ASSOCIATION OF COMMUNITY CANCER CENTERS

MULTIDISCIPLINARY CHRONIC LYMPHOCYTIC LEUKEMIA CARE

Up-to-Date Approaches to Treating the CLL Patient

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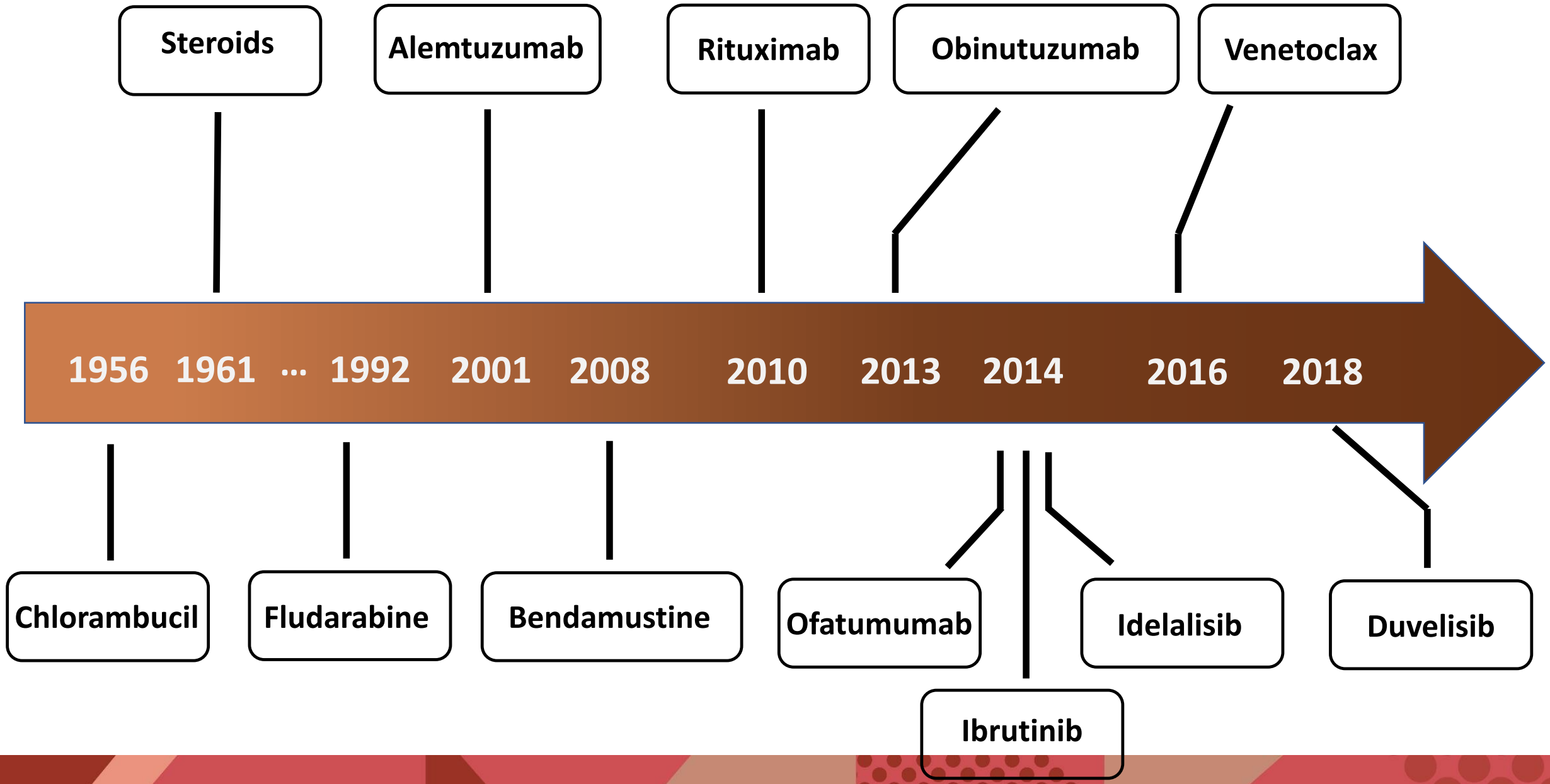
ACCC

Association of Community Cancer Centers


Steroids
Alemtuzumab
Rituximab
Obinutuzumab
Venetoclax
1956
1961
…
1992
2001
2008
2010
2013
2014
2016
2018
Chlorambucil
Fludarabine
Bendamustine
Ofatumumab
Ibrutinib
Idelalisib
Duvelisib

Treatment Options for CLL

Chemotherapy Agents	Anti-CD20 Abs	BCR Inhibitors	BCL-2 Inhibitor

• Fludarabine
• Cyclophosphamide
• Bendamustine
• Chlorambucil
		• **BTK inhibitors**
		  • Ibrutinib
		  • Acalabrutinib
		• **PI3K inhibitors**
		  • Idelalisib
		  • Duvelisib
			• **Venetoclax**

