MAYO CLINIC

MOVING THE FIELD FORWARD IN CLL

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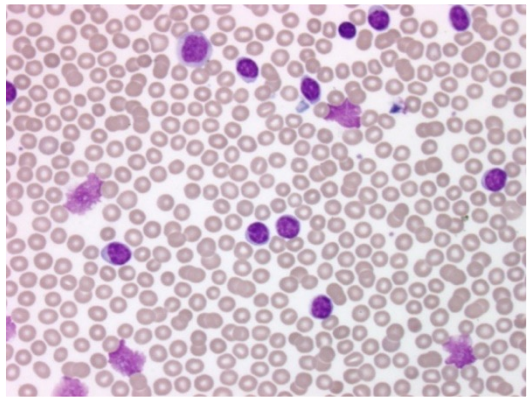
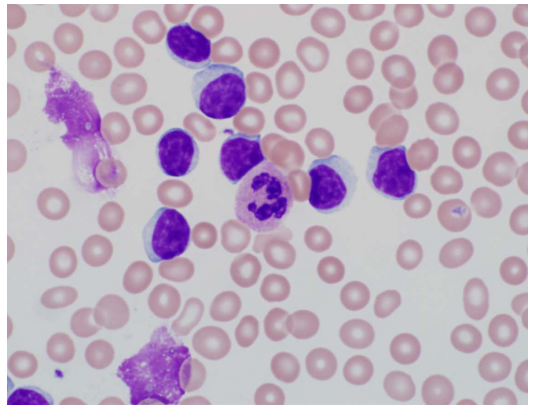
Next Wave Academy
April 29, 2023

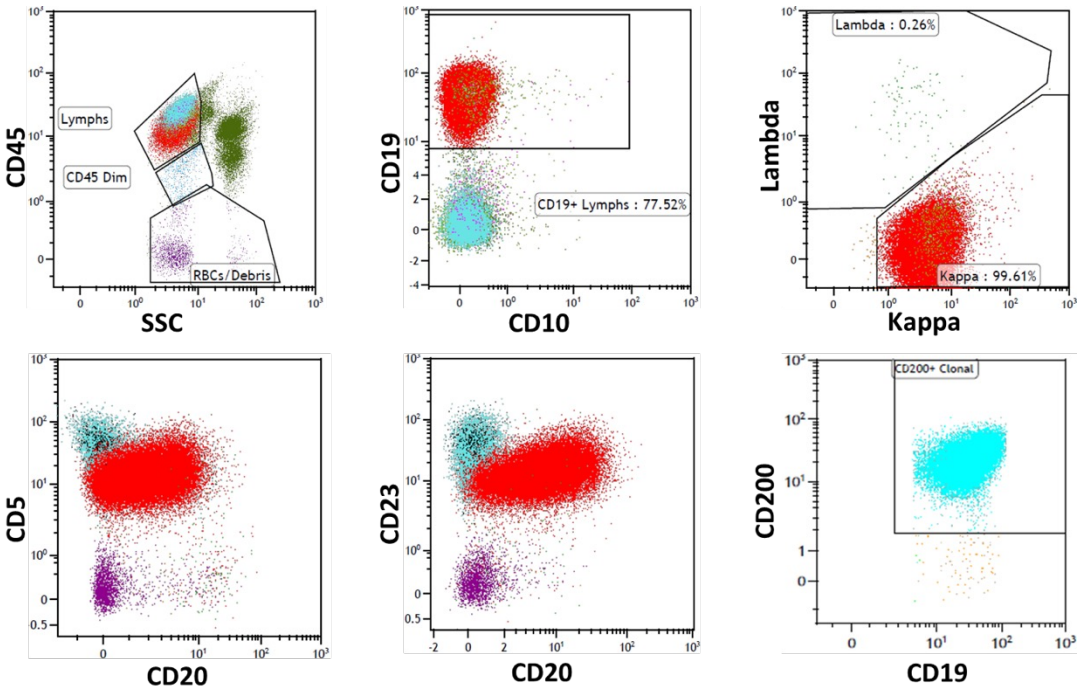
DISCLOSURES

- Research funding (institution): Janssen, AstraZeneca, Merck, and Genentech
- Honoraria (institution): Pharmacyclics, Merck, AstraZeneca, Janssen, BeiGene, Genentech, Amgen, MingSight Pharmaceuticals, TG Therapeutics, Novalgen Limited, Kite Pharma, and AbbVie.

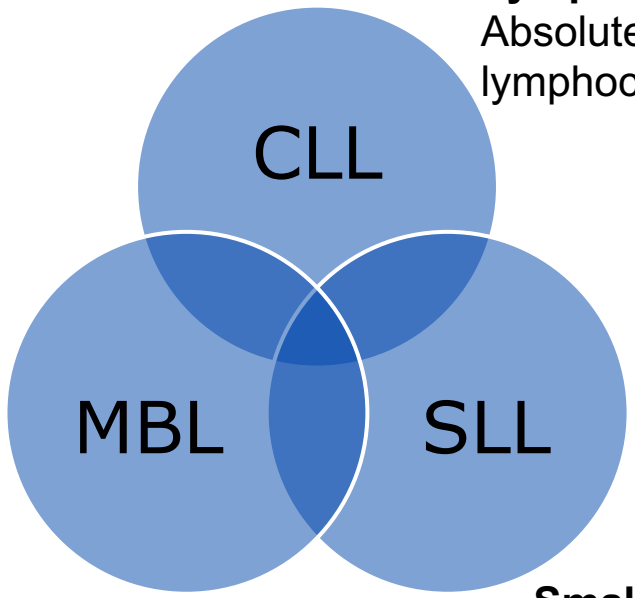
DIAGNOSIS OF CLL/SLL







Chronic Lymphocytic Leukemia:
Absolute clonal B lymphocyte count >5000



Monoclonal B-cell Lymphocytosis:
Absolute clonal B lymphocyte count <5000; **AND** no cytopenia, organomegaly, lymphadenopathy

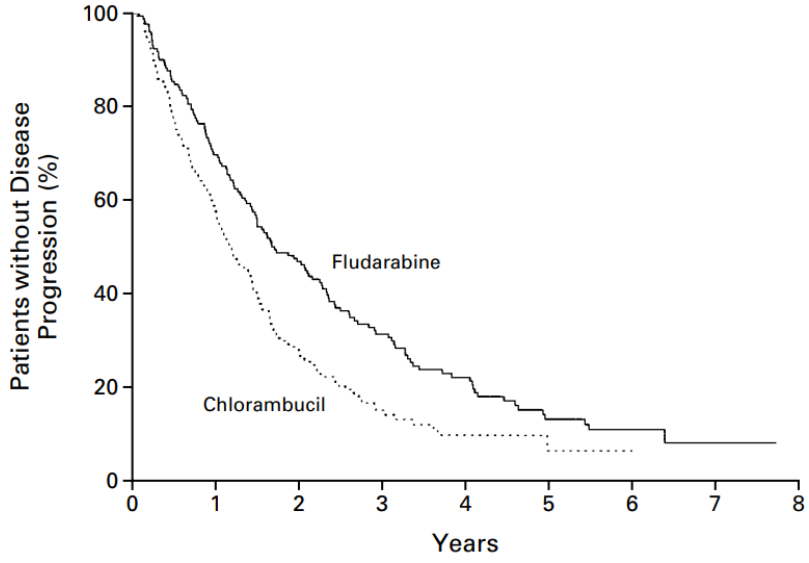
Small lymphocytic lymphoma:
Absolute clonal B lymphocyte count <5000; **AND** no cytopenia, but either organomegaly or lymphadenopathy by scans/exam

CLL TREATMENT

- Prior to 1991:
  - Chlorambucil and cyclophosphamide
  - Patients who stopped responding to these treatments had poor survival

- Fludarabine:
  - Phase II studies in alkylator refractory CLL (Dr. Grever and Dr. Keating) resulted in accelerated approval in 1991

- CALGB 9011[1]:
  - 509 patients untreated, symptomatic CLL
  - Randomized 1:1:1 to 6 (monthly) cycles of:
    - Fludarabine (F) 25 mg/m^2/day IV x 5
    - Chlorambucil (C) 40 mg/m^2 PO
    - Fludarabine + chlorambucil (F+C), 20/20



No. at Risk									
Fludarabine	172	116	74	43	27	13	6	3	0
Chlorambucil	183	99	44	17	7	2	1	0	0

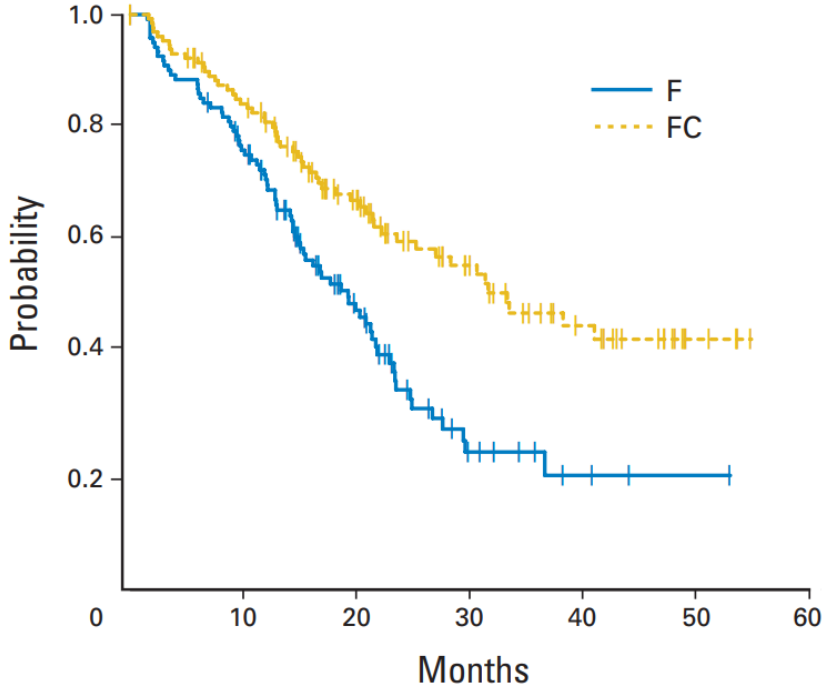
[1]Rai, *N Engl J Med* 2000;343:1750-7

CLL TREATMENT

- ECOG 2997[1]:
  - 278 previously untreated CLL
  - Randomized (1:1) to
    - Fludarabine alone (F) 25 mg/m^2 IV days 1-5, every 28 days
    - Fludarabine + cyclophosphamide (FC); C:600 mg/m^2 IV day 1 and F: 20 mg/m^2 days 1-5

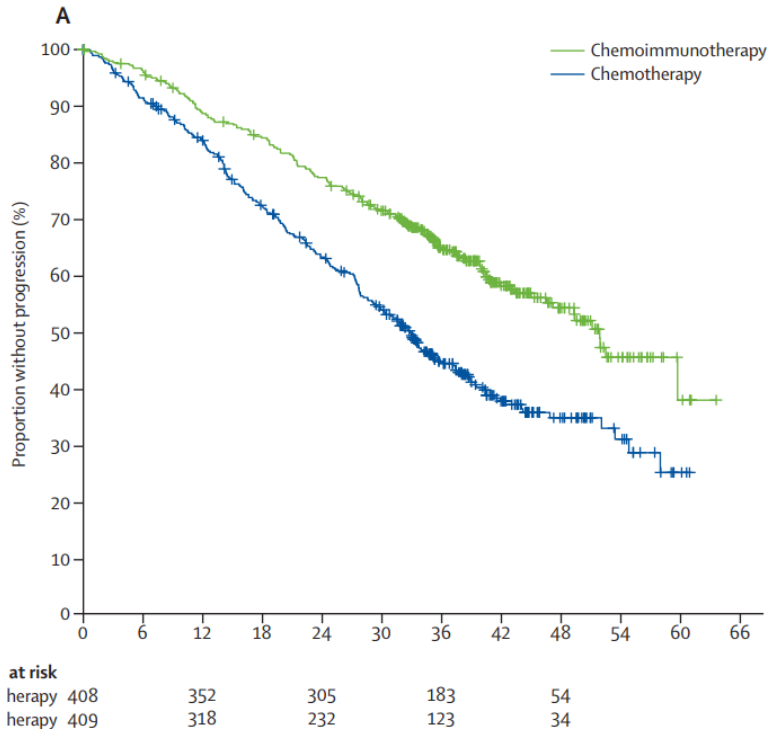
- Rituximab was approved for relapsed low-grade lymphoma in 1997

- CALGB 9712[2]:
  - Concurrent versus delayed treatment with fludarabine and rituximab
  - Higher ORR (90% vs. 77%) and higher CR (47 % vs. 28%) in the concurrent vs. delayed rituximab arm

