Chronic Lymphocytic Leukemia
and
Hairy Cell Leukemia

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Comprehensive Hematology & Oncology Review Course
2021

Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine

Financial Disclosures

- Consulting, Advisory Boards, steering committees or data safety monitoring committees: Abbvie, Genentech, AstraZeneca, Sound Biologics, Pharmacyclics, Beigene, Bristol Myers Squibb, Morphosys, TG Therapeutics, Innate Pharma, Kite Pharma, Adaptive Biotechnologies, Epizyme, Eli Lilly, and Atara Biotherapeutics

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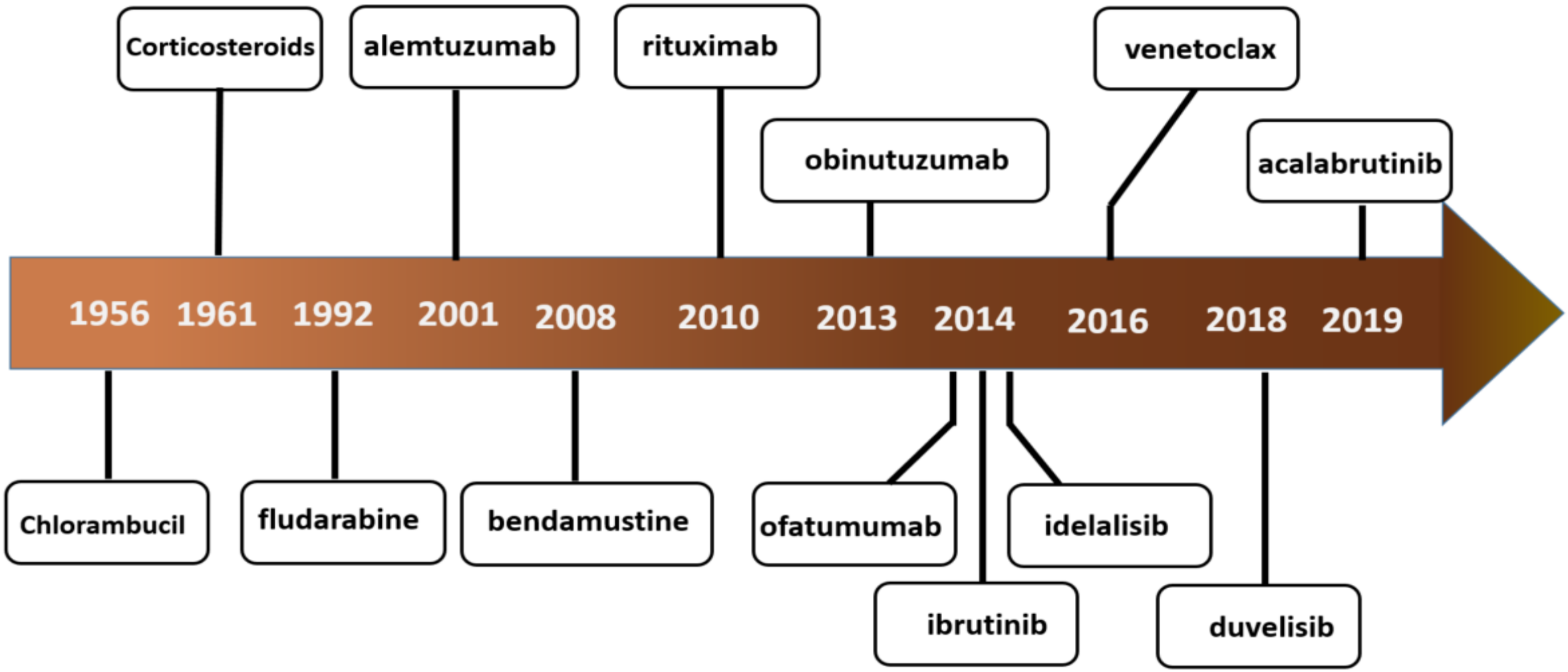
Disclosures

- Main purpose of this presentation is **“Board Review”**
- Will not discuss **investigational** treatments

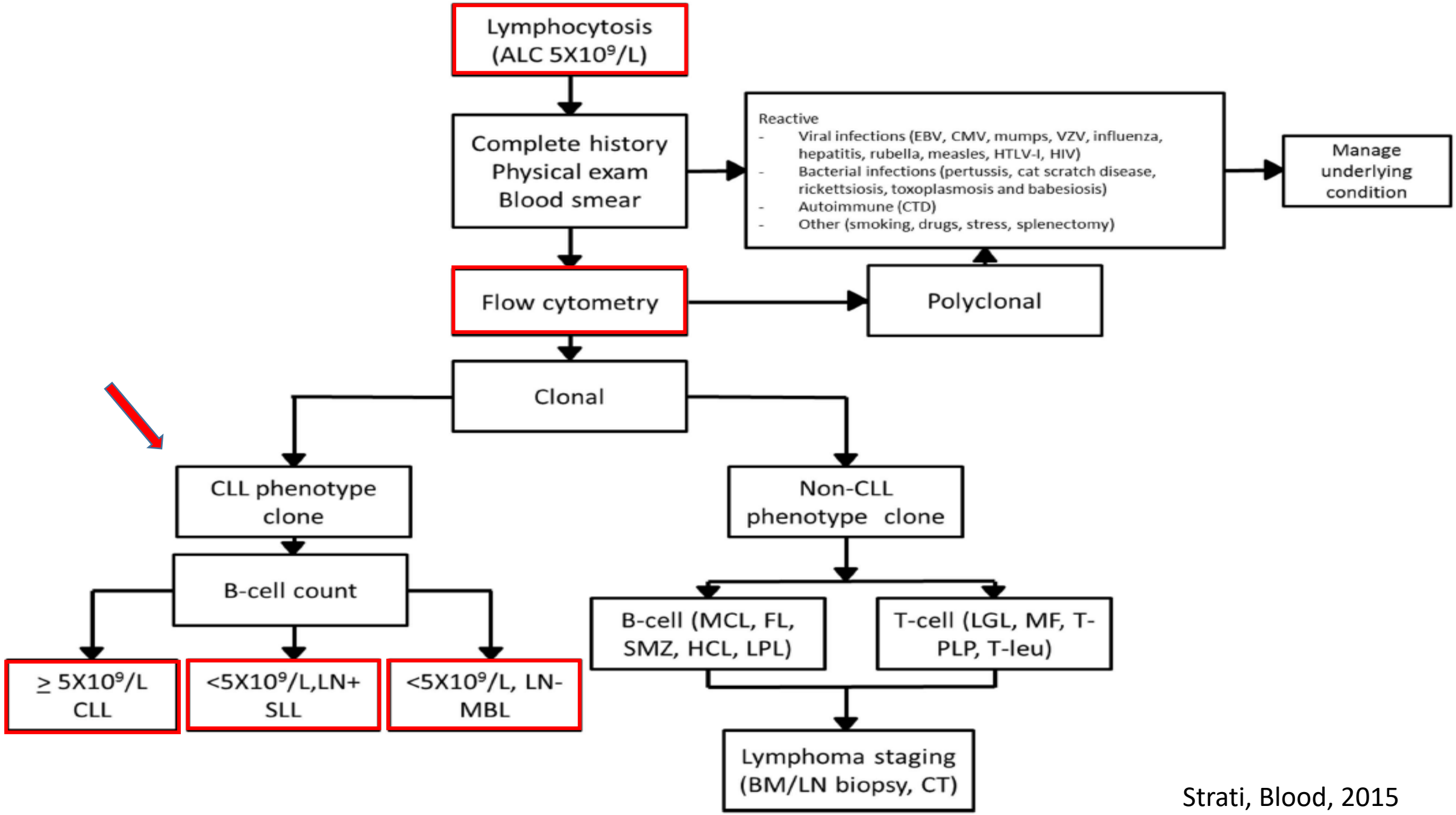
Treatment options for CLL/SLL



Epidemiology

- CLL/SLL is the most common leukemia in adults in western countries
  - 4.5 cases per 100,000
- Median age ~ 70 years
- Slight male predominance (1.7:1)
- Familial risk (7-8 fold)
- Caucasians > African Americans > Asian Pacific Islanders
- Genetic > Environmental

Initial diagnosis and appropriate work-up



Strati, Blood, 2015

Immunophenotypic Features

	CD5	CD10	CD23	CD103	BCL6	CD20	Cyclin D1
CLL/SLL	+	-	+	-	-	+ (weak)	-

Immunophenotypic Features

	CD5	CD10	CD23	CD103	BCL6	CD20	Cyclin D1
CLL/SLL	+	-	+	-	-	+ (weak)	-
MCL	+	-	-	-	-	+	+
LPL	-	-	-	-	-	+	-
sMZL	-	-	-	-	-	+	-
FL	-	+/-	-/+	-	+	+	-
HCL	-	-	-	+	-	+	+/-

	CD23	Cyclin D1	t(11,14)
CLL/SLL	+	-	-
MCL	-	+	+

MBL (monoclonal B cell lymphocytosis)

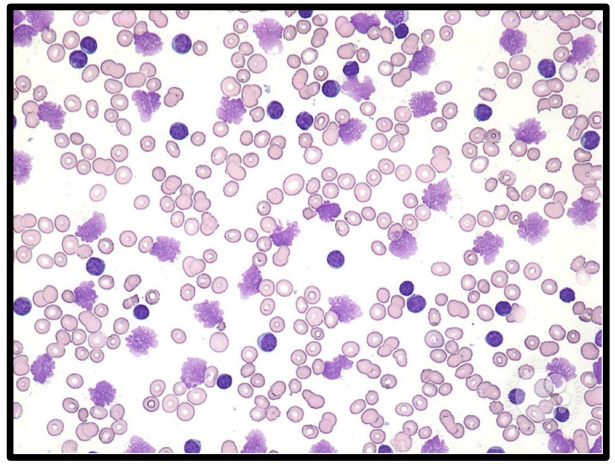
- < 5x 10^9/L monoclonal B- cells in the PB AND no lymphadenopathy
- Almost all cases of CLL are preceded by MBL but only a small percentage of persons with MBL will ultimately develop CLL
- **Low-count MBL (< 0.5x 10^9/L) ➔ rarely progresses to CLL**
- **High-count MBL (≥0.5x 10^9/L) ➔ progresses to CLL at a rate of 1-2% /year**
- Up to 17 percent of first-degree family members of patients with CLL were found by flow cytometry to have MBL
- **Screening of family members is NOT recommended**

Strati, Blood, 2015

Diagnosis

- **Flow cytometry** of **blood** is **essential and adequate** to make the diagnosis
- Biopsy may be needed if PB flow cytometry is not conclusive
- Cytogenetic and molecular studies are informative for prognostic and/or therapy determination .
- Baseline CT scan (or PET) is **NOT** required for asymptomatic patients

  (The ASH "Choosing Wisely" List)



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Prognostic and predictive markers

Staging for CLL

Rai Staging System for Chronic Lymphocytic Leukemia			
Stage	Risk	Clinical Features	Overall Survival, y
Rai			
0	Low	Lymphocytosis in peripheral blood and bone marrow only	>10
I/II	Intermediate	Lymphadenopathy ± hepatosplenomegaly	7
III/IV	High	Anemia ± thrombocytopenia	<4

Use Ann Arbor staging for SLL

Molecular Biomarkers for CLL

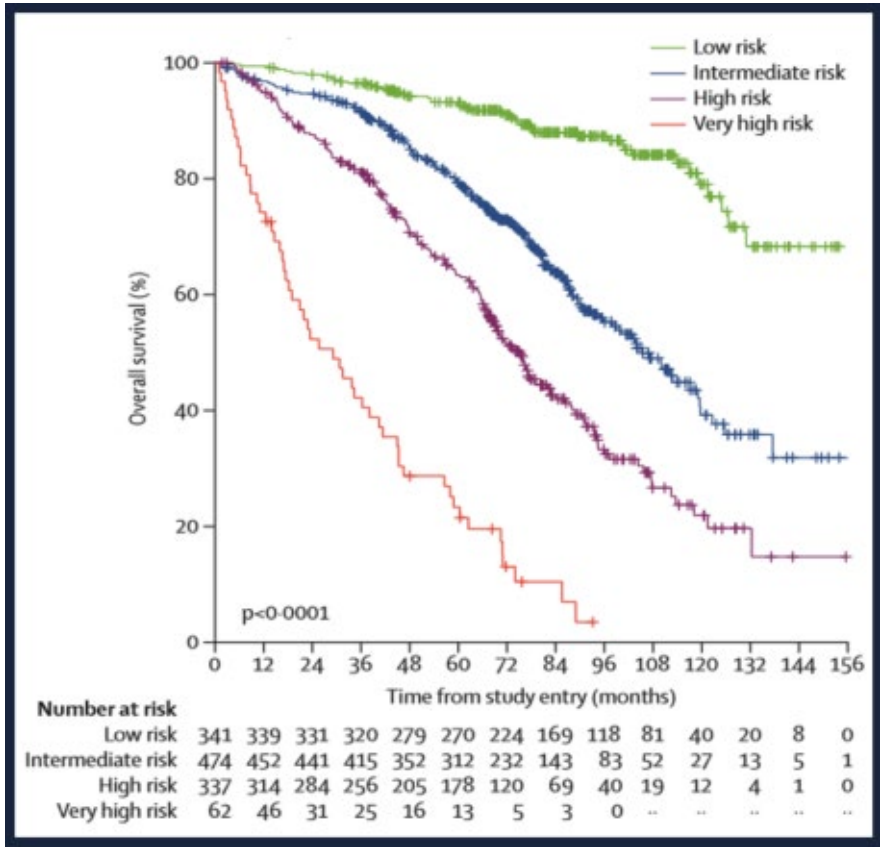
	FISH	Karyotype	Mutations
Unfavorable	del (17p) del (11q)	Complex (>3 abnormalities) (> 5?)	TP53 unmutated IGHV (≤ 2%) * NOTCH-1 SF3B1 BIRC3 ATM
Neutral	Normal +12		
Favorable	del (13q) (sole abnormality)		mutated IGVH (>2%)

* If chemotherapy is used

Prognostic Models: CLL-IPI

Characteristic	Points
Del(17p) or TP53 mutation	4
Serum beta-2-macroglobulin ≥ 3.5mg/L	2
Un-mutated IgVH	2
Rai Stage I-IV	1
Age > 65 years	1

Points	Risk Group	5-y OS (%)	10-yr OS (%)
0-1	Low	93	79
2-3	Int	79	39
4-6	High	63	22
7-10	Very High	23	4



- ✓ Developed for chemoimmunotherapy
- ✓ Not validated for novel agents

CLL-IPI Group, Lancet Oncol 2016

Important therapeutic agents for CLL

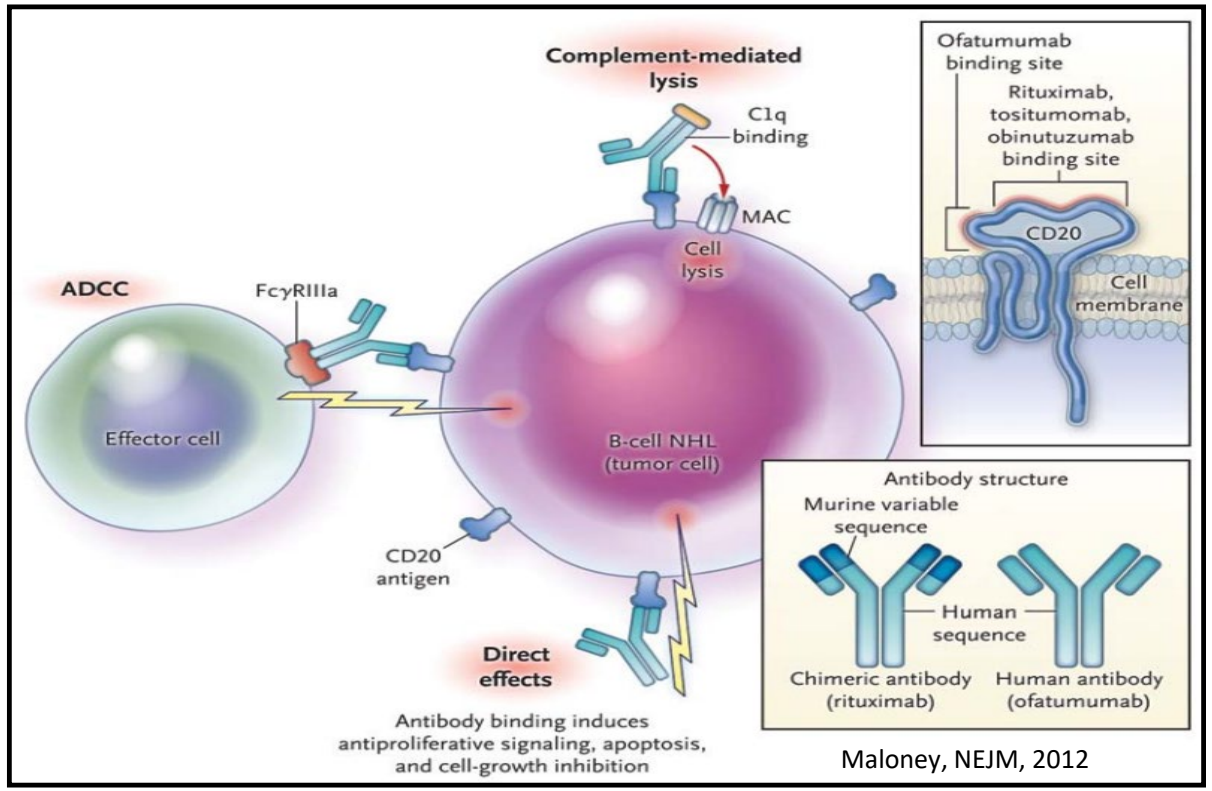
What are the treatment options?

Chemotherapy	anti-CD20 Abs	BCR inhibitors	BCL-2 inhibitor

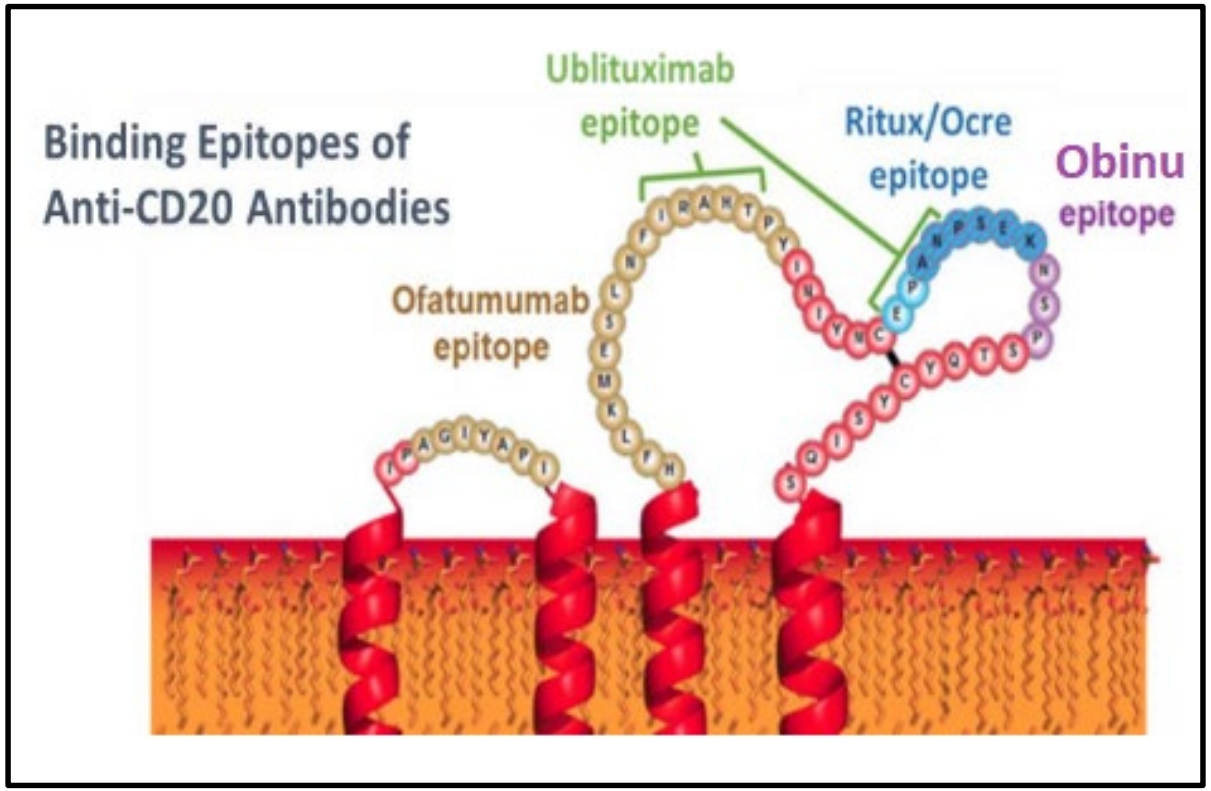
• fludarabine
• cyclophosphamide
• bendamustine
• chlorambucil
	• rituximab
	• ofatumumab
	• obinutuzumab
	• ublituximab *
		• **BTK inhibitors**
		  • ibrutinib
		  • acalabrutinib
		  • zanubrutinib*†
		• **PI3K inhibitors**
		  • idelalisib
		  • duvelisib
		  • umbralisib * ‡
			• **venetoclax**

* Not FDA approved for CLL as of June 2021
† Approved for MCL and WM
‡ Approved for MZL and FL

Anti-CD20 antibodies

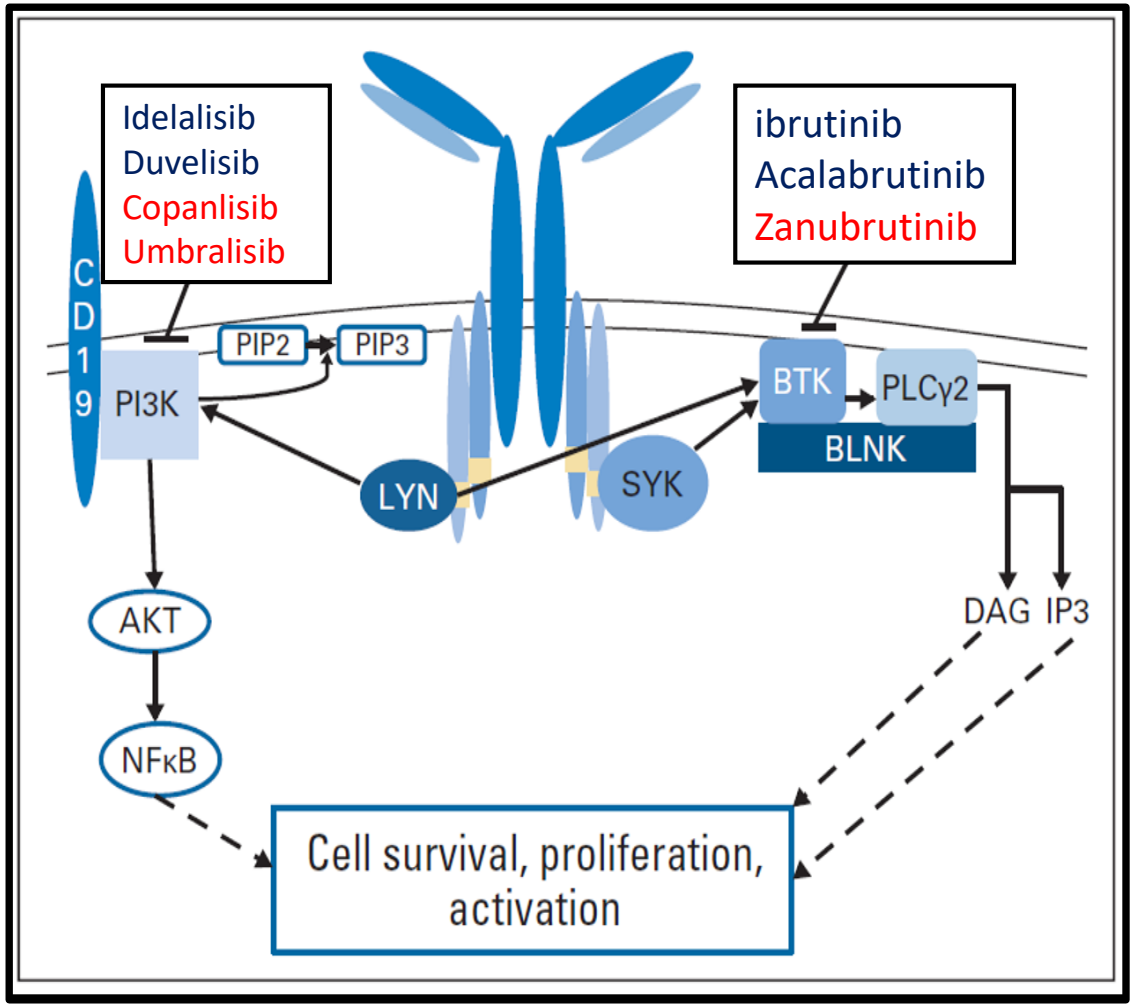


Maloney, NEJM, 2012

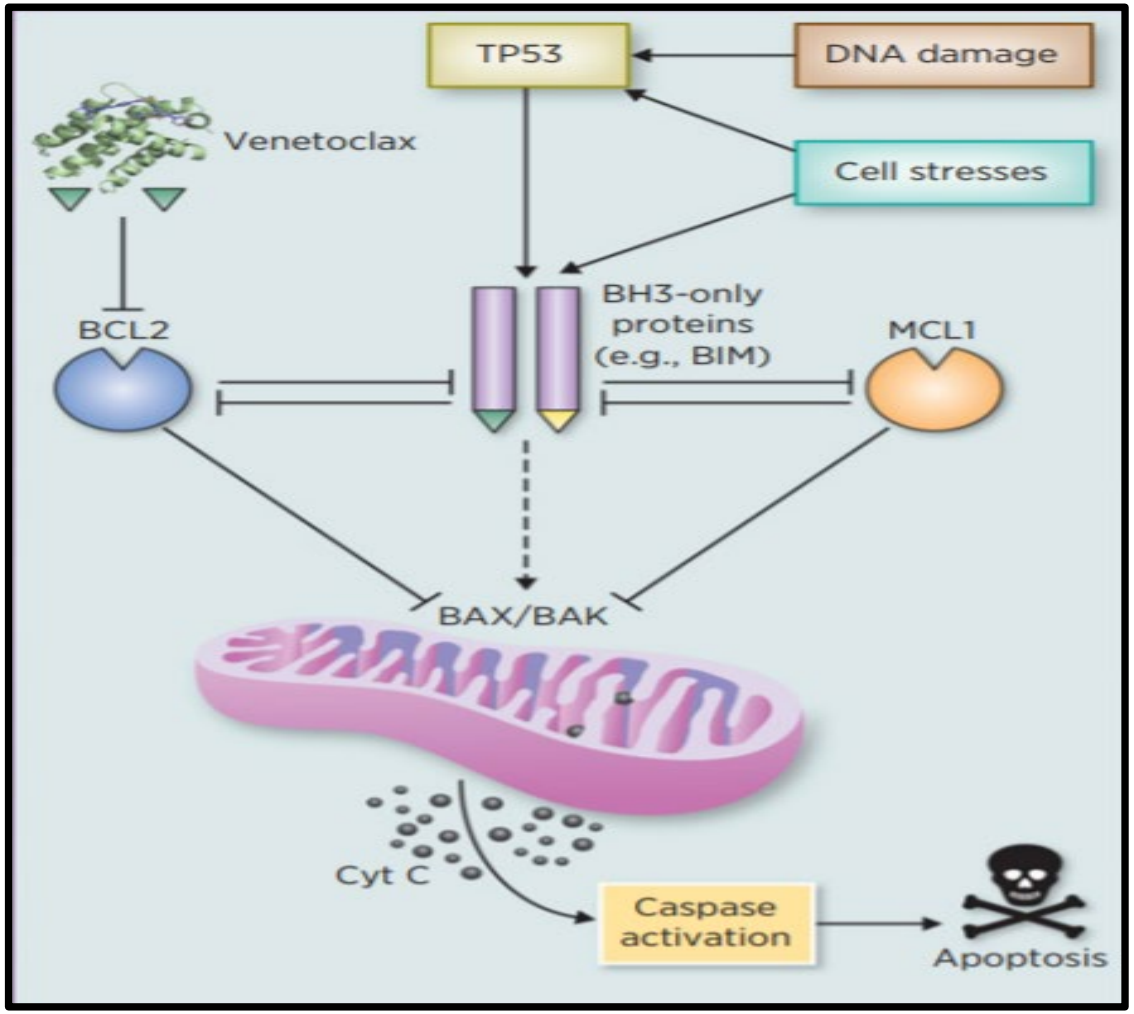


		Glycoengineered	Type	Direct effect	CDCC	ADCC
Rituximab	chimeric	No	I	↑	↑↑↑↑	↑↑
ofatumumab	humanized	No	I	↑	↑↑↑↑	↑↑
obinutuzumab	humanized	Yes	II	↑↑↑↑	↑	↑↑↑
ublituximab	chimeric	Yes	I	↑	↑↑↑↑	↑↑↑↑

BCR Pathway inhibitors vs. BCL2 antagonist



Byrd, JCO,2014



Roberts, CCR Drug Updates,2017

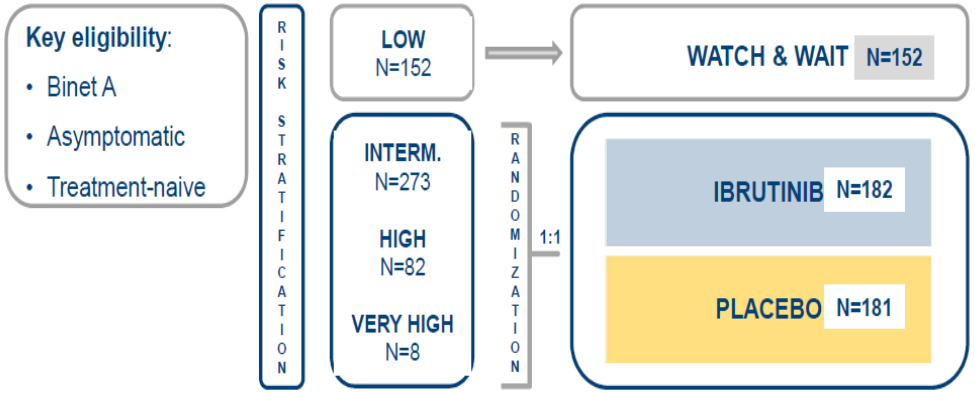
Who needs to be treated?

