Chimeric Antigen Receptor T-cells

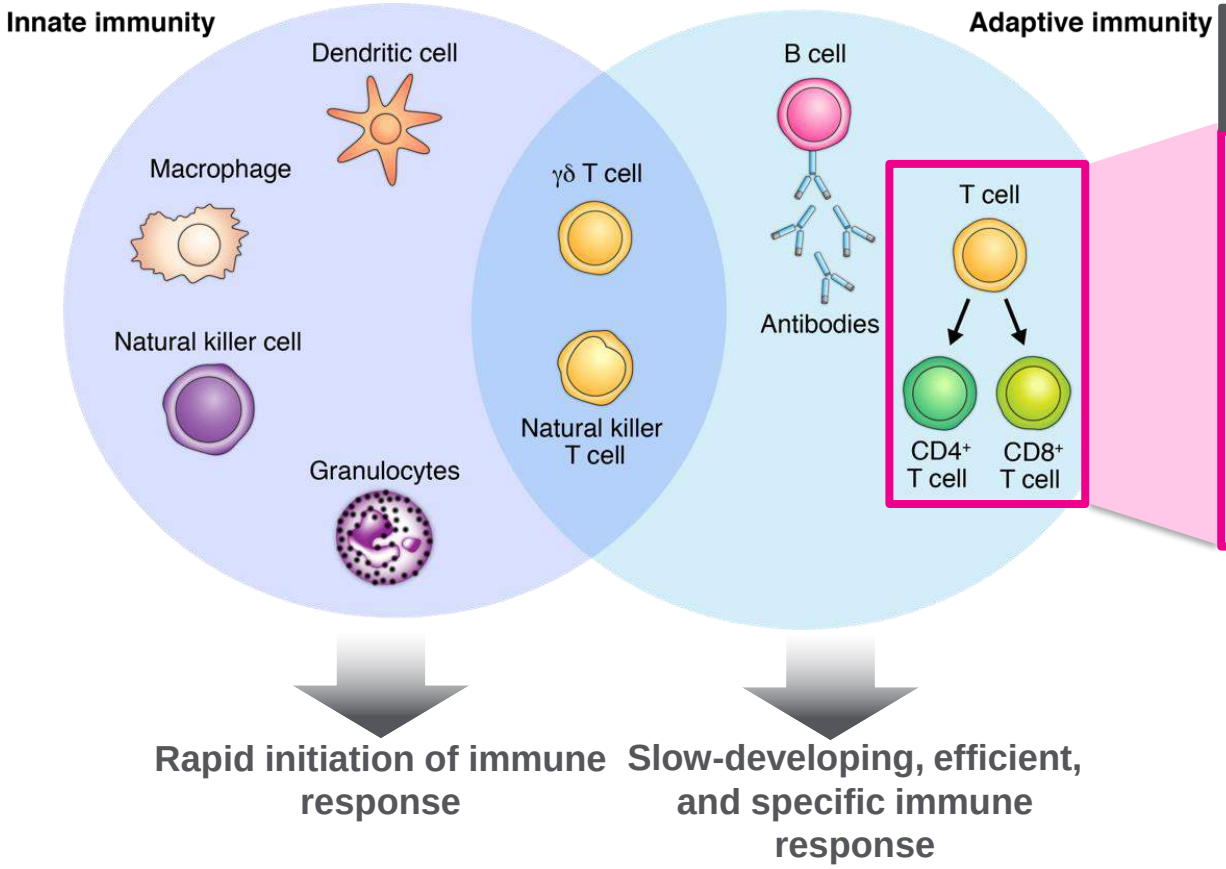
Αποτελεσματικότητα στην υποτροπή Οξείας Λεμφοβλαστικής Λευχαιμίας και Μη Hodgkin Λεμφώματος

Tisagenlecleucel (KYMRIAH, Novartis, Basel, Switzerland), a synthetic bioimmune product of anti-CD19 chimeric antigen receptor - T cells (CAR-T), approved by FDA and EMA, for the treatment of children and young adults with relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL).

Axicabtagene ciloleucel (YESCARTA®, Kite Pharma, a Gilead Company) and tisagenlecleucel (KYMRIAH®, Novartis Pharmaceuticals Corp.) are two CD19-directed chimeric antigen receptor T cell (CD19 CAR T) products that are currently approved by the U.S. Food and Drug Administration, the European Medicines Agency, Health Canada, Ministry of Health, Labor and Welfare (Japan) and Therapeutic Goods Administration (Australia) for treatment of specific subtypes of relapsed/ refractory aggressive B cell non-Hodgkin lymphoma (NHL).

Role of the Immune System in Cancer Control/Eradication

Two distinct forms of immunity



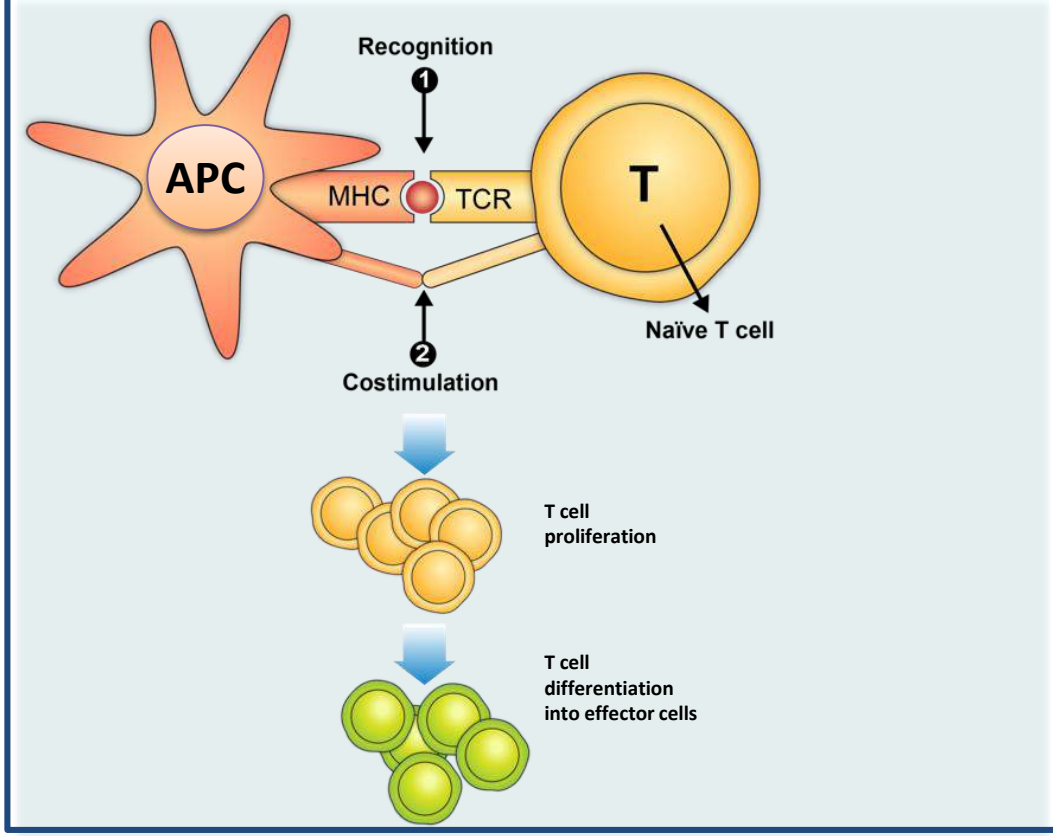
T cells are central players in adaptive immunity

- Active surveillance of pathogens
- Elimination of infected cells

Murphy KM, Weaver C, Mowat A, et al. *Janeways Immunobiology*. 9th ed. Garland Science, Taylor & Francis Group; 2017

T Cell Activation

T cell activation requires two signals[1,2]

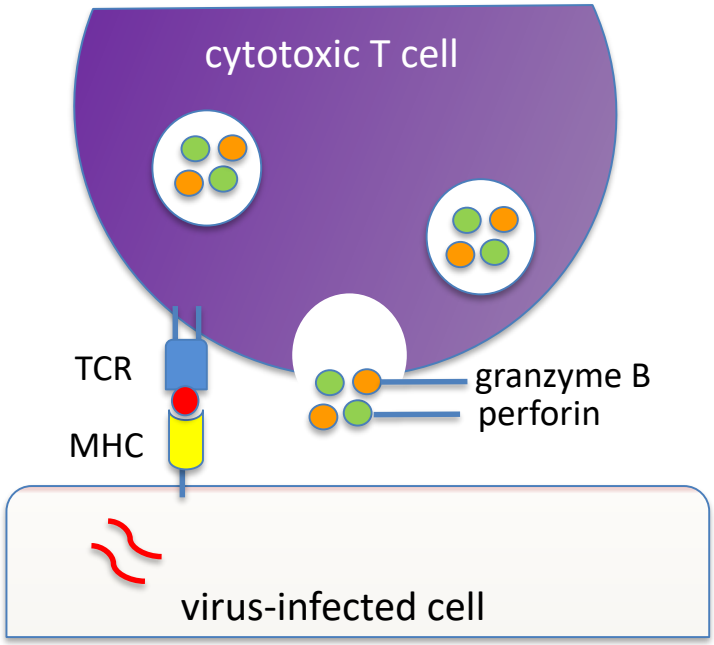


- 1 Activation(Signal 1): TCR binds to MHC:antigen
- 2 Co-stimulation (Signal 2): Co-stimulatory molecule binds to its ligand on APC
- Signal 1 and 2 together lead to
  - T cell activation
  - T cell expansion and differentiation

APC=antigen presenting cell; MHC=major histocompatibility complex; TCR=T cell receptor.

