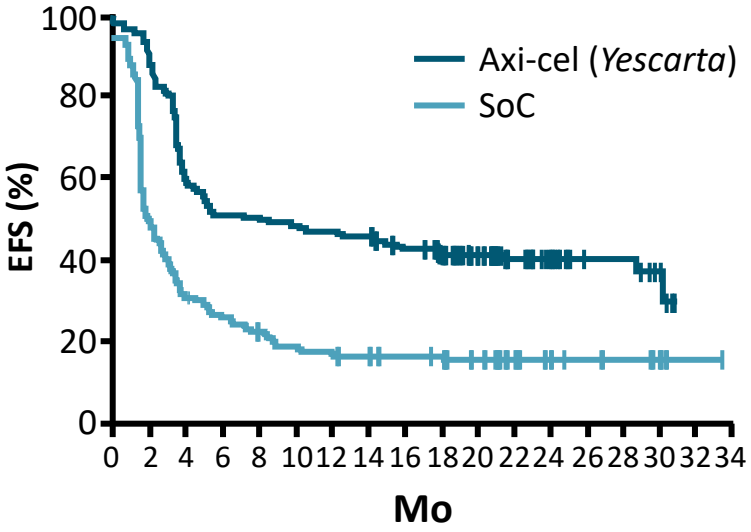
Phase III Trials of CAR T-Cells vs SoC: High-Risk DLBCL Refractory to or Relapsed Within 12 Mo of 1L Tx

ZUMA-7

Optional bridging tx with steroids; crossover not permitted

	Axi-Cel (n = 180)	SoC (n = 179)
Median, mo	8.3	2.0

HR: 0.40 (95% CI: 0.31-0.51; *P* <.0001)



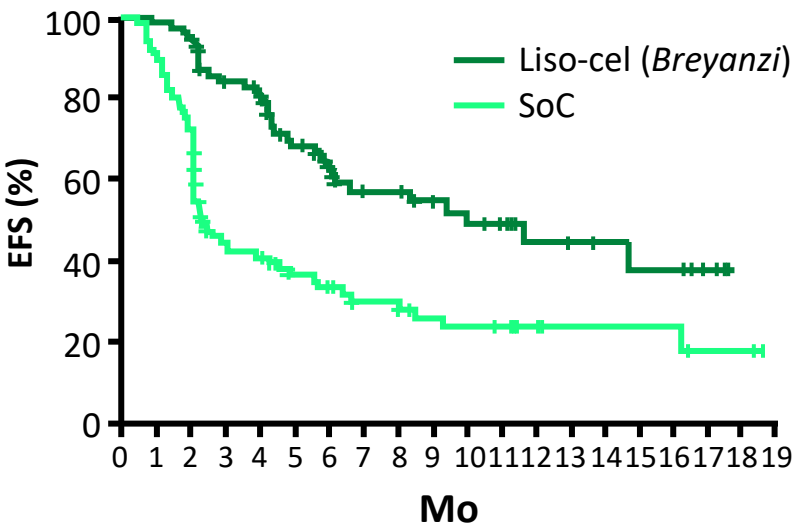
Median follow-up: 24.9 mo

TRANSFORM

Optional bridging tx with platinum CIT; crossover permitted

	Liso-Cel (n = 92)	SoC (n = 92)
Median, mo	10.1	2.3

HR: 0.349 (95% CI: 0.229-0.530; *P* <.0001)



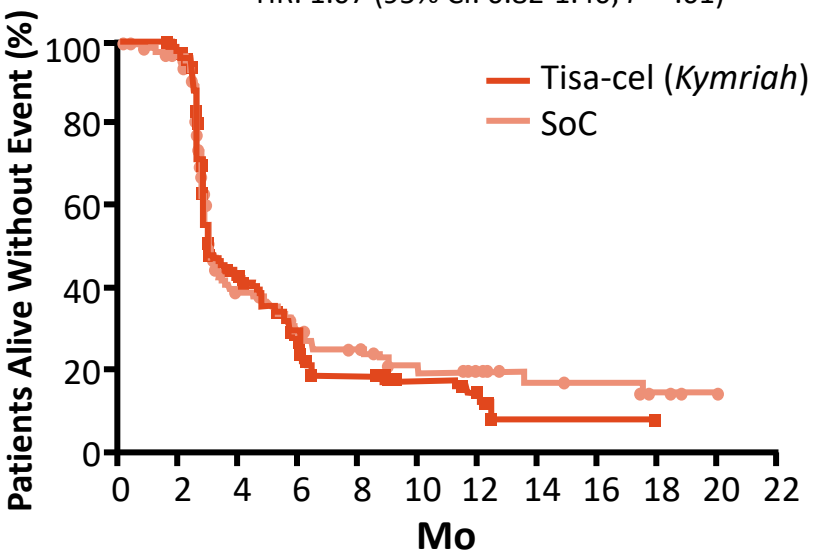
Median follow-up: 6.2 mo

BELINDA

Optional bridging tx with platinum; crossover permitted if SD/PD ≥12 wk

	Tisa-Cel (n = 162)	SoC (n = 160)
Median, mo	3.0	3.0

HR: 1.07 (95% CI: 0.82-1.40; *P* = .61)



Median follow-up: 10 mo

- CAR T-cells generally improve outcomes in R/R disease compared with SoC

Locke. NEJM. 2022;386:640. Locke. ASH 2021. Abstr 2. Kamdar. Lancet. 2022;399:2294.
Kamdar. ASH 2021. Abstr 91. Bishop. NEJM. 2022. 386:629. Bishop. ASH 2021. Abstr LBA-6.