Indications for treatment

- Progressive marrow failure
- Massive , progressive or symptomatic lymphadenopathy or organomegaly
- Constitutional symptoms
- Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
- ~~Lymphocyte doubling time~~

Is there a role for early intervention in “high-risk” patients?

CLL-12 Study – Early intervention with Ibrutinib

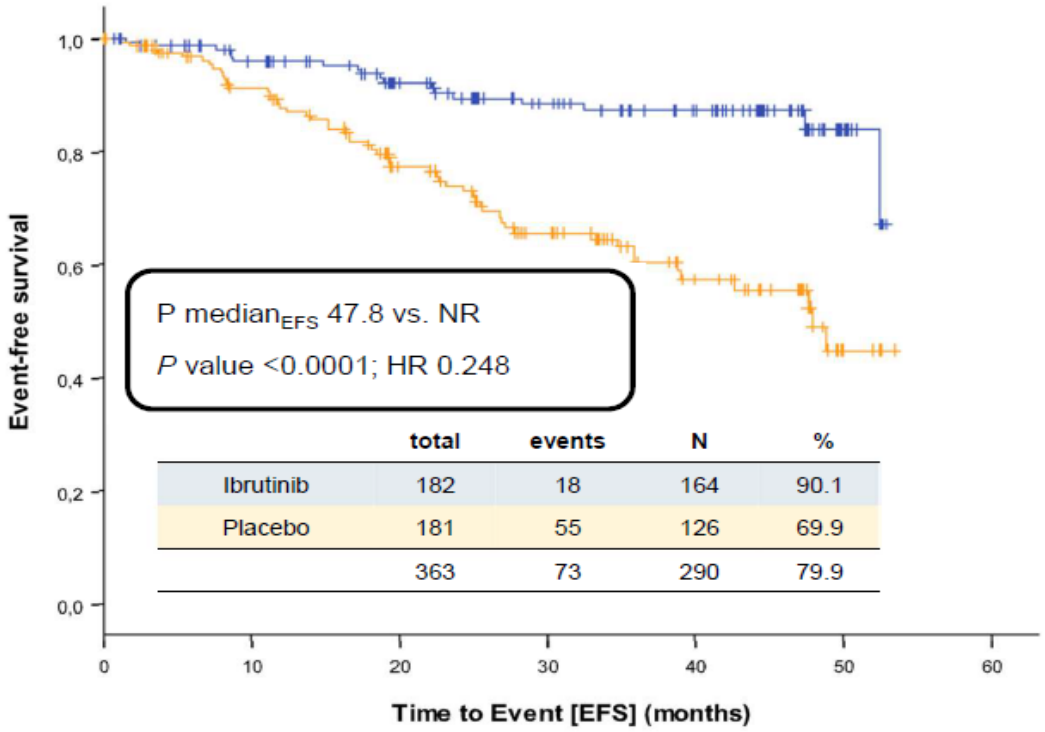


Phase 3, placebo-controlled, double-blind, multicenter trial

Primary endpoint EFS: time from randomization until symptomtatic PD, new treatment, death

Secondary endpoints: survival, PFS, TFS, TTNT, ORR, safety

π_2 : median EFS from 24 to 48 months with ibrutinib (superiority test)



	total	events	N	%
Ibrutinib	182	18	164	90.1
Placebo	181	55	126	69.9
	363	73	290	79.9

- No OS benefit
- Study is powered for OS so longer follow-up would be interesting
- **Early intervention with ibrutinib is NOT recommended at this time**

Langerbeins, Lugano (15-ICML) meeting , 2019

Upcoming US Intergroups Early Intervention Trial with Venetoclax

CLL-IPI

Characteristic	Points
Del(17p) or TP53 mutation	4
Serum beta-2-macroglobulin ≥ 3.5mg/L	2
Un-mutated IgVH	2
Rai Stage I-IV	1
Age > 65 years	1

Points	Risk Group
0-1	Low
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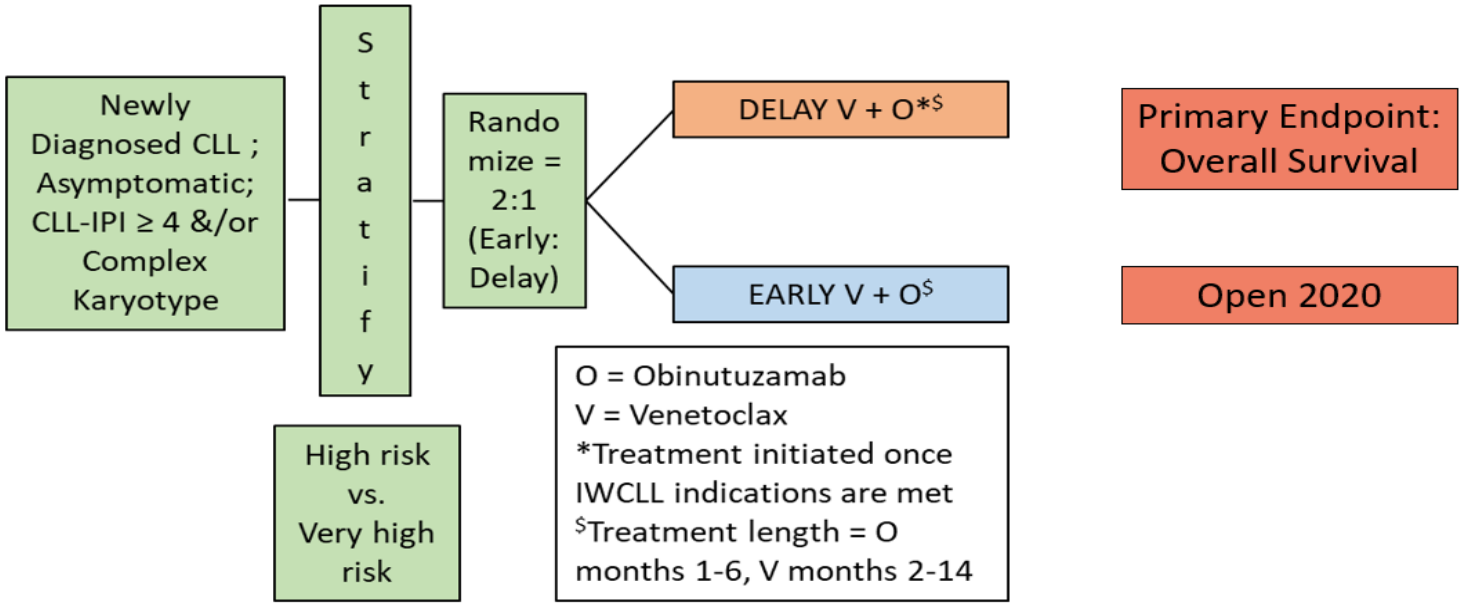


Courtesy: Dr. Deborah Stephens (study PI)

SWOG
Leading cancer research. Together.

Treatment options for treatment-naïve patients (without del17p/P53 mutation)

First line treatment
for patients with normal TP53

For all pts:

Acalabrutinib ± G **OR** **Ibrutinib** **OR** **Venetoclax + G**

FCR is <u>not preferred</u> but can be a <u>reasonable option</u> for selected patients if:

- younger than 65 and fit
- mutated IGHV
- no evidence of del17p or TP53 mutation
- (no evidence of del 11q)

G = Gazyva = obinutuzumab

Frontline (normalTP53)

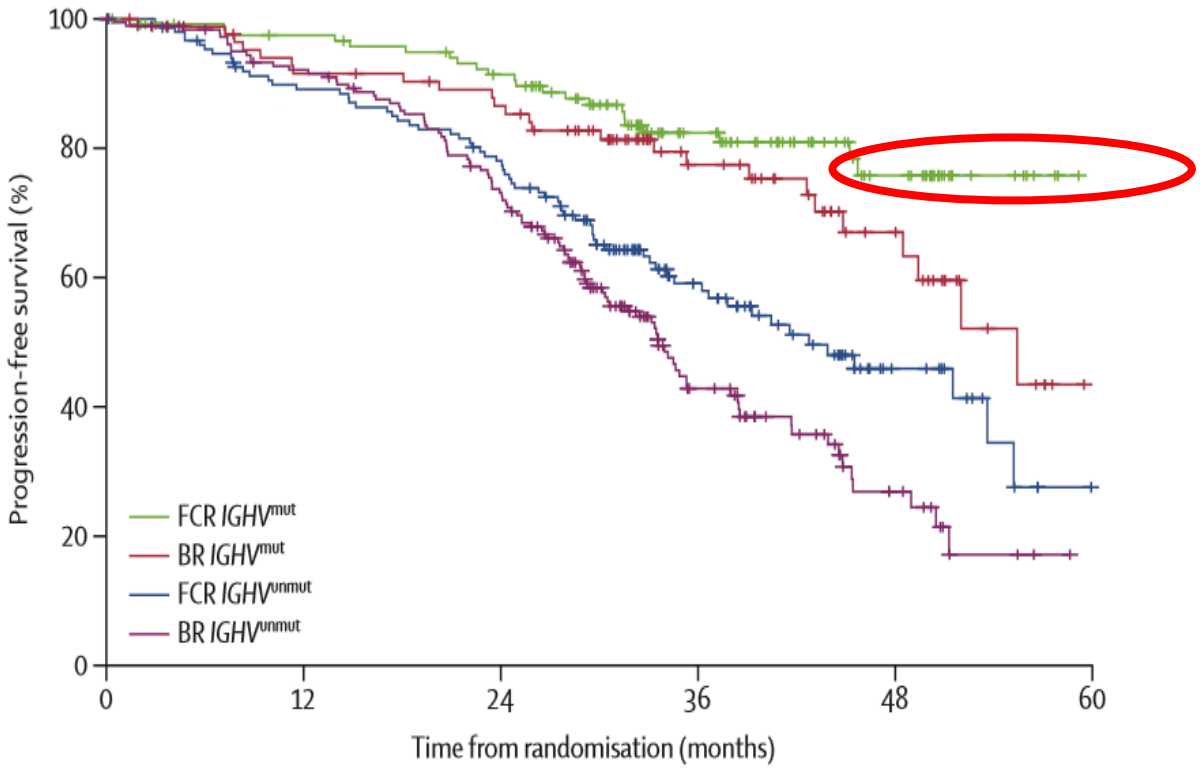
Historical studies from the “chemo era”

Study	Treatments	N	Result	Outcome	Notes
German CLL10	FCR vs. BR	564	FCR > BR	PFS but not OS	No benefit if > 65 AML/MDS: 5% with FCR
German CLL11	CHL-obino vs. CHL-ritux vs. CHL	780	CHL-obino > CHL-ritux > CHL	PFS and OS	
RESONATE-2	Ibrutinib vs. CHL	269	Ibrutinib > CHL	PFS and OS	

Eichhorst, Lancet Oncology, 2016 ; Eichhorst, ASH, 2016; Geode, NEJM, 2014; Geode, Leukemia, 2015; Burger, NEJM,2015

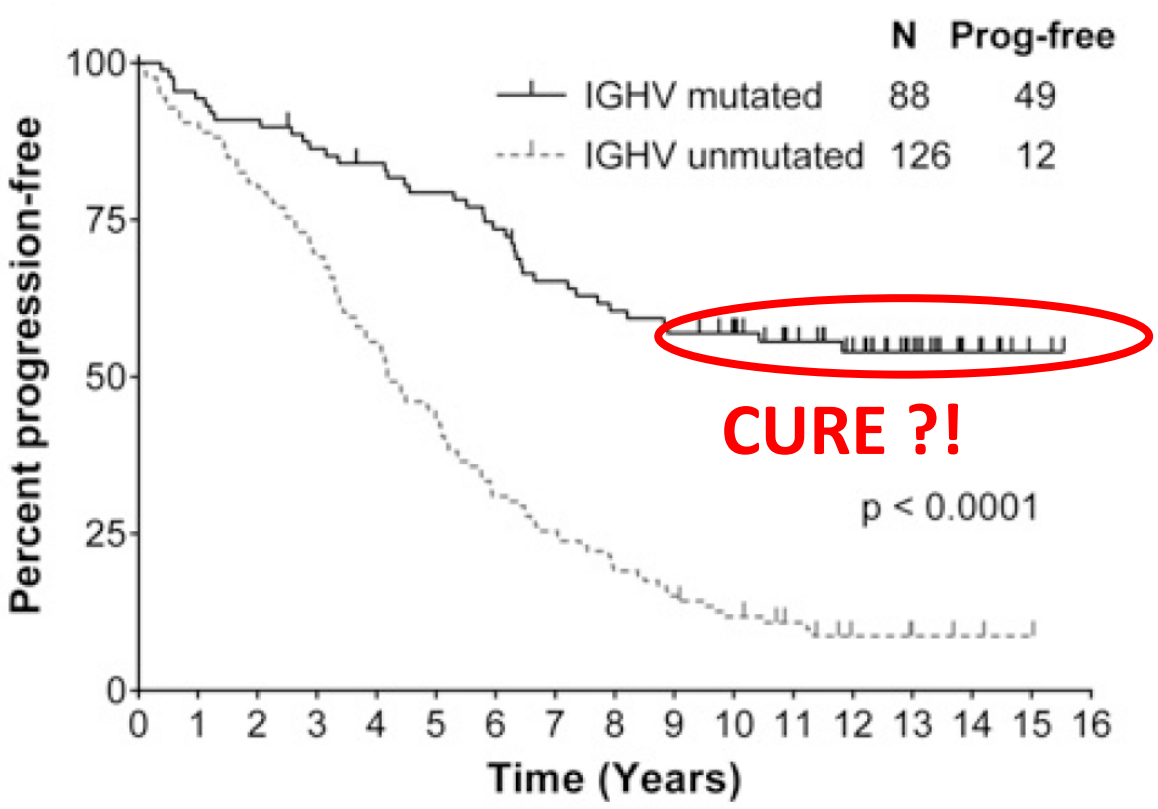
IGHV mutation as a predictive marker for FCR

CLL10 Study



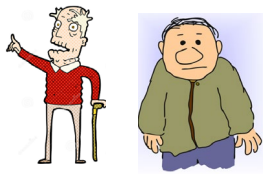
Eichhorst, Lancet Oncology, 2016

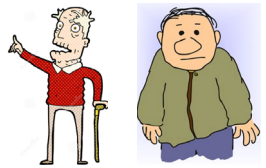
MD Anderson

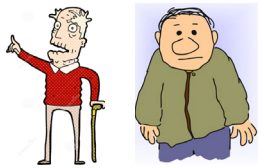


Thompson, Blood, 2106

First line – Summary of novel vs. chemo studies





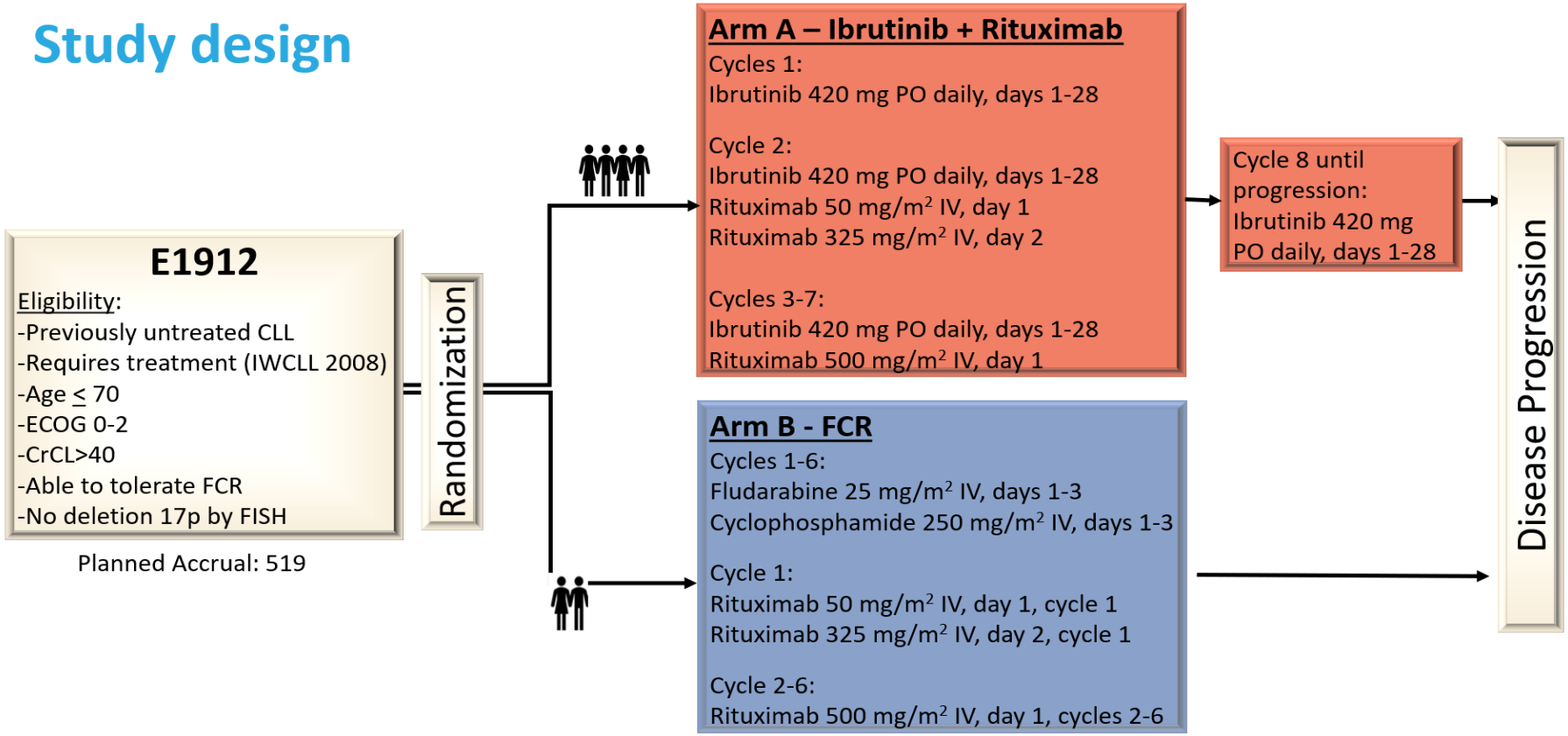


Fit and young	**FCR**	? (E1912)	**Ibrutinib +R**
Older	**BR**	? (A041202)	**Ibrutinib ± R**
Older or with comorbid conditions	**CHL+G**	? (iLLUMINATE)	**Ibrutinib +G**
Older or with comorbid conditions	**CHL+G**	? (ELEVATE)	**acalabrutinib ± G**
with comorbid conditions	**CHL+G**	? (CLL14)	**Venetoclax+ G**

G = obinutuzumab
R = rituximab

FCR vs. IB+R (E1912 Study)

Study design



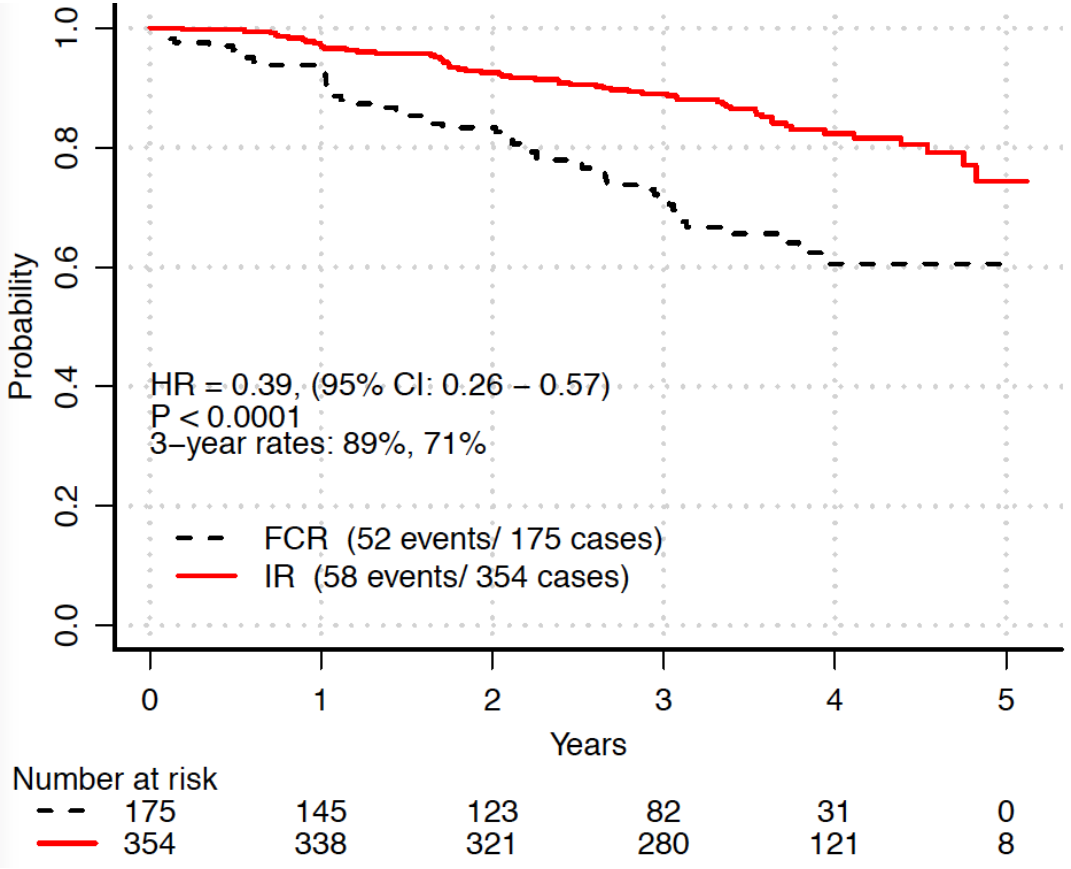
ECOG-ACRIN cancer research group | Reshaping the future of patient care

Shanafelt. NEJM,2019

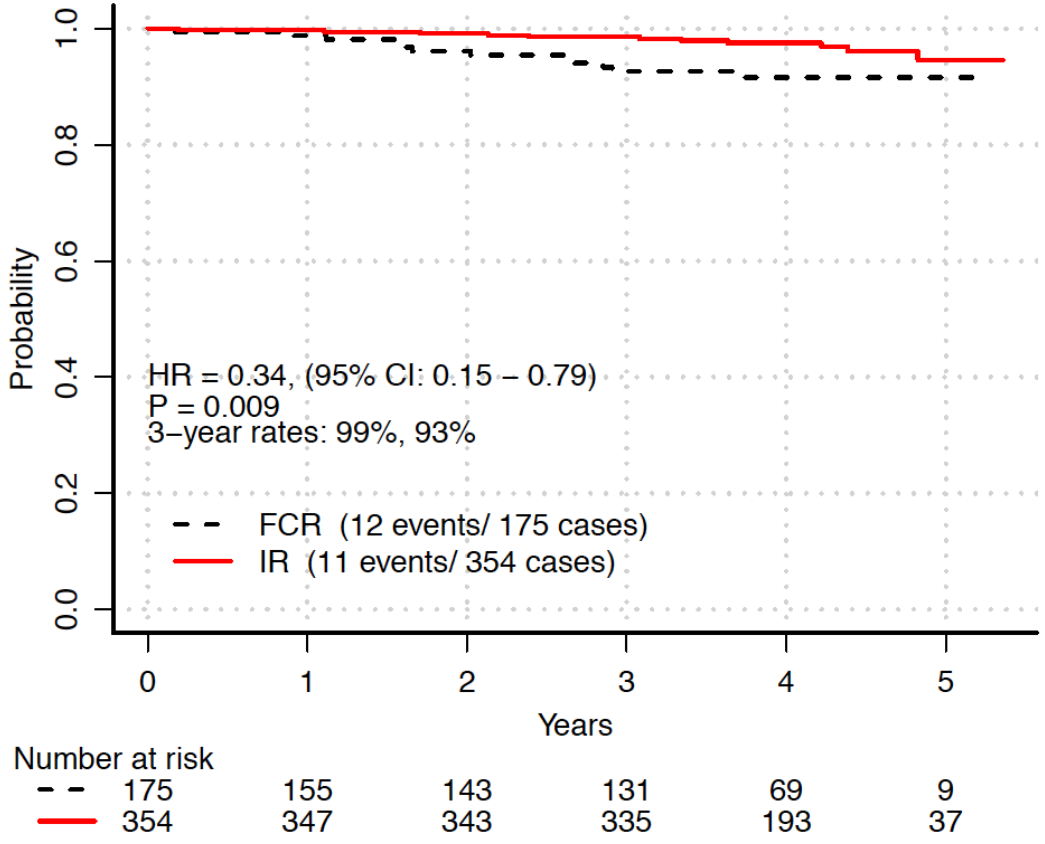
FCR vs. IB+R (E1912 Study)

