REGIONALE SIES – Delegazione Piemonte


# Anti CD19 CAR-T therapy: meccanismo di azione e risultati clinici

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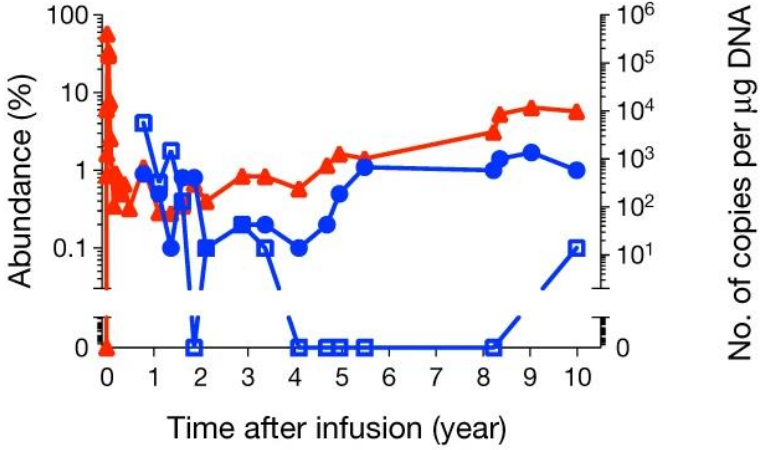
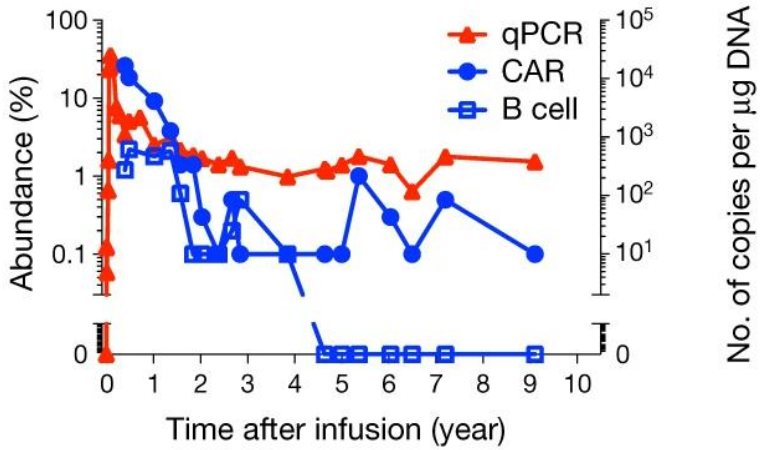
TORINO, ACCADEMIA DI MEDICINA | 4-5 GIUGNO 2026

# Disclosures of Francesca Perutelli

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| AstraZeneca | | | | | x | | |
| | | | | | | | |
| Lilly | | | | | x | | |
| | | | | | | | |
| Takeda | | | | | x | | |
| | | | | | | | |
| Roche | | | | | x | | x |
| | | | | | | | |
| Johnson & Johnson | | | | | | | x |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