Mantle Cell Lymphoma

Standard dose chemotherapy (age>65-70 years)
High dose chemotherapy/autoSCT

R/R

Ibrutinib

R/R

CAR T-cell therapy ⋯⋯▸ R/R **AlloSCT**

Mantle Cell Lymphoma

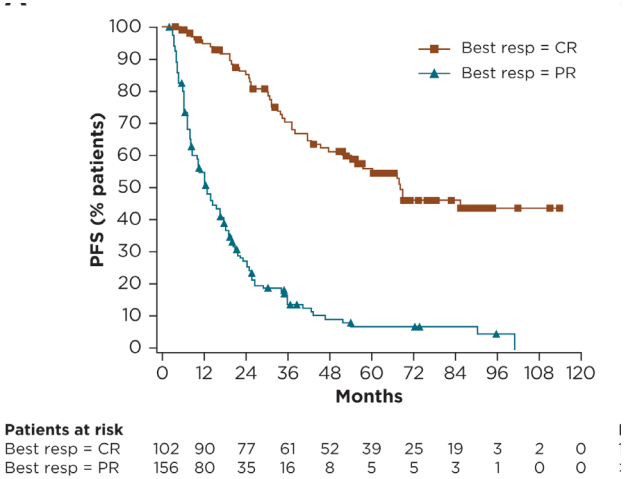
Standard dose chemotherapy (age>65-70 years)
High dose chemotherapy/autoSCT

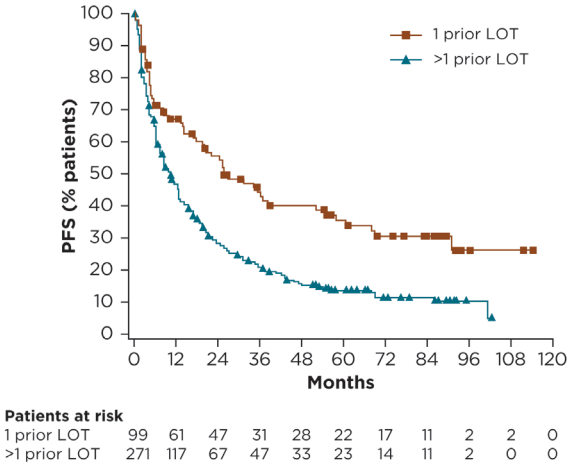
R/R

Ibrutinib

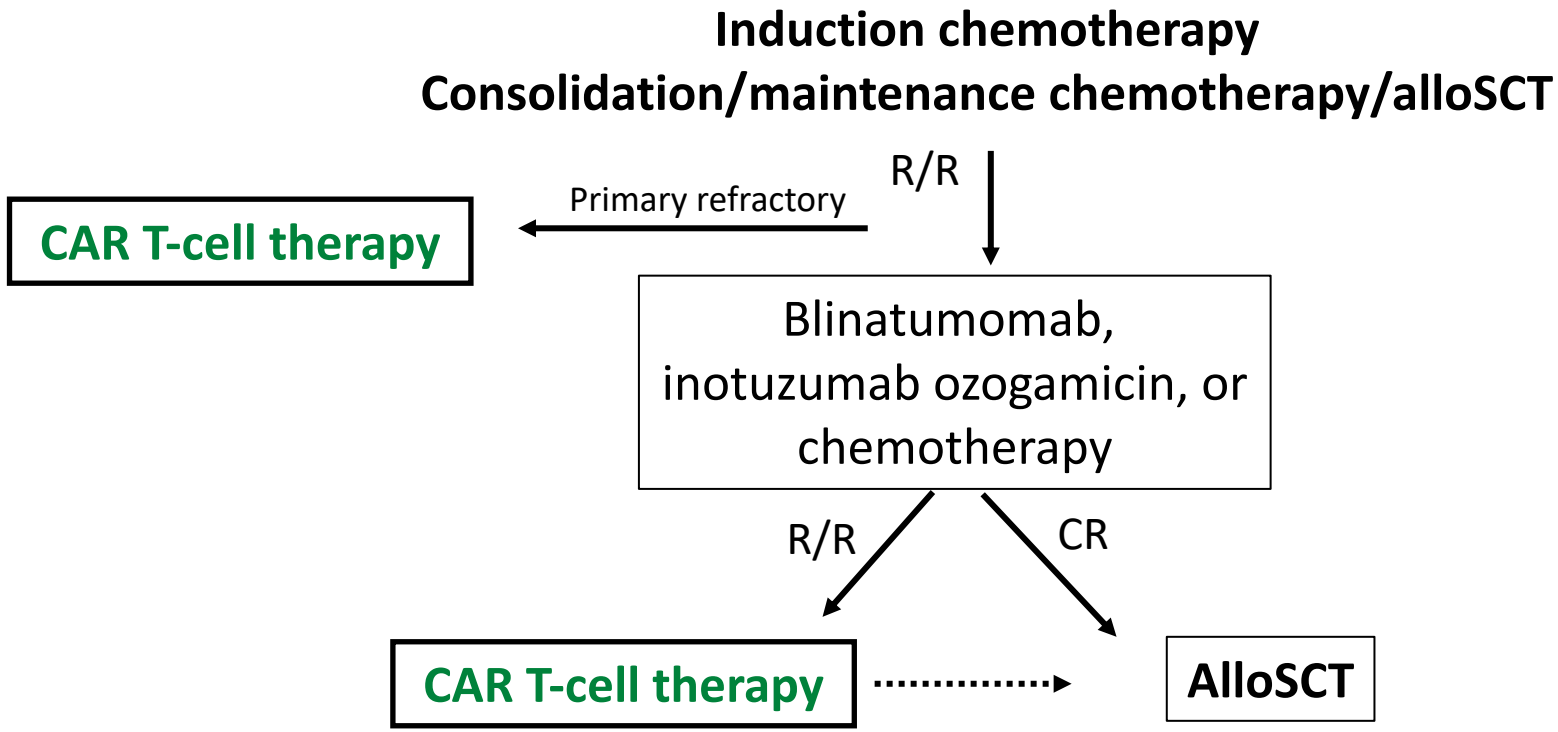
R/R

CAR T-cell therapy R/R **AlloSCT**





B-cell Acute Lymphoblastic Leukemia



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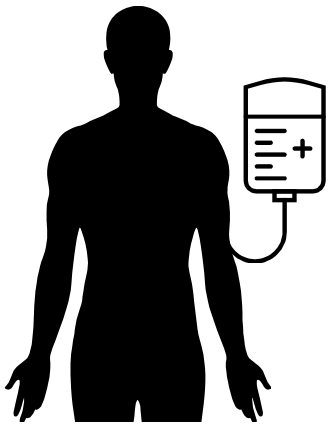
Bird's Eye View: Collection, Manufacturing, and Infusion of CAR T-Cells