(48 months follow-up)

Progression-free Survival



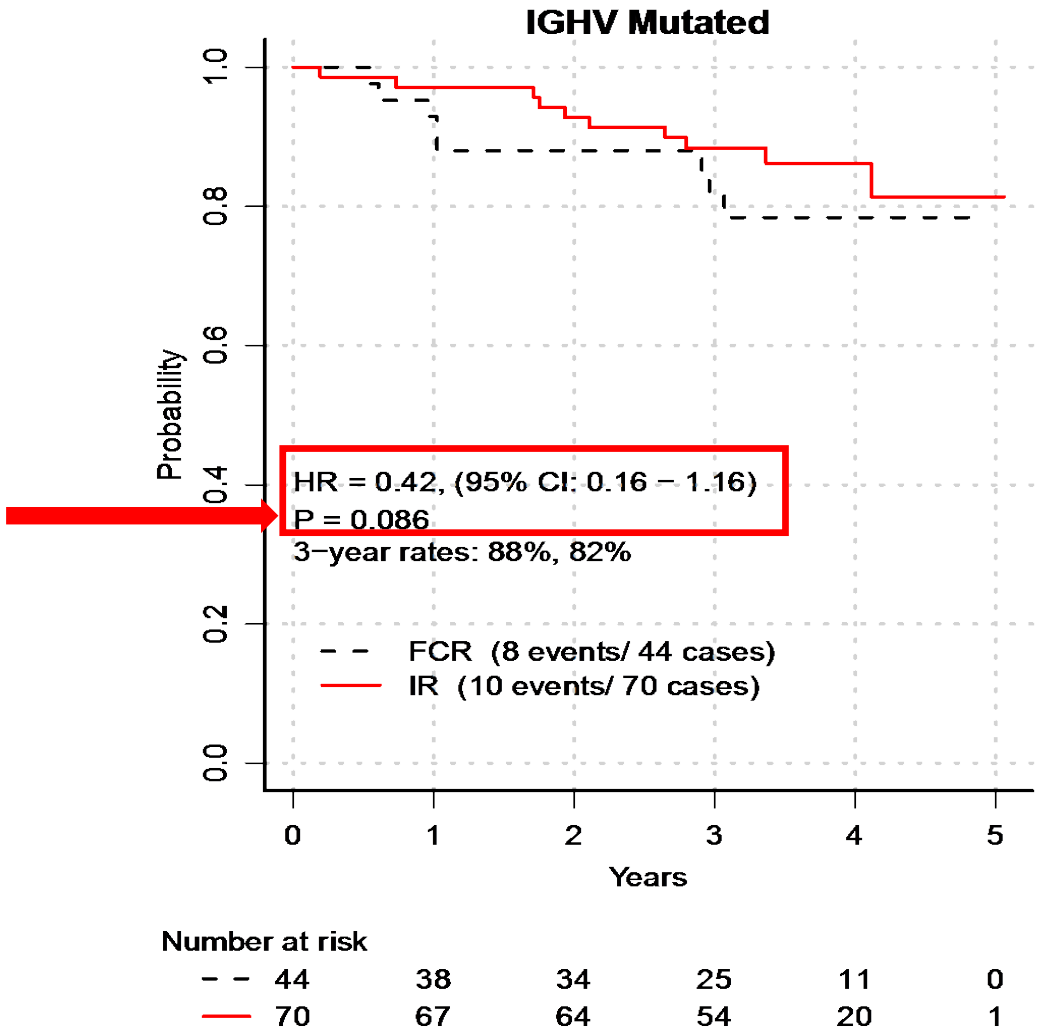
Overall Survival

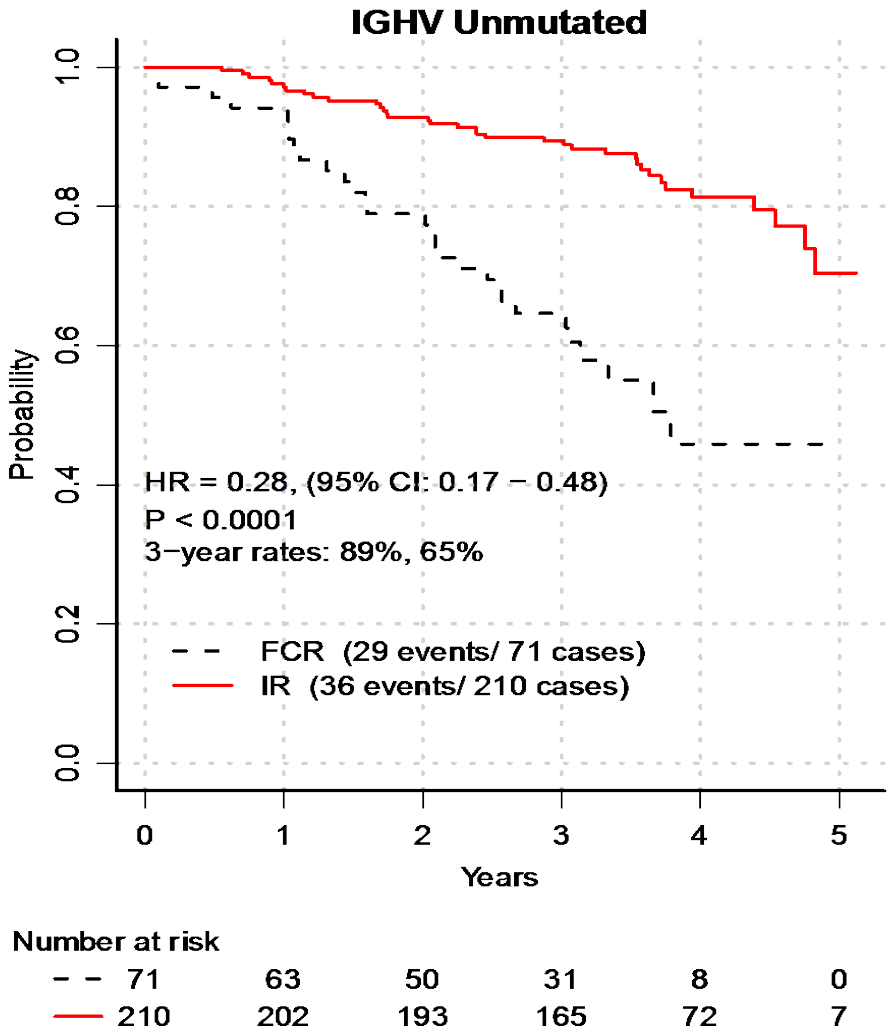


Shanafelt, ASH,2019

FCR vs. IB+R (E1912 Study)

(48 months follow-up)



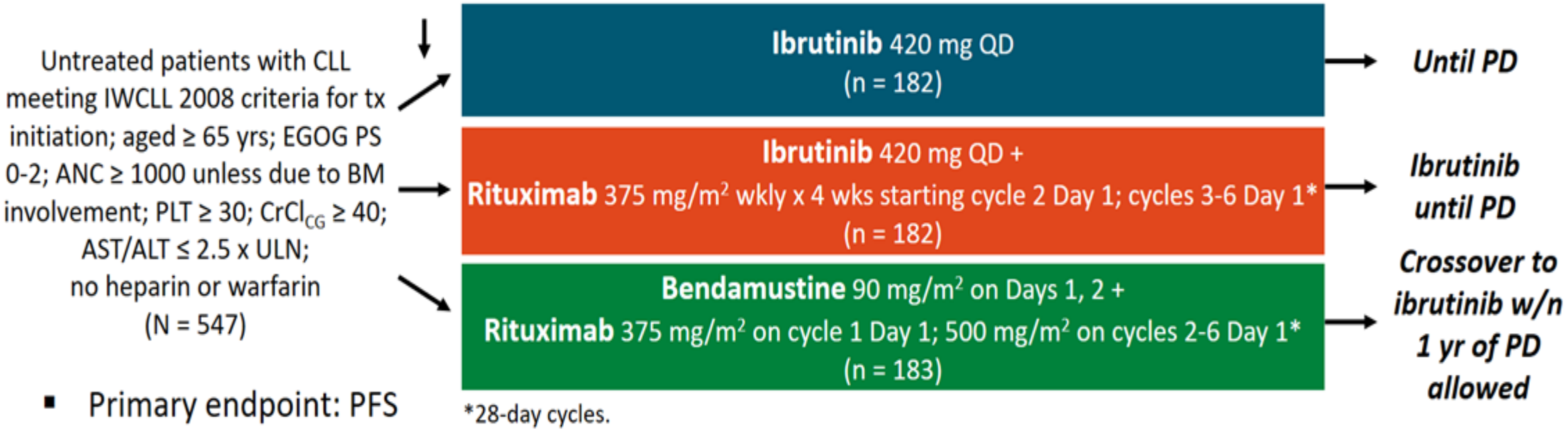


Shanafelt, ASH,2019

BR vs. IB+R vs. IB (A041202 Study)

- Multicenter, randomized, double-blind phase III study (data cutoff: October 4, 2018)

Stratified by Rai stage (high vs intermediate risk), del(11q22.3) or del(17p13.1) (presence vs absence), ZAP-70 methylation (< vs ≥ 20%)



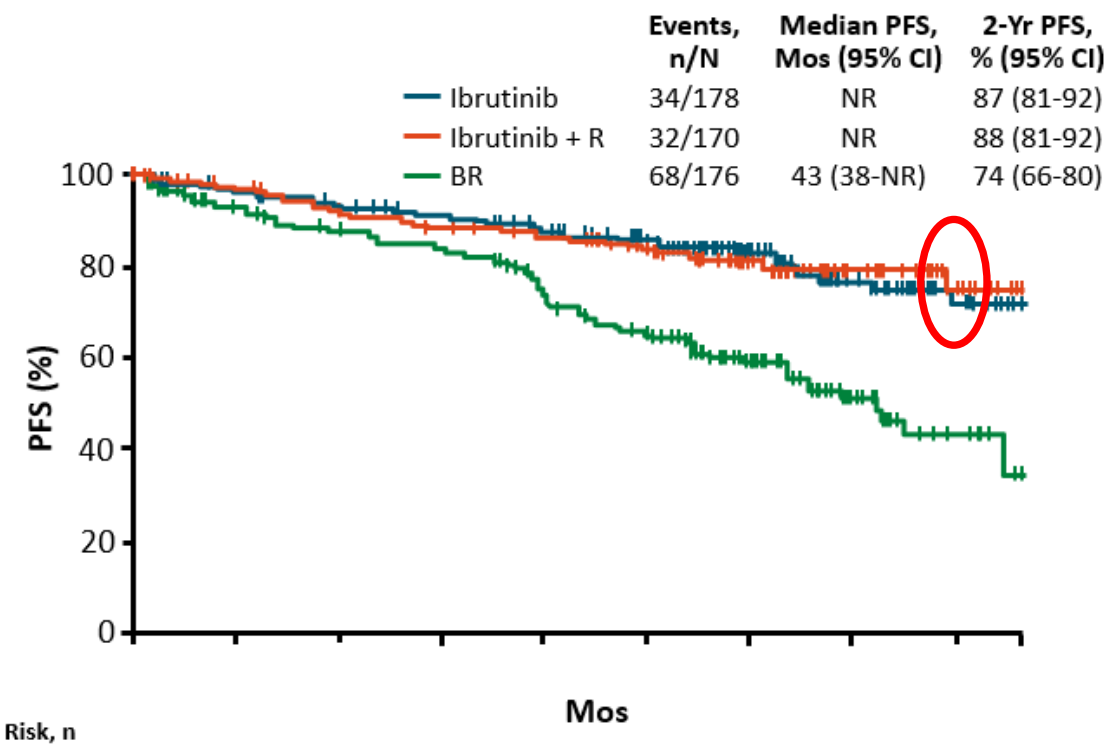
- Primary endpoint: PFS

*28-day cycles.

Woyach,NEJM,2018

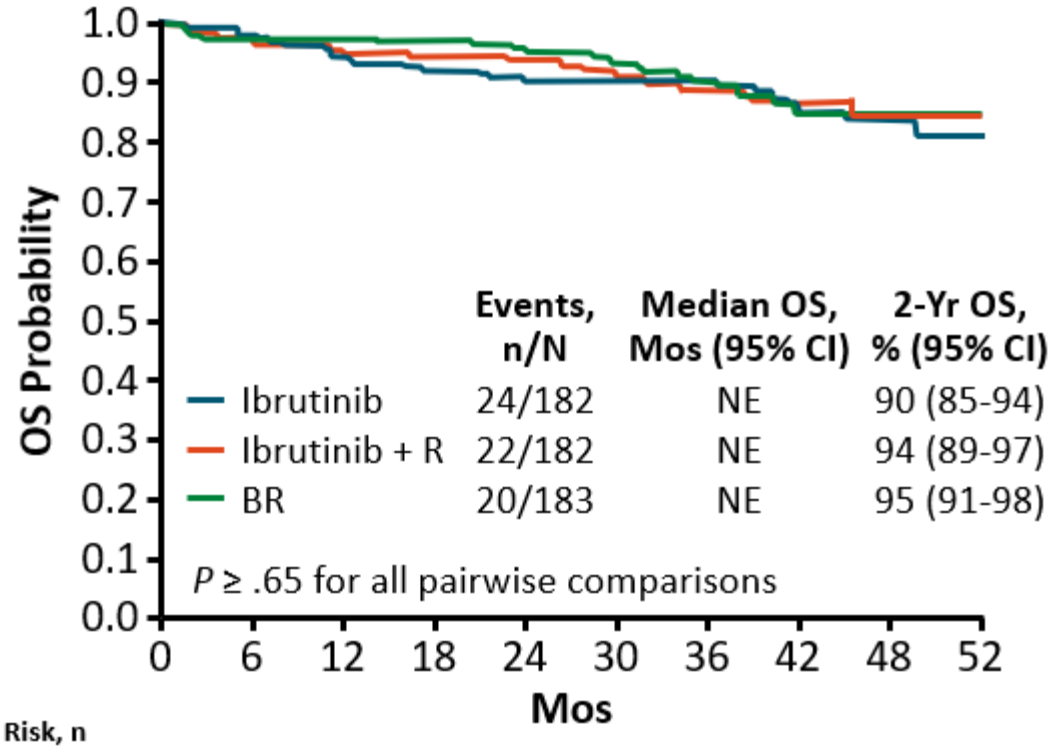
A041202: Results

Progression-Free Survival



Patients at Risk, n										
Ibrutinib	178	165	154	147	136	120	78	45	22	0
Ibrutinib + R	170	159	145	138	132	115	74	40	20	0
BR	176	140	129	122	103	88	57	26	11	0

Overall Survival



Patients at Risk, n										
Ibrutinib	182	175	166	161	156	146	100	62	26	1
Ibrutinib + R	182	172	169	165	161	147	100	55	24	1
BR	183	166	163	160	153	143	98	53	23	1

Woyach,NEJM,2018

IB+G vs. CHL+G (iLLUMINATE)

- Randomized, open-label, multicenter phase III trial

Stratified by ECOG PS (0-1 vs 2), del(17p)/del(11q) (+/+ vs +/- vs -/+ vs -/-)

Untreated patients with CLL/SLL needing treatment by iwCLL criteria, ≥ 65 yrs or < 65 yrs with comorbidities* (N = 229)

Ibrutinib 420 mg PO QD continuously + **Obinutuzumab** IV for 6 cycles† (n = 113) → ***Ibrutinib continued until PD or unacceptable toxicity***

Chlorambucil 0.5 mg/kg PO D1,15 for 6 cycles + **Obinutuzumab** IV for 6 cycles† (n = 116) → ***If IRC-confirmed progression, crossover to next-line single-agent ibrutinib permitted***

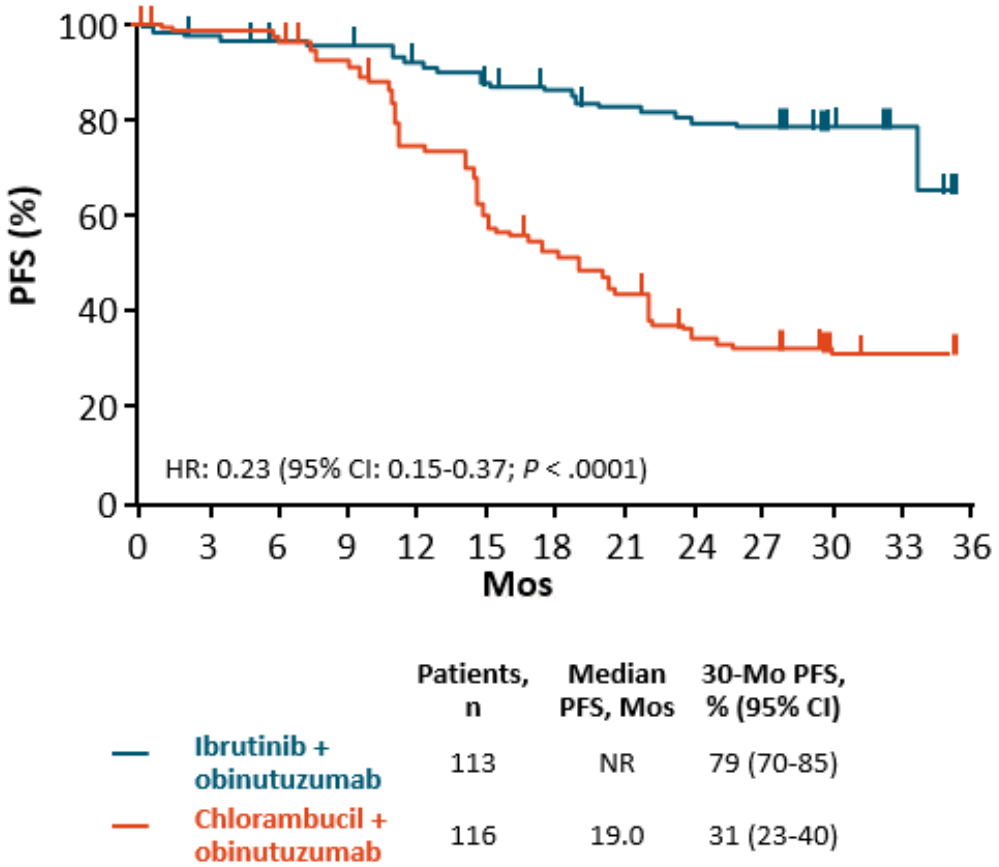
*Cumulative Illness Rating Score > 6, creatinine clearance < 70 mL/min, and/or del(17p)/*TP53* mutation.
†Cycle 1: 100 mg, Days 1; 900 mg, Day 2; 1000 mg, Days 8, 15. Cycle 2-6: 1000 mg, Day 1.

- Primary endpoint: PFS

Moreno, Lancet Oncology, 2018

IB+G vs. CHL+G (iLLUMINATE) Results

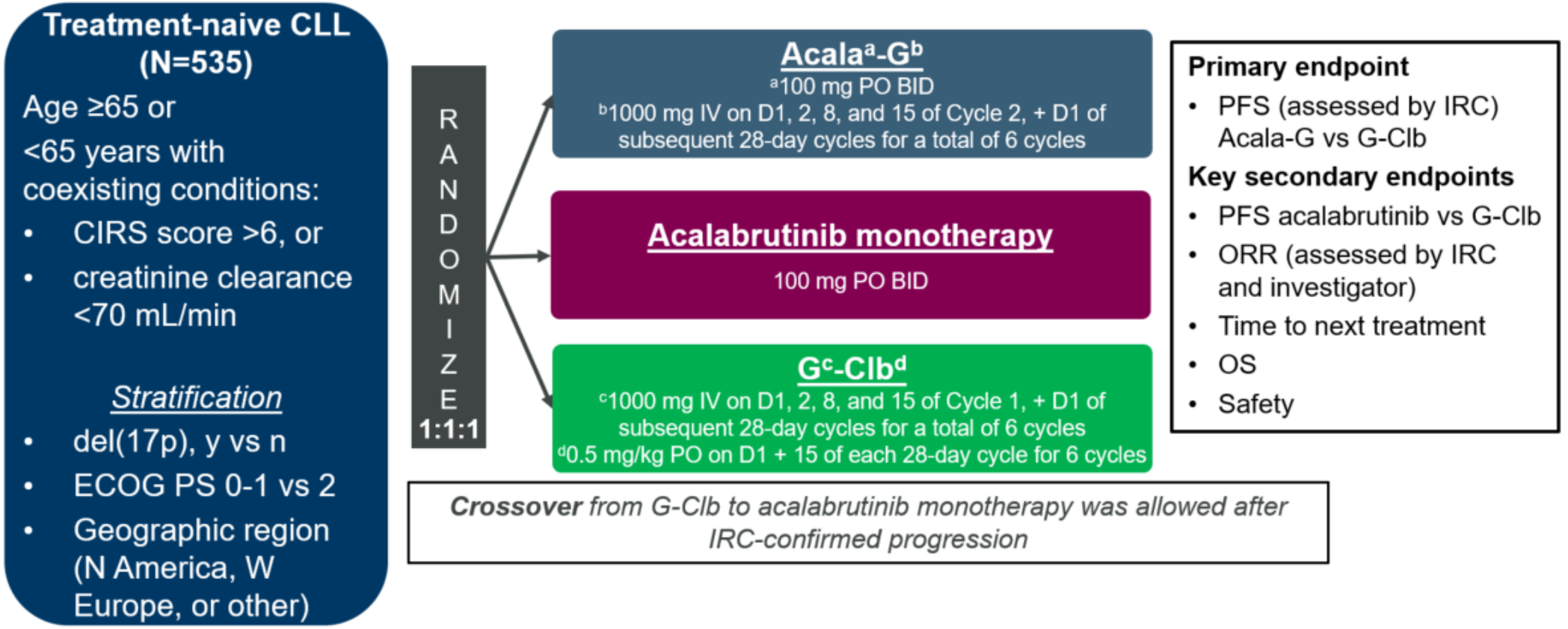
Progression-free Survival



No Overall Survival Benefit

Moreno, Lancet Oncology, 2018

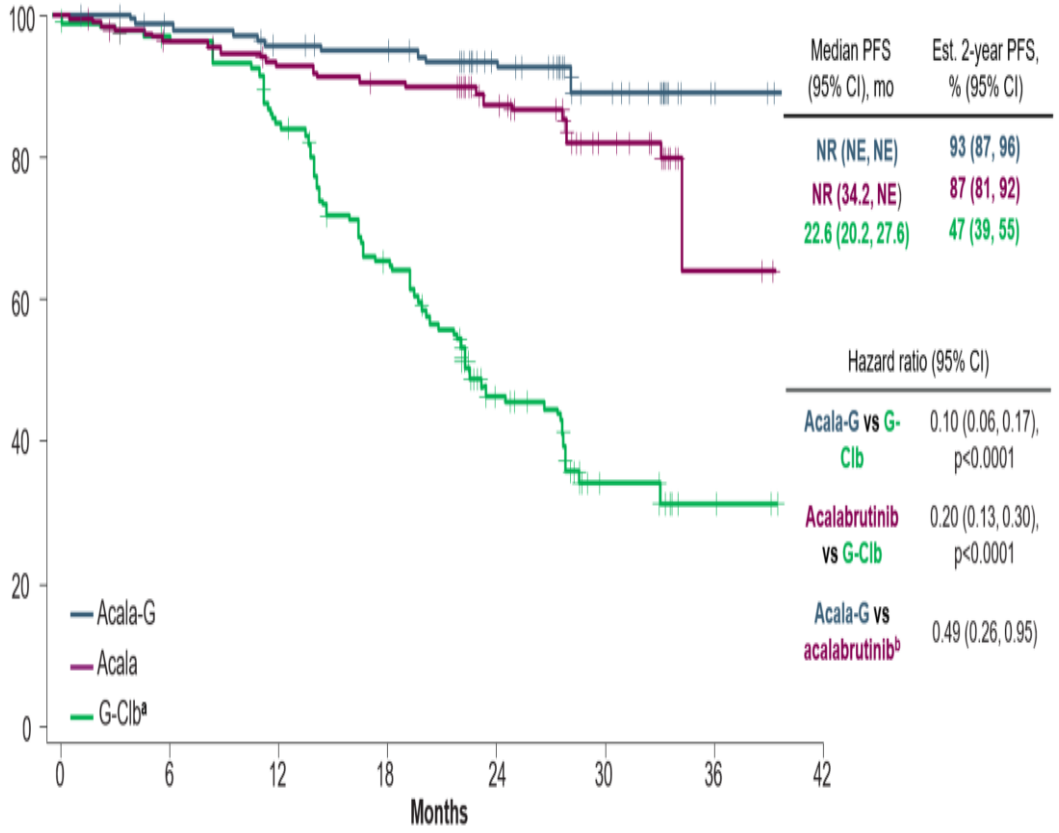
Acalabrutinib ± G vs. CHL+G (ELEVATE)



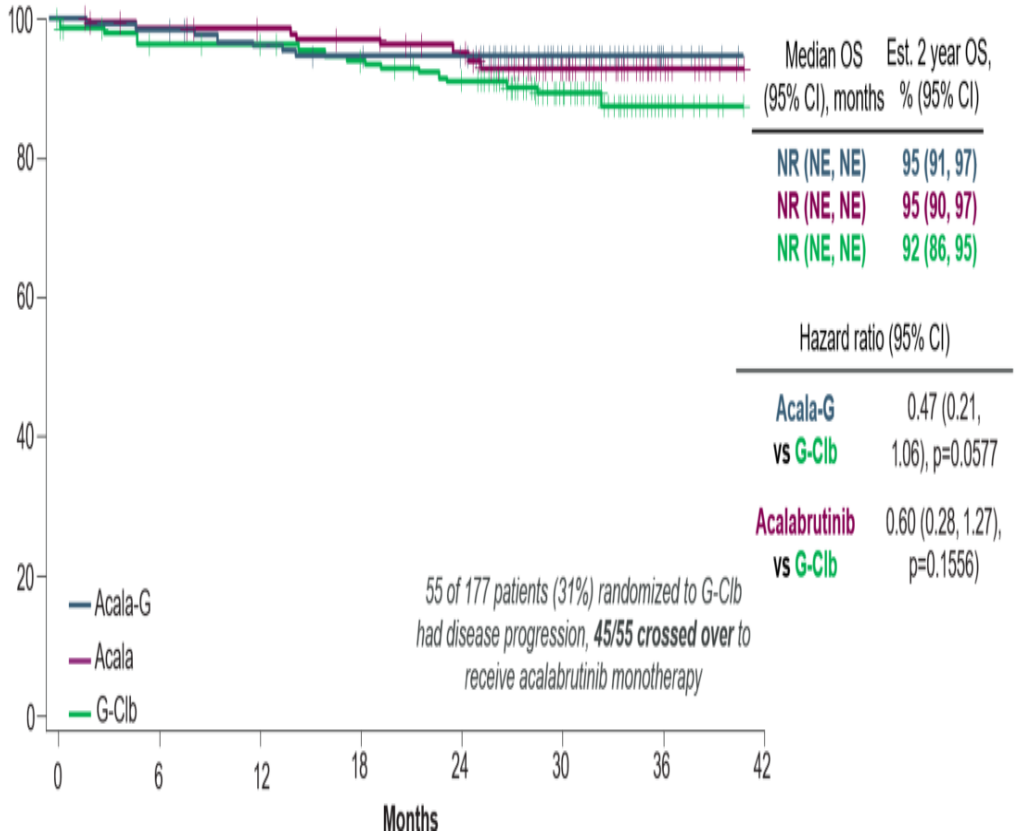
Sharman, Lancet, 2020

Acalabrutinib ± G vs. CHL+G (ELEVATE)