Abbas A, et al (ed). Basic Immunology (fourth edition). 2014. Elsevier Saunders 2. Murphy KM, Weaver C, Mowat A, et al. Janeways Immunobiology. 9th ed. Garland Science, Taylor & Francis Group; 2017

Activated T Cell Subset: Effector CD8 CTLs



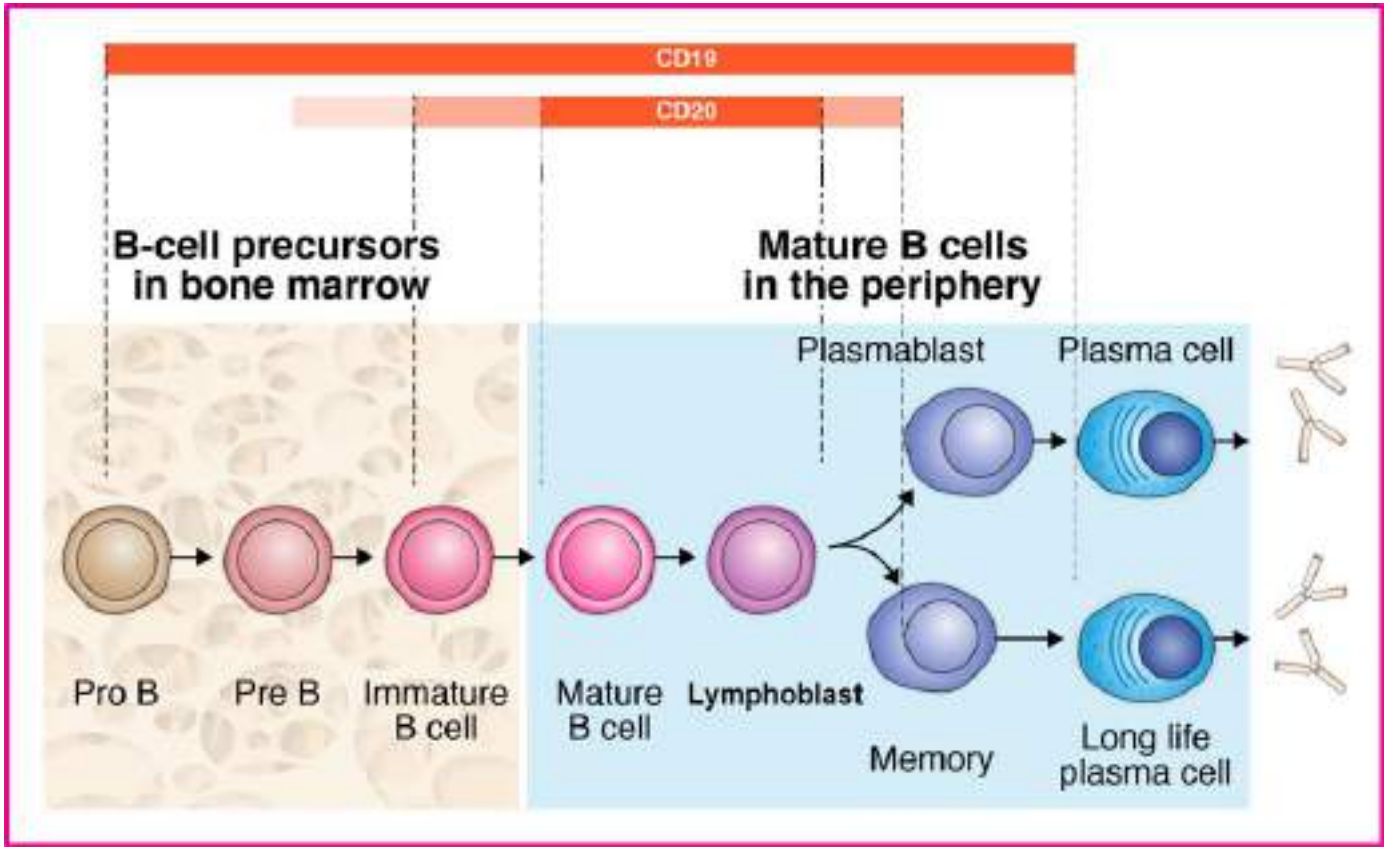
CTLs induce **apoptosis** through multiple mechanisms, including release of cytotoxic granules containing perforin and granzyme B

CTLs are **selective serial killers** of targets expressing a specific antigen

CTL, cytotoxic T lymphocyte; MHC=major histocompatibility complex; TCR, T cell receptor

Murphy KM, Weaver C, Mowat A, et al. Janeways Immunobiology. 9th ed. Garland Science, Taylor & Francis Group; 2017

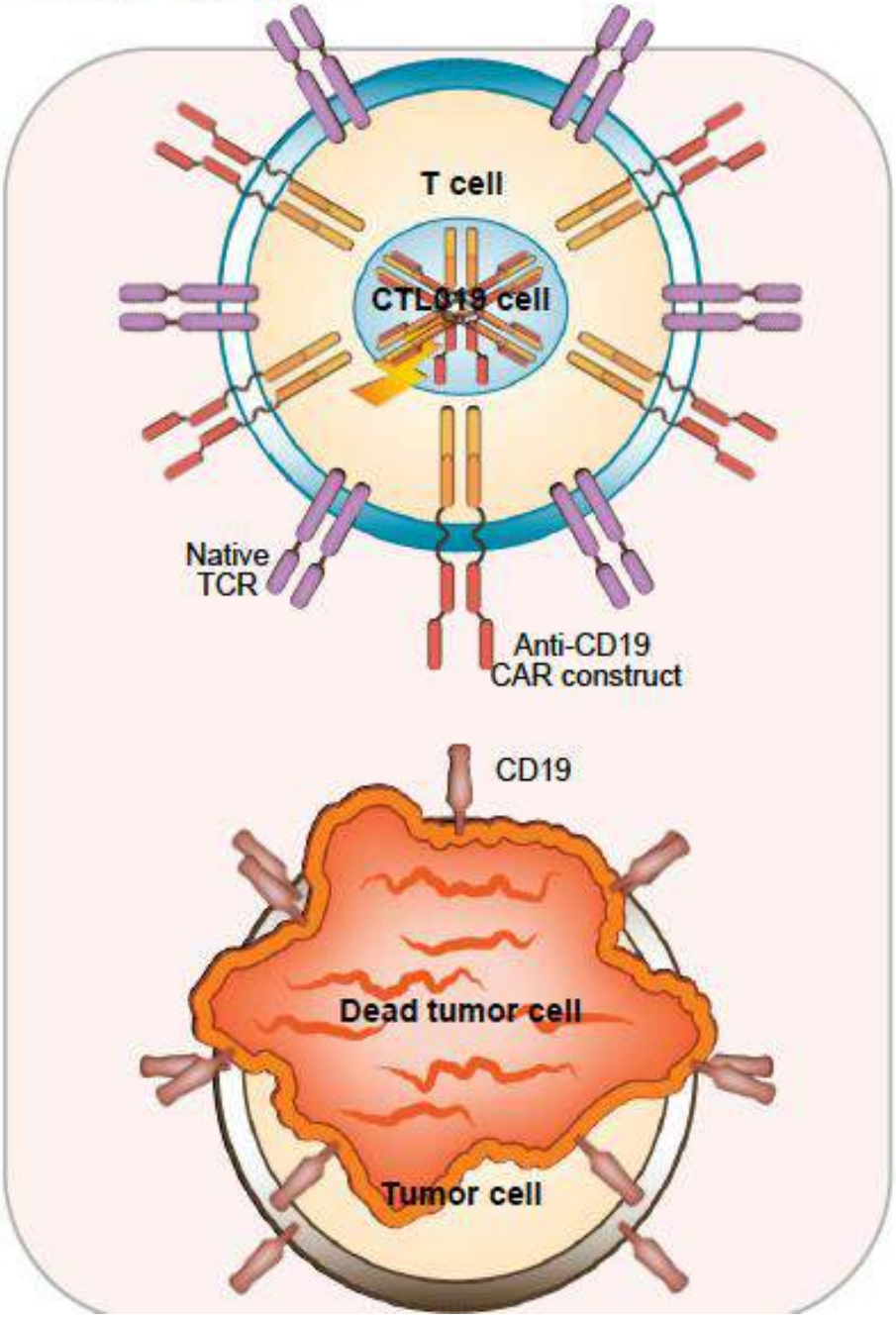
CD19 is a Widely Expressed Antigen in B-lineage Cells



- CD19 is present almost throughout the entire B cell maturation process
- CD19 is present in most B cell leukemias and lymphomas but not in any normal tissue other than the B cell lineage

Mechanism of action of CTL019

- Gene transfer technology is used to stably express CARs on T cells, conferring novel antigen specificity[1,2]
- CTL019 therapy takes advantage of the cytotoxic potential of T cells, thereby killing tumor cells in an antigen-dependent manner[1,3]
- Persistent CTL019 cells consist of both effector (cytotoxic) and central memory T cells[3]



1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464; 2. Hollyman D, et al. *J Immunother.* 2009;32:169-180; 3. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.