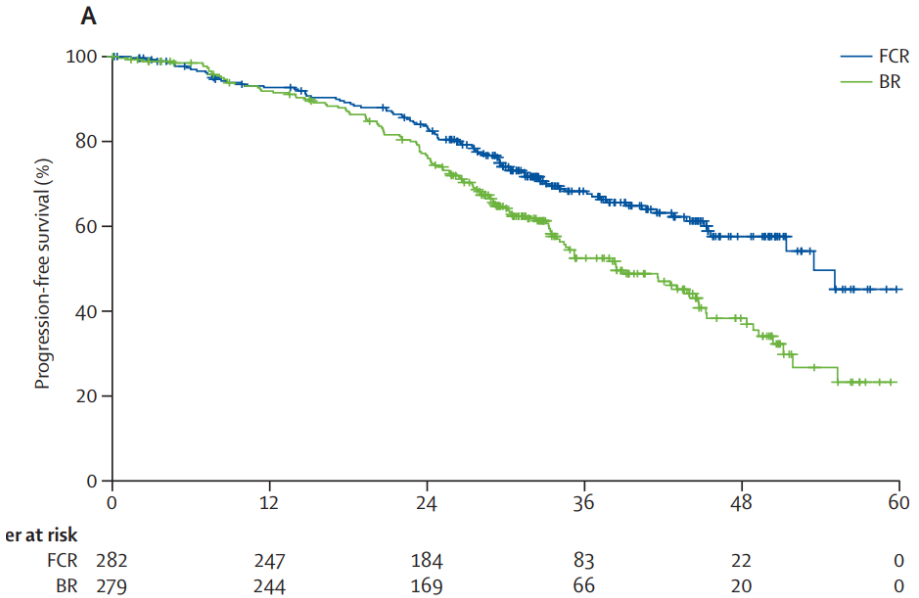


[1]Flinn, *J Clin Oncol*, 2007; 25:793-798
[2]Byrd, *Blood*, 2003; 101 (1): 6–14

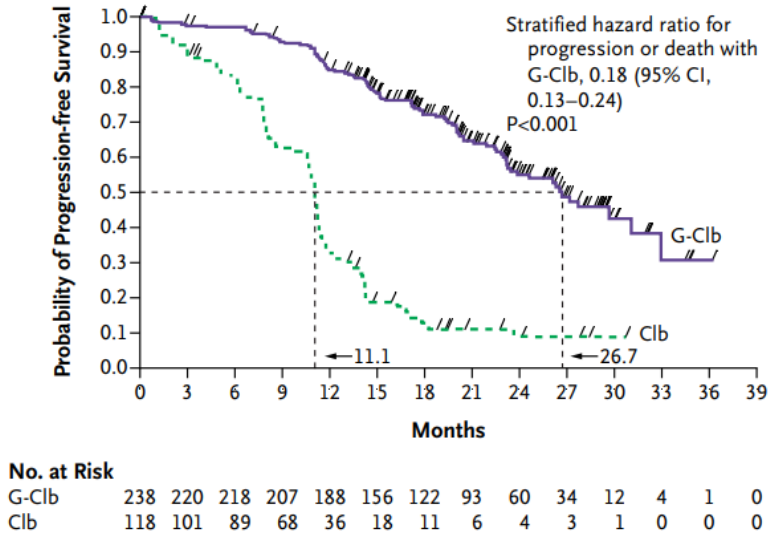
OTHER PIVOTAL TRIALS



CLL8: FCR vs. FC



CLL10: FCR vs. BR



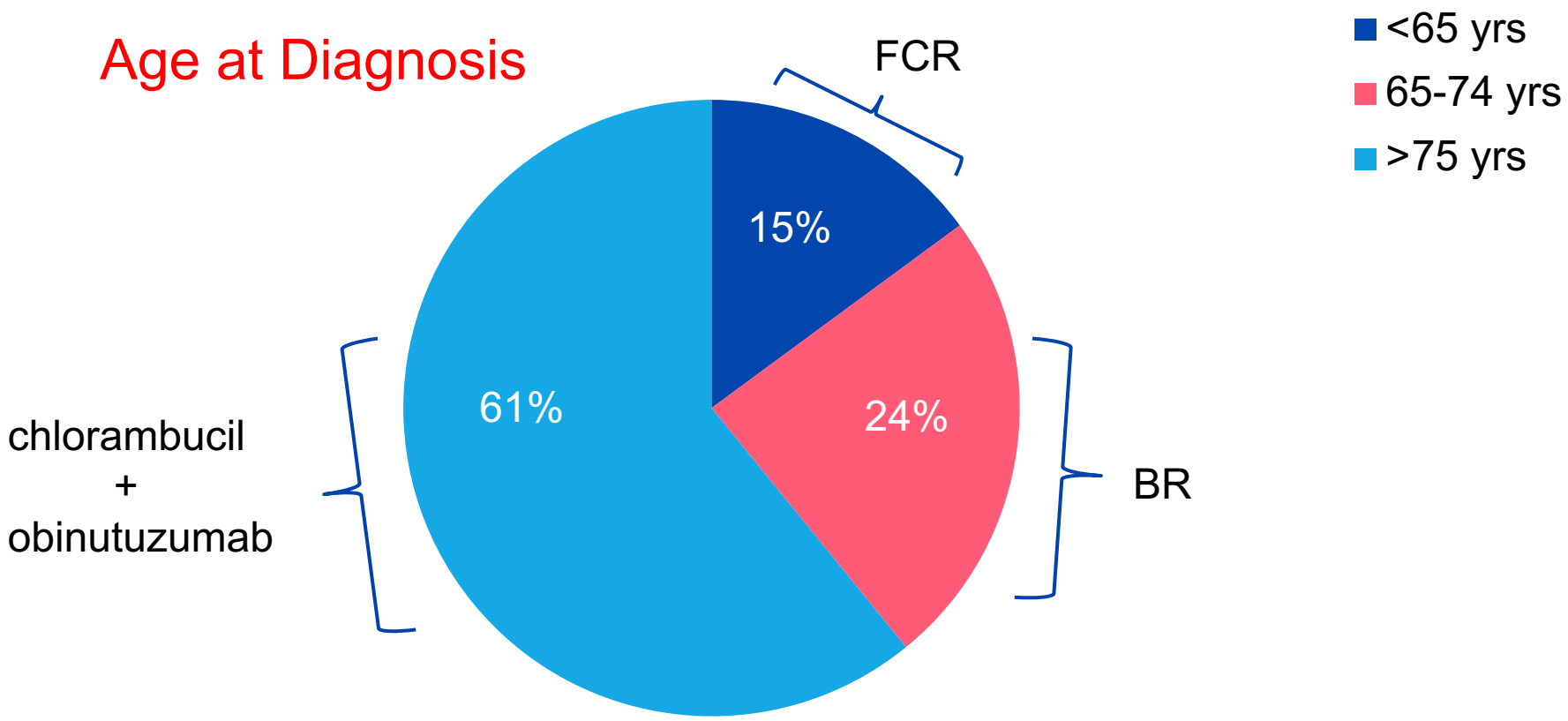
CLL11: chlorambucil vs. chlorambucil-rituximab vs. chlorambucil-obinutuzumab

Hallek, *Lancet* 2010; 376: 1164–74

Eichhorst, *Lancet Oncol* 2016; 17: 928–42

Goede, *N Engl J Med* 2014; 370:1101-1110

MANAGEMENT OF FRONTLINE CLL CIRCA 2013



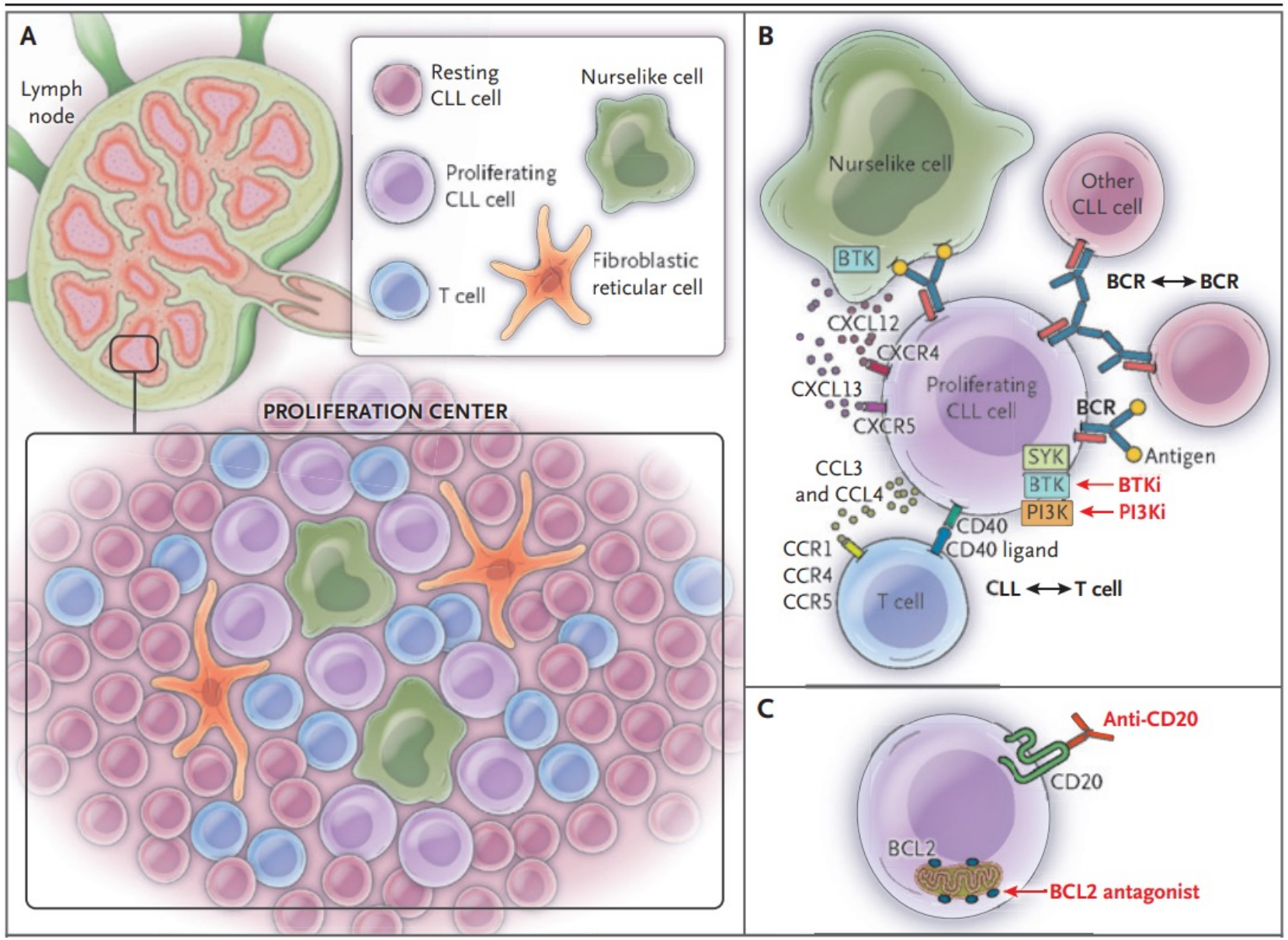
BIG QUESTIONS CIRCA 2013

- Primary goal of treatment to achieve high CR rates = longer PFS and longer OS
  - Add or change the treatment recipe of FCR:
    - Fludarabine + cyclophosphamide + ofatumumab
    - Pentostatin + cyclophosphamide + rituximab
    - FCR + mitoxantrone
    - FCR + alemtuzumab

- Reduce the risk of secondary neoplasms including MDS/AML and Richter's transformation:
  - Risk of secondary AML/MDS: 5% at 12 years
  - Risk of Richter transformation: 2% at 12 years

- Improve outcomes of patients with high-risk genetics:
  - Median PFS with the best frontline therapy (FCR) in del17p = 15-18 months
  - Median PFS in unmutated *IGHV* patients (FCR) = 36-40 months

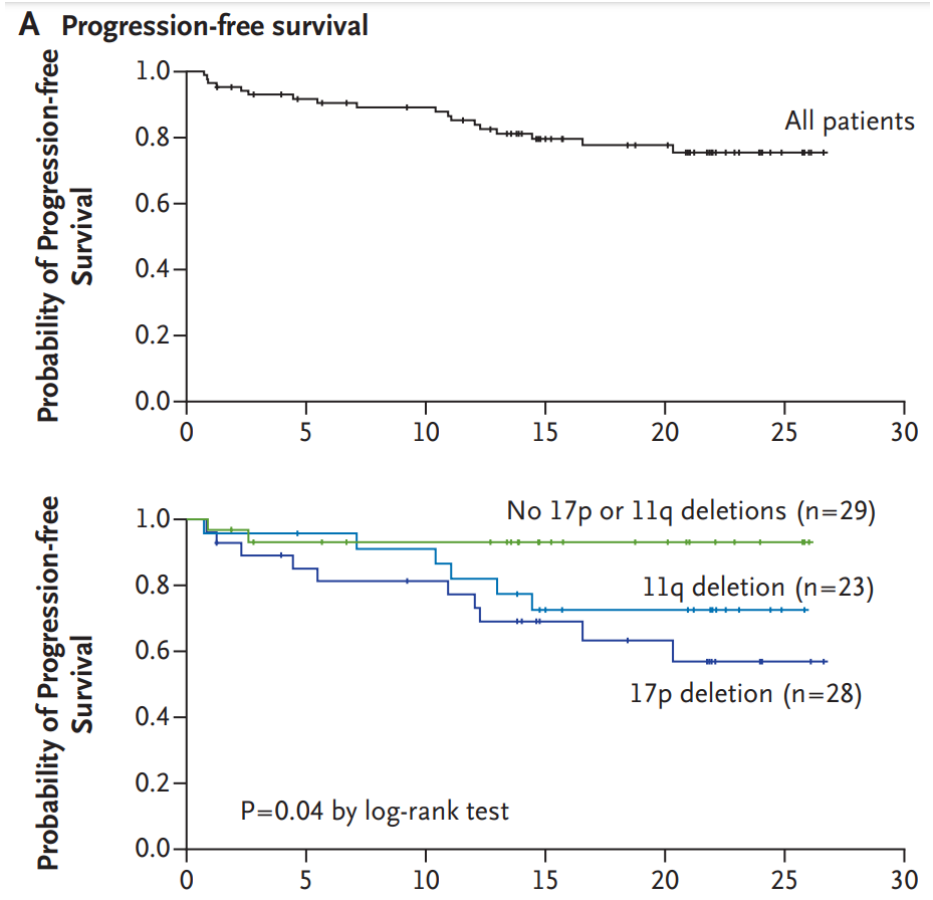
CLL MICROENVIRONMENT



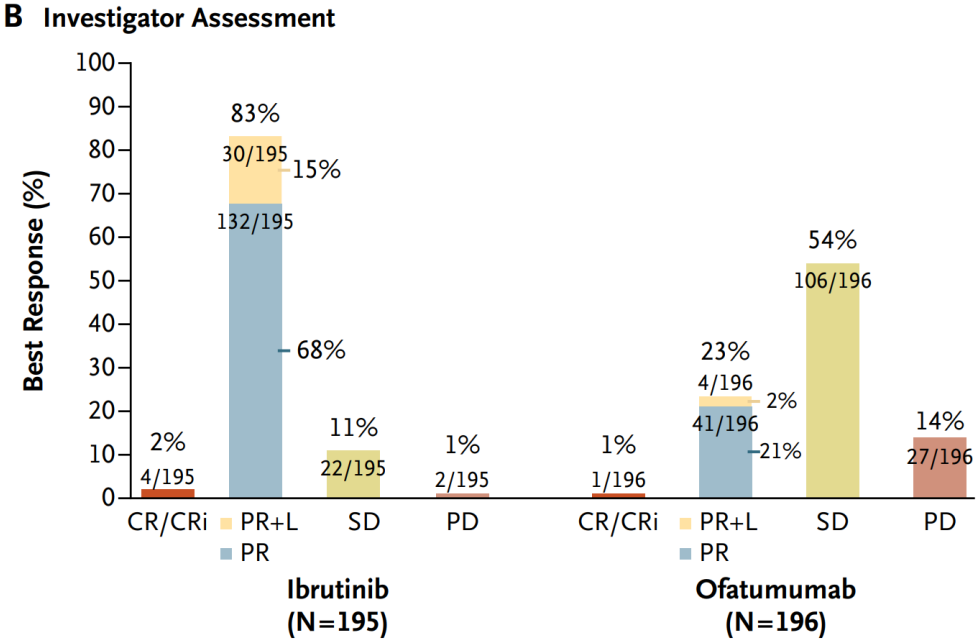
Burger, *NEJM*, 2020

RELAPSED CLL – IBRUTINIB

- Phase 2 study of ibrutinib in relapsed CLL, n=85
- Median prior lines of therapy = 4 (1-12)

