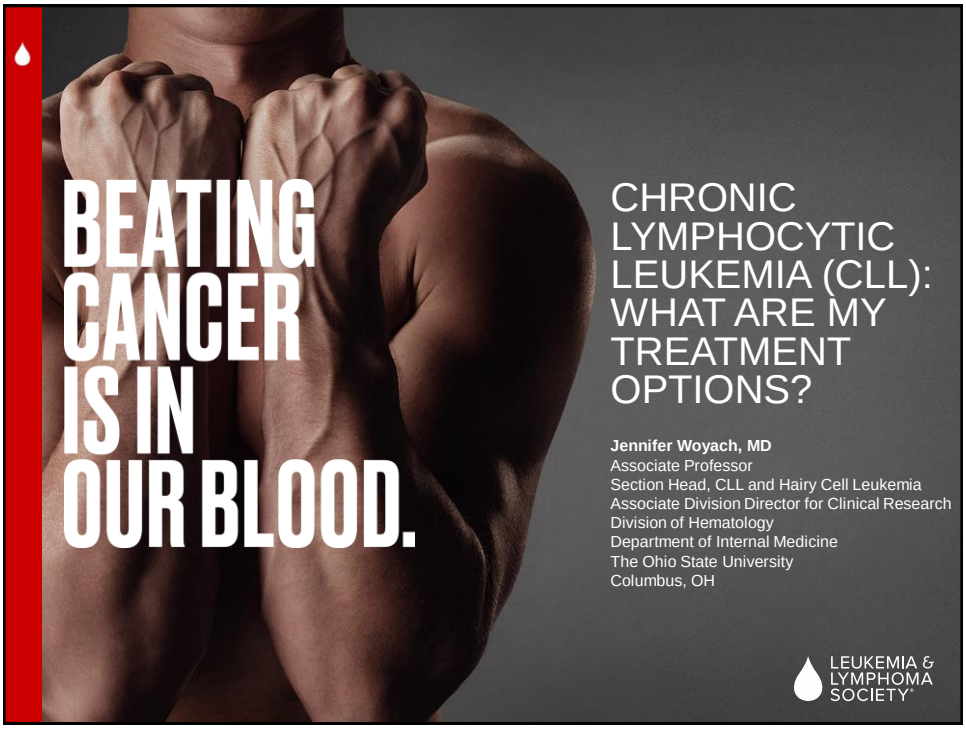

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): WHAT ARE MY TREATMENT OPTIONS?

Jennifer Woyach, MD
Associate Professor
Section Head, CLL and Hairy Cell Leukemia
Associate Division Director for Clinical Research
Division of Hematology
Department of Internal Medicine
The Ohio State University
Columbus, OH

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DISCLOSURES

Chronic Lymphocytic Leukemia (CLL): What Are My Treatment Options?

Jennifer Woyach, MD, has affiliations with AbbVie, ArQule, AstraZeneca, Janssen, Loxo Oncology, and Pharmacyclics.

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Current Treatment of CLL

Jennifer Woyach, MD

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Objectives

- Briefly discuss natural history of CLL
- Discuss useful prognostic markers in CLL
- Discuss criteria for the initiation of therapy
- Discuss specific therapies for CLL
- Discuss what may be coming next

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Chronic Lymphocytic Leukemia: Background and Natural History

- Most prevalent leukemia (~ 15,000 cases per year)
- Disease of older patients, median age at diagnosis 72 years
- 3:2 male-to-female ratio; Caucasian > African American >>> Asian
- ~ 4,500 deaths per year
- Absolute survival has increased during past 2 decades

	1980–1984	2000–2004	*p*
5-Year	54.2%	60.2%	< .0001
10-Year	27.8%	34.8%	< .0001

American Cancer Society, 2008; Rai et al, 1975; Brenner et al, 2008..

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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

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Rai Staging

Rai Stage	Finding	Modified Rai Classification
0	Lymphocytosis	Low Risk
I	Lymphadenopathy	Intermediate Risk
II	Splenomegaly and/or Hepatomegaly	
III	Anemia (<11 g/dL)	High Risk
IV	Thrombocytopenia (<100 k/uL)	
Category is assigned based on highest risk finding		

Rai et al., Blood 1975; Hallek at al., Blood 2018.