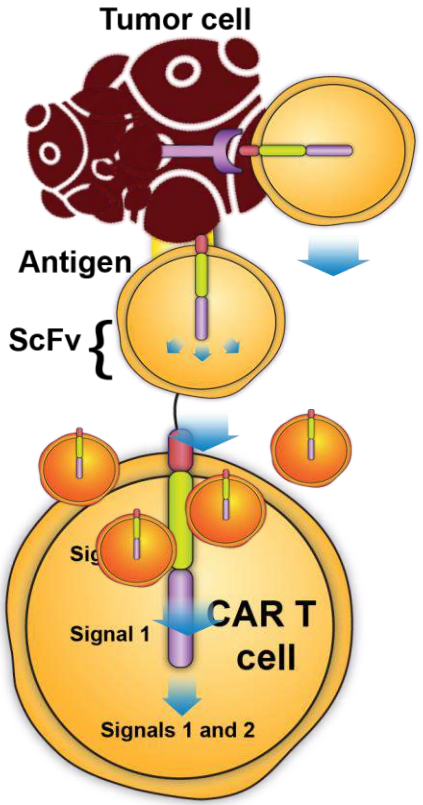
Chimeric antigen receptor (CAR) T cell therapy is a class of immunotherapy that involves engineering patient's own immune cells with a goal of[1,2]:

Recognizing tumor cells

Signaling through the CAR intracellular domains

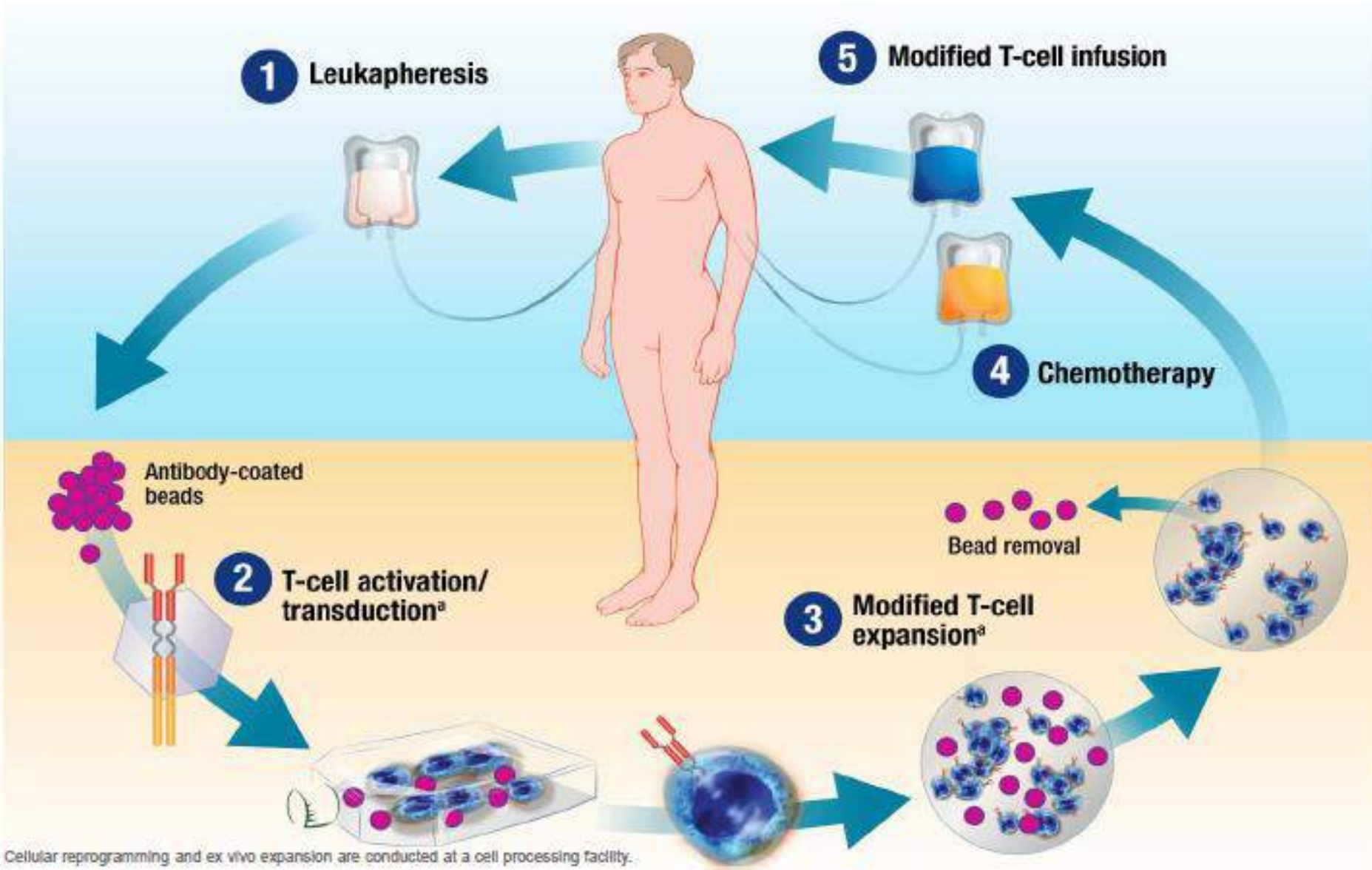
Activating and proliferating CAR T cells

Inducing tumor cell death



scFV= single chain variable fragment.

1. *June CH, Sadelain M. N Engl J Med. 2018;379(1):64-73*
2. *2. Lee DW, et al. Clin Cancer Res. 2012;18:2780-2790.*

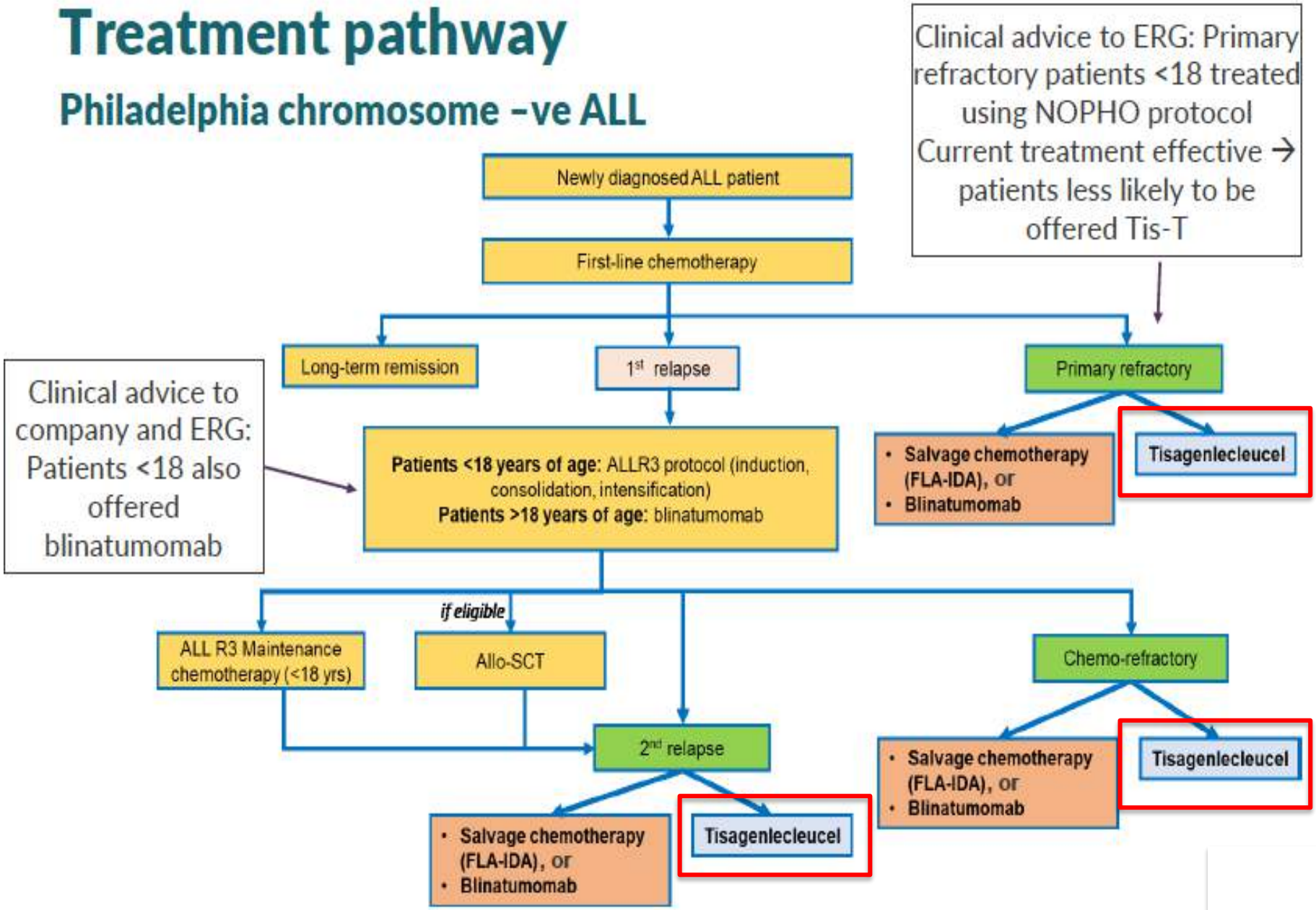


a. Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.

