CLL SOCIETY

Smart Patients Get Smart Care™

CAR-T Ed Forum: The Basic Science and Latest Data

April 21, 2021

10:00 AM PT, 11:00 AM MT,
12:00 PM CT, 1:00 PM ET

This program was made possible by grant support from

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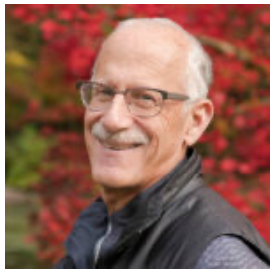
Agenda and Speakers

Patricia Koffman,
CLL Society

John M. Pagel, MD, PhD
Swedish Cancer Institute



Larry Saltzman, MD
Leukemia & Lymphoma Society

Brian Koffman,
MDCM (retired), MSEd
CLL Society

Tanya Siddiqi, MD
City of Hope National Medical Center

Sharon Saltzman
Caregiver

Agenda		
1:00 PM EST	Welcome	Patricia Koffman
1:05 PM	CAR-T and CLL: A Patient and Caregiver Journey	Dr. Larry Saltzman and Sharon Saltzman
1:20 PM	Introduction to the Science and Future of CAR-T and Other Immune Therapies	Dr. John Pagel
1:45 PM	The Present State of the Art in CLL	Dr. Tanya Siddiqi
2:10 PM	CLL Society's Programs & Resources	Patricia Koffman
2:20 PM	Audience Q&A	Drs. Koffman, Pagel, Siddiqi, and Saltzman
2:57 PM	Closing Remarks	Dr. Brian Koffman

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Immunotherapy: A New Paradigm For Treatment

John M. Pagel, MD, PhD

April 21, 2021

Not So Long Ago…

CLL Therapy Toolkit

Chemotherapies

Radiation

Generally applied to CLL patients

Then…

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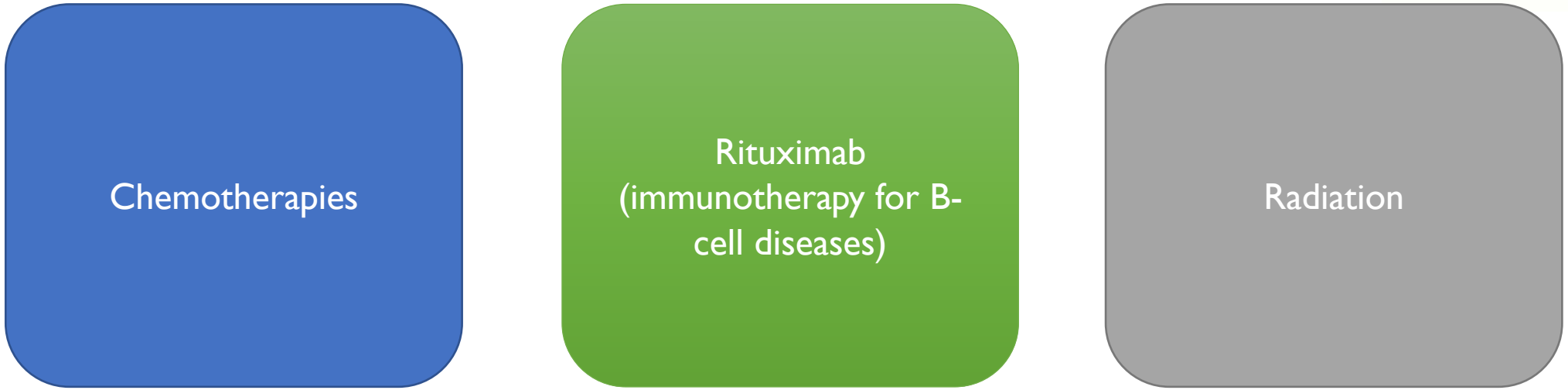
CLL Therapy Toolkit



Rituximab markedly improved outcomes in NHL
Again, these tools largely applied to all CLL

Now…

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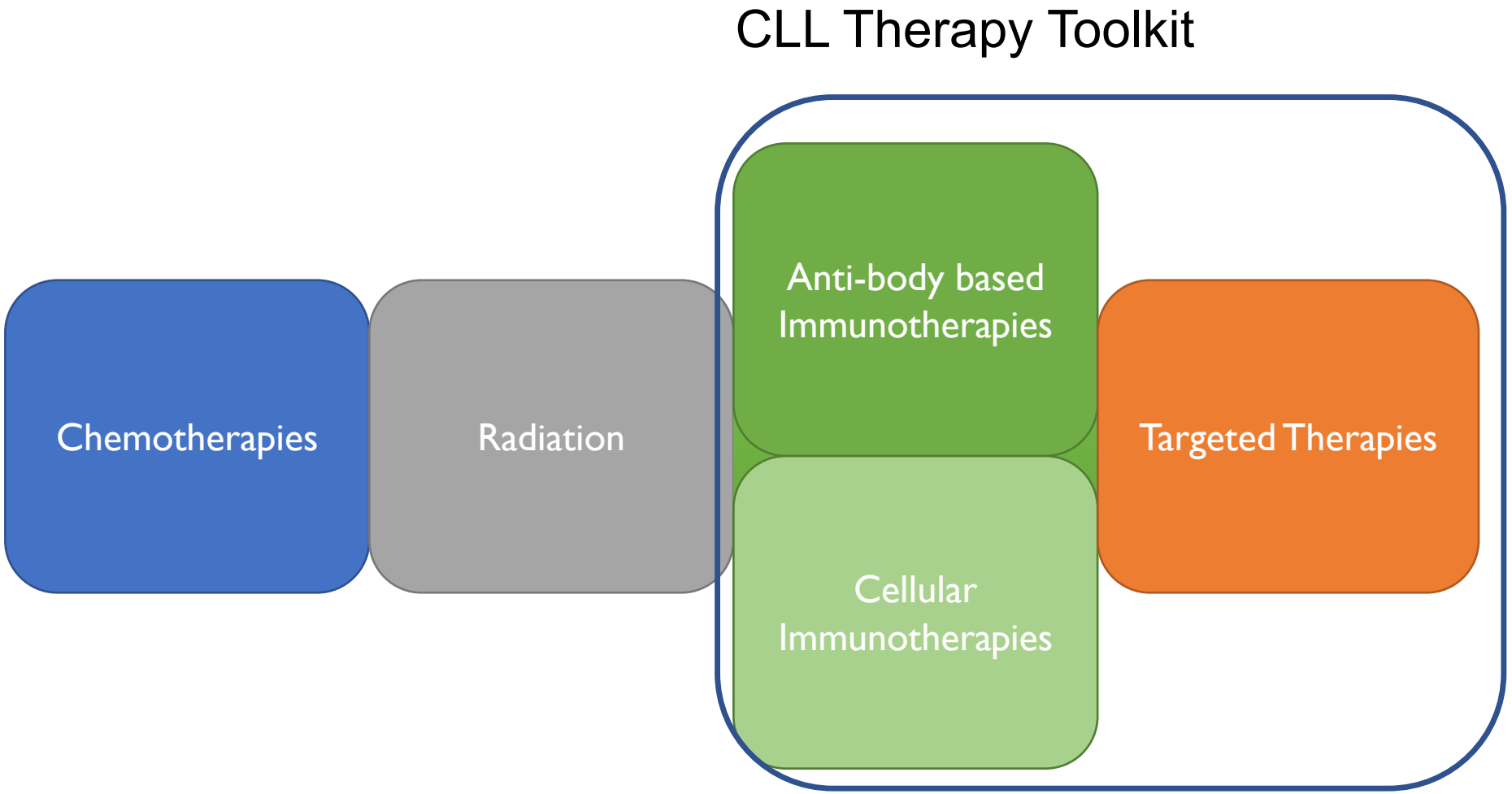

Importantly, these tools are being used in ways specific to CLL


Science
20 December 2013 | $10
Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack
AAAS

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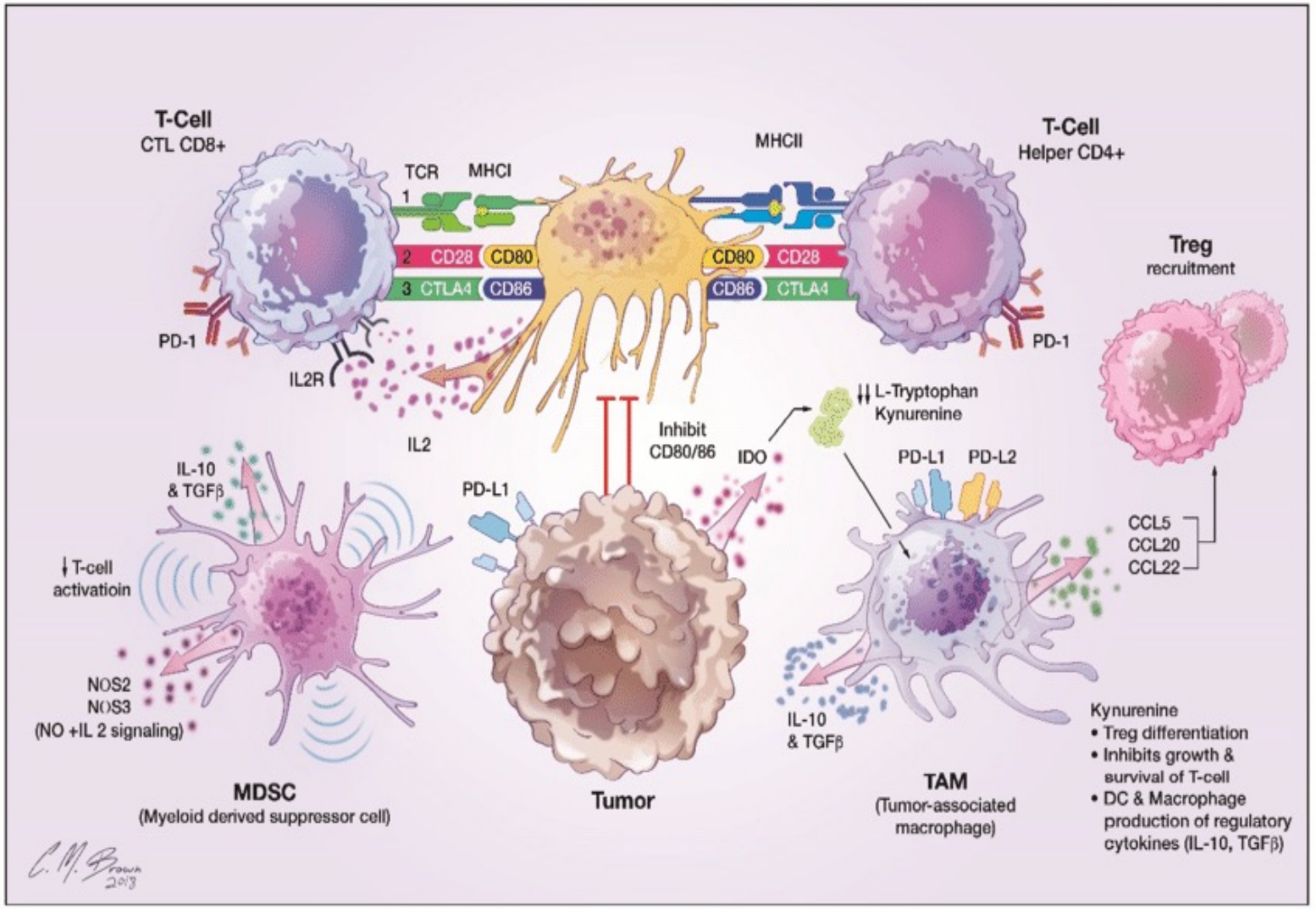
Immunotherapy



- Immune system long recognized as having ability to fight CLL
- CLL (like other cancers) can “hide” from the immune system

Leibold, A, et al. Current Neurobiology 2019

New Paradigm

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The immune system is the “agent” that improves outcome and *CURES* people with systemic cancer.

Fundamental shift in our understanding of cancer

Summary Of The Old Era

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- Therapies are non-specific
- Allogeneic transplant may be the ultimate adoptive immunotherapy
  - Comes with a potential price
- Other therapies (IFN, vaccines, etc.) have more modest benefit
  - Immune responsiveness may be an important concept
  - Disease specific (FL different than DLBCL which is different than HL)

Immunotherapy Types

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Anti-body based Immunotherapies

Medicines (typically infusions) given to enhance native immune activity against lymphoma

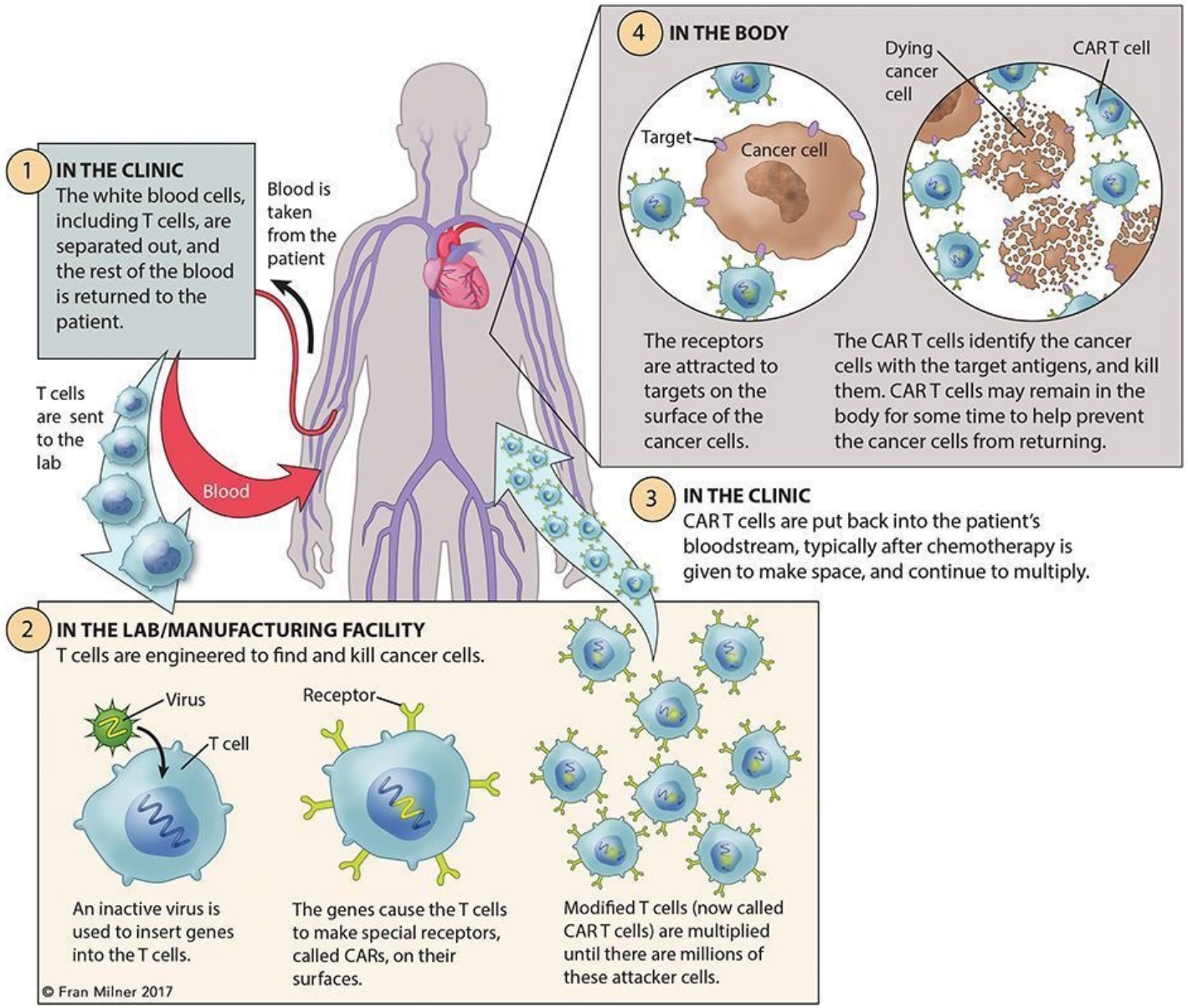
"Off-shelf"