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IGHV Mutational Status

- Indicates the divergence of the immunoglobulin heavy chain variable region from the germline sequence.
- Higher levels indicate greater amounts of normal somatic hypermutation, and suggest a more mature precursor cell
- Currently the strongest predictor of prognosis

Hamblin, Blood 1999.

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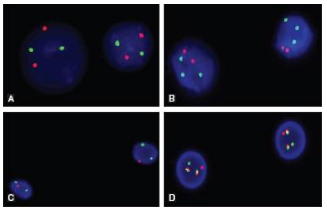
Cytogenetics & Fluorescence In Situ Hybridization

Metaphase spread



A. Normal
B. Trisomy
C. Deletion
D. Translocation

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Implications of FISH/Cytogenetics on Prognosis

- Del(13q), the most common abnormality, indicates indolent disease when detected as the sole abnormality (>50% of pts)
- Trisomy 12 indicates intermediate prognosis (~30% of pts)
- Del(11q) results in loss of the tumor suppressor ATM and is associated with more aggressive disease (~20% of pts)
- Del(17p) results in loss of the tumor suppressor TP53 and is associated with more aggressive disease (~10% of pts)
- Complex karyotype (≥ 3 abnormalities) is associated with more aggressive disease

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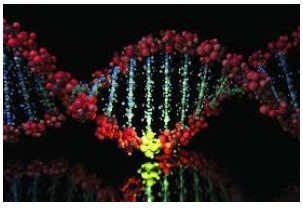
TP53 Mutation

- Mutations are common in CLL, but most mutations are shared infrequently (2-5% of patients)
- TP53 mutations are seen in about 10-15% of patients at diagnosis.
- 80% of the time, mutations co-exist with del(17p)



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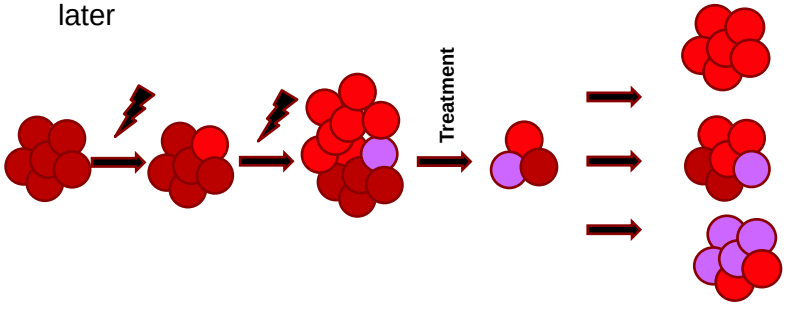
Can Prognosis Change Over Time?

- 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



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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

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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.

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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)

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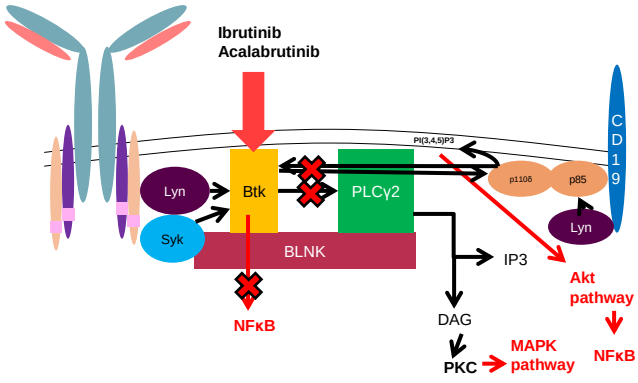
Mechanism of BTK Inhibitors

- Ibrutinib or Acalabrutinib



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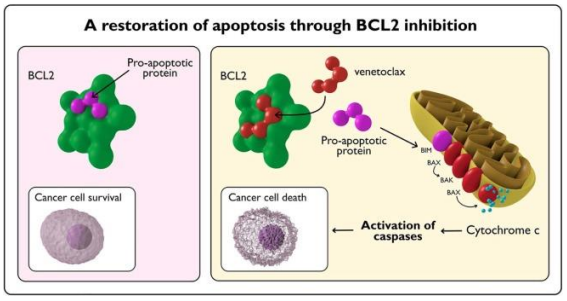
Mechanism of BCL2 Inhibitors

- Venetoclax + Obinutuzumab



Mihalyova et al, 2018.