B cell Acute Lymphoblastic Leukemia

Treatment pathway

Philadelphia chromosome –ve ALL



Allo-SCT, allogenic stem cell transplant; NOPHO Nordic Society of Paediatric Haematology and Oncology

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Taran, M. Leung, K.T. Mueller, Y. Zhang, K. Sen, D. Lebwohl, M.A. Pulsipher, and S.A. Grupp

Kymbriah

N Engl J Med 2018;378:439-48.
DOI: 10.1056/NEJMoa1709866

METHODS

We conducted a phase 2, single-cohort, 25-center, global study of tisagenlecleucel in pediatric and young adult patients with CD19+ relapsed or refractory B-cell ALL. The primary end point was the overall remission rate (the rate of complete remission or complete remission with incomplete hematologic recovery) within 3 months.

ELIANA Study Design

Key Eligibility Criteria

- **Inclusion:**
  - r/r B-cell ALL, aged 3-21 years[a]
  - Bone marrow with ≥ 5% lymphoblasts
- **Exclusion:**
  - Isolated extra-medullary disease relapse
  - Prior CD19-directed or gene therapy

Endpoints

- Primary endpoint: Overall remission rate (CR + CRi) within 3 months
  - IRC assessment4-week maintenance of remission
- Secondary endpoints
  - MRD status, DOR, OS, EFS, cellular kinetics, safety

Study Treatment

- **Lymphodepleting chemotherapy prior to infusion**
  - Fludarabine 30 mg/m^2 IV daily for 4 doses
  - Cyclophosphamide 500 mg/m^2 IV daily for 2 doses
- **Tisagenlecleucel dose range (single infusion)**
  - 0.2 to 5.0 × 10^6 cells/kg for patients ≤ 50 kg
  - 0.1 to 2.5 × 10^8 cells for patients > 50 kg

[a] Age of 3 years at the time of screening to age of 21 years at time of initial diagnosis.

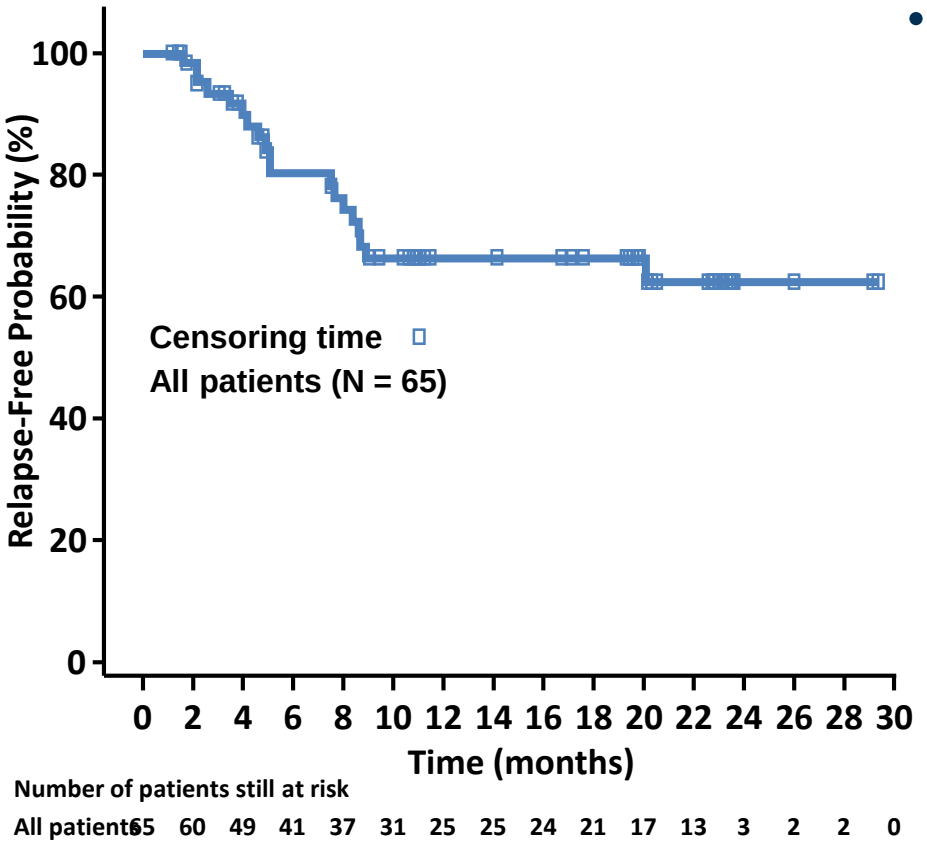
CR, complete response; CRi, CR with incomplete blood count recovery; DOR, duration of response; IRC, Independent Review Committee; MRD, minimal residual disease; OS, overall survival; r/r B-ALL, relapsed or refractory B-cell acute lymphoblastic leukemia.

	Patients (N = 75)
Age, median (range), years	11 (3-23)
Male, n (%)	43 (57)
Prior stem cell transplant, n (%)	46 (61)
Previous line of therapies, median (range), n	3 (1-8)
Disease status, n (%)	
Primary refractory	6 (8)
Chemo-refractory or relapsed	69 (92)
Morphologic blast count in bone marrow, median (range), %	74 (5-99)
CNS status classification, n (%)*	
CNS-1	63 (84)
CNS-2	10 (13)
CNS-3	1 (1)
Unknown	1 (1)
High-risk genomic lesions, n (%)†	28 (37)
Down syndrome, n (%)	6 (8)

CNS, central nervous system.

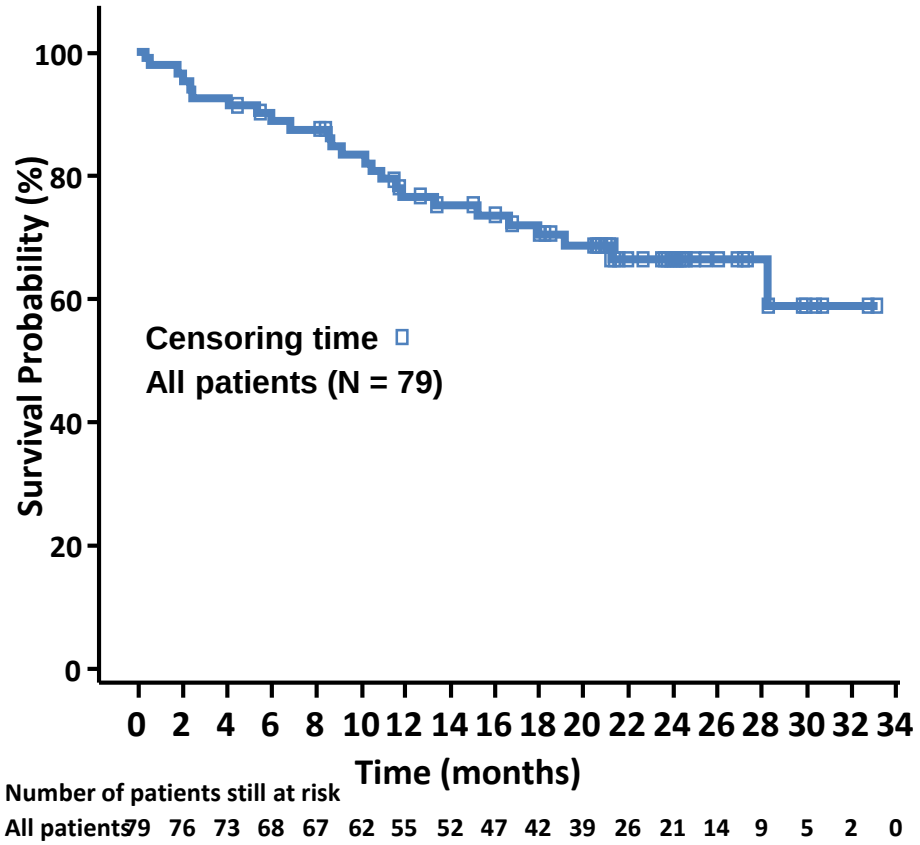
* The most current assessment on or prior to the date of enrollment. † *BCR-ABL1*, *MLL* rearrangement, hypoploidy, lesions associated with *BCR-ABL1*-like gene signature, or complex karyotype (≥5 unrelated abnormalities).