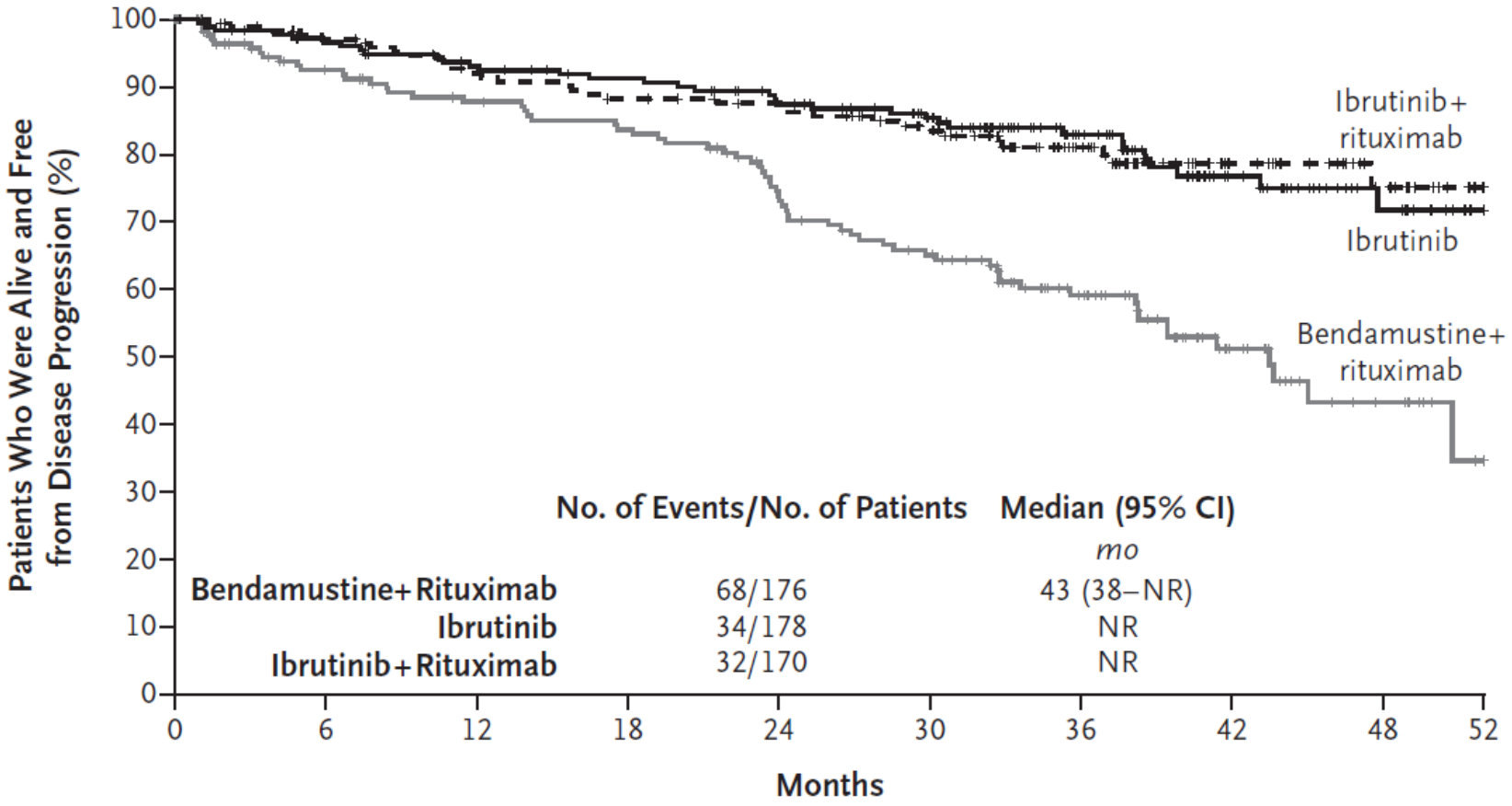


- Ibrutinib vs. ofatumumab in relapsed CLL, n=391
- Median prior lines of therapy = 3 (1-12)



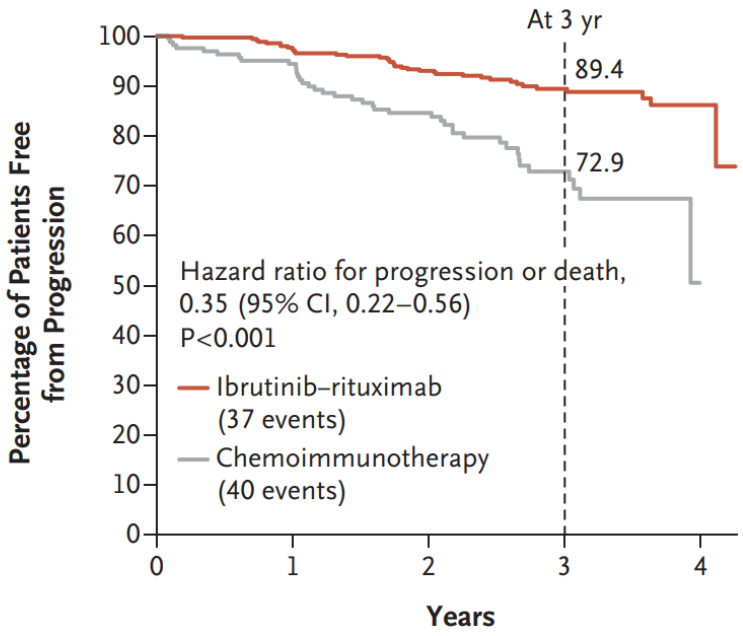
Byrd; *N Engl J Med* 2013; 369:32-42
Byrd; *N Engl J Med* 2014; 371:213-23

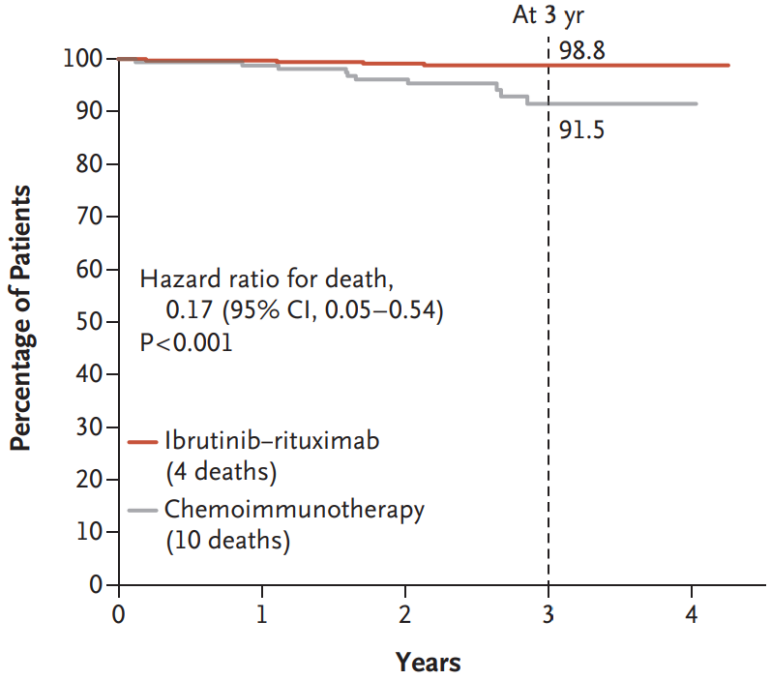
A041202: IBRUTINIB VS. IBRUTINIB-RITUXIMAB VS. BR, MEDIAN AGE = 71 YEARS



Woyach, *NEJM*, 2018; 379:2517

E1912; IBRUTINIB-RITUXIMAB VS. FCR; MEDIAN AGE = 57 YEARS





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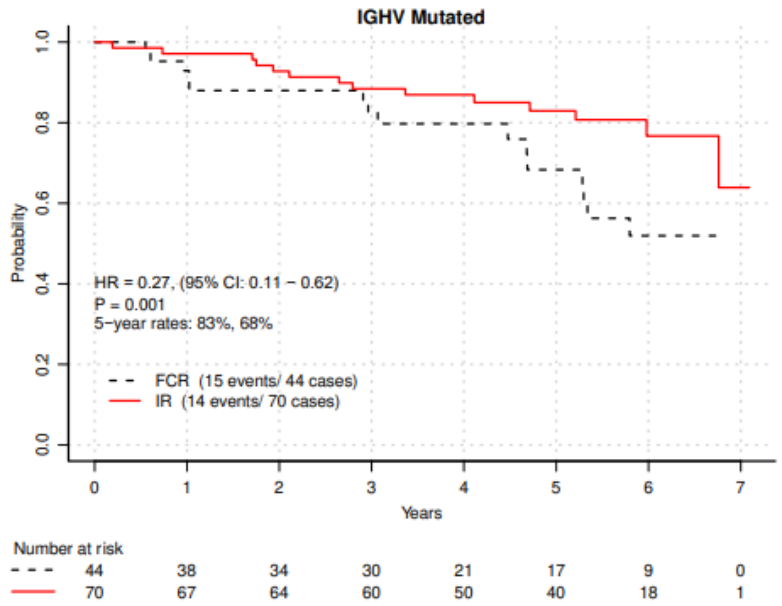
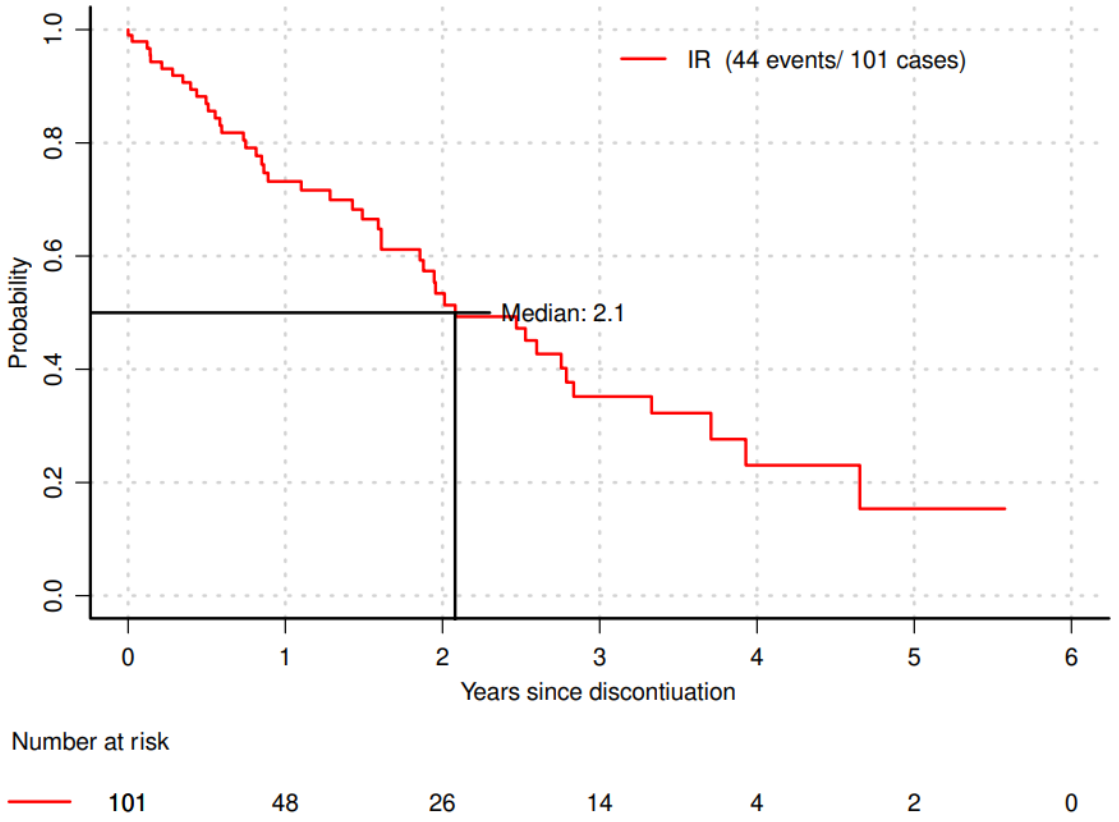


