

CLL SOCIETY

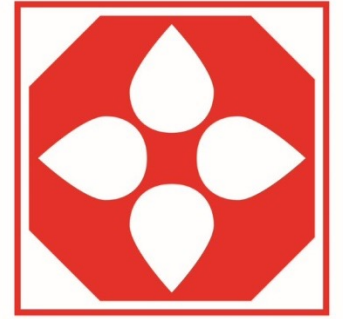
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CAR-T and Other Cellular Therapies in CLL: The Present and Future

August 2, 2022

11 AM PT, 12 PM MT
1 PM CT, 2 PM ET

This program was made possible by grant support from



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Speakers



Mazyar Shadman, MD, MPH

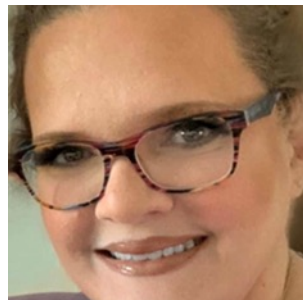
Associate Professor, Division of Medical Oncology
University of Washington School of Medical Oncology
Associate Professor, Clinical Research Division
Fred Hutchinson Cancer Research Center



Moderator

Brian Koffman, MDCM (retired) MS Ed

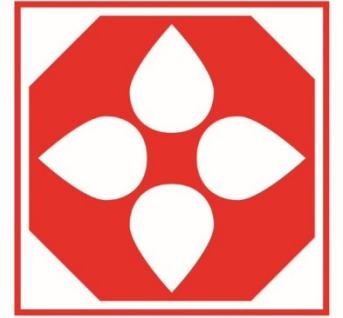
Executive Vice President and Chief Medical Officer
CLL Society



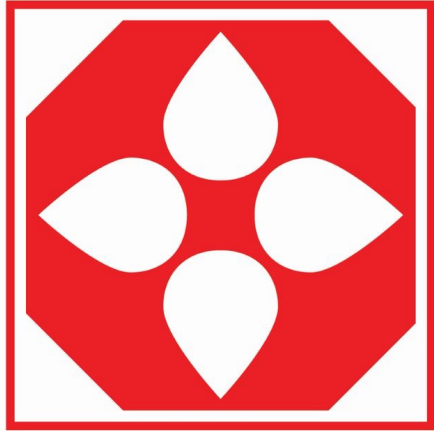
Welcome

Robyn Brumble, MSN, RN

Director of Scientific Affairs and Research
CLL Society



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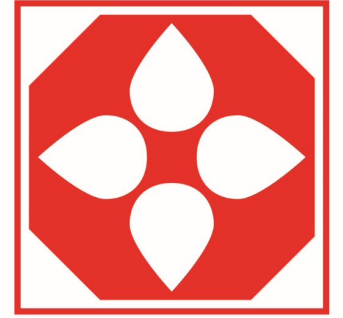
CAR-T and Other Cellular Therapies in CLL: The Present and Future

Mazyar Shadman, MD, MPH

Fred Hutch Cancer Center & University of Washington
Seattle, WA

August 2, 2022

Disclosures



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- **Consulting, Advisory Boards, steering committees or data safety monitoring committees:** Abbvie, Genentech, AstraZeneca, Sound Biologics, Pharmacyclics, Beigene, Bristol Myers Squibb, Morphosys/Incyte, TG Therapeutics, Innate Pharma, Kite Pharma, Adaptive Biotechnologies, Epizyme, Eli Lilly, Adaptimmune, Mustang Bio, Regeneron, Merck, Fate therapeutics, MEI pharma and Atara Biotherapeutic.
- **Research Funding:** Mustang Bio, Celgene, Bristol Myers Squibb, Pharmacyclics, Gilead, Genentech, AbbVie, TG Therapeutics, Beigene, AstraZeneca, Sunesis, Atara Biotherapeutics, Genmab, Morphosys/Incyte

T-cell immunotherapy tied to 10-year remission in two leukemia patients, study finds



By [Jacqueline Howard](#) and [Carma Hassan](#), CNN

Updated 3:23 PM ET, Wed February 2, 2022

DAILY BEAST

CROSS

ALL CHEAT SHEET POLITICS CRIME ENTERTAINMENT MEDIA INNOVATION OPINION WORLD U.S. NEWS SCOUTED TRAVEL

INNOVATION

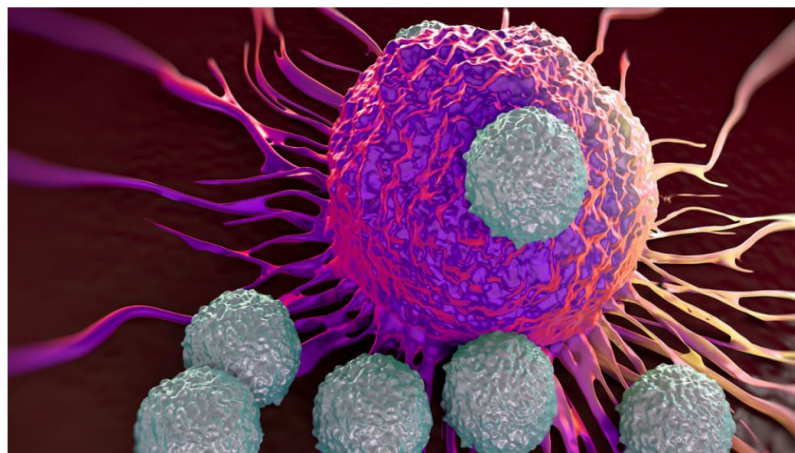
This Breakthrough Cancer Treatment Has Prevented Leukemia Relapse for Over a Decade

SUPER EFFECTIVE

We already knew CAR T-cell treatment was incredibly good at killing tumor cells. But now we know it works for a ridiculously long time.



Sofia Quaglia | Updated Feb. 02, 2022 6:49PM ET / Published Feb. 02, 2022 11:00AM ET



The New York Times

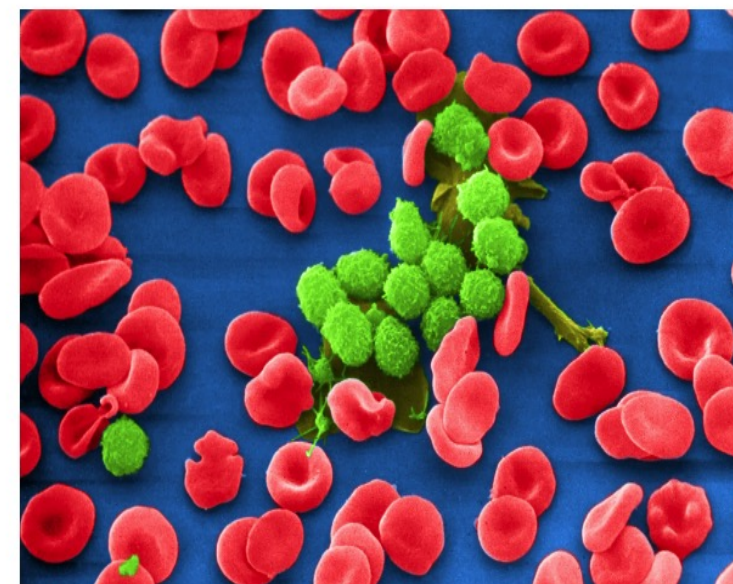
A Cancer Treatment Makes Leukemia Vanish, but Creates More Mysteries

Two early recipients of CAR T immunotherapy were free of a blood cancer nearly a decade after receiving the therapy.