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How Do We Choose Therapy? First Consideration

Targeted therapy **VS** Chemo-immunotherapy

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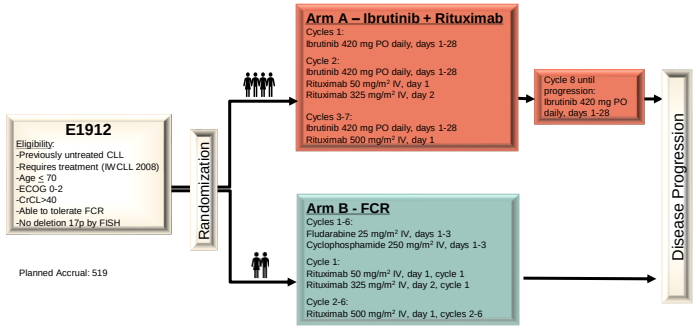
ECOG 1912



Key Points

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

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

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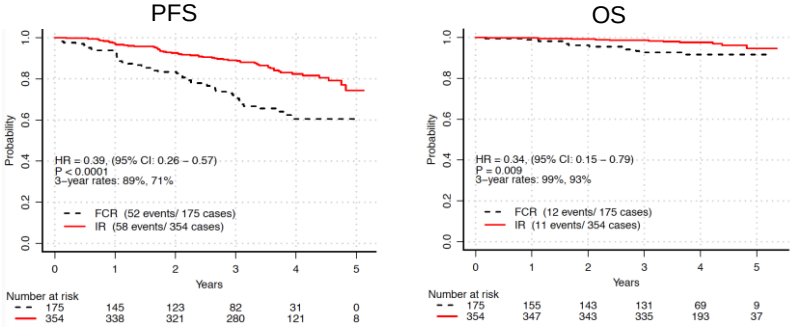
E1912 Progression-Free Survival and Overall Survival



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

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Shanafelt, et al, ASH 2019, abstract 33.

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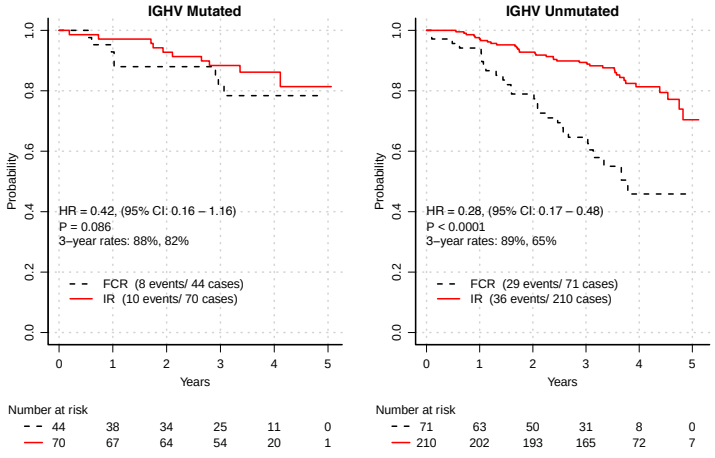
E1912 PFS Based Upon IGHV Mutational Status



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Shanafelt, et al, ASH 2019, abstract 33.

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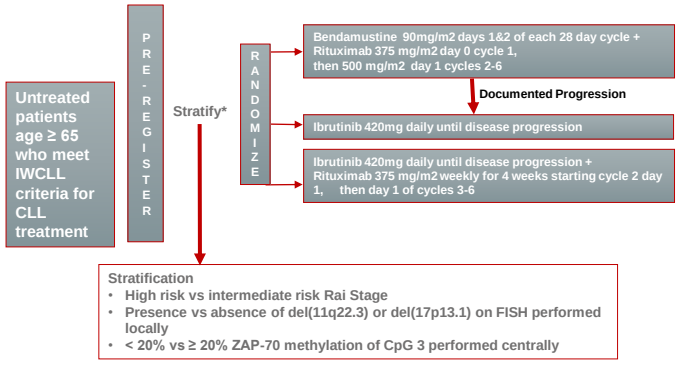
A041202



Key Points

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

Planned accrual: 498

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Woyach et al, NEJM 2018.