Shanafelt, *N Engl J Med* 2019; 381:432-443
Shanafelt, *Blood (2022)* 140 (2): 112–120

TOXICITY WITH IBRUTINIB

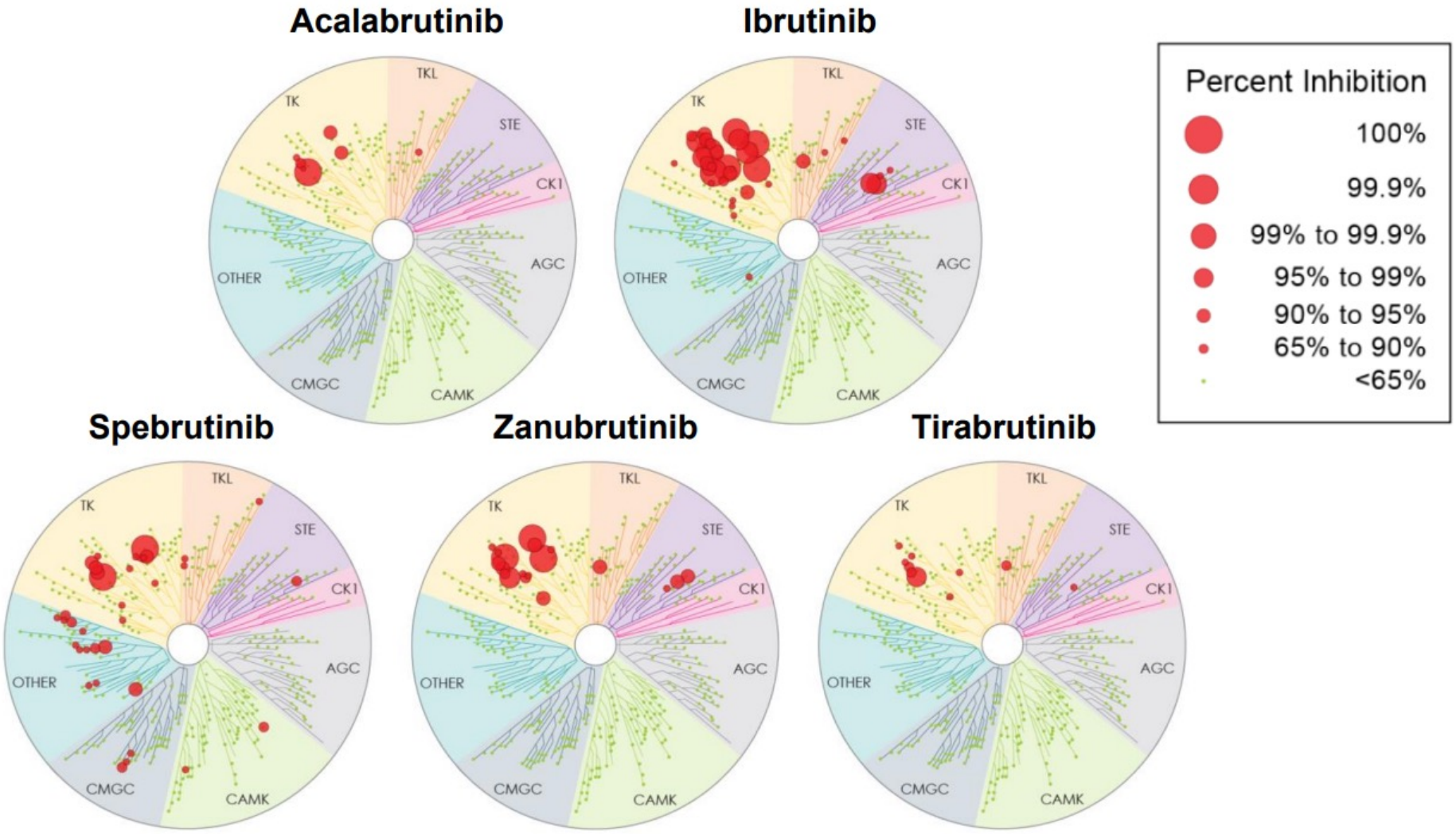
Adverse events	Ibrutinib	
	RESONATE2[5]	RESONATE[83,84]
	TN n = 135	RR n = 195
	f/u = 18.4 mo	f/u = 19 mo
Atrial fibrillation		
All grades	14 (10)	13 (7)
Grade ≥ 3	6 (4)	7 (4)
Bleeding		
All grades	9 (7)	NR
Grade ≥ 3	8 (6)	4 (2)
Hypertension		
All grades	18 (14)	NR
Grade ≥ 3	5 (4)	8 (4)
Arthralgia		
All grades	27 (20)	36 (19)
Grade ≥3	3 (2)	NR
Infection		
All grades	NR	NR
Grade ≥3	21 (23)	59 (30)
Diarrhea		
All grades	57 (42)	105 (54)
Grade ≥3	5 (4)	9 (5)



Lipsky and Lamanna, *ASH Education Book*, 2021
Shanafelt, *Blood (2022)* 140 (2): 112–120

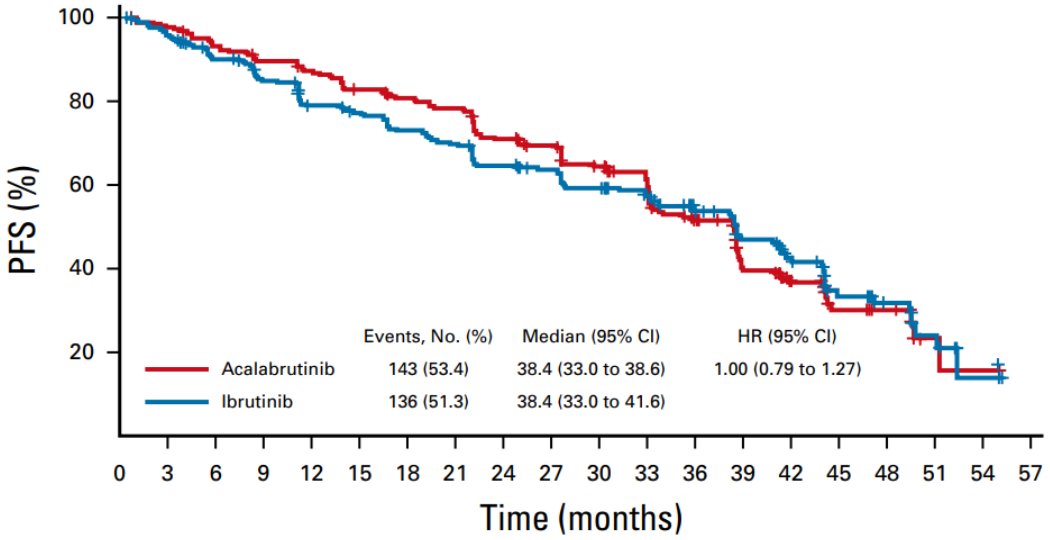
BETTER BTK INHIBITORS?

NOVEL BTK INHIBITORS

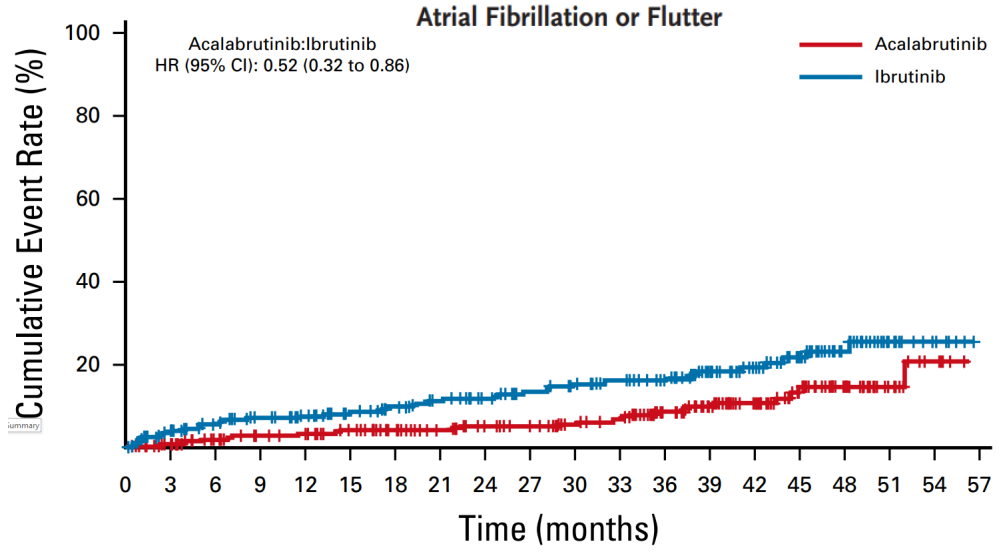


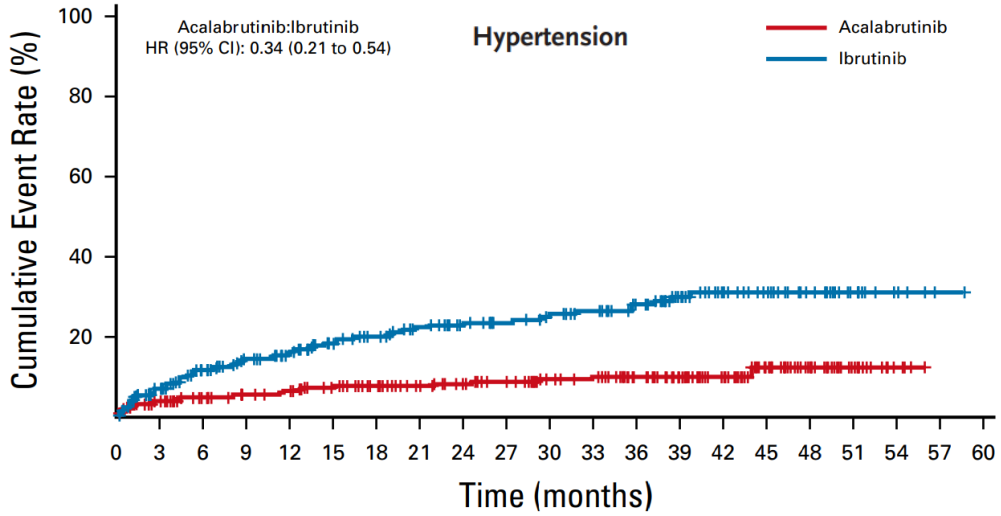
Kaptein, *ASH Annual Meeting*, 2018, Abstract 1871

ACALABRUTINIB VS. IBRUTINIB: ELEVATE-RR STUDY



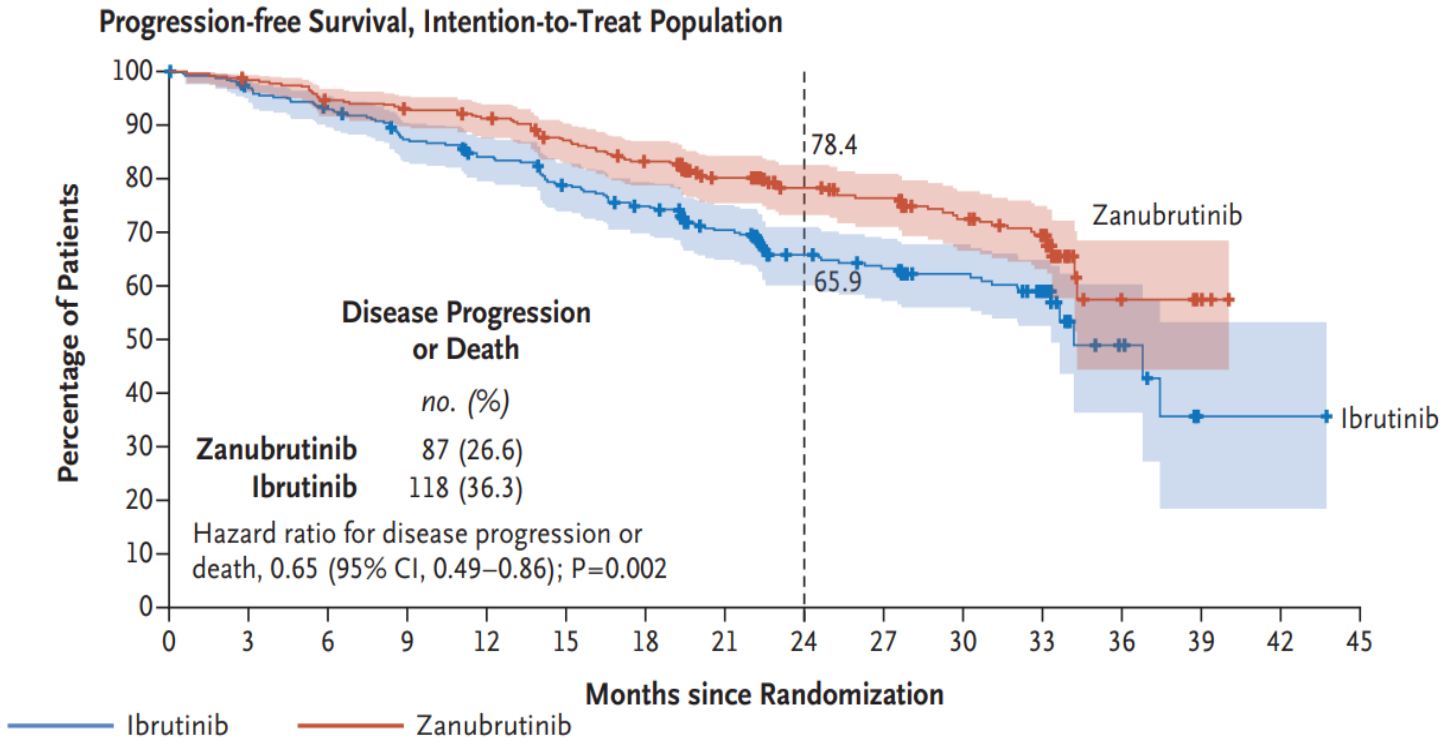
- No difference in OS between the two study arms