# CAR T cells remained detectable after 10y post infusion in 2 CLL pts

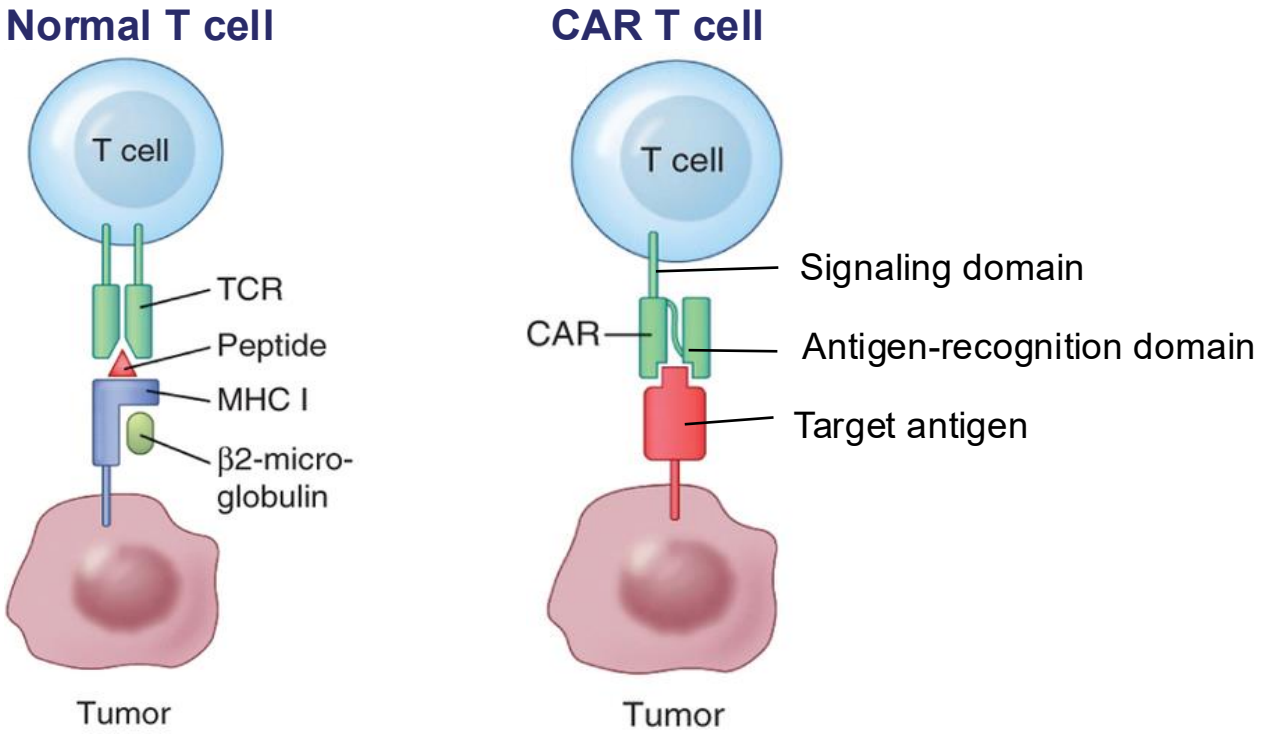



***CAR T-cell therapy a cure for lymphoproliferative disorders?***

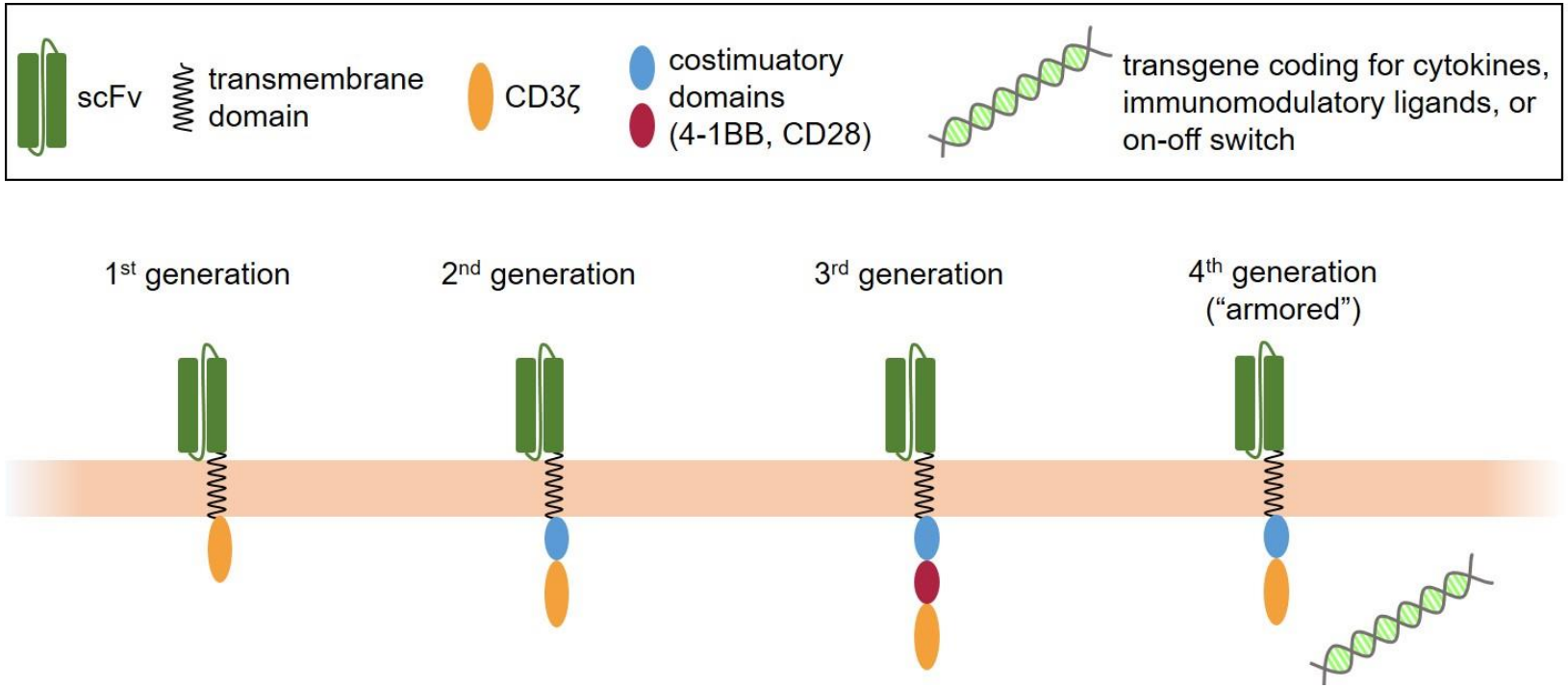
Melenhorst JJ *Nature* 2022

# Chimeric Antigen Receptor (CAR) modified T cells



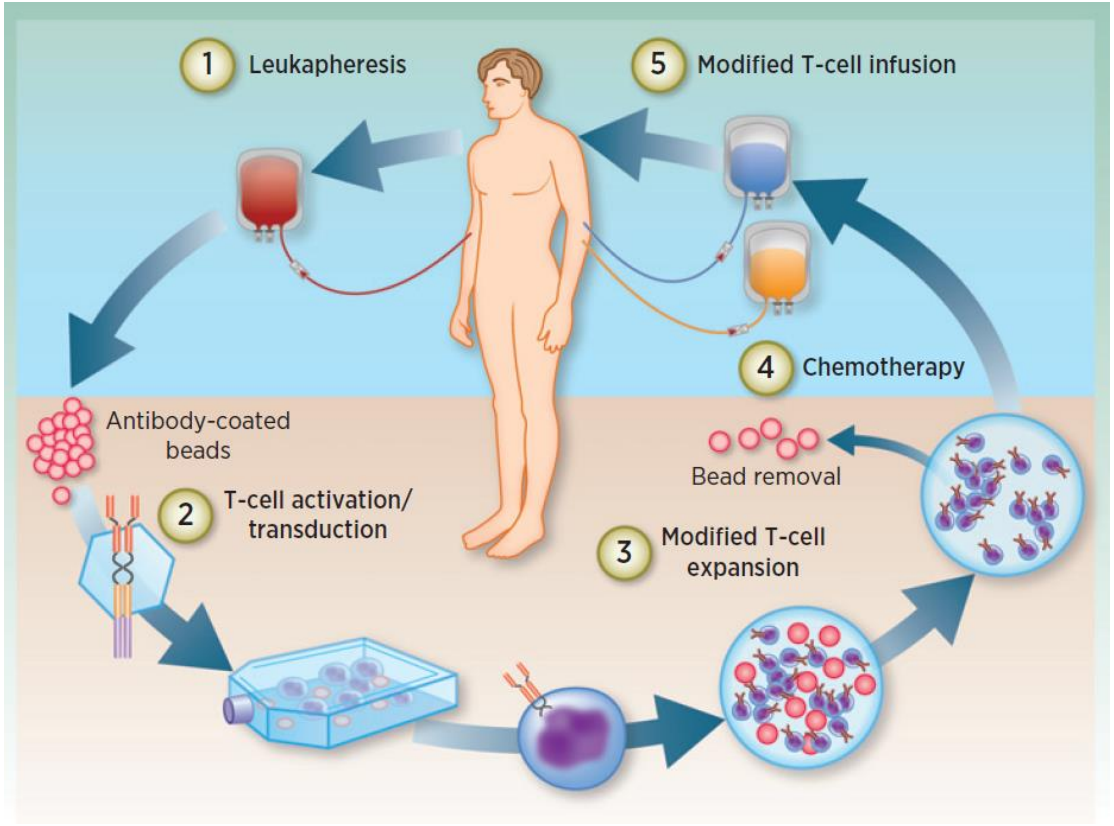

Adapted from Hinrichs & Restifo *Nat Biotech* 2013

# CAR structure development



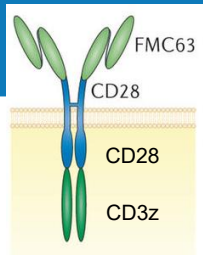

Coscia M *Frontiers in Biosciences* 2019

# CAR T cells production



# CAR T-cell therapy in RR DLBCL

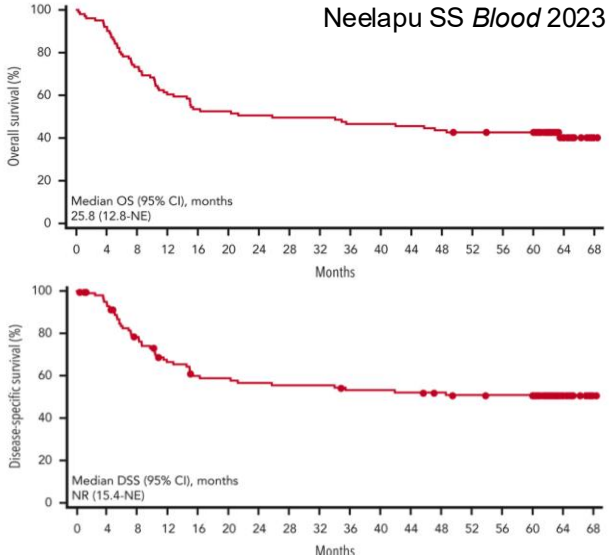
## Axi-cel



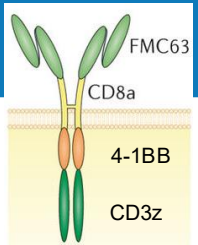

**5y FU – ZUMA 1**

5y OS: 42.6%

Neelapu SS *Blood* 2023



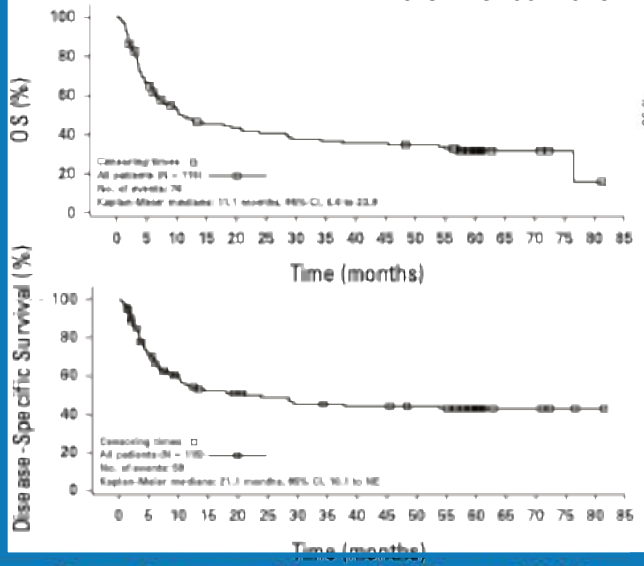

## Tisa-cel



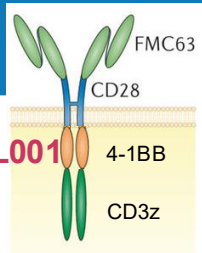

**5y FU – JULIET**

5y OS: 32%

Maziarz RT *J Clin Oncol* 2025



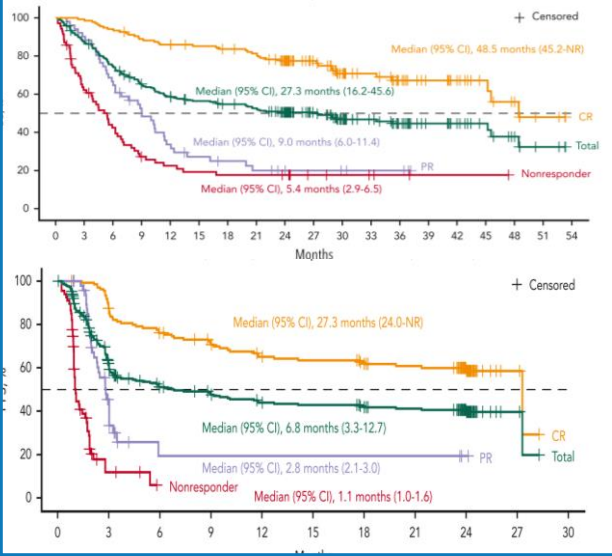

## Liso-cel




**5y FU – TRANSCEND NHL001**

5y OS: 38.1 %

Abramson JS *Blood* 2024



# CAR T-cell therapy vs SOC in 2L DLBCL

| Study name and reference | ZUMA-7[19] | TRANSFORM[21] | BELINDA[20] |
|---|---|---|---|
| CD19-CAR T-cell in experimental arm | Axi-cel | Liso-cel | Tisa-cel |
| Number of patients | 359 | 184 | 322 |
| Patients proceeding to CAR T versus ASCT (%) | 94%/36% | 97%/47% | 96%/32% |
| Median time from registration to CAR T infusion | 29 days | 34 days | 52 days |
| Bridging therapy allowed (% receiving bridging therapy) | Steroids only | One cycle of salvage chemotherapy (63%) | One cycle or more of salvage chemotherapy (97%, including 54% > 1 regimen) |
| Crossover to CAR (% who proceeded) | Not planned (56% received cellular immunotherapy) | Planned per protocol (63%) | Planned per protocol (51%) |
| Median follow-up | 25 months | 17.5 months | 10 months |
| Complete response rate (%) | 65% versus 32% | 74% versus 43% | 28% versus 28% |
| Median event-free survival (months) | 8.3 versus 2 | Not reached versus 2.4 | 3 versus 3 |
| Median progression-free survival (months) | 14.7 versus 3.7 | Not reached versus 6.2 | na |
| Median overall survival (months) | Not reached versus 35.1 (0.73) | Not reached versus 29.9 (0.72) | 16.9 versus 15.3 |
| Any grade CRS/NE (%) | 92%/60% | 49%/11% | 61%/10% |