High Response Rate; Median Duration of Remission Not Reached

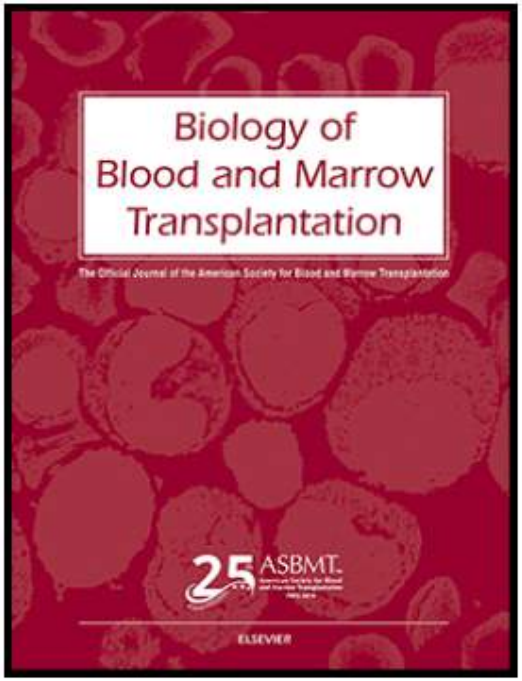


- Overall remission rate (CR + CRi) within 3 months was 82% (65/79; 95% CI, 72-90)[a,b]
  - 98% (64/65) achieved MRD(–)[c] bone marrow
    - Relapse-free survival rate **among responders**
      - 12-month: 66% (95% CI, 52-77)
      - 18-month: 66% (95% CI, 52-77)
      - 24-month: 62% (95% CI, 47-75)

Median Overall Survival Not Reached



- Overall survival rates among all infused patients
  - 12-month: 76% (95% CI, 65-85)
  - 18-month: 70% (95% CI, 58-79)
  - 24-month: 66% (95% CI, 54-76)



Clinical utilization of Chimeric Antigen Receptors T-cells (CAR-T) in B-cell acute lymphoblastic leukemia (ALL) – an expert opinion from the European Society for Blood and Marrow Transplantation (EBMT) and the American Society for Blood and Marrow Transplantation (ASBMT)

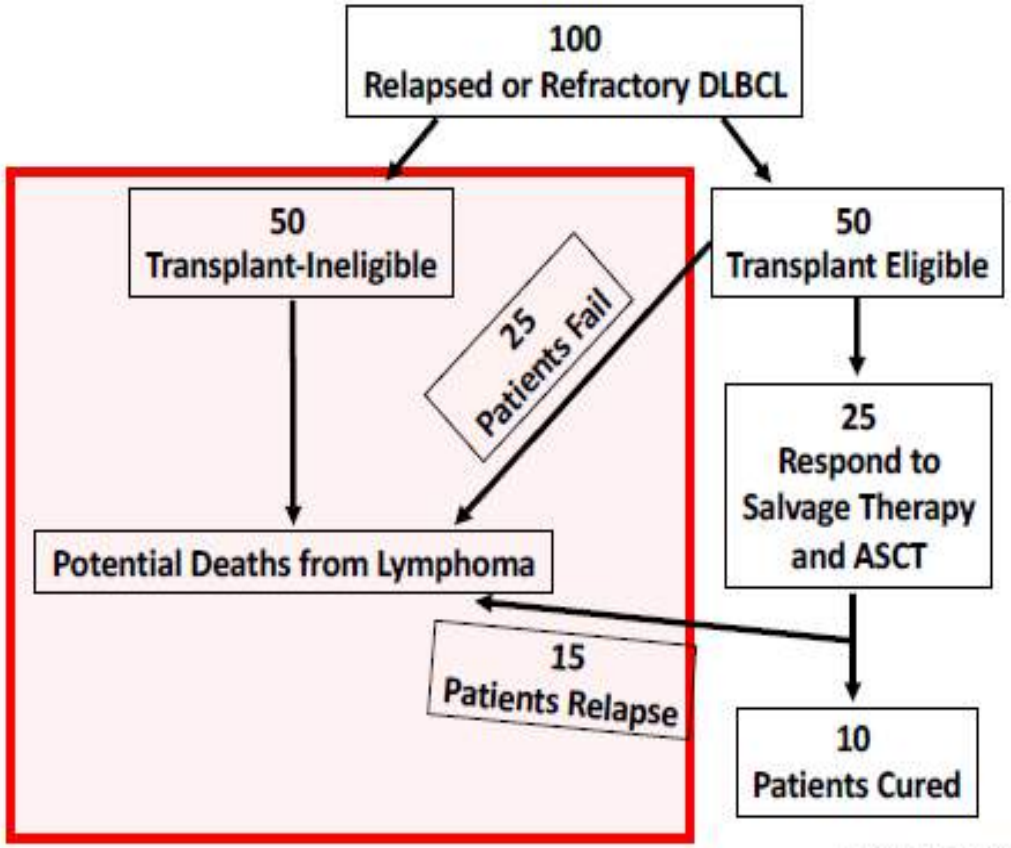
Ankit J. Kansagra , Noelle V. Frey , Merav Bar , Theodore W. Laetsch , Paul A. Carpenter , Bipin N. Savani , Helen E. Heslop , Catherine M. Bollard , Krishna V. Komanduri , Dennis A. Gastineau , Christian Chabannon , Miguel A. Perales , Michael Hudecek , Mahmoud Aljurf , Leslie Andritsos , John A. Barrett , Veronika Bachanova , Chiara Bonini , Armin Ghobadi , Saar I. Gill , Joshua Hill , Saad Kenderian , Partow Kebriaei , Arnon Nagler , David Maloney , Hien D. Liu , Nirali N. Shah , Mohamed A. Kharfan-Dabaja , Elizabeth J Shpall , Ghulam J. Mufti , Laura Johnston , Elad Jacoby , Ali Bazarbachi , John F. DiPersio , Steven Z. Pavletic , David L. Porter , Stephan A Grupp , Michel Sadelain , Mark R. Litzow , Mohamad Mohty , Shahrukh K. Hashmi

PII: S1083-8791(18)30890-5
DOI: https://doi.org/10.1016/j.bbmt.2018.12.068
Reference: YBBMT 55418

1. Where and when should patients be referred for CAR-T in B-cell acute lymphoblastic leukemia?
2. Is the sequence of CAR-T therapy with blinatumomab and/or inotuzumab important?
3. What is the optimal strategy to manage bridging chemotherapy and administer lymphodepleting chemotherapy between T-cell collection and infusion of CAR-T?
4. **Are CAR-T a bridging therapy to allo-HCT or sufficient alone as definitive relapse therapy?**
5. **What are the late effects of CAR-T therapy?**

B-Cell Non Hodgkin Lymphomas

What does AutoSCT achieve in r/r DLBCL in the rituximab era*?



* Estimates based on Gisselbrecht et al. *J Clin Oncol* 2010 28:27;4184-4190.
* Assumes all patients received rituximab as part of primary therapy.

Outcomes in refractory large B cell lymphoma with traditional standard of care are extremely poor

The SCHOLAR-1 analysis demonstrated an ORR of 26%, a CR rate of 7%, and a median OS of 6.3 months in this patient population