What Do You Need to Know About Your CLL Before Starting Treatment

	FISH	Karyotype	Mutations
Unfavorable	**del (17p)** ★ **del (11q)**	**Complex** **(>3 abnormality in more than 1 cell)**	**Unmutated IGHV (≤ 2%)** ★ **TP53** ★ NOTCH-1 SF3B1 BIRC3 ATM
Neutral	**Normal** **+12**		
Favorable	**del (13q)** **(sole abnormality)**		**Mutated IGVH (>2%)**

1. TP53 aberration is the most important marker (check before each treatment).
2. IGHV mutational status (one time test).

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.

Is Early Treatment Reasonable?

Question:

I have high-risk CLL and the new drugs are much safer and more effective these days. Why can't I start treatment earlier (at the time of diagnosis)?

Answer:

- Great Question.
- Studies are ongoing – ASH-2019?
- Other studies are being designed.

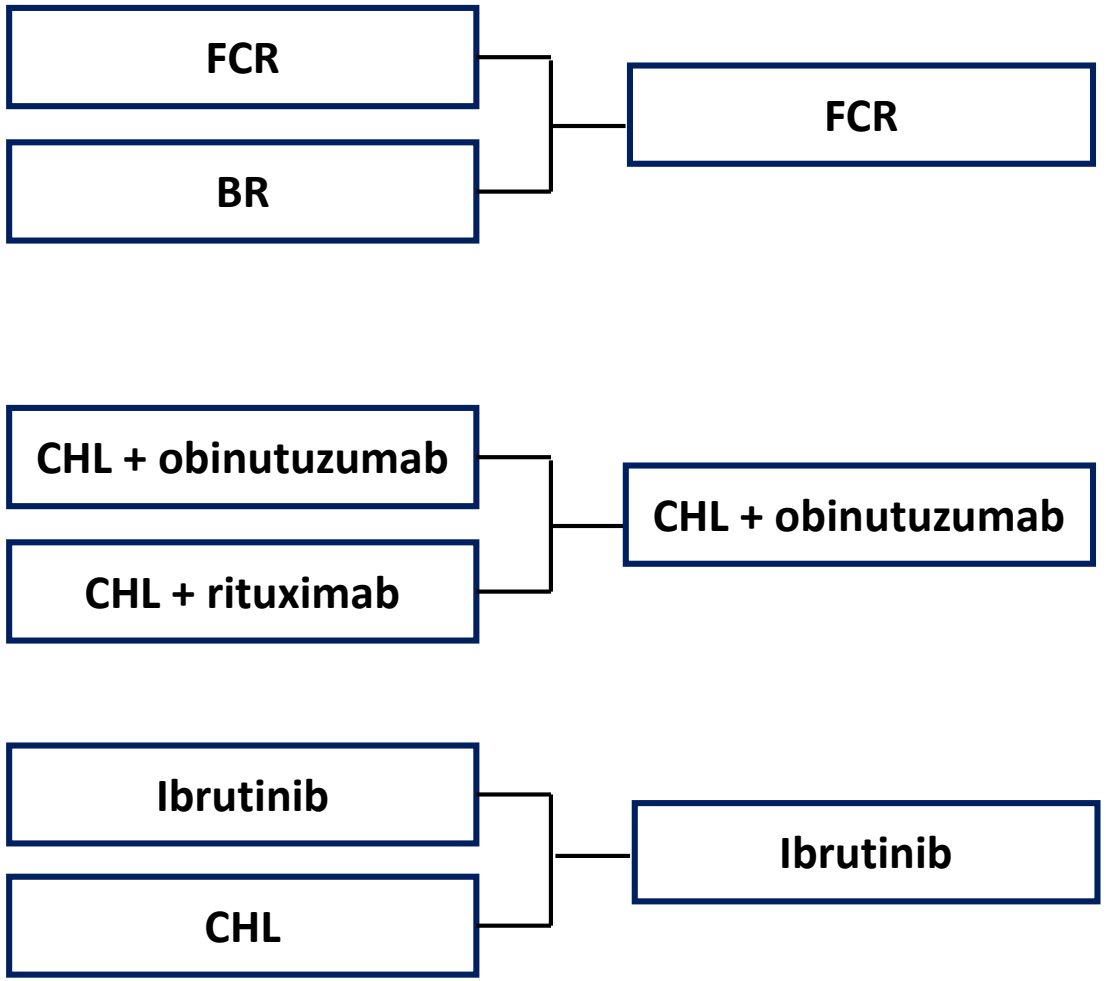
No Algorithm

Ideal Treatment:

- Cures CLL;
- Helps patients live longer;
- Provides long time periods without treatment and without disease;
- Doesn’t interfere with patient’s work/life;
- Is not forever;
- Has minimal toxicity;
- Does not make patient’s other medical conditions worse.