| Grade ≥3 CRS/NE (%) | 6%/21% | 1%/4% | 5%/2% |

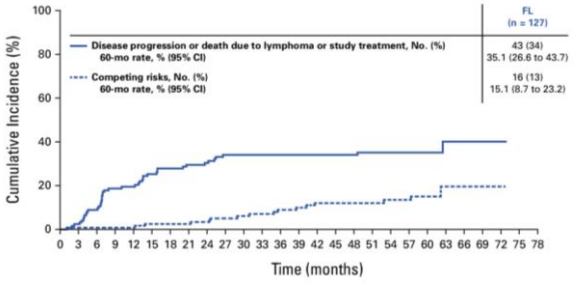
Axi-cel and Liso-cel approved for **primary refractory** or **early relapsed (<12 months)** DLBCL

# CAR T-cell therapy in non Hodgkin lymphomas

## FL

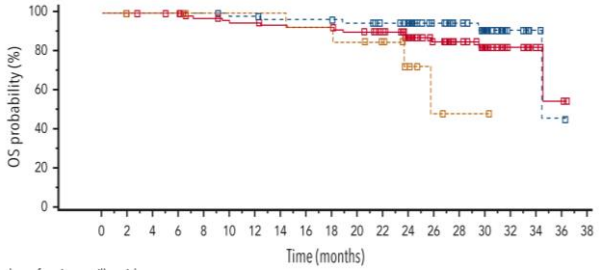
### Axi-cel ≥3 lines

5y FU – ZUMA 5



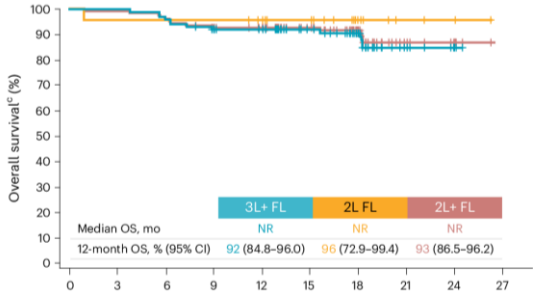

### Tisa-cel ≥2 lines

2y FU – ELARA




### Liso-cel ≥2 lines

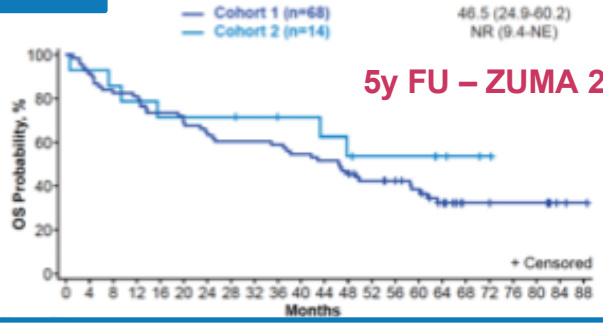
18m FU – TRANSCEND FL

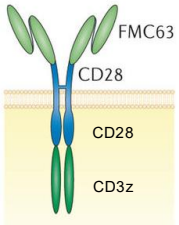



## MCL

### Brexu-cel ≥2 lines (BTKi)

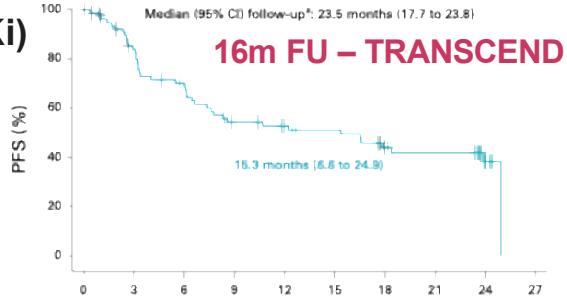
5y FU – ZUMA 2




### Liso-cel ≥2 lines (BTKi)

16m FU – TRANSCEND NHL 001





Neelapu SS *J Clin Oncol* 2025
Dreyling M *Blood* 2024
Morschhauser F *Nature Med* 2024
Munoz J *J Hematol Oncol* 2026
Wang M *J Clin Oncol* 2023

# CAR T-cell therapy in Chronic Lymphocytic Leukemia

| Product administered | Patients evaluable for response, number | ORR | CR rate | Median DOR | Median PFS | Median OS |
|---|---|---|---|---|---|---|
| **Axi-cel** | 4 | 75% (3/4) | 25% (1/4) | 7 months | NA | NA |
| **Tisa-cel** | 14 | 57% (8/14) | 29% (4/14) | CR patients, 40 months<br>PR patients, 7 months | 7 months | 29 months |
| **Tisa-cel** | 32 | 44% (14/32) | 28% (9/32) | NA | 1 month | 64 months |
| **MSKCC CD19 CAR T cells** | 7 | 0% | 0% | NA | NA | NA |
| **MSKCC CD19 CAR T cells** | 15* | 20% (3/15) | 20% (3/15) | NA | 3 months | 17 months |
| **JCAR014** | 24 | 71% (14/24) | 21% (5/24) | NA | 8.5 months | NR |

Adapted from Vitale C *Hemasphere* 2023

# CAR T-cell therapy in Chronic Lymphocytic Leukemia

| Product administered | Patients evaluable for response, number | ORR | CR rate | Median DOR | Median PFS | Median OS |
|---|---|---|---|---|---|---|
| Axi-cel | 4 | 75% (3/4) | 25% (1/4) | 7 months | NA | NA |
| Tisa-cel | 14 | 57% (8/14) | % (4/14) | CR patients, 40 months<br>PR patients, 7 months | 7 months | 29 months |
| Tisa-cel | 32 | 44% (14/32) | % (9/32) | NA | 1 month | 64 months |
| MSKCC CD19 CAR T cells | 7 | 0% | 0% | NA | NA | NA |
| MSKCC CD19 CAR T cells | 15* | 20% (3/15) | 20% (3/15) | NA | 3 months | 17 months |
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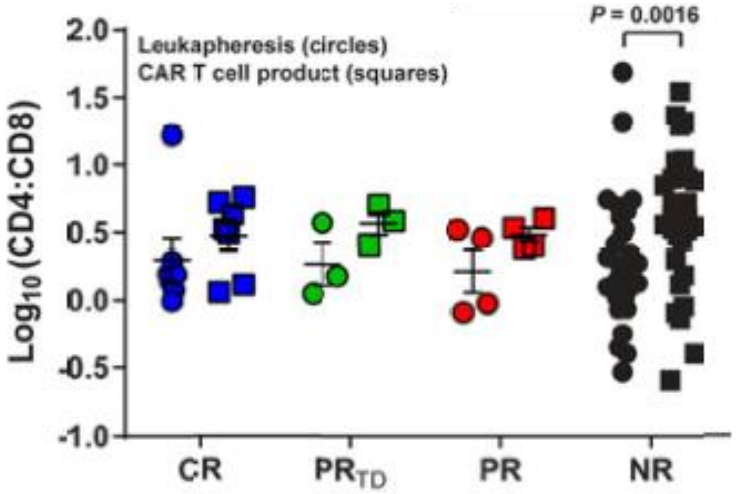
Adapted from Vitale C *Hemasphere* 2023