Cellular Immunotherapies

Genetically modified immune cells ("living drug") given to patients to fight lymphoma

May require time to make specifically for patients

Use of either might depend on the individual circumstances for the patients
Potential for combinations of both types of immunotherapy


1 IN THE CLINIC
The white blood cells, including T cells, are separated out, and the rest of the blood is returned to the patient.
Blood is taken from the patient
T cells are sent to the lab
Blood
4 IN THE BODY
Dying cancer cell
CAR T cell
Target
Cancer cell
The receptors are attracted to targets on the surface of the cancer cells.
The CAR T cells identify the cancer cells with the target antigens, and kill them. CAR T cells may remain in the body for some time to help prevent the cancer cells from returning.
3 IN THE CLINIC
CAR T cells are put back into the patient's bloodstream, typically after chemotherapy is given to make space, and continue to multiply.
2 IN THE LAB/MANUFACTURING FACILITY
T cells are engineered to find and kill cancer cells.
Virus
T cell
Receptor
An inactive virus is used to insert genes into the T cells.
The genes cause the T cells to make special receptors, called CARs, on their surfaces.
Modified T cells (now called CAR T cells) are multiplied until there are millions of these attacker cells.
© Fran Milner 2017

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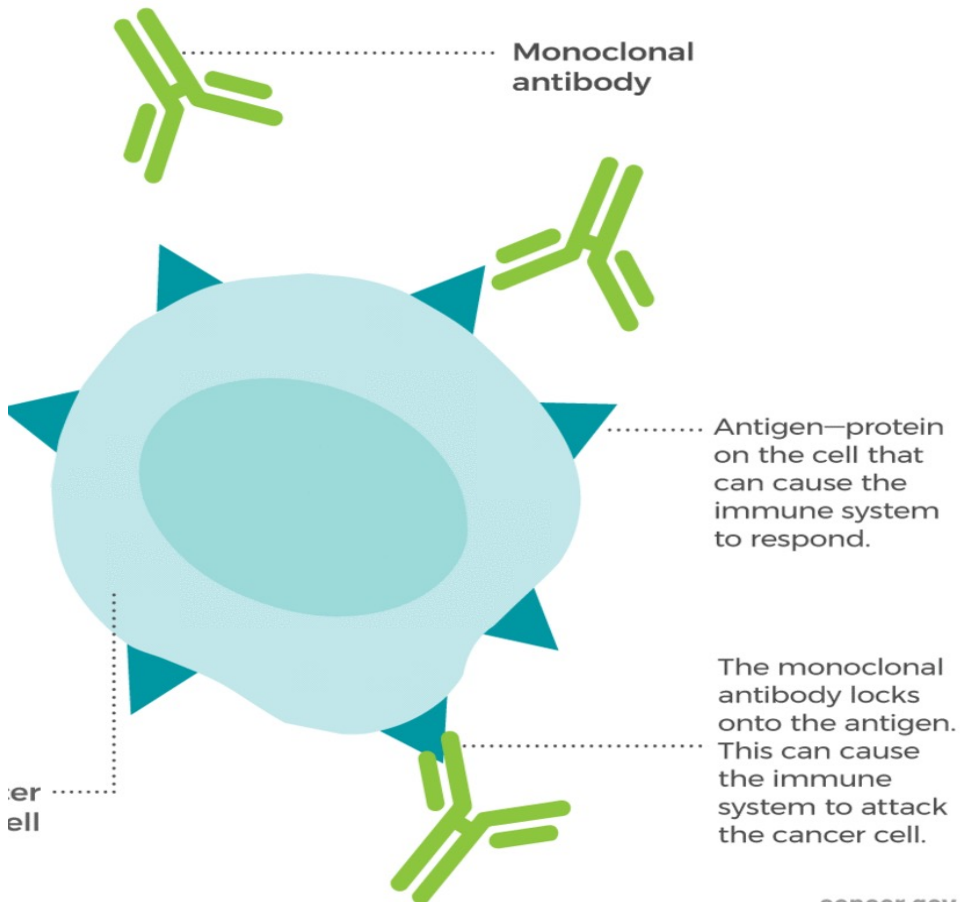
Monoclonal antibody
Antigen—protein on the cell that can cause the immune system to respond.
The monoclonal antibody locks onto the antigen. This can cause the immune system to attack the cancer cell.
cancer.gov

The New Era

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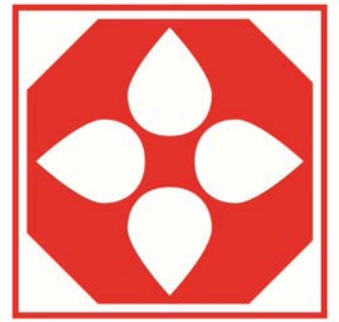
- Checkpoint inhibitors
- A host of other antibody approaches
- Cell-based therapies
- Combination strategies
- Signaling pathway inhibitors (PI3K, BTK as examples)
- CAR-T cell therapy

Antibody Based Immunotherapy



Anti-B-cell Abs (B-cell NHL)

Anti-CD20 mabs
Rituximab
Obinutuzumab
Ublituximab*

Anti-CD19 mabs
Tafasitimab*

Checkpoint Inhibitors

PD1 inhibitors
Nivolumab
Pembrolizumab

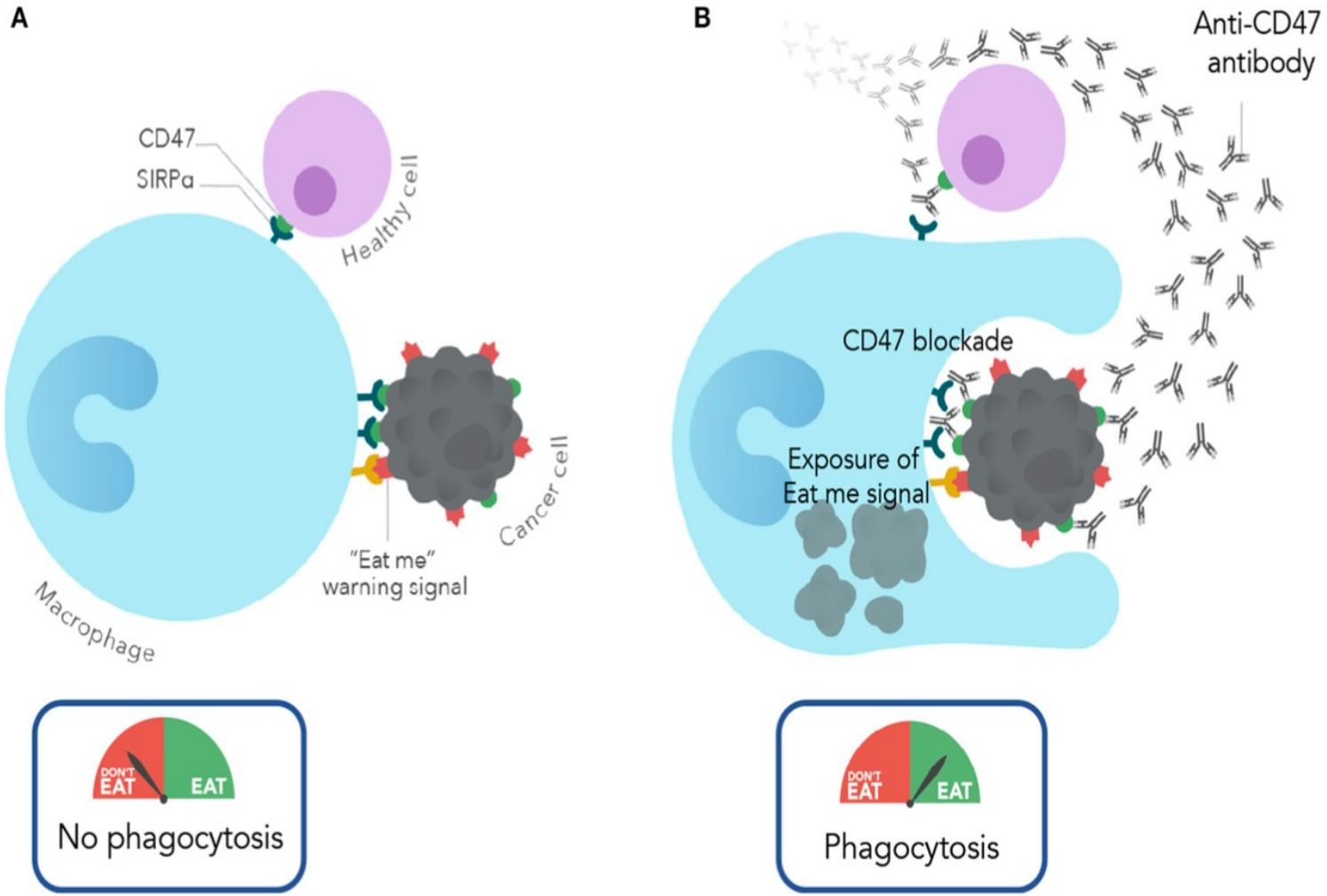
Anti-CD47 agents
Magrolimab*
TTI-622*

Bi-specific Antibodies (bsAbs)

CD3 x CD20 bsAb
Mosenutuzumab*
Glofitamab*
Plamotamab*
Epcoritimab*
REGN1979*

*Investigational agents, not FDA approved

Anti-CD47 Agents

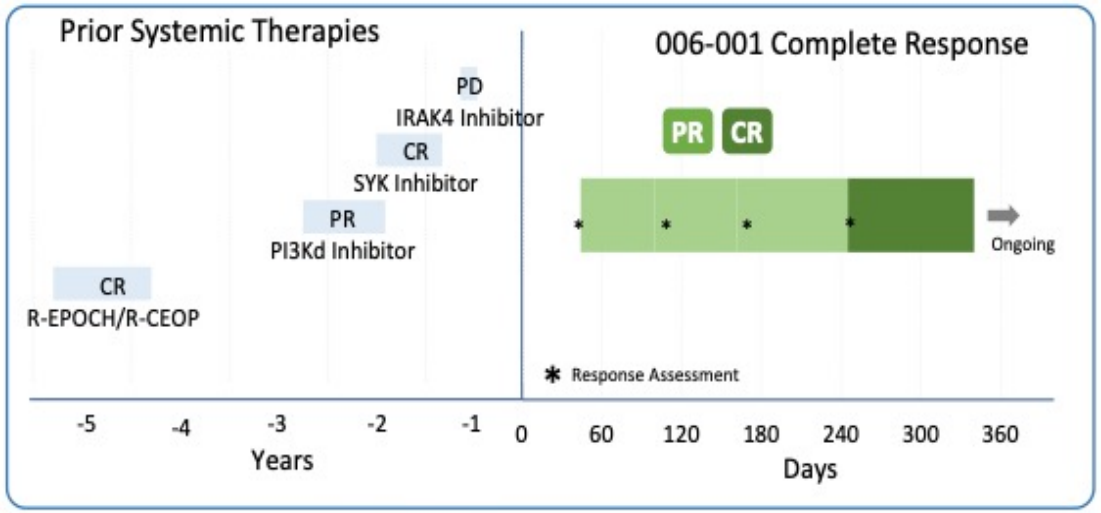


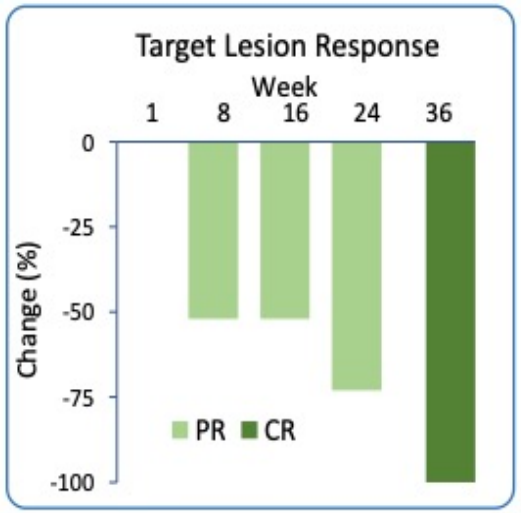
- Immune cells (macrophages) can destroy cells which express an “Eat me” signals (several types)
- Cancer cells express “Eat me” and “Don’t eat me” signals (CD47) to avoid destruction by macrophages
- Normal cells express “Don’t eat me” signals but mostly do not express “Eat me” signal, allowing these treatments to be selective

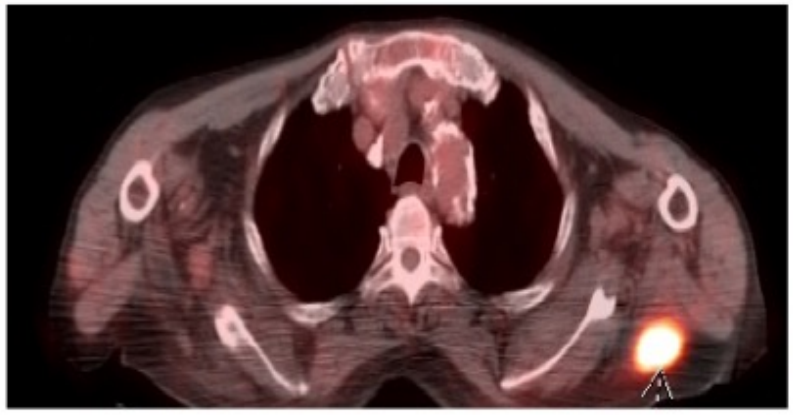
Chao, M. et al Frontiers in Oncology. January 2020

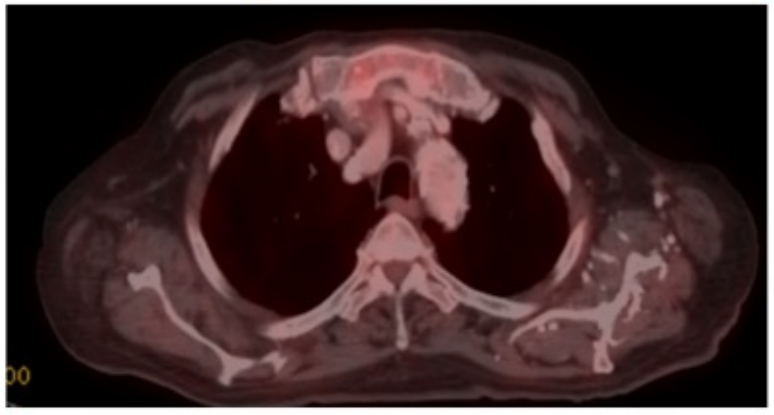
Anti-CD47 Agents

TTI-622 Phase 1 Clinical Trial





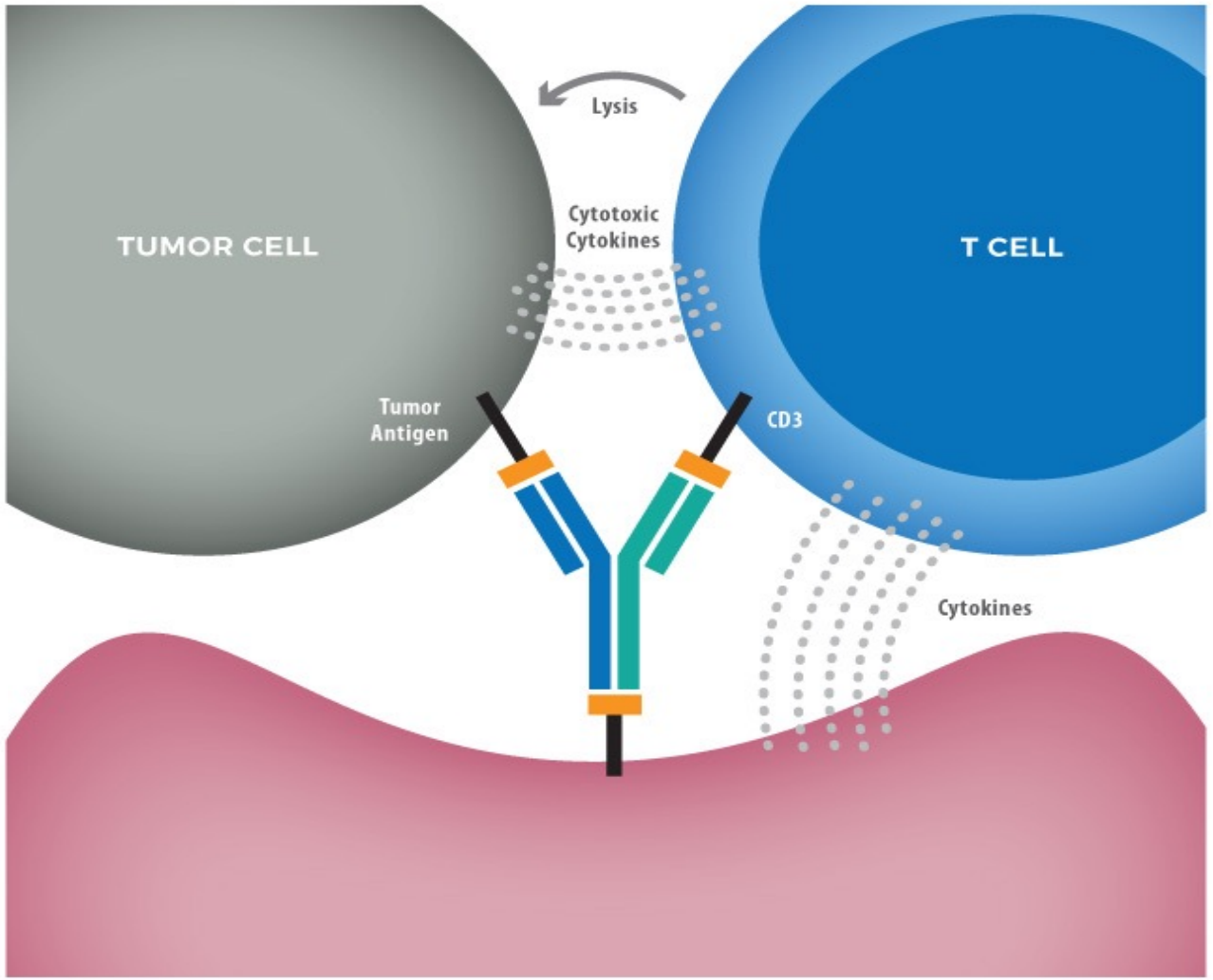




- Anti-CD47 agents have shown clinical **activity in both B-cell and T-cell lymphomas** in early stage studies
- **Side effects appear generally mild and reversible**; these therapies may be reasonable to combine with other therapies
- Further studies needed and underway

Patel, K et al. ASCO 2020

Bispecific Antibodies



- Two-sided antibody
  - One side binds cancer cell
  - One side binds immune cell
- **Helps activate immune cells to destroy cancer cells**
- Lots of different designs to change the properties of these therapies

Bispecific Antibodies

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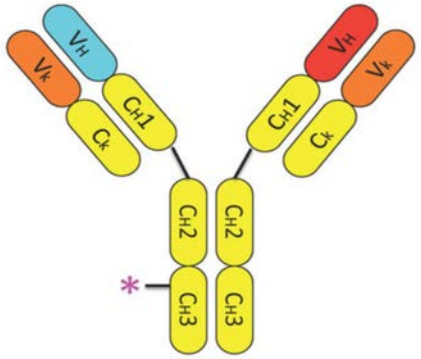
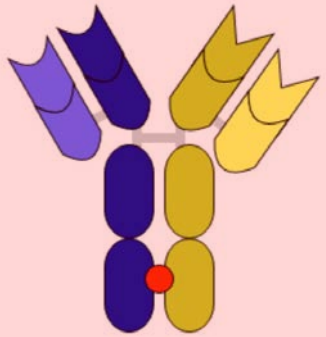
REGN1979



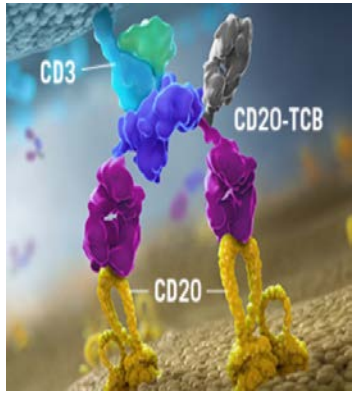
CD3 x CD20 Common LC IgG4 Fc BsAb

Mosunetuzumab



CD3 x CD20 Knobs-in-hole IgG1 Fc BsAb

Glofitimab (CD20-Tcb)



CD3 (Fab) x CD20 (Fab x2) Fc BsAb

Palotamab (Xmab13676)

CD3 (scFv) x CD20 (Fab) Fc BsAb

Data from ASH 2019 *Investigational agents, not FDA approved

Mosunetuzumab in R/R NHL

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Patient population

n (%)	*N=270**
Median age, years (range)	62 (19–96)
Male	172 (63.7%)
ECOG PS 1 at baseline	164 (61.2%)†
Aggressive NHL	180 (66.7%)
DLBCL	117 (43.3%)
trFL	32 (11.9%)
MCL	23 (8.5%)
Other	8 (3.0%)
Indolent NHL	85 (31.5%)
FL	82 (30.4%)
Other	3 (1.1%)
Median prior systemic therapies, n (range)	3 (1–14)†
Prior CAR-T therapy	30 (11.1%)
Prior autologous SCT	77 (28.5%)
Refractory‡ to last prior therapy	194 (71.9%)
Refractory‡ to prior anti-CD20 therapy	233 (86.3%)

30 pts with prior CAR-T therapy

- 17 DLBCL, 8 trFL, 5 FL
- Median 5 lines of prior systemic therapies (range 3–14)
- 29 pts (96.7%) refractory to prior anti-CD20 therapy
- 25 pts (83.3%) refractory to last prior therapy
- 22 pts (73.3%) refractory to prior CAR-T therapy

CCOD (clinical cut-off date): Aug 9, 2019; *safety evaluable pts; †n=268, as two pts did not have data entered by CCOD; ‡no response (PR or CR) or PD within ≤6 months of treatment; trFL, transformed FL;

Schuster, S et al. ASH 2019

Mosunetuzumab in R/R NHL (Indolent)

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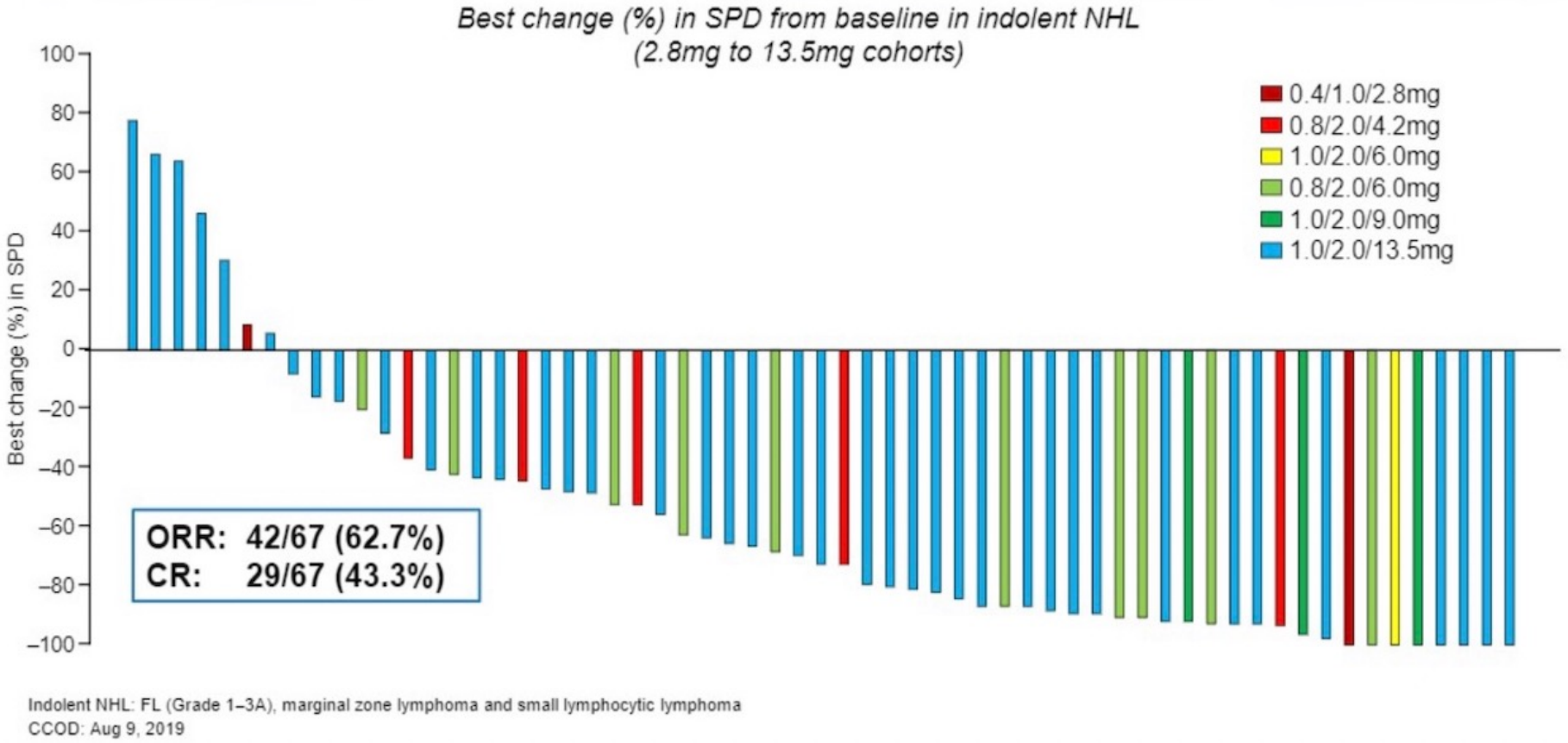
Objective response rate in indolent NHL



Indolent NHL: FL (Grade 1–3A), marginal zone lymphoma and small lymphocytic lymphoma
CCOD: Aug 9, 2019

- In this early stage study, >60% of patients with indolent B-cell lymphoma had responses
- ~40% had complete responses

Schuster, S et al. ASH 2019

Mosunetuzumab in R/R NHL (Aggressive)

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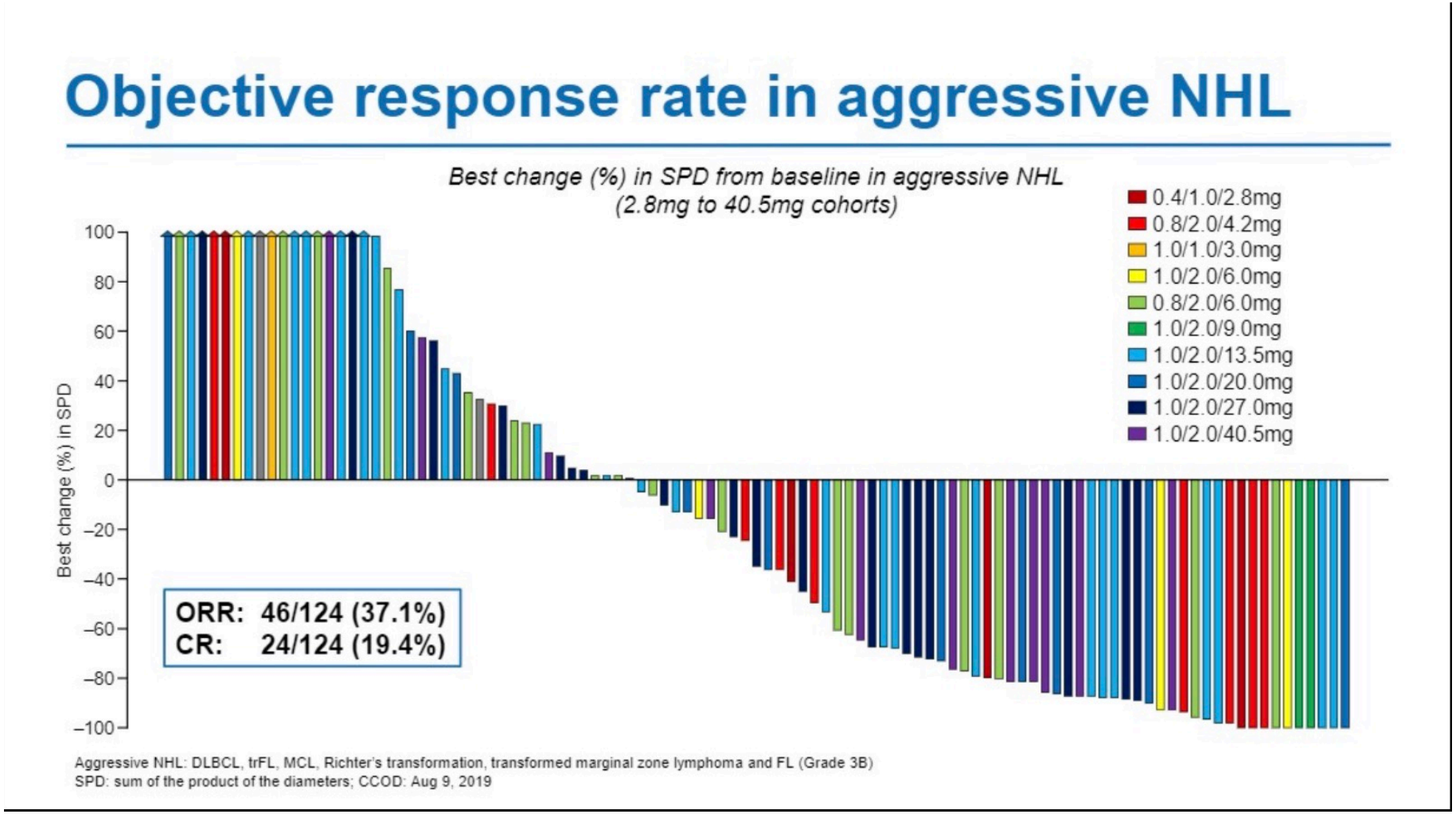
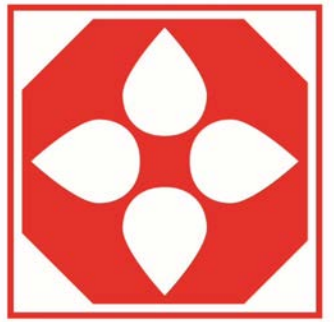


- In this early stage study, ~40% of patients with aggressive B-cell lymphomas had responses
- Half of responders had complete responses

Schuster, S et al. ASH 2019

Antibody Based Immunotherapy



Checkpoint Inhibitors

Anti-CD47 agents

Magrolimab*
TTI-622*

Bi-specific Antibodies (bsAbs)

CD3 x CD20 bsAb

Mosenutuzumab*
Glofitamab*
Plamotamab*
Epcoritimab*
REGN1979*

- Lots to still work out, but generally good activity and manageable side effects
- Promising steps forward

*Investigational agents, not FDA approved

Cellular Immunotherapies

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Autologous CAR T-cells

DLBCL/tFL
Axicabtagene Ciloleucel
Tisagenlecleucel
Lisocabtagene maraleucel*

MCL
Brexucabtagene autoleucel

Allogeneic T-cells

AlloCAR T
UCART19*
AUTO3*

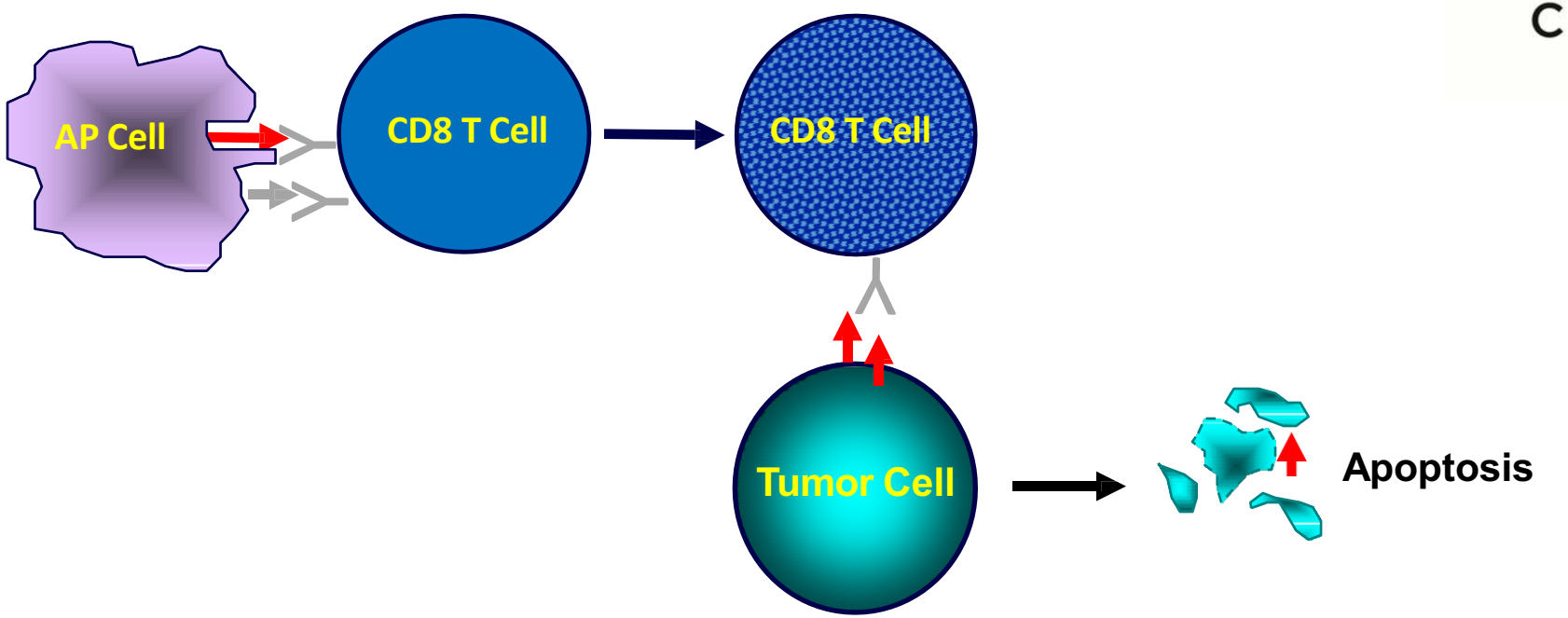
Allogeneic HSCT

Allogeneic Engineered NK Cells

CAR NK Cells (FT596)*
Enhanced NK cells (FT516)*

*Investigational agents, not FDA approved

Mechanisms of Cytotoxic T Cells



Generic Chimeric Antigen Receptor (CAR)

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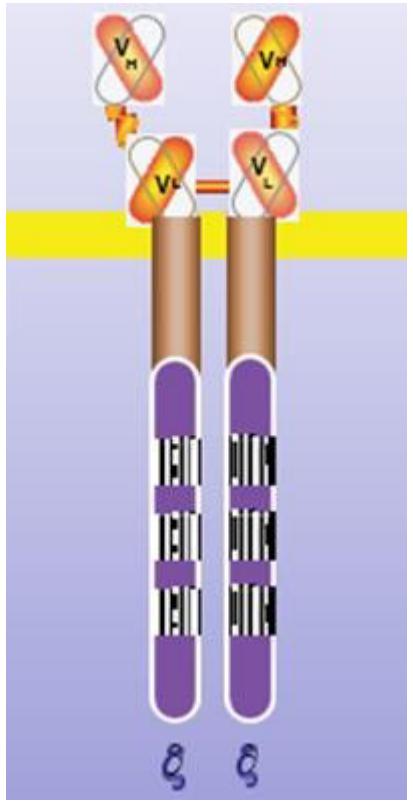
Extracellular Domain

- scFv: monoclonal antibody derivative
- determines receptor specificity

Intracellular Domain

- fusion protein comprised of a T-cell costimulatory receptor signaling domain + a TCRζ activation domain



Transmembrane Domain

- has an extracellular spacer / hinge region

Action of Chimeric Antigen Receptor-Modified (CAR) T Cells

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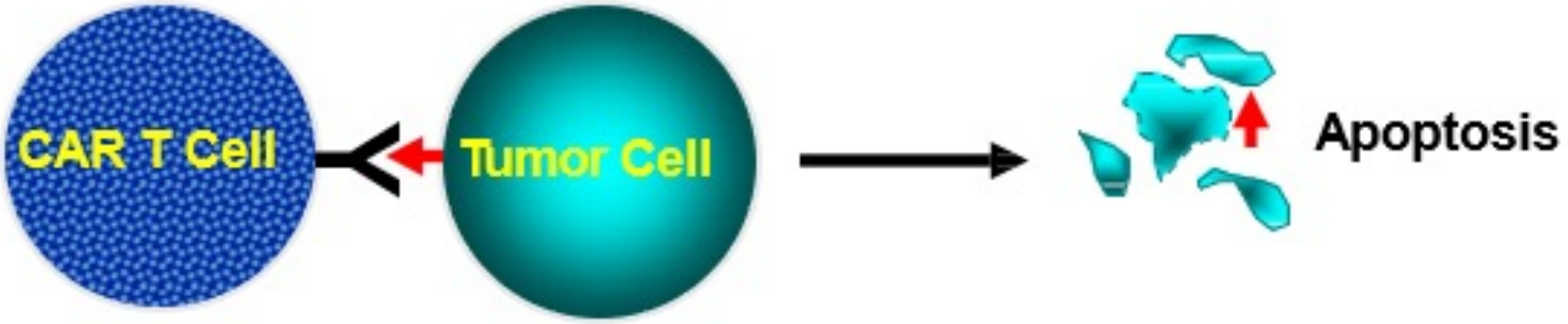

Chimeric Antigen Receptor T-Cells

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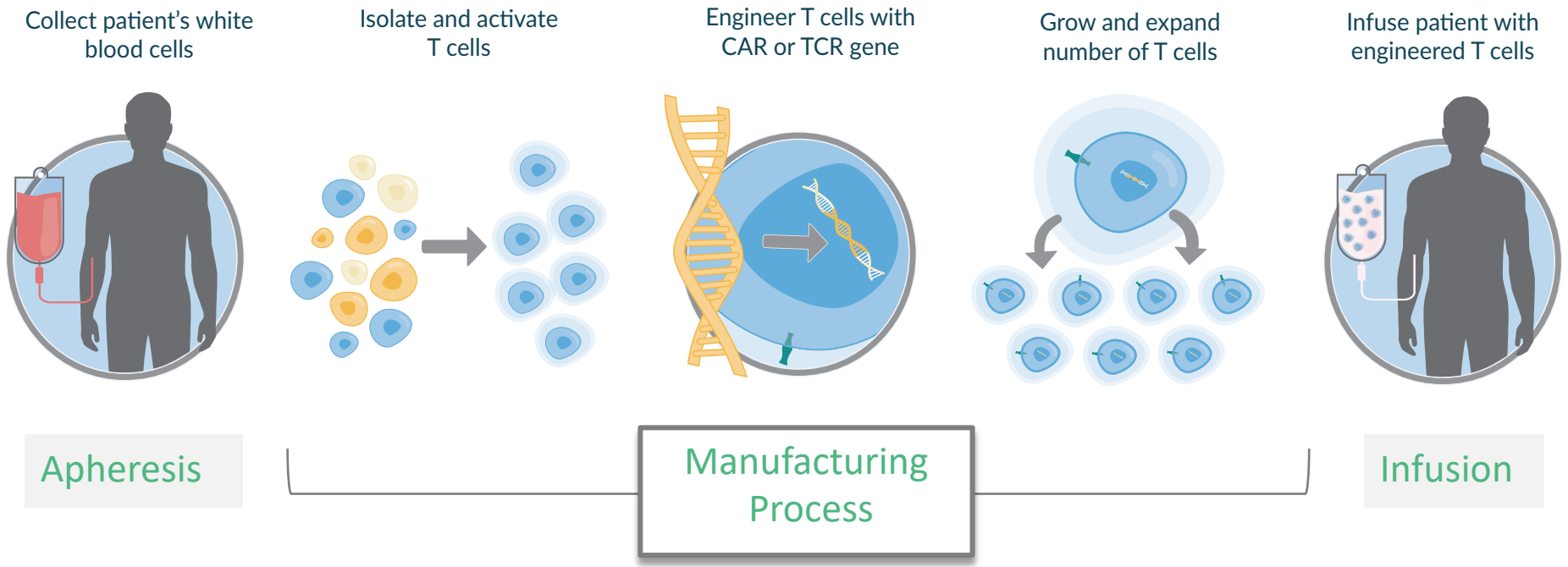
ENGINEERED AUTOLOGOUS CELL THERAPY



Phase I TRANSCEND CLL 004 (Cohort 1): Lisocabtagene Maraleucel in R/R CLL, Including Prior Ibrutinib Treatment

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Outcomes	Patients (n = 23)	Pts Ref to BTKi, Ven (n = 11)
ORR, %	82	80
▪ CR/CRi	45	60
Median DoR, mos	NR	
▪ 15-mo DoR, %	53%	
▪ 18-mo DoR, %	50%	
Median PFS, mos (95% CI)	18 (3.0-NR)	
MRD evaluable, n	n = 20	n = 9
▪ uMRD (blood), %	75	78
▪ uMRD (BM), %	65	67

- Phase I/II trial in R/R CLL with ≥ 3 prior therapies (or ≥ 2 and high risk), including BTKi
- N = 23 (safety), 22 (efficacy)
  - Median 6 prior lines of therapy, 100% prior BTKi, 48% refractory to BTKi and venetoclax
- Three days of lymphodepletion (fludarabine and cyclophosphamide) → liso-cel infusion with 50×10^6 or 100×10^6 CAR+ T-cells
- AEs similar to previous reports

Siddiqi. ASH 2020. Abstr 546.

Phase I Transcend CLL 004 (Combination Cohort): Lisocabtagene Maraleucel + Ibrutinib In R/R CLL

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- Phase I liso-cel + ibrutinib combination cohort (n = 19)
- Start or continue ibrutinib through leukapheresis and for ≥ 90 days after liso-cel infusion (50-100 x 10^6)

Enrollment Criteria:

1) PD on ibrutinib at study enrollment

2) High-risk, no CR on ≥ 6 mos ibrutinib

3) BTK or PLCγ2 mutation, with or without PD on ibrutinib

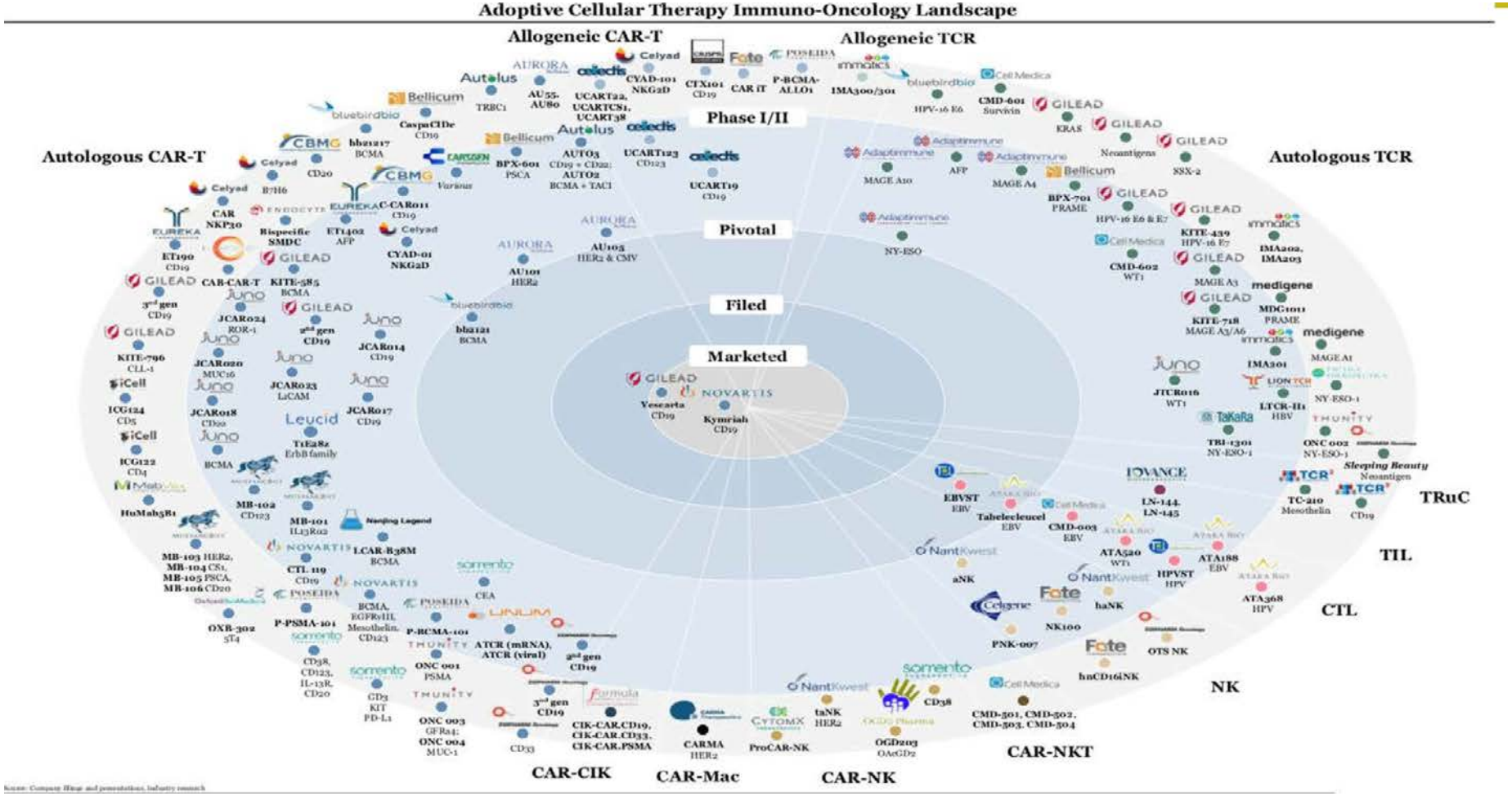
4) Prior ibrutinib, no contraindication to restarting ibrutinib

- Most common grade ≥ 3 TEAEs: Neutropenia or neutrophil count decrease (89%), anemia (47%), and febrile neutropenia (26%)
- CRS: 74% (1 grade 3); neurologic AE (32%)
  - 37% required tocilizumab/corticosteroids
- Ibrutinib-related AEs: Diarrhea (n=7), HTN (n=4), AF (n=1), rash (n = 1)

Outcomes, %	Patients (n = 19)
ORR	95
▪ CR/CRi	47
MRD evaluable, n	n = 19
▪ uMRD (blood), %	89
▪ uMRD (BM), %	79

Wierda. ASH 2020. Abstr 544.

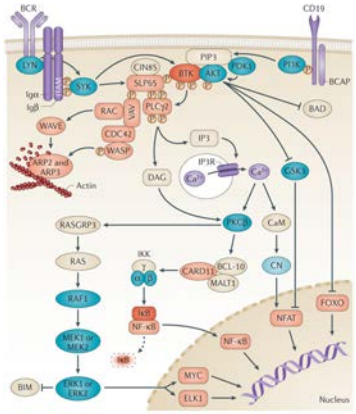
Cellular Immunotherapies: Just the Beginning



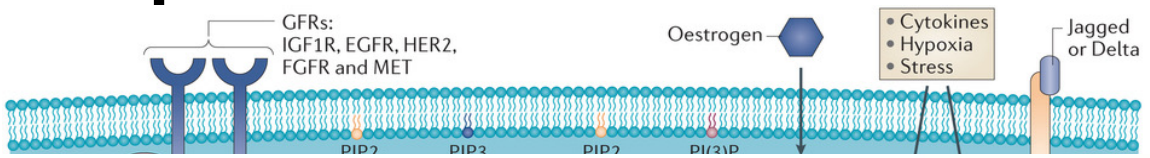
Broad development in Blood cancers and solid tumor cancers

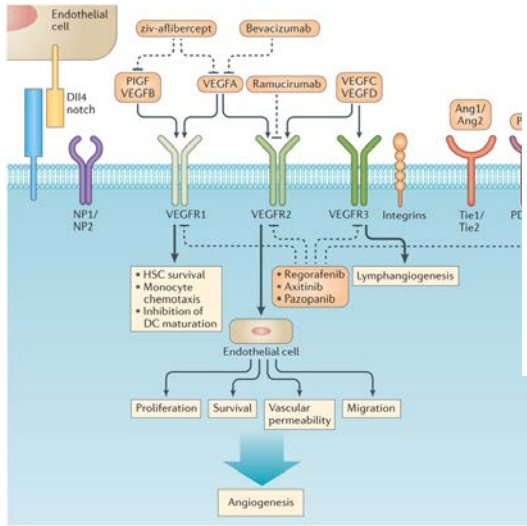
Wierda. ASH 2020. Abstr 544.

Targeted Therapies



Nature Reviews | Cancer





Nature Reviews | Clinical Oncology

Chimeric Antigen Receptor T-Cells

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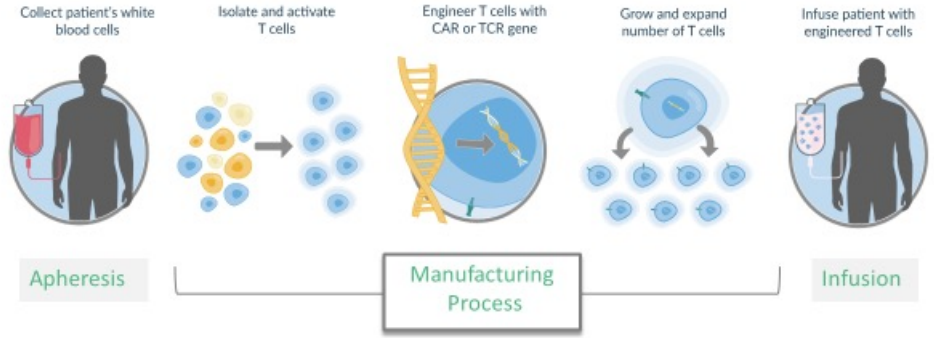
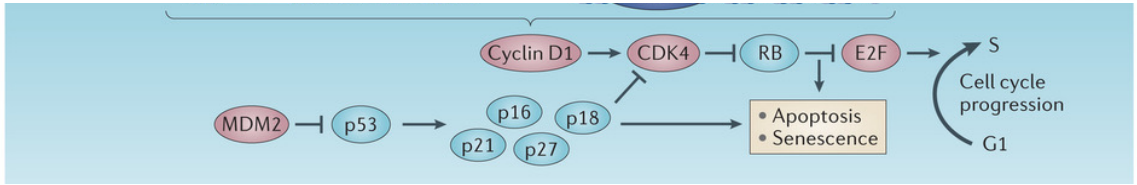
ENGINEERED AUTOLOGOUS CELL THERAPY





Leukemia Lymphoma Society

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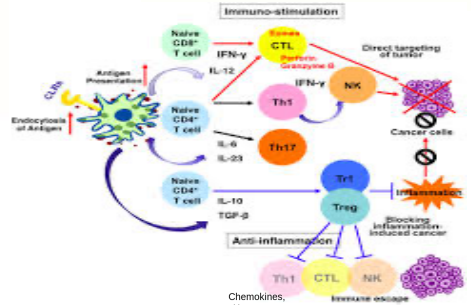

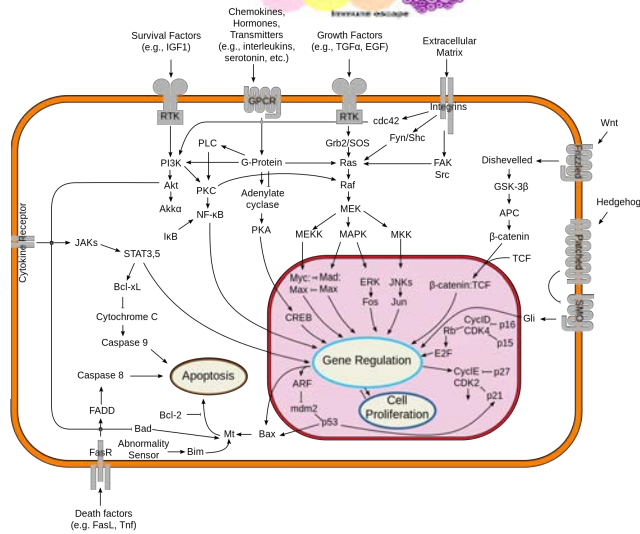

Interfere with specific molecules ("molecular targets") important in the growth, progression, and survival of cancer cells.

Nature Reviews

Targeted Therapies

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Kinase inhibitors

Pi3K inhibitors
Idelalisib, Duvelisib,
Umbralisib*, MEI401*

BTK Inhibitors
Ibrutinib, Acalabrutinib,
Zanubrutinib
Loxo-305*, ARQ531*

Epigenetic Modifiers

Tazemetostat
Belinostat
Romidepsin

Pro-Apoptotic Agents

BCL-2 inhibitors
Venetoclax
BGB-11417*

CDK9/MCL1 inhibitors
Voruciclib*
AZD4573*

Antibody Drug Conjugates

Brentuximab Vedotin
Polatuzumab Vedotin

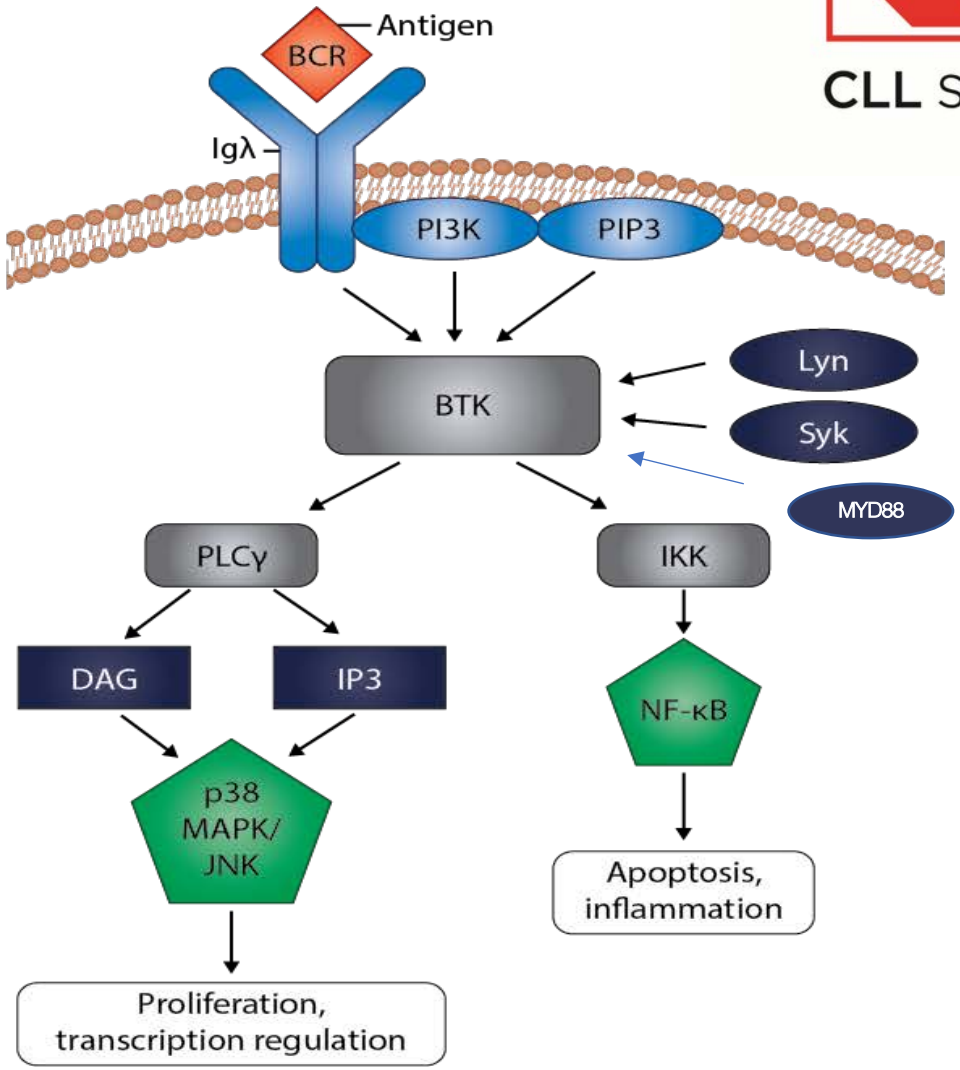
iMIDs

Lenalidomide
Pomalidomide*

*Investigational agents, not FDA approved

Targeting BTK

- Bruton's Tyrosine Kinase key for proliferation survival of several B-cell lymphomas
- Inhibiting BTK leads to improved clinical outcomes in several lymphomas
- However…

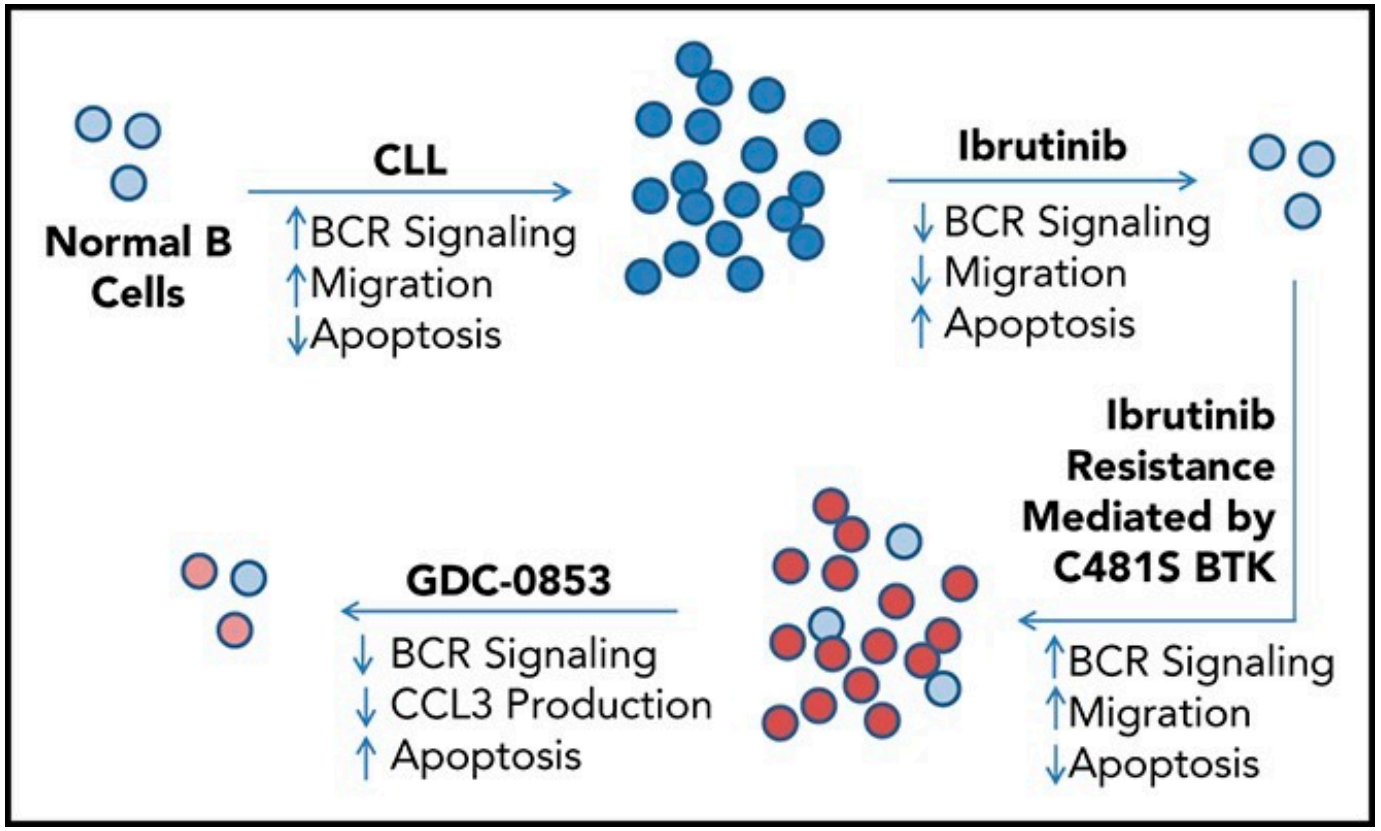


Acquired Resistance to Current BTK Inhibitors

CLL SOCIETY

- Acquired resistance can develop via mutation of C481 of BTK in the binding site of current approved BTK inhibitors

- New BTK inhibitors may not rely upon binding with C481 for activity, and might overcome resistance seen in current BTK inhibitors



LOXO 305 In R/R CLL and NHL

3+3 trial design

- 28-day cycles
- Intra-patient dose escalation allowed
- Additional enrollment permitted at doses deemed safe

Eligibility

- Age ≥18
- ECOG 0-2
- CLL or B-cell NHL
- ≥2 lines of therapy, including BTK intolerant
- All patients must have active disease and in need of treatment

Key endpoints

- Safety/tolerability
- Determine MTD or recommended phase 2 dose
- Pharmacokinetics
- ORR/DOR based on disease criteria (iwCLL, IWWM, Lugano)

CLL, chronic lymphocytic leukemia; ECOG, Eastern Cooperative Group; MTD, maximum tolerated dose; PK, pharmacokinetics; PS, performance score. Mato et al. ASH 2019.

LOXO-305: Response

	CLL	MCL	Other[1]
Treated	16	8	4
Eligible for response evaluation[2]	13	6	2
Overall Response Rate[3]	**10 (77%)**	**3 (50%)**	**1 (50%)**
CR	–	1 (17%)	–
PR	8 (62%)	2 (33%)	–
PR-L	2 (15%)	N/A	–
MR	N/A	N/A	1 (50%)
SD	3 (23%)	–	1 (50%)
PD	–	2 (33%)	–
Not evaluable[4]	–	1 (17%)	–

- Overall Response Rate 66%
- **Responses** at all dose levels and **in BTKi-resistant CLL and MCL**, regardless of C481S status

Mato et al. ASH 2019.

Ongoing Clinical Trials with Novel BTK Inhibitors

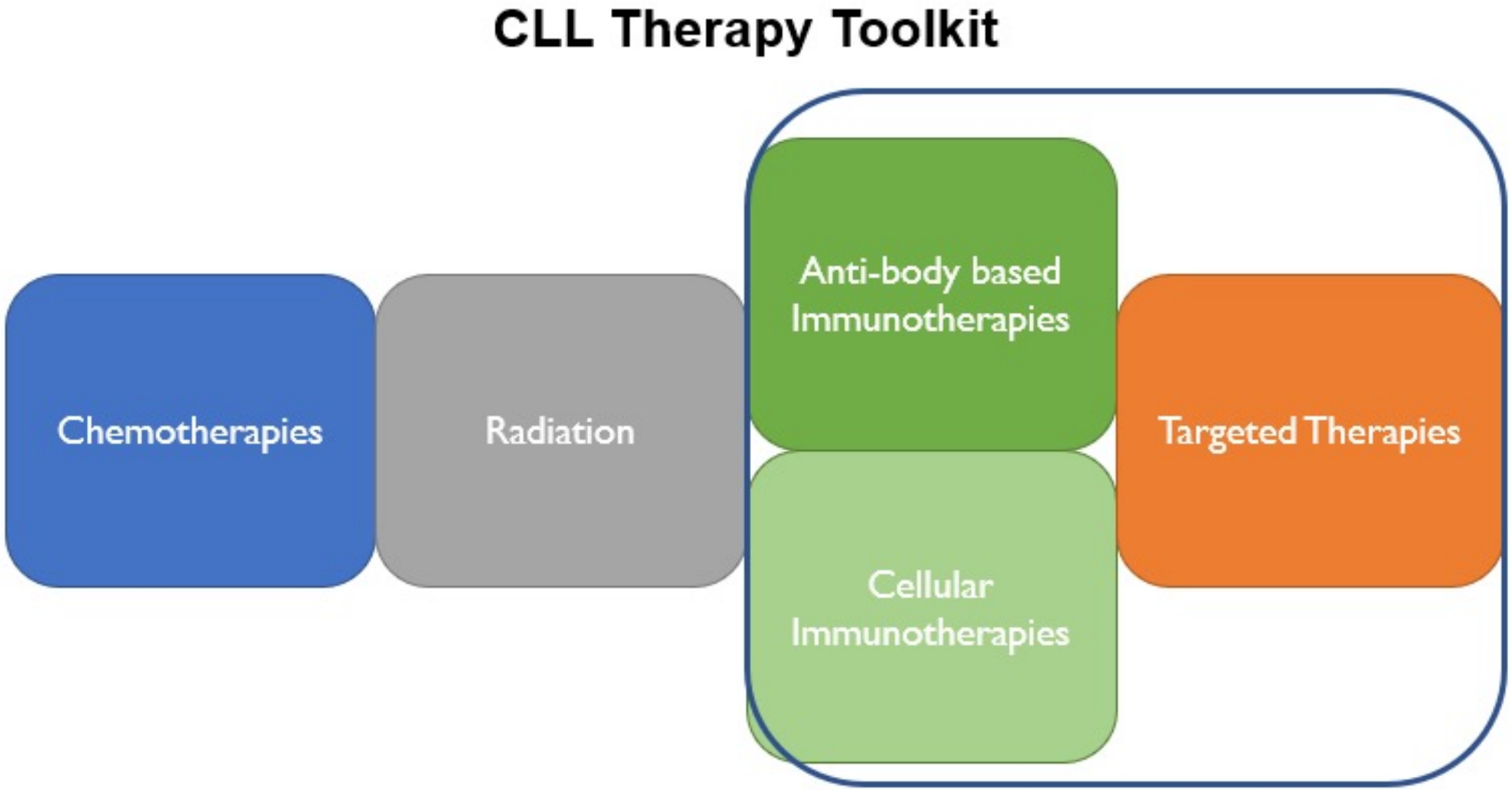
CLL SOCIETY

BTK Inhibitor	Phase	Patient Population
ARQ-531[1]	I/II dose escalation and expansion trial	R/R CLL/SLL, FL, MCL, MZL, or WM who have received ≥ 2 prior systemic tx Expansion cohorts includes R/R CLL after ≥ 2 prior systemic tx including a BTK inhibitor, with or without a C481 mutation
Loxo-305[2]	I/II dose escalation and expansion trial	CLL/SLL or NHL with disease progression after ≥ 2 prior systemic tx or intolerant to standard of care therapies
Orelabrutinib (ICP-022) [3]	I dose escalation	R/R B-cell malignancies (grades1-3a FL, MCL, MZL, and CLL/SLL) after ≥ 1 but ≤ 4 prior lines of systemic tx
Vecabrutinib[4]	I/II dose escalation and expansion trial	R/R CLL/SLL or NHL (DLBCL, FL, MCL, MZL, WM) after ≥ 2 lines of prior standard-of-care therapies including a BTK inhibitor

1. NCT03162536. 2. NCT03740529. 3. NCT04014205. 4. NCT03037645.

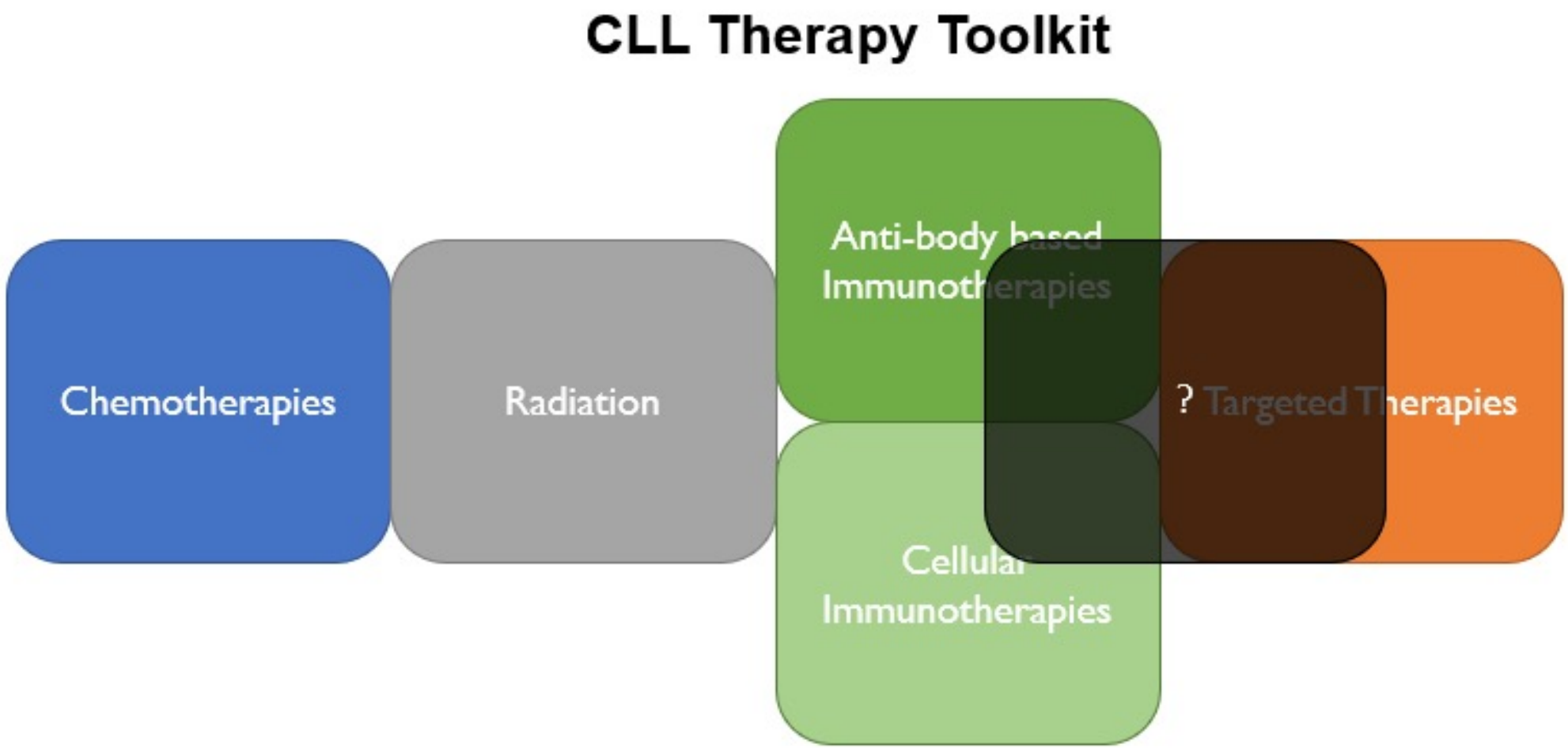
Now…

CLL SOCIETY



Future???

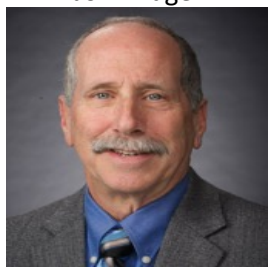
CLL SOCIETY



Thank You


John Pagel


Krish Patel


William Bensinger


Livia Hegerova


Raya Mawad


Daniel Egan

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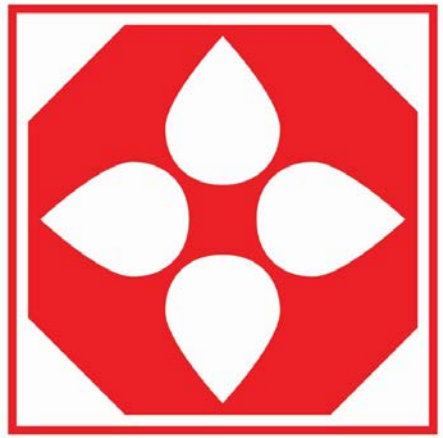
John Pagel, MD, PhD
Krish Patel, MD
William Bensinger, MD
Livia Hegerova, MD
Daniel Egan, MD
Raya Mawad, MD
Vanessa Dunleavy, ARNP
Joey Ferry, ARNP
Sonia Glennie, ARNP
Heather Holdread, ARNP
Joanna Fesler, ARNP
Judson Hall, PA-C
Ami Batchelder, PA-C

Heidi Hohmann, RN
Reagan Kurtz, RN
Hannah Grainger, RN
Summer Clause, RN
Brittany Lutnick, RN
Katelyn Trainor, RN
Carol Dean, RN
Dominque Gandy, RN
Jennifer Kirschler, RN
Stephanie Bardin, PharmD
Kayla Gulley, PharmD
Julia Lewin, PharmD
John Jemison, PharmD

SCI Heme Research

Neil Bailey, MS.c
Tenzin Tsomo, BS
Ngan Trinh, BS
Krystle Pagarigan, BS
Kory Barrow, BS
Jennie Szeto, BS
David Kane, RN
Sunshine Gray, RN
Wezi Longwe, RN

CLL SOCIETY



CLL SOCIETY

Smart Patients Get Smart Care™

CAR-T Cell Therapy in CLL/SLL

Tanya Siddiqi, MD

April 21, 2021

Background

- CLL is generally considered to be incurable and patients eventually relapse or become refractory to available therapies
- Targeted therapies and novel combinations are rapidly changing the treatment landscape, however:
  - CR and undetectable MRD rates are inadequate with monotherapy
  - Patients who progress on novel therapy have poor outcomes
  - Patients with high risk features have poorer outcomes
- Effective therapies are needed for patients with CLL who have failed B-cell receptor inhibitors and/or other novel therapies

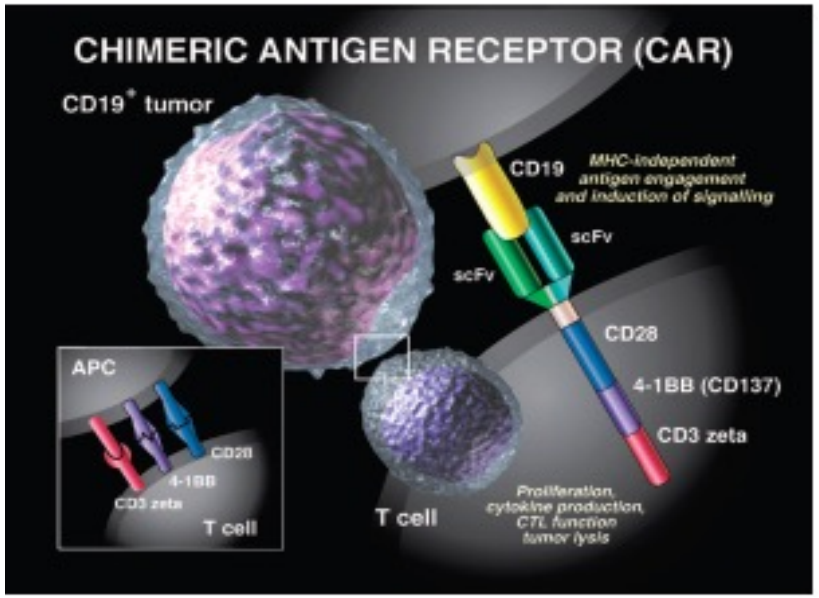
Li XL et al. *Oncol Lett.* 2016;12(5):3051-3054; Landau DA et al. *NatCommun*. 2017;8(1):2185; Byrd JC et al. *Blood*. 2015;125(16):2497-2506; Seymour JF et al. *N Engl J Med*. 2018;378(12):1107-1120; O'Brien SM et al. *Blood.* 2018;131(17):1910-1919; Jain P et al. *Cancer*. 2017;123(12):2268-2273; Mato AR, et al. *Ann Oncol*. 2017;28(5):1050-1056.

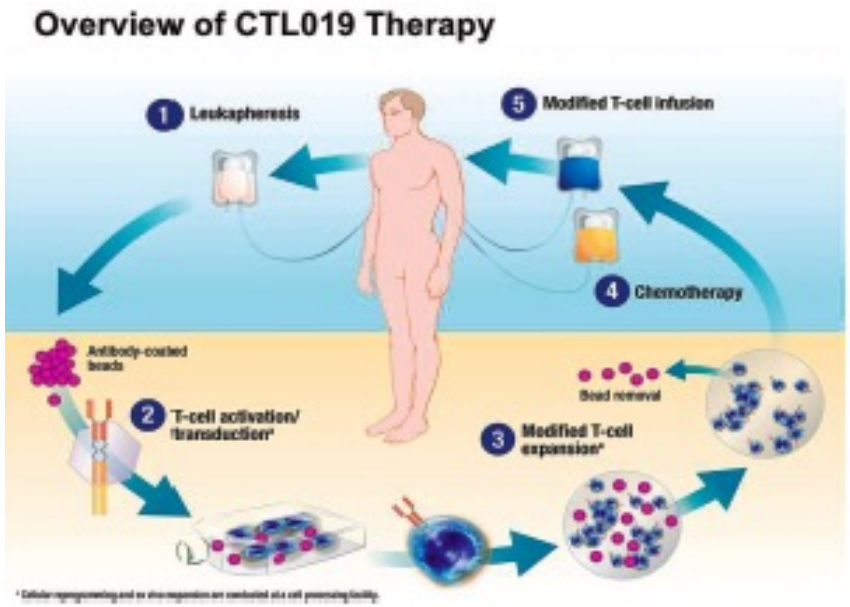
Long-Term Remission of CLL

- Two advanced, chemotherapy-resistant CLL patients with the longest (8+ years) follow-up on any trial of CART19 cells
- Both patients had received five therapies before being treated at the University of Pennsylvania with autologous CART19 cells (tisagenlecleucel) cells in 2010
- Both patients have persistence of CAR-engineered T-cells, and both patients are still in remission as determined by flow cytometry and deep sequencing of IgH rearrangements for over 8 years

Melenhorst JJ, et al. ASGCT Annual Meeting 2019: abs 358

CD19 Specific CAR-T Cells





- N = 14; median prior treatments = 5 [1-11]; median cell dose = 1.6x10^8 cells
- 4 CR (29%), 4 (29%) PR, ORR 57%
- CAR-T cells detectable 4 years later in some
- Expected toxicities: B cell aplasia, delayed tumor lysis syndrome (TLS) and cytokine release syndrome (CRS)
- MRD undetectable in CR patients

Porter D, et al. Blood 2013; ASH abs. 4162, Porter D, et al. Blood 2013; ASH abs. 873
Porter D, et al. Sci Transl Med 2015; 7(303):303ra139.doi: 10.1126/scitranslmed.aac5415

CAR-T Cells After Failure of Ibrutinib

CLL SOCIETY

- Phase 1/2 open label trial of JCAR014
- R/R CLL pts with ibrutinib exposure [19 PD, 3 intolerant; 2 without PD]; 6 also venetoclax refractory
- n = 24 (96% [23/24] with high risk cytogenetics); med age = 61 years [40-73 years]; med prior lines of treatment = 5 [3-9]; 3 dose levels evaluated
- Ibrutinib discontinued in all prior to lymphodepleting chemotherapy (majority got fludarabine and cyclophosphamide)
- 83% CRS (20/24) and 33% neurotoxicity (8/24); 1 gr 5 CRS/NT
- At 1 month, ORR = 71% (17/24); med f/u = 6.6 month; 17 patients restaged; 88% with marrow disease at baseline were MRD neg and did not progress

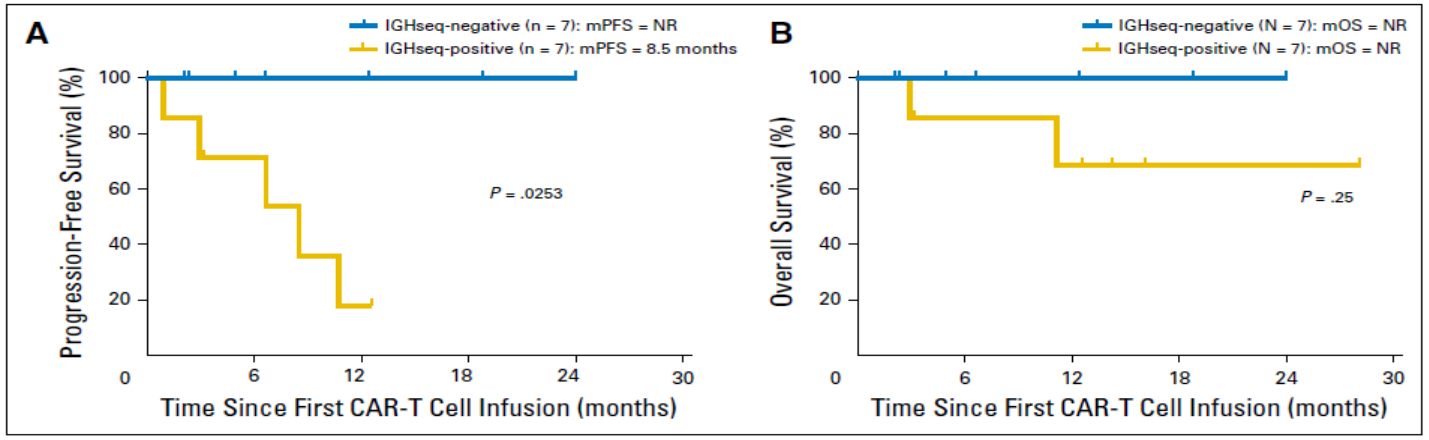


Fig 4. (A) Progression-free survival and (B) overall survival in patients who cleared disease from bone marrow 4 weeks after CAR-T cell infusion by flow cytometry and had no detectable malignant IGH copies (IGHseq-negative) compared with those who had detectable malignant IGH copies (IGHseq-positive). mOS, median OS; mPFS, median PFS; NR, not reached.

Turtle C, et al. JCO 2017; 35: 3010-20

CAR-T Cells with Concurrent Ibrutinib After Ibrutinib Failure

- Pilot cohort of JCAR014 with concurrent ibrutinib on a Phase 1/2 study
- R/R CLL pts; med age 65 [56-69] years; med prior treatments = 5 [4-7]
- N = 19; 89% (17/19) with high risk cytogenetics
- Ibrutinib began >/= 2 weeks prior to leukapheresis and continued for >/= 3 months after JCAR014
- 2×10^6 CD19 CAR-T cells/kg
- Fludarabine and cyclophosphamide lymphodepletion
- Ibrutinib effects:
  - Mobilize lymphocytes
  - Improve CAR-T cell function
  - Decrease CRS
  - Prevent tumor flare

Gauthier J, et al. BBMT 2018; 25: S9-10
Gauthier J, et al. *Blood* (2020) 135 (19): 1650–1660

CAR-T Cells with Ibrutinib

- Well tolerated; 13 patients (68%) received ibrutinib as planned without dose reduction
- One death from probably cardiac arrhythmia in the setting of grade 2 CRS not requiring vasopressors
- Four-week ORR was 83% (15/18); 61% achieved MRD-negative marrow response by IGH sequencing (13/18)
- In this subset, the 1-year OS and PFS probabilities were 86% and 59%, respectively
- JCAR014 plus ibrutinib led to lower CRS severity and lower serum concentrations of CRS-associated cytokines despite equivalent in vivo CAR-T cell expansion

Gauthier J, et al. BBMT 2018; 25: S9-10
Gauthier J, et al. *Blood* (2020) 135 (19): 1650–1660

CAR-T Cells with or without Ibrutinib

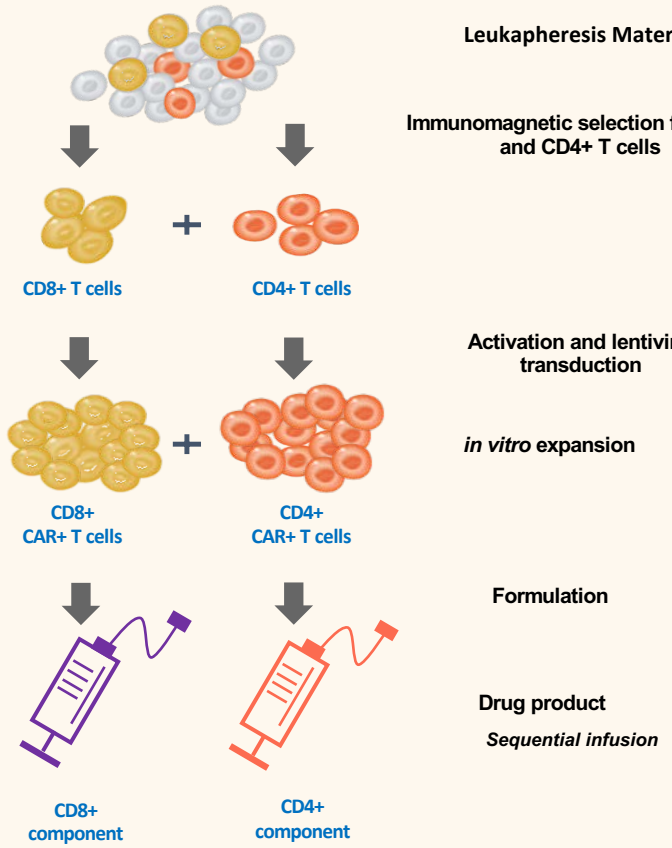
- Compared with CLL patients treated with CAR-T cells without ibrutinib, CAR-T cells with concurrent ibrutinib were associated with lower CRS severity and lower serum concentrations of CRS-associated cytokines, despite equivalent in-vivo CAR-T cell expansion

- One-year PFS probabilities in all evaluable patients were 38% and 50% after CD19 CAR-T cell therapy, with and without concurrent ibrutinib, respectively (P = .91)

Turtle C, et al. JCO 2017; 35: 3010-20. Gauthier J, et al. BBMT 2018; 25: S9-10.
Gauthier J, et al. *Blood* (2020) 135 (19): 1650–1660.

Lisocabtagene Maraleucel (Liso-cel; JCAR017)

CD19-Directed, Defined Composition, 4-1BB CAR-T Cell Product



CD8+ and CD4+ CAR+ T cell components are administered separately at equal target doses of CD8+ and CD4+ CAR+ T cells

The defined composition of liso-cel results in:

- Consistent administered CD8+ and CD4+CAR+ T cell dose
- Low variability in the CD8+/CD4+ ratio

Dose and ratio of CD8+ and CD4+ CAR+ T cells may influence the incidence and severity of CRS and neurological events[1–3]

1. Turtle CJ, et al. *Sci Transl Med*. 2016;8(355):355ra116; 2. DeAngelo DJ, et al. *J Immunother Cancer*. 2017;5(Suppl 2):116: Abstract P217 3. Neelapu SS, et al. *N Engl J Med*. 2017;377:2531–2544.

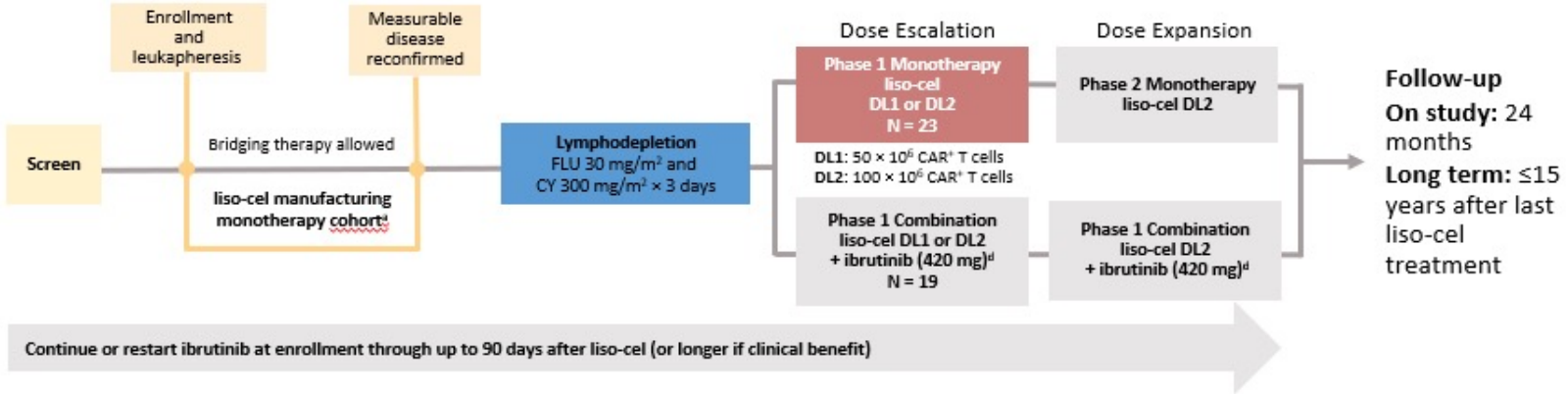
Updated Follow-Up of Patients with Relapsed/Refractory CLL/SLL Treated with Lisocabtagene Maraleucel in the Phase 1 Monotherapy Cohort of TRANSCEND CLL 004, Including High-Risk and Ibrutinib-Treated Patients

Tanya Siddiqi,[1] Jacob D. Soumerai,[2] Kathleen A. Dorritie,[3] Deborah M. Stephens,[4] Peter A. Riedell,[5] Jon Arnason,[6] Thomas J. Kipps,[7] Heidi H. Gillenwater,[8] Lucy Gong,[8] Lin Yang,[8] Ken Ogasawara,[9] William G. Wierda[10]

[1]City of Hope National Medical Center, Duarte, CA, USA; [2]Center for Lymphoma, Massachusetts General Hospital Cancer Center, Boston, MA, USA; [3]UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA; [4]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA; [5]University of Chicago Medical Center, Chicago, IL, USA; [6]Beth Israel Deaconess Medical Center, Boston, MA, USA; [7]Moores Cancer Center, University of California San Diego Health, San Diego, CA, USA; [8]Bristol Myers Squibb, Seattle, WA, USA; [9]Bristol Myers Squibb, Princeton, NJ, USA; [10]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Virtual ASH Annual Meeting 2020: Presentation 546

TRANSCEND CLL 004 Phase 1/2 Study Design of Liso-cel: A CD19-Directed, Defined Composition, CAR-T Cell Product



Key Eligibility for Monotherapy Cohort

- R/R CLL/SLL
- Ineligible for BTKi or prior BTKi failure[b]
- High-risk disease[c]: ≥2 prior therapies failed
- Standard-risk disease: ≥3 prior therapies failed
- ECOG PS of 0—1

Dose Escalation: mTPI-2 Design[2]

28-day dose-limiting toxicity period

Primary objectives

- Safety
- Determine recommended dose

Exploratory objectives

- Antitumor activity (iwCLL 2018)[3]
  - Testing for MRD[e]
- Cellular kinetic profile (qPCR)

[a]Liso-cel conforming product was successfully manufactured for 23 of 24 patients in the monotherapy phase 1 cohort; one patient who received nonconforming product was excluded from the safety-evaluable population (N = 23). [b]Defined as patients whose disease progressed on BTKi. [c]Complex cytogenetic abnormalities, del(17p), *TP53* mutated, or unmutated *IGHV*. [d]Lower dose was used if prior dose reduction was necessary to manage toxicity. [e]MRD was assessed in blood by flow cytometry and/or in bone marrow by next-generation sequencing (both with a sensitivity of ≤10^{-4}). CY, cyclophosphamide; DL, dose level; FLU, fludarabine; iwCLL, International Workshop on CLL; mTPI, modified toxicity probability interval.

ClinicalTrials.gov. NCT03331198; 2. Guo W, et al. Contemp Clin Trials. 2017;58:23–33; 3. Hallek M, et al. Blood. 2018;131:2745–2760.Siddiqi T, et al. Virtual ASH Annual Meeting 2020: Presentation 546

Demographic and Baseline Disease Characteristics

Characteristic	Monotherapy Cohort (N = 23)	BTKi Progression/Venetoclax Failure Subgroup[c] (n = 11)
Median age, y (range)	66 (50–80)	68 (59–76)
Male, n (%)	11 (48)	6 (55)
Median time since diagnosis, mo (range)	87.5 (30–209)	106 (30–209)
Bulky disease ≥5 cm, n (%)[a]	8 (35)	4 (36)
Median SPD, cm^2 (range)	25 (2–197)	41 (2—197)
Median BALL risk score[1] (range)	2 (0–3)	2 (0–3)
Median LDH, U/L (range)	235 (1–1956)	240 (1–1956)
Stage, n (%)		
Rai stage III/IV	15 (65)	7 (64)
Binet stage C	16 (70)	8 (73)
High-risk feature (any), n (%)	19 (83)	10 (91)
Del(17p)	8 (35)	4 (36)
TP53 mutated	14 (61)	8 (73)
Complex karyotype[b]	11 (48)	5 (45)
Median no. of lines of prior therapy (range)	4 (2–11)	5 (4–10)
Ibrutinib progression, n (%)	17 (74)	11 (100)
Ibrutinib intolerant, n (%)	6 (26)	0
Received bridging therapy, n (%)	17 (74)	8 (73)

[a]Defined as ≥1 lesion with longest diameter of >5 cm. [b]At least 3 chromosomal aberrations. [c]Defined as patients whose disease progressed on BTKi and failed venetoclax due to progression, intolerance, or failure to respond after at least 3 months of therapy. BALL, β_2 microglobulin, anemia, LDH, last therapy; SPD, sum of the product of perpendicular diameters.

1. Soumerai JD, et al. *Lancet Haematol*. 2019;6:e366-e374.

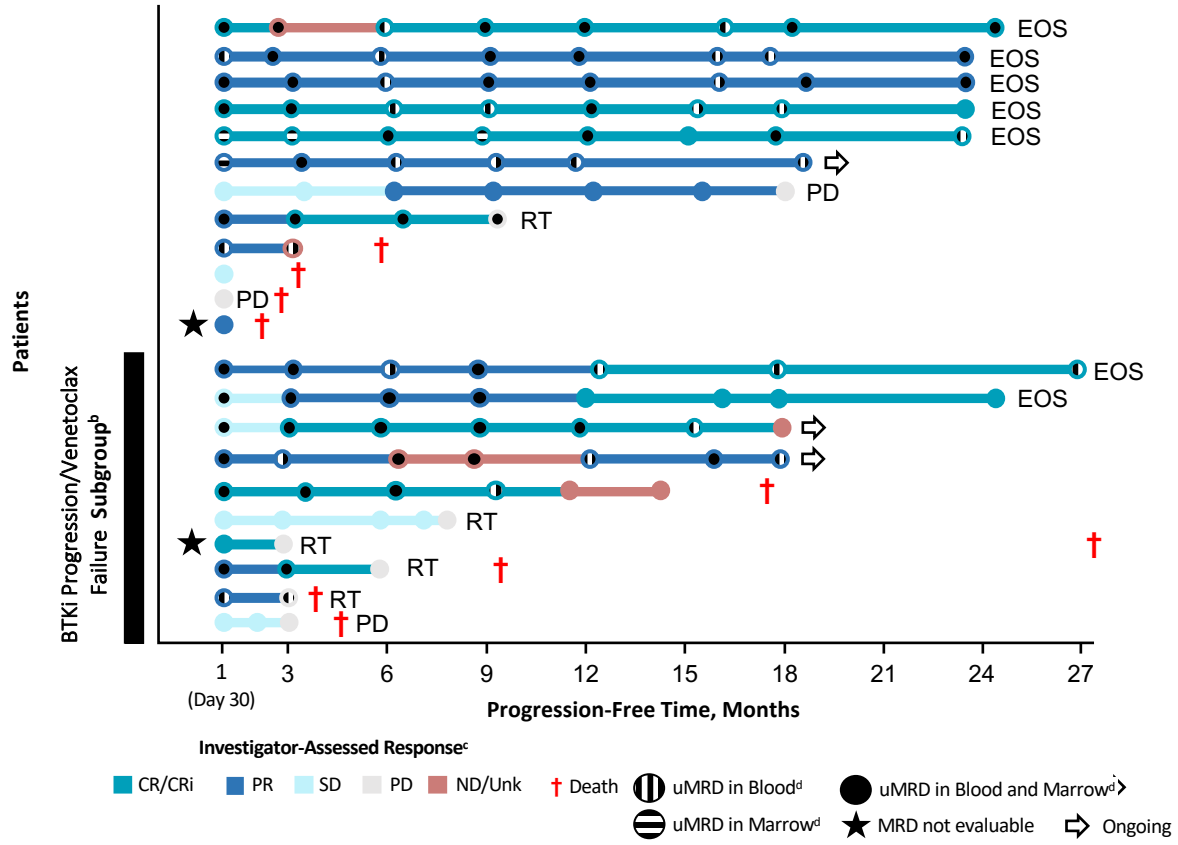
Treatment-Emergent Adverse Events, Cytokine Release Syndrome, and Neurological Events

- Dose-limiting toxicities were reported for two patients at DL2, which resolved
- No late or delayed AEs of concern have emerged with longer follow-up

Parameter	Monotherapy Cohort (N = 23)	BTKi Progression/Venetoclax Failure Subgroup[c] (n = 11)
Common grade 3/4 treatment-emergent AEs (TEAEs), n (%)		
Anemia	17 (74)	7 (64)
Thrombocytopenia	16 (70)	6 (55)
Neutropenia/neutrophil count decrease	16 (70)	8 (73)
Leukopenia	10 (43)	2 (18)
Cytokine release syndrome (CRS)[d]		
All-grade CRS, n (%)	17 (74)	7 (64)
Median time to CRS onset, days (range)	3 (1–10)	1 (1–10)
Median duration of CRS, days (range)	12 (2–50)	15 (5–50)
Grade 3 CRS,[a] n (%)	2 (9)	2 (18)
Neurological events (NEs)		
All-grade NEs, n (%)	9 (39)	5 (46)
Median time to NE onset, days (range)	4 (2–21)	4 (2–21)
Median duration of NE, days (range)	20.5 (6–50)	38 (6–50)
Grade ≥3 NEs,[b] n (%)	5 (22)	3 (27)
Management of CRS and/or NEs, n (%)		
Tocilizumab only	6 (26)	1 (9)
Corticosteroids only	1 (4)	1 (9)
Tocilizumab and corticosteroids	8 (35)	4 (36)

[a]No grade 4 or 5 CRS events were reported. [b]NEs were not mutually exclusive: encephalopathy (n = 3), aphasia (n = 1), confusional state (n = 1), muscular weakness (n = 1), and somnolence (n = 1). [c]Defined as patients whose disease progressed on BTKi and failed venetoclax due to progression, intolerance, or failure to respond after at least 3 months of therapy. [d]Based on Lee criteria (Lee et al, *Blood.* 2014;124:188–195).

Patient Response at 24-Month Median Follow-Up



- ORR was 82% (CR/CRi, 46%; PR, 36%), with 68% (n = 15/22)[a] of patients achieving a rapid response within 30 days
- 27% (n = 6/22) of patients had a deepening of response
- Response was durable; at 12 months, 50% (n = 11/22) were in response and only 2 of these responders progressed beyond 12 months
- Four of the 15 patients with uMRD (blood) response (CR or PR) have progressed, with 3 due to Richter's Transformation (RT)
- The subgroup also demonstrated rapid and durable responses
- Four of 6 progression events in the subgroup were due to RT

[a]One patient had RT before lymphodepleting chemotherapy and was excluded from the efficacy analysis. [b]Defined as patients whose disease progressed on BTKi and failed venetoclax due to progression, intolerance, or failure to respond after at least 3 months of therapy. [c]Evaluated according to iwCLL 2018 criteria. [d]Assessed in blood by flow cytometry and/or in bone marrow by next-generation sequencing (both with a sensitivity of $\leq 10^{-4}$). CRi, CR with incomplete blood count recovery; EOS, end of study; ND, not done; Unk, unknown.

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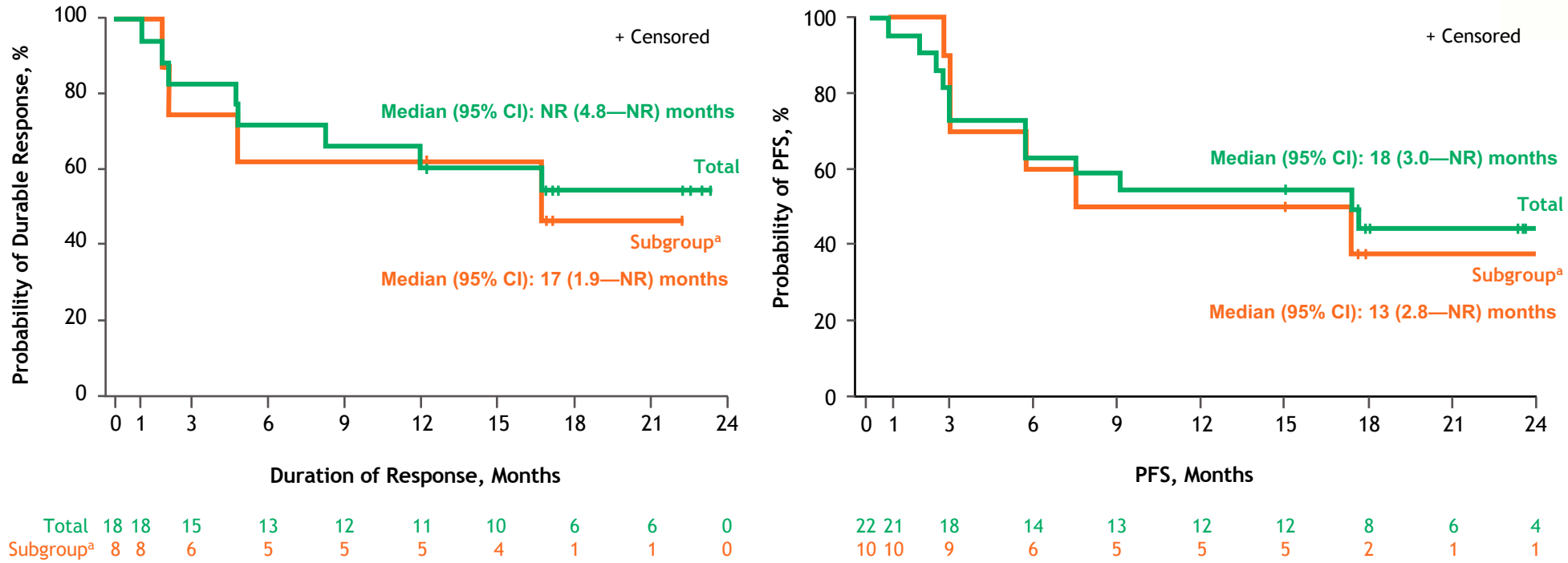
Duration of Response and PFS at 24-Month Median Follow-Up



[a]Defined as patients whose disease progressed on BTKi and failed venetoclax due to progression, intolerance, or failure to respond after at least 3 months of therapy. NR, not reached.

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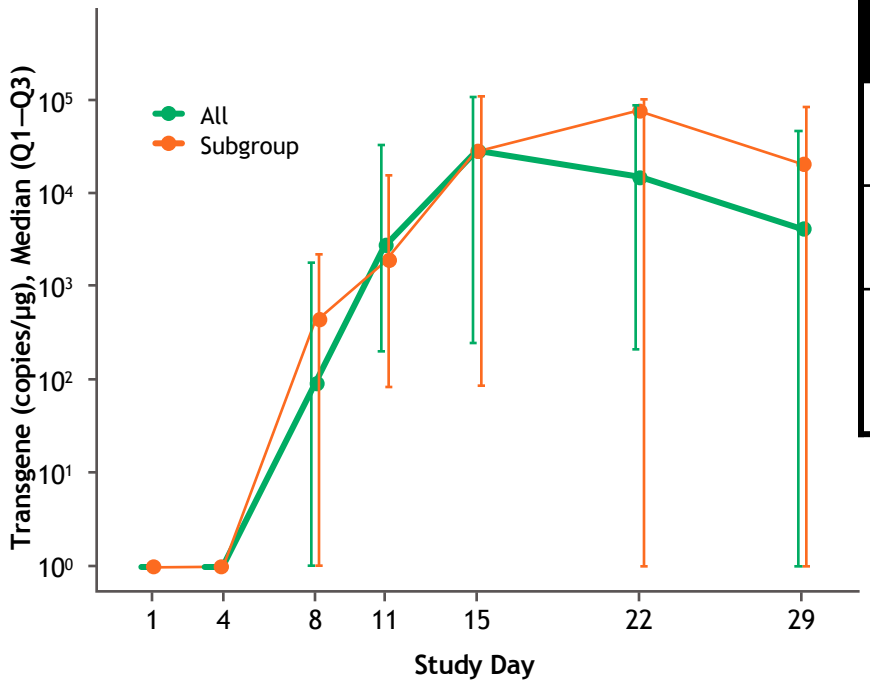
Cellular Kinetics-Expansion and Persistence



$AUC_{0—28d}$, area under the curve for transgene levels from 0 to 28 days postinfusion; C_{max}, maximum transgene levels; Q, quartile; t_{max}, time to C_{max}.

Parameter[a,b]	Monotherapy Cohort (N = 23)	**BTKi Progression/Venetoclax Failure** Subgroup[c] (n = 11)
C_{max} (copies/µg)	67,300 (2510–139,000)	67,300 (982–163,000)
t_{max} (day)	15 (14–21)	20 (15–21)
$AUC_{0—28d}$ (day × copies/µg)	470,000 (17,400–1,740,000)	664,000 (7810–1,960,000)

[a]Median (interquartile range, Q1–Q3). [b]Evaluated using qPCR. [c]Defined as patients whose disease progressed on BTKi and failed venetoclax due to progression, intolerance, or failure to respond after at least 3 months of therapy.

- Long-term persistence
  - 50% of patients (n = 6/12) at 12 months
  - 18% of patients (n = 2/11) at 18 months

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Summary

- Liso-cel treatment elicited rapid, deep, and durable responses in this updated analysis with 24-month median follow-up
- Of the patients who achieved response and have ≥12 months of follow-up, most have maintained their response; all 7 patients who completed the 24-month study maintained their response
- As previously reported, liso-cel treatment resulted in a high rate of uMRD in this heavily pretreated, high-risk population of patients with R/R CLL/SLL, including those whose disease progressed on BTKi and failed to respond to venetoclax
- No late or delayed safety signals were reported with longer follow-up
- The phase 2 monotherapy expansion of the study is currently enrolling at DL2 (100×10^6 CAR-T cells)

Siddiqi T, et al. *Blood*. 2019;134 (suppl 1): ASH annual meeting 2019: Abstract 503
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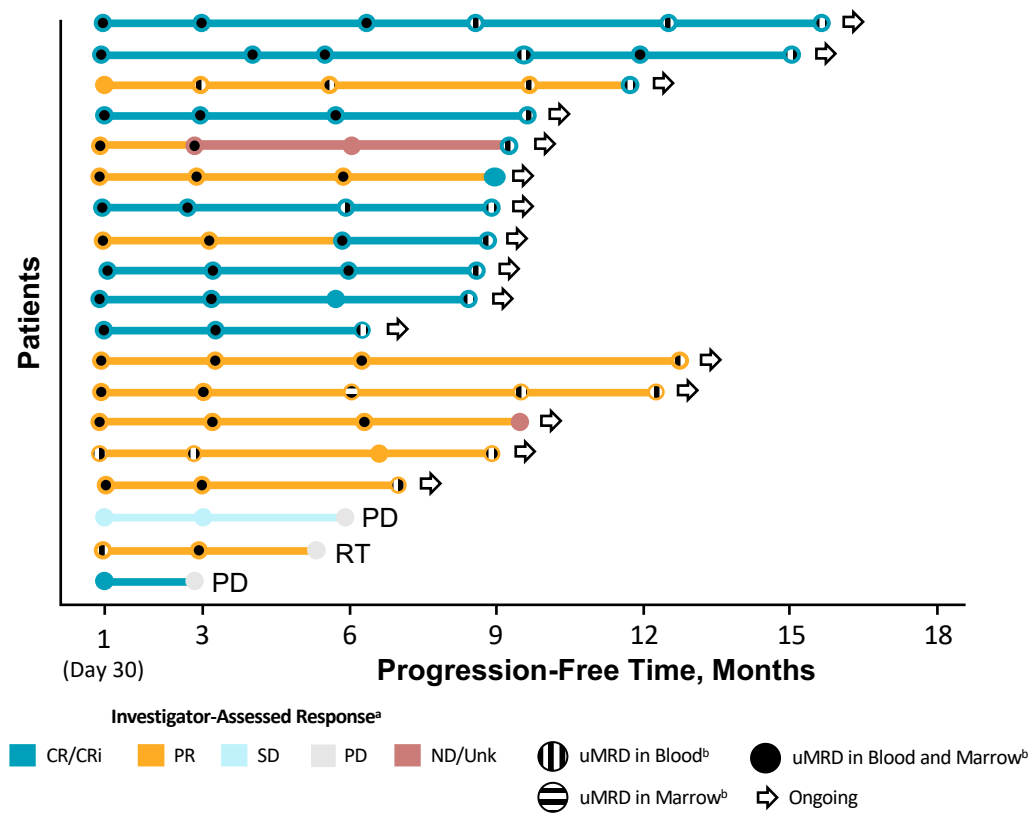
Patient Responses Over Time at the 10-Month Follow-Up



- All responders (n = 18/19) achieved a response by Day 30 after liso-cel
- Among 18 patients with ≥6 months of follow-up, 89% (n = 16/18) maintained or improved response from Day 30
- Of 17 patients who achieved uMRD in blood:
  - All achieved this response by Day 30
  - Only 1 later progressed due to Richter transformation (RT)

[a]Evaluated according to iwCLL 2018 criteria. [b]Assessed in blood by flow cytometry and/or in bone marrow by NGS.
ND, not done; Unk, unknown.

Wierda W, et al. ASH Annual Meeting 2020

Other Ongoing CAR-T Trials for CLL

- ZUMA-8 (axi-cel)
- JCAR014 + ibrutinib (University of Washington, Seattle)
- CTL019 + ibrutinib (University of Pennsylvania)
- Novel CAR-T targets like ROR1 and CD22
- Off-the-shelf allogeneic CAR-T cell trials
- Bispecific antibodies

Thank You

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Thank You for Attending!

Please take a moment to complete our **Ed Forum survey**, your feedback is important to us.

Join us on May 27th for our webinar **Getting Maximum Benefit from Doctor Appointments**. Registration is open on our homepage.

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