LIVING WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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WELCOMING REMARKS

LIVING WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Lizette Figueroa-Rivera, MA
Sr. Director, Education & Support
The Leukemia & Lymphoma Society

Upcoming Programs: Registration available soon: www.LLS.org/Programs

June 9, 2022- Spotlight on Caregiving: Chronic Lymphocytic Leukemia (CLL)
June 16, 2022- Caregiving Over Coffee: An Interactive Q&A With Dr. Applebaum
June 21, 2022- Addressing the Financial Impact of Cancer

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WELCOMING REMARKS

LIVING WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Kristin Fuhrmann-Simmons, MSW
CLL Caregiver
LLS Policy Advocate, State of Maine

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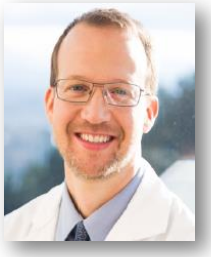
DISCLOSURES

LIVING WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)



Program Research Support: Acerta, Gilead Sciences, Celgene-BMS, Janssen, Velos-bio Inc., Genentech, BeiGene, Verastem, Pharmacyclics

Paid Consultancy: Flamingo Therapeutics, Kyropharm, VelosBio, Pharmacyclics, Innate Pharma, Genentech

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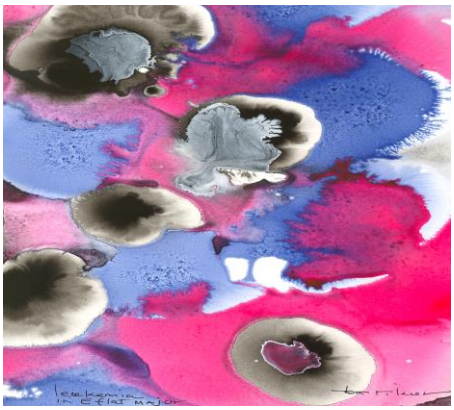
Chronic Lymphocytic Leukemia



Stephen E. Spurgeon MD
Associate Professor of Medicine
Lymphoma Program Director
Distinguished Scholar in Leukemia and Lymphoma Research
Knight Cancer Institute at Oregon Health & Science University

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Talk Overview

- Background/Disease Overview
- “Best” Initial Therapy
- Minimal Residual Disease (MRD)
- Next wave of therapeutics
- CLL and COVID

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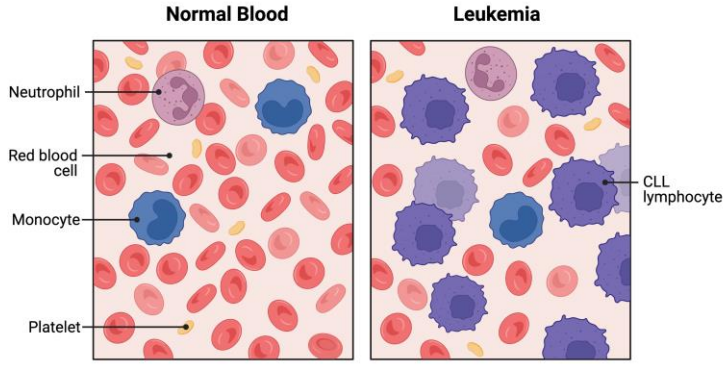
Chronic Lymphocytic Leukemia (CLL)

Most common type of leukemia in western countries



Characterized by: Uncontrolled proliferation of B-cells within the peripheral blood, lymphoid tissue and bone marrow.

Results in severe immune dysfunction.

CLL patients at a higher risk of infection

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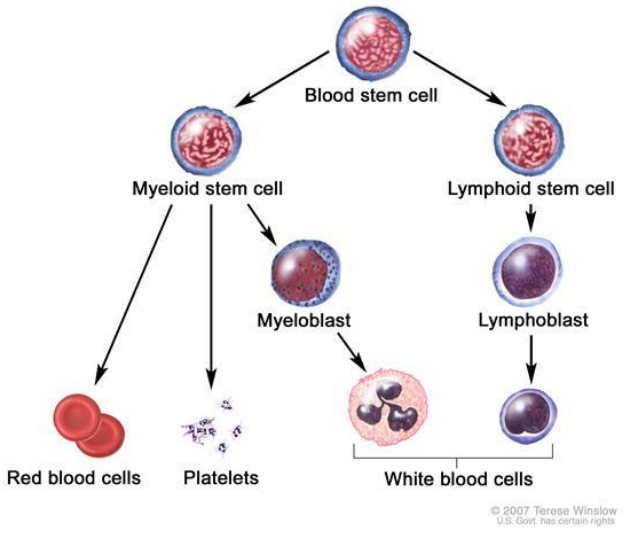
Hematopoiesis (how blood cells are made)



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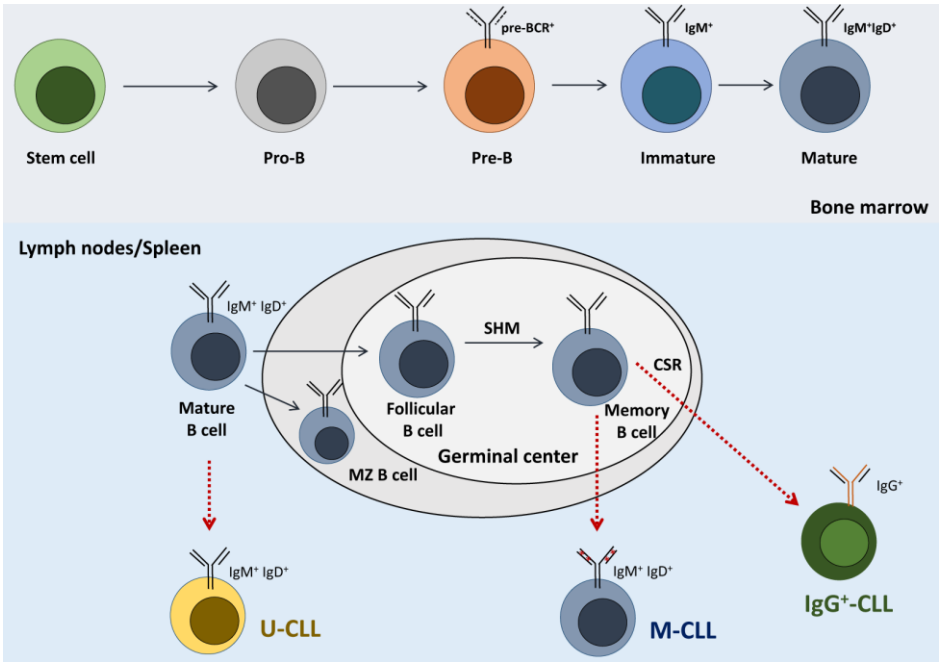

Leukemia **33**, pages287–298(2019)

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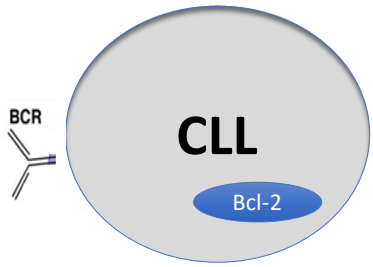
The "old" model of CLL



- CLL cells "accumulate"
- Defective apoptosis due to increased bcl-2
- Limited activity of the B-cell Receptor (BCR)

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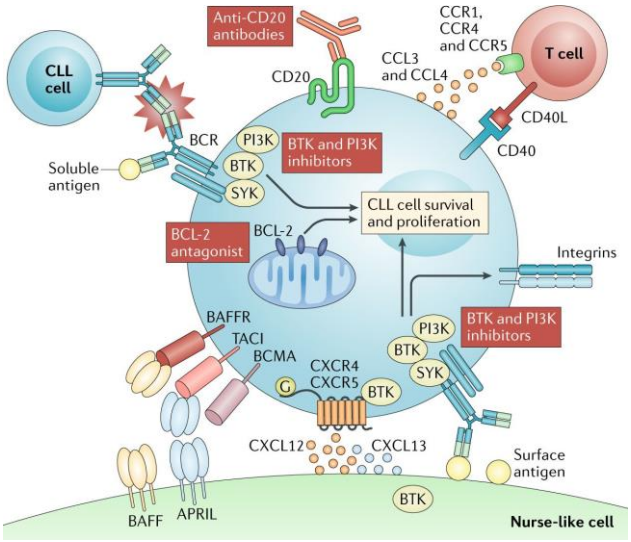
CLL is a complex disease



We have been able to use this knowledge to target CLL cells

Nature Reviews Clinical Oncology 15, 510-527 (2018)

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Clinical Manifestations of CLL

- Lymphadenopathy
- Early satiety/LUQ fullness
- Fatigue
- Weight loss
- Fever
- Night sweats
- Recurrent infections
- Bleeding
- Autoimmune (anemia, thrombocytopenia)

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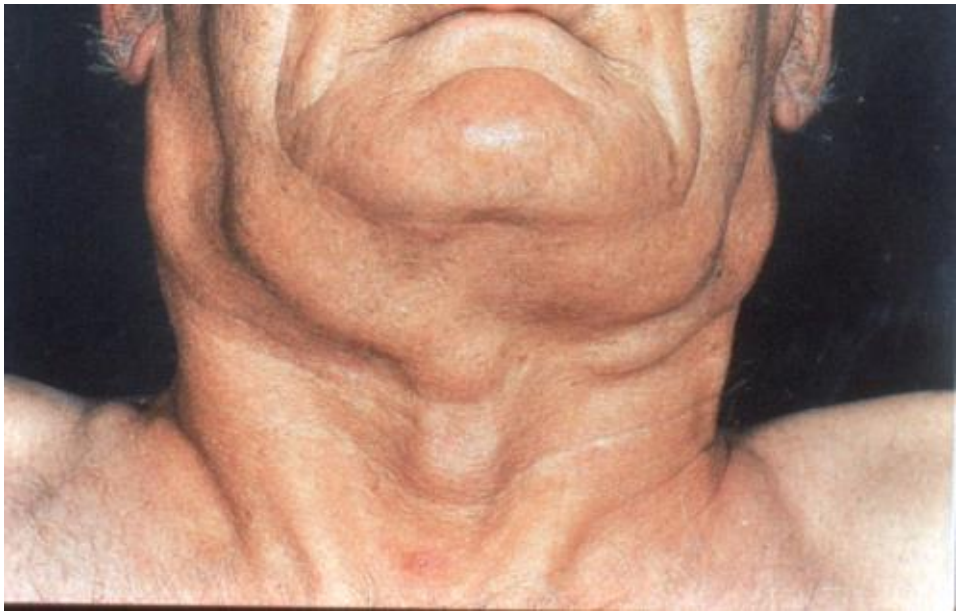
Cervical Lymphadenopathy in CLL