# Determinants of response to CAR T-cell therapy

## 1) Cellular composition




**CD4:CD8 ratio**

Clinical outcome

Fraietta JA *Nat Med* 2018

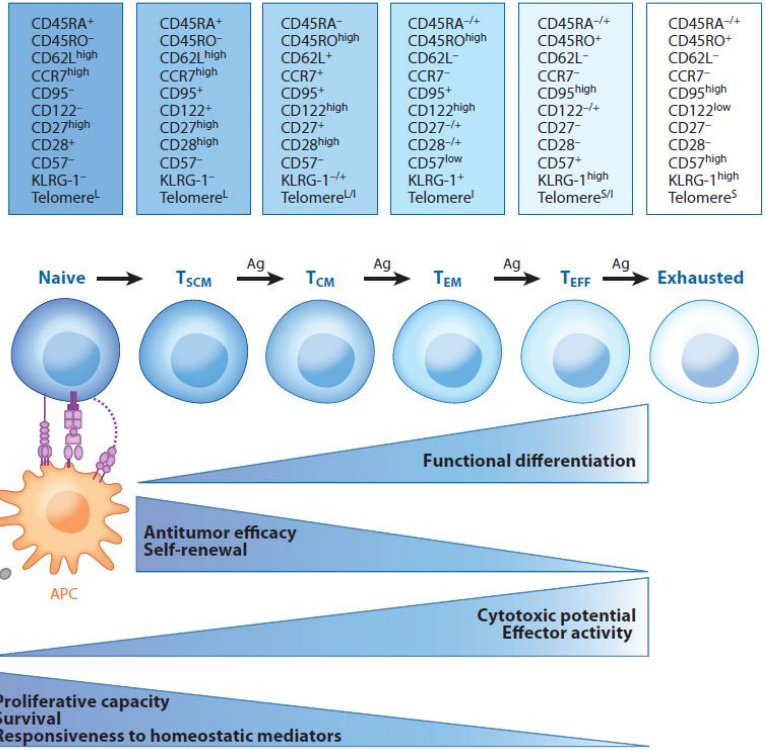
# Determinants of response to CAR T-cell therapy

1) Cellular composition

**2) T-cell subset distribution**

Increased frequency of $CD27^{+}CD45RO^{-}$ $CD8^{+}$ T cells before CAR T generation associated with durable remission

$CD27^{+}PD\text{-}1^{-}CD8^{+}$ CAR T cells associated with better response



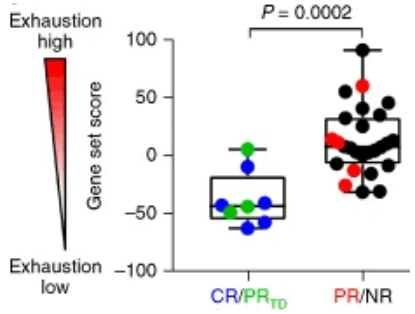

Maus MV *Annu. Rev. Immunol* 2014
Fraietta JA *Nat Med* 2018

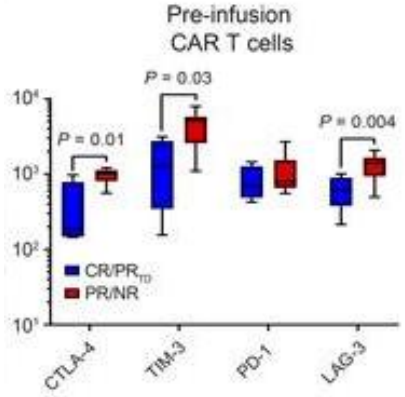
# Determinants of response to CAR T-cell therapy

1) Cellular composition

2) T-cell subset distribution

**3) Presence of exhaustion markers**

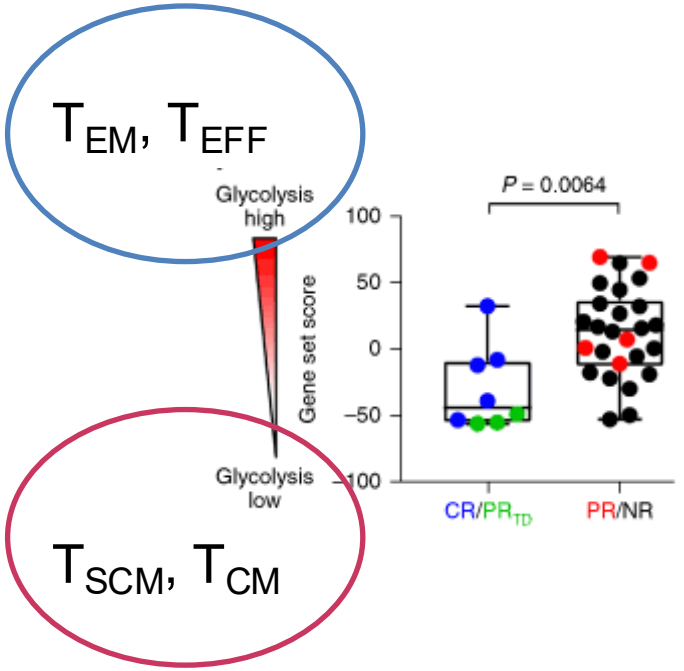



Kong W *JCI* 2021
Fraietta JA *Nat Med* 2018

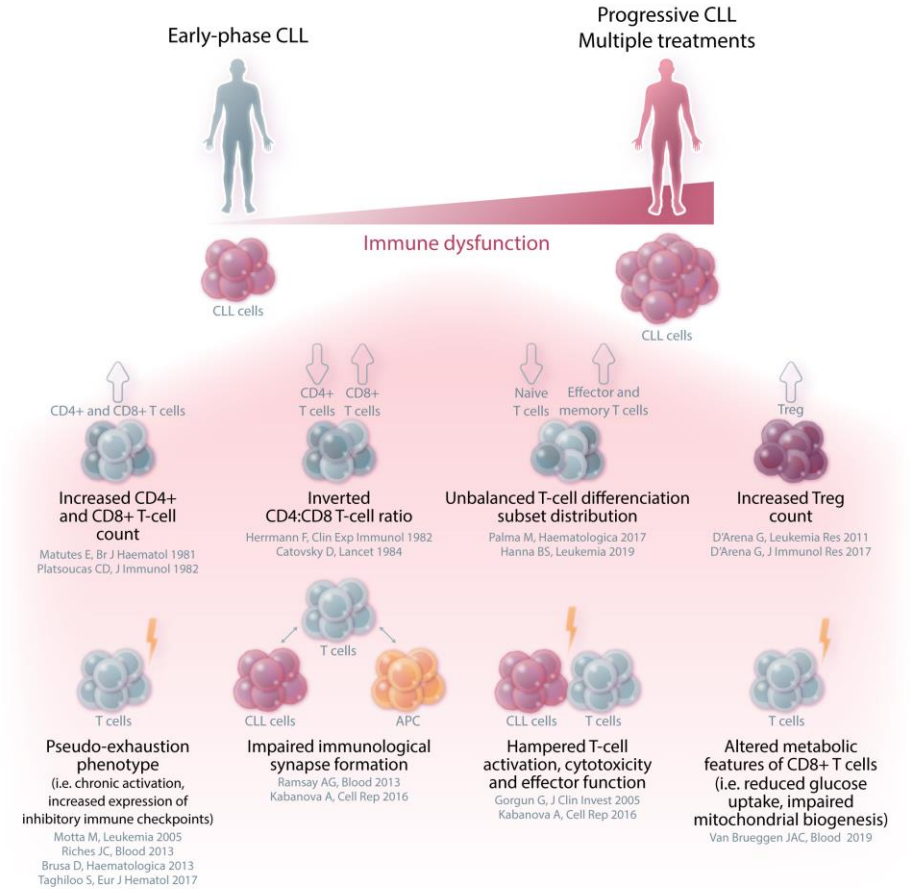
# Determinants of response to CAR T-cell therapy

1) Cellular composition
2) T-cell subset distribution
3) Presence of exhaustion markers
4) **T-cell metabolism**




Fraietta JA *Nat Med* 2018

Intrinsic **immune deterioration** of **T cells** in CLL patients




Vitale C *Hemasphere* 2023


Selection
Of T cells

T-cell fitness
improvement


Selection
Of T cells

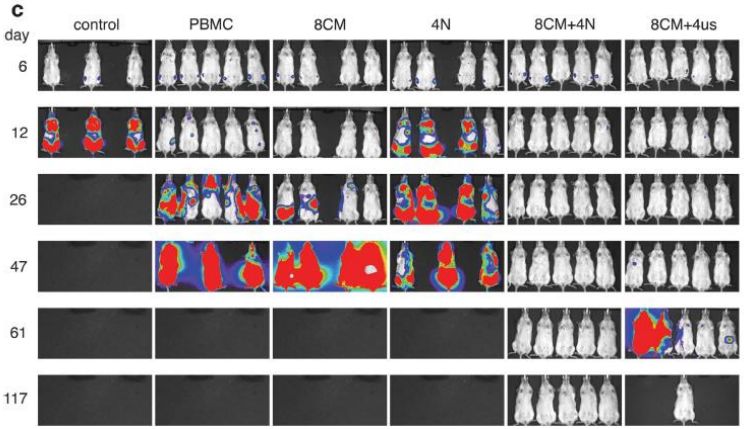
T-cell fitness
improvement

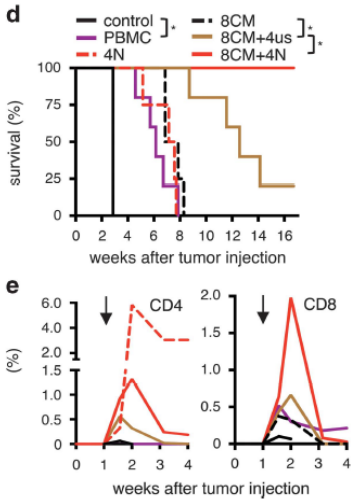
# Selection of T cells

Chimeric antigen receptor-modified T cells derived from defined $CD8^+$ and $CD4^+$ subsets confer superior antitumor reactivity *in vivo*