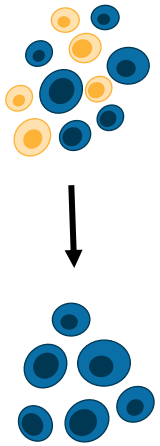
Leukapheresis

Collect patient's own white blood cells

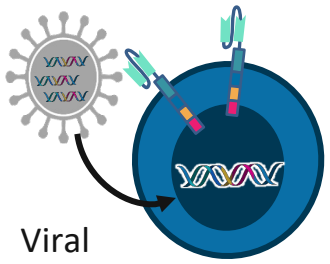


Manufacturing

Isolate and activate T-cells

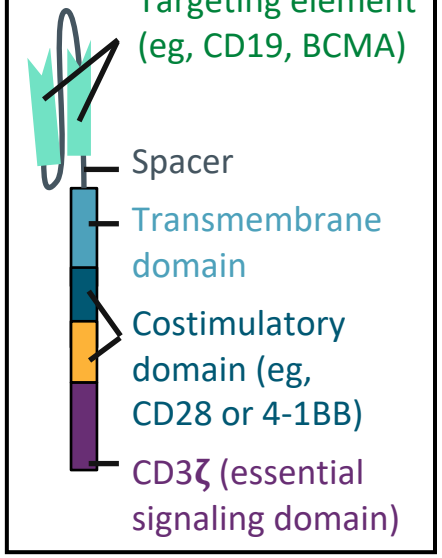


Engineer T-cells with CAR gene

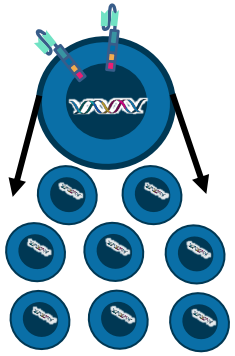


Viral vector with CAR DNA

CAR-engineered T-cell



Expand CAR T-cells

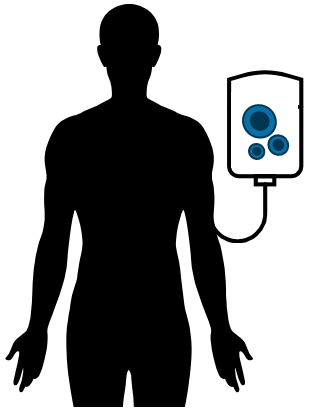


Median manufacturing time: 13-44 days

Patients undergo lymphodepleting (and possibly salvage/bridging) therapy

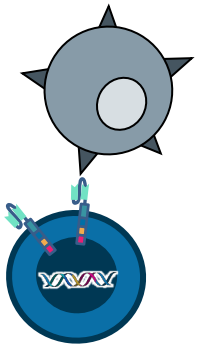
Infusion

Infuse same patient with CAR T-cells



Activity

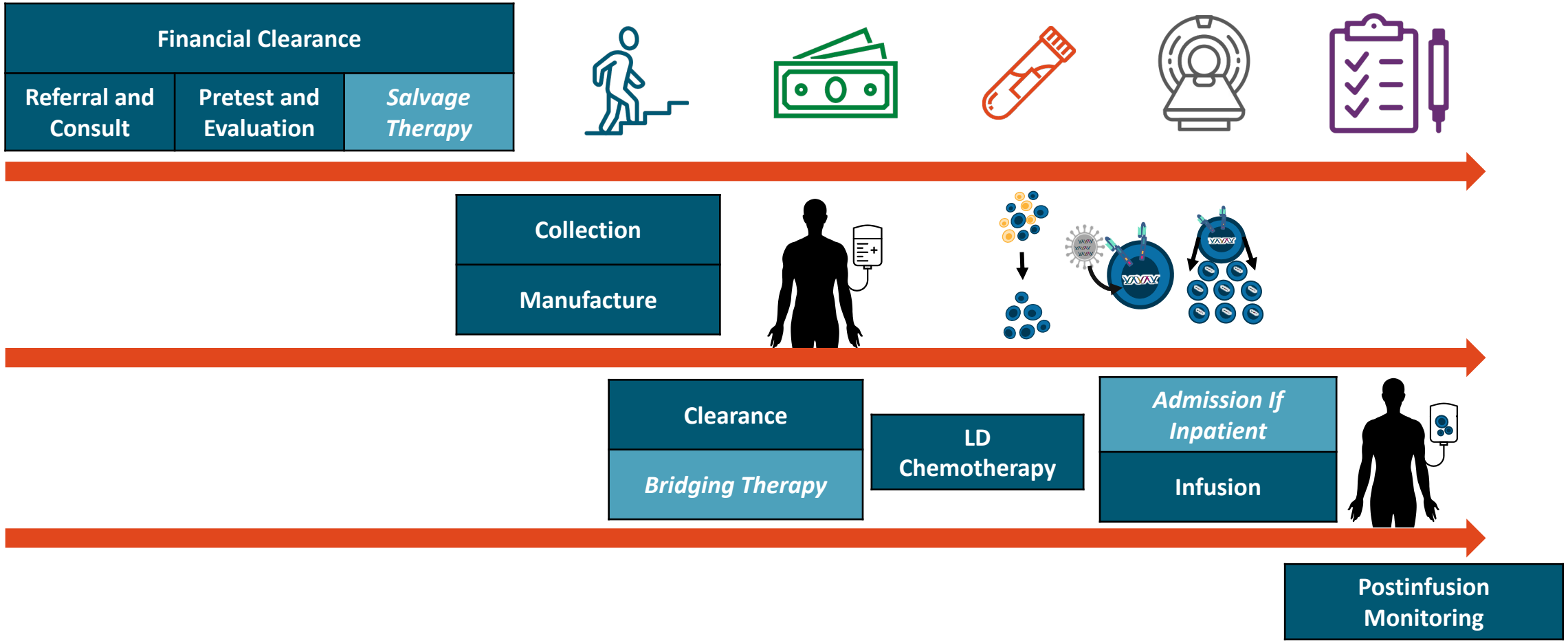
eg, CD19, BCMA



Majors. EHA 2018. Abstr PS1156. Lim. Cell. 2017;168:724. Sadelain. Nat Rev Cancer. 2003;3:35. Brentjens. Nat Med. 2003;9:279. Park. ASH 2015. Abstr 682. Axicabtagene ciloleucel PI. Tisagenlecleucel PI. Neelapu. NEJM. 2017;377:2531. Locke. NEJM. 2022;386:640. Jacobson. Lancet Oncol. 2022;23:91. Wang. NEJM. 2020;382:1331. Shah. Lancet. 2021;398:491. Abramson. ASH 2019. Abstr 241. Kamdar. Lancet. 2022;399:2294. Sehgal. Lancet Oncol. 2022;23:1066. Westin. Am J Hematol. 2021;96:1295.