Progression-free Survival

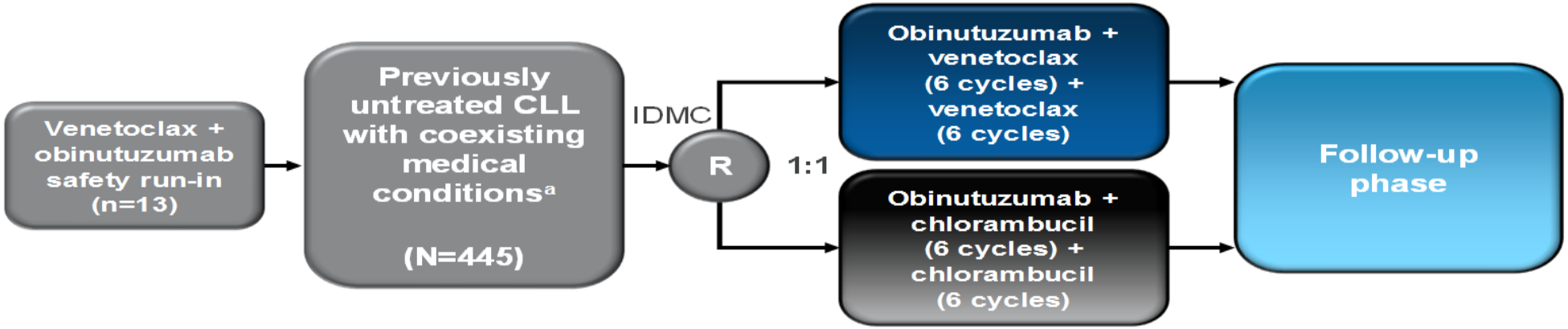


Overall Survival



Sharman, Lancet, 2020

Venetoclax + G vs CHL + G (CLL-14)



Primary endpoint:

- PFS as assessed by investigator[3]

Secondary endpoints[3]:

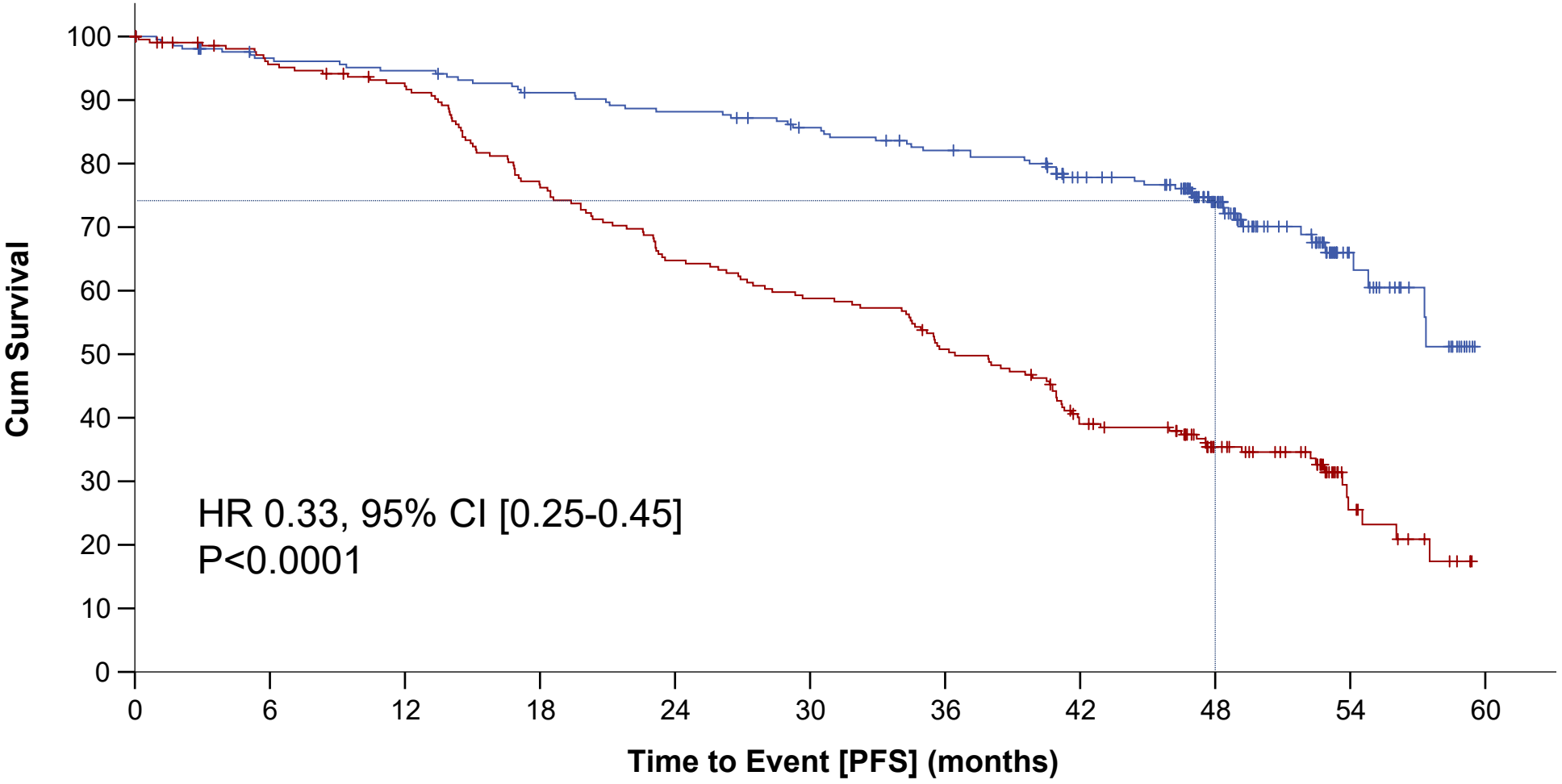
- PFS as assessed by IRC
- MRD
- ORR
- CR rate
- DOR
- EFS
- OS
- TTNT
- Safety

[a]CIRS >6 and/or CrCl <70 mL/min

Fischer, NEJM,2019

Venetoclax + G vs CHL + G (CLL-14)

(52.4 months follow-up)



Median PFS

Ven-Obi: not reached

Clb-Obi: 36.4 months

4-year PFS rate

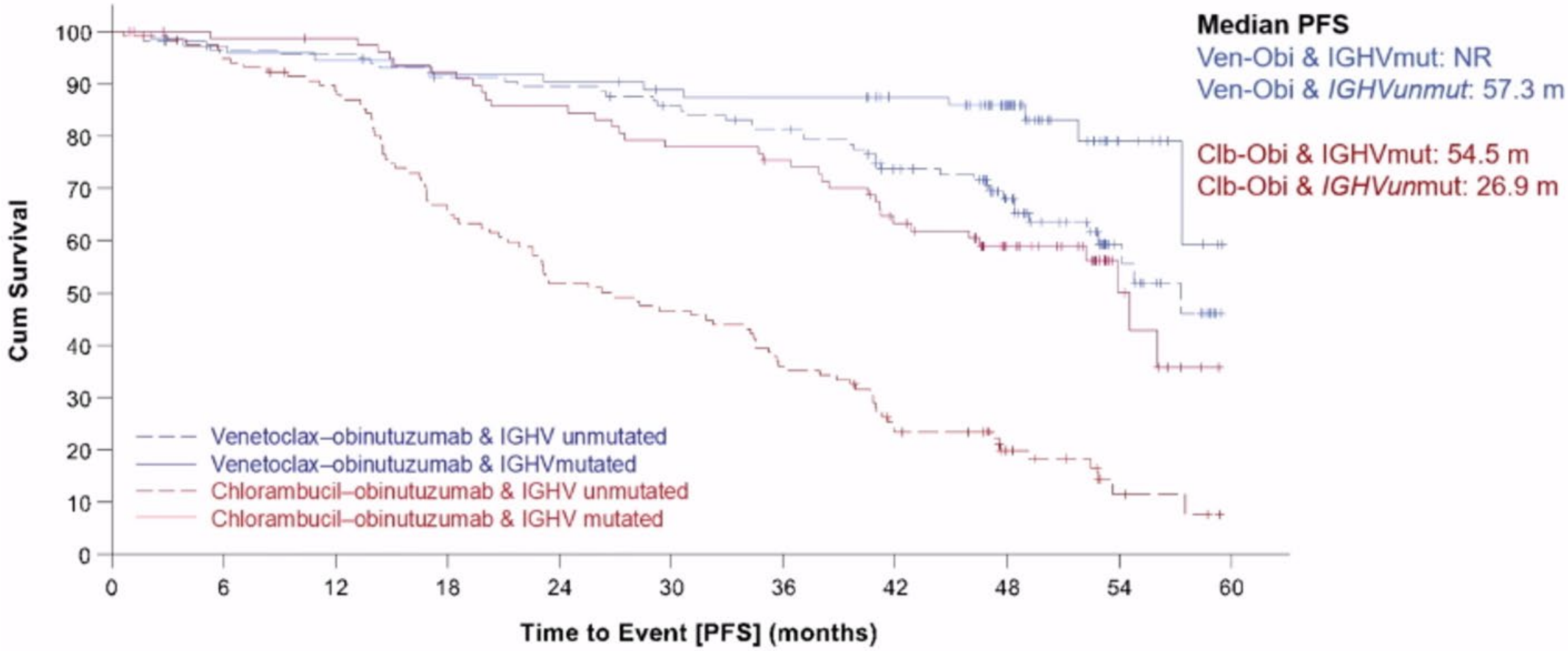
Ven-Obi: 74.0%

Clb-Obi: 35.4%

Al-Sawaf, EHA, 2021

4-YEAR FOLLOW-UP: PFS – IGHV STATUS

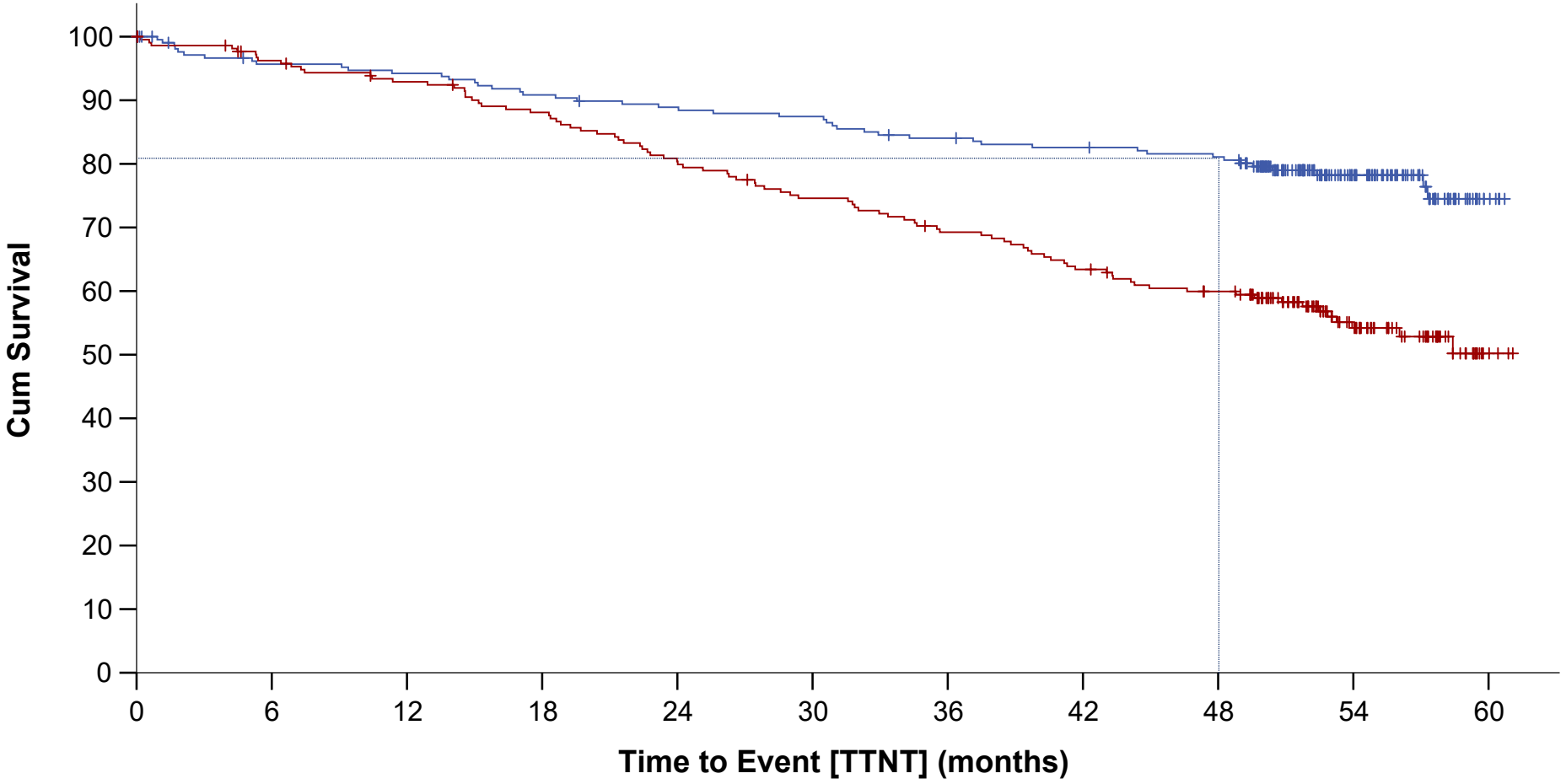
Median observation time 52.4 months



Al-Sawaf, EHA, 2021

4-YEAR FOLLOW-UP: TIME TO NEXT TREATMENT

Median observation time 52.4 months



Median TTNT
Ven-Obi: not reached
Clb-Obi: not reached

4-year TTNT rate
Ven-Obi: 81.08%
Clb-Obi: 59.9%

Next anti-leukemic therapy:
Ven-Obi: 35 PDs – 17 NLT
Clb-Obi: 122 PDs – 70 NLT

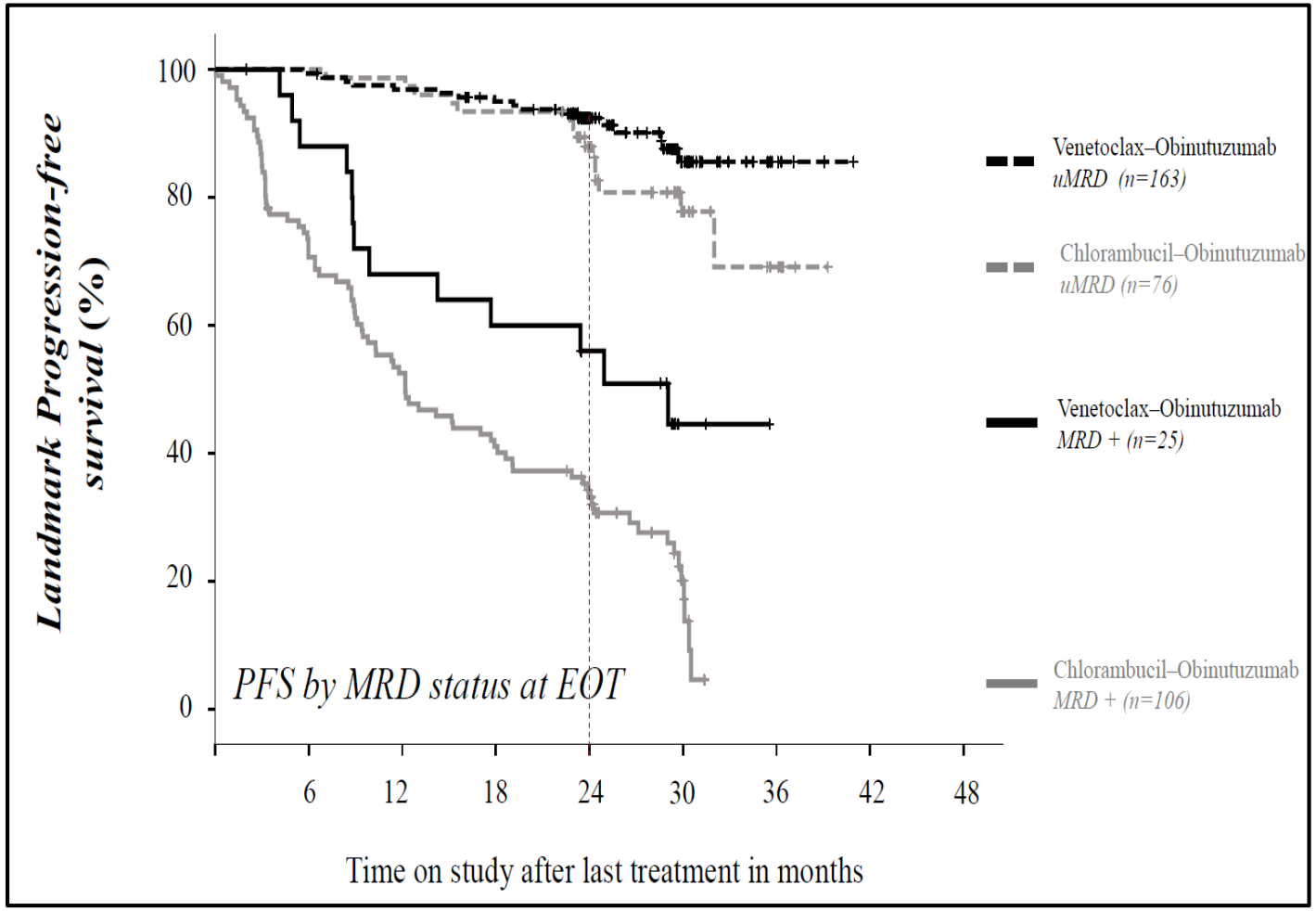
HR 0.46, 95% CI [0.32-0.65]
P<0.0001

Al-Sawaf, EHA, 2021

uMRD4 at the end of treatment (12 months) and PFS

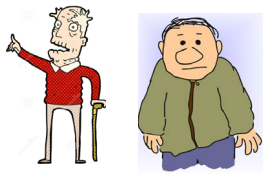
	Venetoclax-Obinutuzumab	Chlorambucil-Obinutuzumab	*P* value
Number of patients, N	216	216	
Peripheral blood			
Negative ($<10^{-4}$)	76 %	35 %	< 0.001
Negative ($<10^{-4}$) in complete response	42 %	14 %	< 0.001
Bone marrow			
Negative ($<10^{-4}$)	57 %	17 %	< 0.001
Negative ($<10^{-4}$) in complete response	34 %	11 %	< 0.001

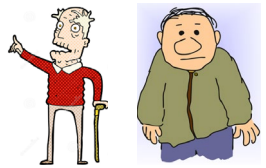
By ASO-PCR 3 months after completion of treatment

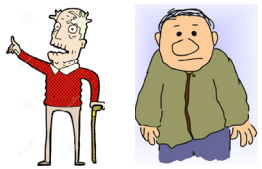


Fischer, ASH,2019

First line – Summary of novel vs. chemo studies







Fit and young	**FCR**	< (E1912)	**Ibrutinib +R**
Older	**BR**	< (A041202)	**Ibrutinib ± R**
Older or with comorbid conditions	**CHL+G**	< (iLLUMINATE)	**Ibrutinib +G**
Older or with comorbid conditions	**CHL+G**	< (ELEVATE)	**acalabrutinib ± G**
with comorbid conditions	**CHL+G**	< (CLL14)	**Venetoclax+ G**

G = obinutuzumab
R = rituximab

First line treatment
for patients normal TP53

For all pts:

Acalabrutinib ± G

OR

Ibrutinib

OR

Venetoclax + G

FCR is <u>not preferred</u> but can be a <u>reasonable option</u> for selected patients if:

- younger than 65 and fit
- mutated IGHV
- no evidence of del17p or TP53 mutation
- (no evidence of del 11q)

G = Gazyva = obinutuzumab

BTKis vs. Ven-Obino

BTKi (Acalabrutinib/Ibrutinib)	Ven-G
Indefinite treatment (responses mostly PR)	Fixed-duration ; High CR and uMRD rate
Easier to start	Time-limited treatment
Preferred in patients who: • Can't follow the ramp-up schedule for venetoclax • Significant/unstable renal issues	Preferred in patients with: • Cardiac (arrythmia, HTN) • Bleeding issues
uMRD achievement is irrelevant	uMRD status after treatment is important
Can use after Ven and is effective	Can use after BTKi and is effective
Favored in patients with del17p or mutated TP53	If uses for del17p/mTP53, prefer continuous treatment

- **No head-to-head comparison**
- **Both are reasonable options**
- **Consider patient and disease factors**
- **Look at pros and cons for each**

Treatment options for previously treated patients (without del17p/P53 mutation)

Previously Treated CLL Summary

For all pts:

Acalabrutinib OR **Ibrutinib** OR **Venetoclax + R**

Duvelisib OR **Idelalisib**

R = rituximab

Previously Treated CLL Summary

1. **First**
   - **Venetoclax + Rituximab**
     or
   - **BTKi : acalabrutinib or Ibrutinib**

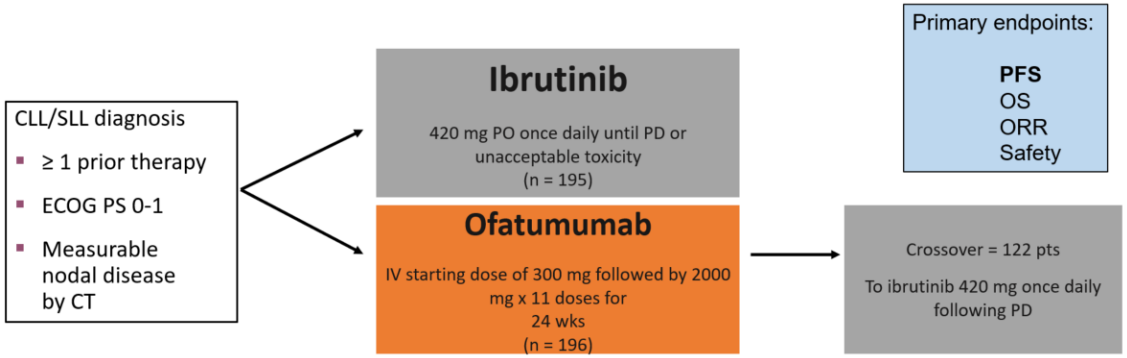
2. **Second**
   - **Ibrutinib/acalabrutinib if previously treatment with Ven**
   - **Ven-R if previously treated with BTKi (ibrutinib or acalabrutinib)**

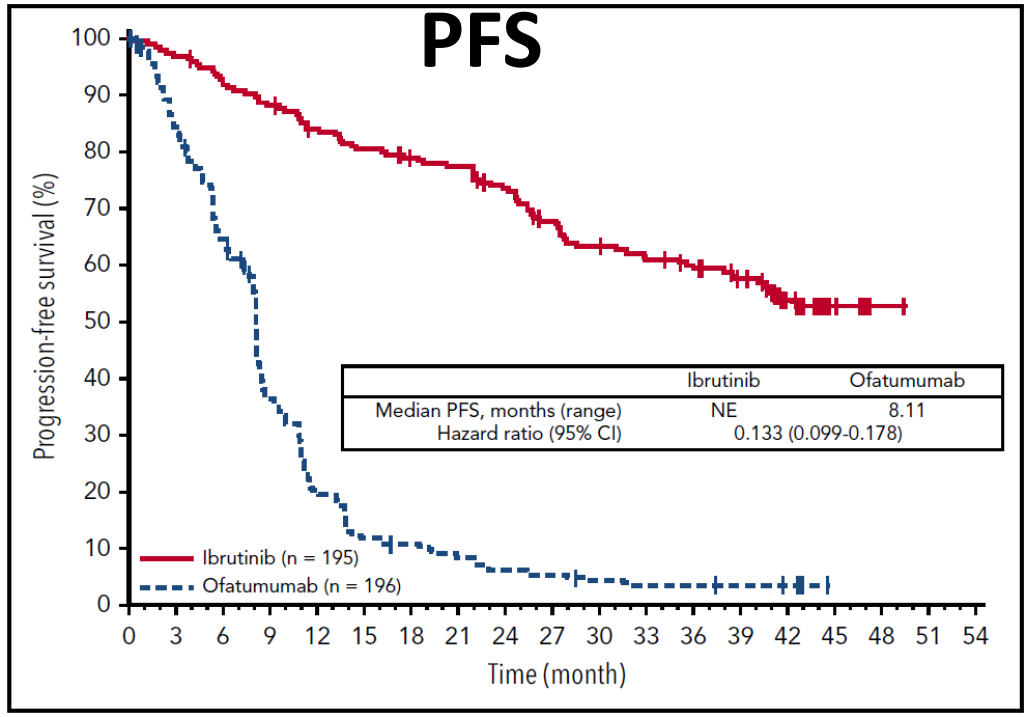
3. **Third**
   - **Idelalisib+ rituximab OR duvelisib**

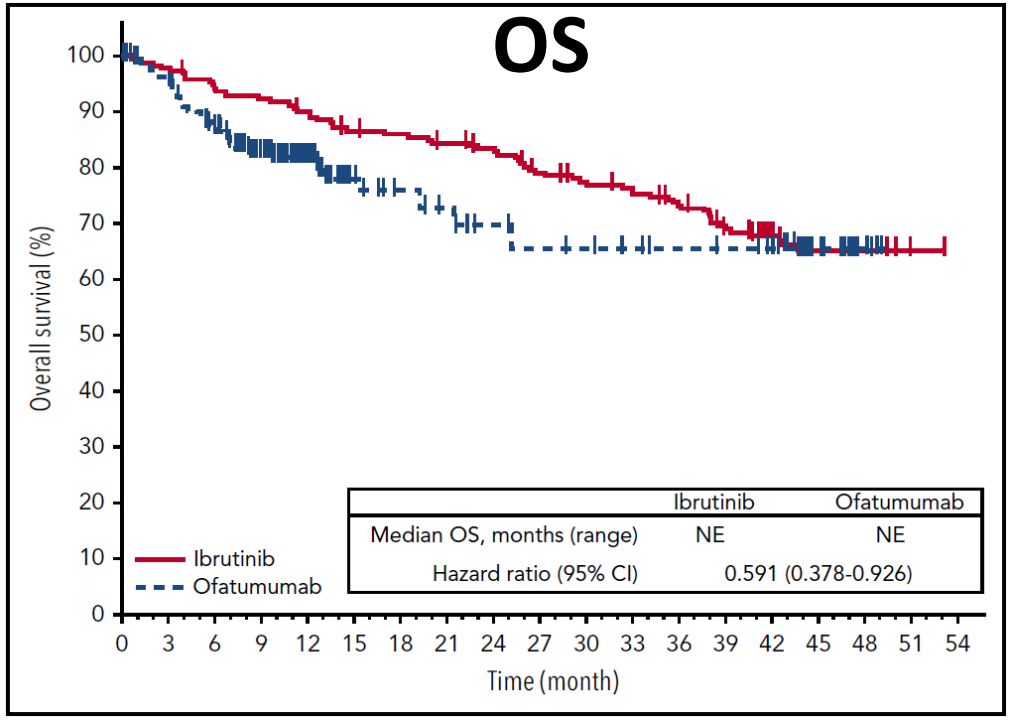
Previously treated CLL : Principles

1. **Repeat FISH panel - look for del (17p) or TP53 mutation**
2. Bone marrow needs to be repeated to assess for MDS if prior FCR
3. Very limited role for chemoimmuntherapy (almost never)