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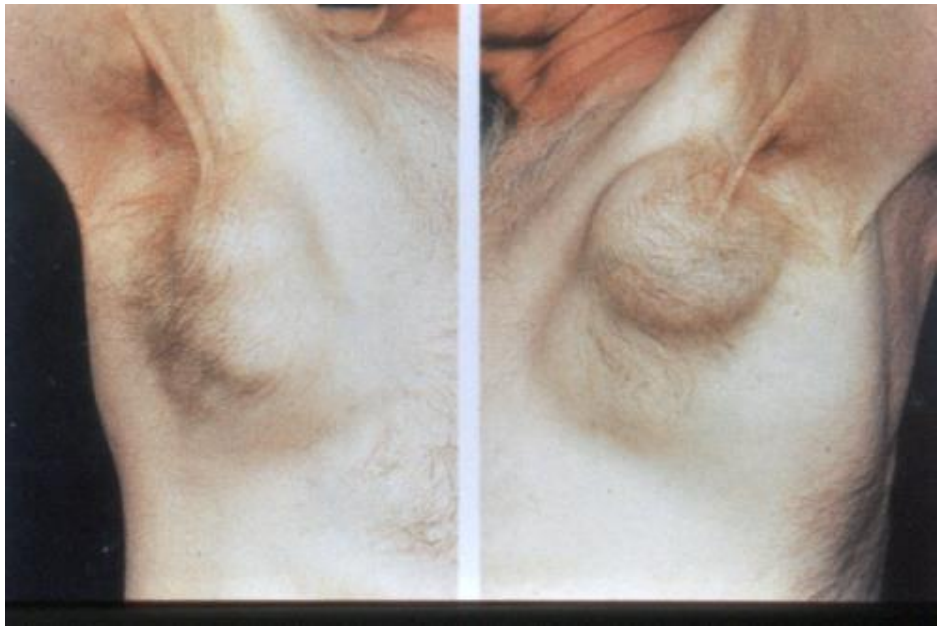
Axillary Lymphadenopathy in CLL



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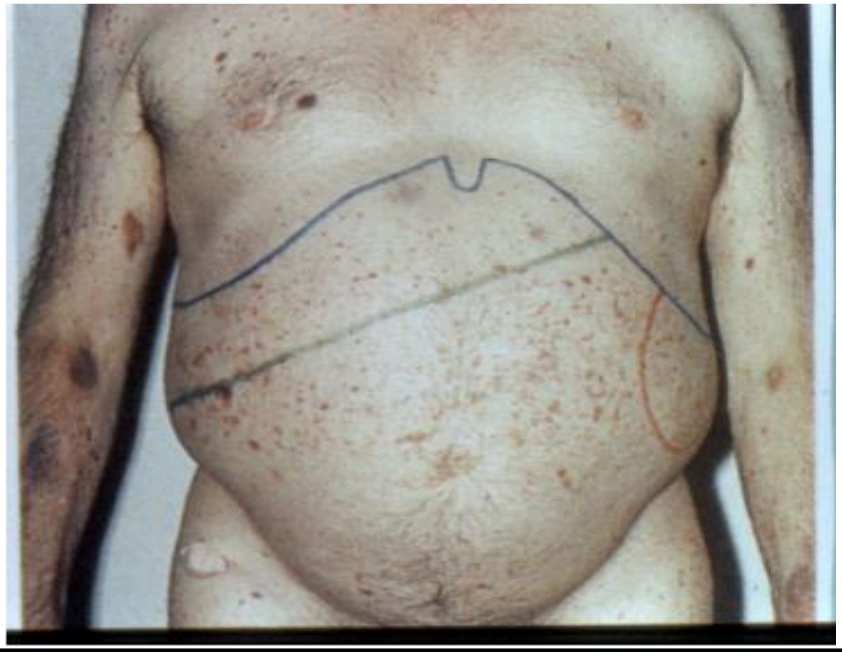
Hepato-splenomegaly in CLL



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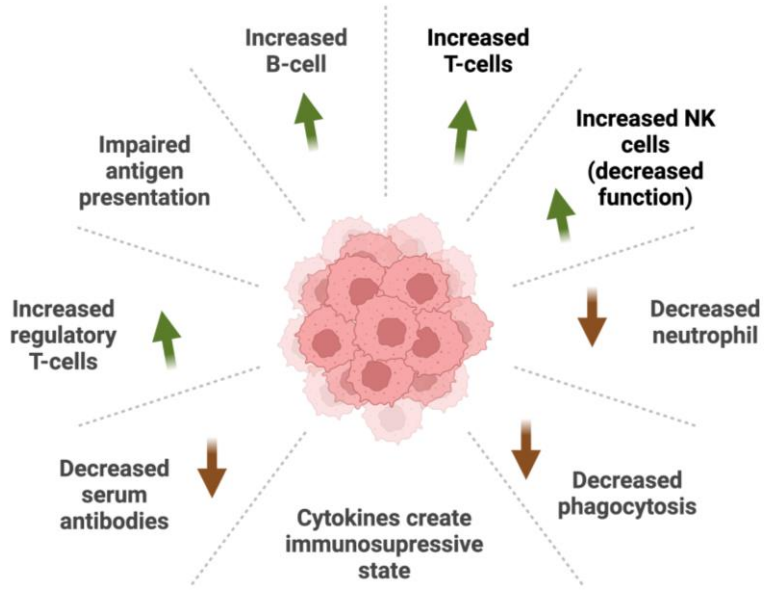
CLL is characterized by immune disfunction



Vaccines!
IVIG?

PNA (PCV13, PPV 23)
Shingles
COVID
No live virus vaccines

IVIG – recurrent infections
Acyclovir with active Rx

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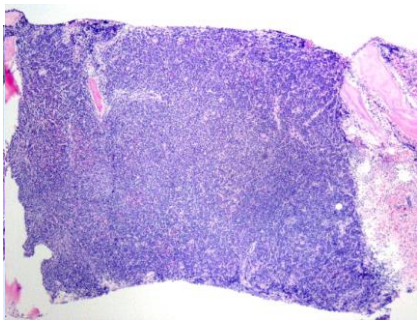
Clinical Considerations



- **Cytopenias (anemia and thrombocytopenia)**
  - Marrow infiltration with CLL
  - Inhibitory activity of CLL (anemia of chronic disease)
  - AIHA (autoimmune hemolytic anemia), ITP
  - Pure red cell aplasia
  - Marrow suppression from treatment
- **Transformation to aggressive lymphomas**
- **Secondary Malignancies**

Skin exams
Cancer screening

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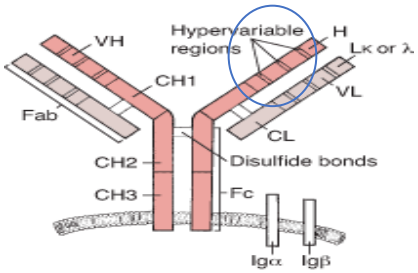
Biologic markers
-additional prognostic features-

- B-cell receptor

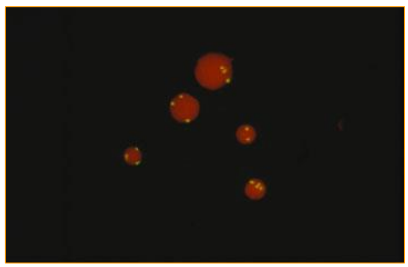
  Mutation of the variable region of Immunuglobulin heavy chain (IgV_H)

  UNMutated = unfavorable



- FISH/CYTOGENETICS

  unfavorable=
  17 p deletion,
  > 3 abnormalities



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Treatment Principles

- Standard therapy is not curative
- Absolute white count # not used for treatment (rate of change is)
- Therapy reduces symptoms
- Therapy has side-effects
  - alters types of infections seen
- Treat when meet IWCLL criteria
  - Enlarged lymph nodes, spleen, low blood counts, B symptoms
- "Watch and wait" approach

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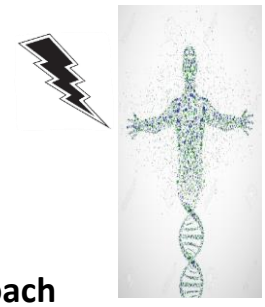
Rapidly Evolving Treatment Landscape



Old Approach

DNA damaging chemotherapy was King

Eventually stops working

Increased risk of long-term toxicity

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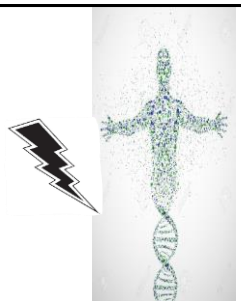
Treatment

-chemotherapy-



- Alykylating agents
  - Cytoxan
  - chlorambucil
- Nucleoside (purine) analogs
  - Fludarabine
  - Cladribine
  - Pentostatin
- Bendamustine
  - Properties of alkylators and purine nucleoside analogues
  - High response rates

FCR and Bendamustine most commonly used

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Current Approach

Chemotherapy is (largely) obsolete

Inhibit the BCR pathway

Target bcl-2

Immune based therapy

Spare the DNA

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Important Drugs

- BTK inhibitors (ibrutinib, acalabrutinib)
- PI3k inhibitors (idelalisib, duvelisib)
- Bcl-2 inhibitors (venetoclax)
- Anti-CD20 monoclonal antibodies (mAb)- rituximab, obinutuzumab

- Effective in up-front and relapsed treatment setting
- Superior to chemotherapy

? Continuous therapy vs. fixed duration therapy?