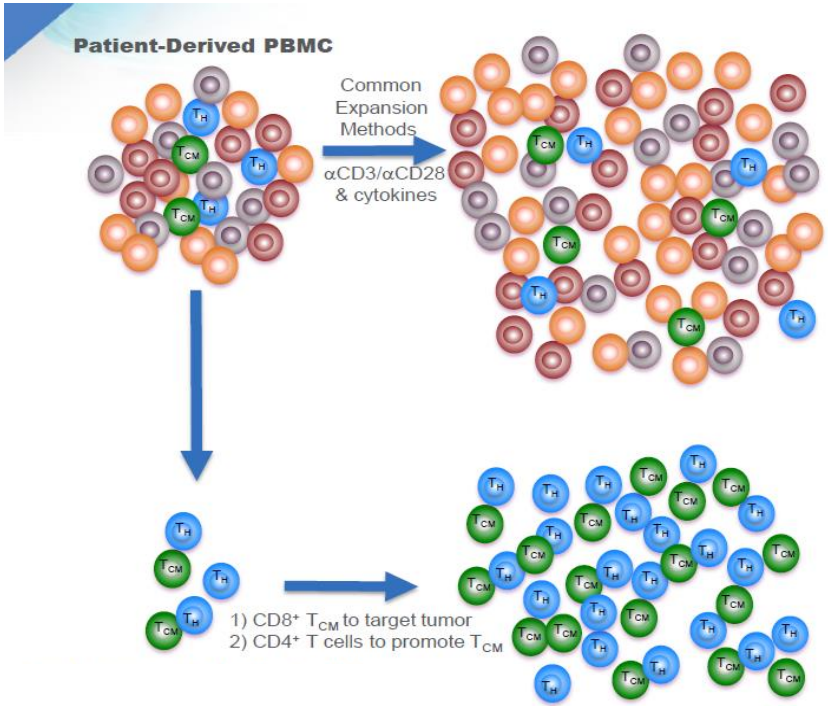
D Sommermeyer[1,5], M Hudecek[1,2,5], PL Kosasih[1], T Gogishvili[2], DG Maloney[1,3], CJ Turtle[1,3] and SR Riddell[1,3,4]

Leukemia, 2016

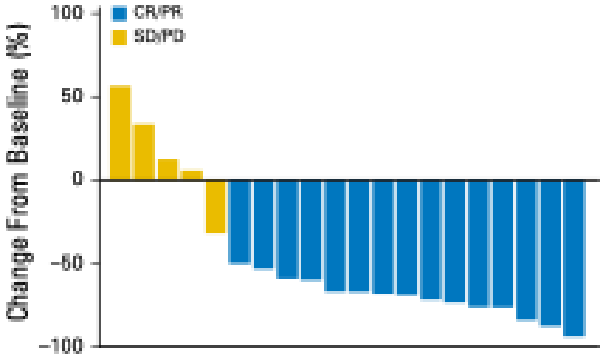


# JCAR014



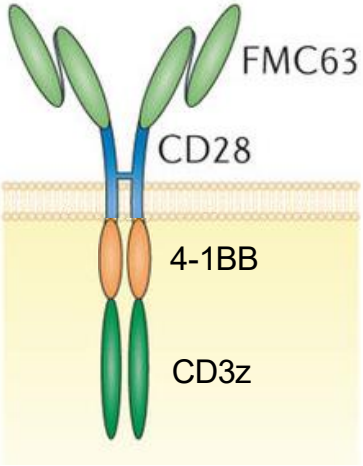

19 pts
@4 weeks:
- ORR 70%, CR 17%
- mFU 6.6 months
- mPFS 8.5 months



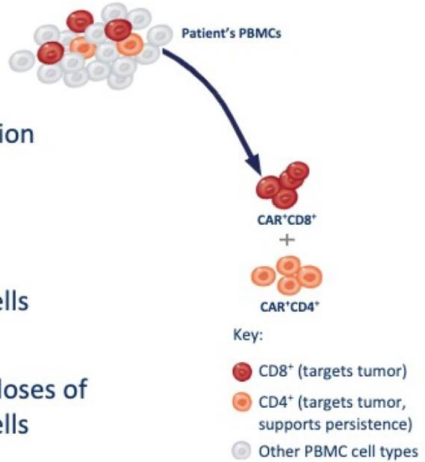

Turtle CJ *J Clin Oncol* 2017

# Selection of T cells

## Lisocabtagene maraleucel (JCAR017)




- Immunomagnetic selection
- Lentiviral transduction
- Expansion
- CD4+ and CD8+ CAR T cells formulated separately
- Administered at target doses of CD4+ and CD8+ CAR T cells



# TRASCEND CLL 004 study

## Liso-cel in RR CLL

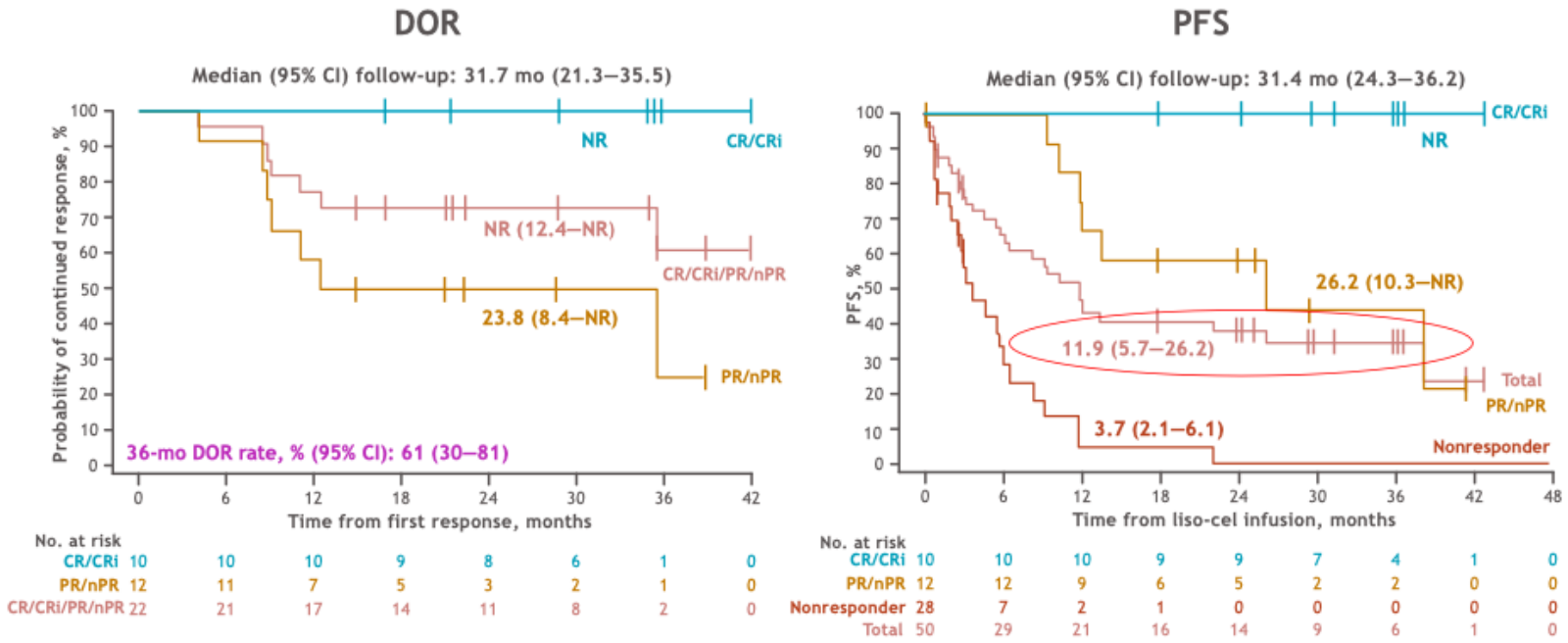
| | Full study population at DL2 (n = 88) | BTKi progression/venetoclax failure subset at DL2 (n = 50) | Prior BTKi exposure and venetoclax-naïve subset at DL2 (n = 18) |
|---|---|---|---|
| **Primary endpoint: IRC-assessed CR/CRi rate per iwCLL 2018, n (%) [95% CI]** | 18 (20) [13–30] | 10 (20) [10–34] | 4 (22) [6–48] |
| **Key secondary endpoints** | | | |
| IRC-assessed ORR, n (%) [95% CI] | 42 (48) [37–59] | 22 (44) [30–59] | 11 (61) [36–83] |
| uMRD4 rate in blood, n (%) [95% CI] | 58 (66) [55–76] | 32 (64) [49–77] | 12 (67) [41–87] |
| **Exploratory endpoint: uMRD4 rate in marrow, n (%) [95% CI]** | 53 (60) [49–70.5] | 30 (60) [45–74] | 12 (67) [41–87] |
| **Other secondary endpoints** | | | |
| Best overall response, n (%) | | | |
| CR/CRi | 18 (20) | 10 (20) | 4 (22) |
| PR/nPR | 24 (27) | 12 (24) | 7 (39) |
| SD | 34 (39) | 21 (42) | 6 (33) |
| PD | 6 (7) | 4 (8) | 0 |
| Not evaluable | 6 (7) | 3 (6) | 1 (6) |
| Median (range) time to first response, months | 1.3 (0.8–17.4) | 1.2 (0.8–17.4) | 2.6 (0.9–6.3) |
| Median (range) time to first CR/CRi, months | 4.4 (0.8–18.0) | 2.1 (0.8–18.0) | 9.0 (3.2–15.2) |