Ibrutinib vs Ofatumumab in R/R CLL (RESONATE: Phase III)

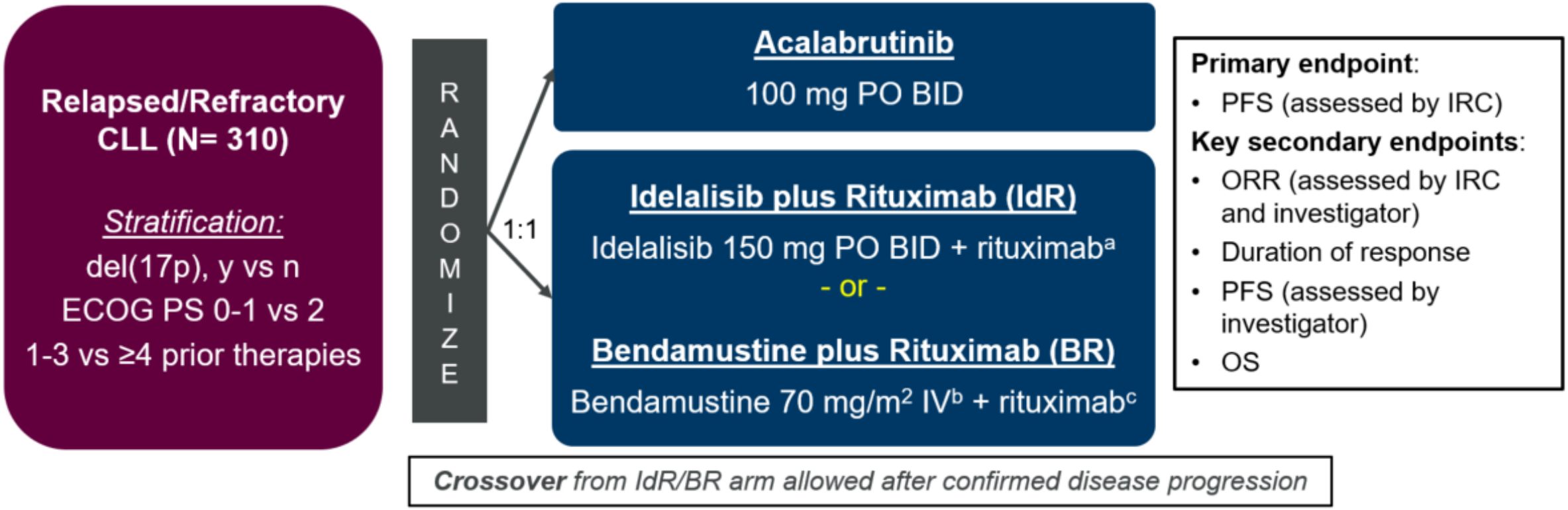






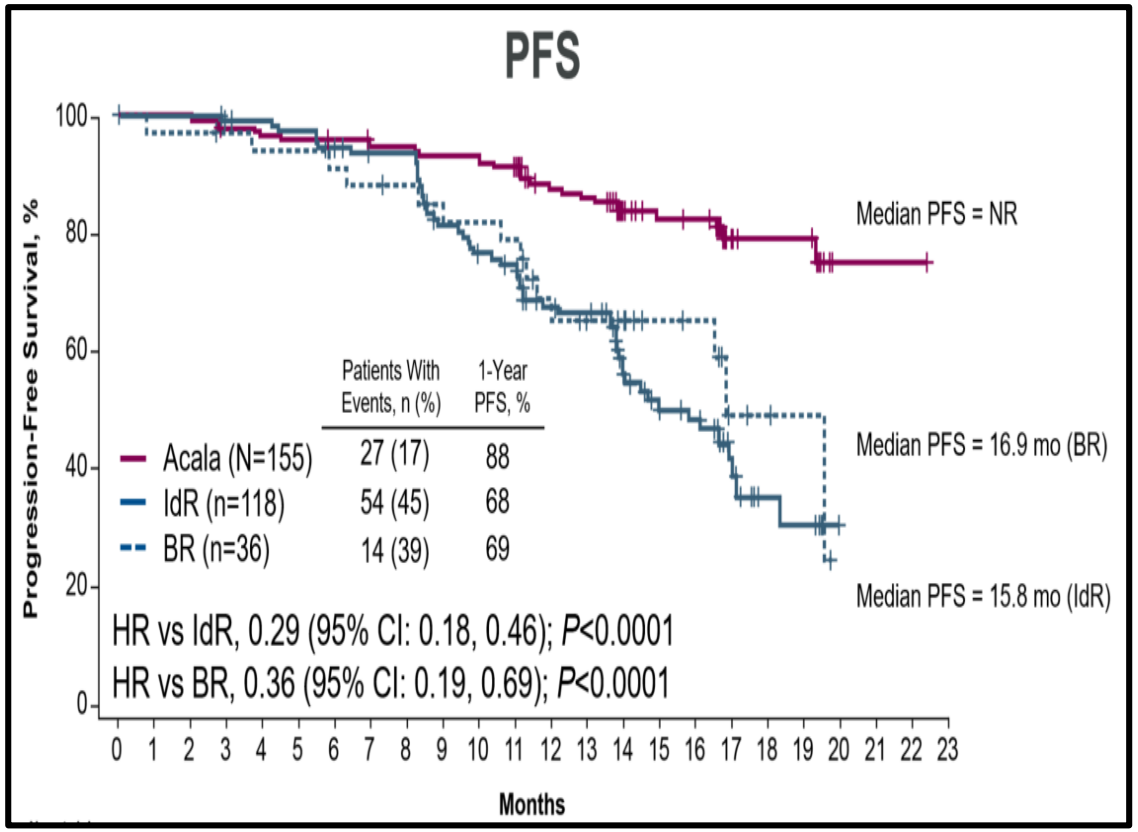
Byrd, NEJM, 2014 ; Byrd, Blood, 2019

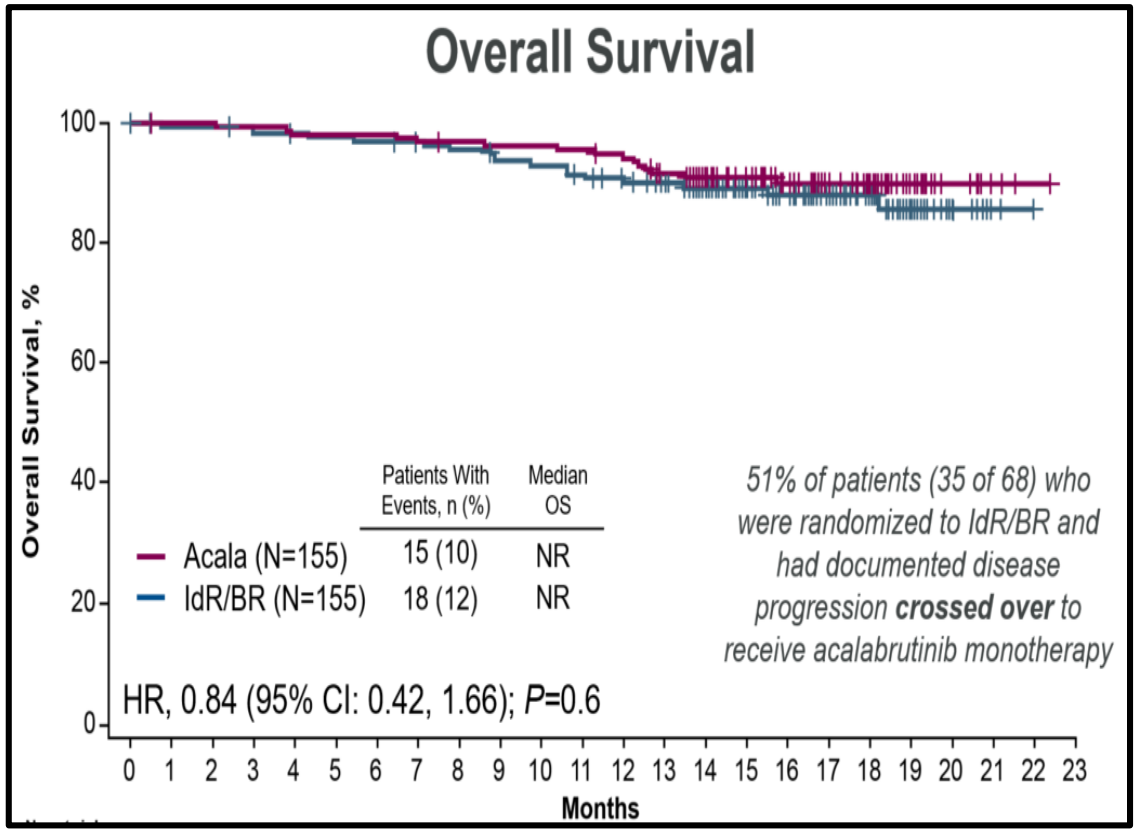
Acalabrutinib vs. Investigator choice for relapsed CLL (ASCEND Study)



Ghia,JCO,2020[52]

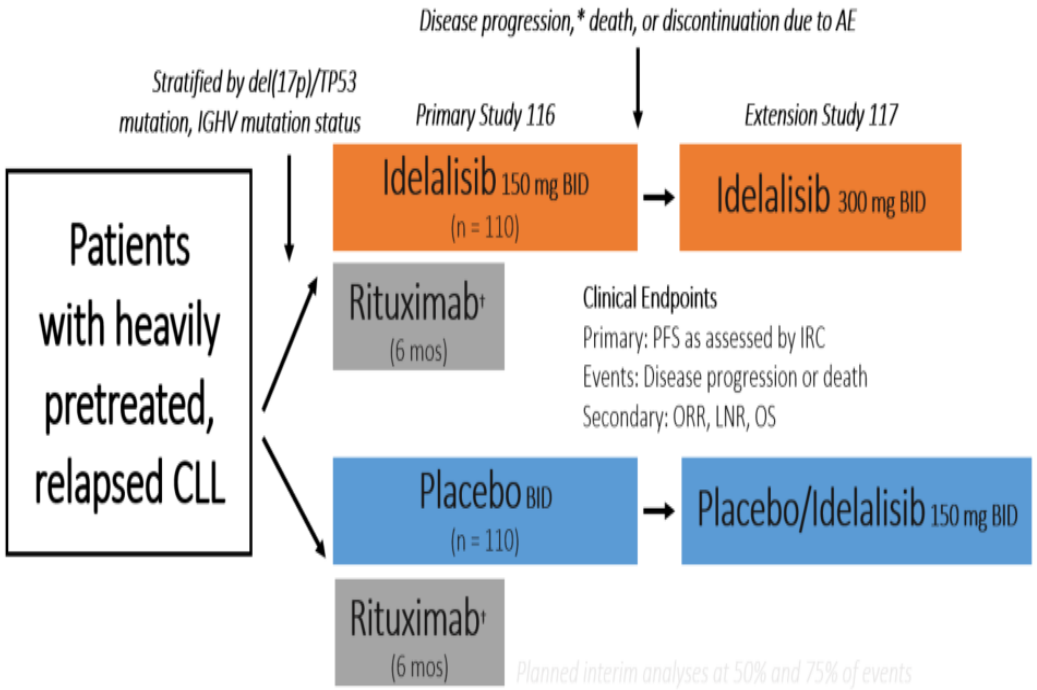
Acalabrutinib vs. Investigator choice for relapsed CLL (ASCEND Study)

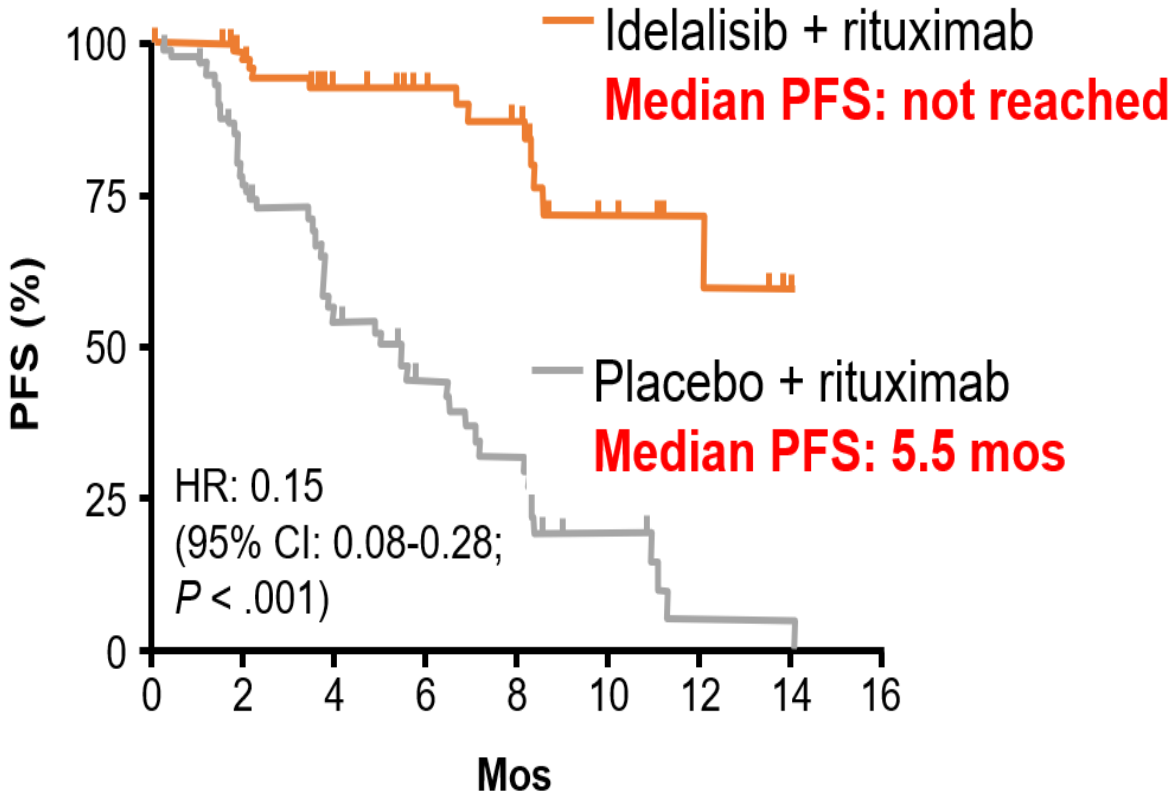




Ghia, JCO, 2020

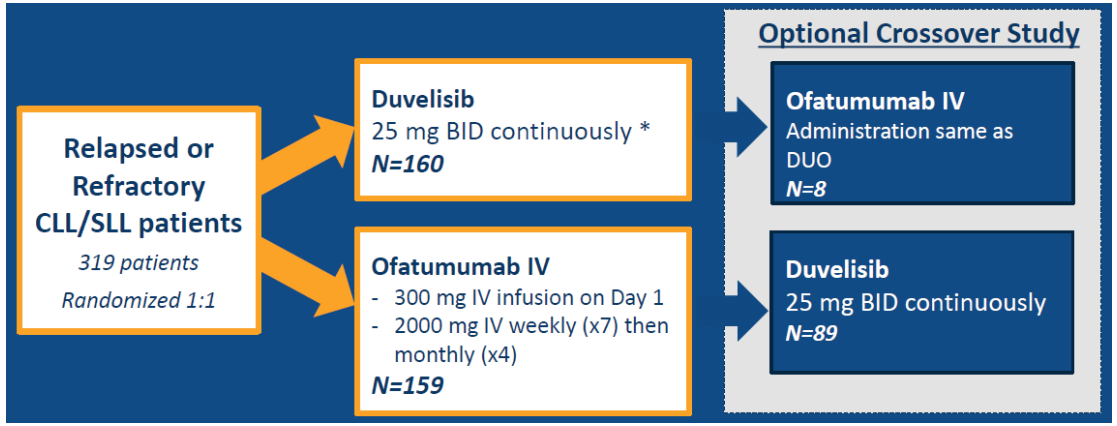
Idelalisib and Rituximab for Previously Treated Patients

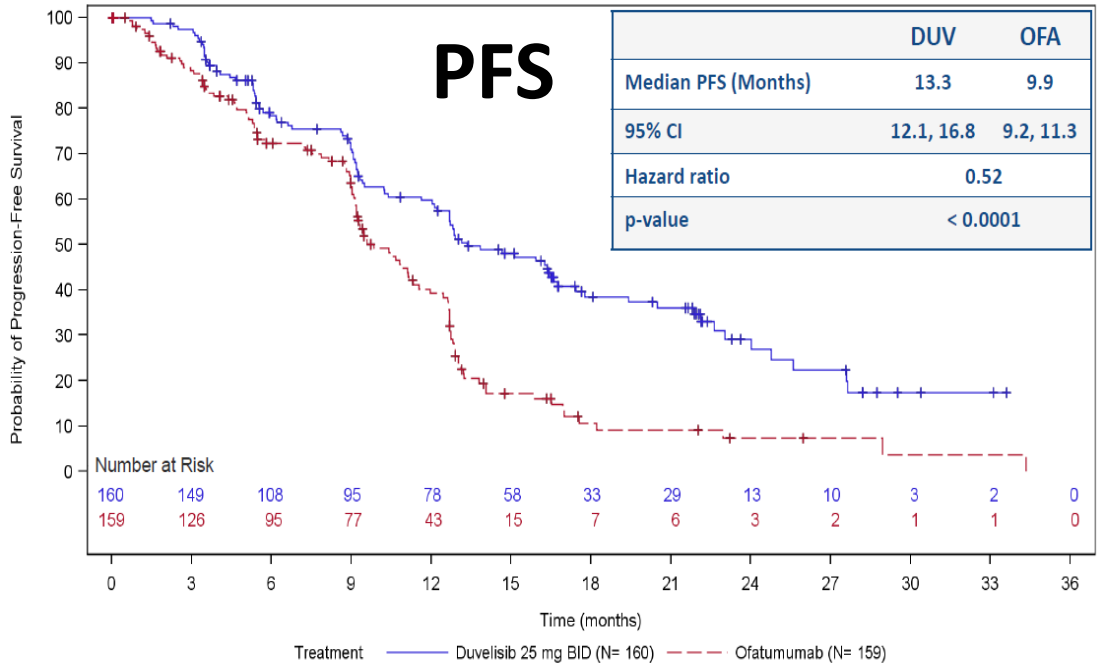


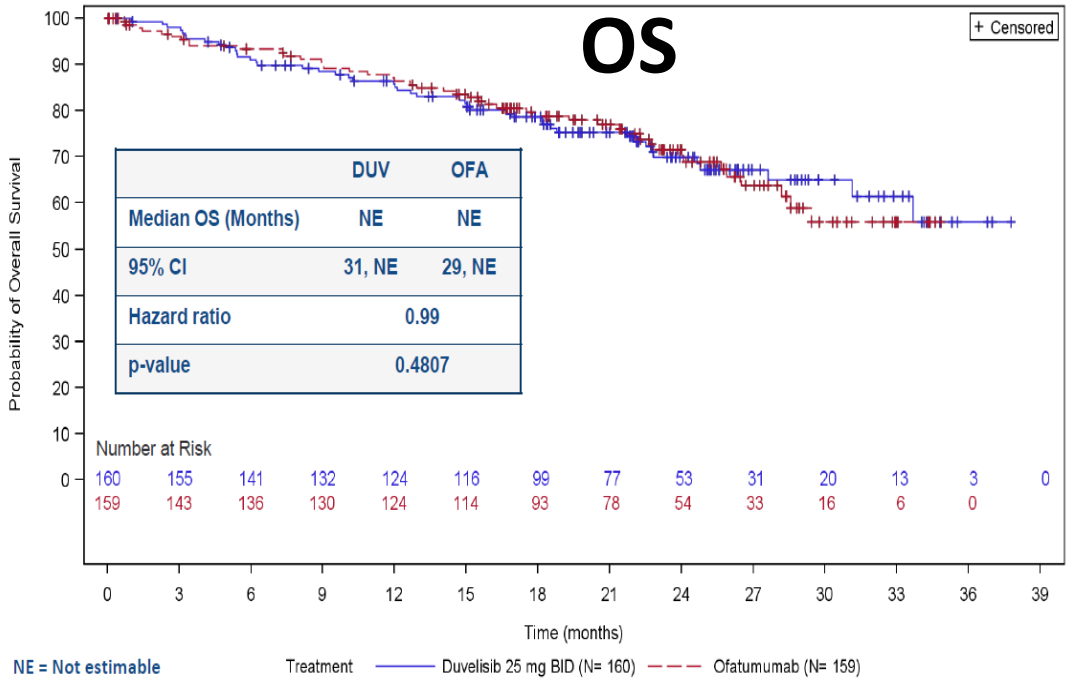


Furman, NEJM,2014

Duvelisib vs Ofatumumab (DUO trial) - Relapsed/Refractory

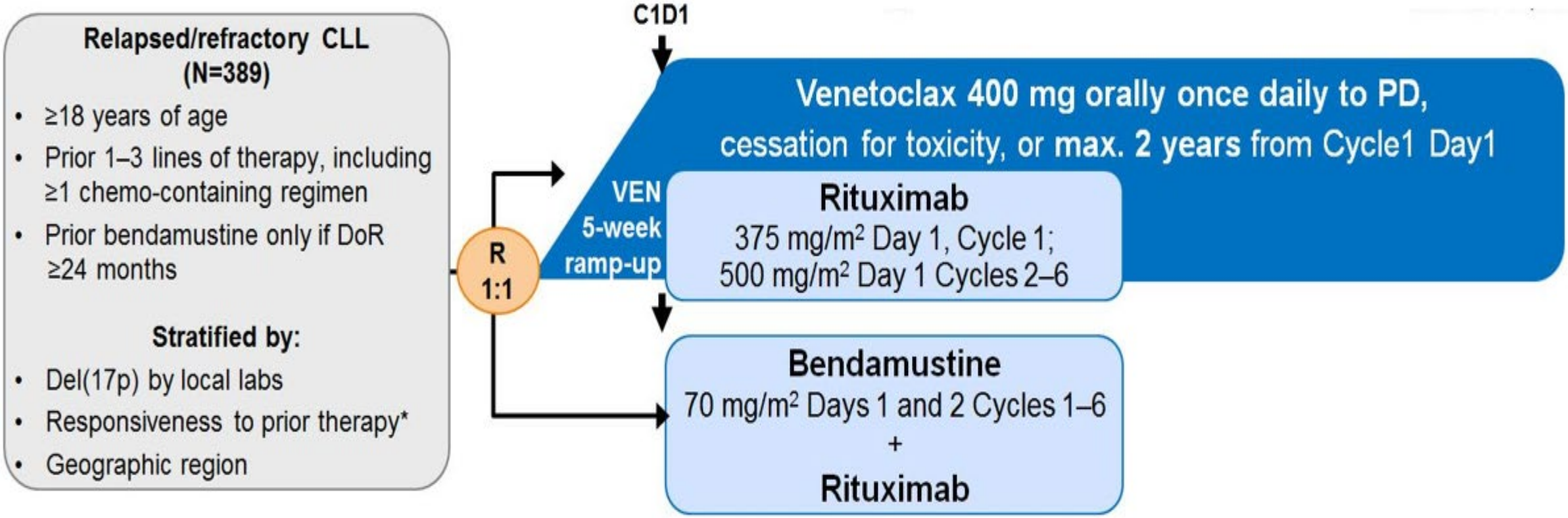






Flinn, Blood, 2018

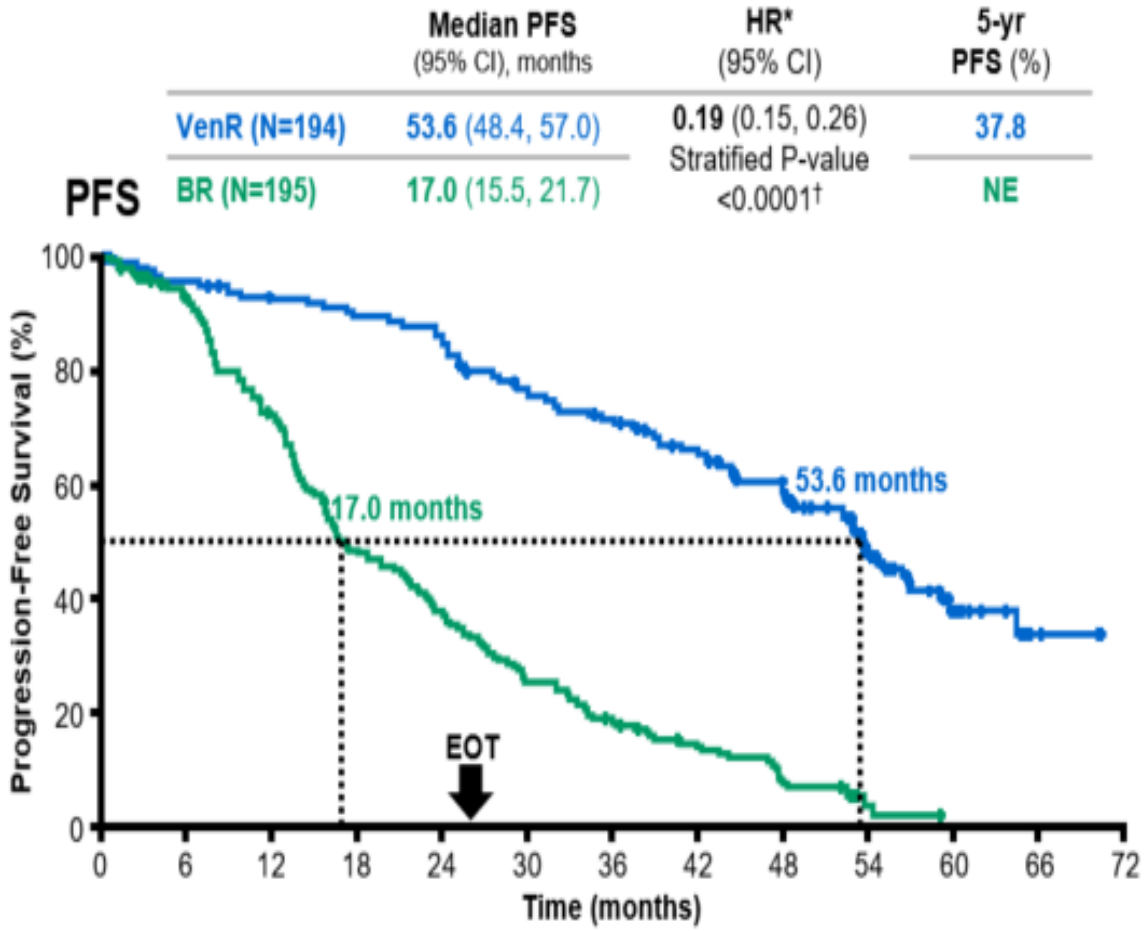
Ven-R vs. BR in R/R CLL (MURANO Study)