Slide credit: clinicaloptions.com

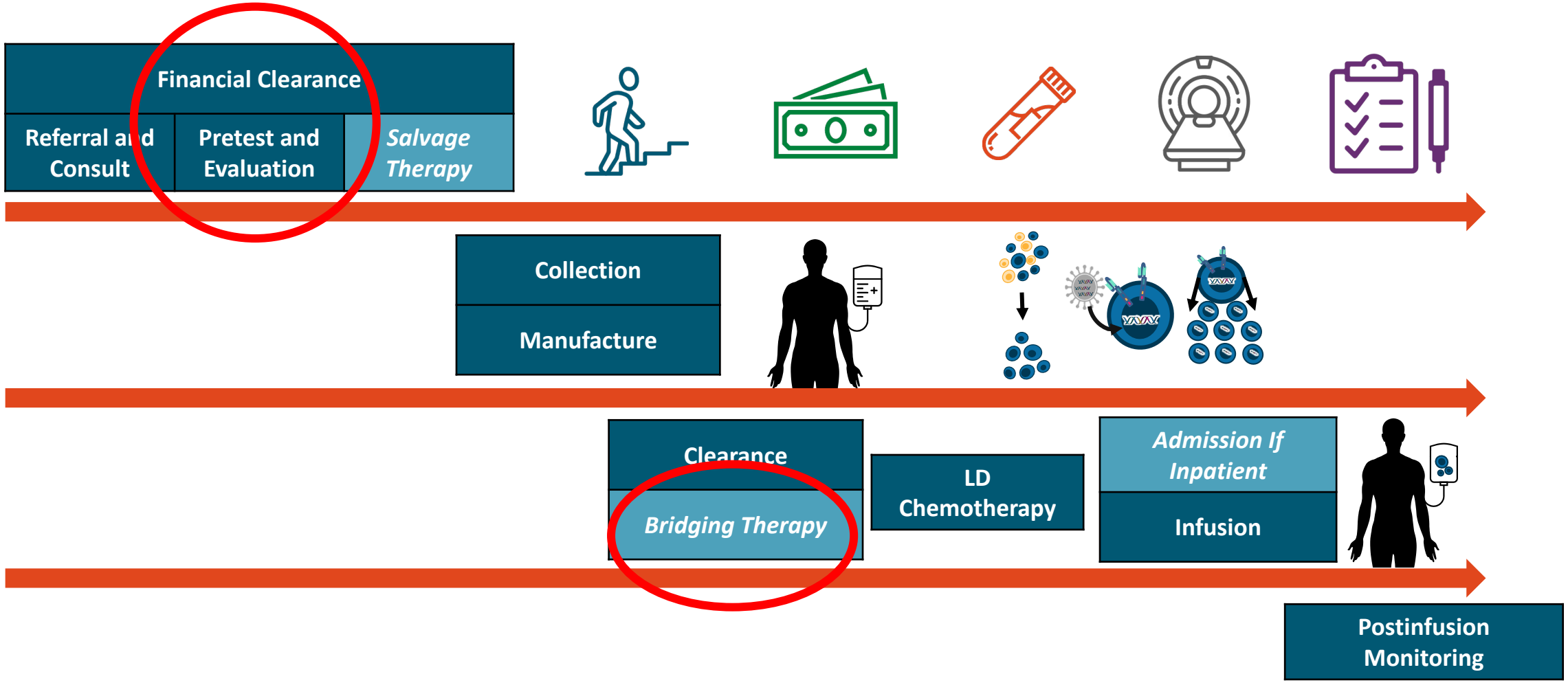
Patient Journey: A Closer Look



Beaupierre. J Adv Pract Oncol. 2019;10(suppl 3):29.

Slide credit: clinicaloptions.com

Patient Journey: A Closer Look



Beaupierre. J Adv Pract Oncol. 2019;10(suppl 3):29.

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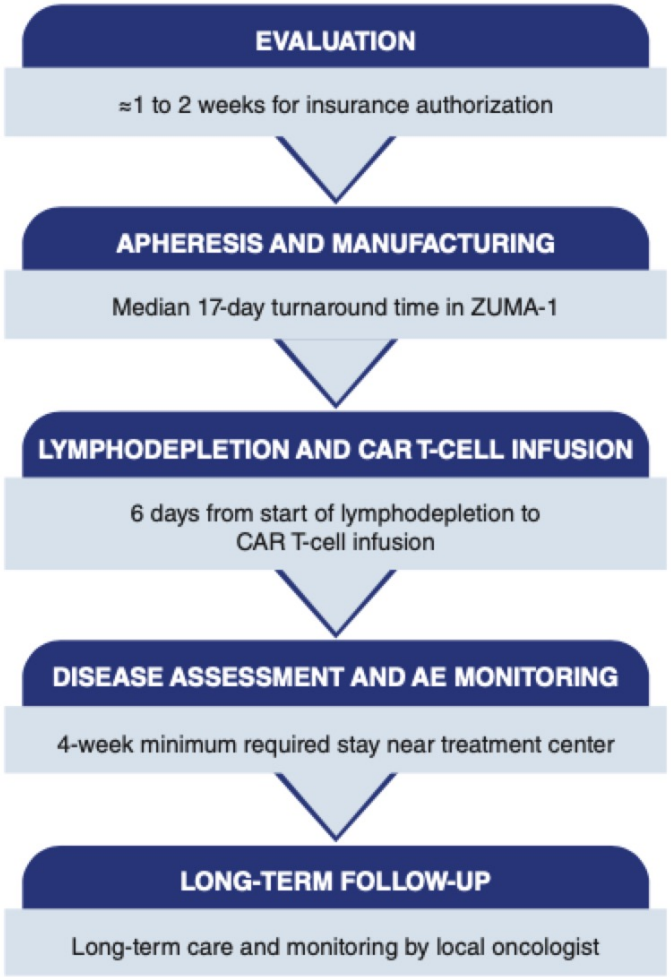


How do we select the candidate patient?