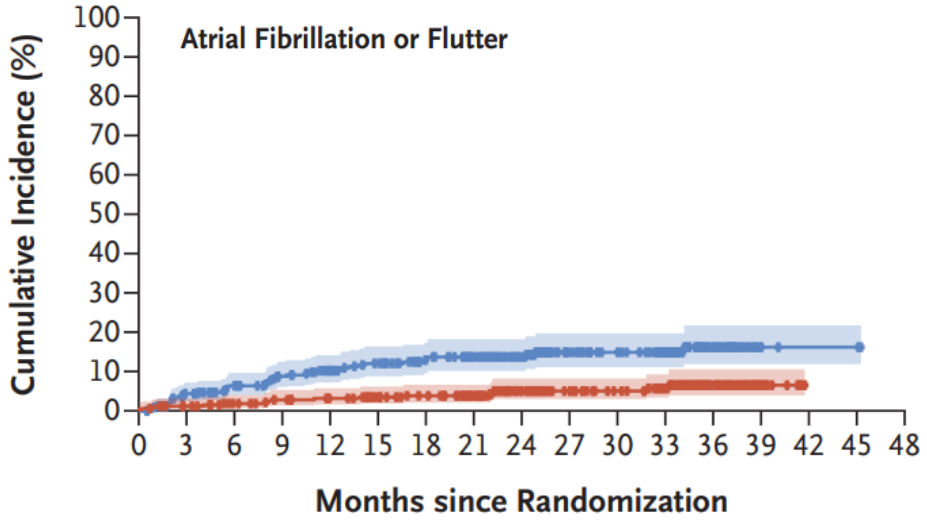


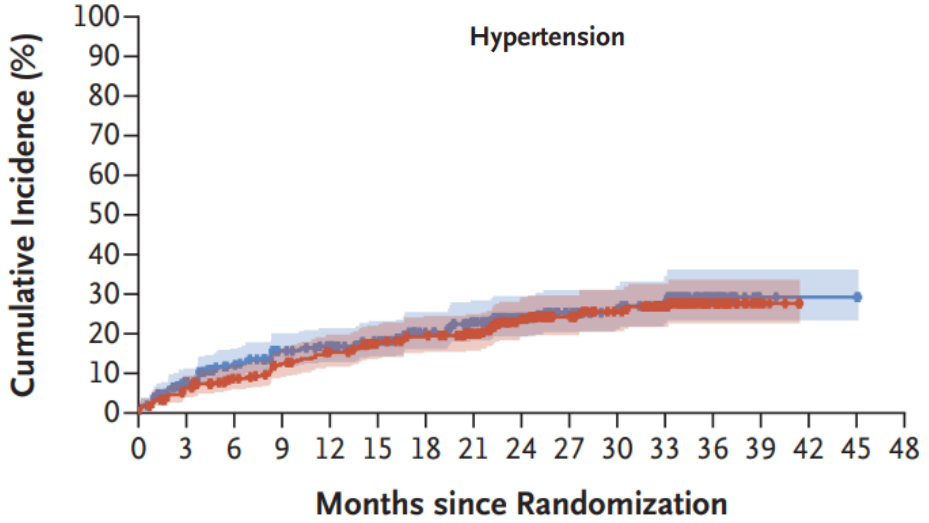


Byrd, *J Clin Oncol* 39:3441-3452

ZANUBRUTINIB VS. IBRUTINIB: ALPINE STUDY



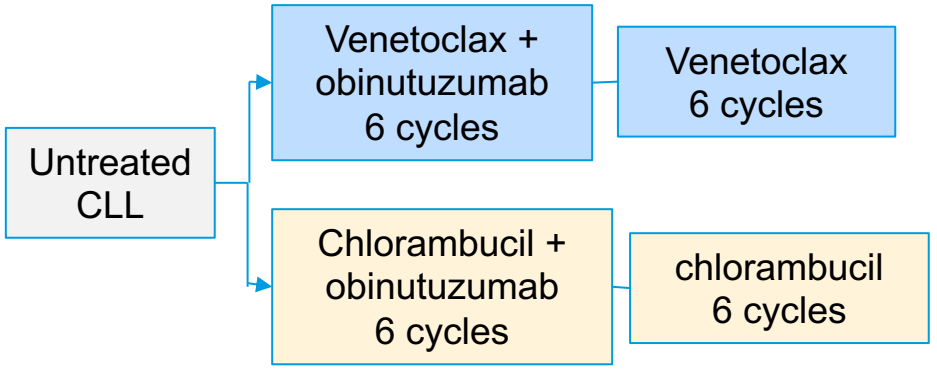


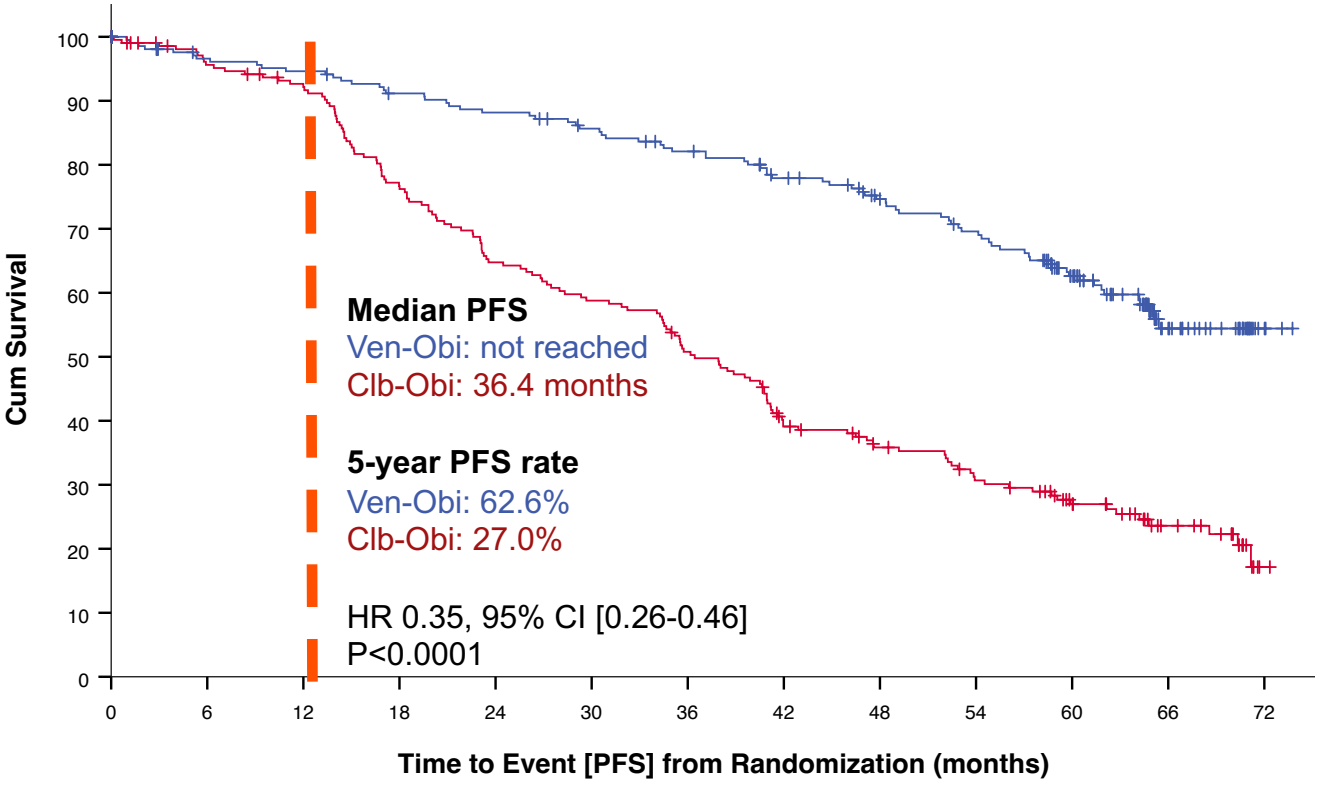


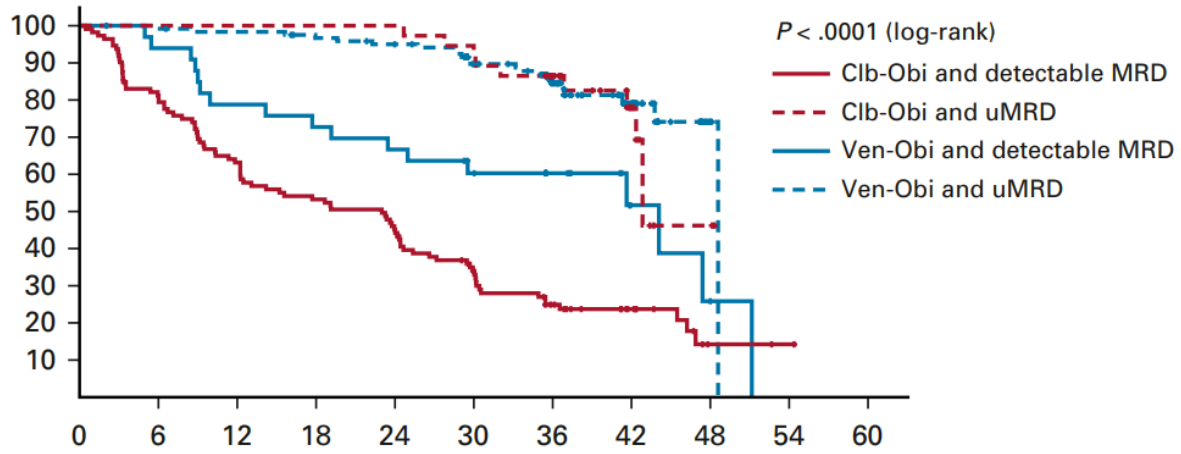
Brown, *NEJM*; epub December 2022

SHORTER DURATION OF THERAPY?

VENETOCLAX + OBINUTUZUMAB (CLL14, N=432)