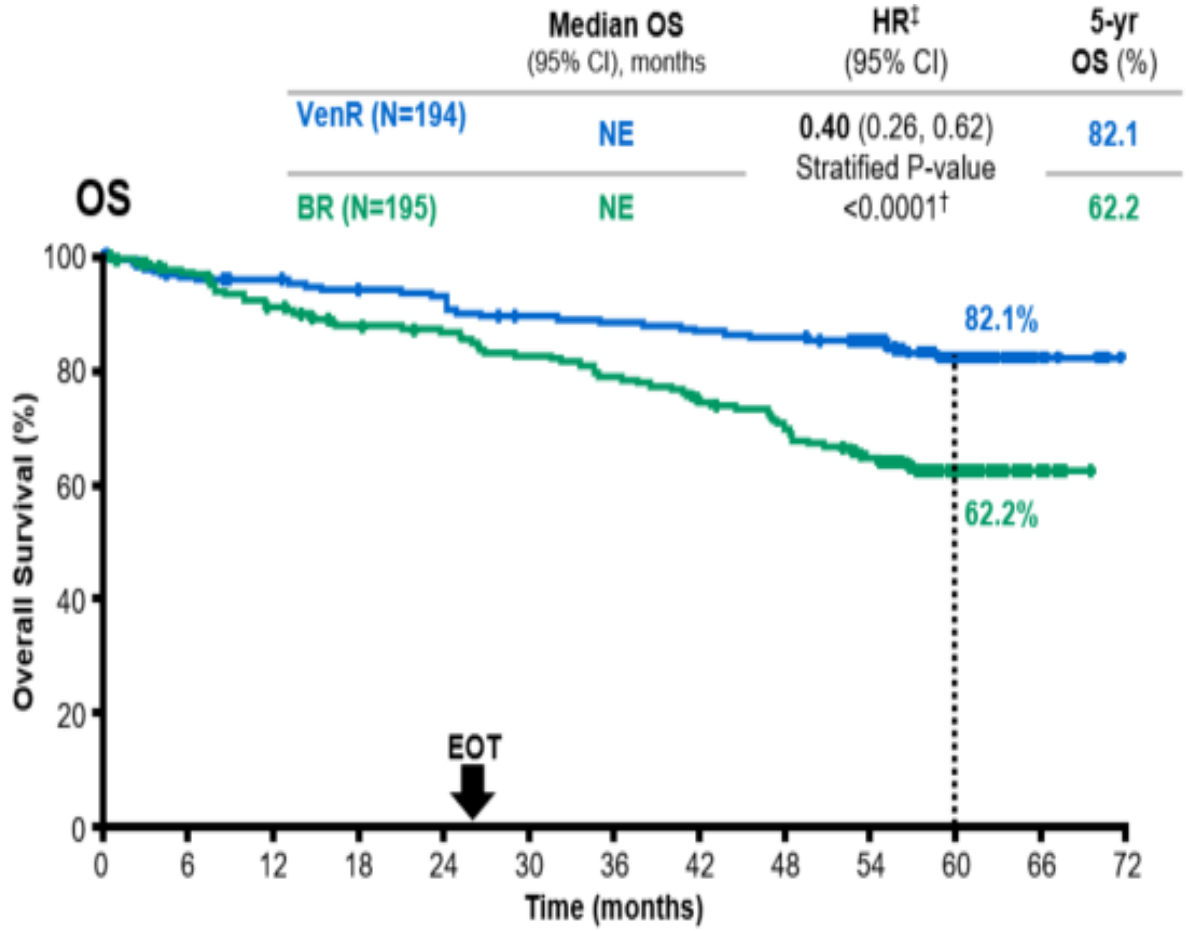


Primary Endpoint	INV-assessed PFS

Seymour, NEJM,2018

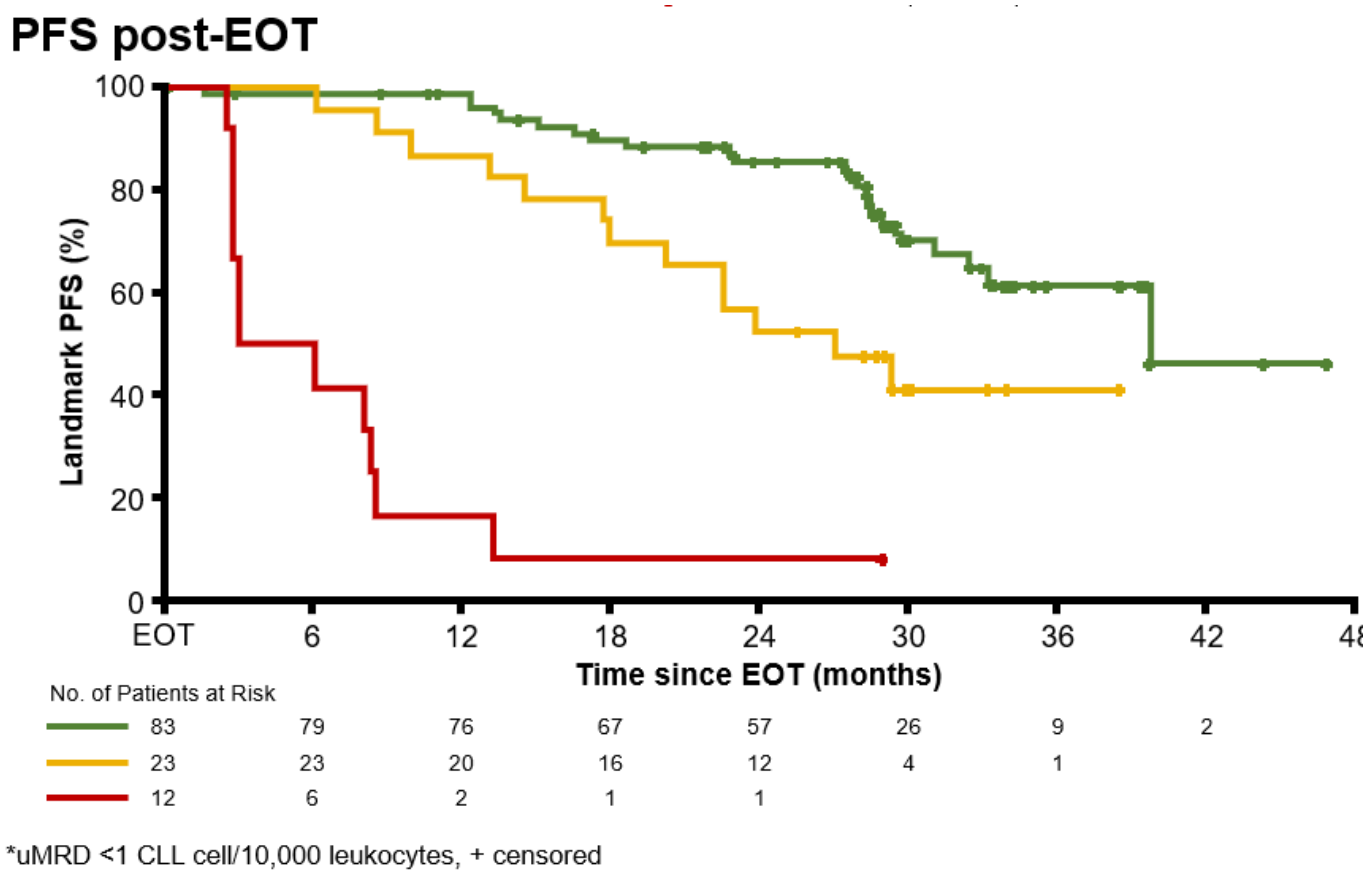
Ven-R vs. BR in R/R CLL (MURANO Study)
5-year follow-up





Kater, ASH, 2020

Ven-R outcomes (MRD and PFS)

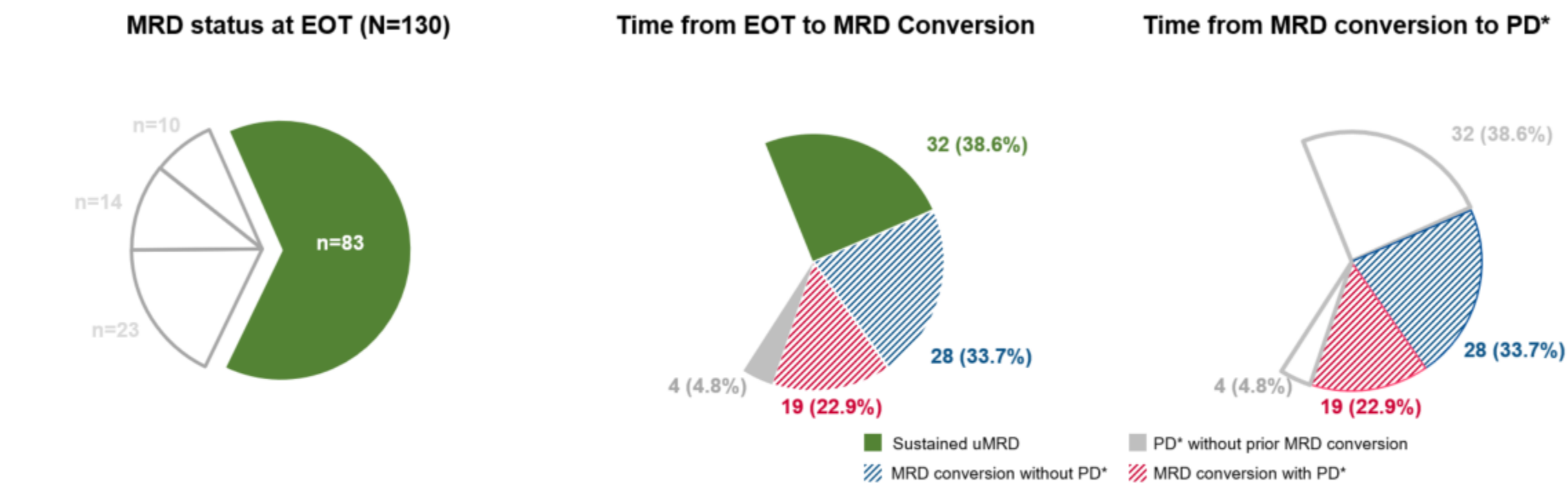


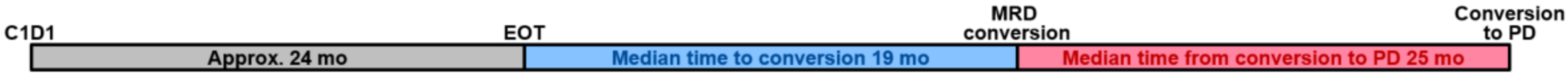
*uMRD <1 CLL cell/10,000 leukocytes, + censored

	PFS (95% CI) since EOT	
Category	**24 month**	**36 month**
uMRD ($<10^{-4}$)* (N=83)	85.4% (77.4, 93.4)	61.3% (47.3, 75.2)
Low-MRD+ (10^{-4}–10^{-2}) (N=23)	52.2% (31.8, 72.6)	40.7% (19.2, 62.2)
High-MRD+ ($>10^{-2}$) (N=12)	8.3% (0.0, 24.0)	NE
	HR (95% CI)	**P-value**
uMRD vs Low-MRD+	0.40 (0.18, 0.91)	0.0246
uMRD vs High-MRD+	0.02 (<0.01, 0.18)	<0.0001
Low-MRD+ vs High-MRD+	0.32 (0.10, 0.99)	0.0410

Kater, ASH, 2020

Delay between MRD Conversion and Clinical Progression





N=130; uMRD <1 CLL cell/10,000 leukocytes

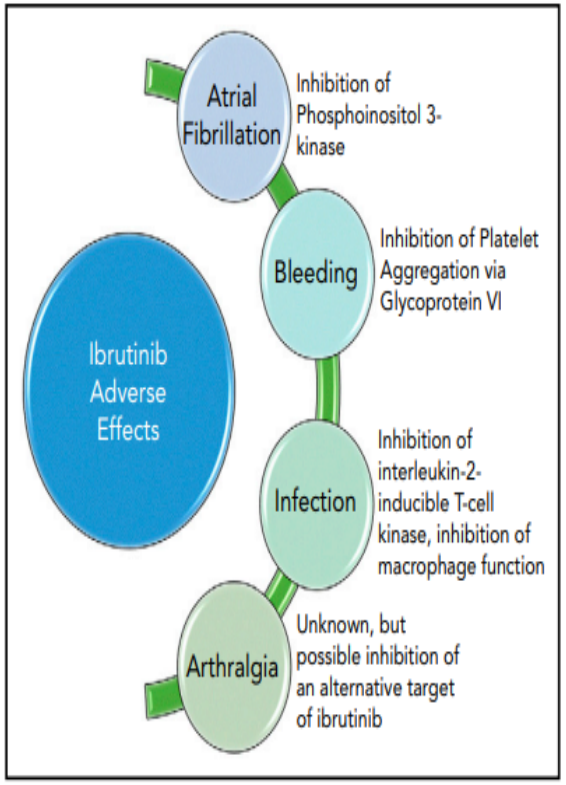
Kater, ASH, 2020

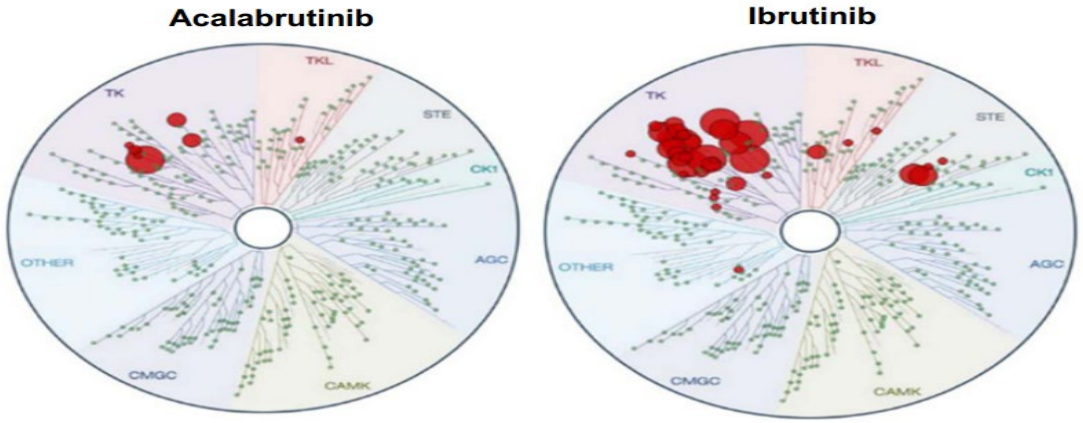
Novel Agents for R/R setting

	Acalabrutinib/ Ibrutinib	Venetoclax	Duvelisib/ Idelalisib
Target	BTK	BCL-2	PI3K delta+gamma / delta
Duration	Indefinite	2-years	Indefinite
Addition of Anti CD20 Ab	No major benefit Faster "response"	Recommended	Idelalisib + R Duvelisib monotherapy
Major side effect (concern)	Bleeding (anticoagulation)	TLS (initially)	Colitis (diarrhea) Infections (FDA alert)
Other side effects	• Body pain • Fatigue • Hypertension • A fib	• Neutropenia	• Pneumonitis • Transaminitis (mainly idela) • PJP • CMV
FDA label for CLL	All settings	All settings	Relapsed

Acalabrutinib or Ibrutinib

- Head-to-head trial is done in the relapsed setting and will be reported “soon”



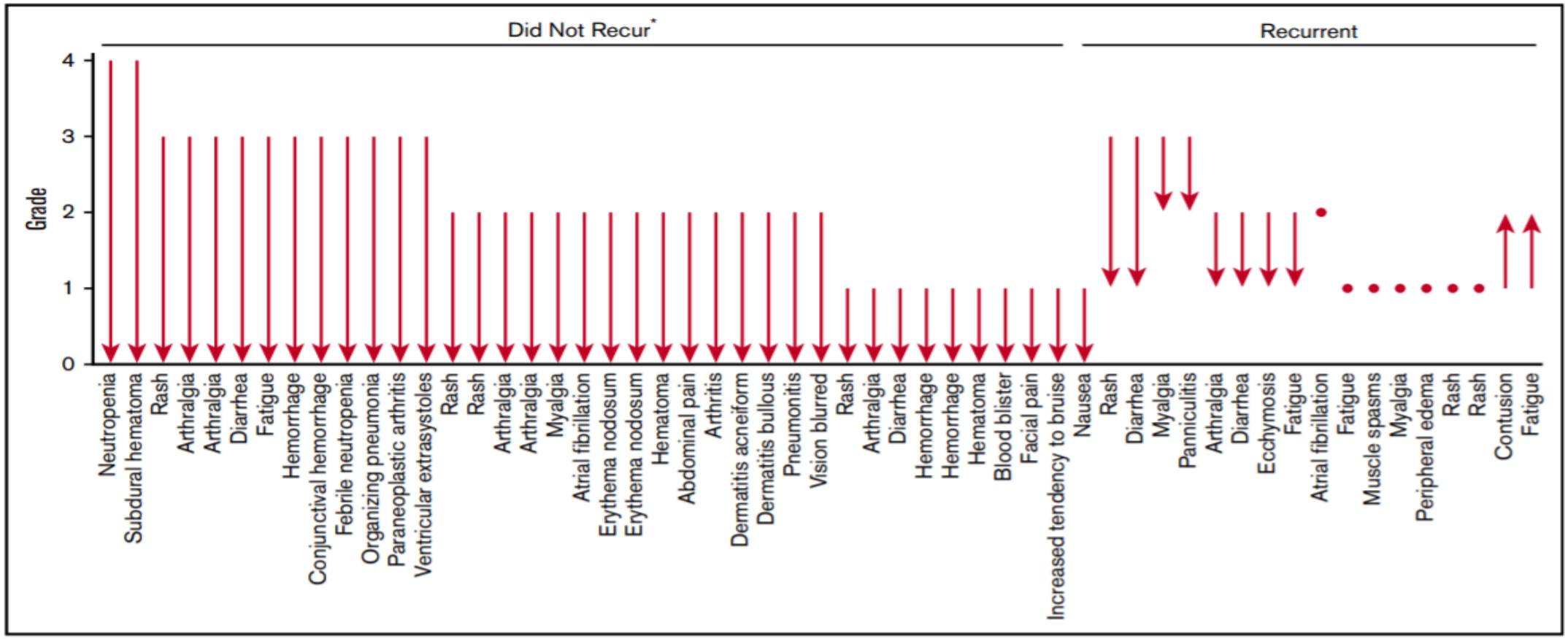


Treatment discontinuation rates due to toxicity

Ibrutinib	Frontline: 15% Relapsed: 22%
Acalabrutinib	Frontline: no data Relapsed: 12%

Mato, Haematologica, 2018 ; Yazdi,ASH,2019; Roeker, Clin Cancer Research, 2019 ;Shadman, ASH,2019; Stephens, Blood, 2019

Acalabrutinib in Ibrutinib intolerant patients



of 61 ibrutinib-related AEs associated with intolerance, 72% did not recur and 13% recurred at a lower grade with acalabrutinib

Awan, Blood Adv, 2019

Ibrutinib vs. Acalabrutinib (ELEVATE-RR)

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**

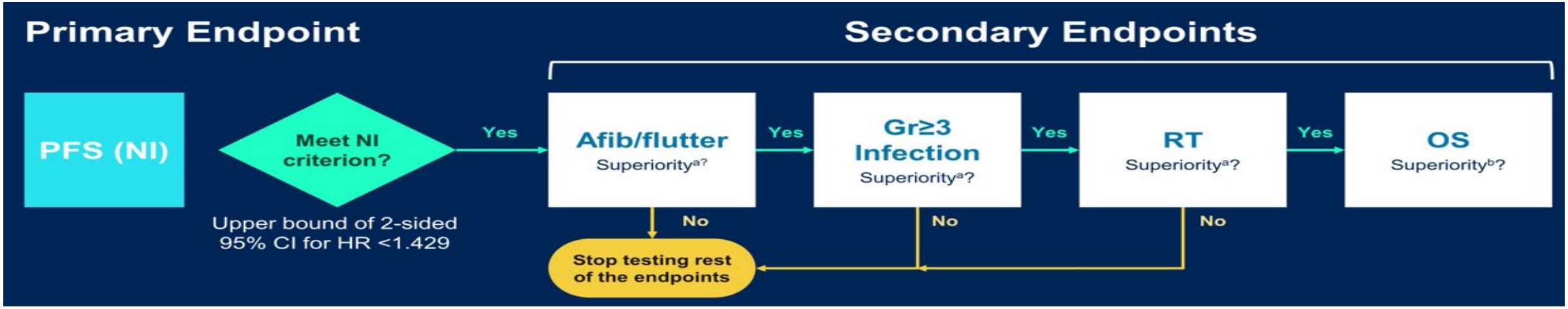
Primary endpoint

- Non-inferiority on IRC-assessed PFS[c]

Secondary endpoints (hierarchical order):

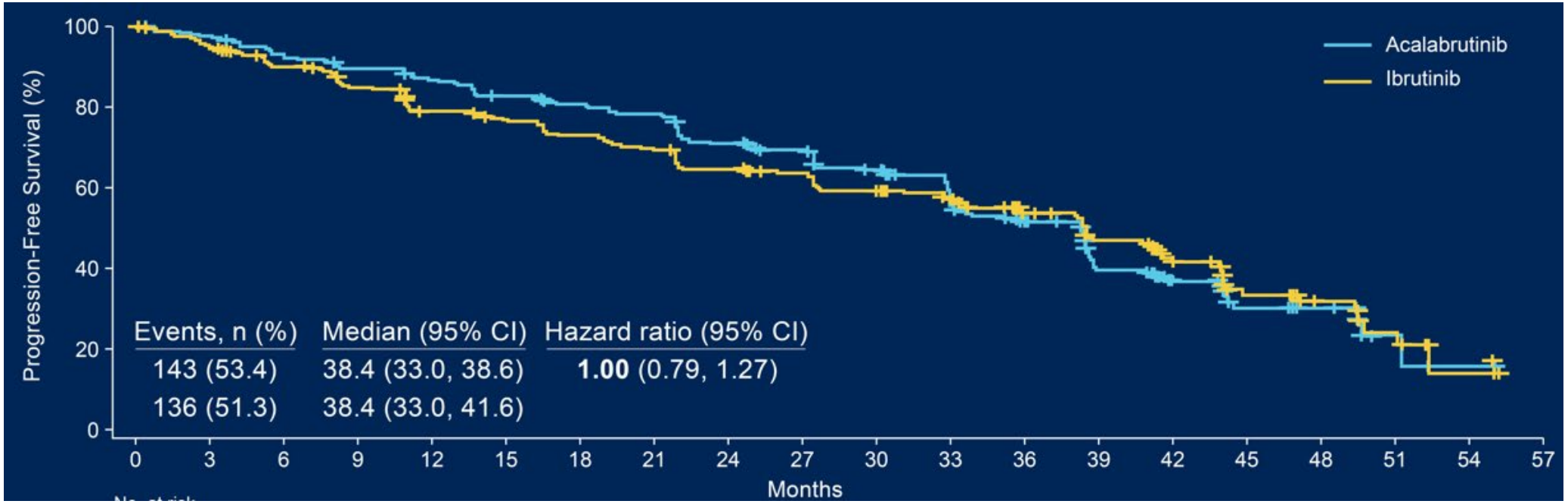
- Incidence of any grade atrial fibrillation/flutter
- Incidence of grade ≥3 infection
- Incidence of Richter transformation
- Overall survival

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)



Byrd, ASCO, 2021

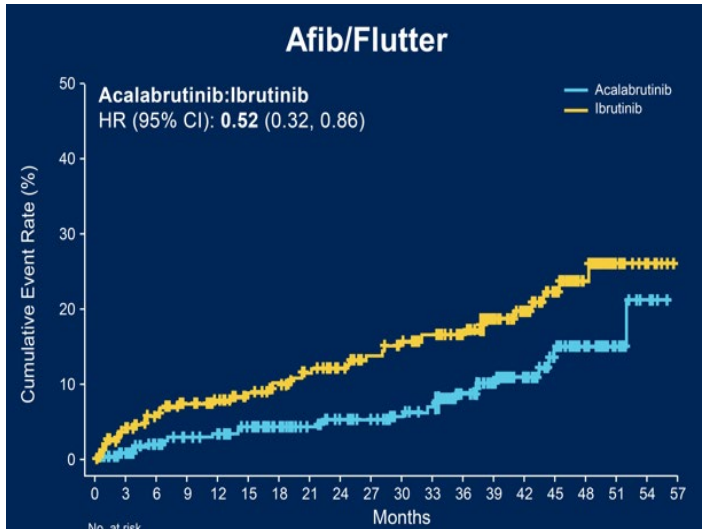
Ibrutinib vs. Acalabrutinib (ELEVATE-RR)

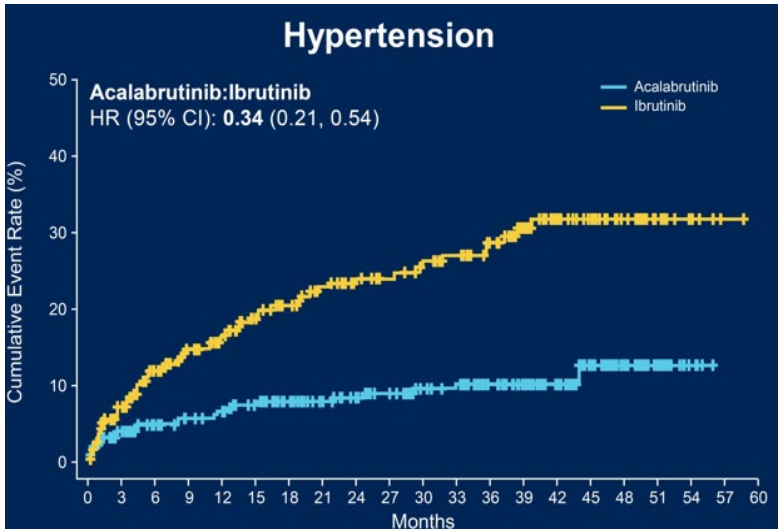


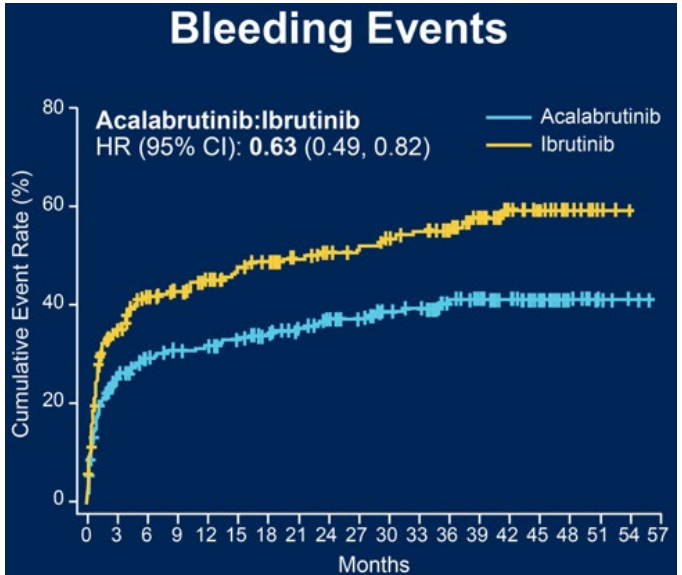
- High-risk patients only:
  - Del 17p: 45%
  - TP53 mutated 37-42%
  - Unmutated IGVH 82-89%
- Stopped because of adverse events:
  - 14.9% in acalabrutinib and 22.3% in ibrutinib group