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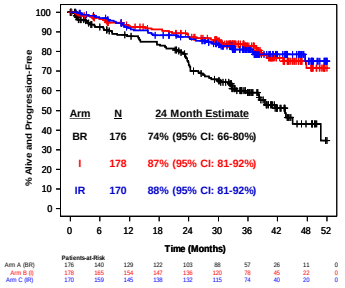
A041202 Progression-Free Survival and Overall Survival

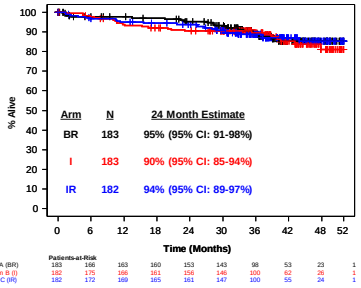


Pairwise Comparisons

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)



Median Follow-up: 38 months

Woyach et al, NEJM 2018

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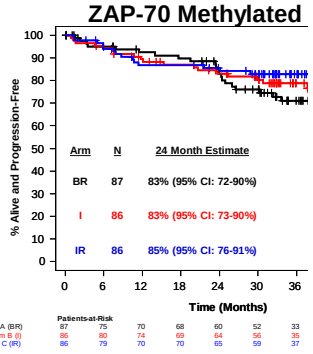
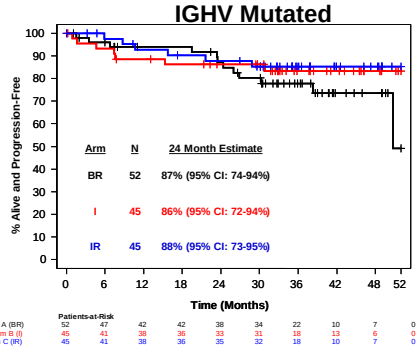
IGHV Mutated and ZAP-70 Methylated Subgroups PFS





Woyach et al, NEJM 2018.

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ELEVATE TN (ACE-CL-007)

Treatment-naive CLL (N=535)

Age ≥65 or

<65 years with coexisting conditions:

- CIRS score >6, or
- creatinine clearance <70 mL/min

Stratification

- del(17p), y vs n
- ECOG PS 0-1 vs 2
- Geographic region (N America, W Europe, or other)

RANDOMIZE 1:1:1

Acala-G
100 mg PO BID
1000 mg IV on D1, 2, 8, and 15 of Cycle 2, + D1 of subsequent 28-day cycles for a total of 6 cycles

Acalabrutinib monotherapy
100 mg PO BID

G-Clb
1000 mg IV on D1, 2, 8, and 15 of Cycle 1, + D1 of subsequent 28-day cycles for a total of 6 cycles
0.5 mg/kg PO on D1 + 15 of each 28-day cycle for 6 cycles

***Crossover** from G-Clb to acalabrutinib monotherapy was allowed after IRC-confirmed progression*

Primary endpoint
- PFS (assessed by IRC) Acala-G vs G-Clb

Key secondary endpoints
- PFS acalabrutinib vs G-Clb
- ORR (assessed by IRC and investigator)
- Time to next treatment
- OS
- Safety

Sharman et al, ASH 2019 Abstract 31.

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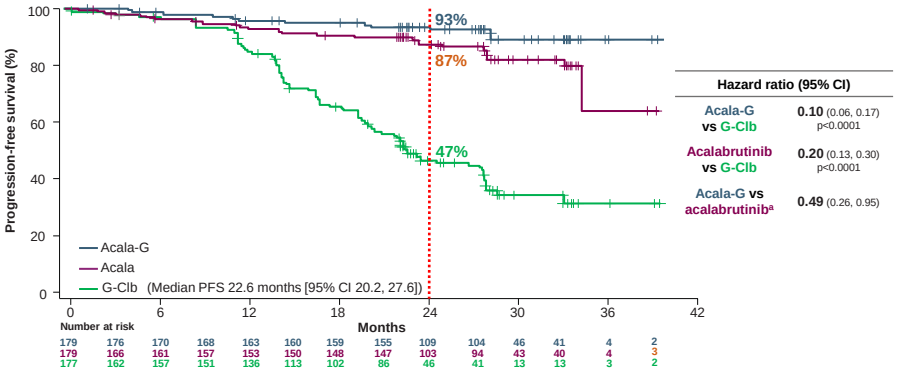
ELEVATE-TN Progression-Free Survival

Median Follow-Up 28.3 Months



Kaplan-Meier estimates performed by IRC and all analyses for the intention-to-treat population. No. of events: Acala-G, 14 (7.8%); Acala, 26 (14.5%); G-Clb, 93 (52.5%)
[a]*Post hoc* analysis.
Richter's transformation occurred in: Acala-G n=1, Acala n=5, G-Clb n=1