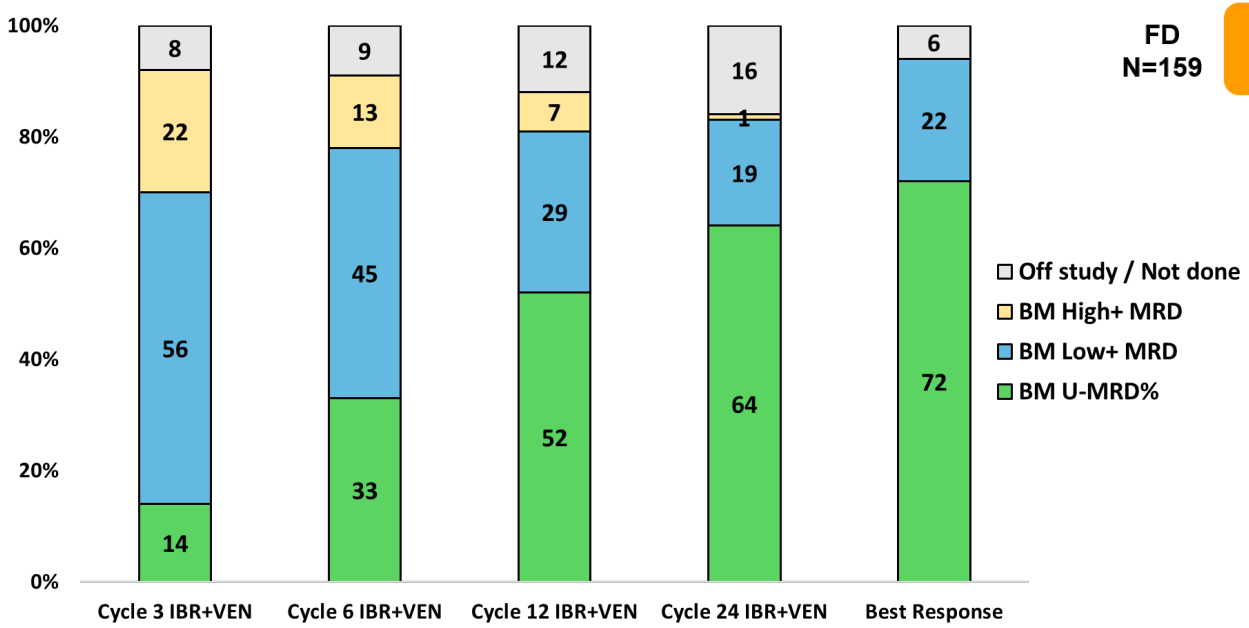




Fischer, NEJM 2019;380:2225
Al-Sawaf, *EHA Abstracts*, 2022

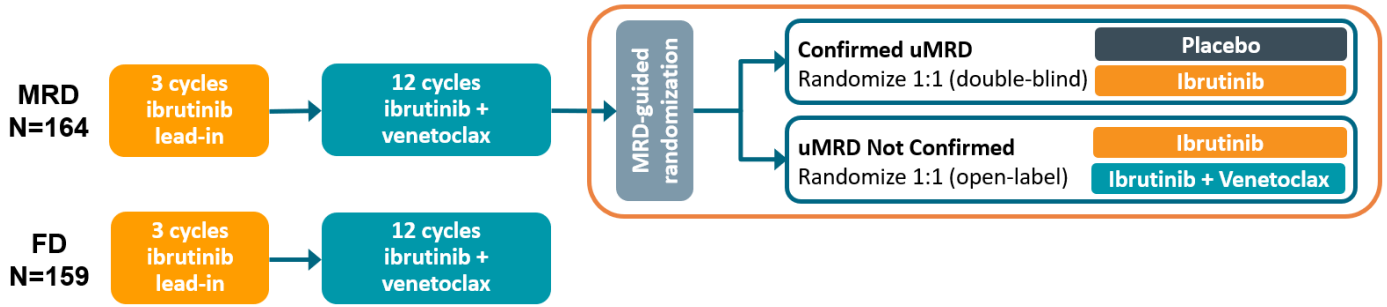
IBRUTINIB + VENETOCLAX IN FRONTLINE CLL

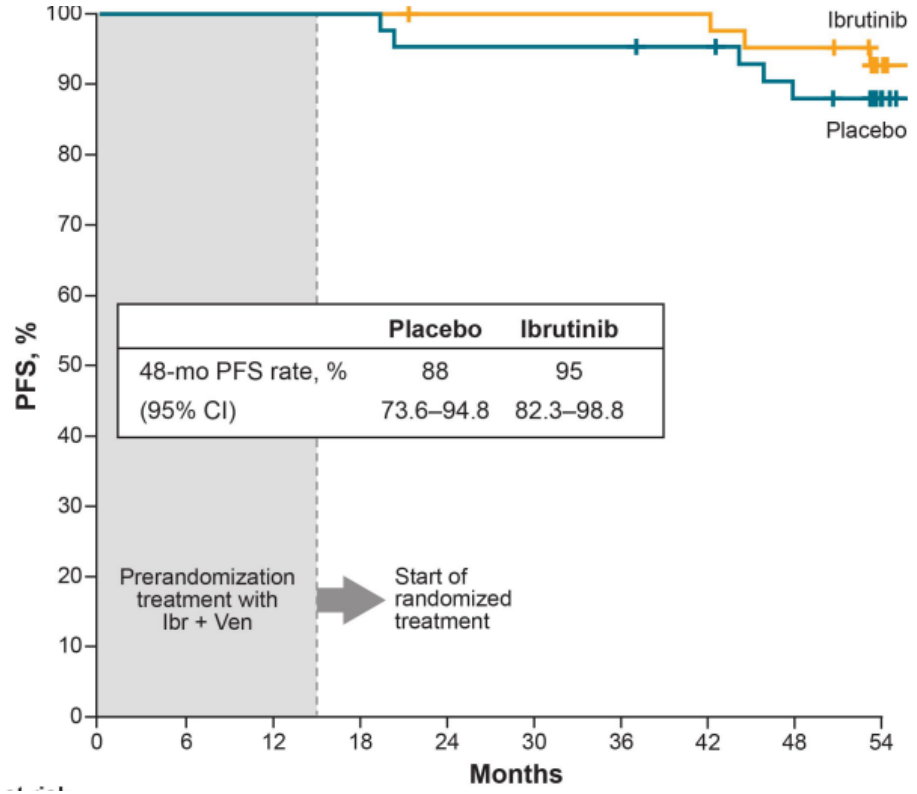
Phase 2 study of ibrutinib + venetoclax for 24 months (n=120)



MRD by flow-cytometry in marrow (10^{-4} sensitivity)

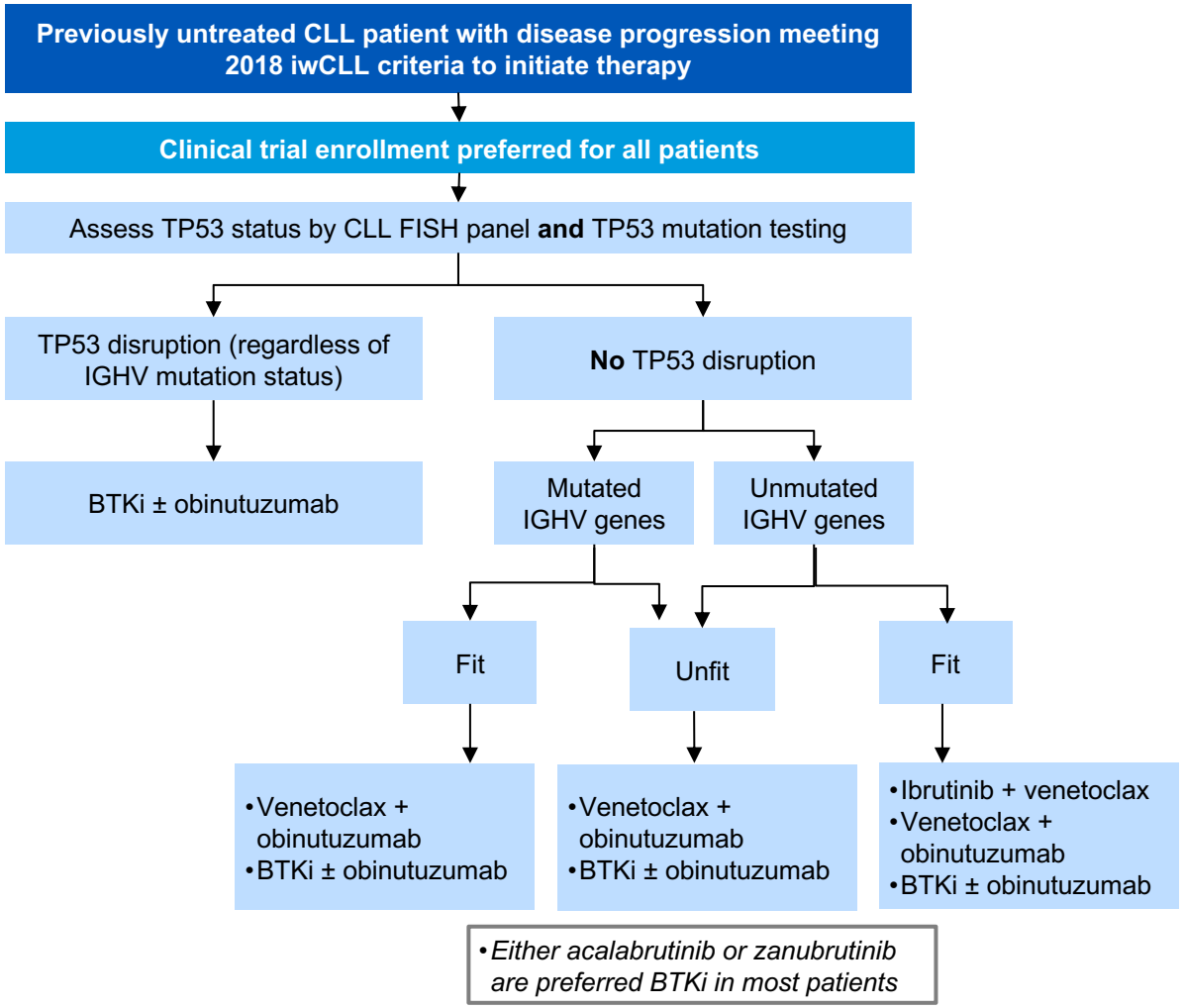
U-MRD4: <0.01%
Low+ MRD: 0.01% to <1%
High+ MRD: ≥1%





Jain, *ASH Abstracts*, 2022
Allan, ASH Abstracts, 2022

TREATMENT OF CLL IN 2023

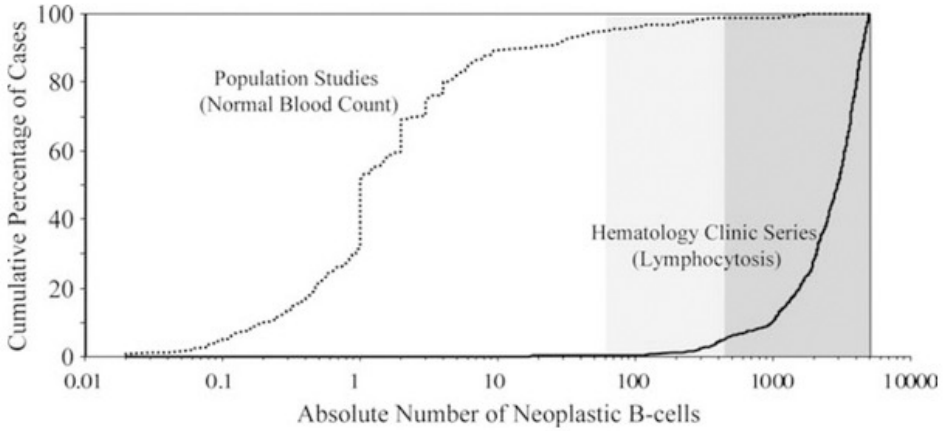


- No mention of chlorambucil, or CIT treatment approaches in frontline or relapsed CLL treatment options
- CD20 antibody not always necessary
- Second generation BTKi generally preferred
- Fixed duration therapy with venetoclax-obinutuzumab typically preferred in most patients
  - Except in those with *TP53* disruption where continuous BTKi therapy is better

Hampel, *Blood Cancer Journal* (2022) 12:161

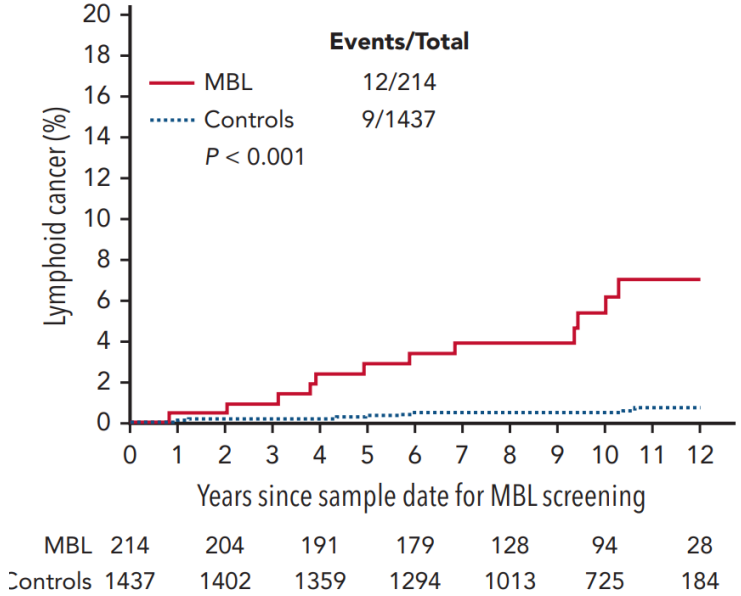
WHAT NEXT IN CLL?

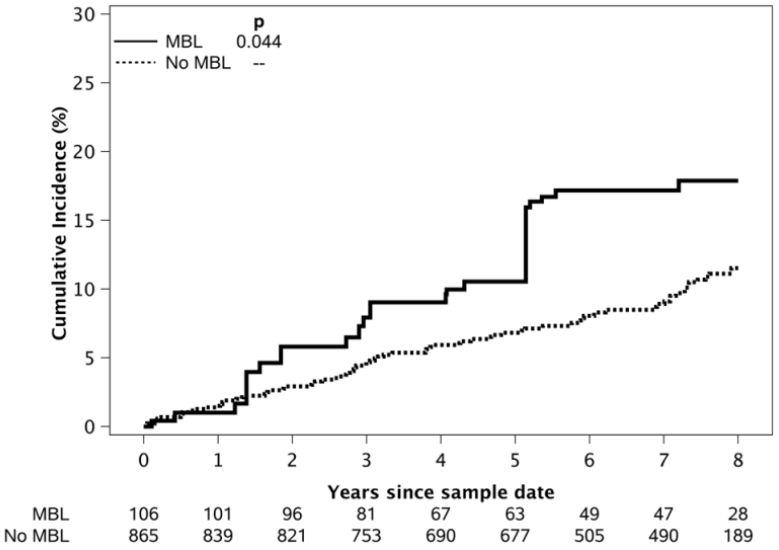
EARLY DIAGNOSIS



Clonal B cell count <0.5 x 10^9/L	Clonal B cell count 0.5 - 4.9 x 10^9/L	Clonal B cell count > 5 x 10^9/L
Low count MBL (Screening MBL)	High count MBL (Clinical MBL)	CLL

- 10,139 individuals (>40 years of age) in the Mayo Clinic Biobank were screened using a sensitive 8 color flow cytometry assay
- 1712 (17%) individuals were identified to have MBL (94% with LC MBL)





7-fold* higher risk of **lymphoid malignancies** in LC MBL compared to controls

1.5-fold* increased risk of **serious infections requiring hospitalization** in LC MBL compared to controls

Shanafelt, *Leukemia*, 2021; 239-244
Slager, *Blood (2022)* 140 (15): 1702–1709

EARLY INTERVENTION STRATEGIES

Key eligibility:
- Binet A
- Asymptomatic
- Treatment-naive

CLL12 Trial

RISK STRATIFICATION

LOW N=152 → WATCH & WAIT N=152

INTERM. N=273

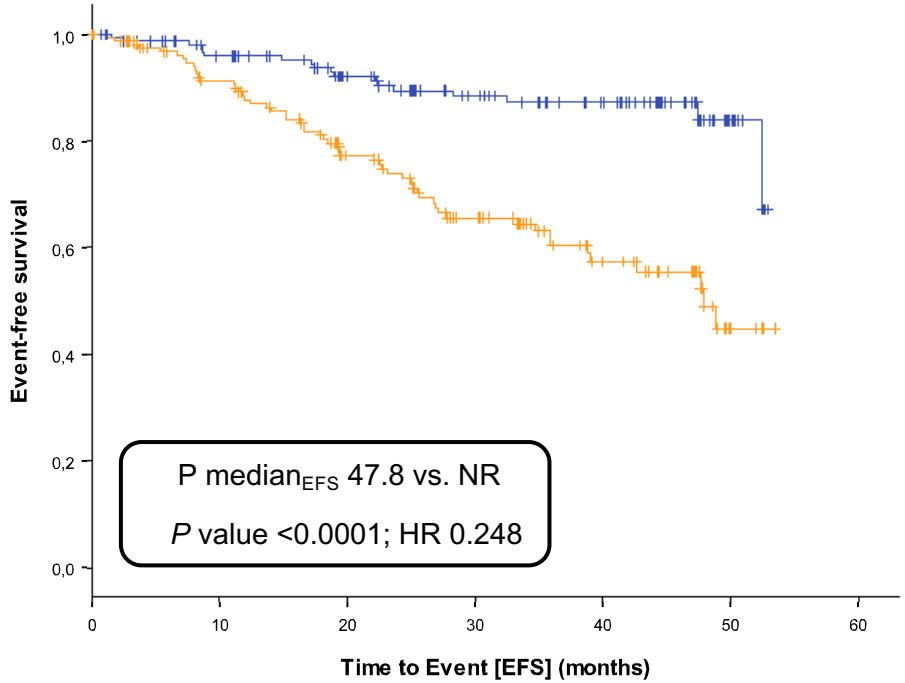
HIGH N=82

VERY HIGH N=8

RANDOMIZATION 1:1

IBRUTINIB N=182

PLACEBO N=181



S1925: EVOLVE Study

Newly Diagnosed CLL ; Asymptomatic; CLL-IPI ≥ 4 &/or Complex Cytogenetics

Stratify: High risk vs. Very high risk

Randomize = 2:1 (Early: Delay)