ORR 44%

- **uMRD4 was achieved in MRD-evaluable patients in the full population at DL2 by:**
  - **16/16 (100%) patients with CR/CRi in blood and 16/17 (94%) in marrow**
  - 23/23 (100%) patients with PR/nPR in blood and 22/22 (100%) in marrow
  - 19/32 (59%) patients with SD in blood and 15/32 (47%) in marrow

Siddiqi T *ASH 2024* [Abstract #4633]

# TRASCEND CLL 004 study




→ CAR-T isn't curing most patients

Siddiqi T *ASH 2024* [Abstract #4633]


Selection
Of T cells

T-cell fitness
improvement

# T-cell fitness improvement

**Apheresis product → *in vivo* T-cell modulation**

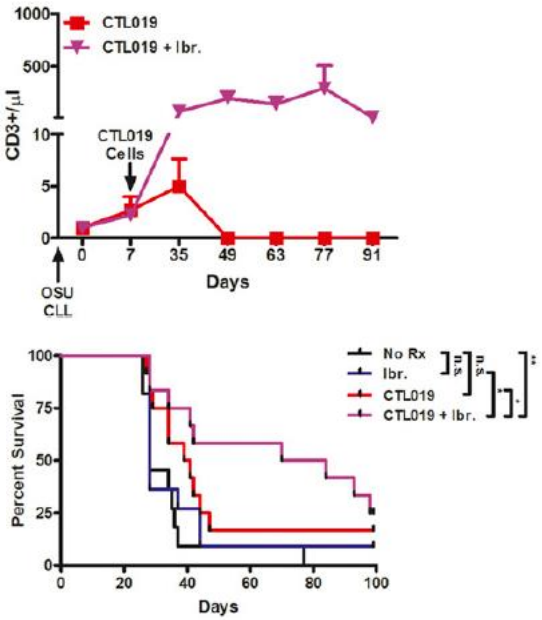

**IBRUTINIB** (Imbruvica®) - BTK inhibitor

Approved for the treatment of Chronic Lymphocytic Leukemia

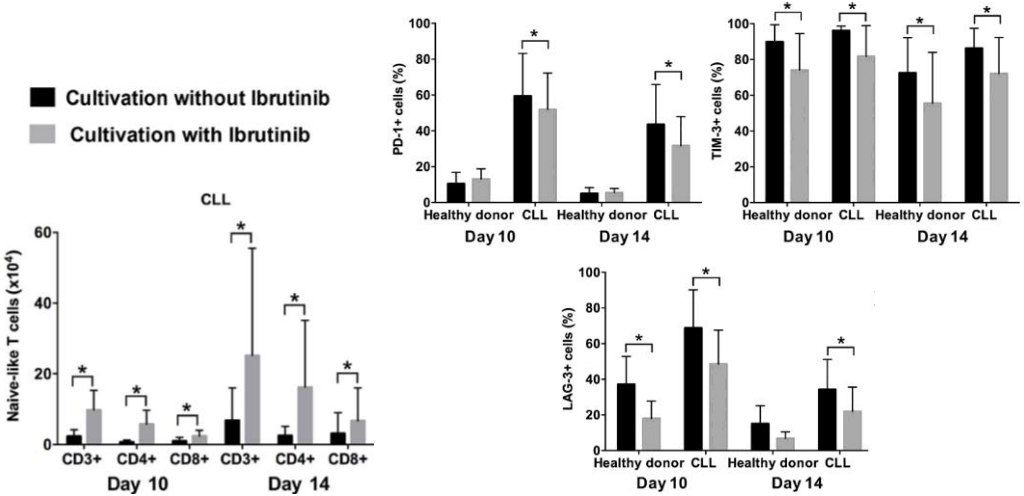
In addition to its **anti-neoplastic effect**, ibrutinib exerts an **off-tumor effect that modulates different immune compartments**, particularly T cells.

Dubovsky *Blood* 2013
Long *J C Invest* 2017
Griggio V ASH 2019

# T-cell fitness improvement




The combination with **Ibr** enhances **CAR T-cell engraftment** and significantly prolongs the **survival**




The addition of **Ibr** increases **naïve-like T-cell subsets** and mitigates the expression of **exhaustion markers**


Fraietta JA *Blood* 2016
Fan F *Int J Cancer* 2021

# JCAR014 + Ibrutinib in RR CLL/SLL

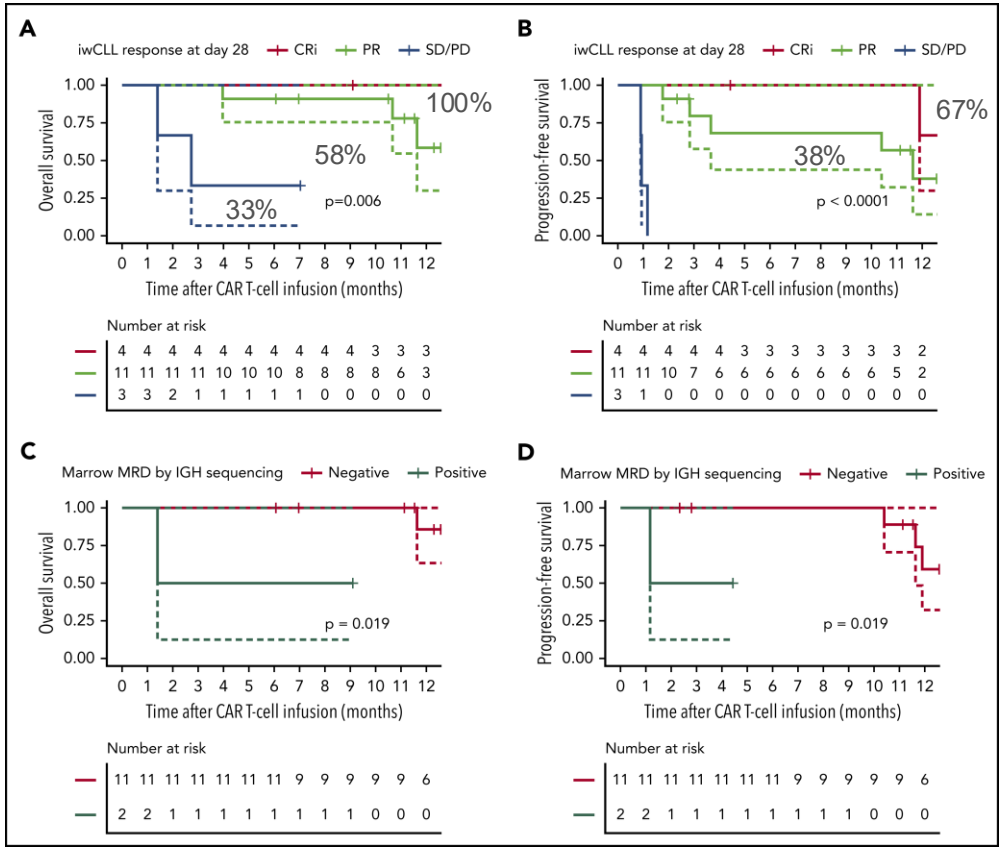
**Con-ibr cohort**
19 patients with RR CLL(high-risk disease)
Ibrutinib 420 mg/day from ≥2 weeks pre-leukapheresis and until ≥3 months after CAR T-cell infusion