ZUMA-1 study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

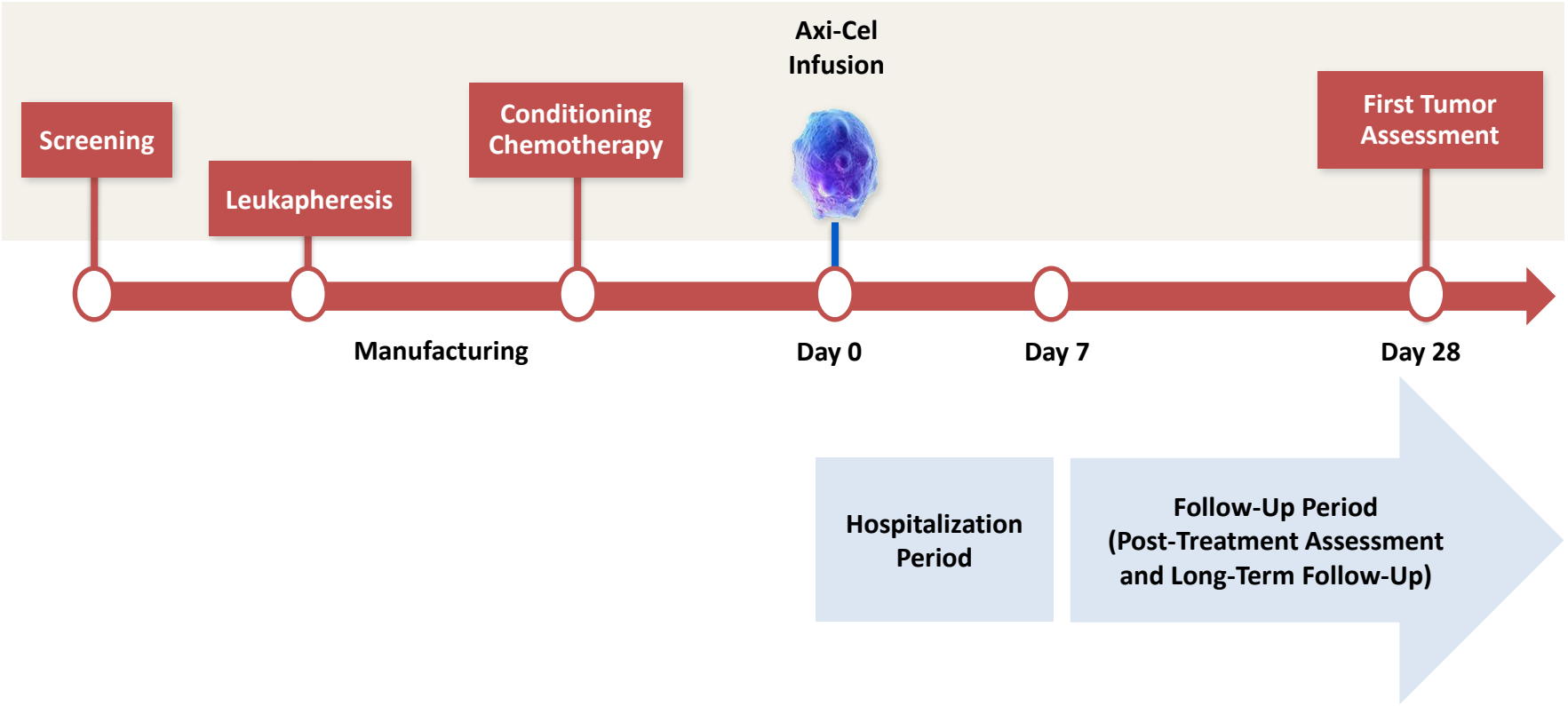
S.S. Neelapu, F.L. Locke, N.L. Bartlett, L.J. Lekakis, D.B. Miklos, C.A. Jacobson, I. Braunschweig, O.O. Oluwole, T. Siddiqi, Y. Lin, J.M. Timmerman, P.J. Stiff, J.W. Friedberg, I.W. Flinn, A. Goy, B.T. Hill, M.R. Smith, A. Deol, U. Farooq, P. McSweeney, J. Munoz, I. Avivi, J.E. Castro, J.R. Westin, J.C. Chavez, A. Ghobadi, K.V. Komanduri, R. Levy, E.D. Jacobsen, T.E. Witzig, P. Reagan, A. Bot, J. Rossi, L. Navale, Y. Jiang, J. Aycock, M. Elias, D. Chang, J. Wiezorek, and W.Y. Go

METHODS

In this multicenter, phase 2 trial, we enrolled 111 patients with diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma who had refractory disease despite undergoing recommended prior therapy. Patients received a target dose of 2×10^6 anti-CD19 CAR T cells per kilogram of body weight after receiving a conditioning regimen of low-dose cyclophosphamide and fludarabine. The primary end point was the rate of objective response (calculated as the combined rates of complete response and partial response). Secondary end points included overall survival, safety, and biomarker assessments.

Variable	Patients with DLBCL	Patients with PMBCL or TFL	All Patients
Refractory subgroup at study entry — no. (%)			
Primary refractory	2 (3)	0	2 (2)
Refractory to second-line or subsequent therapy	59 (77)	19 (79)	78 (77)
Relapse after autologous stem-cell transplantation	16 (21)	5 (21)	21 (21)

ZUMA-1 Treatment Schema



- Bridging chemotherapy was not allowed per study protocol

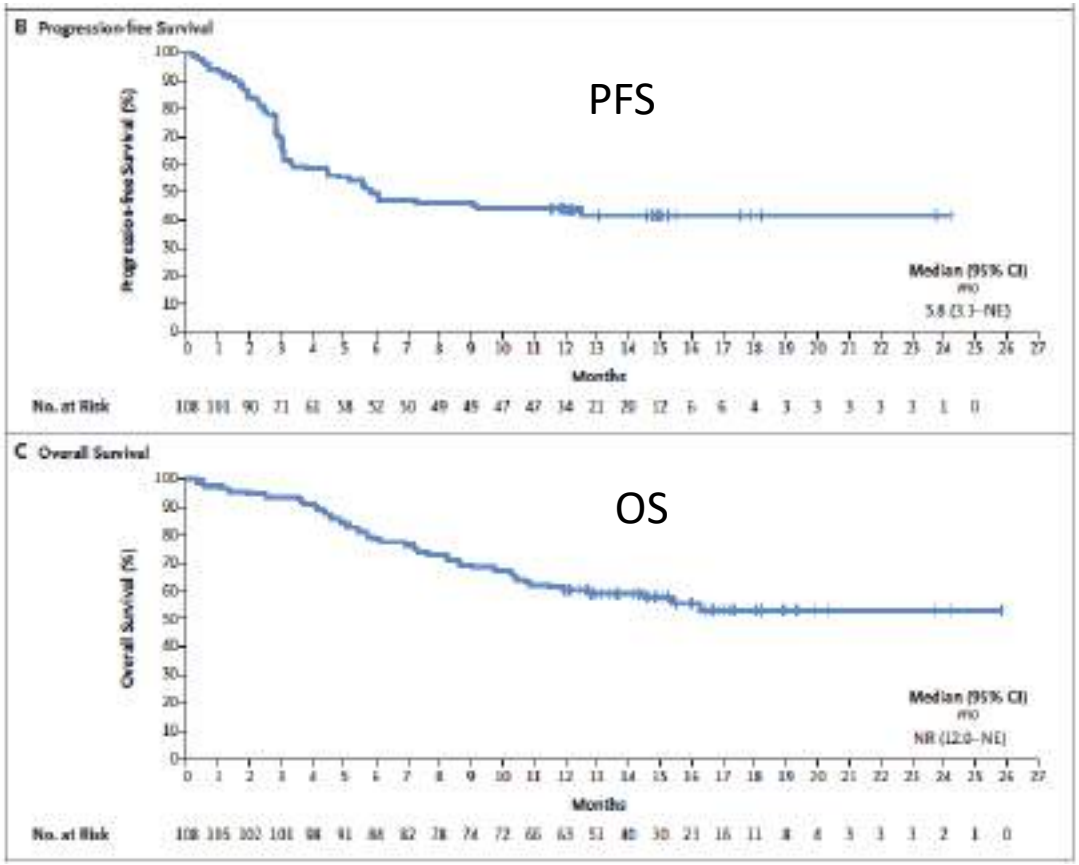
ZUMA-1 Results

objective response rate 82%

complete response rate 54%

With a median follow-up of 15.4 months:

42% of the patients continued to have a response, with **40% continuing to have a complete response. The overall rate of survival at 18 months was 52%.**



JULIET Study

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 380;1 NEJM.ORG JANUARY 3, 2019

ORIGINAL ARTICLE

Kymbriah

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

Stephen J. Schuster, M.D., Michael R. Bishop, M.D., Constantine S. Tam, M.D., Edmund K. Waller, M.D., Ph.D., Peter Borchmann, M.D., Joseph P. McGuirk, D.O., Ulrich Jäger, M.D., Samantha Jaglowski, M.D., Charalambos Andreadis, M.D., Jason R. Westin, M.D., Isabelle Fleury, M.D., Veronika Bachanova, M.D., Ph.D., S. Ronan Foley, M.D., P. Joy Ho, M.B., B.S., D.Phil., Stephan Mielke, M.D., John M. Magenau, M.D., Harald Holte, M.D., Ph.D., Serafino Pantano, Ph.D., Lida B. Pacaud, M.D., Rakesh Awasthi, Ph.D., Jufen Chu, Ph.D., Özlem Anak, M.D., Gilles Salles, M.D., Ph.D., and Richard T. Maziarz, M.D., for the JULIET Investigators*