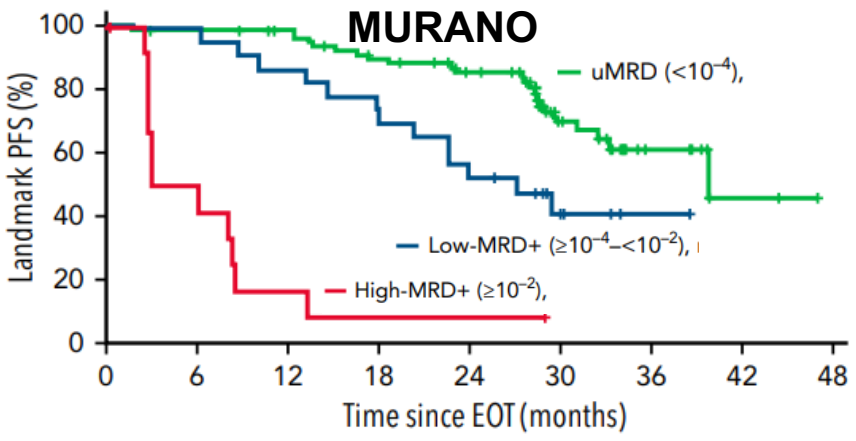
EARLY V + O$^{\$}$

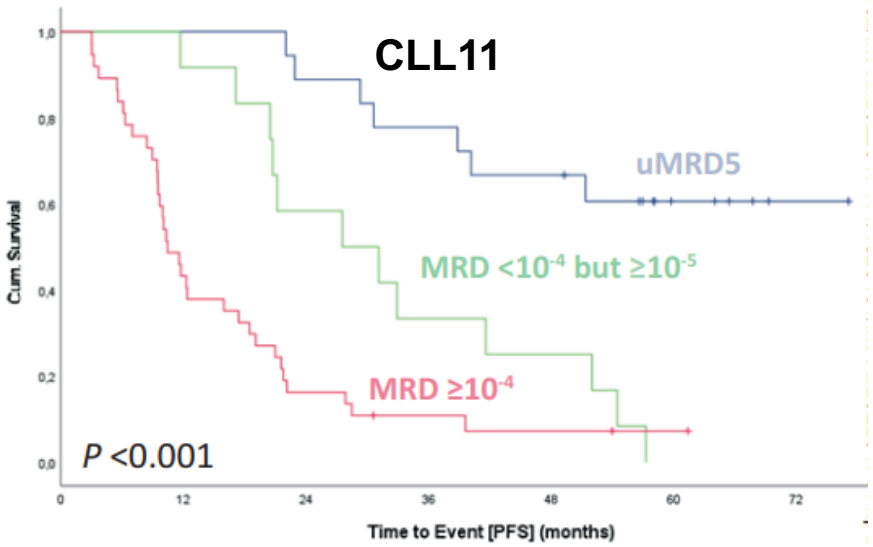
DELAYED V + O*$^{\$}$

O = Obinutuzamab
V = Venetoclax
*Treatment initiated once IWCLL indications are met
$^{\$}$Treatment length = O months 1-6, V months 1-12

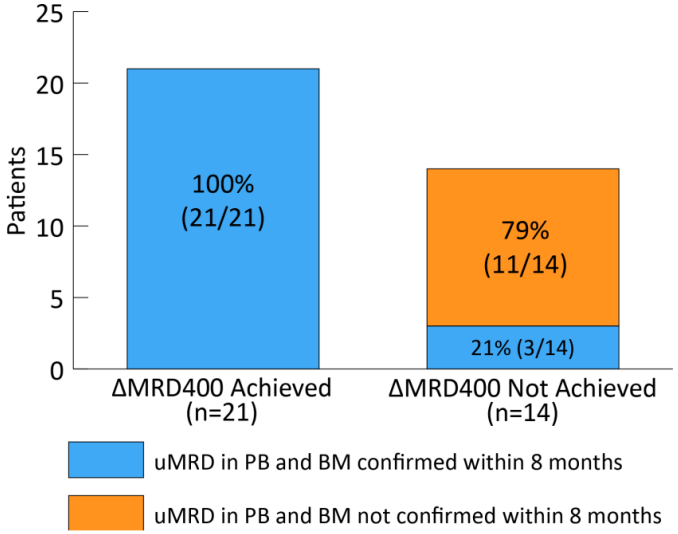
1◦ Endpoint: Overall Survival =
Accrual goal → 247 patients

HOW BEST TO INCORPORATE MRD IN TRIALS/PRACTICE?





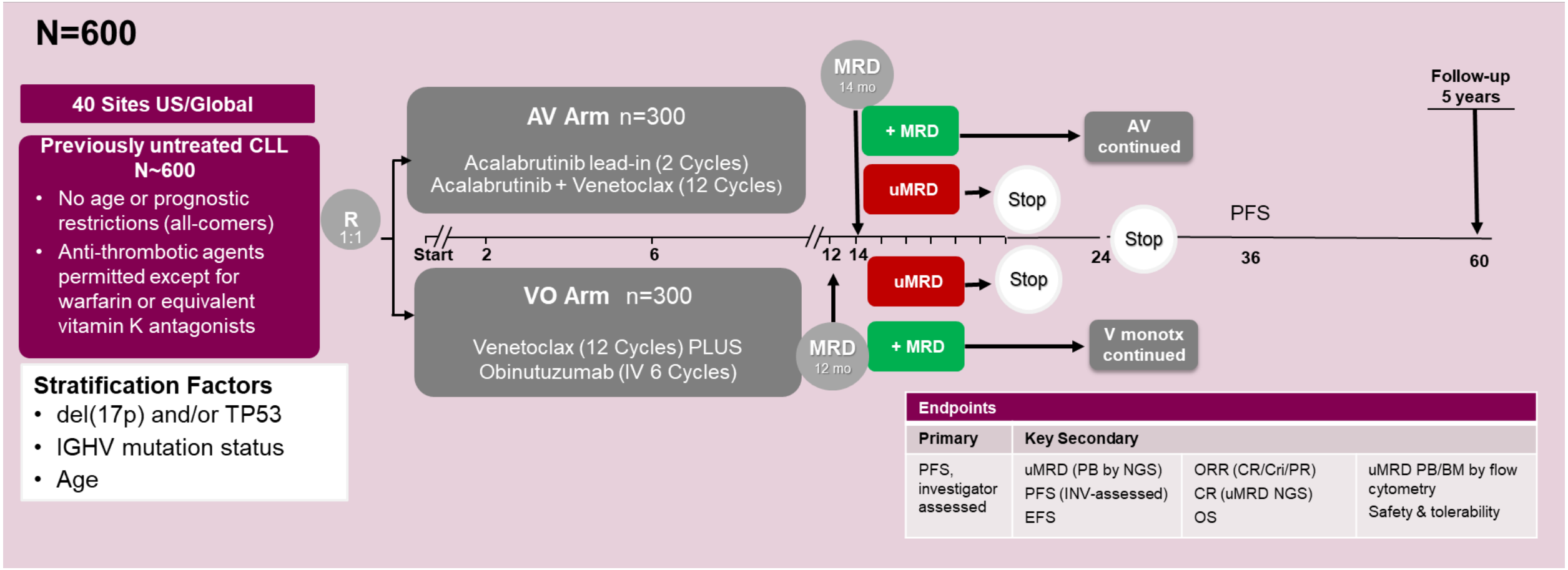
- ΔMRD was measured as the decrease in MRD by immunosequencing from baseline to cycle 5, day 1
- This ΔMRD was used to predict which patients are more likely to achieve uMRD at cycle 8



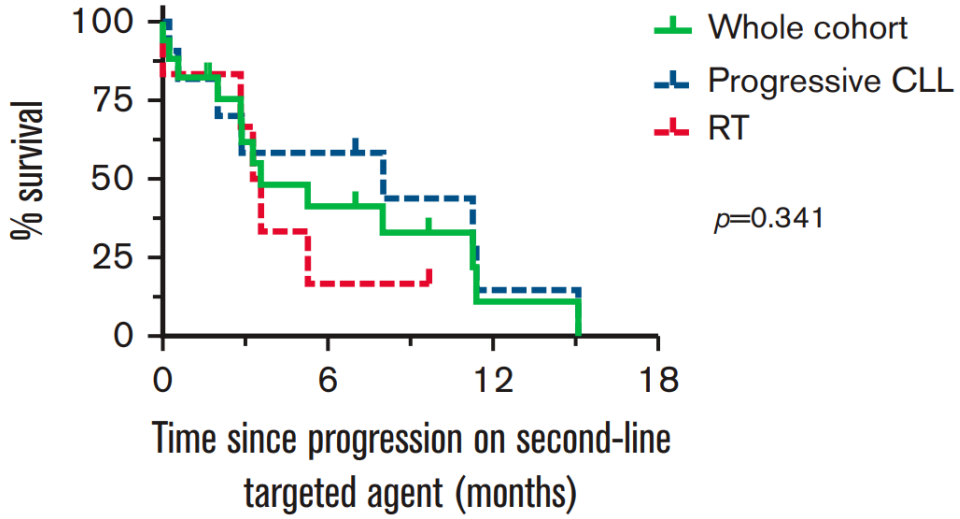
Seymour; *Blood* (2022) 140 (8): 839–850
Hengevold; Blood (2022) 140 (8): 839–850
Soumerai; *Lancet Haematology;* Volume 8, Issue 12, Pages e879