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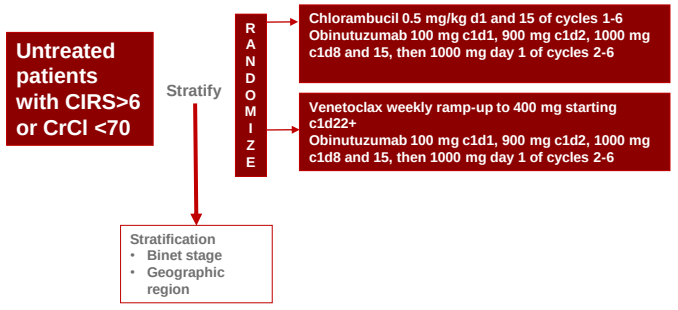
CLL14



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

Fischer et al, NEJM 2019.

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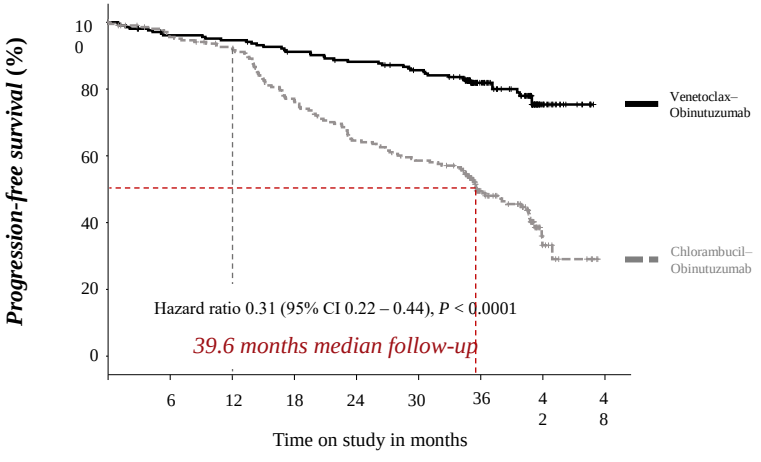
CLL14 Progression Free and Overall Survival



36 month PFS: 82% vs 50%

OS: no difference

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What Do These Trials Tell Us?

- BTKi +/- anti-CD20 antibody is more effective than chemoimmunotherapy in the treatment of CLL
  - For the subset of IGHV mutated, this may not be true, especially with FCR
- Anti-CD20 antibodies may be better combined with acalabrutinib than ibrutinib
- Venetoclax + obinutuzumab is more effective than chlorambucil + obinutuzumab
- At 2 years, PFS for VO is similar to what is reported for ibrutinib
- Long term results will be critical to determine which regimen is more effective

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Second Consideration: How to Choose Between Targeted Therapies?

Ibrutinib
VS
Acalabrutinib
VS
Venetoclax

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Efficacy Considerations

- At 2 years, ibrutinib, acalabrutinib, and venetoclax/obinutuzumab appear relatively equivalent
  - There might be a difference in TP53 altered patients
  - IGHV?
- There is much more long-term data with ibrutinib than either venetoclax or acalabrutinib
- Acalabrutinib and ibrutinib are being compared head to head in relapsed CLL, and venetoclax/obin will be compared to ibrutinib, so data on these will be available…someday

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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%), Bleeding (significant <5%)
- Venetoclax toxicities: Neutropenia (significant 50%), Febrile neutropenia (5%), Diarrhea (significant <5%)

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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

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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

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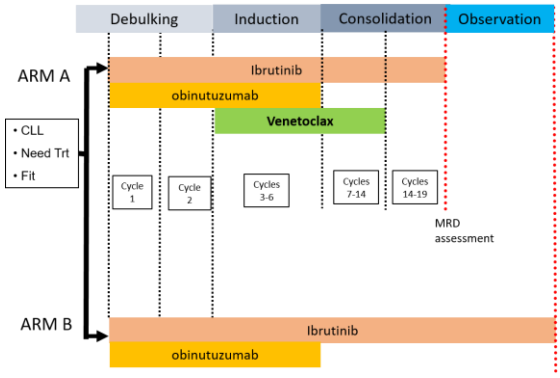
NCTN Study: EA9161