AIFA Criteria (+ Others)

Patient related

- Age
- ECOG PS
- Comorbidities
- Organ function
- Family/social support

Disease related

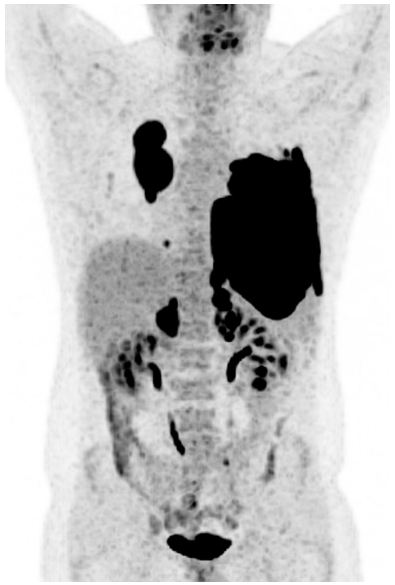
- Tumor burden
- LDH
- Number of prior CHT
- Type of prior CHT
- History of CNS involvement

B.N. male, 39 yrs

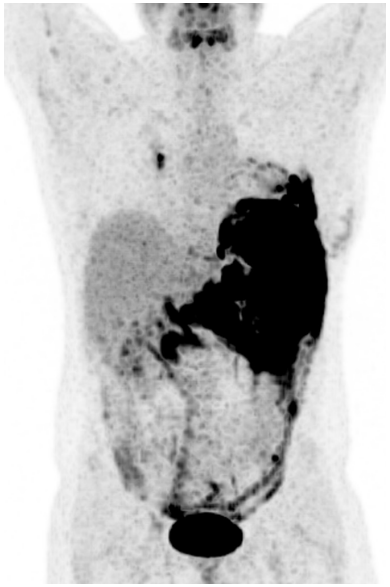
2017 Hodgkin Lymphoma
2 ABVD→ PET +
6 BEACOPP +RT → RC

2018 PMBCL/DBCL
IV-AEX aaIPI high
2 R-OxaDHA → SD
2 R-ICE → PD
Revlimid→ PD

At time of yescarta infusion:
- High LDH
- Myocardial, hepatic ang gastric infiltration



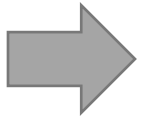
before Yescarta



3 months after Yescarta

Predictors of Outcome

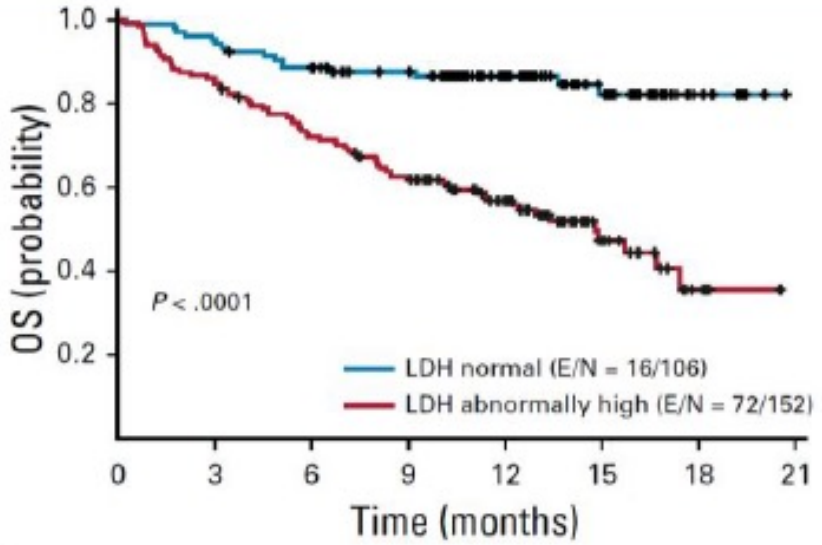
- Pre-infusion high tumor burden
- Highly aggressive disease
- Adequate lymphodepleting conditioning



- Need of bridging therapy
- PS ECOG
- Elevated LDH level
- High total metabolic tumor volume (NHL)
- BM infiltration/MRD (ALL)
- Bone marrow function/leukopenia (previous treatments)

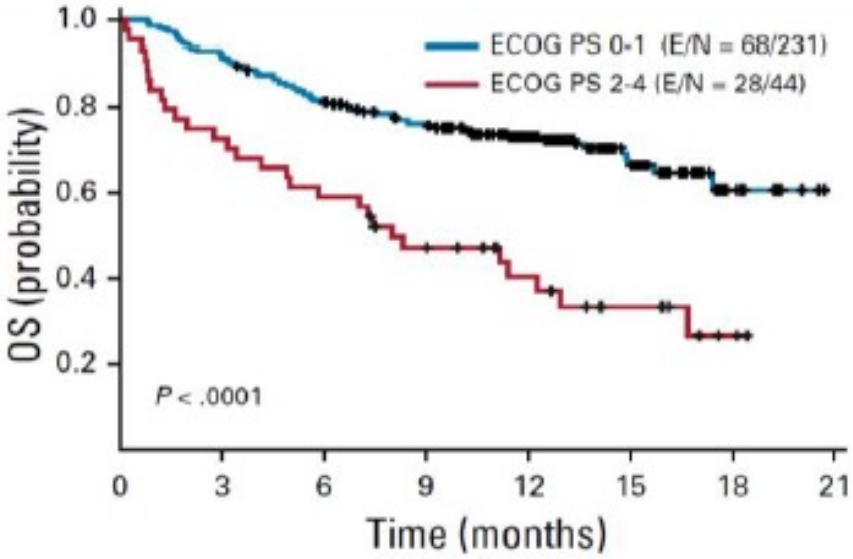
Overall survival by LDH and by ECOG

OS Stratified by LDH[1]



No. at risk:								
LDH normal	106	101	93	84	61	32	8	0
LDH abnormally high	152	129	107	88	57	19	4	0

OS Stratified by ECOG PS[1]

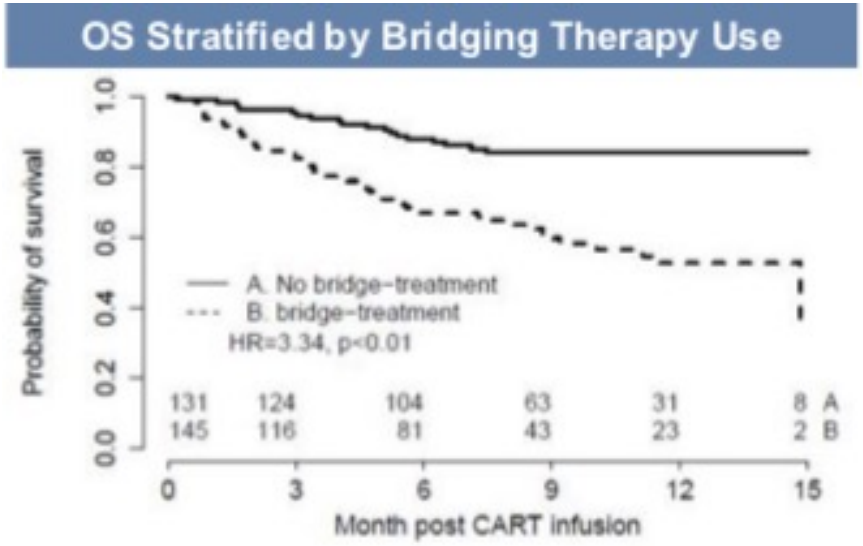


No. at risk:								
ECOG PS 0-1	231	212	184	162	113	47	10	0
ECOG PS 2-4	44	32	26	19	12	7	2	0

Nastoupil LJ, et al. J Clin Oncol. 2020;38(27):3119-3128.