MRD GUIDED FRONTLINE TREATMENT

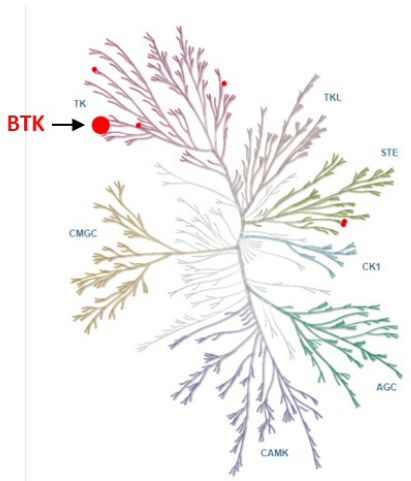
- MAJIC trial

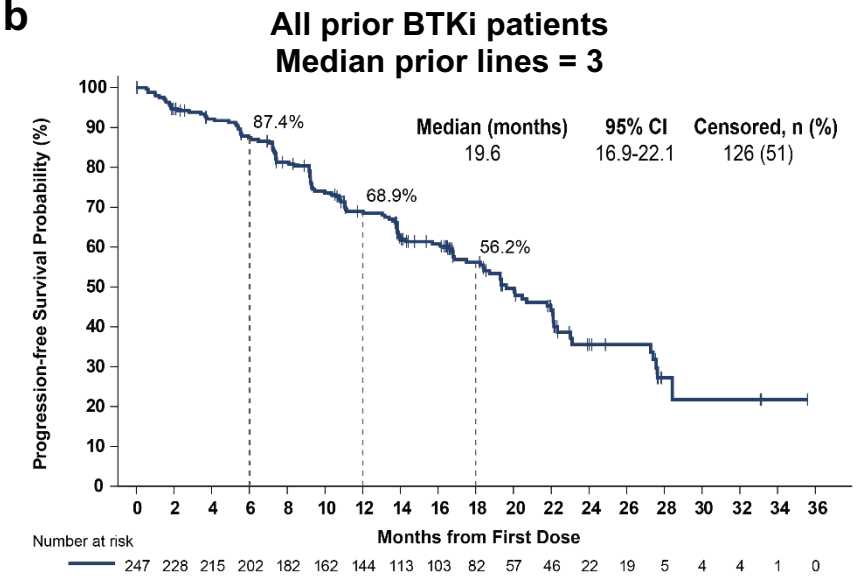


DOUBLE REFRACTORY CLL

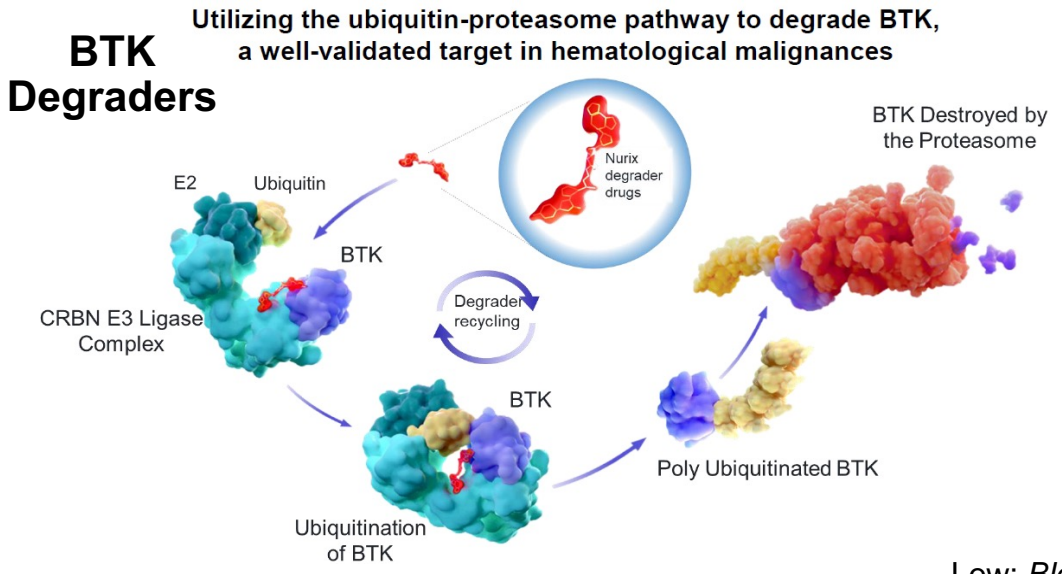


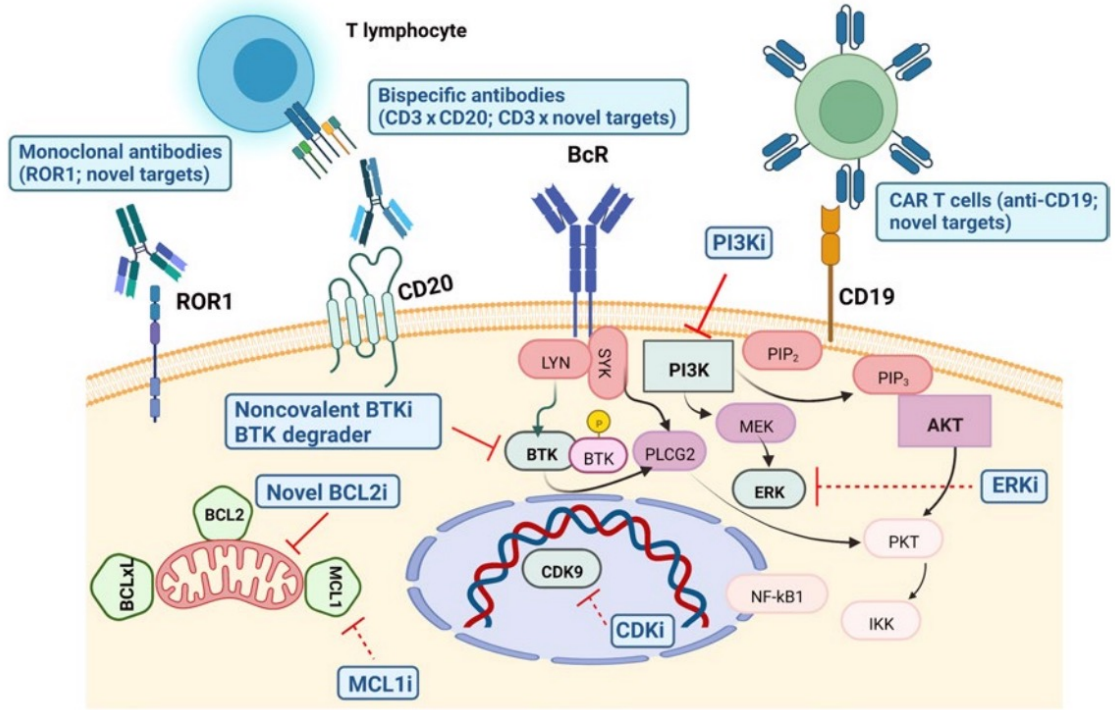
Pirtobrutinib





BTK Degraders





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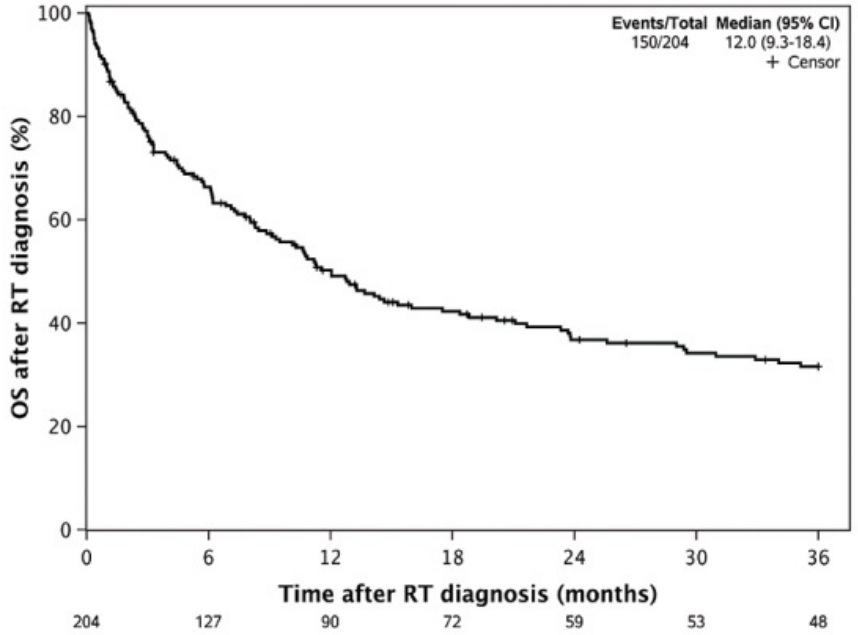
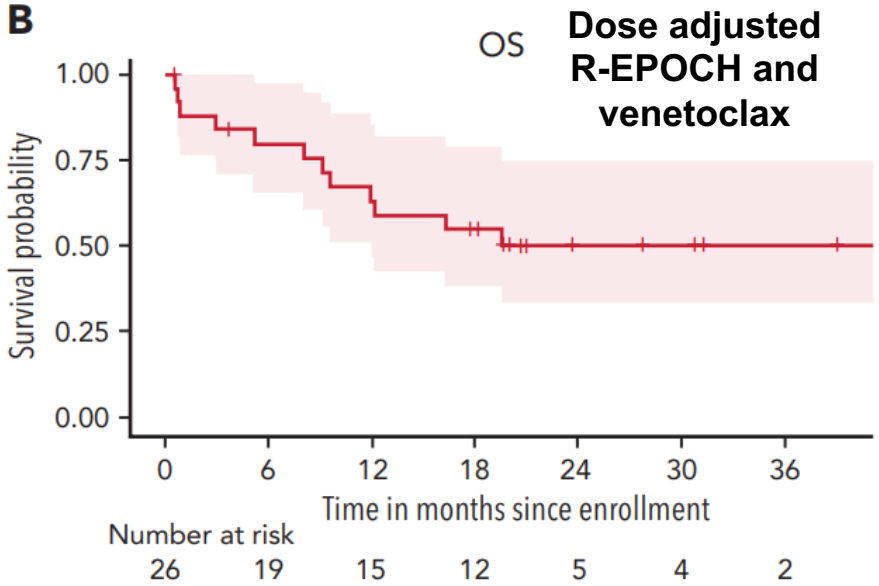
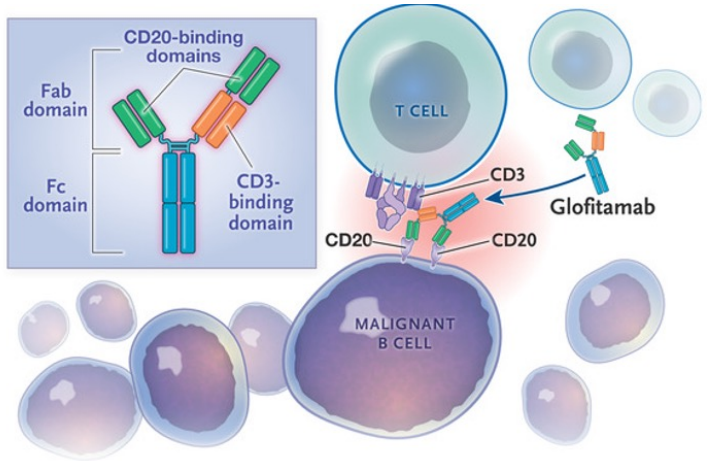
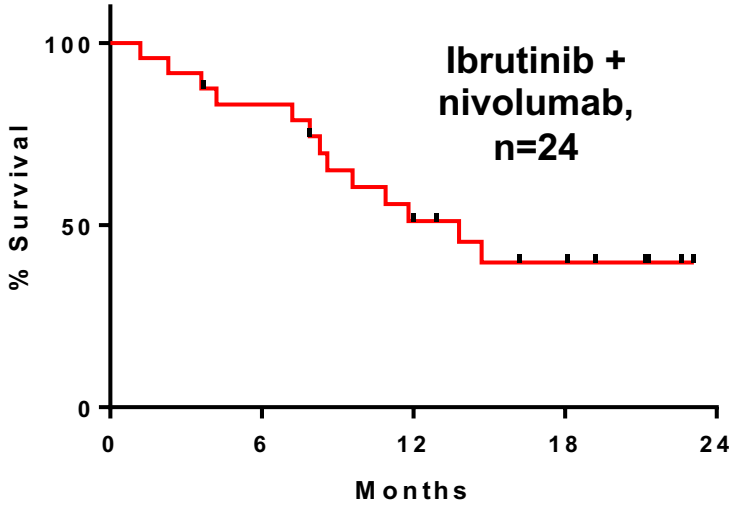
RICHTER TRANSFORMATION





Bispecific antibodies





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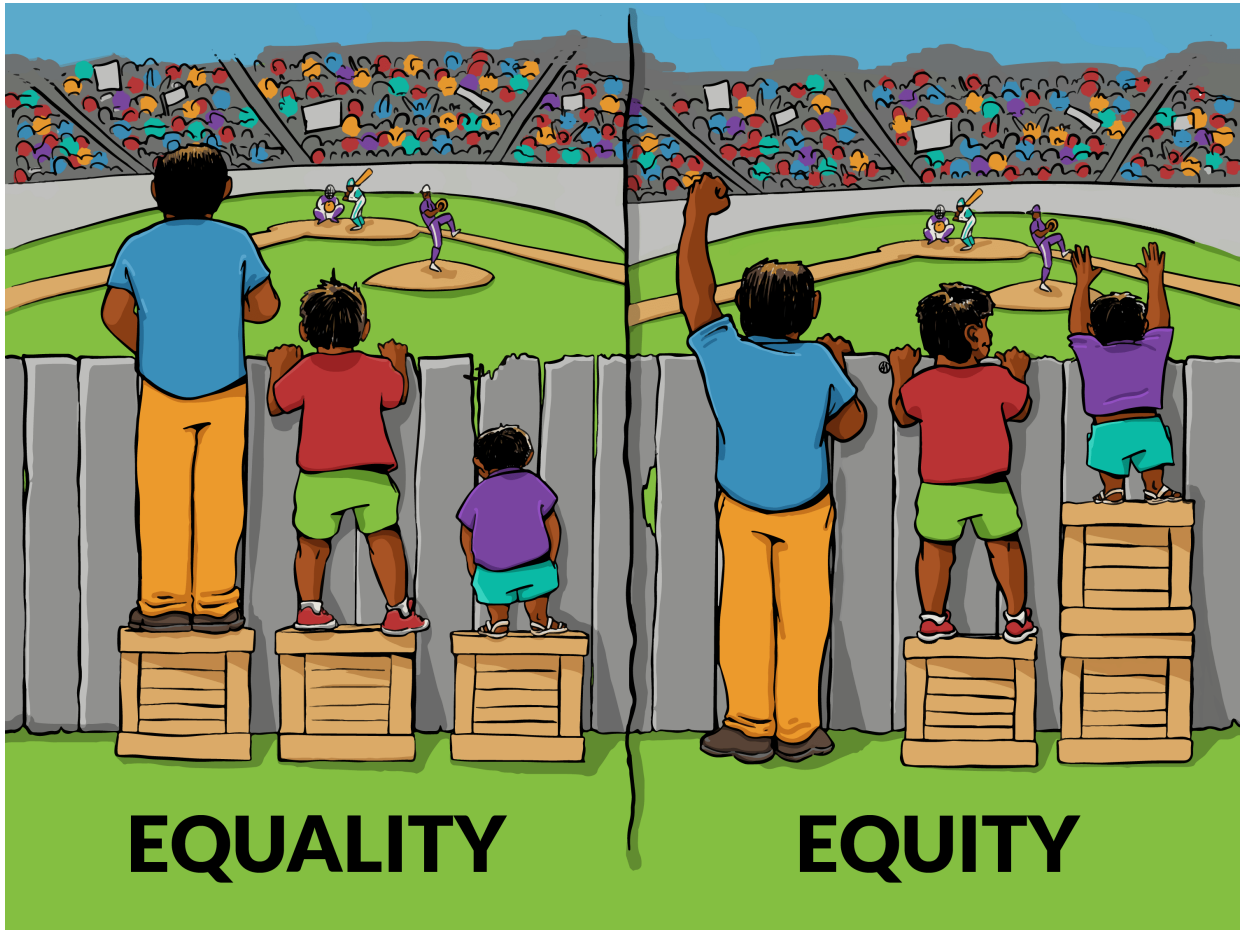
INCLUSION AND EQUITY



AT THE END OF THE DAY

- We are here for OUR patients

- Two things that matter the most to patients:
  - Improve quality of life, **AND**
  - Improve quantity of life

- "The best interest of the patient is the only interest to be considered, and in order that the sick may have the benefit of advancing knowledge, union of forces is necessary."
  - William J. Mayo, M.D. Commencement Address, Rush Medical College, University of Chicago, June 15, 1910.

THANK YOU!

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