**No-ibr cohort**
19 patients with RR CLL
Previously treated in the same trial (NCT01865617)
Same lymphodepletion and CAR T-cell dose

| | Con-ibr cohort | No-ibr cohort |
|---|---|---|
| **Response at 4 wk** | | |
| iwCLL 2018, CR/CRi/PR† | 15/18 (83) | 10/18 (56) |
| iwCLL 2018 CT response, CR/PR‡ | 10/14 (71) | 9/17 (53) |
| Marrow CR by flow cytometry | 13/18 (72) | 12/18 (67) |
| Marrow CR by *IGH* sequencing§ | 11/13 (85) | 6/10 (60) |

Gauthier J *Blood* 2020

# JCAR014 + Ibrutinib in RR CLL/SLL

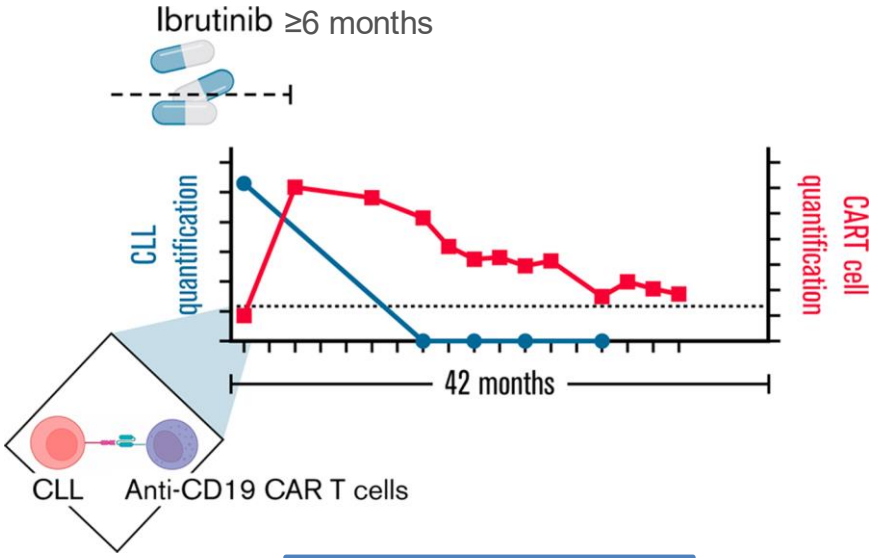



1y-OS: 64%
1y-PFS: 38%

Responding patients had superior long-term outcomes

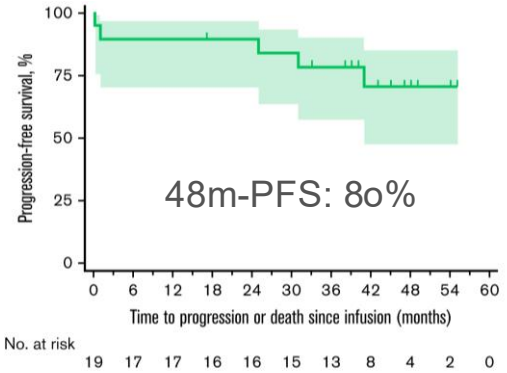
Gauthier J *Blood* 2020

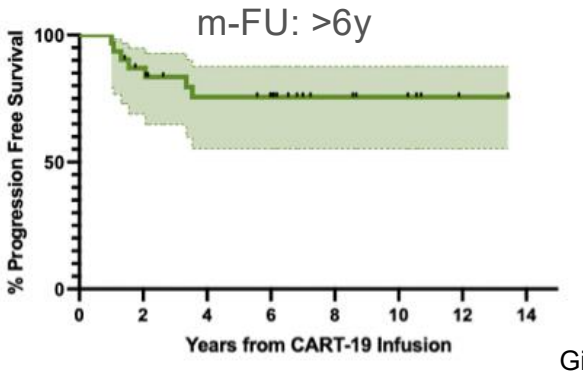
# huCART19 in combination with Ibrutinib in patients with CLL/SLL
# NCT 02640209 trial




CLL pts
not in CR

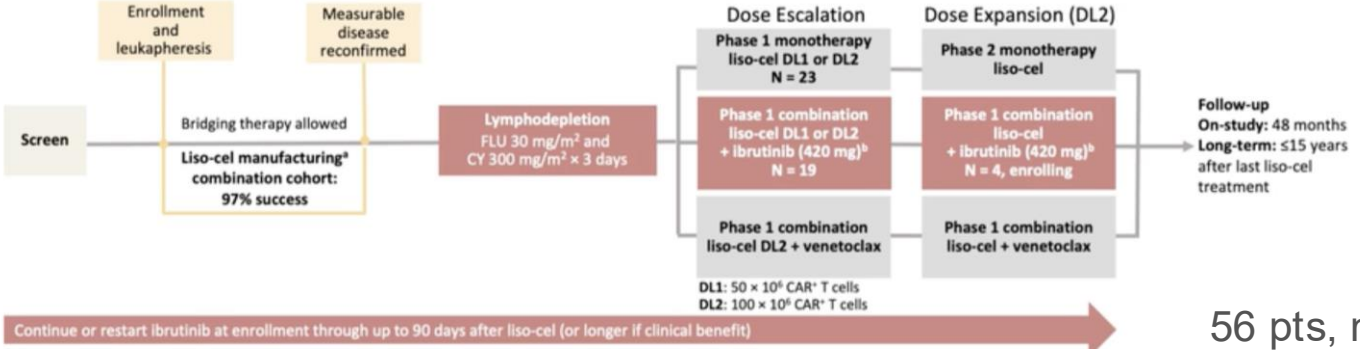
19 pts
@12 months
CR 50%
uMRD 72%




Gill S *Blood Adv* 2022
Frost BJ *ASH 2024*

# Liso-cel in combination with Ibrutinib in patients with RR CLL/SLL: phase 1/2 TRANSCEND CLL 004 Study




56 pts, mFU 24.8 mo

**Key Eligibility:**

- RR CLL/SLL **and**
- Progressing on Ibr at enrollment ***or***
- High-risk features and received Ibr for ≥6 mo with less than a CR ***or***
- *BTK*/*PLCγ2* mutation ***or***
- Prior BTKi with no contraindications to ibr ***or***
- PD on BTKi and received prior venetoclax

Wierda W *ASH 2024* [Abstract #887]

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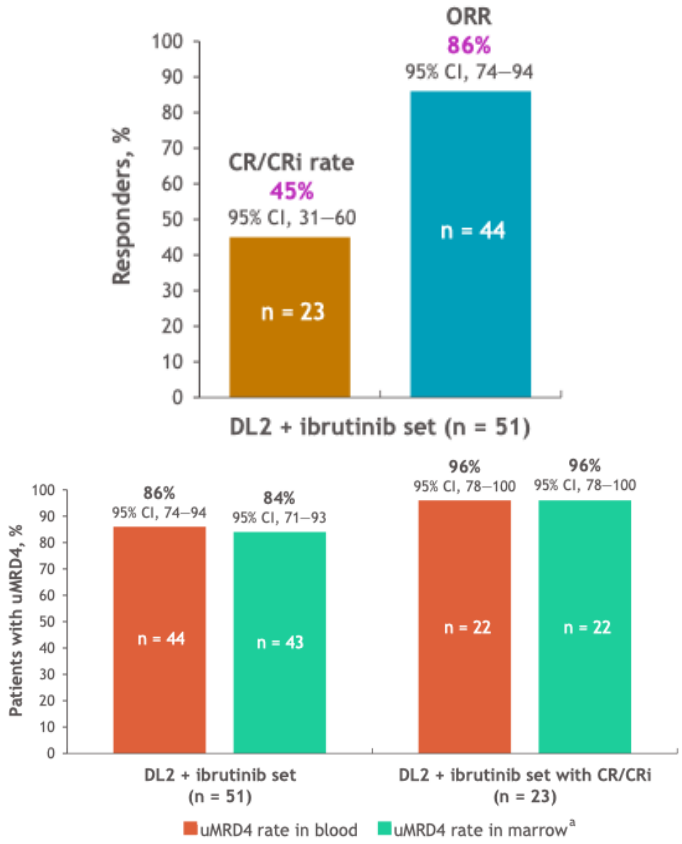