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CLL-"Best" initial therapy

- Is watchful waiting still the best option at diagnosis?
- Any role for chemotherapy?
- MRD negativity as a treatment goal?
- Ongoing Treatment with BTKi
  - Which BTKi?
  - In combination?
  - Does this really need to continue forever?
- Fixed duration therapy – incorporating MRD

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Watchful Waiting (worrying)

- original watchful waiting data based primarily on older chemotherapy (chlorambucil)

- Can we define a high risk subset that would benefit from earlier treatment?

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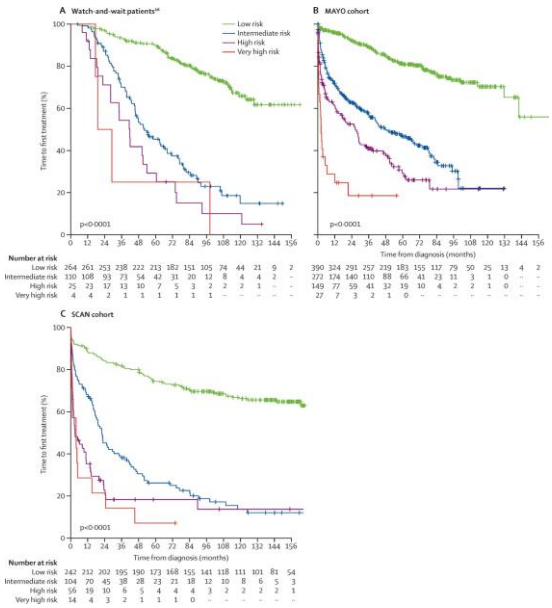
Defining High Risk Disease – CLL IPI

Characteristic	Points (10)
Age > 65	1
Rai Stage I-IV	1
B2M ≥ 3.5	2
IGHV UNmutated	2
17p deletion or p53 mutation	4

Low risk: 0-1
Intermediate Risk: 2-3
High Risk: 4-6
Very High Risk: 6-10



Lancet Oncology Volume 17, Issue 6, June 2016, Pages 779-790

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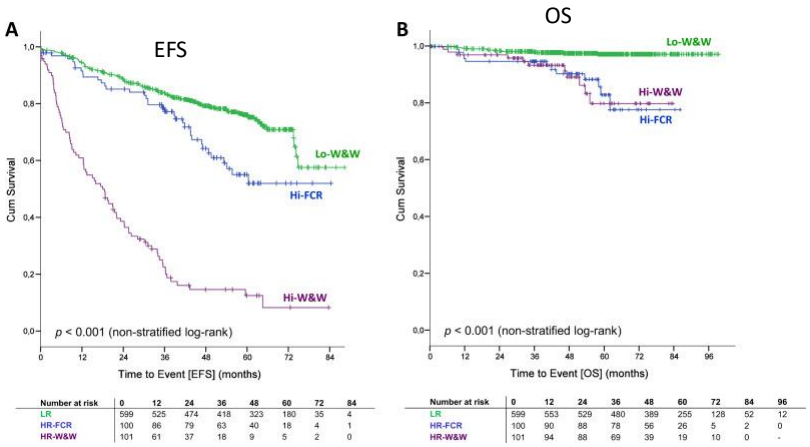
Early treatment with FCR versus watch and wait in patients with stage Binet A high-risk chronic lymphocytic leukemia (CLL): a randomized phase 3 trial



High risk = ≥ 2 risk factors: Doubling time <12 months, serum thymidine kinase >10 U/L, unmutated IGHV genes, and unfavorable cytogenetics (del(11q)/del(17p)/trisomy 12).

Leukemia. 2020; 34(8): 2038–2050.

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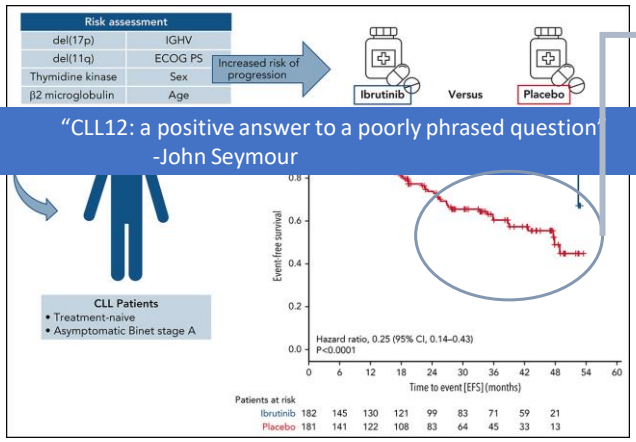
The CLL12 trial: ibrutinib vs placebo in treatment-naïve, early-stage chronic lymphocytic leukemia



"CLL12: a positive answer to a poorly phrased question"
-John Seymour

Better than expected EFS

EVOLVE CLL (NCTN study)
Early vs. late Obi-Ven
CLL-IPI score ≥4 and/or complex cytogenetics
OS and QOL primary outcomes

Blood Volume 139, Issue 2, 13 January 2022, Pages 177-187

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CLL-"Best" initial therapy

- Is watchful waiting still the best option? -→ YES, unless on study
- Any role for chemotherapy?
- Ongoing Treatment with BTKi
  - Which BTKi?
  - In combination?
  - Does this really need to continue forever?
- Fixed duration therapy
- MRD negativity as a treatment goal

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Ibrutinib based Regimens vs. Chemo

Study	Arms	Clinical Data	Notes
E1912 Trial (Ph III) (<70 years old + no del17p) N=529	• **Ibrutinib**/ritux • FCR	**36 mo PFS:** 89% vs 73% **36 mo OS:** 99% vs 92%	• Ibrutinib/ritux superior to FCR • Outcomes independent of high-risk features (except IGHV-mutated)
A041202 (Ph III) (≥65 years old, including del17p) N=547	• **Ibrutinib** • **Ibrutinib**/ritux • BR	**24 mo PFS:** 87% vs 88% vs 74% (I vs IR vs BR) I vs BR (HR: 0.39); I vs IR (HR: 1.00) IR vs BR (HR: 0.38) **24 mo OS:** 90% vs 94% vs 95% (I vs IR vs BR)	• Ibrutinib and ibrutinib/ritux PFS are superior to BR [regardless of high-risk features (except ZAP70)]; no significant difference with ibrutinib vs ibrutinib/ritux • No statistically significant difference in OS

BTKis have largely supplanted chemotherapy

Woyach JA, et al. *N Engl J Med*. 2018; Shanafelt TD, et al. *N Engl J Med*. 2019; Moreno C, et al. *Lancet Oncol.* 2019; Tam CS, et al. *Hematologica*. 2020.

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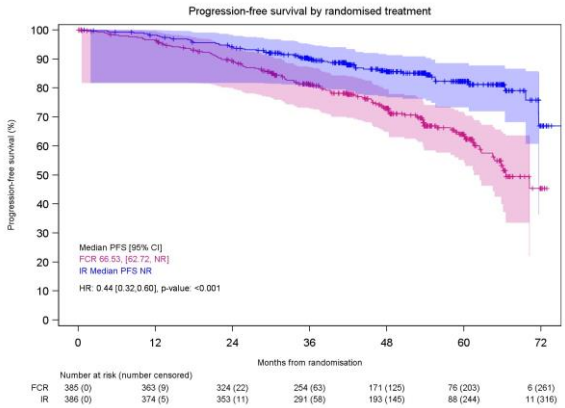
Ibrutinib Plus Rituximab Is Superior to FCR in Previously Untreated CLL: Results of the Phase III NCRI FLAIR Trial



N = 771
Median age = 62
FCR vs. IR
Follow up = 57 months

- **The PFS significantly better for IR in patients with IGHV unmutated CLL (HR: 0.41; p<0.001), but not for patients with IGHV mutated CLL**
- No OS difference
  - **-8 vs. 2 cardiac/sudden deaths in ibrutinib arm (7 of 8 hx of HTN)**
  - -6 cases (1.6%) of MDS/AML in FCR (1 in IR)
  - -Significantly improved OS compared to prior FCR studies

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CLL-"Best" initial therapy

- Is watchful waiting still the best option? → YES, unless on study
- Any role for chemotherapy?→ nope….*
- Ongoing Treatment with BTKi
  - Which BTKi? Mitigate Side effects?
  - In combination?
  - Does this really need to continue forever?
- MRD negativity as a treatment goal
- Fixed duration therapy

*more to come with ven based Rx

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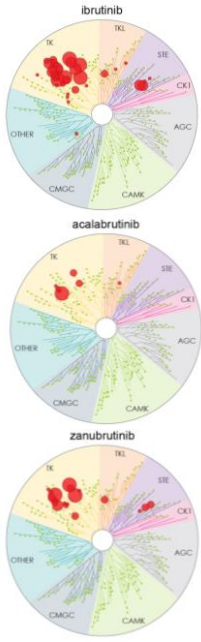
BTK Inhibitor Toxicity Differs Based on Selectivity



All Grades

A

	Ibru	Acala	Zanu
Anemia	27	14	22
Neutropenia	23	10.6	53
Thrombocytopenia	16	7.3	32
Infection	83	79.4	75.8
Diarrhea	53	34.6	23.8
Fatigue	36	18.4	/
Upper respiratory infection	29	18.4	39
Arthralgia	22	15.6	17.4
Pneumonia	18	7.3	25
Hypertension	21	6.7	15.4
Headache	17	36.9	/
Atrial fibrillation	11	3.9	/
Rash	35	14	36
Bleeding/Bruising	55	39.1	28.4
Median treatment exposure	29mon	27.7mon	6mon
Numbers	330	179	118
Patients	CLL/SLL	CLL/SLL	MCL

≥40 ≥30 ≥20 ≥10

Grades 3–5

B

	Ibru	Acala	Zanu
Anemia	7	6.7	8
Neutropenia	18	9.5	15
Thrombocytopenia	6	2.8	5
Infection	31	14	10.8
Diarrhea	5	0.6	0.8
Fatigue	3	1.1	/
Upper respiratory infection	1	0	0
Arthralgia	2	0.6	3.4
Pneumonia	12	2.2	10
Hypertension	7	2.2	3.4
Headache	2	1.1	/
Atrial fibrillation	5	0	/
Rash	3	0.6	0
Bleeding/Bruising	6	1.7	3.4
Median treatment exposure	29mon	27.7mon	6mon
Numbers	330	179	118
Patients	CLL/SLL	CLL/SLL	MCL

≥10 ≥7.5 ≥5 ≥2.5

FDA Prescribing

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ELEVATE-RR: Phase 3 Randomized Non-inferiority Open-Label Trial[1,2]

Patients (N=533)

Key Inclusion Criteria

- Adults with previously treated CLL requiring therapy (iwCLL 2008 criteria[1])
- Presence of del(17p) or del(11q)[a]
- ECOG PS of ≤2

Stratification

- del(17p) status (yes or no)
- ECOG PS (2 vs ≤1)
- No. prior therapies (1-3 vs ≥4)

RANDOMIZE 1:1

- Acalabrutinib[b] 100 mg PO BID
- Ibrutinib[b] 420 mg PO QD

Primary endpoint

- Noninferiority on IRC-assessed PFS[c]

Secondary endpoints (hierarchical order):

- Incidence of Any Grade afib/flutter
- Incidence of Grade ≥3 infection
- Incidence of Richter transformation
- Overall survival

Key exclusion criteria: Significant CV disease; concomitant treatment with warfarin or equivalent vitamin K antagonist; prior treatment with ibrutinib, a BCR inhibitor, (eg, BTK , PI3K, or Syk inhibitors) or a BCL-2 inhibitor (eg, venetoclax)

NCT02477696 (ACE-CL-006). [a]By central laboratory testing. [b]Continued until disease progression or unacceptable toxicity. [c]Conducted after enrollment completion and accrual of ≈250 IRC-assessed PFS events.
Afib, atrial fibrillation; BCL-2, B-cell leukemia/lymphoma-2; BCR, B-cell receptor; BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CV, cardiovascular; del, deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; iwCLL, International Workshop on CLL; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PO, orally; QD, once daily; Syk, spleen tyrosine kinase.
1. Hallek M, et al. *Blood*. 2008;111:5446-56. 2. Byrd JC, et al. Presented at ASCO Virtual Annual Meeting; June 4-8, 2021.

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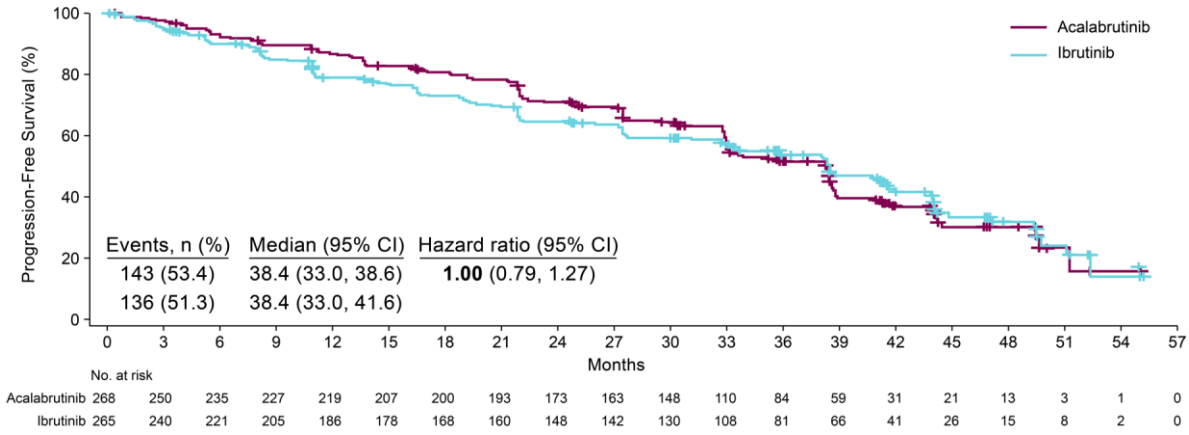
Primary Endpoint: Noninferiority Met on IRC-Assessed PFS



Median follow-up: 40.9 months (range, 0.0-59.1)

CI, confidence interval; IRC, independent review committee; PFS, progression-free survival.
Byrd JC, et al. Presented at ASCO Virtual Annual Meeting; June 4-8, 2021.

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Events of Clinical Interest

Events, n (%)	Any Grade		Grade ≥3	
	Acalabrutinib (n=266)	Ibrutinib (n=263)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
Atrial fibrillation[a,f]	25 (9.4)	**42 (16.0)**	13 (4.9)	10 (3.8)
Ventricular arrhythmias[b]	0	3 (1.1)	0	1 (0.4)
Bleeding events[f]	101 (38.0)	**135 (51.3)**	10 (3.8)	12 (4.6)
Major bleeding events[c]	12 (4.5)	14 (5.3)	10 (3.8)	12 (4.6)
Hypertension[d, f]	25 (9.4)	**61 (23.2)**	11 (4.1)	**24 (9.1)**
Infections[e]	208 (78.2)	214 (81.4)	82 (30.8)	79 (30.0)
ILD/pneumonitis[f]	7 (2.6)	**17 (6.5)**	1 (0.4)	2 (0.8)
SPMs excluding NMSC	24 (9.0)	20 (7.6)	16 (6.0)	14 (5.3)

All Grade cardiac arrhythmias of unspecified origin were reported including tachycardia (2.6%), arrhythmia (0.8%) and extrasystoles (0.8%) for acalabrutinib; tachycardia (2.7%), arrhythmia (0.8%), and extrasystoles (0.4%) for ibrutinib

Higher incidence indicated in **bold red** for terms with statistical differences.
[a]Includes events with preferred terms atrial fibrillation and atrial flutter.
[b]Includes events with preferred terms: ventricular arrhythmia, ventricular extrasystoles, and ventricular fibrillation.
[c]Defined as any hemorrhagic event that was serious, Grade ≥3 in severity, or a central nervous system hemorrhage (any severity grade).
[d]Included events with the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased.
[e]Most common Grade ≥3 infections were pneumonia (acalabrutinib, 10.5%; ibrutinib, 8.7%), sepsis (1.5% vs 2.7%, respectively), and UTI (1.1% vs 2.3%).
[f]Two-sided *P* value for event comparisons <0.05 without multiplicity adjustment.
ILD, interstitial lung disease; NMSC, nonmelanoma skin cancer; SPM, second primary malignancy; UTI, urinary tract infection.
Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.

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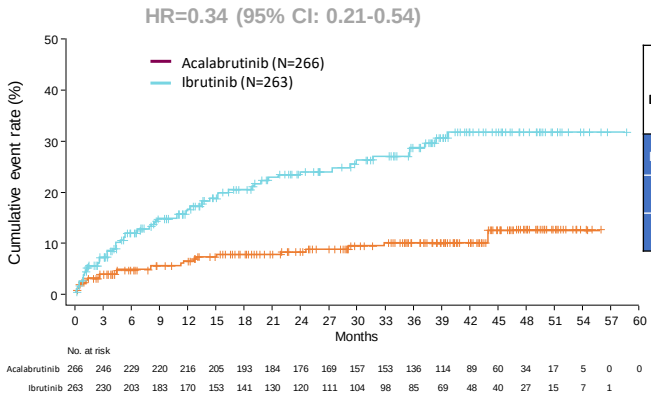
Cumulative Incidence and Summary of HTN



Events	Acalabrutinib (n=266)		Ibrutinib (n=263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
HTN events[a]	25 (9.4)	11 (4.1)	61 (23.2)	24 (9.1)
Events/100 person-months	0.444	0.133	1.243	0.435
Patients with a history of HTN	16 (64.0)	9 (81.8)	30 (49.2)	16 (66.7)

Percentages are based on the number of patients with the event.

[a]Includes events with the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased.
CI, confidence interval; HR, hazard ratio; HTN, hypertension.
Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.

Blood (2021) 138 (Supplement 1): 3721

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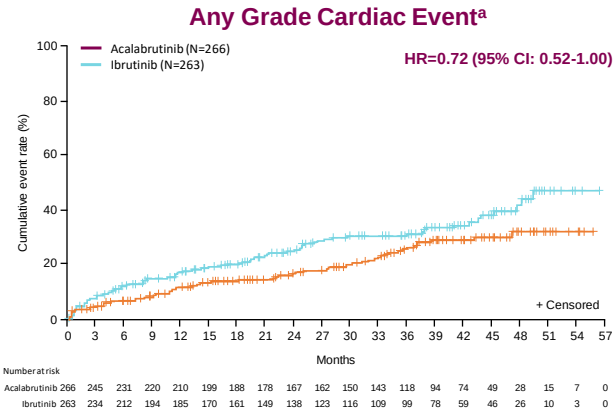
Cumulative Incidence of Cardiac Events



[a]Cardiac events include cardiac arrhythmias, cardiac disorders, signs and symptoms not elsewhere classifiable, coronary artery disorders, heart failures, pericardial disorders, cardiac valve disorders, and myocardial disorders.
CI, confidence interval; HR, hazard ratio.
Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.