Give this article



76



A colorized scanning electron micrograph of chronic lymphocytic leukemia, a type of leukemia that affects B cells and accounts for a quarter of new leukemia cases each year. Keith R. Porter/Science Source

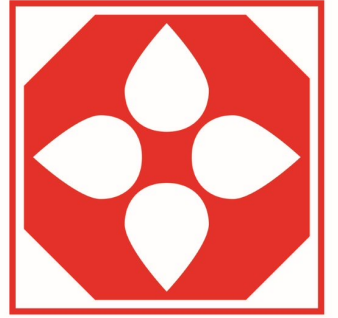
Cancer patients cured a decade after gene therapy, doctors say

The two examples show the treatment, called CAR-T cell therapy, can attack cancer immediately, then stay inside the body and evolve there to keep cancer at bay.



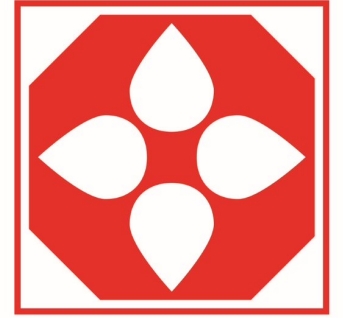
Outline

- What are CAR-T cells?
- Why do we need them in CLL?
- How are they made?
- When are they used in CLL?
- What are the risks?
- What is the latest on other cellular therapies?
- What is available now in trials?
- What is expected in the future?
- Summary and takeaways



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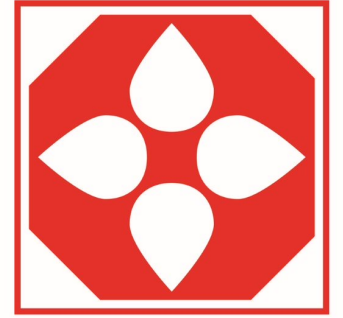
What Are CAR-T Cells?



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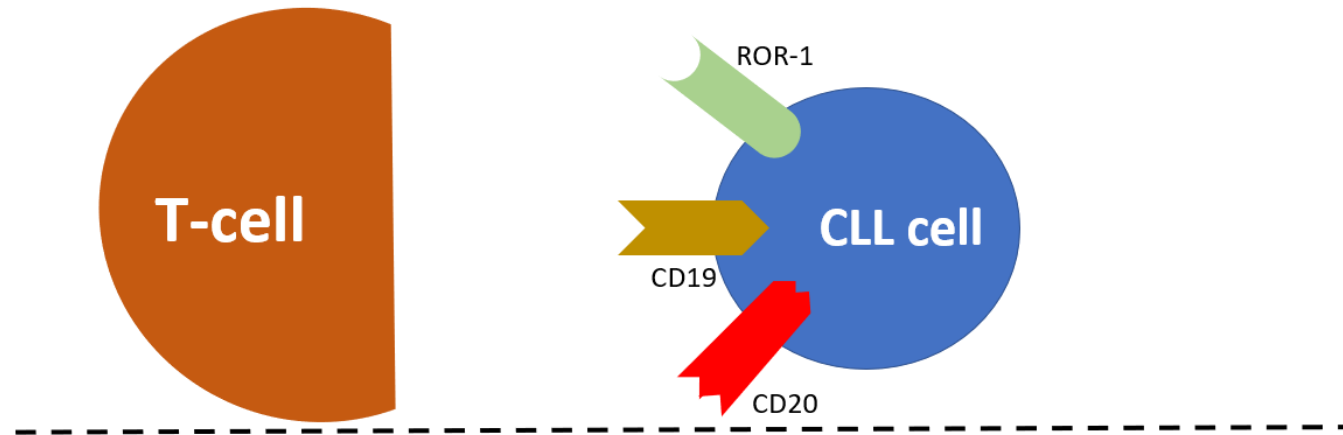
- Chimeric antigen receptors (CARs) are engineered proteins that enable T-cells to target the cancer cells
- CAR-T cell therapy has been a major advancement in treatment of B-cell lymphoma in recent years
- Currently approved by the FDA for treatment of:
 - Diffuse large B-cell lymphoma
 - Follicular lymphoma
 - Mantle cell lymphoma
 - Acute lymphoblastic leukemia
 - Multiple myeloma
- CAR-T remains an investigational option for CLL in August 2022
 - Patients with CLL can have access to CAR-T by participating in clinical trials

What Are CAR-T Cells?

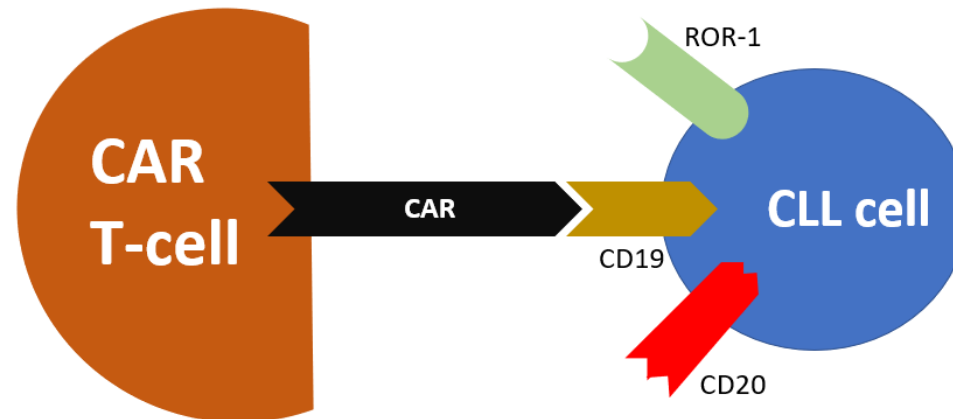


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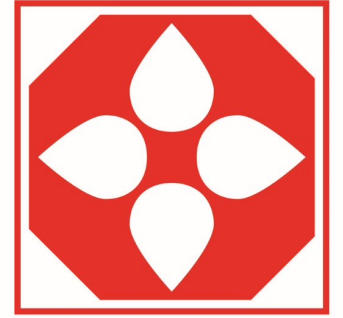
BEFORE



AFTER

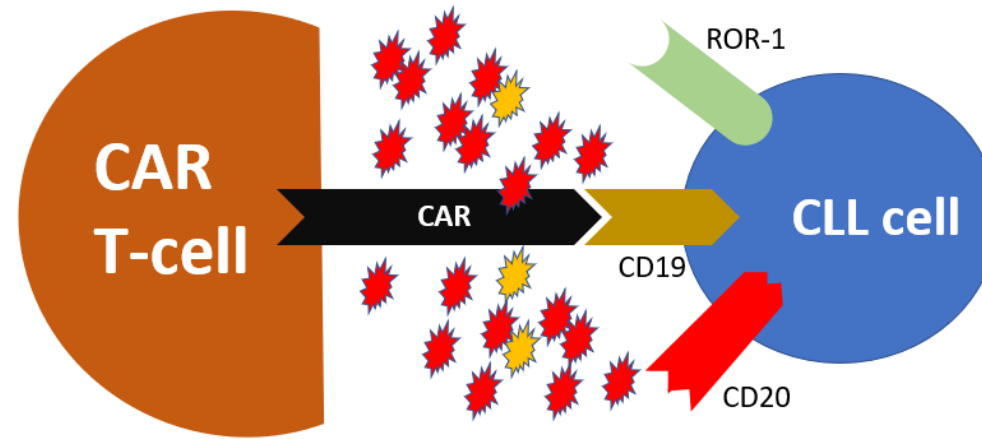


What Are CAR-T Cells?