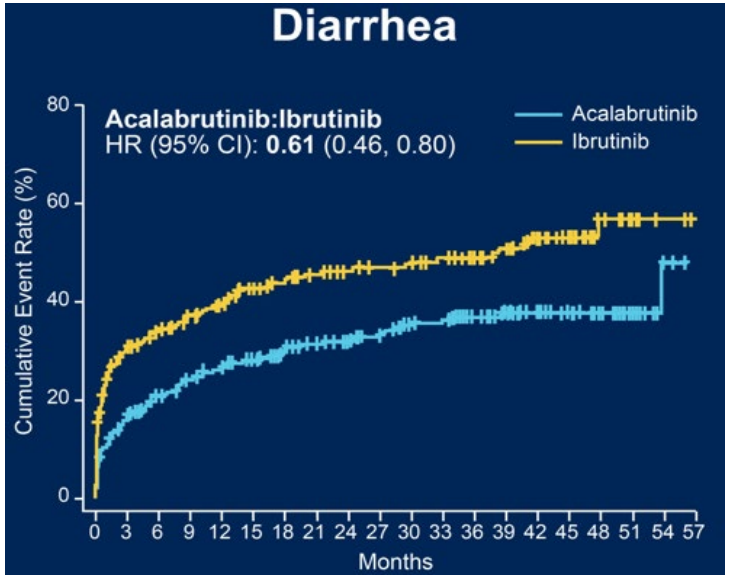
Byrd, ASCO, 2021

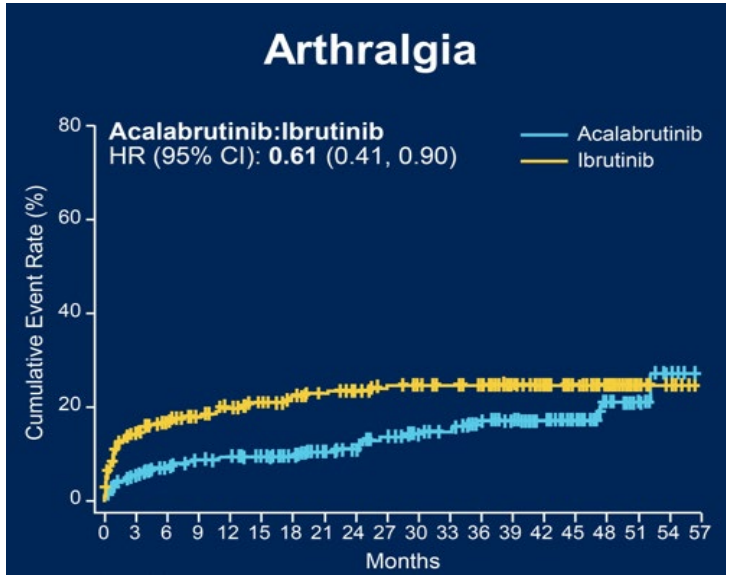
Ibrutinib vs. Acalabrutinib (ELEVATE-RR)











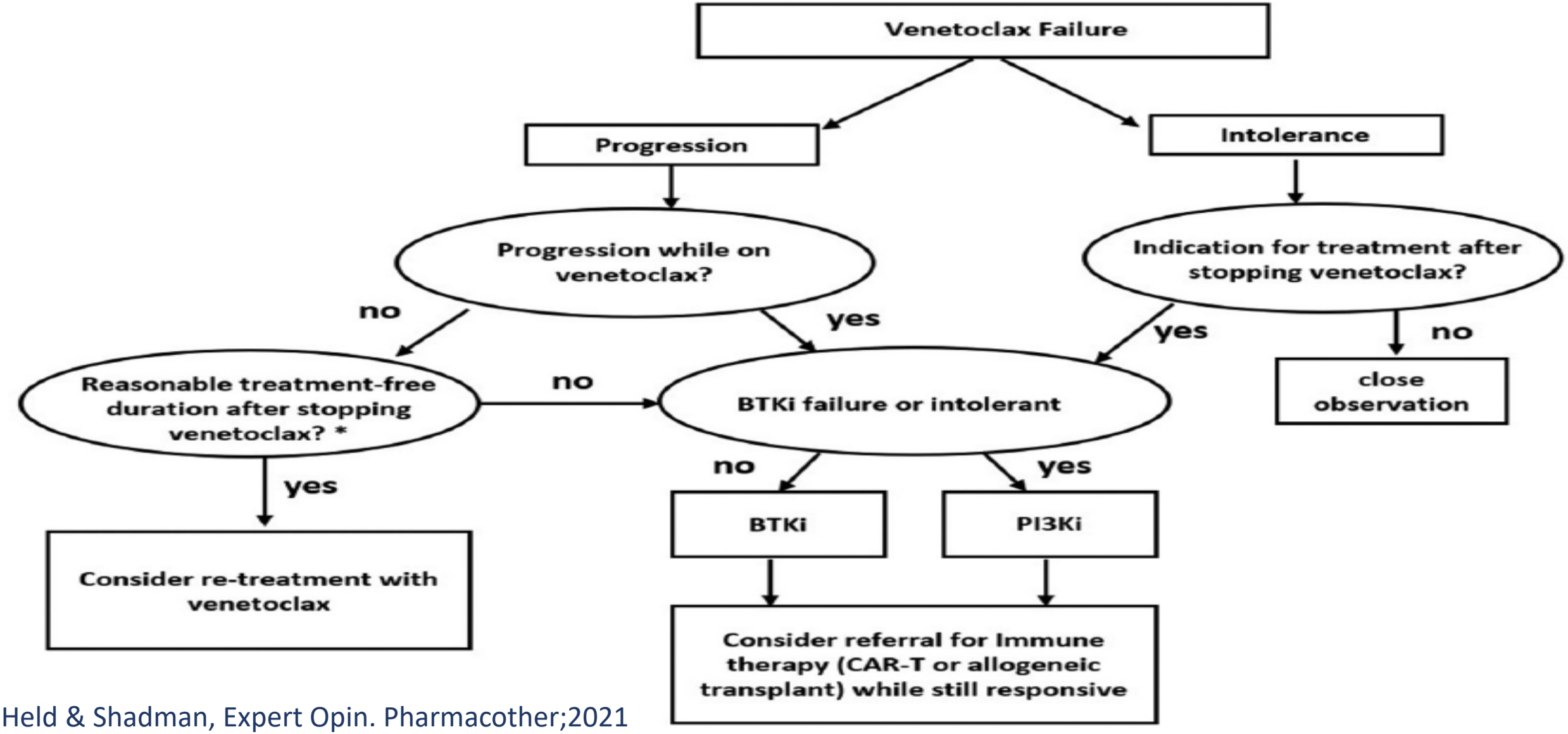
Previously Treated CLL Summary

1. **First**
   - **Venetoclax + Rituximab**
     or
   - **Ibrutinib or acalabrutinib**

2. **Second**
   - **Ibrutinib/acalabrutinib if previously treatment with Ven**
   - **Ven-R if previously treated with BTKi (ibrutinib or acalabrutinib)**

3. **Third**
   - **Idelalisib+ rituximab OR duvelisib**

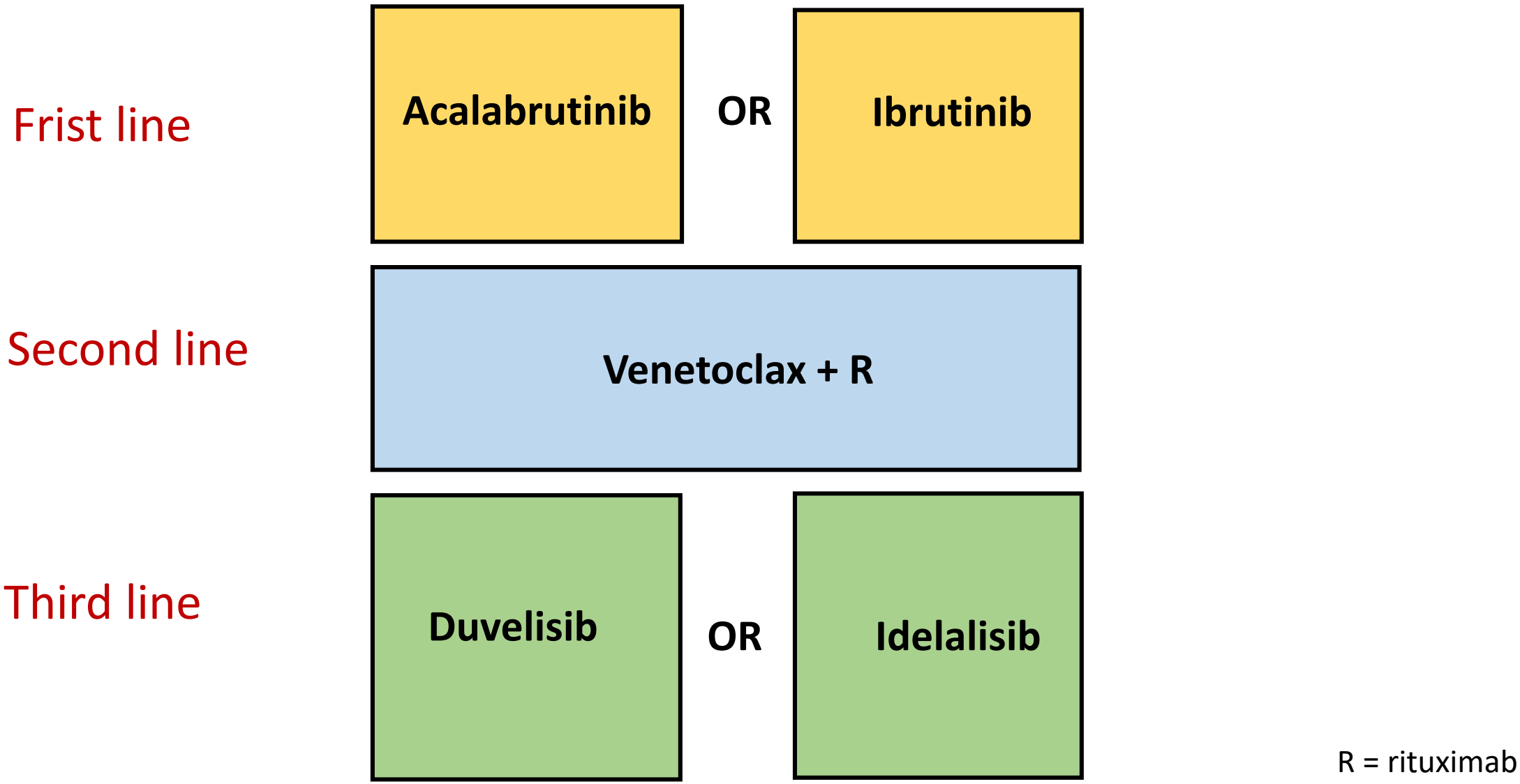
After Venetoclax…



Held & Shadman, Expert Opin. Pharmacother;2021

Treatment options for patients with del17p/P53 mutation

CLL with del17p or TP53



R = rituximab

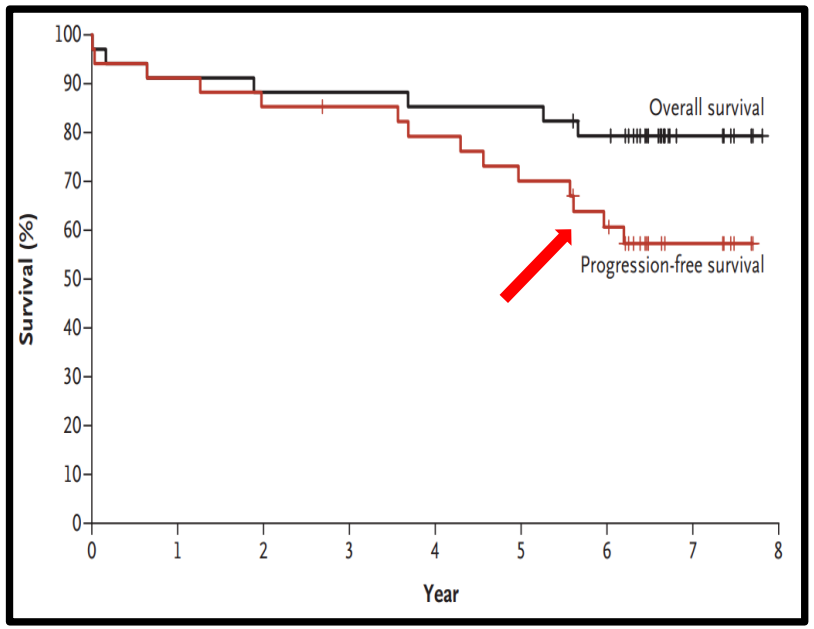
There is no role for chemotherapy in abnormal TP53 (deletion or mutation)

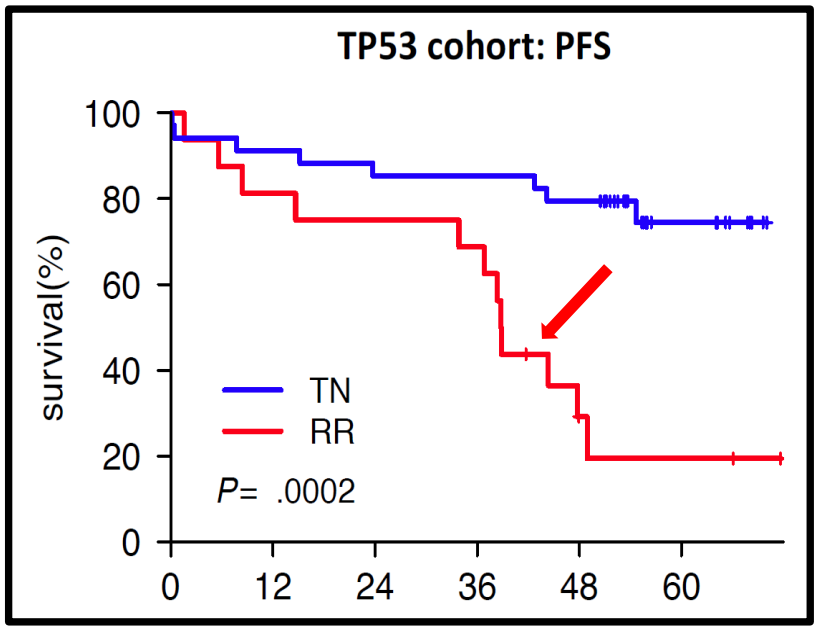
Regimen	PFS
FCR (frontline)	11.3 m
Alemtuzumab (frontline)	11 m
BR (frontline)	7.9 m
HDMP + R	7.5m
BR (relapsed)	7 m
FC (frontline)	6.5 m
FCR (relapsed)	5 m

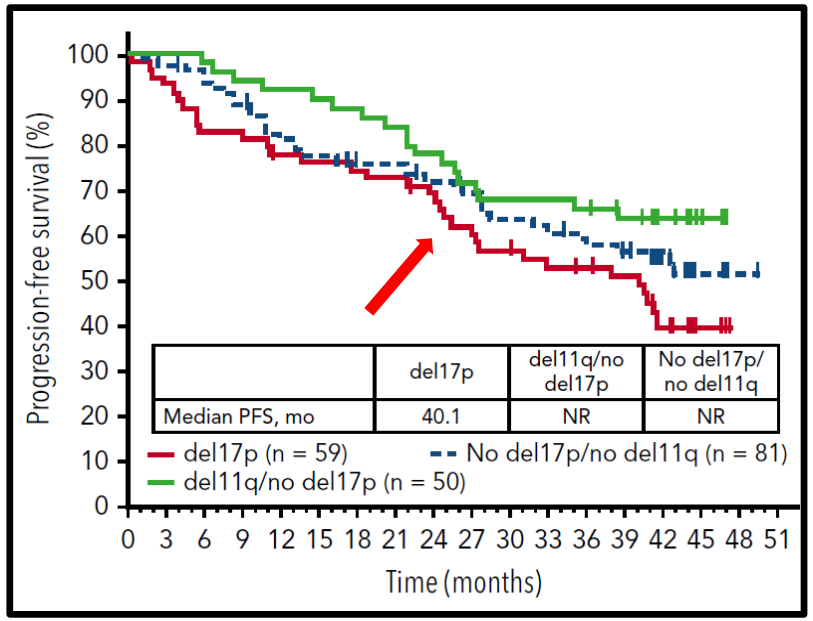
5 – 11 months

Ibrutinib for abnormal TP53

Study	Setting	Outcome
NIH study	TN R/R	6-year PFS 61% 5-year PFS 19%
PCYC-1102/1103 5-year f/u	R/R	median PFS 26 m
RESONATE f/u	R/R	Median PFS 40 m



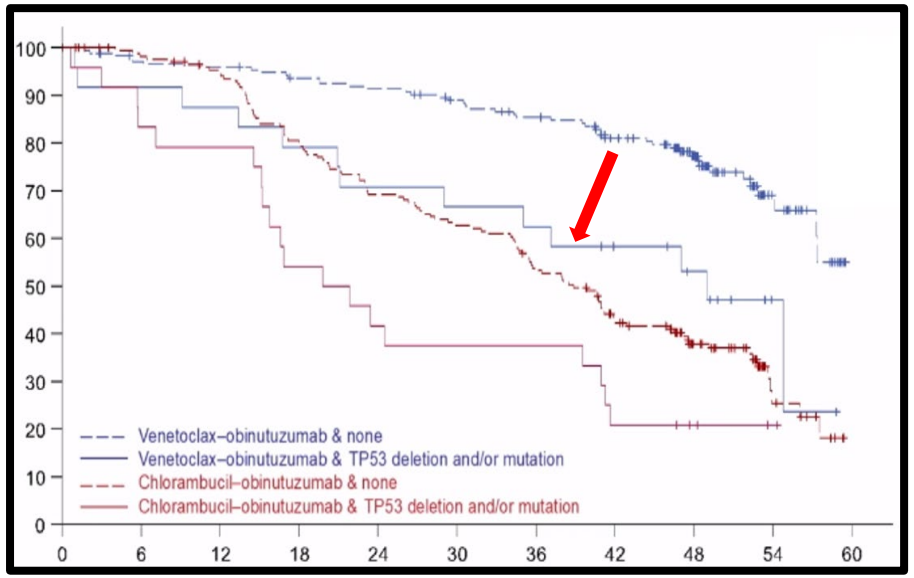


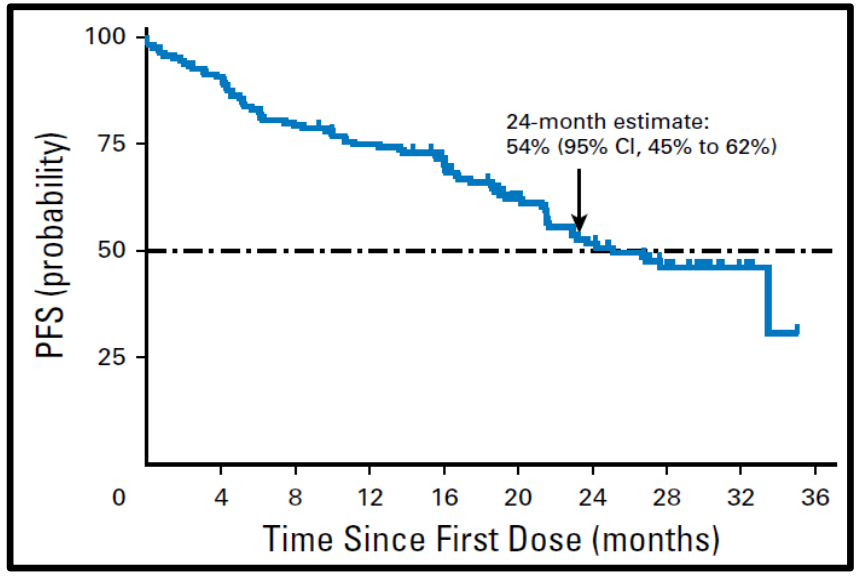


Ahn,Blood,2018; Ahn,NEJM,2020 ; O'Brien, Blood, 2018; Byrd, Blood, 2019

Venetoclax for abnormal TP53

Study	Setting	Outcome
CLL14	TN	m PFS 49m
M13-982 study	R/R	24 m PFS 54% m PFS 27 m
MURANO	R/R	m PFS 48 m

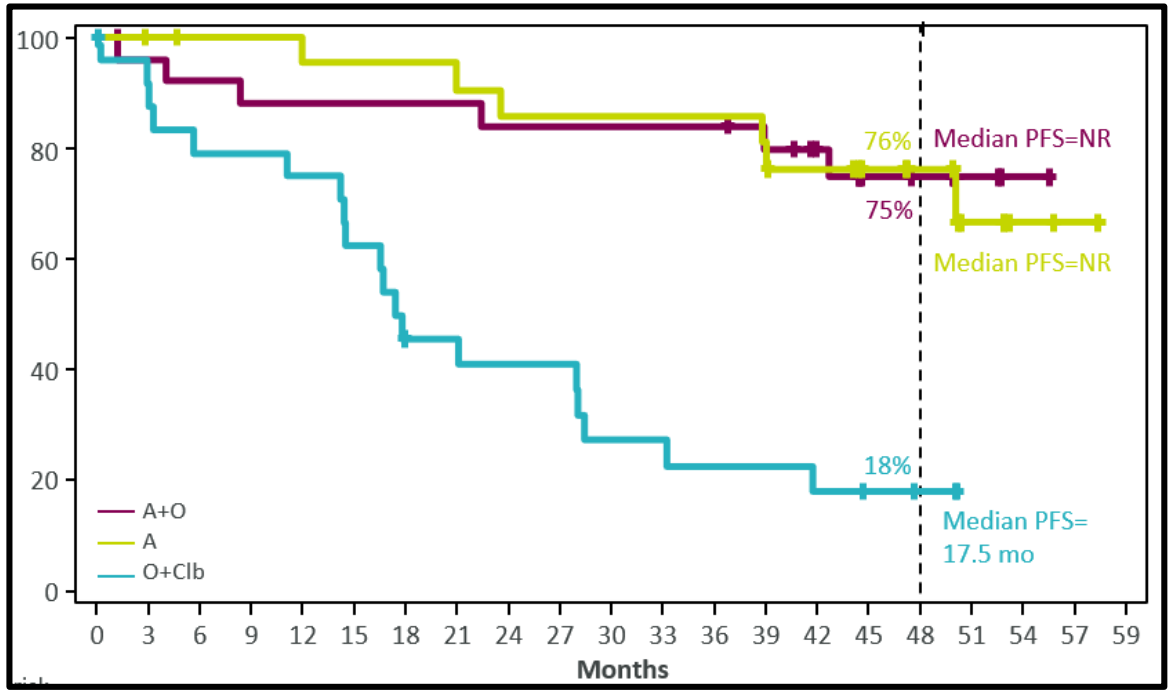




Al-Sawaf, EHA, 2021; Stilgenbauer, JCO,2018; Seymour, ASH, 2019

Acalabrutinib for abnormal TP53

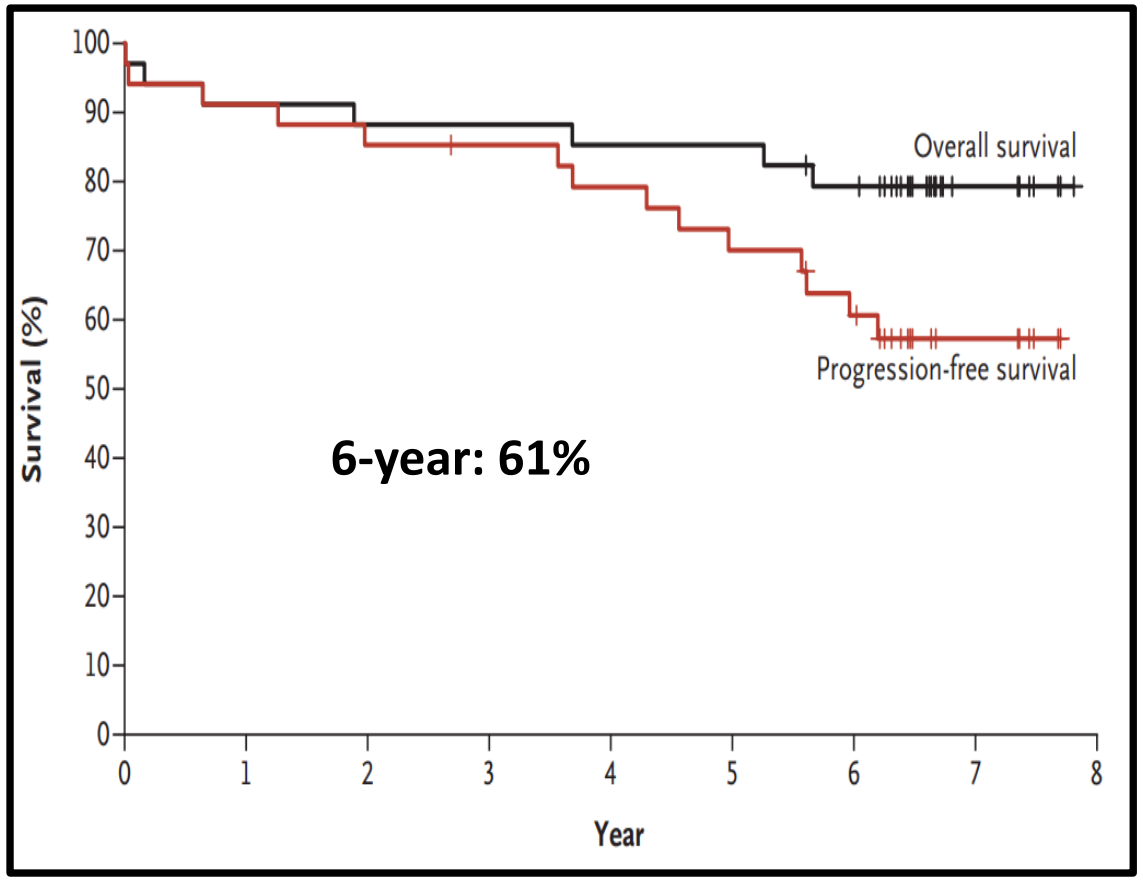
Study	Setting	Outcome
ELEVATE TN	TN	4-year PFS 75%
ACE-CL-001	R/R	PFS 36m (21 – NR)
ASCEND	R/R	Not reported