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

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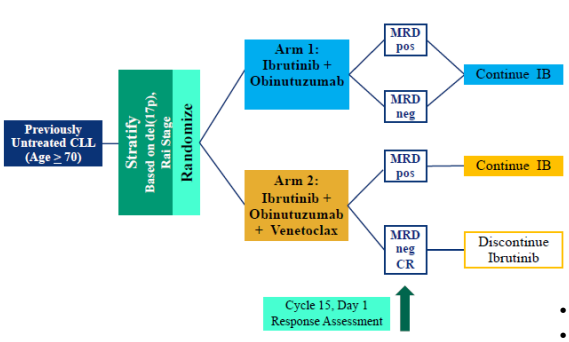
NCTN Study: A041702



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

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

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What Happens If the CLL Comes Back?

- It depends…
  - What do we mean by relapse?
  - What are the prognostic factors?
  - What was the initial treatment?

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What Was the Initial Treatment?

- Chemotherapy?
- Venetoclax/obinutuzumab (or other time-limited targeted treatment)?
- Ibrutinib or acalabrutinib given continuously?

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If Initial Treatment Was Chemotherapy…

- Lots of options!!
  - Ibrutinib
  - Acalabrutinib
  - Venetoclax/rituximab
  - Idelalisib/rituximab
  - Duvelisib
  - Repeat chemotherapy regimen (not my top choice)

But will they work?

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Answer: Yes!

- Most of the data we have for outcomes comes from patients who were previously treated with chemotherapy.
- Ibrutinib: Average progression-free survival 52 months
- Acalabrutinib: At 45 months, 62% were progression-free
- Venetoclax/rituximab: At 48 months, 57% were progression-free

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If Initial Treatment Was Venetoclax/Obinutuzumab…

- Many options for targeted therapies
  - Ibrutinib
  - Acalabrutinib
  - Venetoclax/rituximab
  - Idelalisib/rituximab
  - Duvelisib
  - Could also consider repeating initial therapy depending on remission duration

But will they work?

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Answer: Probably

- No clinical trials have been performed specifically to address second-line therapy in patients previously on venetoclax/obinutuzumab
  - But, there is no reason why other therapies would not work
- Recent data from ASH 2019 shows that BTK inhibitors are effective after venetoclax. PI3K inhibitors are less so, but still have activity
- Repeating venetoclax is not clearly effective (yet)

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If Initial Treatment Was Ibrutinib or Acalabrutinib…

- Options remain for targeted therapies
  - Acalabrutinib
  - Venetoclax/rituximab
  - Idelalisib/rituximab
  - Duvelisib

But will they work?

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Answer Is Dependent on Context of Progression

- If progression occurs after ibrutinib discontinued for toxicity, treatment with acalabrutinib is effective
- If progression occurs after acalabrutinib discontinued for toxicity, other treatments (venetoclax, PI3K inhibitor) are likely effective
- If progression occurs during treatment with ibrutinib/acalabrutinib, venetoclax has been shown to be effective. PI3K inhibitors less so

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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

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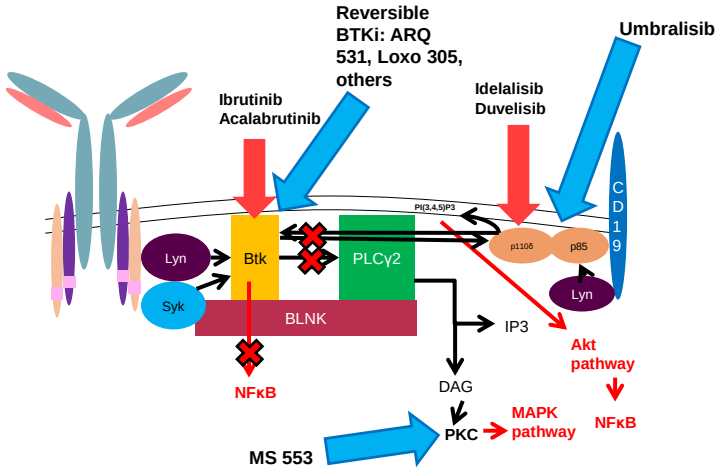
New Ways to Target the B-Cell Receptor Signaling Pathway



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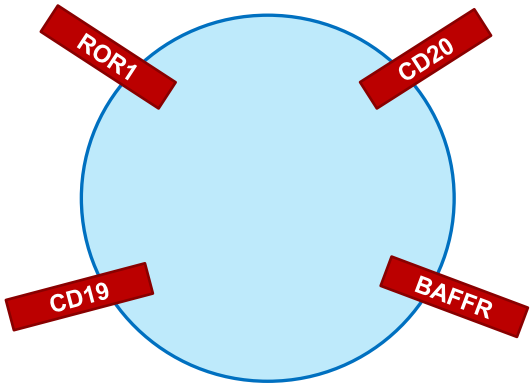
New Antibody Targets



New Antibody Techniques:
- Bispecific antibodies

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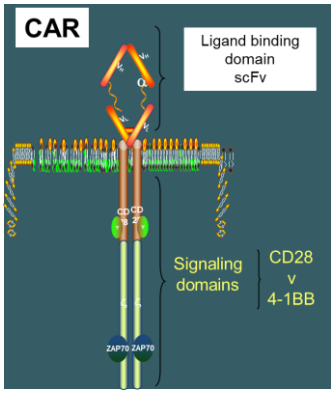
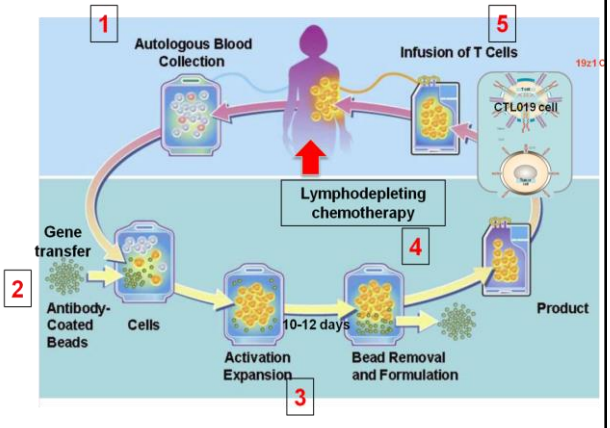
Harnessing the Immune System





CAR-T cells (or CAR-NK cells)

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Thank You!

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Question & Answer Session

BEATING CANCER IS IN OUR BLOOD.

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RESOURCES

- **Information Specialists**

  Master's level oncology professionals, available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.

  – **Email: infocenter@LLS.org**

  – **Toll-Free Phone: 1-800-955-4572**

- **Clinical Trial Support Center**

  Work one-on-one with an LLS Clinical Trial Nurse Navigator who will personally assist you throughout the entire clinical-trial process. Clinical Trial Nurse Navigators are registered nurses with expertise in blood cancers.

  – **Email: www.LLS.org/CTSC**

- **Additional Information about Leukemia:**
  – **www.LLS.org/leukemia**

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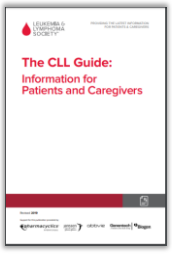
FREE LLS EDUCATION & SUPPORT RESOURCES

- **Education Booklets about CLL:**
  – **www.LLS.org/booklets**

- **Telephone/Web Programs:**
  – **www.LLS.org/programs**



- **Weekly Chronic Lymphocytic Leukemia Online Chat:**
  – **www.LLS.org/chat**

- **Additional LLS Information about Coronavirus:**
  – **www.LLS.org/coronavirus**

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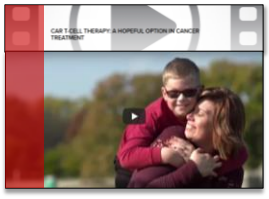
FREE LLS EDUCATION & SUPPORT RESOURCES



- **LLS Podcast, *The Bloodline with LLS***

  Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: **www.thebloodline.org**

- **Education Videos**

  Free education videos about survivorship, treatment, disease updates and other topics: **www.LLS.org/educationvideos**

- **Patti Robinson Kaufmann First Connection Program**

  Peer-to-peer program that matches newly diagnosed patients and their families: **www.LLS.org/firstconnection**

- **Nutrition Consults**

  Telephone and email consultations with a Registered Dietitian: **www.LLS.org/nutrition**

- **What to Ask**

  Questions to ask your treatment team: **www.LLS.org/whattoask**

- **Other Support Resources**

  LLS Community, discussion boards, blogs, support groups, financial assistance and more: **www.LLS.org/PatientSupport**

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