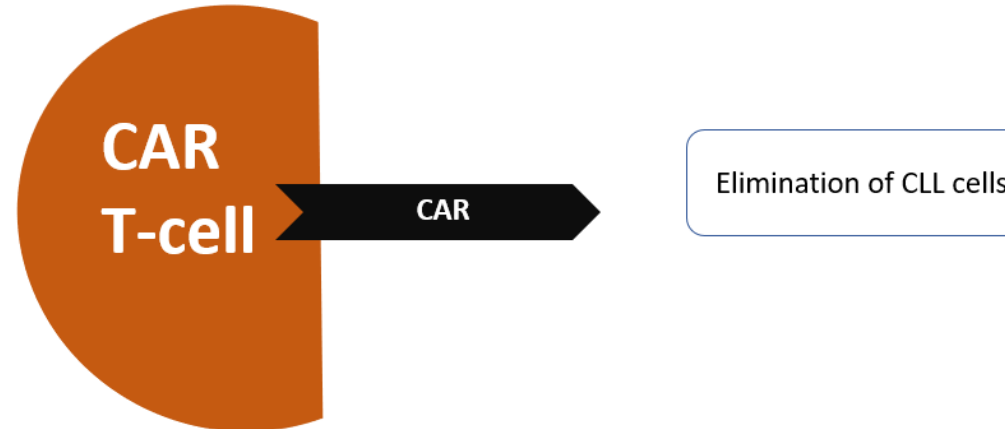


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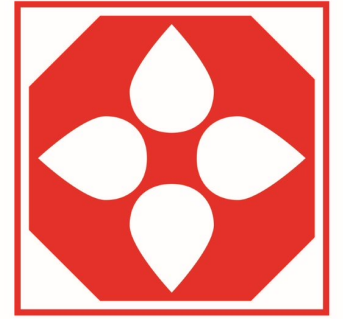
**Immune
storm**



**Cancer
killing**

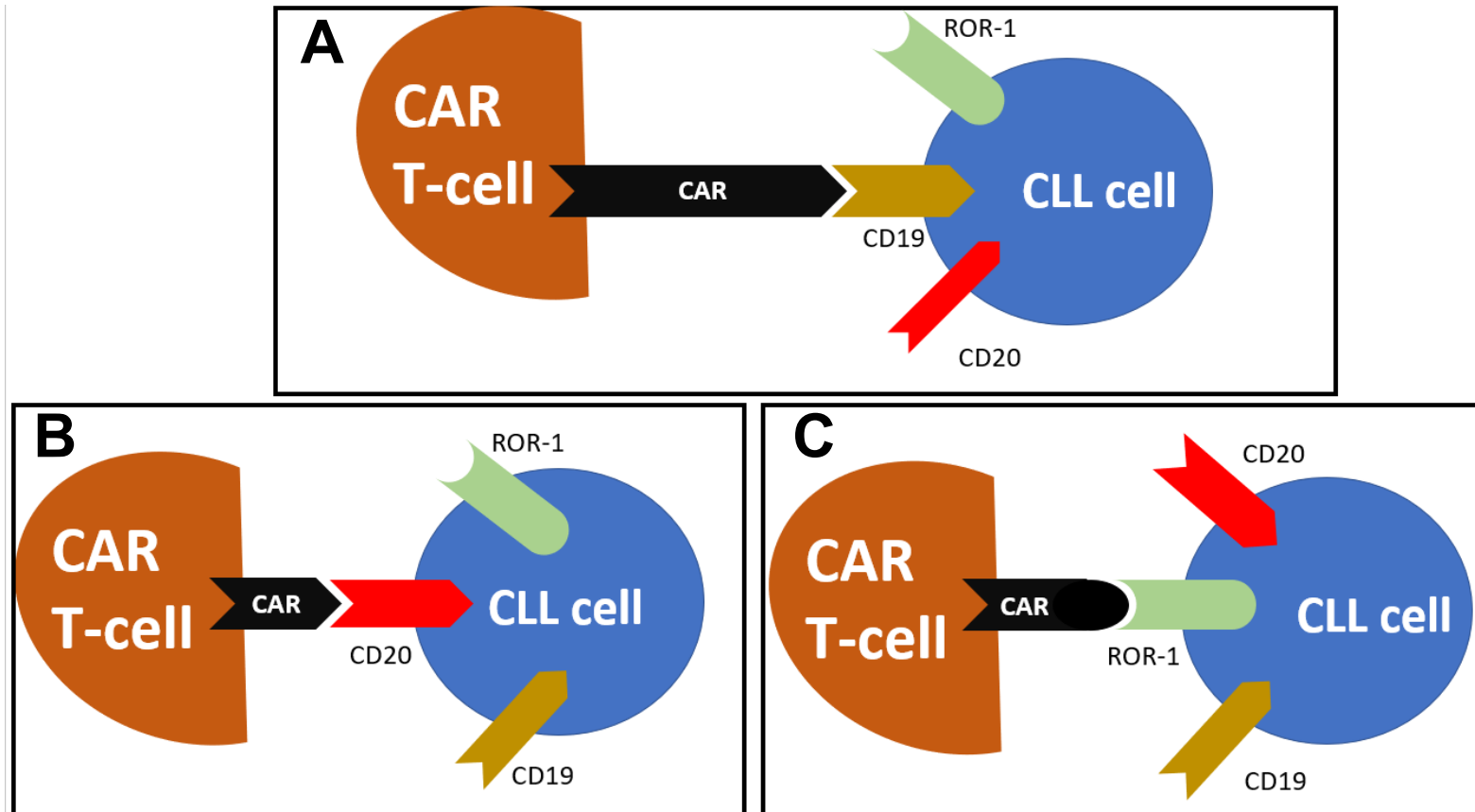


What Are CAR-T Cells?