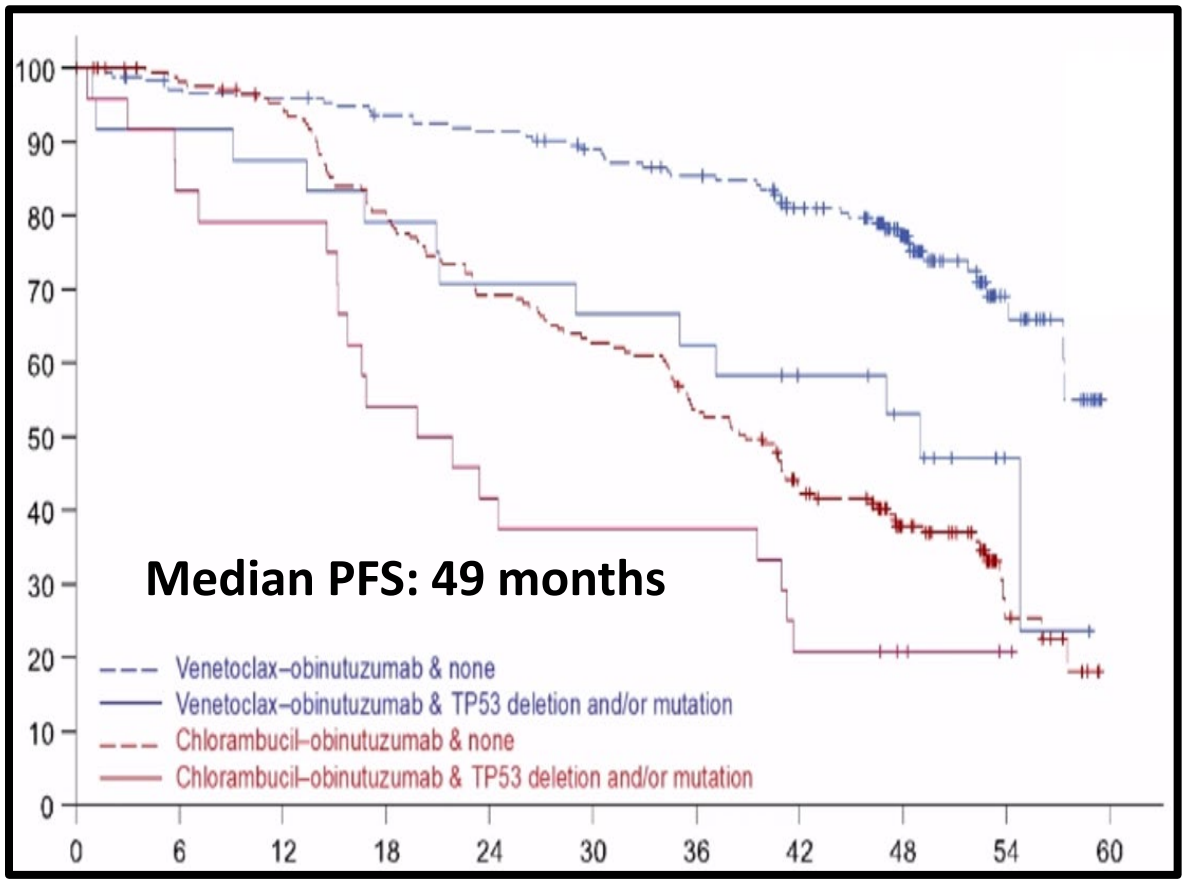
Sharman,EHA, 2021; Byrd, Blood, 2020; Ghia,15-ICML,2019

Ibrutinib vs. Ven-G for first-line treatment in CLL patients with abnormal TP53

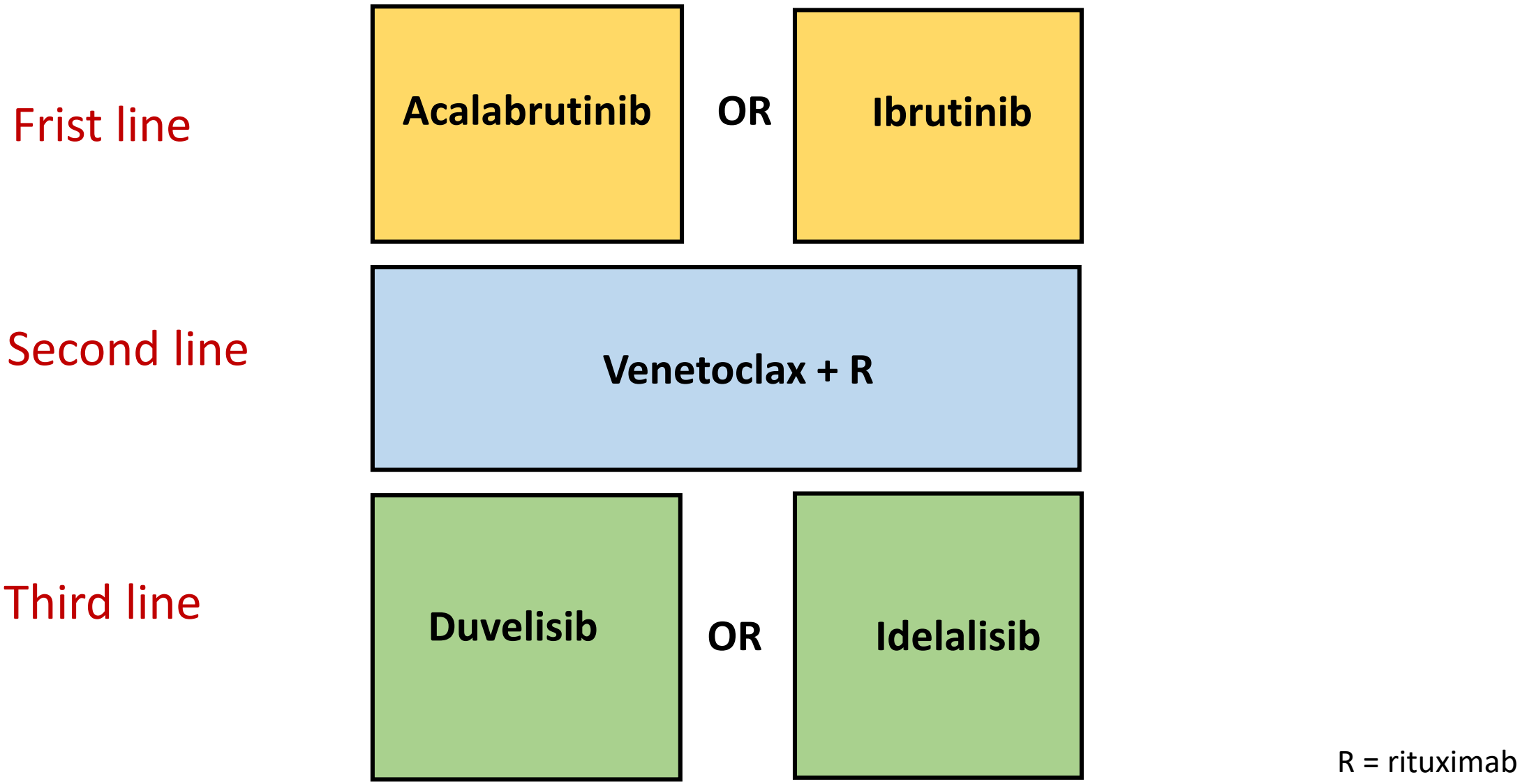
Ibrutinib



Venetoclax + Obinutuzumab



CLL with del17p or TP53

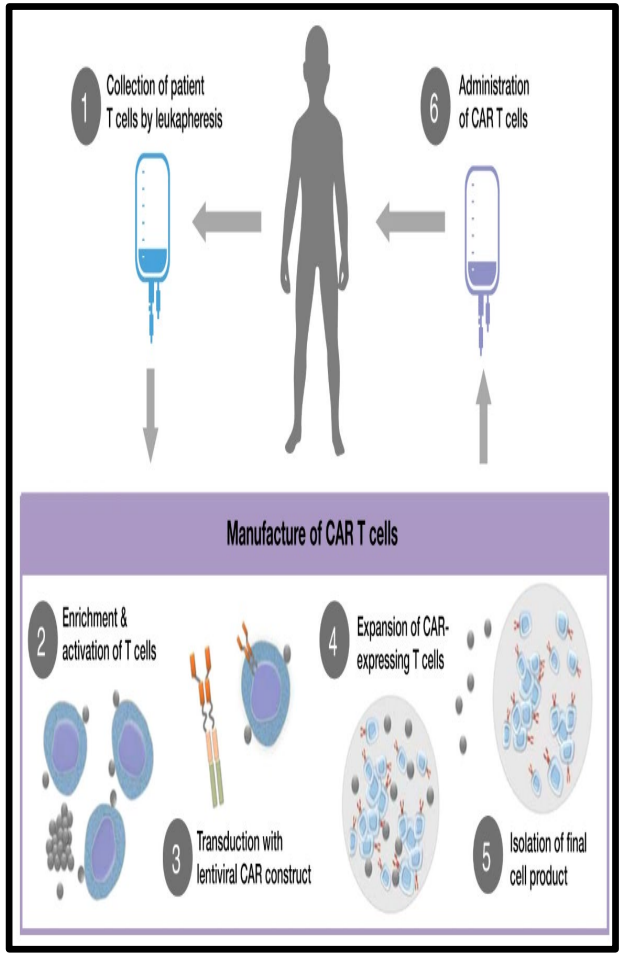


R = rituximab

Cellular therapies for CLL

CAR-T for CLL

- Investigational, not FDA approved
- Registration studies are currently ongoing
- Long-term remissions ~ 30-35%
- Best predictor od response: MRD neg after treatment
- Recommend before alloSCT, if available



Allogeneic SCT for High Risk CLL

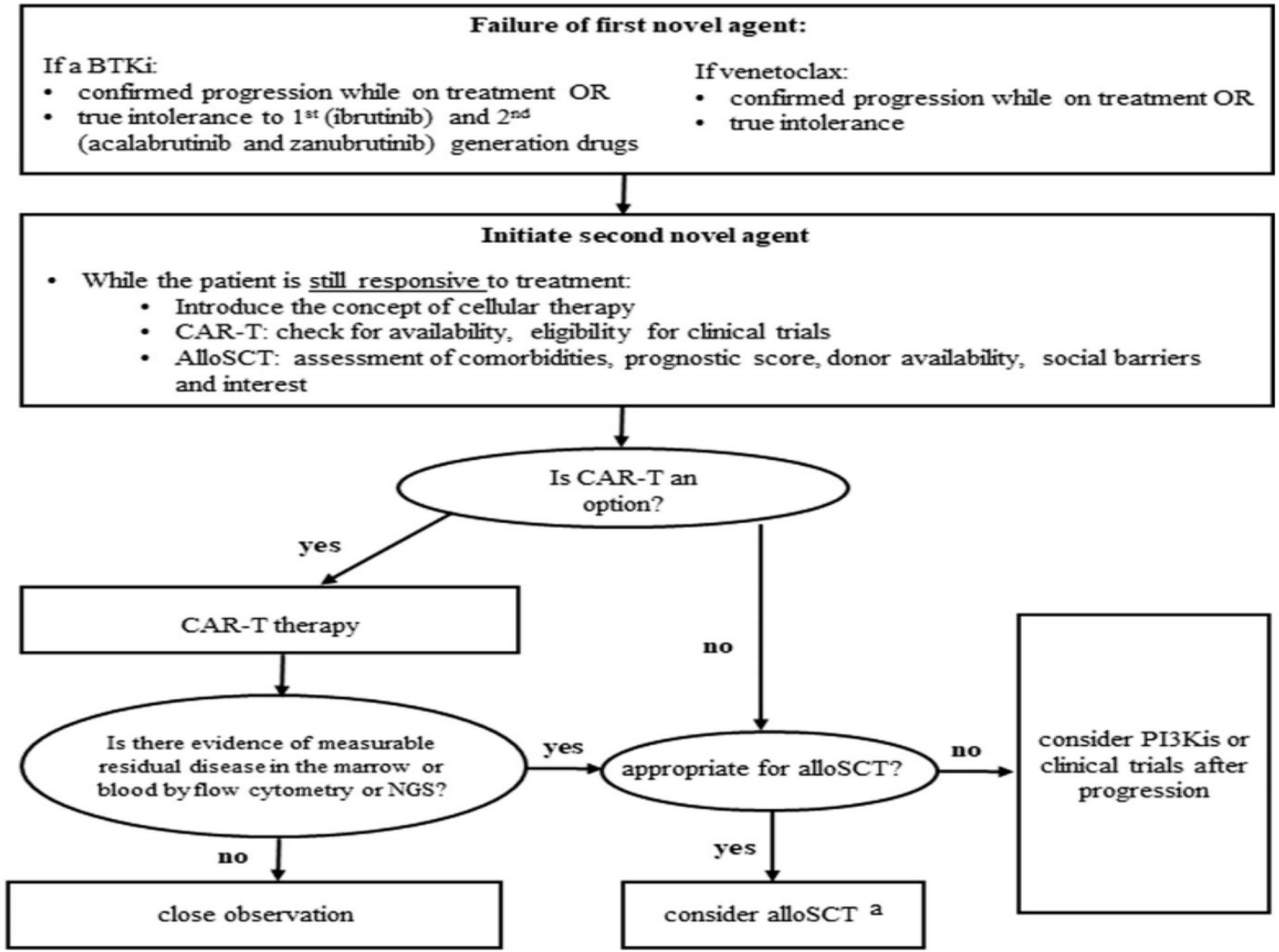
- Reduced intensity/ Nonmyeloablative allogeneic transplant

Author	Kim	Roeker	Paul	Shadman	Andersen
Year	**2020**	**2020**	**2020**	**2019**	**2019**
N	108	65	64	55	432
Conditioning	RIC	RIC	RIC (haplo)	NMA	RIC/NMA
Follow-up (yr)	3	2	4	3	5
OS	**69-87**	**81**	**52**	**54**	**46-52**
PFS	**58-72**	**63**	**37**	**45**	**38-43**
NRM	**7-17**	**13**	**24**	**38 (<12)***	**32-35**
aGVHD (3-4)	8-13	24	3	20	?
Extensive cGVHD	45-57	27	7	66	?

50
40
20-25

*** in pts without comorbidities**

Shadman, Hematol Oncol Clin N Am, 2021



Shadman, Hematol Oncol Clin N Am, 2021

Practical points about novel drugs

New Agents: Practical Considerations

- BTKi: ibrutinib and acalabrutinib
- PI3Ki: idelalisib and duvelisib
- BCL2i:venetoclax

BTKis (ibrutinib/acalabrutinib)

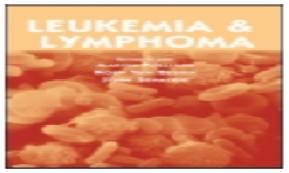
- **Common side effects:**
  - Muscle/bone pain
  - Cytopenia
  - Hypertension
  - Diarrhea (early , reversible)
- **Serious side effect:**
  - Bleeding: (peri-procedural management)
  - Atrial fibrillation
  - Opportunistic infections: PJP, aspergillosis (?) (case reports)

- **Second generation BTKi, acalabrutinib has a better toxicity profile**
  - **Acalabrutinib**

PI3Kis (idelalisib/duvelisib)

- Important side effects
  - LFT abnormalities (idelalisib)
  - Pneumonitis
  - CMV reactivation and PJP (FDA alert 2016)

- Colitis/Diarrhea
  - Median time to grade III/IV : 7 months
  - Not responsive to anti-motility agents
  - Corticosteroids ; treat as aGVHD



Management of adverse events associated with idelalisib treatment: expert panel opinion

Steven E. Coutré, Jacqueline C. Barrientos, Jennifer R. Brown, Sven de Vos, Richard R. Furman, Michael J. Keating, Daniel Li, Susan M. O'Brien, John M. Pagel, Martin H. Poleski, Jeff P. Sharman, Nai-Shun Yao & Andrew D. Zelenetz

Don’t use Idelalisib in treatment naïve patients!

Toxicity Frequency

	Phase I	Overall relapsed	Upfront Pts ≥ 65 yo	Upfront younger Pts
Number of patients	54	760	64	24
Median prior treatments	5 (2-14)	≥ 1	0	0
Median age	63 (37-82)	66 (21-91)	71 (65-90)	67 (58-85)
Median time to therapy (months)	15 (0.2-49)	-	22 (0.8 – 46)	8 (0.7-16)
Grade≥ 3 transaminitis	1.9%	14%	23%	52%
Grade ≥3 Colitis/diarrhea	5.6%	14%	42%	13%
Any grade pneumonitis	5.6%	3%	3%	13%
Reference	Brown Blood 2014	Coutre EHA 2015	O’Brein Blood 2015	Lampson ASH 2015

Venetoclax

Figure 1: Dosing Schedule for Ramp-up Dose

Tumor Burden		Prophylaxis		Blood Chemistry Monitoring[c]
		Hydration[a]	Anti-hyperuricemics	Setting and Frequency of Assessments
Low	All LN <5 cm AND ALC <25 × 10^9/L	Oral (1.5-2 L)	Allopurinol[b]	**Outpatient** • Pre-dose, 6-8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp up doses
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 × 10^9/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	**Outpatient** • Pre-dose, 6-8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp up doses • Consider hospitalization for patients with CrCl <80 mL/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 × 10^9/L AND any LN ≥5 cm	Oral (1.5-2 L) and intravenous (150-200 mL/hr as tolerated)	Allopurinol;consider rasburicase ifbaseline uric acid is elevated	**In hospital at first dose of 20 mg and 50 mg** • Pre-dose, 4, 8,12 and 24 hours **Outpatient at subsequent ramp-up doses** • Pre-dose, 6-8 hours, 24 hours

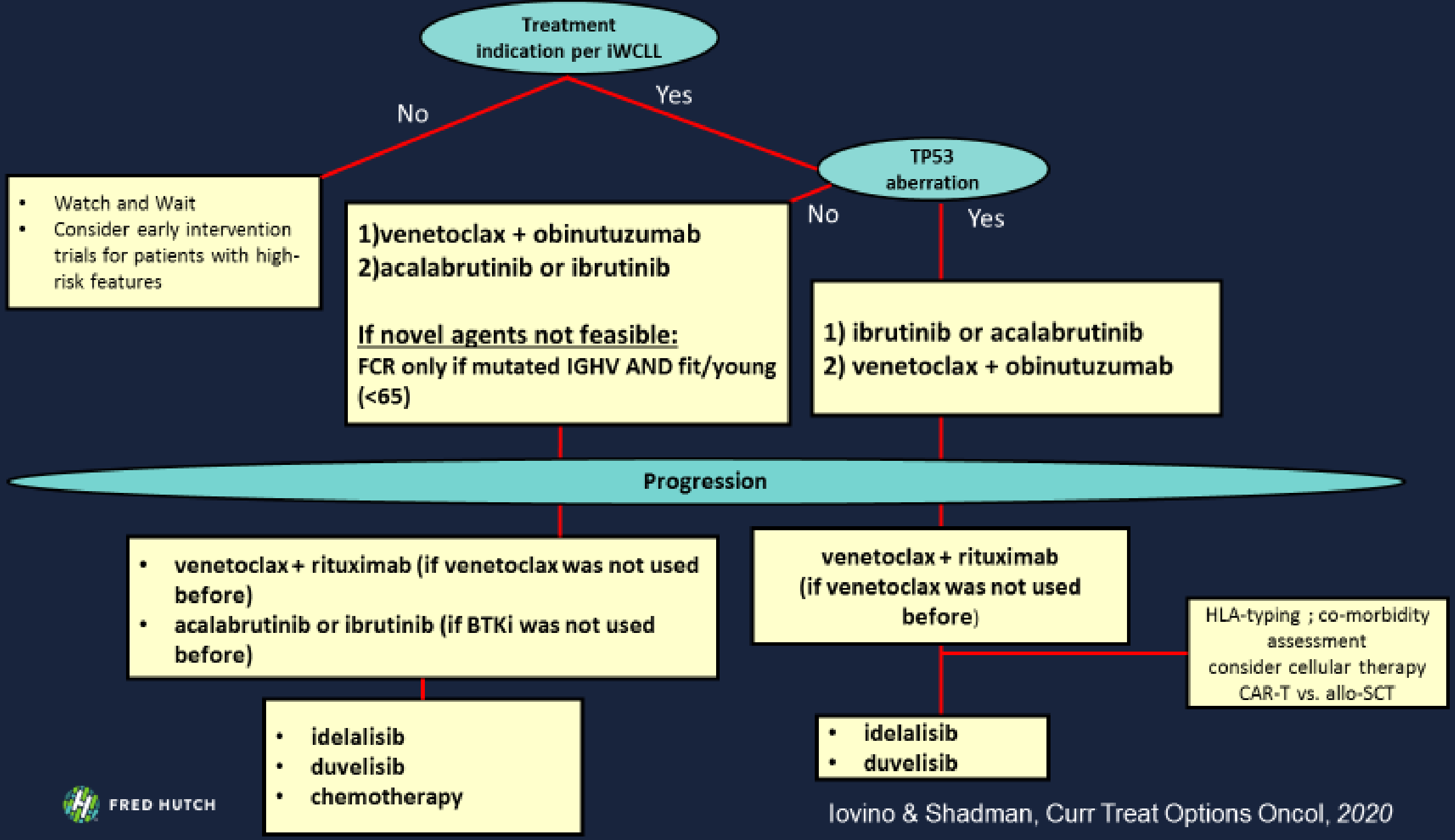
- For patients at risk of TLS, monitor blood chemistries at 6-8 hours and at 24 hours after each subsequent ramp-up dose

Venetoclax

- Consider debulking strategies
- Follow the standard ramp-up schedule
- Coordinate with the inpatient team
- Selected patients can be treated using the “escalated inpatient ramp-up” *
- Follow ALL TLS labs (not just uric acid!)

- Will take some effort to start

* Jones. Lancel Onc, 2017


Treatment indication per iWCLL
No
Yes
Watch and Wait
Consider early intervention trials for patients with high-risk features
TP53 aberration
No
Yes
1)venetoclax + obinutuzumab
2)acalabrutinib or ibrutinib
If novel agents not feasible:
FCR only if mutated IGHV AND fit/young (<65)
1) ibrutinib or acalabrutinib
2) venetoclax + obinutuzumab
Progression
venetoclax + rituximab (if venetoclax was not used before)
acalabrutinib or ibrutinib (if BTKi was not used before)
idelalisib
duvelisib
chemotherapy
venetoclax + rituximab (if venetoclax was not used before)
HLA-typing ; co-morbidity assessment
consider cellular therapy
CAR-T vs. allo-SCT
idelalisib
duvelisib
FRED HUTCH
Iovino & Shadman, Curr Treat Options Oncol, 2020

What is new?

- Upcoming approvals:
  - Zanubrutinib
  - Umbralisib and Ublituximab

- Important drug in development
  - Pirtobrutinib (LOXO-305)

- Important regimens in development
  - Combination therapy: venetoclax + BTKi (GLOW trial, CAPTIVATE,etc)

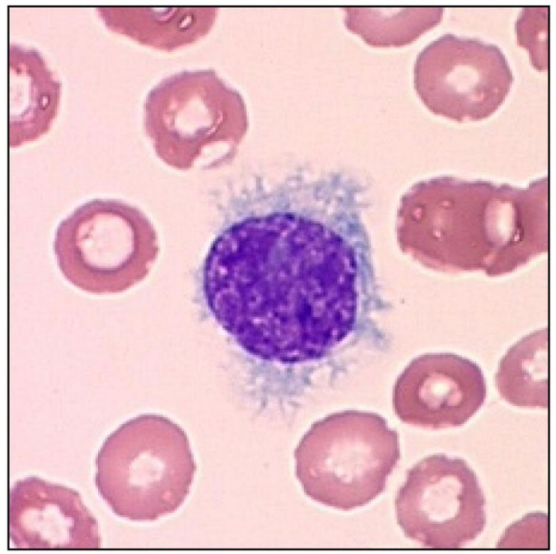
- CAR-T trials

CLL (Night before the test)

1. Flow cytometry is critical (and adequate) to make the diagnosis
2. Remember CLL immunophenotype (and differences with MCL and other lymphomas)
3. Review Indications for treatment. This hasn't change even with new agents.
4. Check FISH before each line of treatment (r/o del 17p/P53 mutation)
5. Frontline (no del17p or P53mutation): Ven-G or BTKi (acalabrutinib is better tolerated). FCR reasonable for: fit,<65 and mutated IGHV.
6. Relapsed setting: Ven-R or BTKi (acalabrutinib better tolerated), idelalisib/duvelisib.
7. For del 17p patients: BTKi, Ven-R, cellular therapy, idelalisib/duvelisib.
8. BTKi: initial lymphocytosis (is OK), bleeding, Afib, HTN, body pain (acalabrutinib is better tolerated)
9. Idelalisib/duvelisib: lymphocytosis (is OK), colitis, pneumonitis, hepatitis (more with idela), PJP, CMV – Don't use in frontline setting
10. Venetoclax: watch for TLS at the beginning. Ramp-up HAS to be done!

Hairy Cell Leukemia

- Uncommon chronic B cell lymphoid neoplasm
- Small mature B cell lymphoid cells with abundant cytoplasm and "hairy" projections within the peripheral blood, bone marrow, and splenic red pulp
- Splenomegaly and cytopenias



Hairy cell Leukemia
(Diagnosis)

	CD11c	CD25	CD103	CD123	CD10	CD21	CD23	CD5	CD20	CD19	CD22	Annexin A1
HCL	+	+	+	+	-	-	-	-	+	+	+	+

BRAF V600E mutation is a disease-defining event

HCL variant:

CD25 (-) , CD123 (-), annexin A1 (-) and BRAF V600E (-)

Hairy cell Leukemia

- **Clinical presentation**
  - Splenomegaly
  - Cytopenias (infections, bleeding)
  - Constitutional symptoms

- **Treatment Indications:**
  - Systemic symptoms
  - Splenic discomfort
  - Recurrent infections
  - Cytopenias (Hb <11, ANC < 1000, bleeding due to plt <100,000)

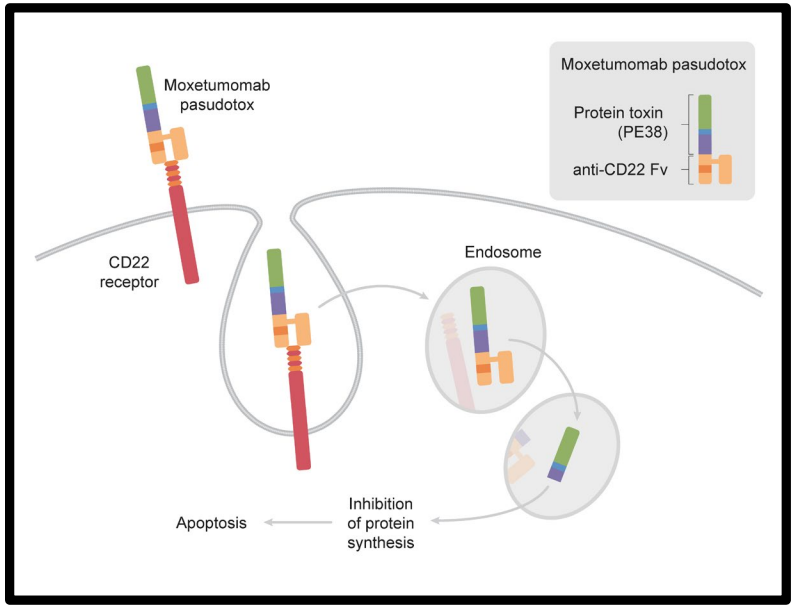
Hairy Cell Leukemia

Treatment

- **First Line**
  - Purine analogs
    - **Cladrabine (2-CdA) + rituximab** – Up to 80% CR with a CR duration of 57 months (7 – 246) after a single cycle
    - **Pentostatin**
- **Refractory (failure in less than a year) or Relapsed disease**
  - purine analogs ± Rituximab
  - INF-alfa
  - rituximab
  - **BRAF targeting agents (Vemurafenib) ± rituximab**
  - **moxetumomab Pasudotox** (anti CD22 immunotoxin conjugate)

Moxetumomab Pasudotox for R/R HCL

- Anti CD22 immunotoxin conjugate
- IV ; D1,3,5 of 28D cycle (up to 6 cycles)
- At least 2 prior systemic therapies, including a purine analog
- **Efficacy:**
  - ORR: 75%
  - durable CR: 30%
  - MRD eradication 34% of all CRs
- **Unique side effects**
  1. Hemolytic-uremic syndrome
  2. Capillary leak syndrome
  - supportive care and discontinuation were effective
  - could occur at any cycle



Please Consider Clinical Trials!

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FRED HUTCH

W Medicine
UNIVERSITY of WASHINGTON

Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine