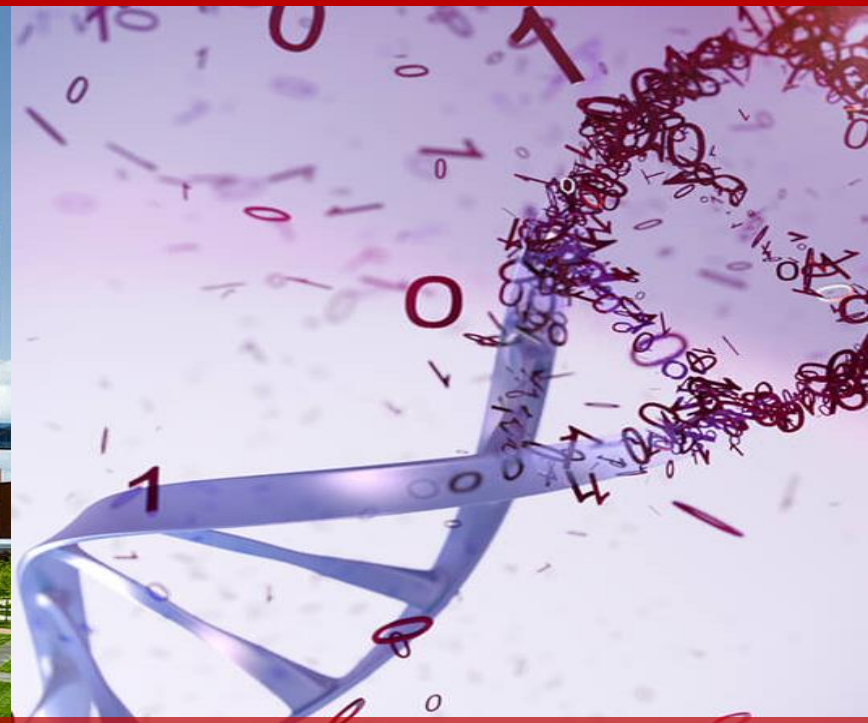

Creating a Cancer-free World. One Person, One Discovery at a Time.

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WEXNER MEDICAL CENTER

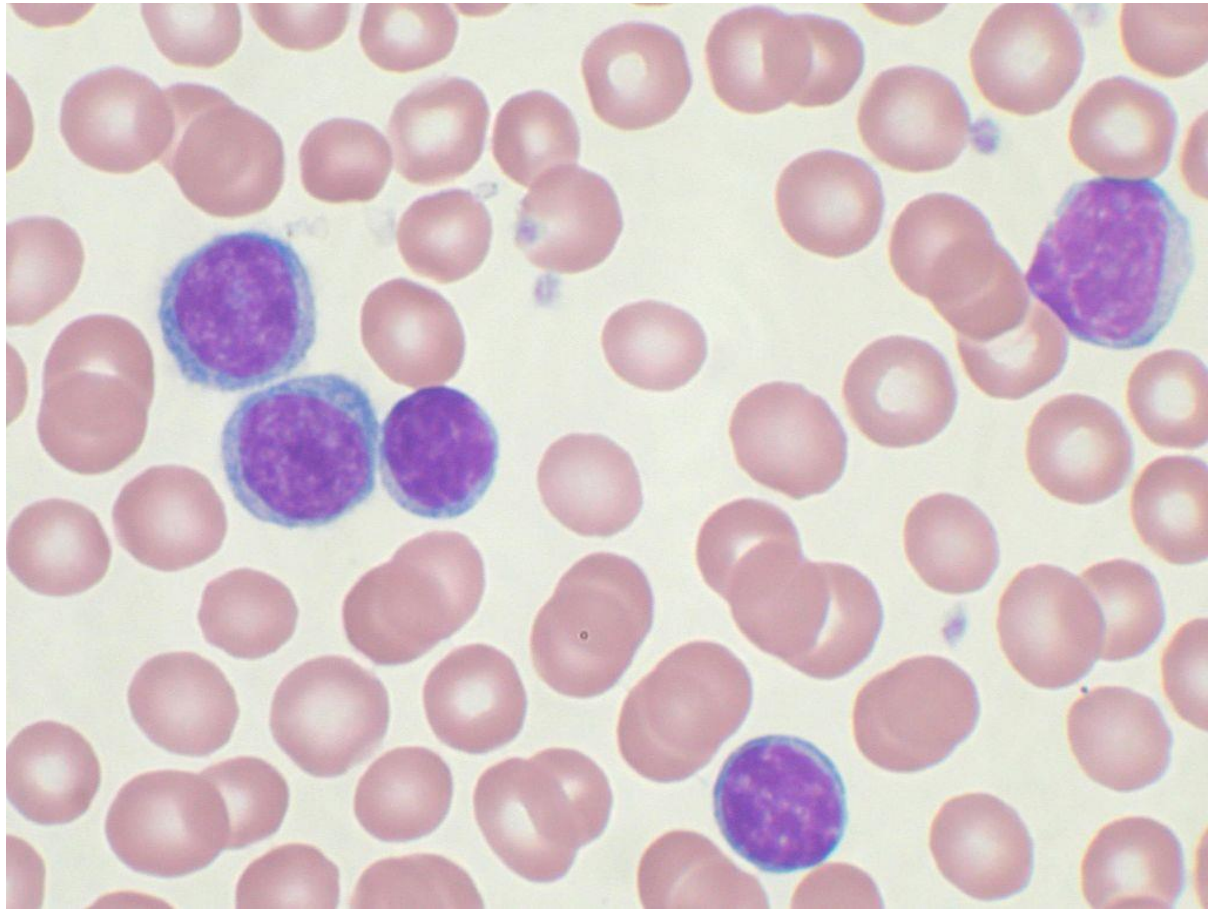
Chronic lymphocytic leuekmia

Jennifer Woyach, MD

Objectives

- Discuss the biology and natural history of CLL/SLL
- Discuss criteria for the initiation of therapy
- Discuss specific therapies for CLL/SLL
- Discuss what may be coming next

CLL



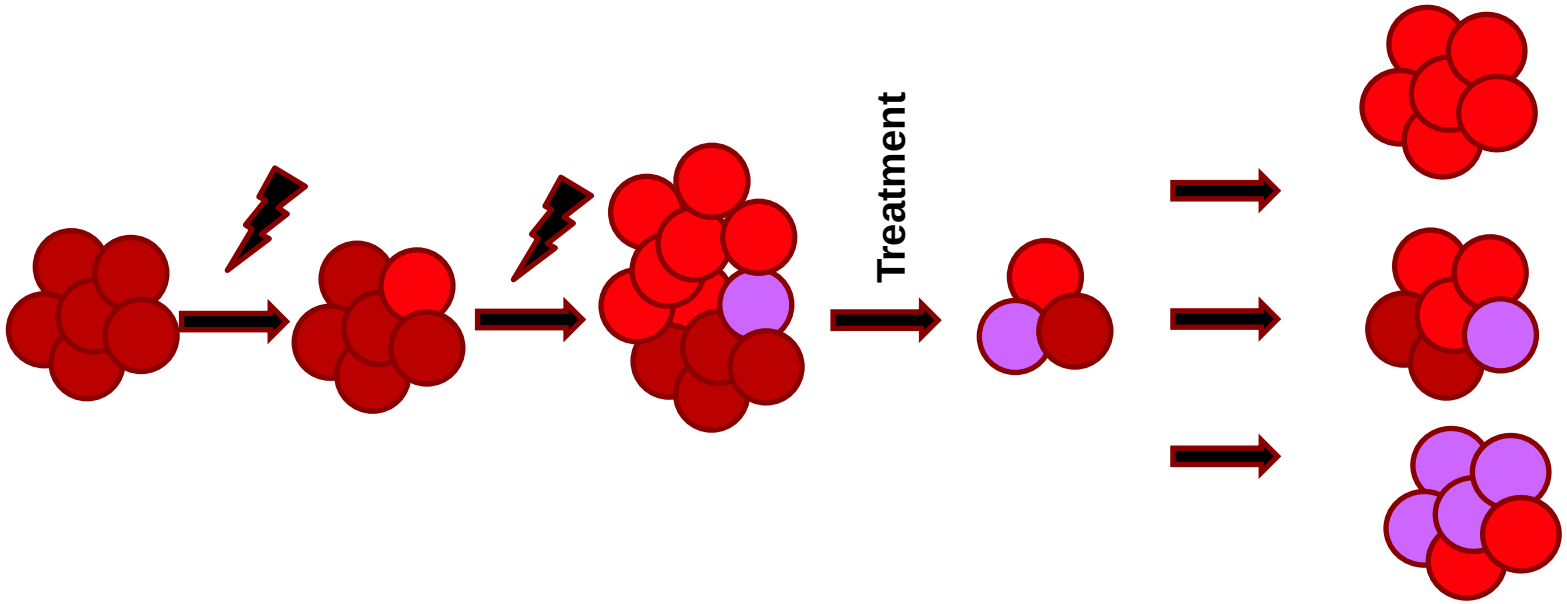
- CLL is often considered a disease of disordered apoptosis—> cells do not die
- Cells accumulate in lymph nodes, blood, spleen, and bone marrow, all of which cause symptoms
- CLL cells also disrupt normal immune cells
- SLL is the same disease, but with less blood involvement

CLL Prognostic Factors

- Heterogeneous disease with survival ranging from months to 25+ years from diagnosis
- Prognostic factors commonly used
  - Stage
  - Lymphocyte doubling time
  - Beta 2 microglobulin
  - IGHV mutational status
  - FISH/Stimulated karyotype
  - TP53 mutation

Can Prognosis Change Over Time?

- IGHV mutational status does not change
- Cytogenetic abnormalities and gene mutations can, a process called clonal evolution
  - TP53 abnormalities seen in 10% at baseline, but ~40% later



Indications for Therapy

Category	Reasons for Treatment
CLL-related symptoms	• Significant B symptoms (eg, night sweats, weight loss, fever without infection, severe fatigue)
Tumor burden	• Progressive lymphadenopathy • Progressive splenomegaly Lymphocyte doubling time <6 months (if ALC >30 x 10^9/L) • Threatened end-organ function (eg, enlarged lymph node obstructing biliary tree)
Bone marrow failure	• Progressive anemia (Hgb <11 mg/dL) • Progressive thrombocytopenia (platelets <100K)
Immune dysfunction	• Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroids or other standard therapy

Why Don’t We Treat at Diagnosis?

- Multiple clinical trials have investigated this question—none yet have shown a survival advantage to early treatment.
- This remains a question of interest, especially with advances in prognosis (so high risk patients can be targeted) and with newer better tolerated therapies.
- **SWOG 1925** is a new early intervention trial of venetoclax/obinutuzumab for high risk patients early vs standard timing of therapy

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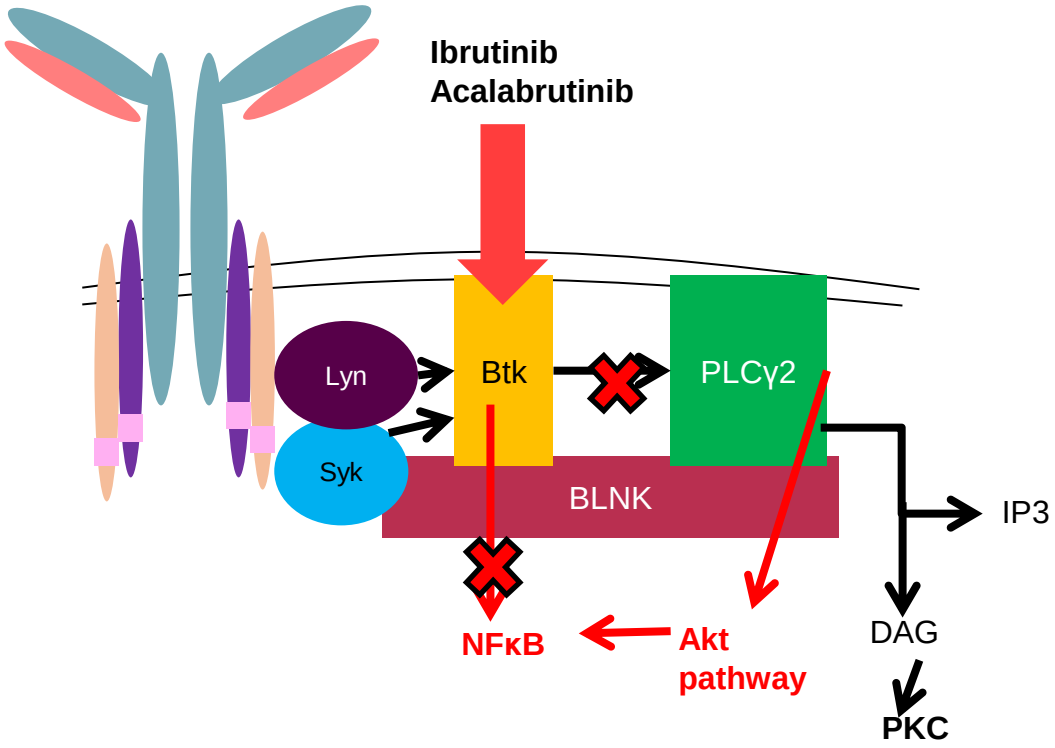
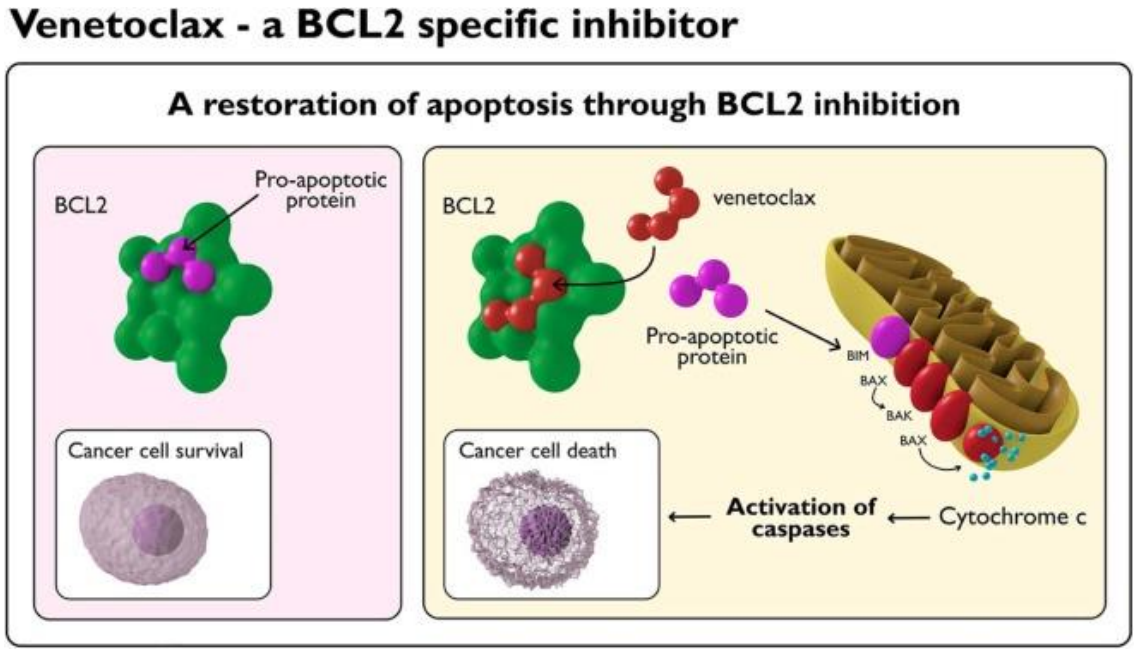
Natural history of CLL has been changed by targeted therapy

- Therapies used in the front line setting
  - Ibrutinib
  - Ibrutinib/rituximab
  - Ibrutinib/obinutuzumab
  - Acalabrutinib
  - Venetoclax/obinutuzumab
  - FCR
  - Other CIT (BR, Chlorambucil/obinutuzumab)

Mechanism of Targeted Therapies

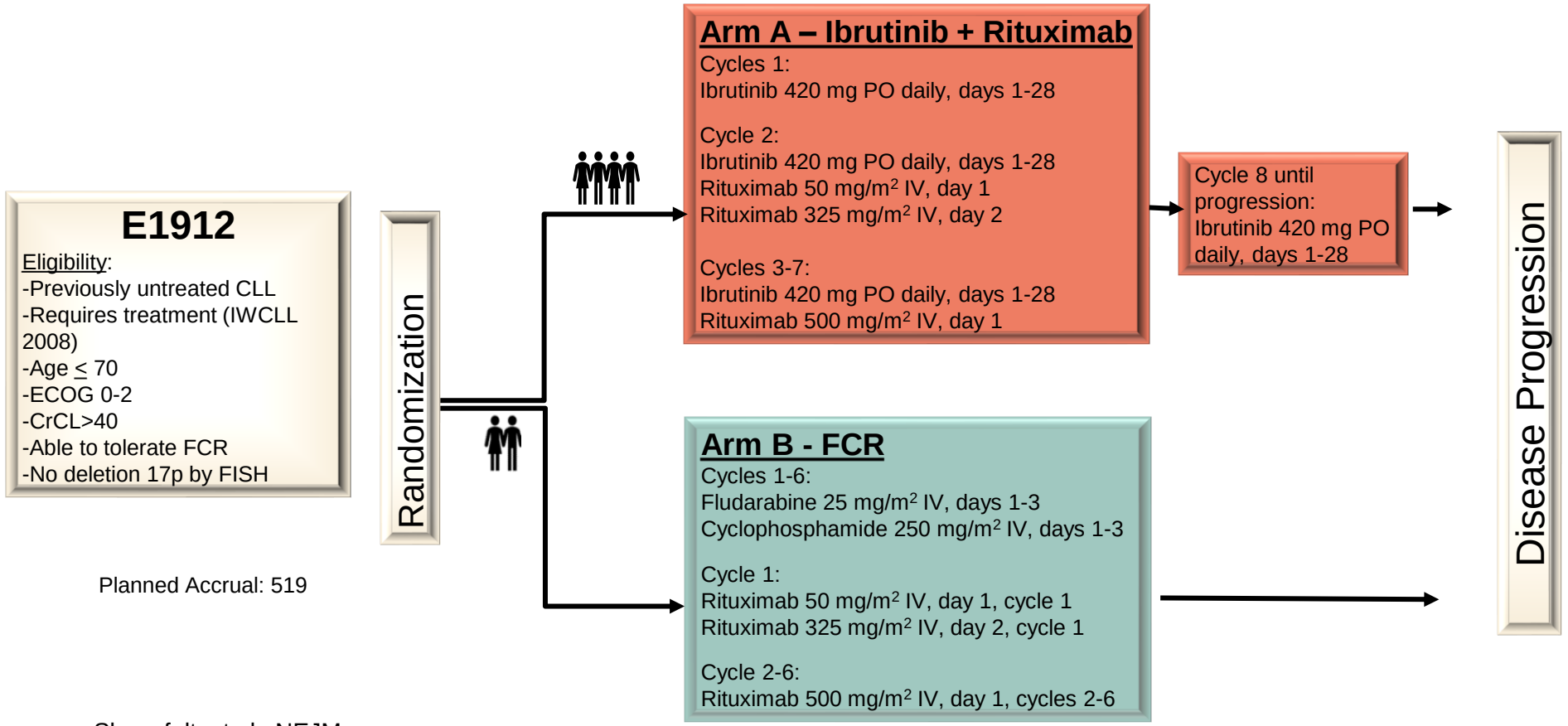




How do we choose therapy? First consideration:

Targeted therapy **VS** Chemo-immunotherapy

ECOG 1912



Planned Accrual: 519

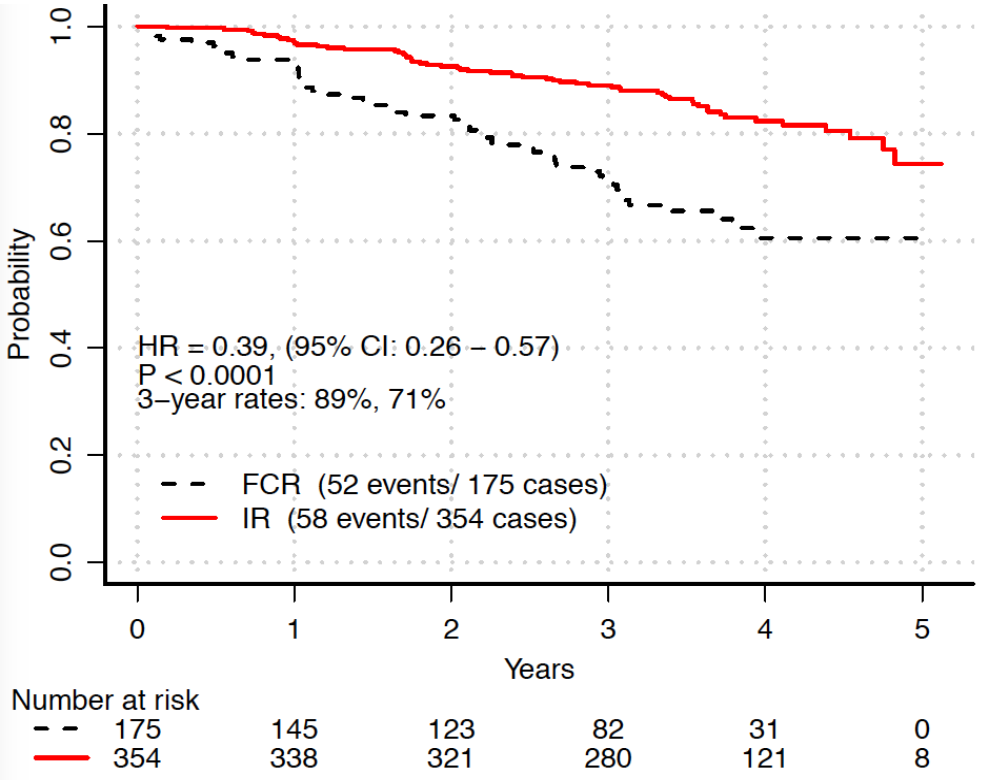
Key Points

- No del(17p)
- Median age 58
- 71% IGHV unmutated

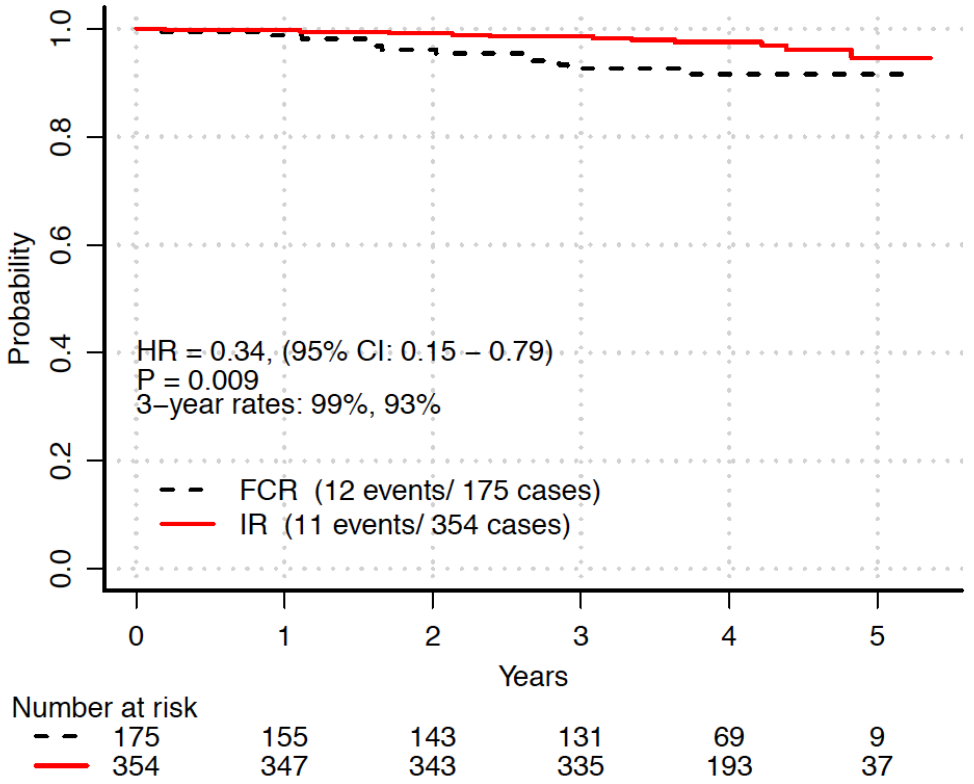
Shanafelt, et al., NEJM 2019
ASH 2019, abstract 33

E1912 Progression Free Survival and Overall Survival

PFS



OS

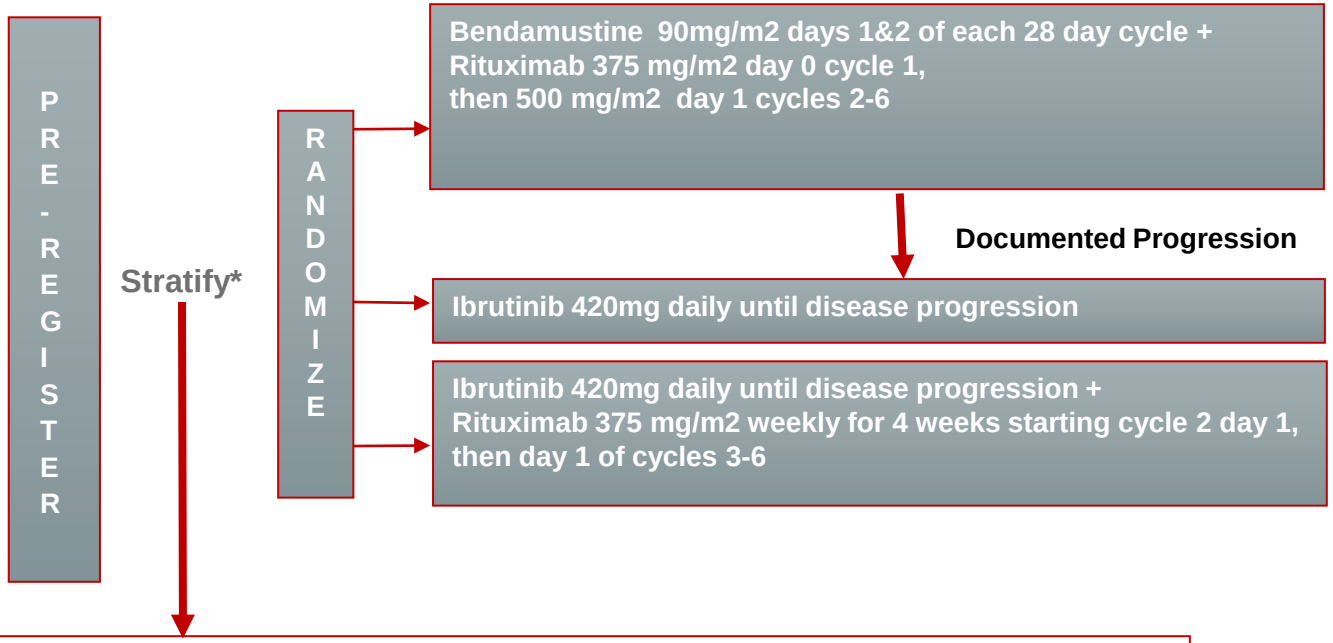


3 yr PFS 89% vs 71%
3 yr OS 99% vs 93%

Shanafelt, et al, ASH 2019, abstract 33

A041202

Untreated patients age ≥ 65 who meet IWCLL criteria for CLL treatment



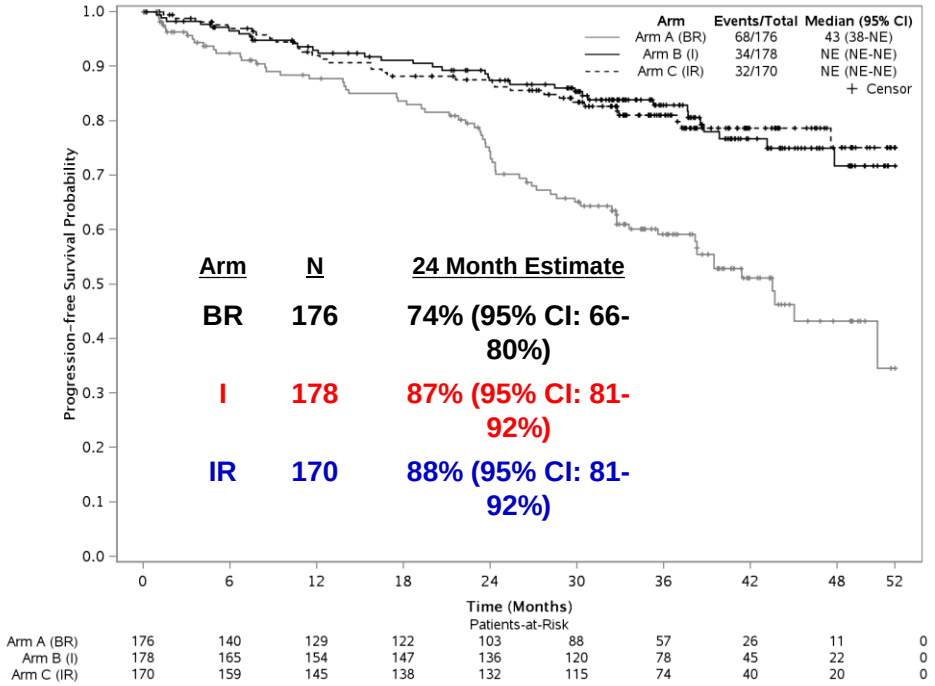
Stratification
- High risk vs intermediate risk Rai Stage
- Presence vs absence of del(11q22.3) or del(17p13.1) on FISH performed locally
- < 20% vs ≥ 20% Zap-70 methylation of CpG 3 performed centrally

Key Points
- Median age 71
- 6% del(17p), 10% TP53 mutated
- 61% IGHV unmutated

Planned accrual: 498

Woyach et al, NEJM 2018

A041202 Progression Free Survival and Overall Survival



Arm	N	24 Month Estimate
BR	176	74% (95% CI: 66-80%)
I	178	87% (95% CI: 81-92%)
IR	170	88% (95% CI: 81-92%)

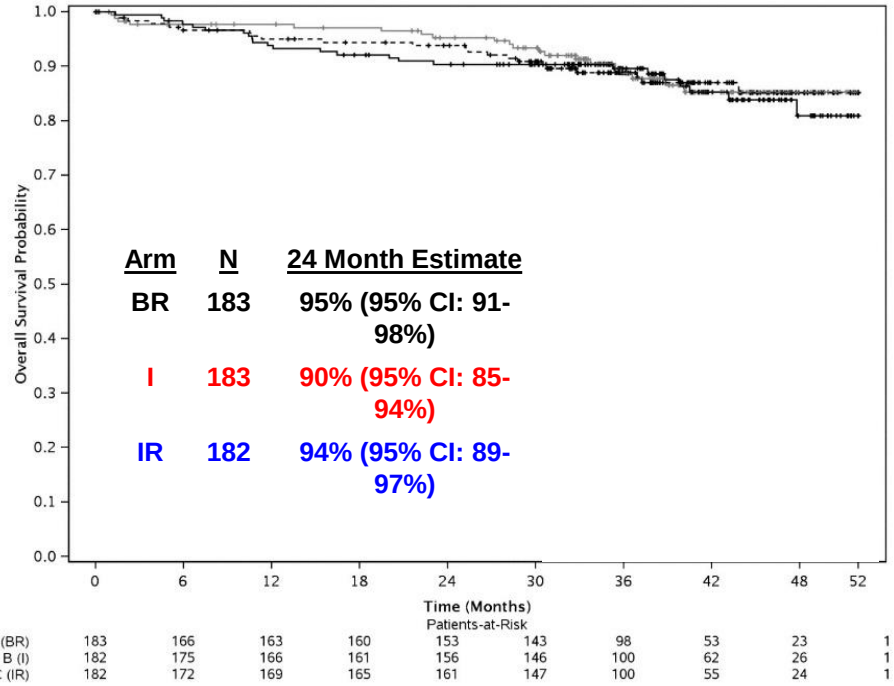
Woyach et al, NEJM 2018

Pairwise Comparisons

I vs BR:
Hazard Ratio 0.39
95% CI: 0.26-0.58
(1-sided P-value <0.001)

IR vs BR:
Hazard Ratio 0.38
95% CI: 0.25-0.59
(1-sided P-value <0.001)

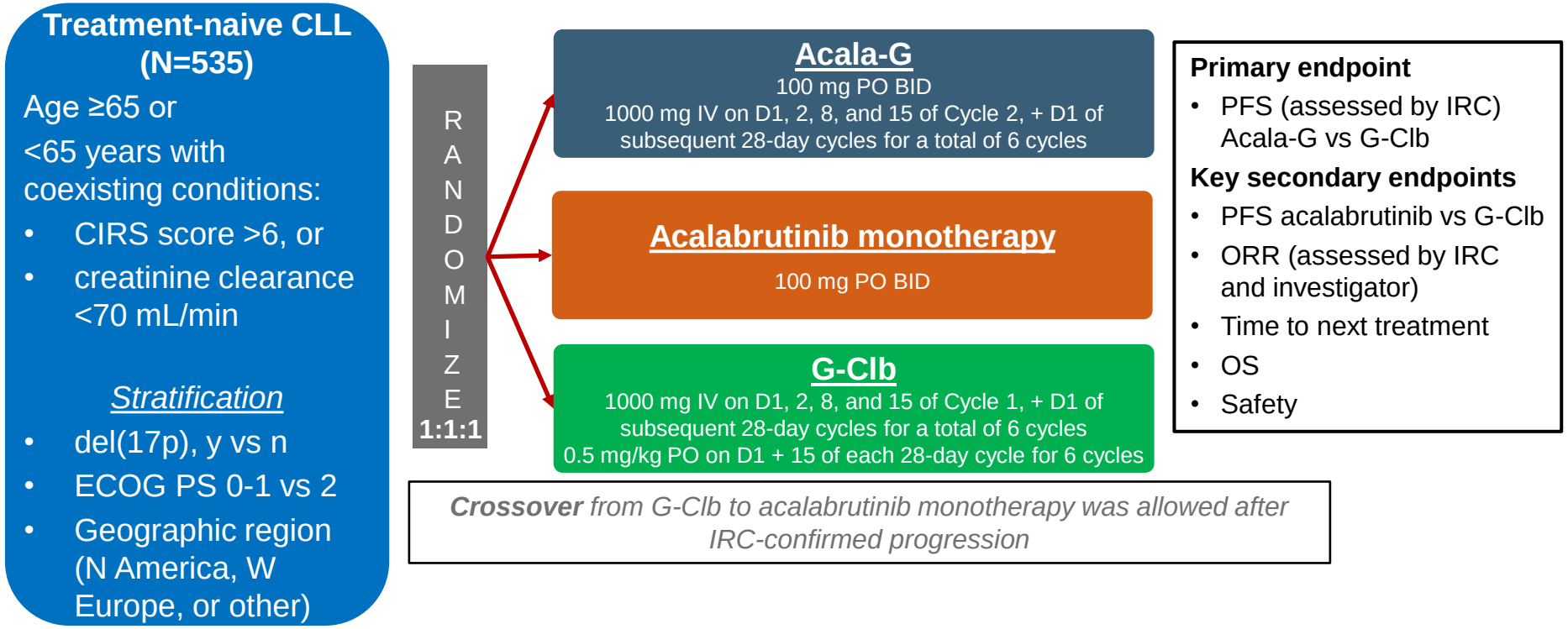
IR vs I:
Hazard Ratio 1.00
95% CI: 0.62-1.62
(1-sided P-value 0.49)



Arm	N	24 Month Estimate
BR	183	95% (95% CI: 91-98%)
I	183	90% (95% CI: 85-94%)
IR	182	94% (95% CI: 89-97%)

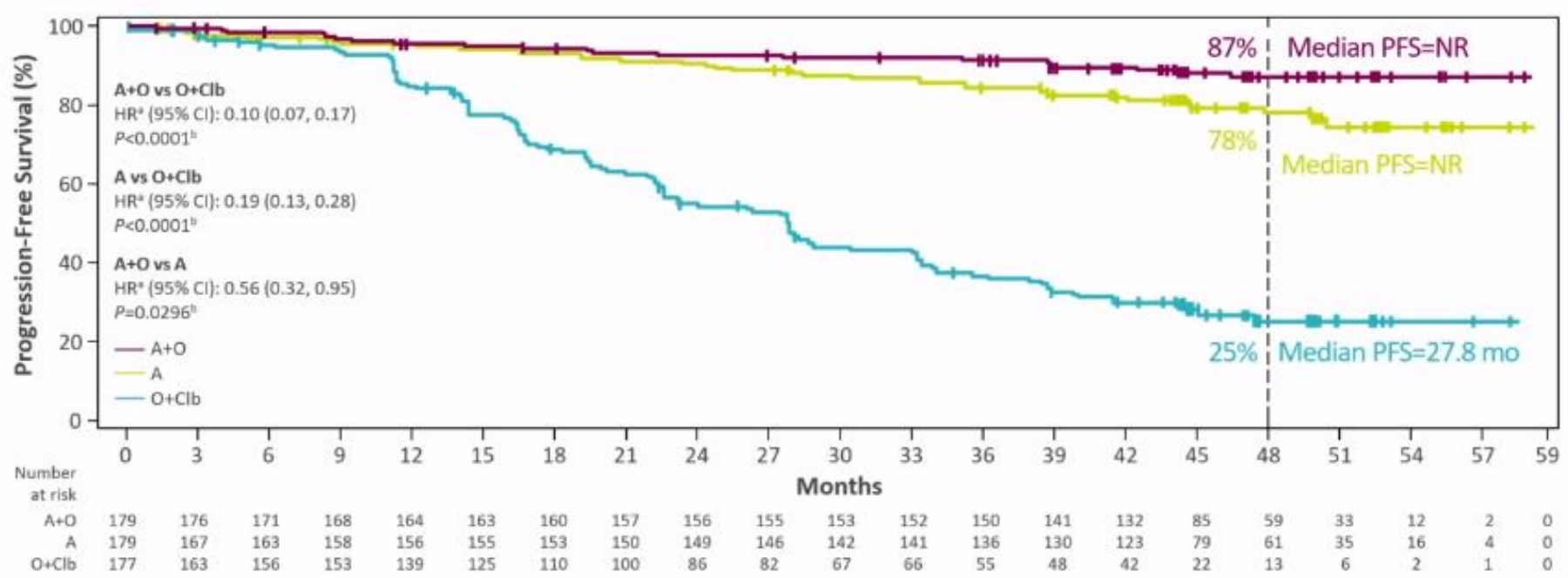
Median Follow-up: 38 months

ELEVATE TN (ACE-CL-007)



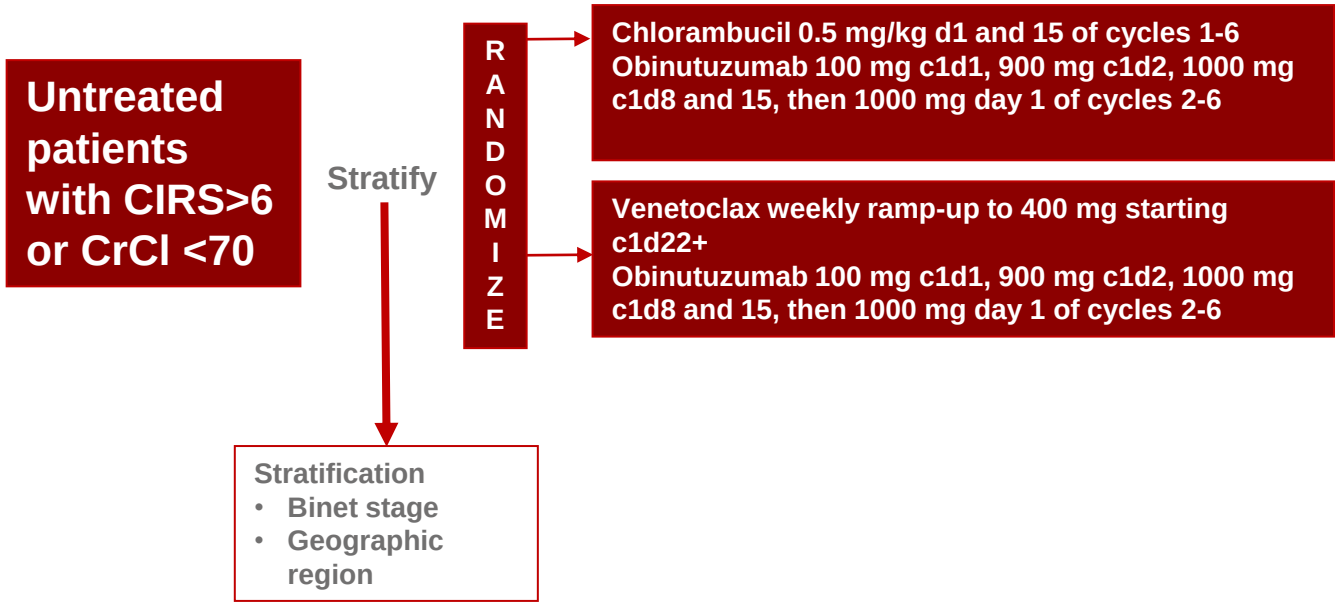
Sharman et al, ASH 2019 Abstract 31

ELEVATE-TN Progression-Free Survival



Sharman et al, EHA 2021

CLL14

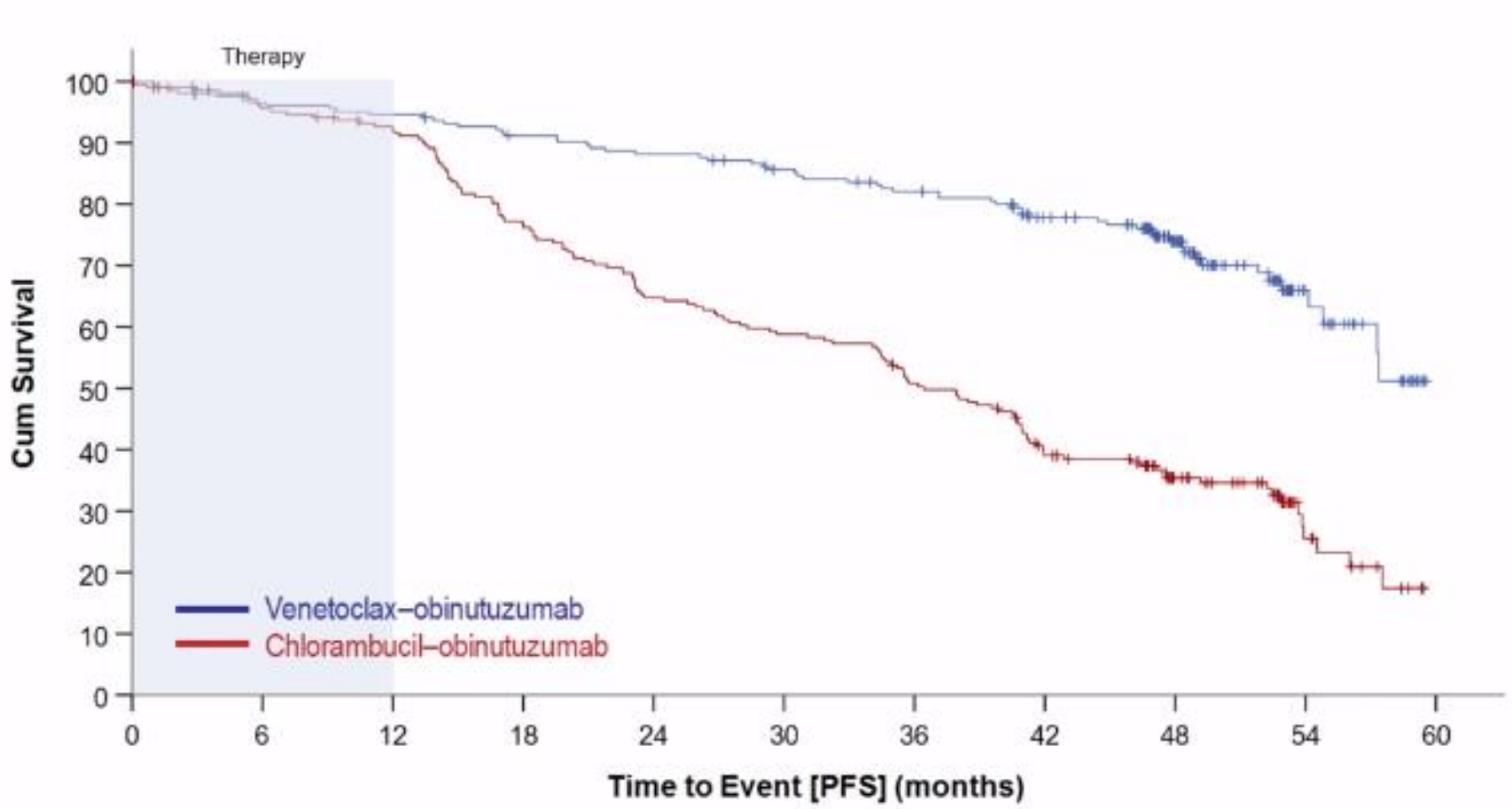


Key Points

- Median age 72
- 7-9% del(17p), 8-11% TP53 mutated
- 60% IGHV unmutated

Fischer et al, NEJM 2019

CLL14 Progression Free and Overall Survival



What do these trials tell us?

- BTKi +/- anti-CD20 antibody is more effective than chemoimmunotherapy in the treatment of CLL
- Venetoclax + obinutuzumab is more effective than chlorambucil + obinutuzumab
- With current follow-ups PFS for VO is similar to what is reported for ibrutinib
- Long term results will be critical to determine which regimen is more effective

Second Consideration: How to Choose Between Targeted Therapies?

Ibrutinib

vs

Acalabrutinib

vs

Venetoclax

Efficacy Considerations

- At 4 years, ibrutinib, acalabrutinib, and venetoclax/obinutuzumab appear relatively equivalent
  - There might be a difference in TP53 altered patients and IGHV unmutated patients
- There is more long-term data with ibrutinib than either venetoclax or acalabrutinib
- Acalabrutinib and Ibrutinib are equally effective

Safety Considerations

- Ibrutinib toxicities: Atrial fibrillation (10-15%, more with older patients), Hypertension (7-30% significant), Bleeding (G3+ <5%), Ventricular arrhythmias (<1%, risk factors unclear)
  - There is much more long term data with ibrutinib
- Acalabrutinib toxicities: Atrial fibrillation (5-10%), Bleeding (significant <5%)
- Venetoclax toxicities: Neutropenia (significant 50%), Febrile neutropenia (5%), Diarrhea (significant <5%)

Intangibles

- Fixed duration venetoclax/obin vs indefinite BTKi
- More intensive run-in venetoclax/obin vs BTKi
- Once daily ibrutinib vs twice daily acalabrutinib
- Cost

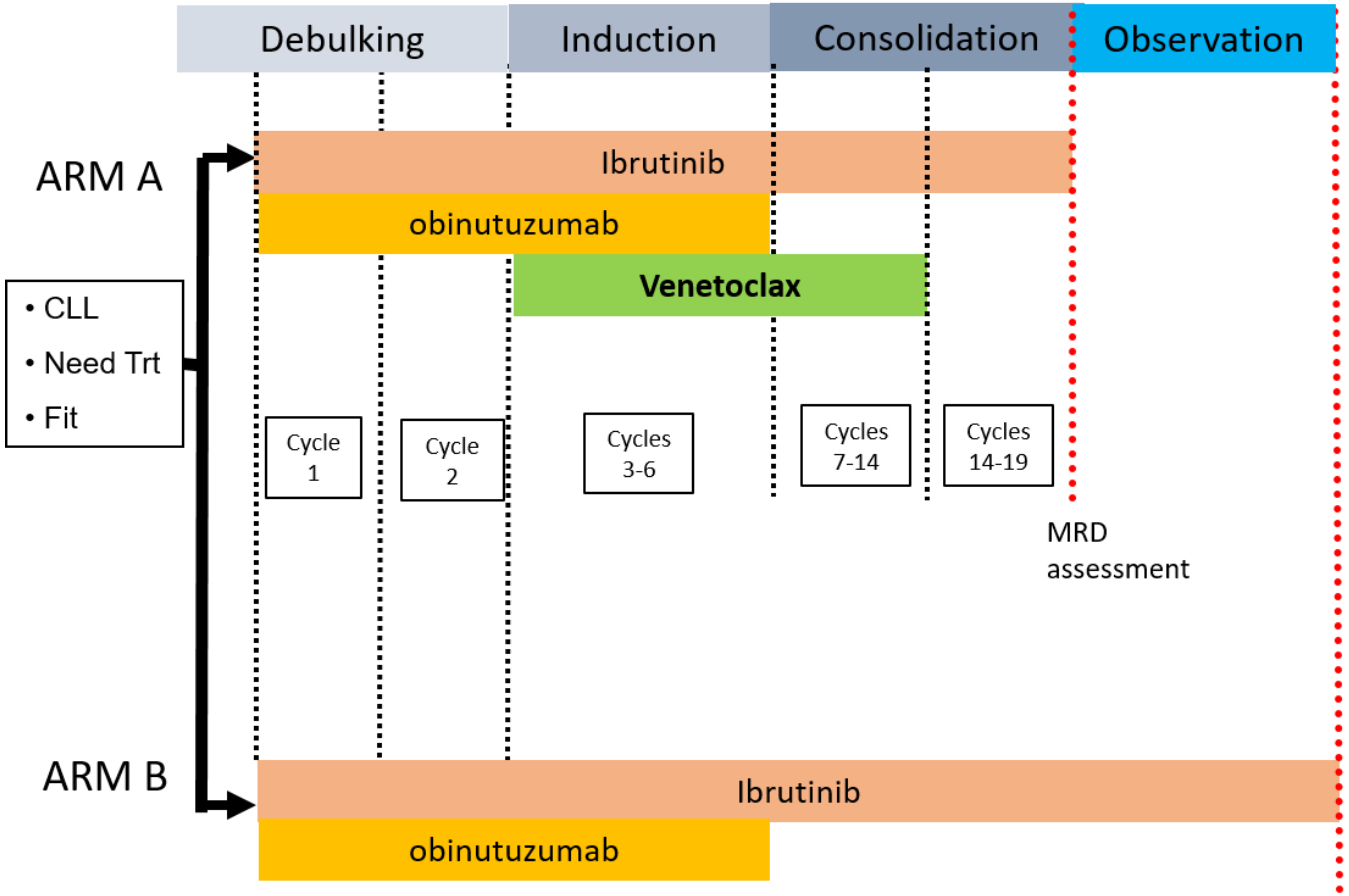
Conclusion: Choice of BTKi vs Venetoclax/obin is patient-specific and involves discussion of data and considerations of pros/cons with each therapy

What is the future of CLL frontline therapy?

- Combination vs single targeted therapy to allow BTKi discontinuation
  - Excellent data from single arm studies of IVO, IV, AVO

- Combinations of CIT and novel therapies: I-FCG, others
- New therapies or strategies

NCTN Study: EA9161



- Age <70
- No del(17p)
- Primary Endpoint: PFS

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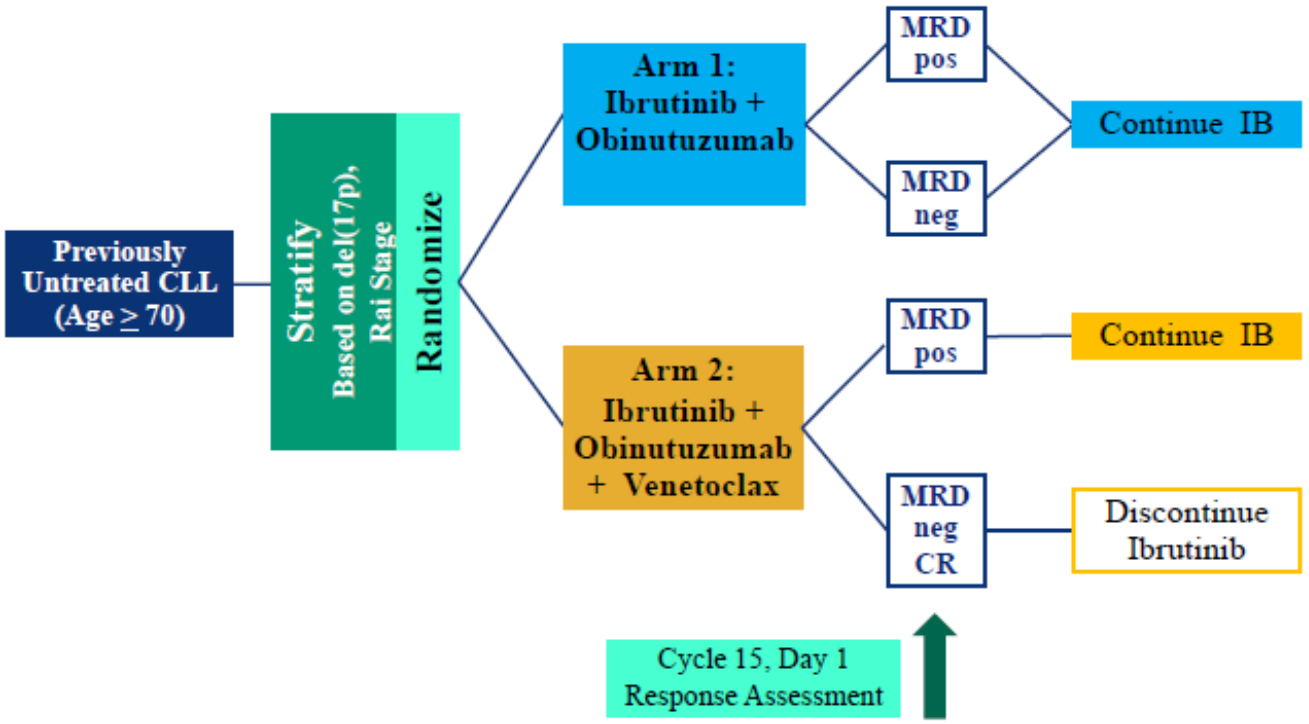
NCTN Study: A041702



Arm 1

Ibrutinib 420 mg PO daily days 1-28 for 15 cycles

Obinutuzumab 100 mg IV 100 mg on C1D1, 900 mg on C1D2, 1000 mg on Cycle1D8 & C1D15, C2-6D1

Arm 2

Ibrutinib 420 mg PO daily days 1-28 for 15 cycles

Obinutuzumab 100 mg IV 100 mg on C1D1, 900 mg on C1D2, 1000 mg on C1D8 & C1D15, C2-6D1

Venetoclax 20 mg daily PO beginning C3D1, dose escalated weekly to a final dose of 400 mg on C4D1, then 400 mg daily PO C4D1-C14D28

All drugs for CLL treatment are provided by the study at no cost to the patients

- Age ≥ 70
- Primary Endpoint: PFS
- Planned Enrollment 494

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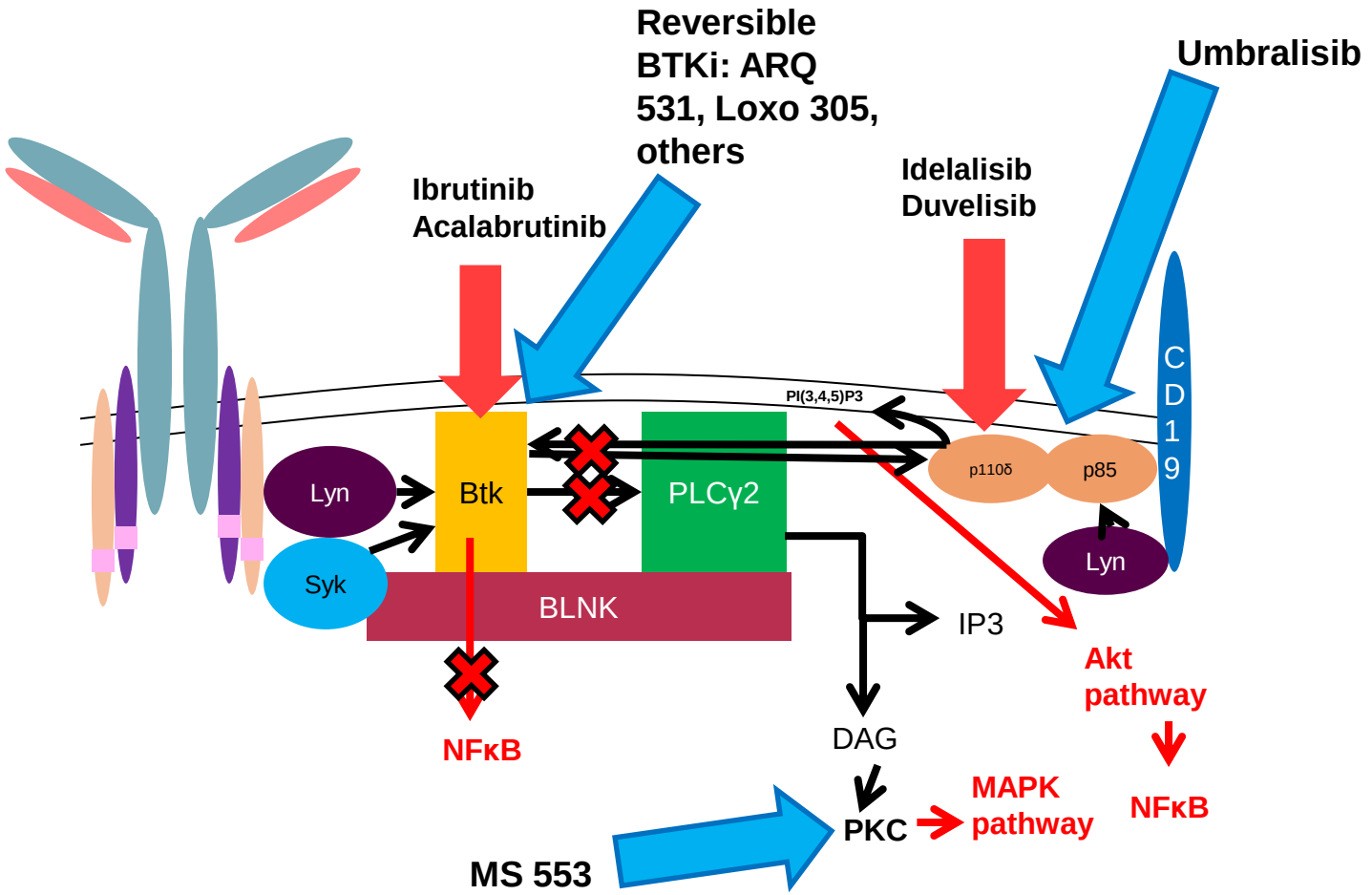
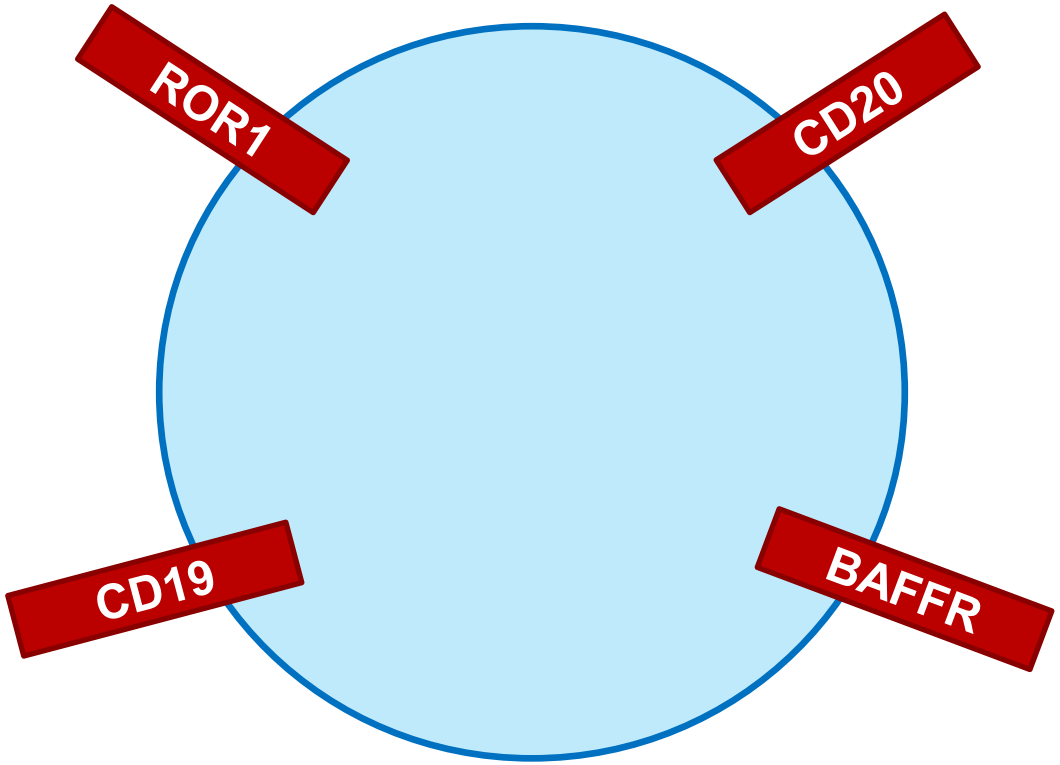
Exciting Treatments/Strategies Currently in Trials

- New ways to target the B cell receptor signaling pathway
- New antibody treatments
- Harnessing the immune system to combat CLL

New ways to target the B cell receptor signaling pathway



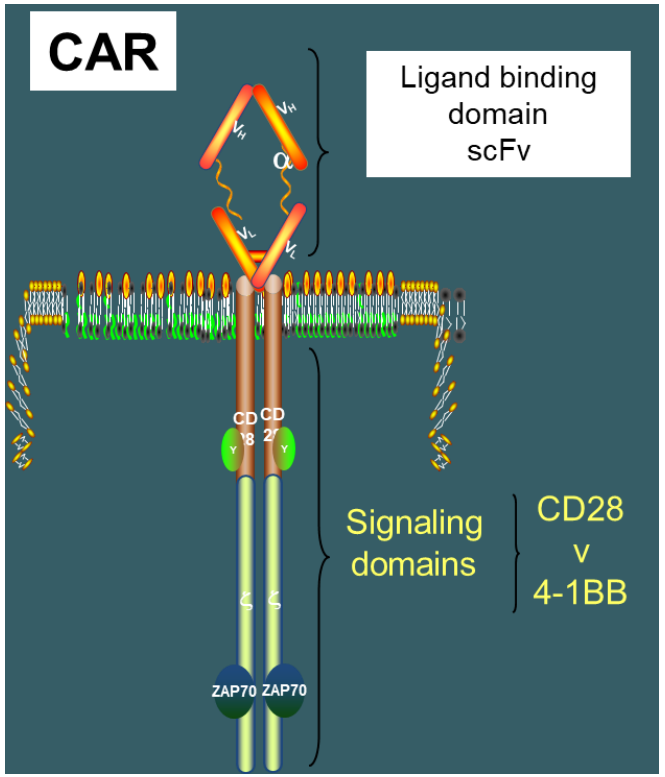
New Antibody Targets

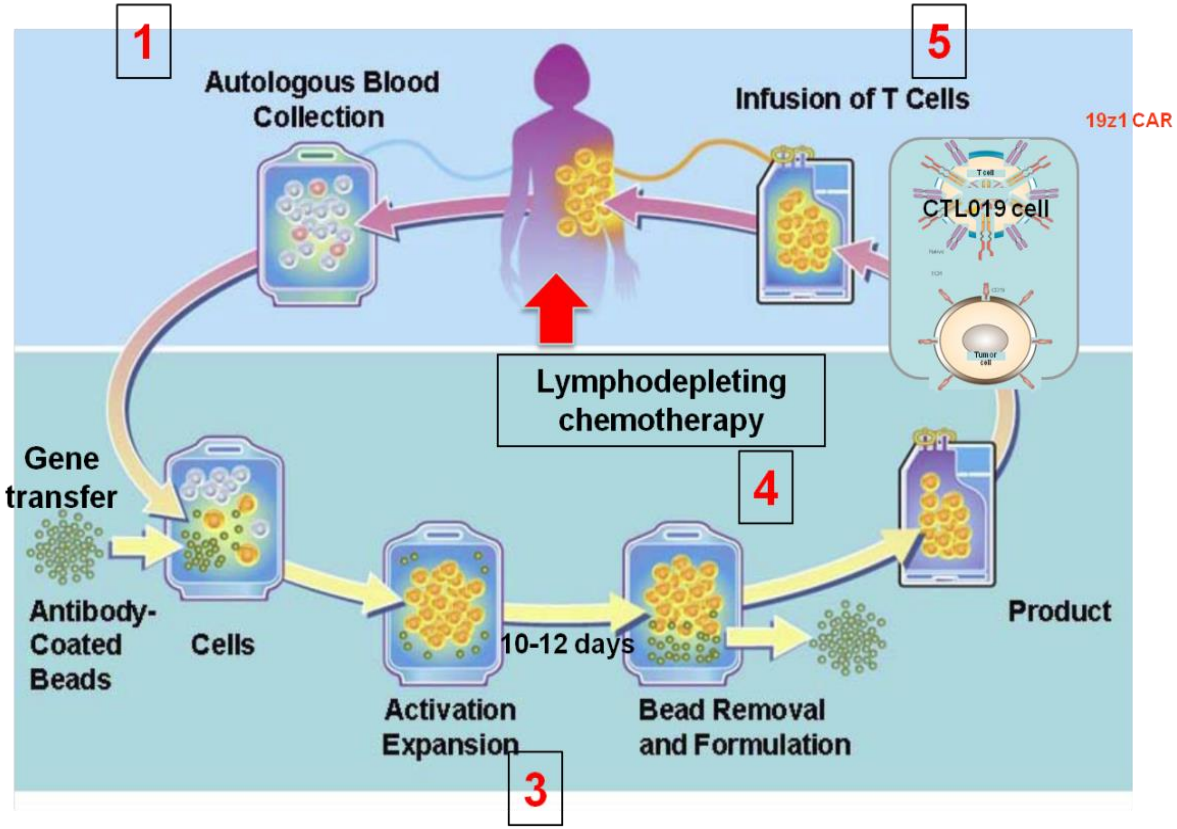


New Antibody Techniques:

- Bispecific antibodies

Harnessing the Immune System





CAR-T cells (or CAR-NK cells)

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Take-away Points

- CLL is a cancer of the blood, bone marrow, lymph nodes, and spleen
- Currently, there is no advantage to treating CLL early
- When it is time for therapy, there are many excellent non-chemotherapy options
- As our CLL therapy gets better, other supportive care issues, like infection prevention and secondary cancer screening becomes even more important
- Ask about clinical trials—this is how we will make the next big leap in CLL therapy!

Thank You!

The James

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