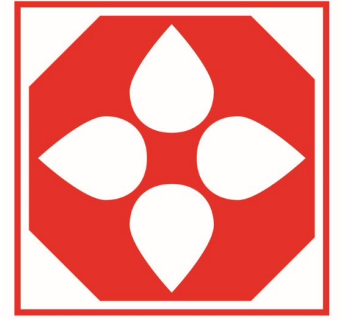


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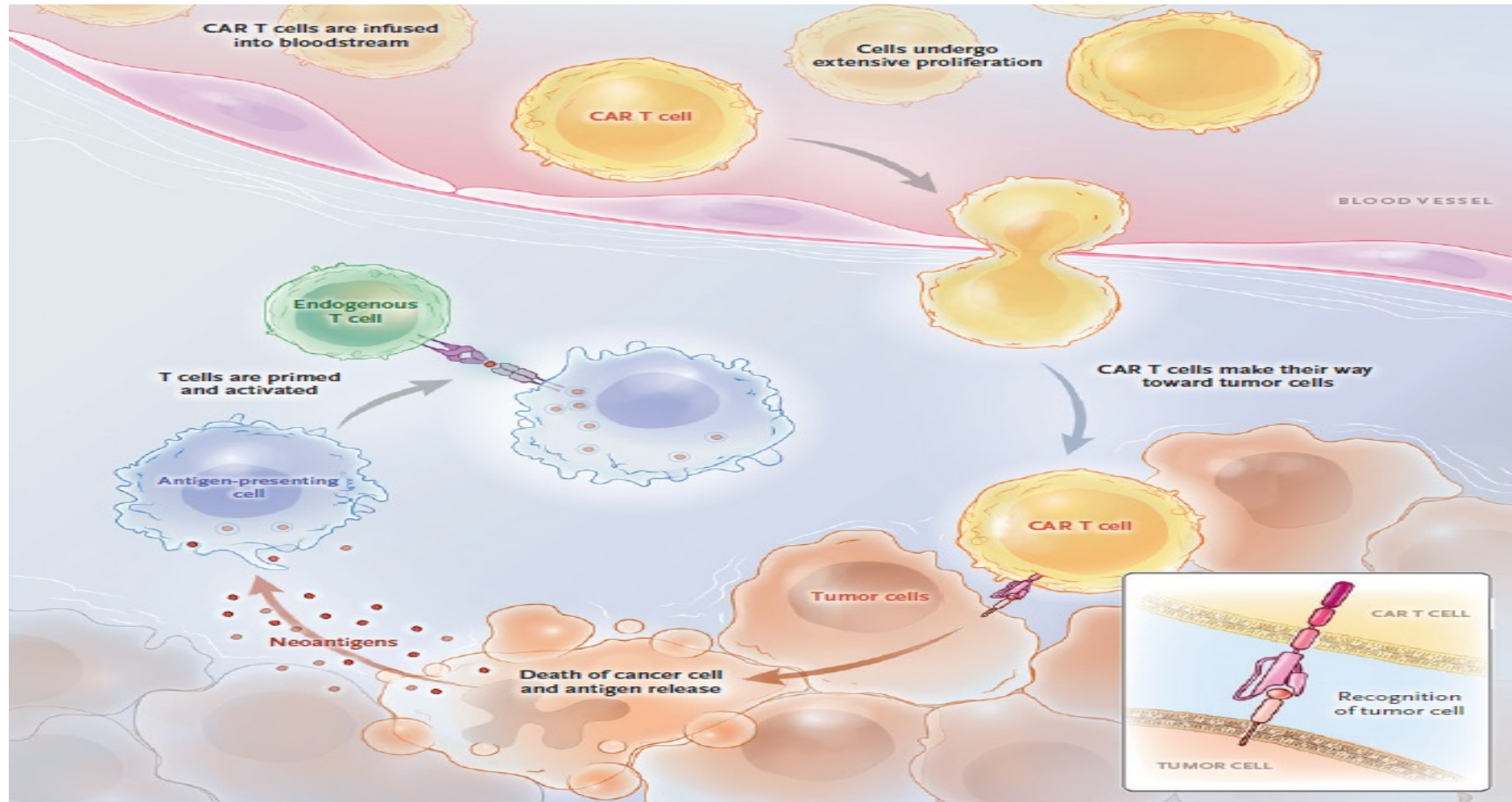
- CAR-T is the name of the process not a specific drug
- Different Proteins can be targeted (CD19, CD20, CD22, ROR-1, etc.)
- Different CAR-T products can be designed. Each specific for 1 (or more) protein(s)



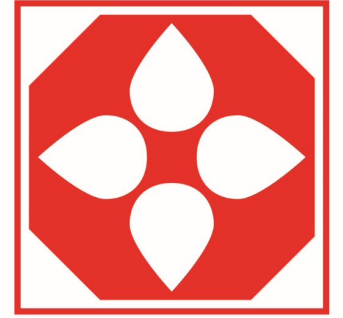
What Are CAR-T Cells?



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Why Do We Need Them in CLL/SLL?



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■ Immediate Need

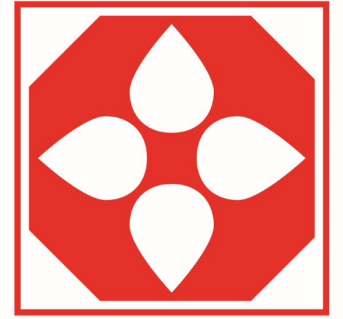
- Treatment of patients with relapsed disease
- Current options:
 - BTK inhibitors:
 - Covalent: ibrutinib, acalabrutinib, zanubrutinib * (can't switch within class after progression)
 - Non-covalent: pirtubrutinib *
 - BCL2 inhibitor: Venetoclax
 - PI3K inhibitors: duvelisib, idelalisib (unknown future)
 - Monoclonal antibodies: rituximab, obinutuzumab
 - Chemotherapy (limited role if any in the relapsed setting)

■ Future Potential Role

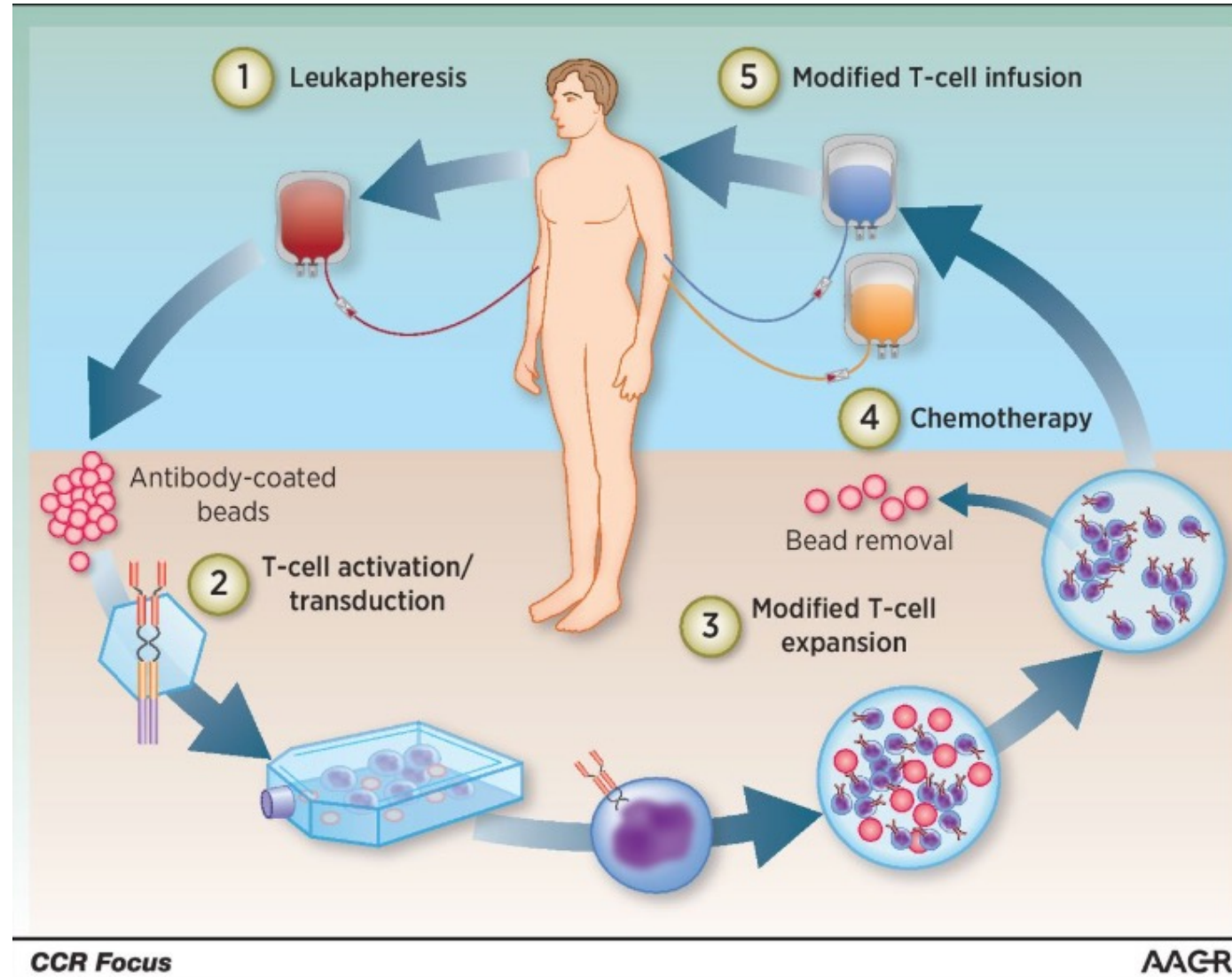
- A component of combination therapy for fixed-duration regimens
- Important to have an improved safety profile before being used in early lines

* Not FDA approved as of Aug 2022

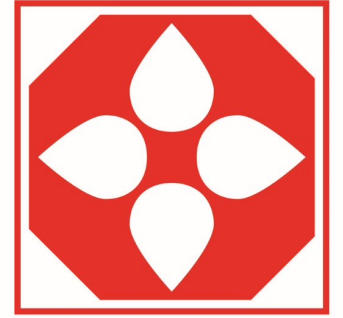
How Are CAR-T Cells Made?



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When Are They Used in CLL?



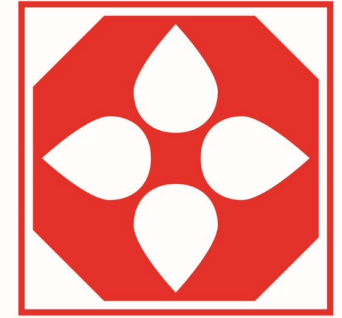
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- A number of factors need to be considered when making a decision about the timing of CAR-T therapy
- Physical fitness, access, alternative trial options, support, etc.

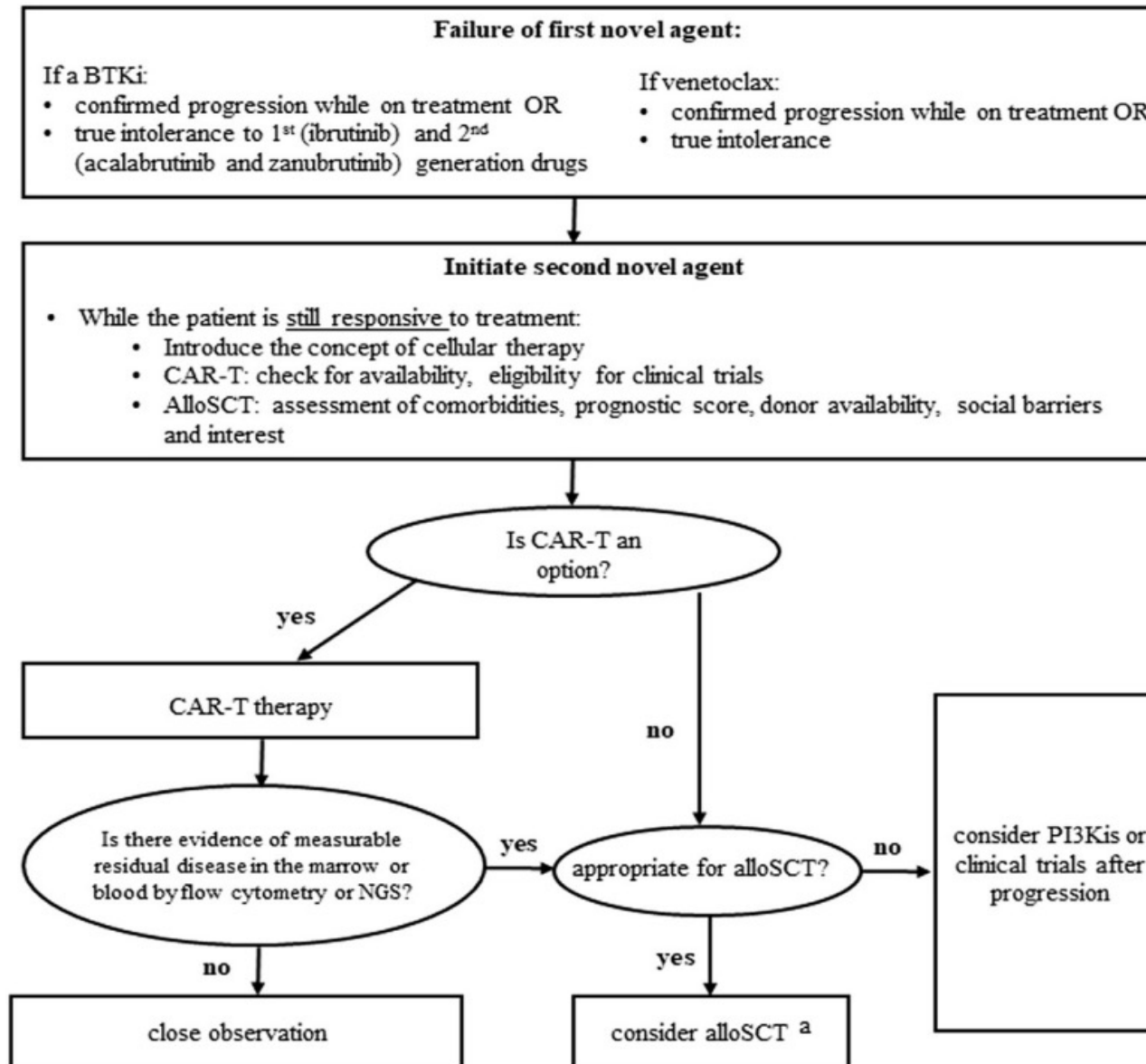
Most importantly:

- 1. Referral should be made when disease is under control/stable and not with progressive and active disease**
- 2. It is highly recommended that CAR-T is utilized when there are reliable standard options left for the patient and not after exhausting all options**

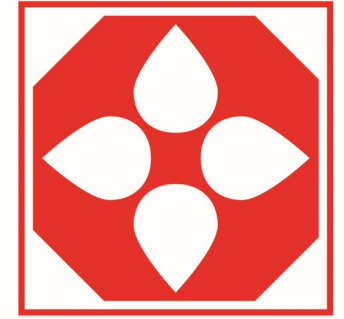
When Are They Used in CLL?



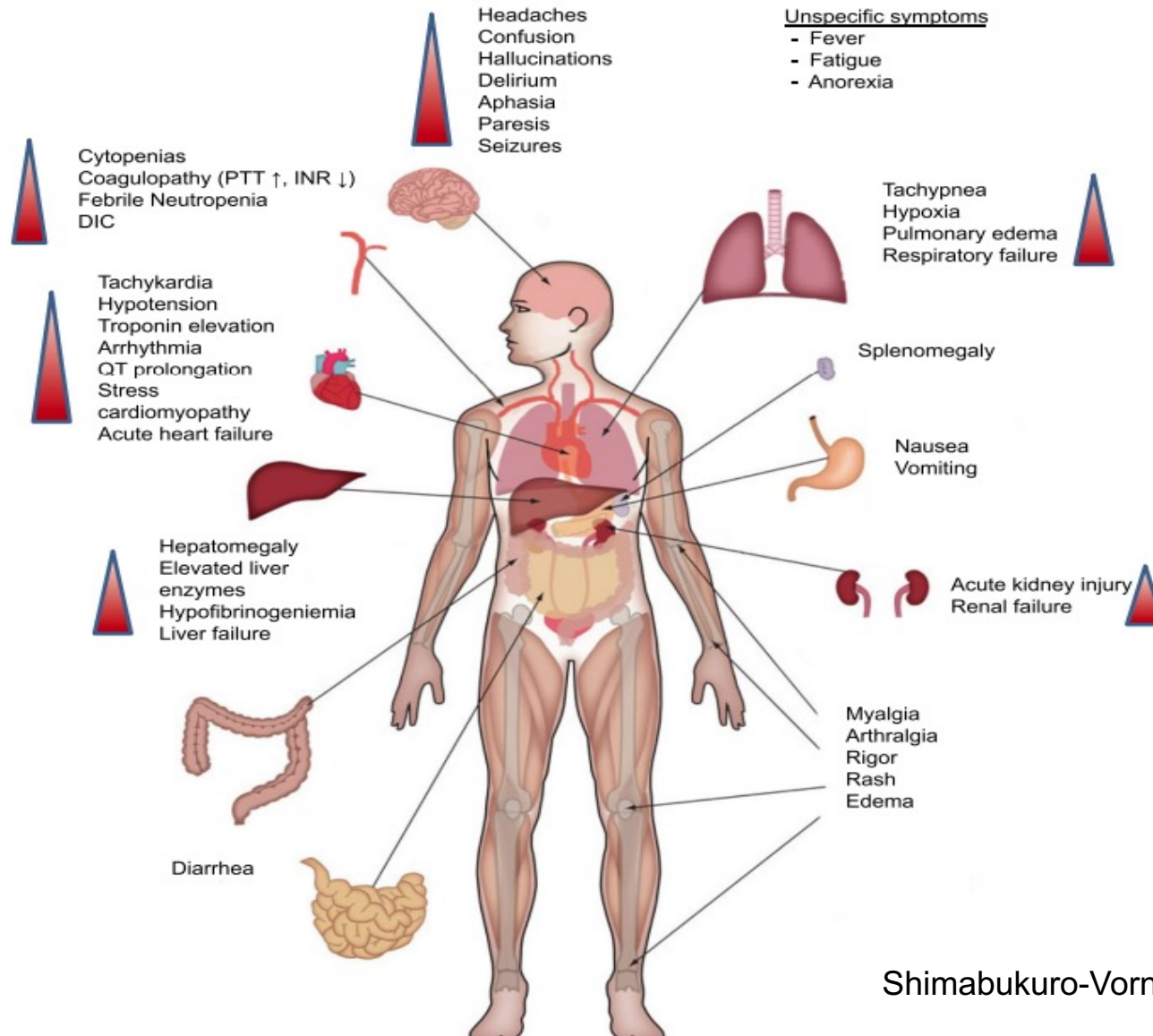
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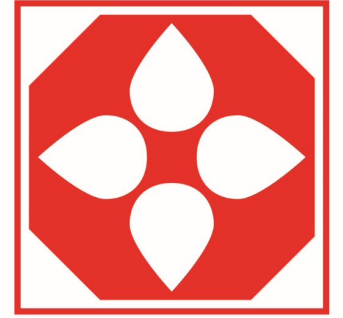
What Are the Risks?



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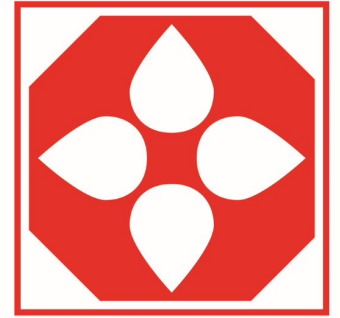
Lisocabtagene Maraleucel (Liso-cel)



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- CD19 directed CAR-T
- High-risk features:
 - del17p (35%), mutated TP53 (61%), complex karyotype (48%)
 - Ibrutinib refractory (91%), Venetoclax refractory (65%), double refractory (65%)
- Side effects
 - Grade 3 CRS: 9% , grade 3-4 neurotoxicity: 22%
- Responses:
 - **Overall response: 82% , complete response: 45%**
 - Undetectable MRD in blood (76%) and bone marrow (65%)
- Follow-up
 - Median follow-up 24 months
 - Median duration of response (not reached) – more than half of the responders have not relapsed

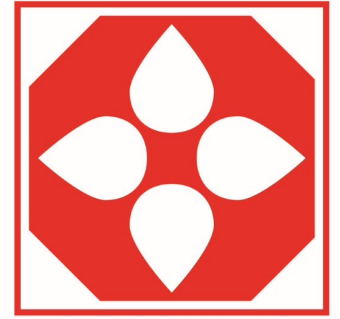
CAR-T in Combination With Ibrutinib



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- Pre-clinical studies showed that concurrent use of ibrutinib with CAR-T may improve the T-cell quality and function
- In clinical studies, ibrutinib was successfully combined with CAR-T with no unexpected toxicity
- There may be some improvement in safety profile of CAR-T when combined with ibrutinib
- Newer BTKis are expected to be combined with CAR-T in various clinical trials

What is the Latest on Other Cellular Therapies?

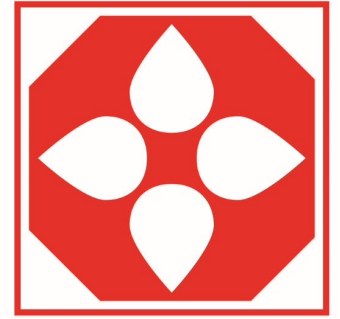


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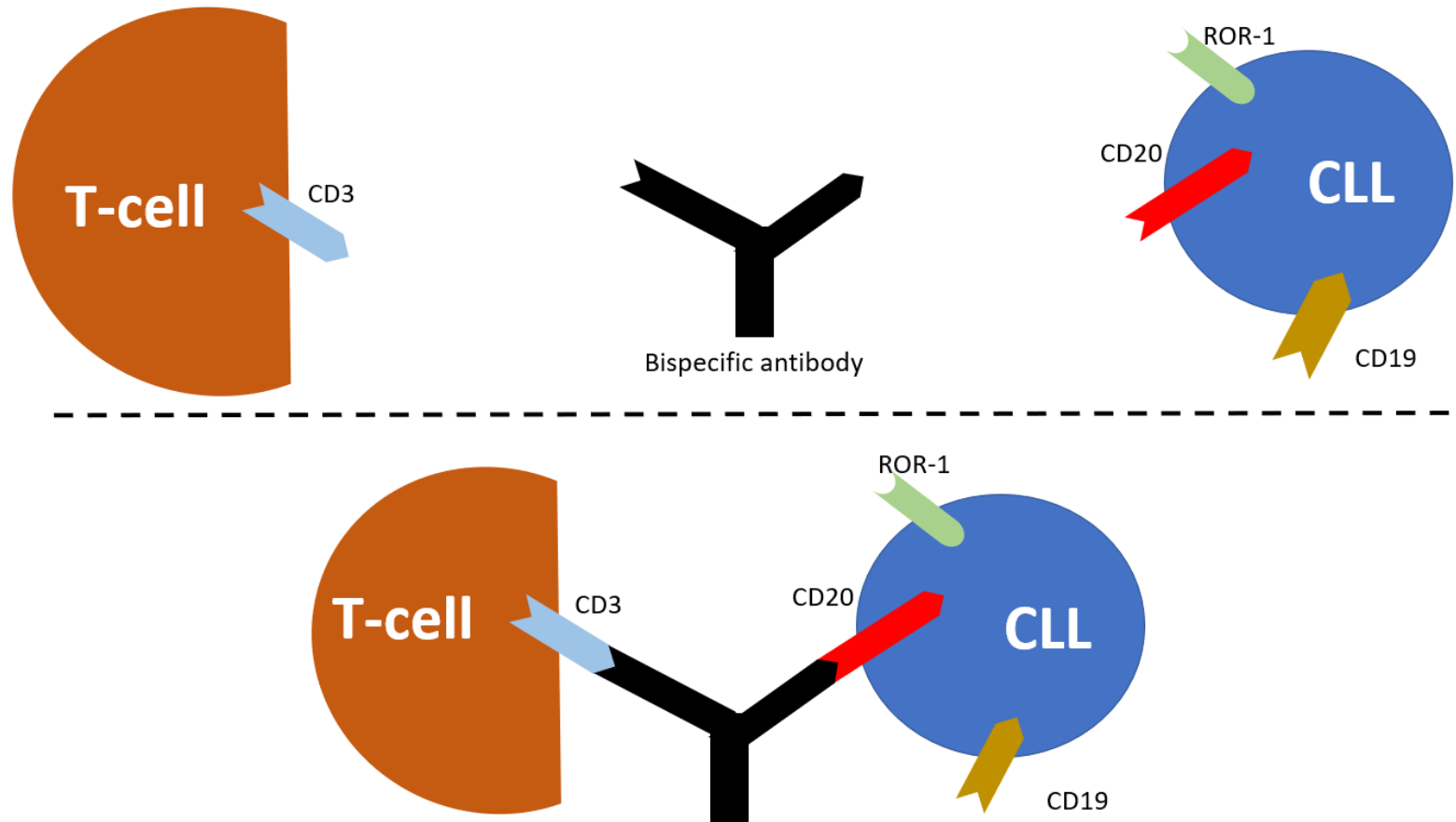
- **Allogeneic CAR-T, CAR-NK or CAR-NKT**
 - Unlike the autologous CARs, immune cells from healthy donors are used
 - Still investigational for CLL and not approved by the FDA
 - Patients with CLL can have access to bispecific antibodies after enrollment in clinical trials

- **Bispecific Antibodies**
 - Bispecific antibodies engage T-cells by physically bringing them to cancer cells
 - Still investigational for CLL and not approved by the FDA
 - Patients with CLL can have access to bispecific antibodies after enrollment in clinical trials

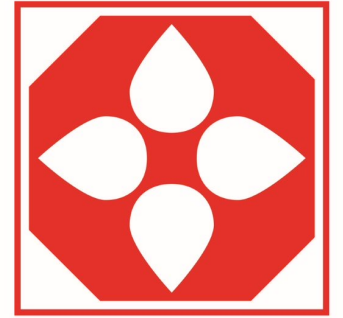
Bispecific Antibodies



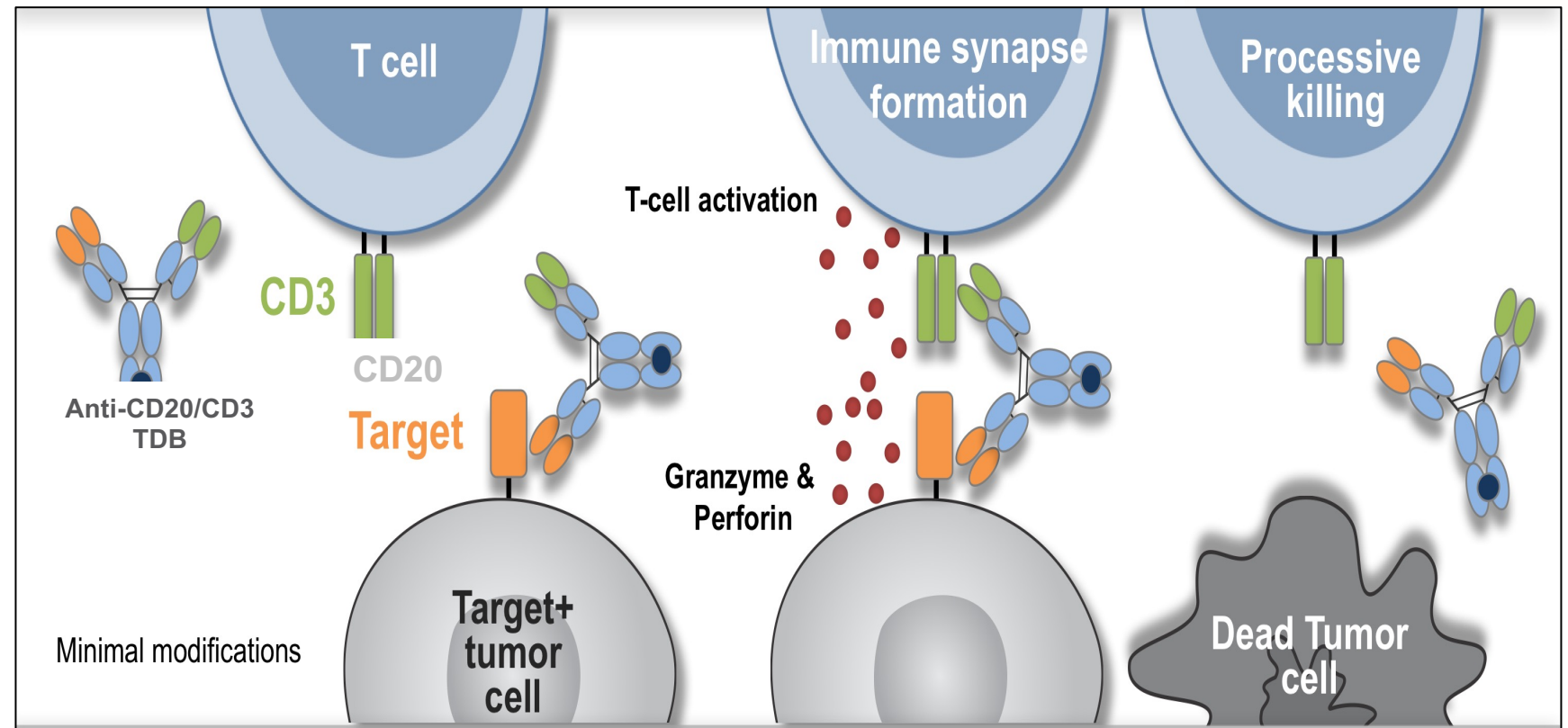
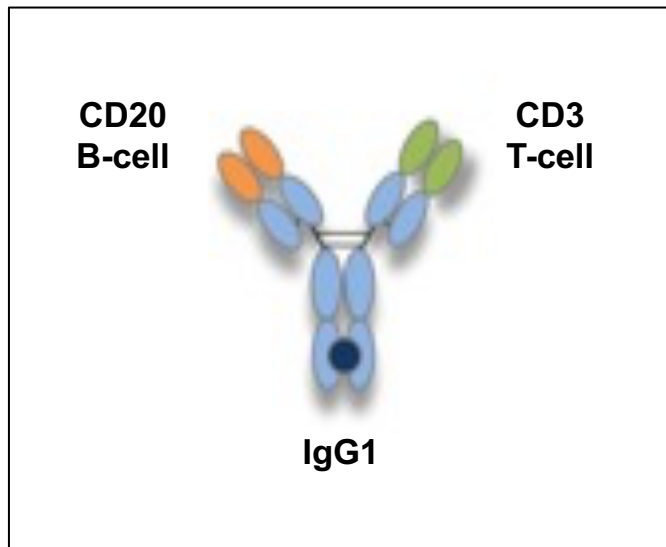
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Bispecific Antibodies



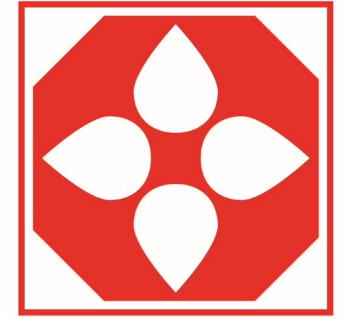
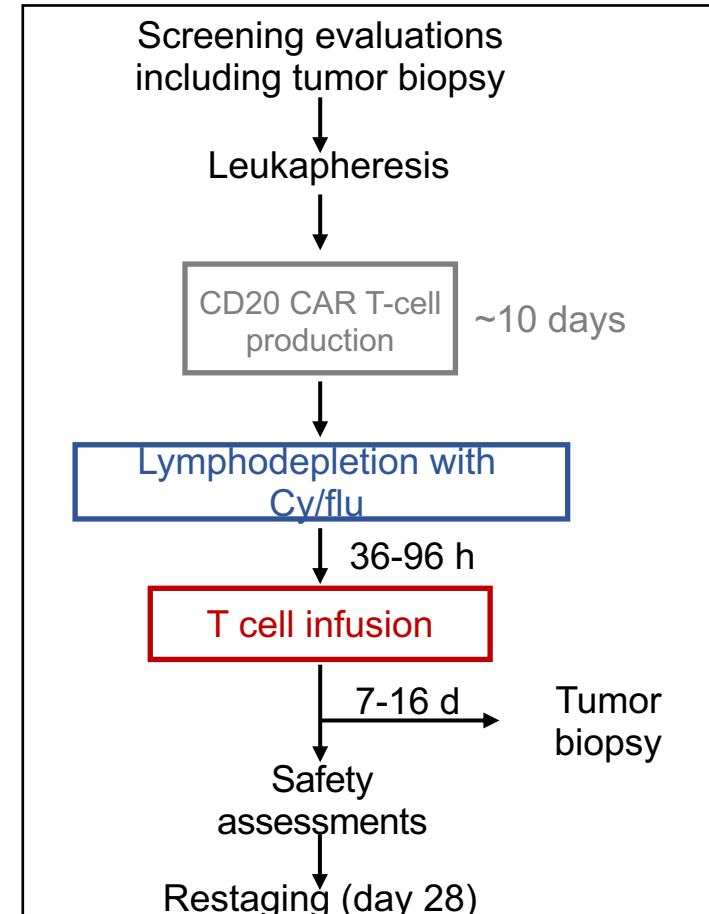
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What Is Available Now in Trials?

- Autologous
 - CD19
 - CD20
 - CD19/CD20
 - CD19/CD22
 - Kappa light chain
 - CD5
- Allogeneic
 - CAR T
 - CAR NK
 - CAR NKT

Example: CD20 CAR-T Trial



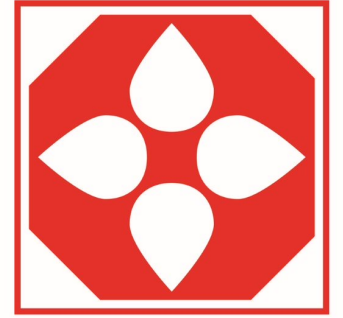
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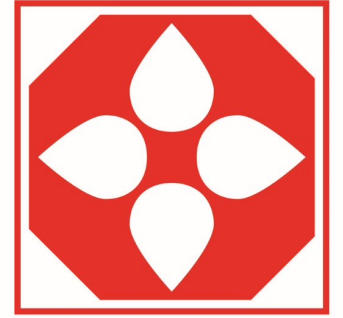
What Do You See as the Future?



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- CD19 CAR-T maybe approved for CLL but the timing is not known
- Number of autologous and allogeneic CAR studies are in clinical trials
- An important option for patients with relapsed disease
 - One time treatment with possible long-term remission
 - Effective in patients after BTKi and/or venetoclax
- Ideally and when safety/efficacy profile is optimized, can be utilized in earlier (first?) line of treatment as part of time-limited regimens

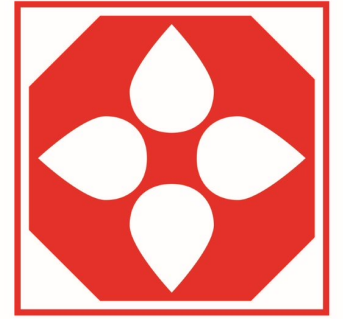
Summary and Takeaways



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- CAR-T cell therapy is an effective treatment strategy for relapsed CLL
- Still investigational but access is possible by participation in clinical trials
- Optimal time for consideration/referral for CAR-T:
 - When disease is under control/stable
 - Before exhausting all treatment options
- Various targets on CLL cells can be targeted by different CAR-T products

Thank You!



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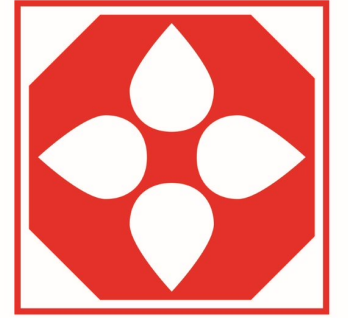


@mshadman



mshadman@fredhutch.org

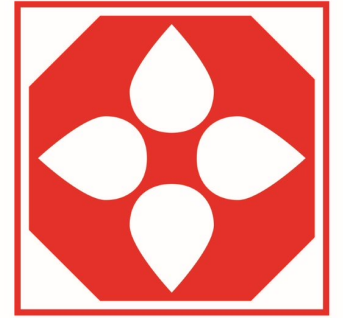




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Audience Questions & Answers

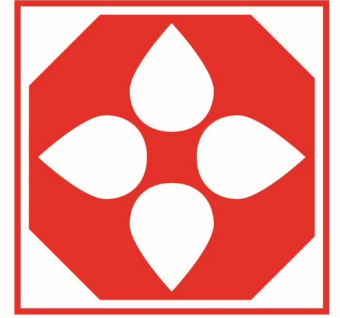
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Thank You for Attending!



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Please take a moment to complete our **post-event survey**, your feedback is important to us

If your question was not answered, please feel free to email asktheexpert@cllsociety.org

Check out our free CAR-T Therapy brochure and join us on October 26th for our virtual event on therapy sequencing

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cllsociety.org/donate-to-cll-society/