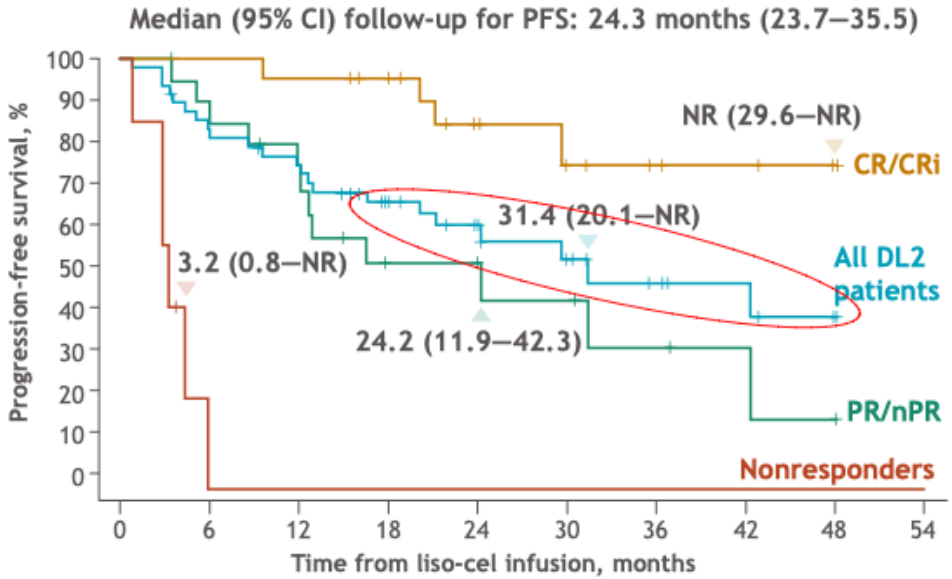


Wierda W *ASH 2024* [Abstract #887]

# T-cell fitness improvement

## cBTKi

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Author Information

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Signal Transduction and Targeted Therapy www.nature.com/sigtrans

ARTICLE OPEN

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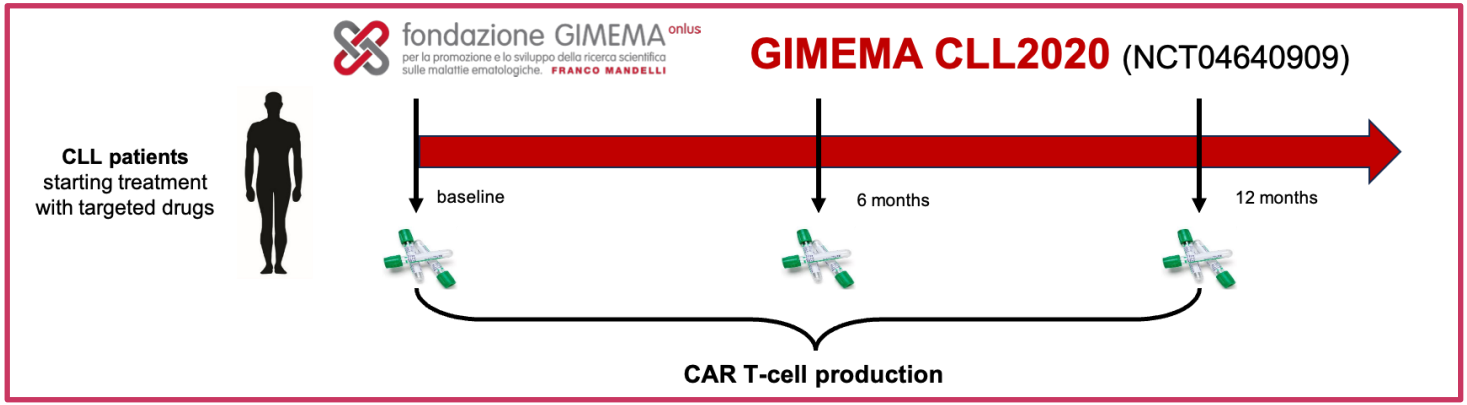

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**Authors**: Fateeha Furqan, Katie Palen, Bryon Johnson, Tyce Kearl, Peiman Hematti, Walter L. Longo, Mehdi Hamadani, Timothy S. Fenske, and Nirav Niranjan Shah | AUTHORS INFO & AFFILIATIONS

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## PI3Ki

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Sophia Stock, Rudolf Übelhart, Maria-Luisa Schubert, Fuli Fan, Bailin He, Jean-Marc Hoffmann, Lei Wang, Sanmei Wang, Wenjie Gong, Brigitte Neuber, Angela Hückelhoven-Krauss ... See all authors

First published: 09 February 2019 | https://doi.org/10.1002/ijc.32201 | VIEW METRICS

National Comprehensive Cancer Network®

# NCCN 2026

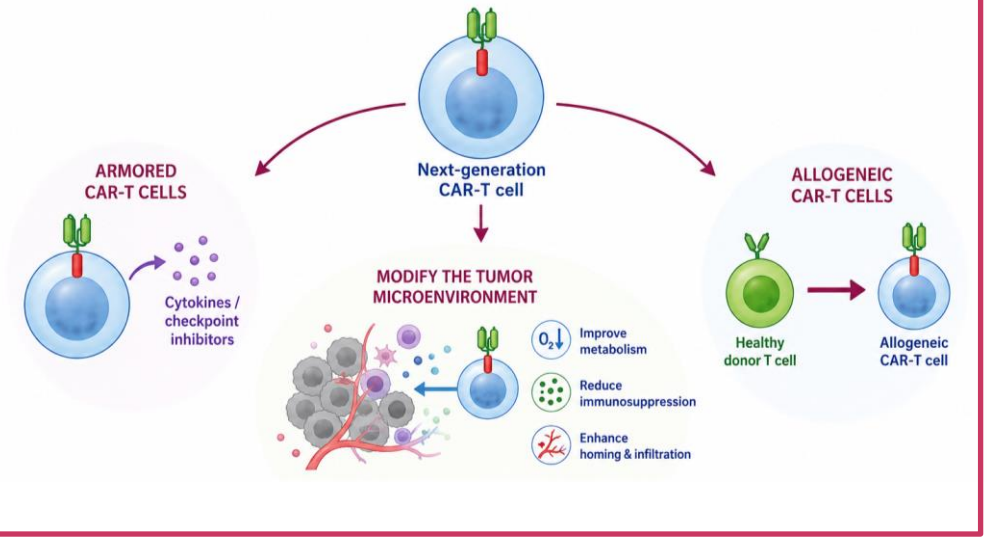
**THERAPY FOR RELAPSED OR REFRACTORY DISEASE**
**AFTER PRIOR cBTKi-BASED AND BCL2i-CONTAINING REGIMENS[a,f]**

| Preferred | Other Recommended |
|---|---|
| • Chimeric antigen receptor (CAR) T-cell therapy<br>▸ Lisocabtagene maraleucel (CD19-directed)[aa] ± Ibrutinib[f]<br>• ncBTKi-based regimen:<br>▸ Pirtobrutinib (continuous) (category 1) (if not previously given) | • PI3Ki-based regimens<br>▸ Duvelisib<br>▸ Idelalisib[bb] ± Rituximab<br>• FC + Rituximab[b,f,cc]<br>• Lenalidomide[dd] ± Rituximab<br>• Obinutuzumab<br>• Alemtuzumab[ee] ± Rituximab (with del(17p)/TP53 mutation)<br>• Bendamustine[p] + Rituximab[ff] (category 2B for patients ≥65 y or patients <65 y with significant comorbidities)<br>• HDMP + anti-CD20 mAb[ff] (category 2A with del[17p]; category 2B without del[17p]) |

## *Take-home Messages*

- **Anti-CD19 CAR-T cells** have transformed the treatment landscape of B-cell malignancies, achieving **long-term disease control.**
- Clinical efficacy depends not only on CAR design, but also on **T-cell quality.**
- A **T-cell dysfunction** as in CLL may impact the efficiency of CAR T-cell therapy.
- **Optimizing T-cell fitness** before/during CAR-T manufacturing may improve CAR T-cell therapy.

**Not only engineering better CARs, but also making better T cells.**

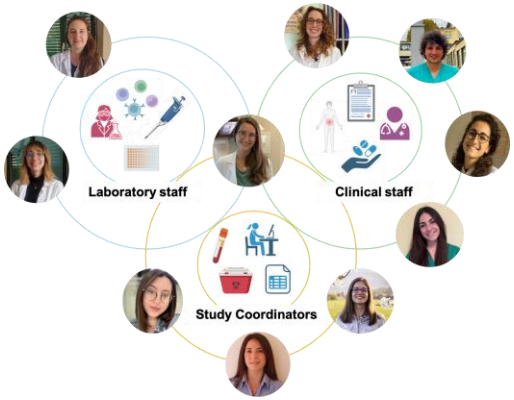


# SC Ematologia U

## AOU Città della Salute e della Scienza di Torino

## Laboratorio di Ematologia Traslazionale

## Gruppo Malattie Linfoproliferative

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DBMSS
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