Outcome by bridging therapy

Patient Characteristic (mITT)	Bridging (n = 146)	No Bridging (n = 130)	*P*
ECOG PS 2-4	24.8%	6.1%	<.001
IPI score 3-5	67.6%	34.3%	<.001
Bulky disease >10 cm	28.2%	13.0%	.002
MYC/BCL2 DE	42.5%	24.6%	.004
Safety Outcome (mITT)	**Bridging (n = 146)**	**No Bridging (n = 130)**	***P***
Grade ≥3 CRS	8.2%	5.3%	.34
Grade ≥3 ICANS	35.2%	28.2%	.25
ICU admission	41.4%	22.9%	.001
Median hospital stay, days	15	14	.02
Death due to lymphoma	33.1%	13.0%	<.001
Death due to TRM	6.9%	1.5%	<.001



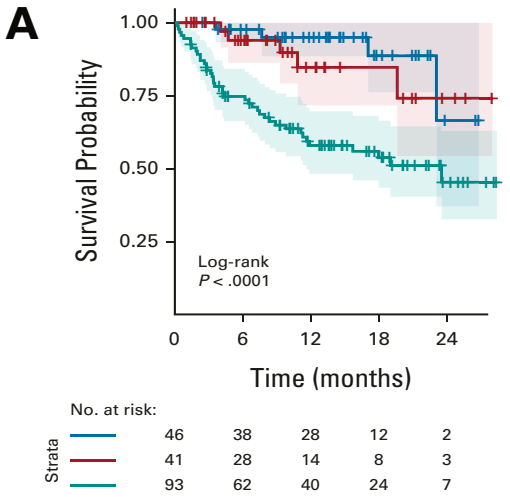
Nastoupil LJ, et al. J Clin Oncol. 2020;38(27):3119-3128.

Disease Burden Affects Outcomes in Pediatric and Young Adult B-Cell ALL After Commercial Tisagenlecleucel: A Pediatric Real-World Chimeric Antigen Receptor Consortium Report

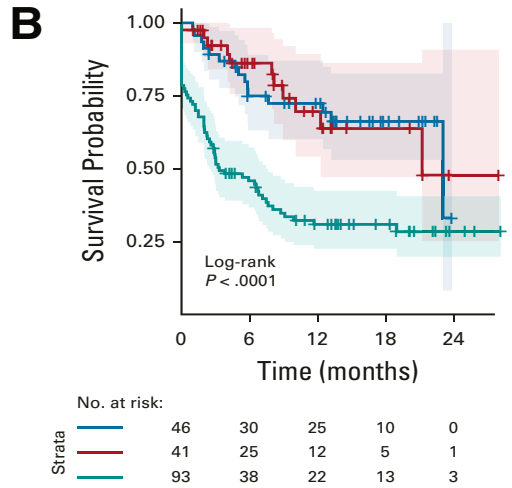
- No detectable disease(no BM blasts)
- Low-disease burden(< 5% BM blasts)
- High-disease burden(≥ 5% BM blasts)

Schultz LM, et al. J Clin Oncol. 2022 Mar 20;40(9):945-955

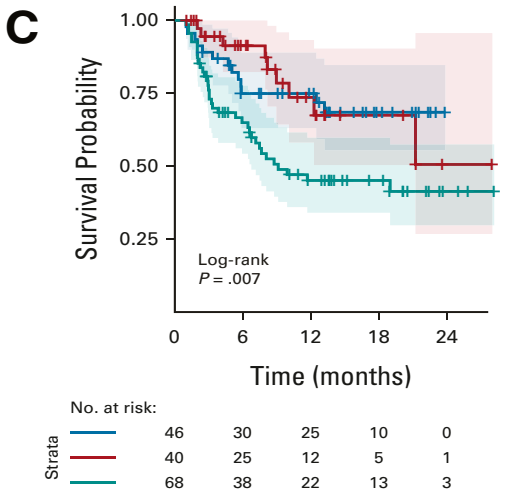
OS, overall survival



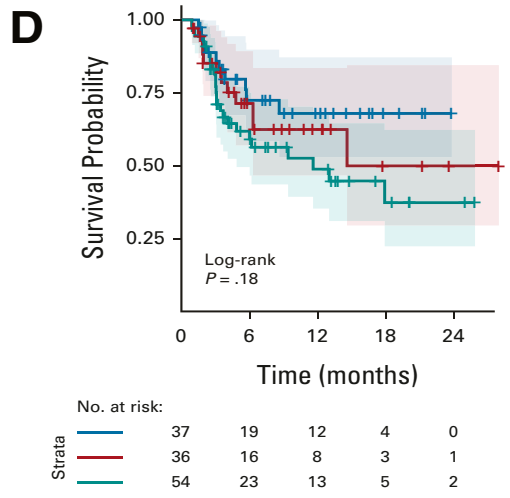
EFS, event-free survival



DOR, duration of remission



DBA, duration of B-cell aplasia



Salvage and Bridging Therapy

- **Goals of salvage therapy:** to stabilize disease
  - Requires washout period before apheresis

Salvage therapy may be recommended during time between referral and consult and apheresis*