JULIET Study

N ENGL J MED 380;1 NEJM.ORG JANUARY 3, 2019

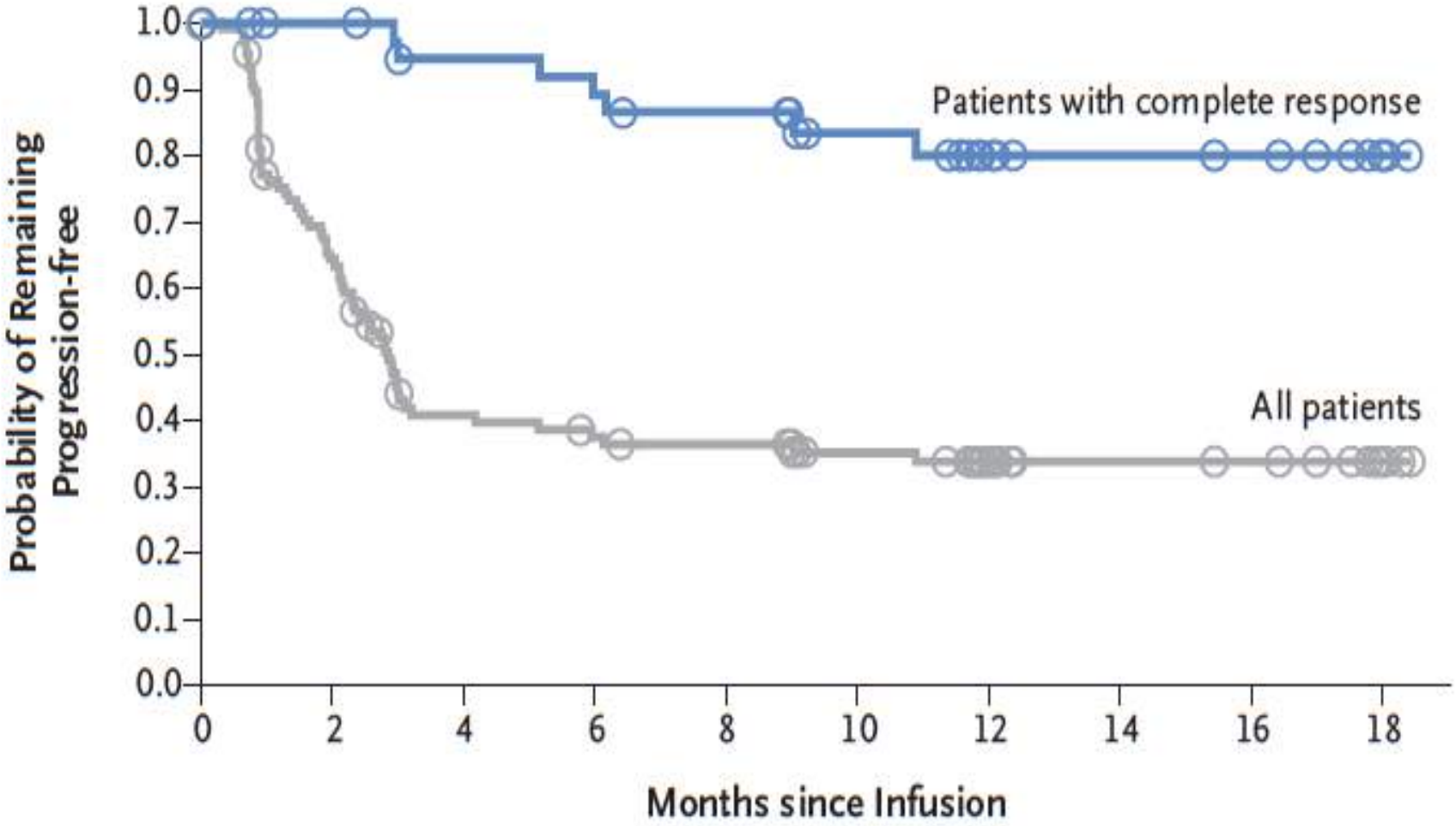
METHODS

We conducted an international, phase 2, pivotal study of centrally manufactured tisagenlecleucel involving adult patients with relapsed or refractory diffuse large B-cell lymphoma who were ineligible for or had disease progression after autologous hematopoietic stem-cell transplantation. The primary end point was the best overall response rate (i.e., the percentage of patients who had a complete or partial response), as judged by an independent review committee.

RESULTS

A total of 93 patients received an infusion and were included in the evaluation of efficacy. The median time from infusion to data cutoff was 14 months (range, 0.1 to 26). The best overall response rate was 52% (95% confidence interval, 41 to 62); 40% of the patients had complete responses, and 12% had partial responses. Response rates were consistent across prognostic subgroups. At 12 months after the initial response, the rate of relapse-free survival was estimated to be 65% (79% among patients with a complete response). The most common grade 3 or 4 adverse events of special inter-

B Progression-free Survival



No. at Risk

Patients with complete response	40	39	39	36	35	35	33	31	31	29	24	23	15	9	9	9	8	7	2
All patients	111		65		38		34		32		25		16		10		9		3

Tisagenlecleucel (KYMRIAH, Novartis, Basel, Switzerland), a synthetic bioimmune product of anti-CD19 chimeric antigen receptor - T cells (CAR-T), approved by FDA and EMA, for the treatment of children and young adults with relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL).

Axicabtagene ciloleucel (YESCARTA®, Kite Pharma, a Gilead Company) and tisagenlecleucel (KYMRIAH®, Novartis Pharmaceuticals Corp.) are two CD19-directed chimeric antigen receptor T cell (CD19 CAR T) products that are currently approved by the U.S. Food and Drug Administration, the European Medicines Agency, Health Canada, Ministry of Health, Labor and Welfare (Japan) and Therapeutic Goods Administration (Australia) for treatment of specific subtypes of relapsed/ refractory aggressive B cell non-Hodgkin lymphoma (NHL).

Another CAR T-cell product, liso-cel (JCAR017) is currently being studied in clinical trials with promising efficacy.

THE PROMISE AND PRICE OF CELLULAR THERAPIES

A revolutionary class of **'living drugs'** now promises to cure once incurable cancers.
But can we afford them?

In **CAR T-therapy** a patient's own immune cells are genetically engineered to recognize and attack cancer.

Siddhartha Mukherjee, MD
THE NEW YORKER
JULY 22, 2019

CD19-directed CAR T cells gain traction

www.thelancet.com/oncology Vol 20 January 2019

"…It is also important to keep in mind that available anti-CD19 CAR T-cell products **are only the beginnings of progress in this field** and that, together with the addition of B-cell targets other than CD19, CAR T cells will be amenable to modulation of their function to improve efficacy and enhance safety.

The current status of CD19-directed CAR T-cell therapies brings to mind a quote from the late **Carroll Shelby**, an innovative American automotive designer, who said, **"I've always been asked, 'what is my favorite car?', and I've always said 'the next one.'"**

Response Rates	Patients (N = 75)
Primary endpoint	
ORR (CR + CRi) within 3 months, n (%)*	61 (81)
95% CI, %	71 to 89
BOR, n (%)	
CR	45 (60)
CRi	16 (21)
No response	6 (8)
Unknown†	8 (11)

N Engl J Med 2018;378:439-48.
DOI: 10.1056/NEJMoa1709866

DISCUSSION

In this global, multicenter, pivotal study of CAR T-cell therapy, high response rates were shown in children and young adults with relapsed or refractory B-cell ALL, 61% of whom had had a relapse after allogeneic hematopoietic stem-cell transplantation. Effective distribution of tisagenlecleucel across four continents with the use of a global supply chain was shown to be feasible and resulted in efficacy and safety similar to those observed in the previous, single-center study.[1]

DISCUSSION

This updated analysis showed an overall remission rate of 81% among 75 patients with at least 3 months of follow-up after a single infusion of tisagenlecleucel. The remissions were durable, with a 6-month relapse-free survival rate of 80%. The durability of the clinical response was associated with persistence of tisagenlecleucel in peripheral blood and with persistent B-cell aplasia.

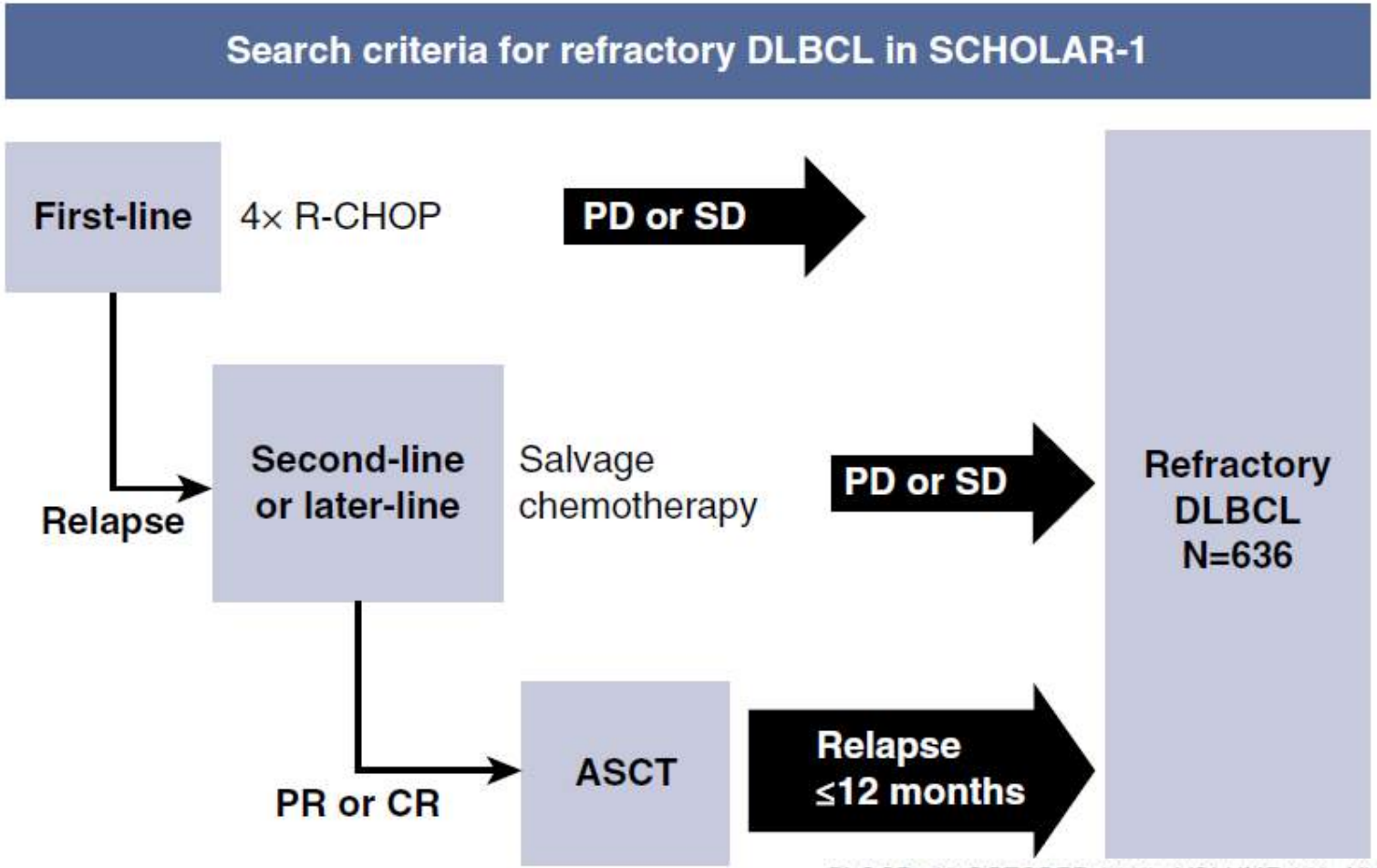
Abstract

On August 30, 2017, the U.S. Food and Drug Administration (US-FDA) approved tisagenlecleucel (KYMRIAH, *Novartis, Basel, Switzerland*), a synthetic bioimmune product of anti-CD19 chimeric antigen receptor - T cells (CAR-T), for the treatment of children and young adults with relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL). With this new era of personalized cancer immunotherapy, multiple challenges are present ranging from implementation of a CAR-T program to safe delivery of the drug, long-term toxicity monitoring and disease assessments. To address these issues, experts representing the American Society for Blood and Marrow Transplant (ASBMT), the European Group for Blood and Marrow Transplantation (EBMT), the International Society of Cell and Gene Therapy (ISCT), and the Foundation for the Accreditation of Cellular Therapy (FACT), formed a global CAR-T task force to identify and address key questions pertinent for hematologists and transplant physicians regarding the clinical use of anti CD19 CAR-T therapy in patients with B-ALL. This article presents an initial roadmap for navigating common clinical practice scenarios that will become more prevalent now that the first commercially available CAR-T product for B-ALL has been approved.

Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study

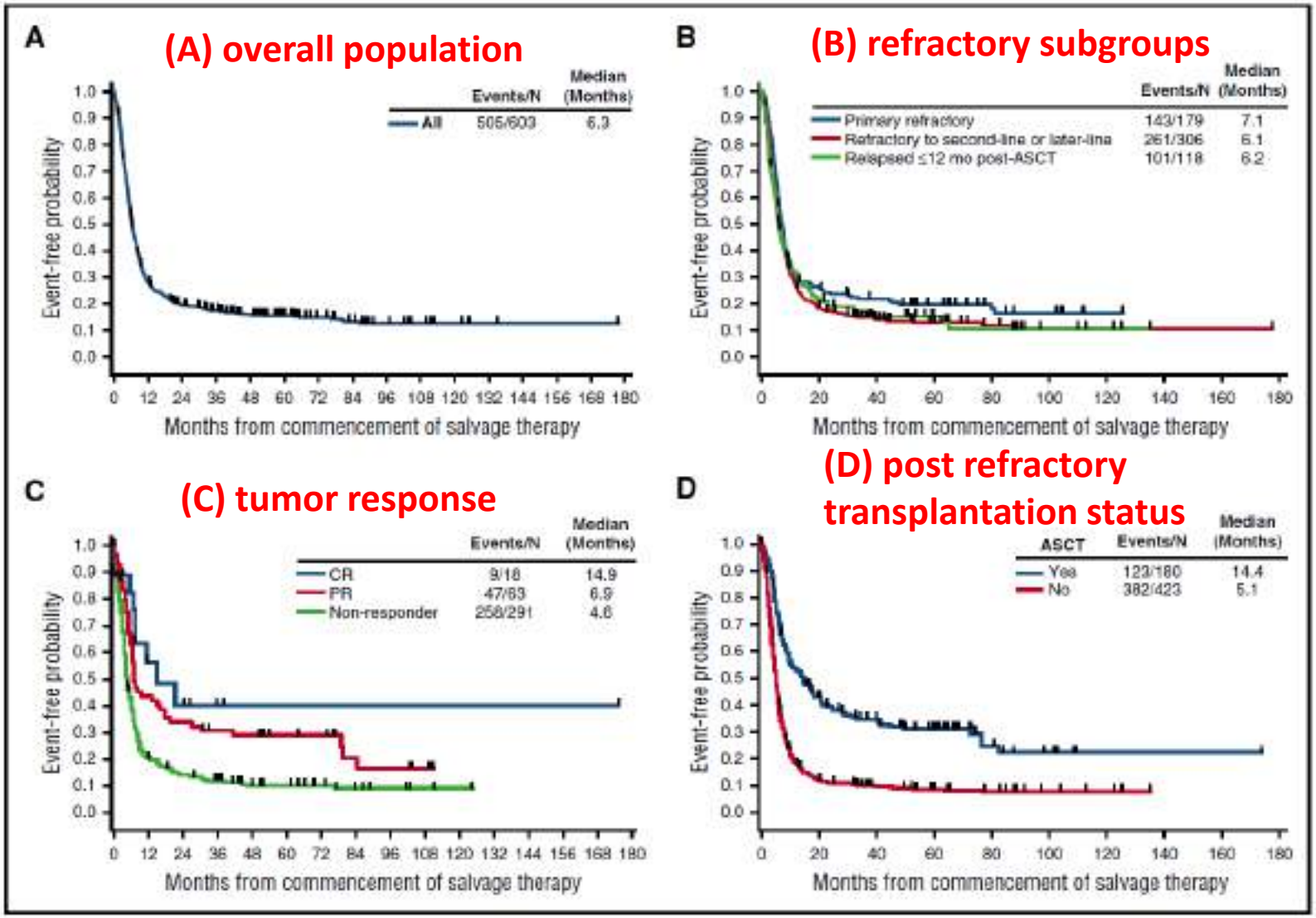
Michael Crump,[1] Sattva S. Neelapu,[2] Umar Farooq,[3] Eric Van Den Neste,[4] John Kuruvilla,[1] Jason Westin,[2] Brian K. Link,[3] Annette Hay,[1] James R. Cerhan,[5] Liting Zhu,[1] Sami Boussetta,[4] Lei Feng,[2] Matthew J. Maurer,[5] Lynn Navale,[6] Jeff Wiezorek,[6] William Y. Go,[6] and Christian Gisselbrecht[4]

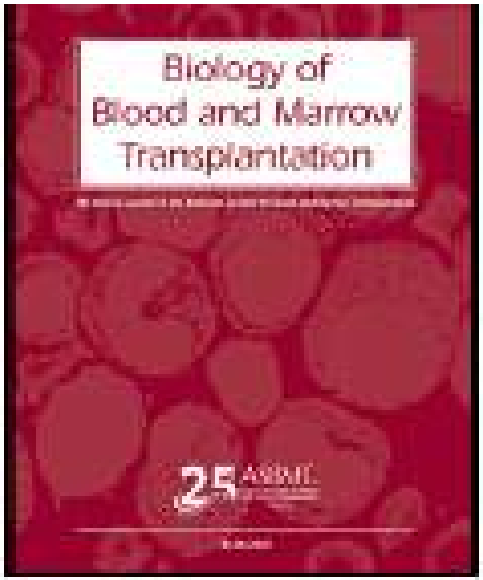
[1]Canadian Cancer Trials Group, Queen's University, Kingston, ON, Canada; [2]Division of Cancer Medicine, Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Division of Hematology, Oncology, and Blood and Marrow Transplantation, Department of Internal Medicine, University of Iowa, Iowa City, IA; [4]Lymphoma Academic Research Organization, Pierre-Bénite, France; [5]Department of Health Sciences Research, Mayo Clinic, Rochester, MN; and [6]Kite Pharma, Santa Monica, CA



Outcomes in refractory large B cell lymphoma with traditional standard of care are extremely poor[1]

The SCHOLAR-1 analysis demonstrated an ORR of 26%, a CR rate of 7%, and a median OS of 6.3 months in this patient population





Utilization of Chimeric Antigen Receptor (CAR) T Cell Therapy in Clinical Practice for Relapsed/Refractory Aggressive B cell non-Hodgkin Lymphoma: An Expert Panel Opinion from the American Society for Transplantation and Cellular Therapy

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