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Zanubrutinib on the way

OncLive

Final Response Analysis of ALPINE Trial Shows Superior ORR With Zanubrutinib Vs Ibrutinib in CLL

April 11, 2022
Kristi Rosa

	ORR	12 month PFS	Afib/aflutter	discontinuation
Zanubrutinib	80.4%	94.9%	4.6%	13%
Ibrutinib	72.9%	84%	12.0%	17.6%

Median f/u 24 months

Phase 3 Alpine study in R/R CLL, n = 415, median age 67

39

+

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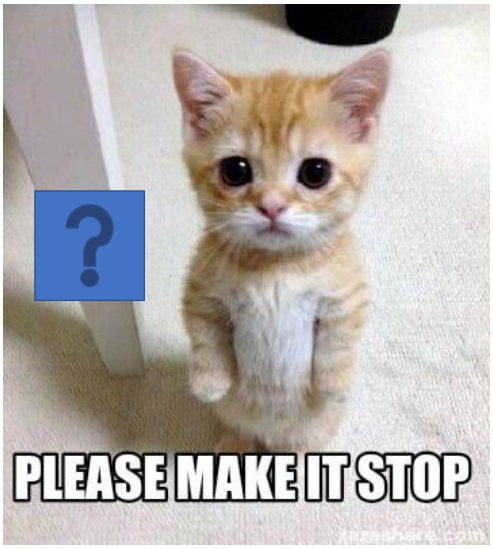
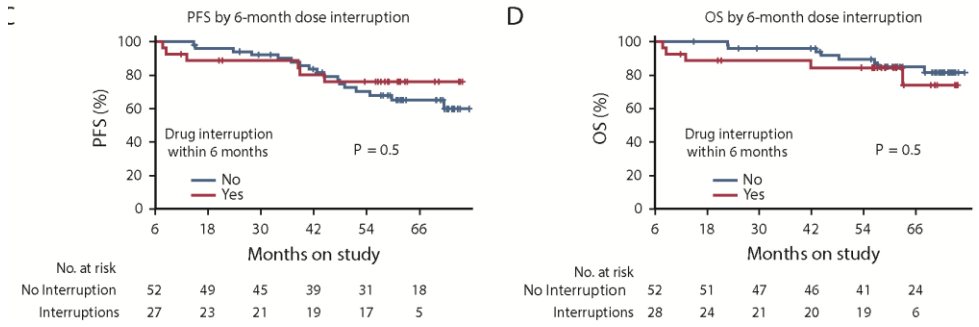
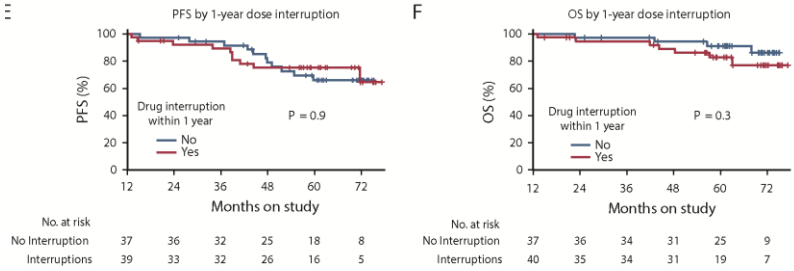


Holding vs. Discontinuation?

41



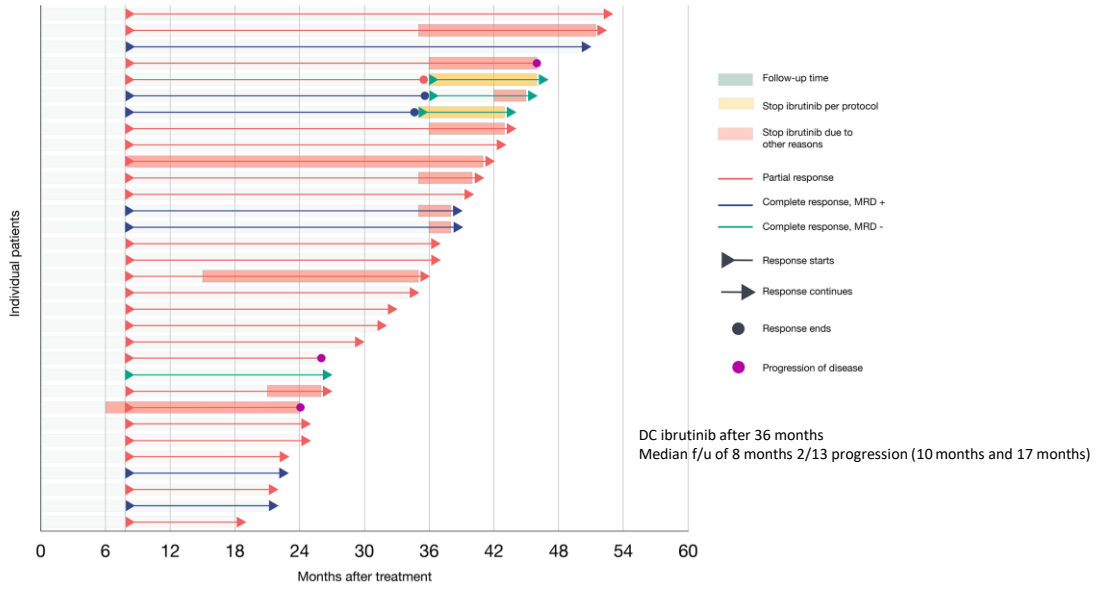
Missed ibrutinib:
> 8 days 68%
> 15 days 48%



Blood (2019) 133 (22): 2452–2455.

42

Stopping Ibrutinib



DC ibrutinib after 36 months
Median f/u of 8 months 2/13 progression (10 months and 17 months)

Figure 1. Swimmers plot of patients enrolled
This figure provides a snapshot of all patients enrolled in the study that received medication. Each bar represents one subject in the study. Patients started treatment at time point zero. First response assessment occurred eight months after initiation of therapy according to iWCLL 2018 guidelines.

Blood 2020 Suppl (1) 33-34

43

CLL-"Best" initial therapy

- Is watchful waiting still the best option? → YES, unless on study
- Any role for chemotherapy?→ not really….
- Ongoing Treatment with single agent BTKi
  - Which BTKi? → acalabrutinib
  - In combination? → no
  - Treatment interruption? → ? Perhaps ? But standard of care remains continuous therapy
- MRD negativity as a treatment goal
- Fixed duration therapy

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Minimal Residual Disease (MRD)- Is this the goal of CLL directed therapy?

https://youtu.be/t1Z4vF0EL74

https://www.youtube.com/watch?v=rkTnrEHwpKI

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MRD

- Not applicable to continuous BTKi
- MRD negativity is associated with longer remissions with fixed duration therapy
  - MCF* (10^{-4}) in marrow has been the gold standard
  - -if MRD negative outcomes the same irrespective of number of chemo/FCR cycles
- What is the best platform to use?
  - MCF or NGS?
- What should one do with the information?
- Should I monitor MRD serially?

MCF = 6 color multi color flow cytometry

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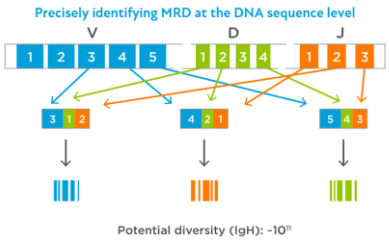
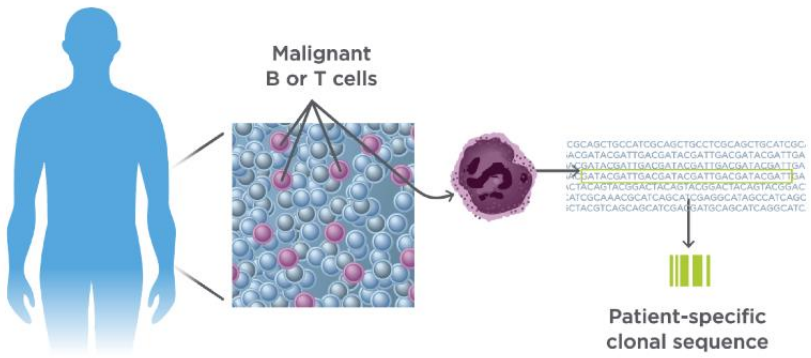
clonoSEQ By Adaptive





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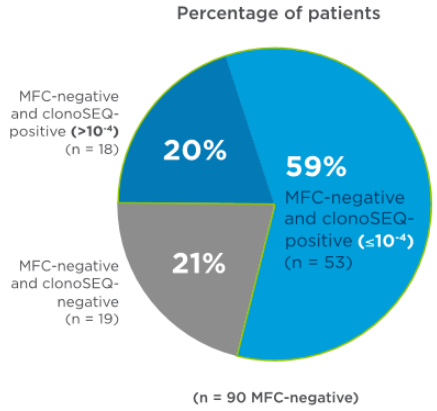
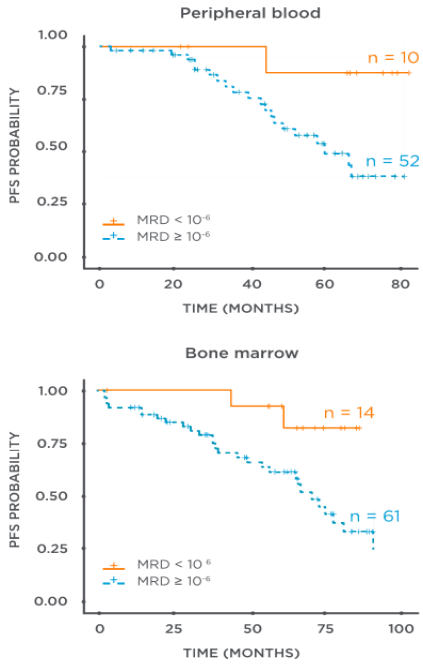
NGS more sensitive than MCF





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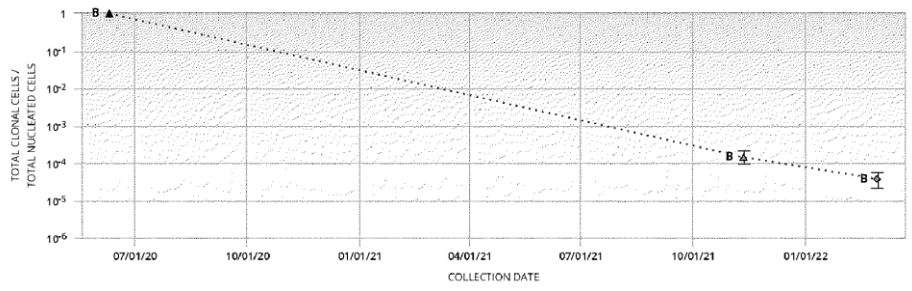
NGS (clonoSEQ®) is highly quantitative

RESULTS SUMMARY

- Genomic DNA was extracted from a blood sample.
- 6 of the 6 dominant sequences identified in a diagnostic sample from this patient were still present in this current sample.
- 121 copies of the dominant sequence determining the MRD result (IGK Sequence C) were observed out of 3,275,992 total nucleated cells evaluated from this sample.
- **The results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.**

SAMPLE-LEVEL MRD TRACKING *(shows only the sequence determining the MRD result for each time point)*



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Fixed Duration Therapy

MRD as a meaningful endpoint

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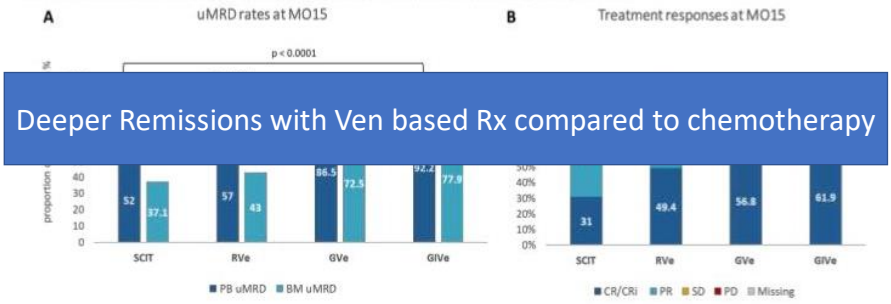
A Randomized Phase III Study of Venetoclax-Based Time-Limited Combination Treatments (RVe, GVe, GIVe) Vs Standard Chemoimmunotherapy (CIT: FCR/BR) in Frontline Chronic Lymphocytic Leukemia (CLL) of Fit Patients: First Co-Primary Endpoint Analysis of the International Intergroup GAIA (CLL13) Trial

Figure 1. Comparison of uMRD rates by flow and treatment responses (CR: complete response; CRi: complete response with incomplete bone marrow recovery; PR: partial response; SD: stable disease; PD: progressive disease)



Deeper Remissions with Ven based Rx compared to chemotherapy

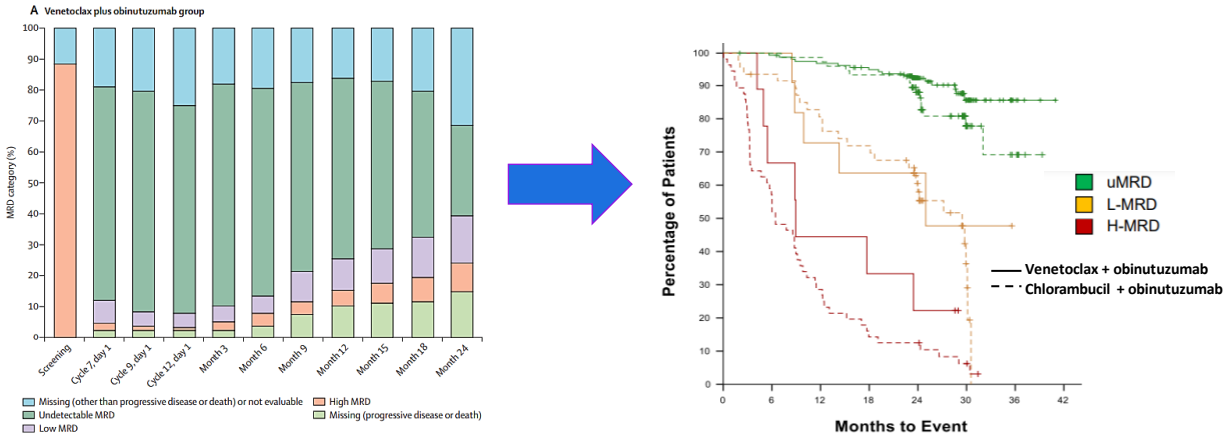
N=926 pts (CIT: 229 (150 FCR, 79 BR), RVe: 237, GVe: 229, GIVe: 231

TUMOR LYSIS IS A RISK OF VENETOCLAX

51

Venetoclax + Obinutuzumab in TN CLL
Phase III, CLL14 Trial

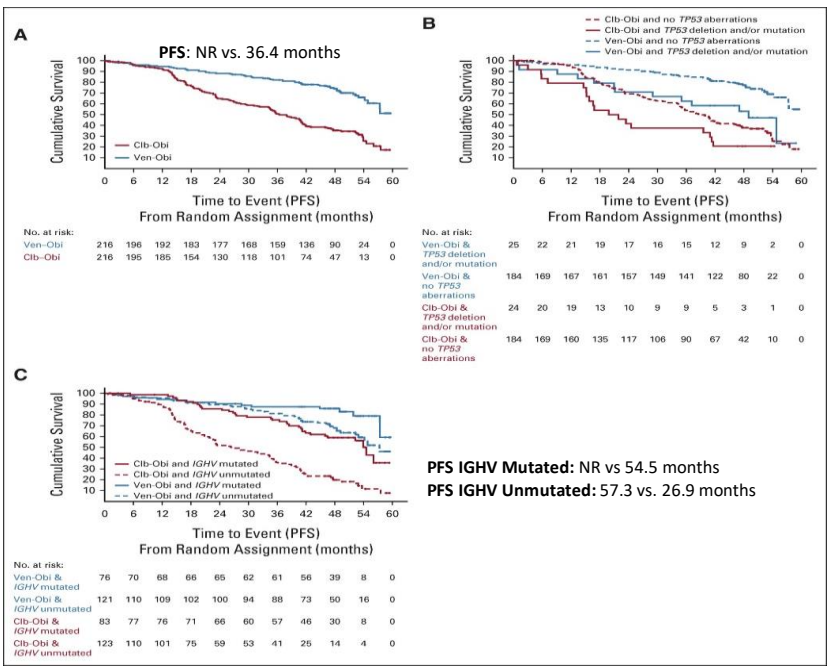
≥65 years or older or <65 years + coexisting conditions (N=432)



Conclusion: MRD negative disease with venetoclax correlates with improved PFS

Fischer K, et al. *N Engl J Med*. 2019; Al-Sawaf O, et al. *Lancet Oncol*. 2020.

52



PFS IGHV Mutated: NR vs 54.5 months
PFS IGHV Unmutated: 57.3 vs. 26.9 months

PFS 17p/p53: 49 vs 21 months (p = .03)

NOT AS GOOD IN PATIENTS WITH HIGH RISK FEATURES

Median follow up 52.4 months

J. Clin Onc. 2021 Dec 20;39(36):4049-4060

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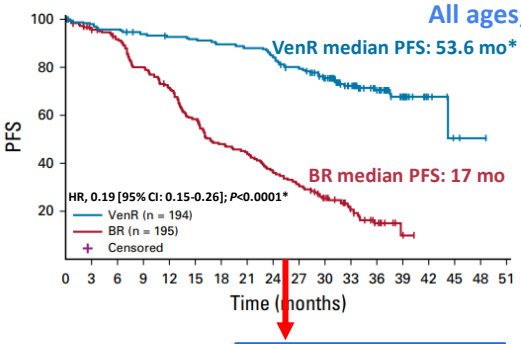
MRD in the relapsed setting: Venetoclax + Rituximab in R/R CLL *Phase III, MURANO Trial*

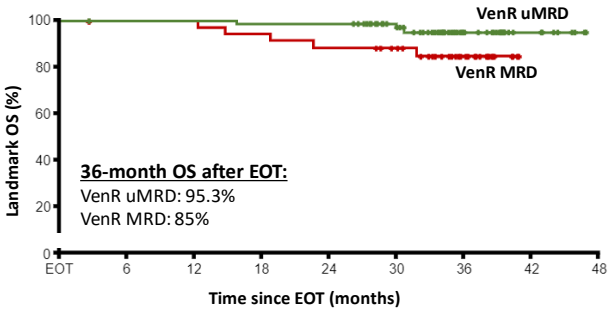
All ages; (median age: 65); N=389



48% of VenR arm had uMRD at EOT

Baseline del17p, unmutated IGVH, genomic complexity (≥3 copy # variations) associated with increased risk of MRD conversion post-EOT

Landmark OS by PB MRD Status at EOT in Patients that Completed Ven Tx without PD



High rates of uMRD with venetoclax combination correlates with improved OS

*Updated ASH 2020
uMRD, undetectable minimal residual disease; EOCT, end of combination therapy; EOT, end of therapy; NR, not reached.

Kater AP, et al. *J Clin Oncol.* 2019; Kater AP, et al. *ASH.* 2020. Abstract 125.

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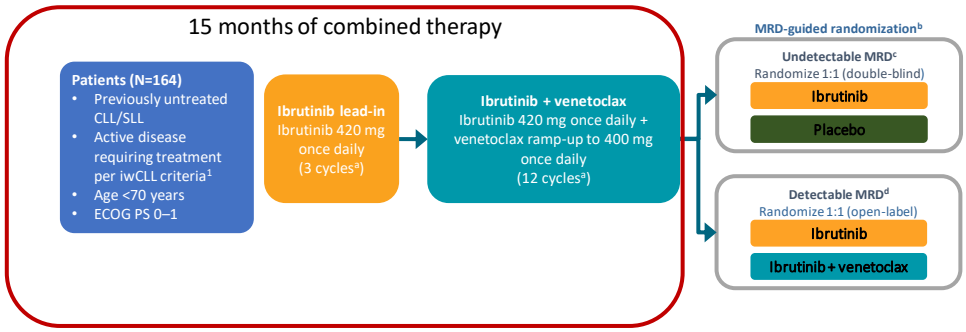
Ibrutinib plus venetoclax

CAPTIVATE-MRD Cohort: Study Design



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First-Line Treatment with Ibrutinib (Ibr) Plus Venetoclax (Ven) for Chronic Lymphocytic Leukemia (CLL): 2-Year Post-Randomization Disease-Free Survival (DFS) Results from the Minimal Residual Disease (MRD) Cohort of the Phase 2 Captivate Study

No need to continue Ibrutinib if MRD negative

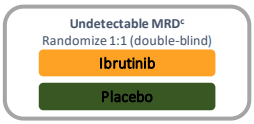
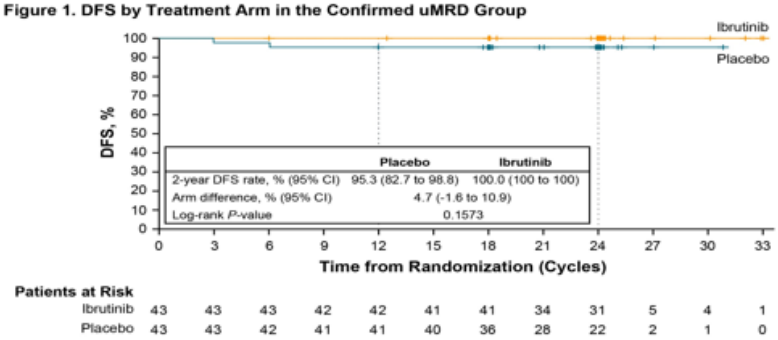


Figure 1. DFS by Treatment Arm in the Confirmed uMRD Group



Similar Study with zanubrutinib Fully accrued in poor risk patients (**SEQUOIA (BGB-3111-304) Trial)**

Blood (2021) 138 (Supplement 1): 68.

56

Fixed Duration and How do I use MRD in 2022

- Prefer clonoSEQ platform
  - Avoids the need for BM bx, quanititative
- Can I stop treatment early??
- Continue therapy in high risk patients and/or those who continue to have a response
- No role for continuous/surveillance monitoring in the majority of patients outside of a clinical trial
  - exception: patients with history of *AIHA/ITP?

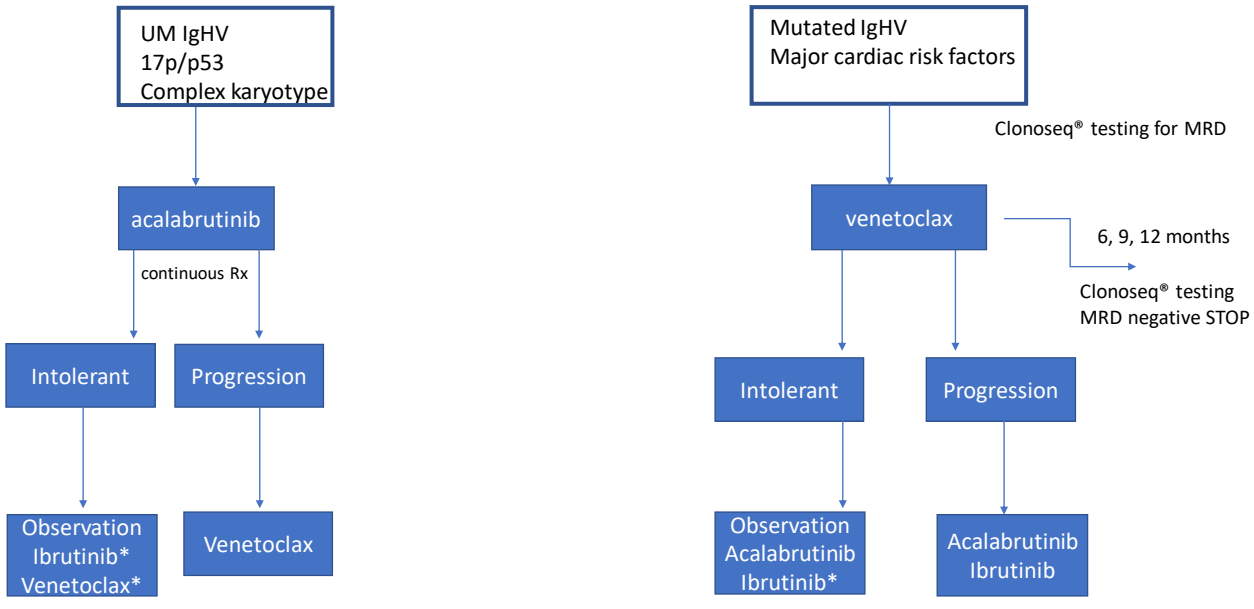
*Autoimmune hemolytic anemia, immune thrombocytopenia

57

CLL-"Best" initial therapy

- Is watchful waiting still the best option? → YES, unless on study
- Any role for chemotherapy?→ not really….
- Ongoing Treatment with single agent BTKi
  - Which BTKi? → acalabrutinib
  - In combination? → no
  - Treatment interruption? → ? Perhaps ? But standard of care remains continuous therapy
- MRD negativity as a treatment goal→ yes for venetoclax based Rx
- Fixed duration therapy→ yes, venetoclax in good risk folks

58



*If early in treatment course, change BTKI, dose reduction

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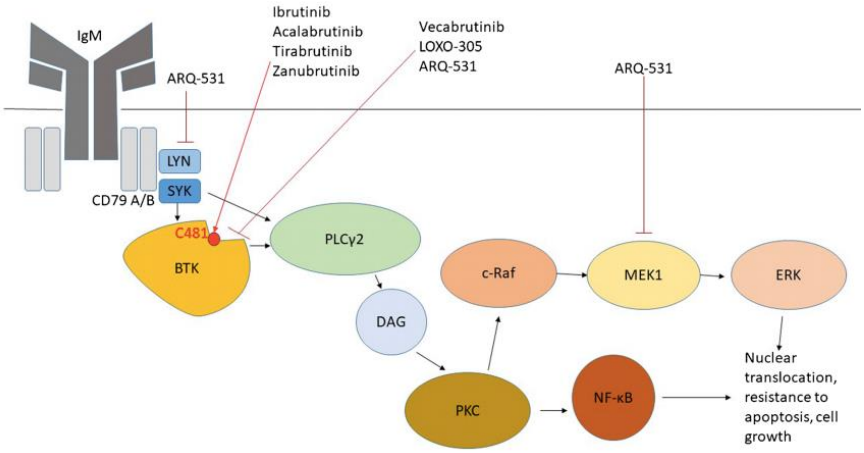
The Next Phase
Drugs in Development that also target BTK



Bond DA, Woyach JA. *Curr Hematol Malig Rep.* 2019.

60

Pirtobrutinib, A Highly Selective, Non-covalent (Reversible) BTK Inhibitor In Previously Treated CLL/SLL: Updated Results From The Phase 1/2 BRUIN Study

Anthony R. Mato[1], John M. Pagel[2], Catherine C. Coombs[3], Nirav N. Shah[4], Nicole Lamanna[5], Talha Munir[6], Ewa Lech-Maranda[7], Toby A. Eyre[8], Jennifer A. Woyach[9], William G. Wierda[10], Chan Y. Cheah[11], Jonathan B. Cohen[12], Lindsey E. Roeker[1], Manish R. Patel[13], Bita Fakhri[14], Minal A. Barve[15], Constantine S. Tam[16], David J. Lewis[17], James N. Gerson[18], Alvaro J. Alencar[19], Chaitra S. Ujjani[20], Ian W. Flinn[21], Suchitra Sundaram[22], Shuo Ma[23], Deepa Jagadeesh[24], Joanna M. Rhodes[25], Justin Taylor[19], Omar Abdel-Wahab[1], Paolo Ghia[26], Stephen J. Schuster[18], Denise Wang[27], Binoj Nair[27], Edward Zhu[27], Donald E. Tsai[27], Matthew S. Davids[28], Jennifer R. Brown[28], Wojciech Jurczak[29]

[1]Memorial Sloan Kettering Cancer Center, New York, USA; [2]Swedish Cancer Institute, Seattle, USA; [3]University of North Carolina at Chapel Hill, Chapel Hill, USA; [4]Medical College of Wisconsin, Milwaukee, USA; [5]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, USA; [6]Department of Haematology, St. James's University Hospital, Leeds, UK; [7]Institute of Hematology and Transfusion Medicine, Warsaw, Poland; [8]Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Center, Oxford, UK; [9]The Ohio State University Comprehensive Cancer Center, Columbus, USA; [10]MD Anderson Cancer Center, Houston, USA; [11]Linear Clinical Research and Sir Charles Gairdner Hospital, Perth, Australia; [12]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [13]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, USA; [14]University of California San Francisco, San Francisco, USA; [15]Mary Crowley Cancer Research, Dallas, USA; [16]Peter MacCallum Cancer Center, Royal Melbourne Hospital, and University of Melbourne, Melbourne, Australia; [17]Plymouth Hospitals NHS Trust - Derriford Hospital, Plymouth, UK; [18]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, USA; [19]University of Miami Miller School of Medicine, Miami, USA; [20]Fred Hutchinson Cancer Research Center, [21]Sarah Cannon Research Institute, Nashville, USA; [22]Department of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, [23]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA; [24]Cleveland Clinic, Cleveland, OH, USA; [25]Northwell Health Cancer Institute, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Health, New Hyde Park, NY; [26]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy; [27]Loxo Oncology at Lilly, Stamford, CT, USA; [28]Dana-Farber Cancer Institute and Harvard Medical School, Boston, USA; [29]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland

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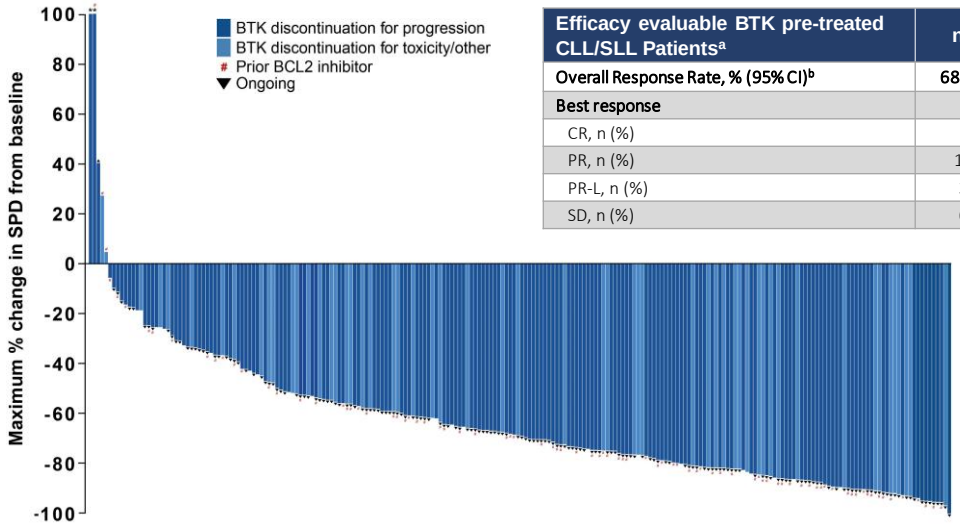
Pirtobrutinib Efficacy in BTK Pre-treated CLL/SLL Patients



Efficacy evaluable BTK pre-treated CLL/SLL Patients[a]	n = 252
Overall Response Rate, % (95% CI)[b]	68 (62 – 74)
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

Data cutoff date of 16 July 2021. *Patients with >100% increase in SPD. Data for 30 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to investigator assessment. Total % may be different than the sum of the individual components due to rounding.

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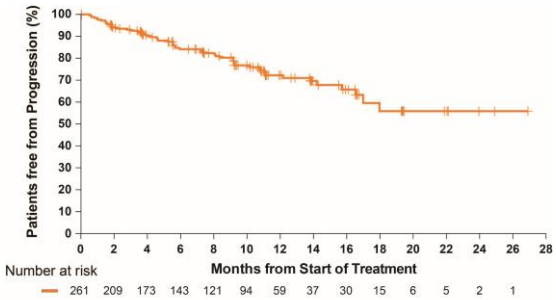
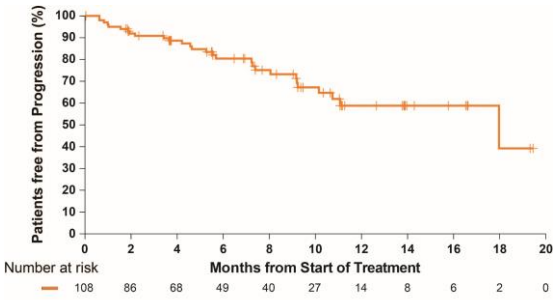
Progression-free Survival in BTK Pre-treated CLL/SLL Patients

PFS in at least BTK pre-treated patients
Median prior lines = 3



Median PFS: Not Estimable (95% CI: 17.0 months – Not Estimable)

PFS in at least BTK and BCL2 pre-treated patients
Median prior lines = 5



Median PFS: 18 months (95% CI: 10.7 months – Not Estimable)

- 74% (194/261) of BTK pre-treated patients remain on pirtobrutinib
- Median follow-up of 9.4 months (range, 0.3 – 27.4) for all BTK pre-treated patients

Very effective in patients who develop BTKi mutations on ibrutinib and acalabrutinib
VERY WELL TOLERATED (low risk of afib/HTN)

Data cutoff date of 16 July 2021. Response status per iwCLL 2018 according to investigator assessment.

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COVID and CLL

- ≈ 70-90% hospitalized, 25-30% die from COVID (pre-vaccine)[1,2]
  - Age > 75 and co-morbidities increase risk for death
- Patients may have active infection for months/difficulty clearing the virus
- Survival in CLL patients has improved significantly over the course of the pandemic (even pre-vaccine)[3]
- Antibody response rate 39% (15-80%) after initial series[4,5]
  - Low IgG, ongoing BTKi, rituximab or obinutuzumab within 1 year
  - Improved with 3rd dose (25% seroconversion)

1. *Blood*. 2020 Sep 3;136(10):1134-1143
2. Leukemia. 2020 Sep;34(9):2354-2363.
3. *Blood* (2021) 138 (18): 1768–1773.
4. *Blood* 2022 Feb 3;139(5):678-685.
5. Blood. 2021 Jun 10;137(23):3165-3173.

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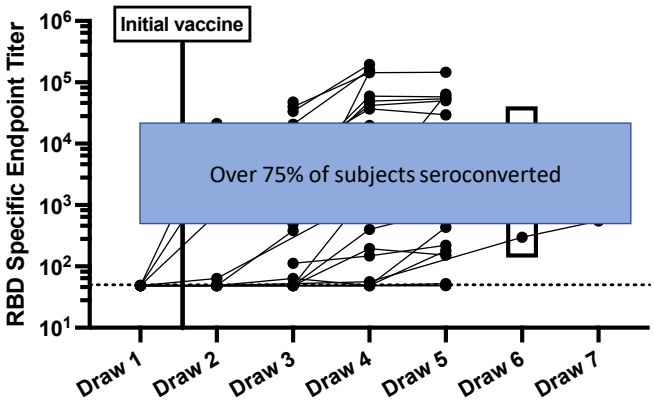
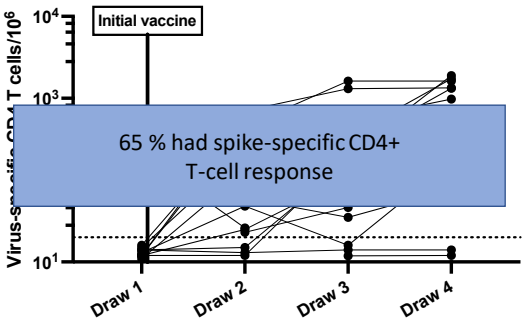
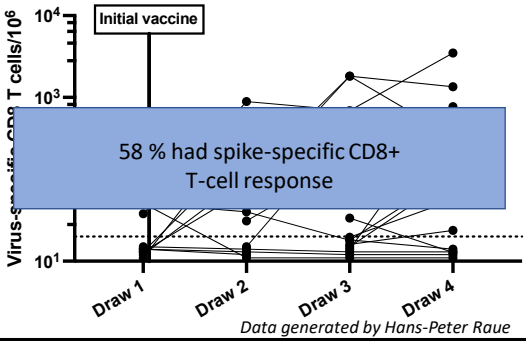


These antibody responses are neutralizing

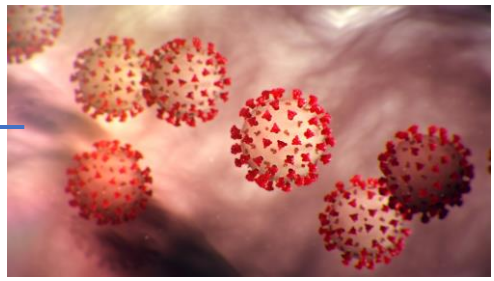
Data generated by David Xthona Lee





Data generated by Hans-Peter Raue

65



Prevention

Vaccination

-4 doses of vaccine*

*Revaccinate all patients (including boosters) receiving mAb within 12 months

Antibody

-on active treatment
-< 12 months of Rituximab or obinutuzumab
-observation patients without antibody response

Treatment

Oral antiviral within 5 days

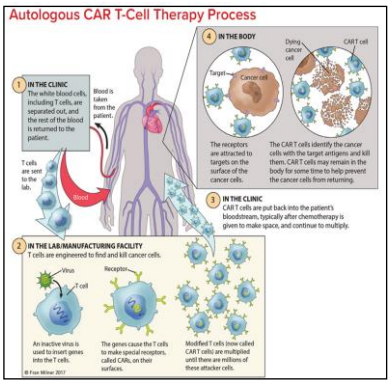
IV antibody
> 5 days
Drug interactions
kidney dz liver disease

66

THANK YOU

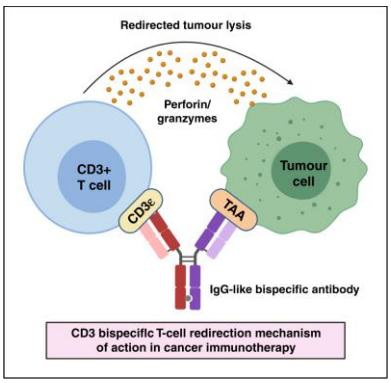
2023…….Immunotherapy

CAR-NK and CAR-T



The Leukemia and Lymphoma Society

Bi-specific antibodies



British Journal of Cancer (*Br J Cancer*) ISSN 1532-1827 (online)

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ASK A QUESTION

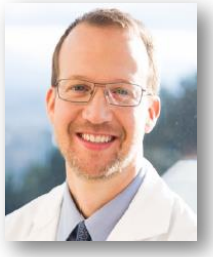
LIVING WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Ask a question by phone:

Press star (*) then the number 1 on your keypad.

Ask a question by web:

Click “Ask a question”
Type your question
Click “Submit”



Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

LEUKEMIA & LYMPHOMA SOCIETY®

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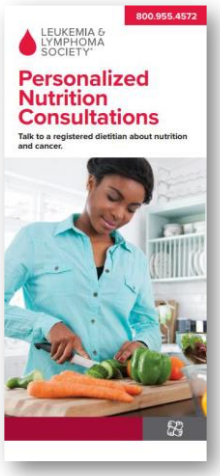
LLS EDUCATION & SUPPORT RESOURCES

HOW TO CONTACT US:

To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials:

Call: (800) 955-4572
Monday to Friday, 9 a.m. to 9 p.m. ET
Chat live online: www.LLS.org/InformationSpecialists
Monday to Friday, 10 a.m. to 7 p.m. ET
Email: www.LLS.org/ContactUs
All email messages are answered within one business day.

CLINICAL TRIAL SUPPORT CENTER
Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process.
www.LLS.org/Navigation



NUTRITION CONSULTATIONS
Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.
www.LLS.org/Consult.

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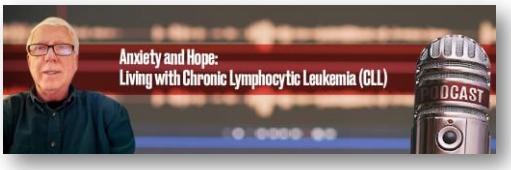
LLS EDUCATION & SUPPORT RESOURCES

Online Chats

Online Chats are free, live sessions, moderated by oncology social workers. To register for one of the chats below, or for more information, please visit **www.LLS.org/Chat**

Education Videos

View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit **www.LLS.org/EducationVideos**



Patient Podcast

The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit **www.TheBloodline.org**

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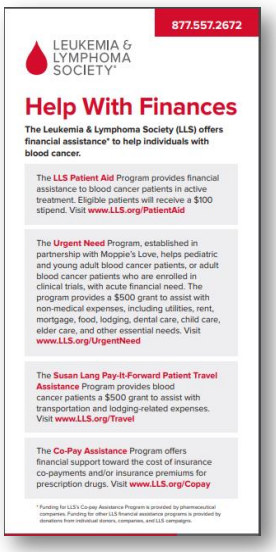
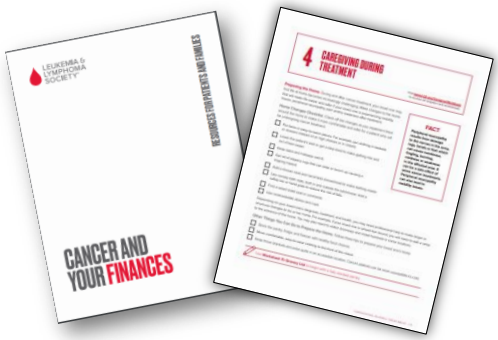
LLS EDUCATION & SUPPORT RESOURCES



The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: www.LLS.org/Finances



To order free materials: **www.LLS.org/Booklets**

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THANK YOU
We have one goal: A world without blood cancers
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