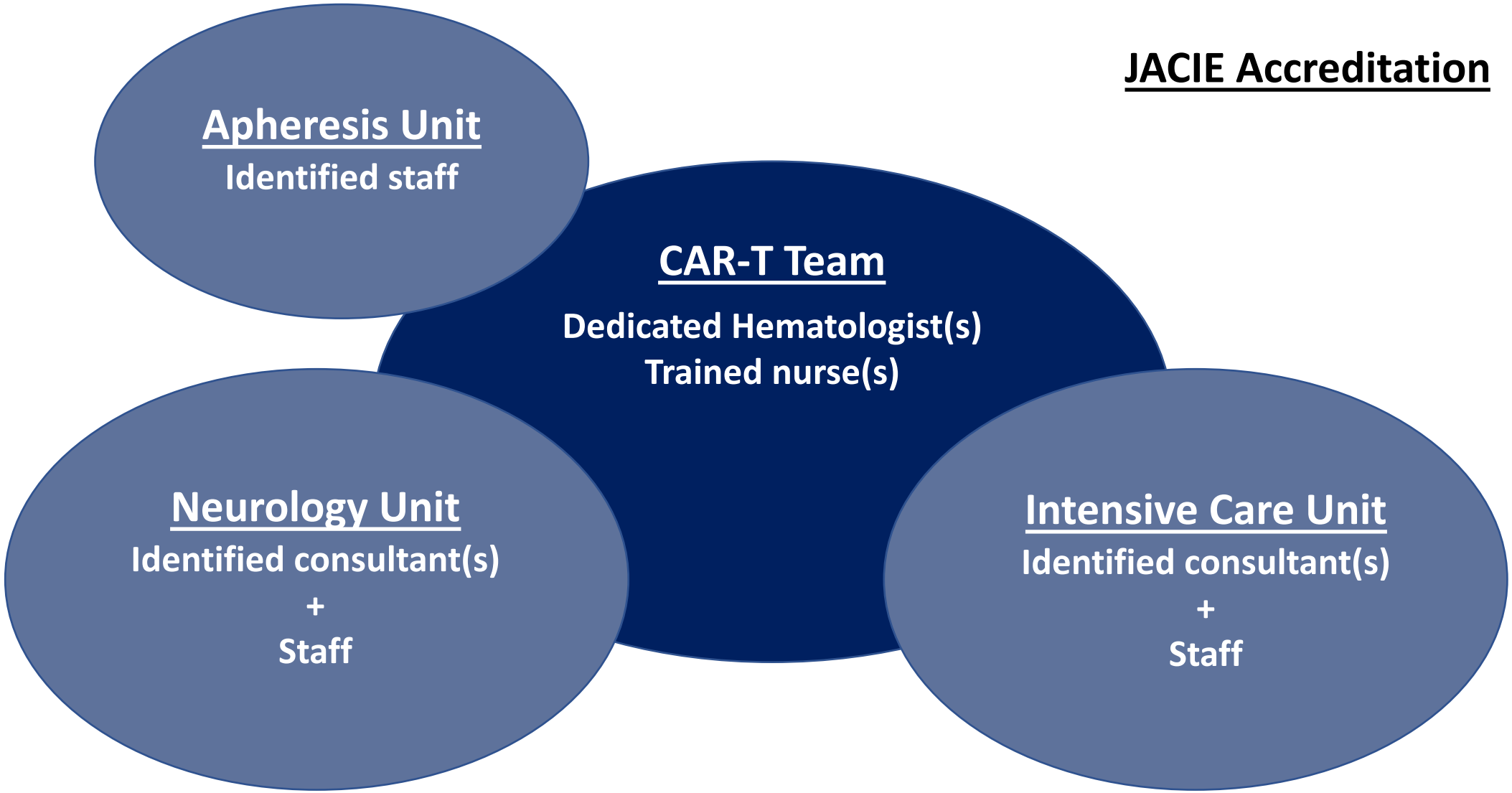
For patients with rapidly proliferating disease, bridging therapy may be recommended during time between apheresis and lymphodepletion

- **Goals of bridging therapy:** reduce tumor burden, palliate symptoms, stabilize disease and QoL, and to **maintain functional reserve during manufacturing period**
  - Limit CRS/ICANS severity by debulking
  - Potential impact on CAR T-cell efficacy
- Maintain frequent communication with patient, primary oncologist, and manufacturer
  - Ensure workup completed
  - Monitor patient's status
- Choose least toxic therapy, if possible, and allow hematologic recovery prior to LDC
  - Real-life time from pheresis to infusion is >30 days
- Consider avoiding immunosuppressive therapy, checkpoint inhibitors, blinatumomab/anti CD19

Jain. Biol Blood Marrow Transpl. 2019;25:2305. Kansagra. Bone Marrow Transplant. 2019;54:1868.

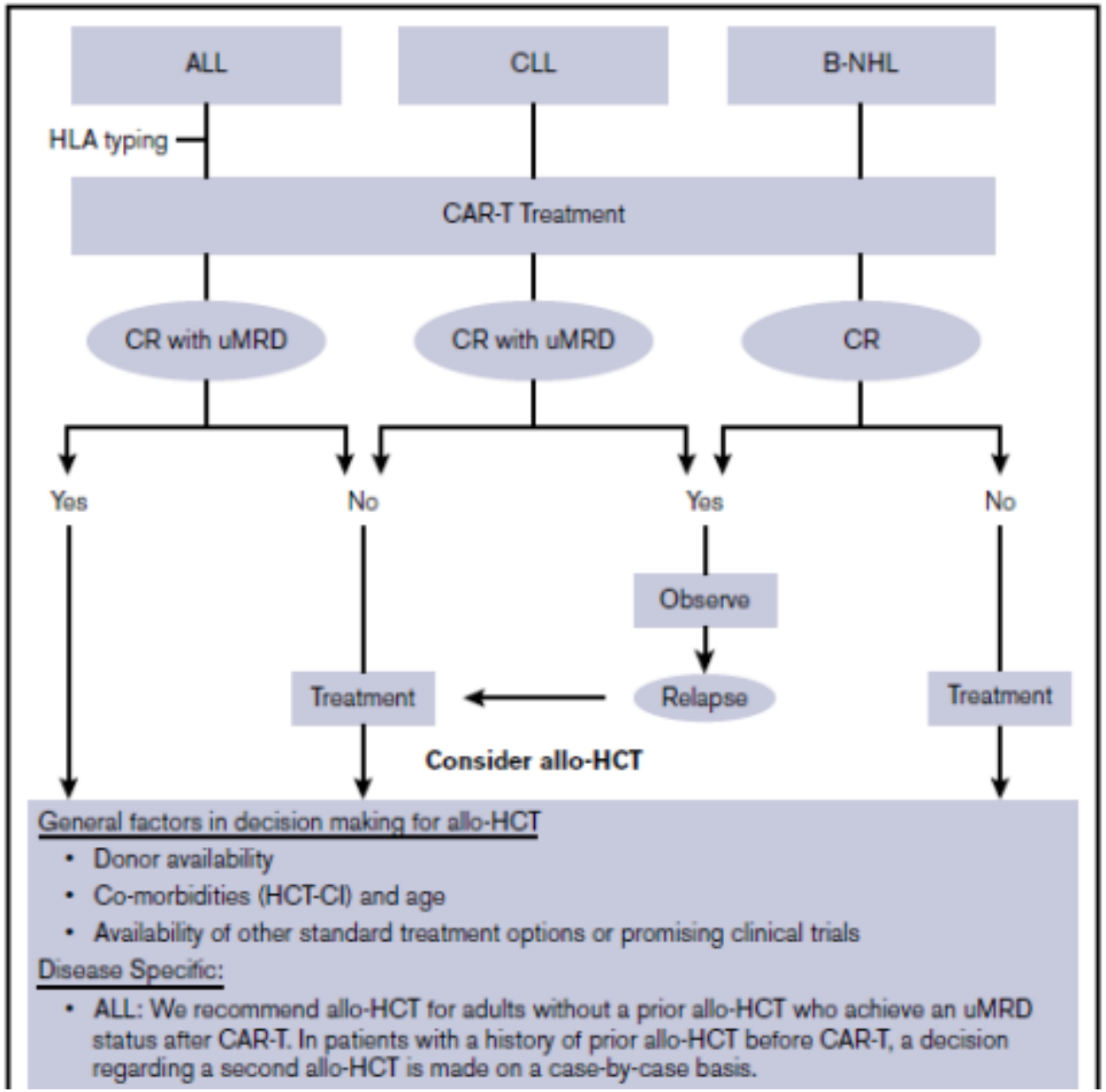
Slide credit: clinicaloptions.com

JACIE Accreditation

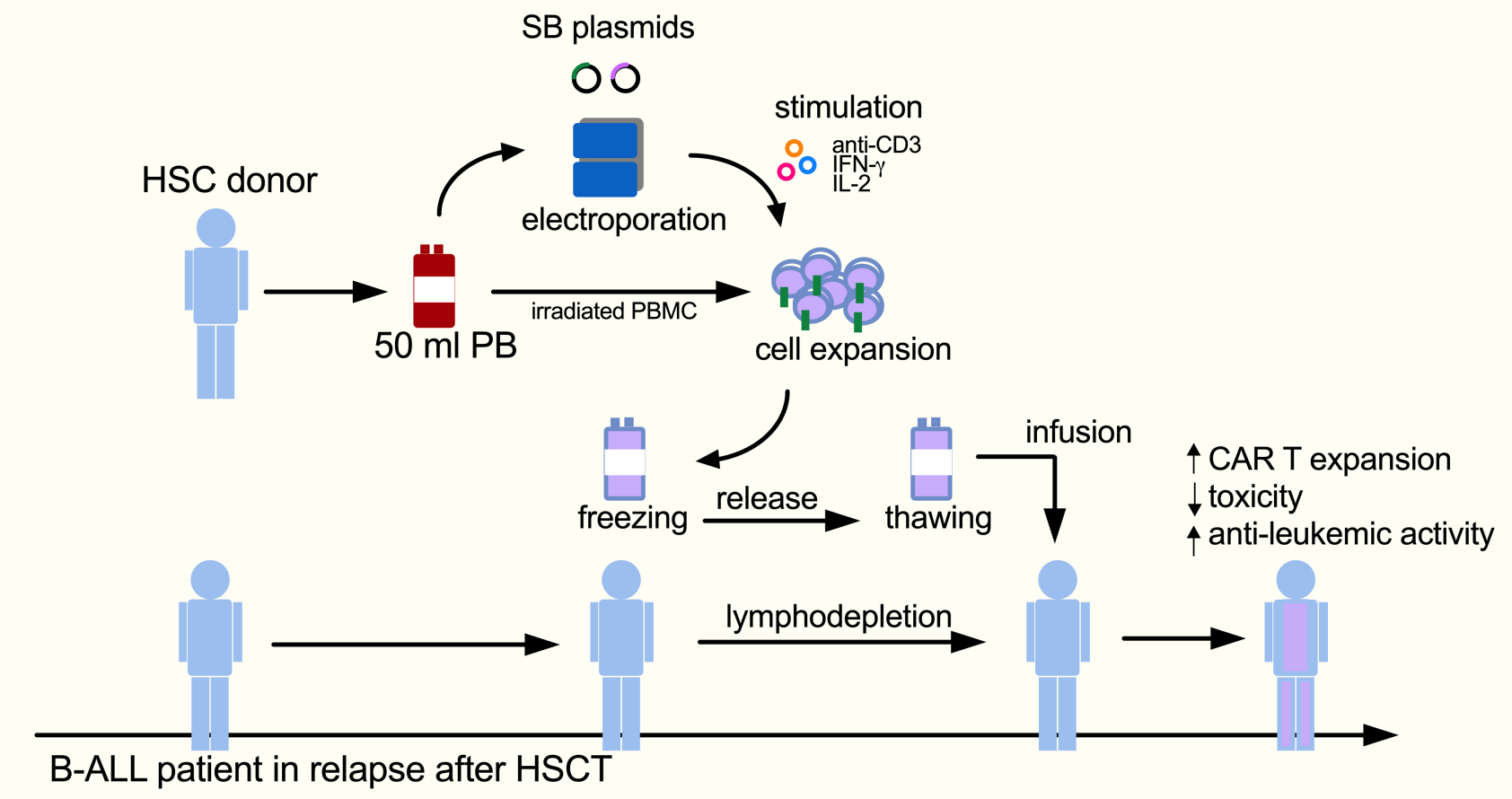


By courtesy of Dr. Filippo Milano, MD

General approach to utilization of allo-HCT in patients treated with CD19-targeted CAR-T



SLEEPING BEAUTY-ENGINEERED CARCIK CELLS ACHIEVE ANTI-LEUKEMIC ACTIVITY WITHOUT SEVERE TOXICITIES



Magnani, J Clin InvestJ Clin Invest. 2020;130(11):6021-6033

Summary

- Expanding indications of CAR-T cell therapy (B-NHL, B-ALL, MM)
- Complex treatment involving several clinical units
- Issues in patient selection and salvage/bridging therapy
- Role of allogeneic SCT/additional treatments
- Finanacial sustainability

Thank you!