First Line Treatment

Before ASH 2018



Young and Fit

- FCR
- most beneficial in pts with mutated IGHV
- ibrutinib for selected patients

Less Fit

- BR
- ibrutinib for selected patients

Unfit

- ibrutinib
- chlorambucil + obinutuzumab
- ibrutinib for selected patients

FCR

BR

FCR

CHL + obinutuzumab

CHL + rituximab

CHL + obinutuzumab

Ibrutinib

CHL

FCR

FCR

Ibrutinib

BR

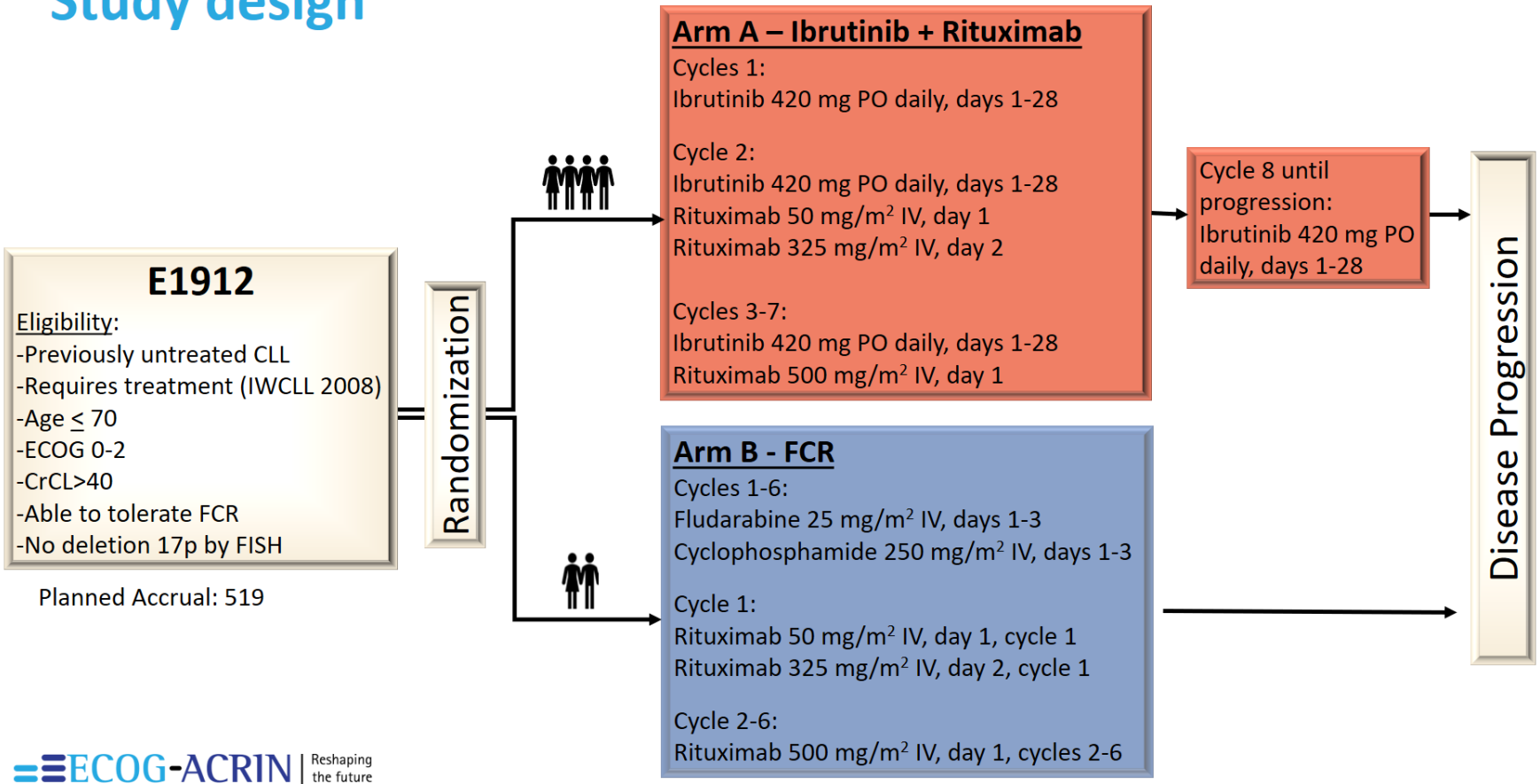
Ibrutinib

CHL + obinutuzumab

Ibrutinib

FCR vs. IB+R (E1912 Study)

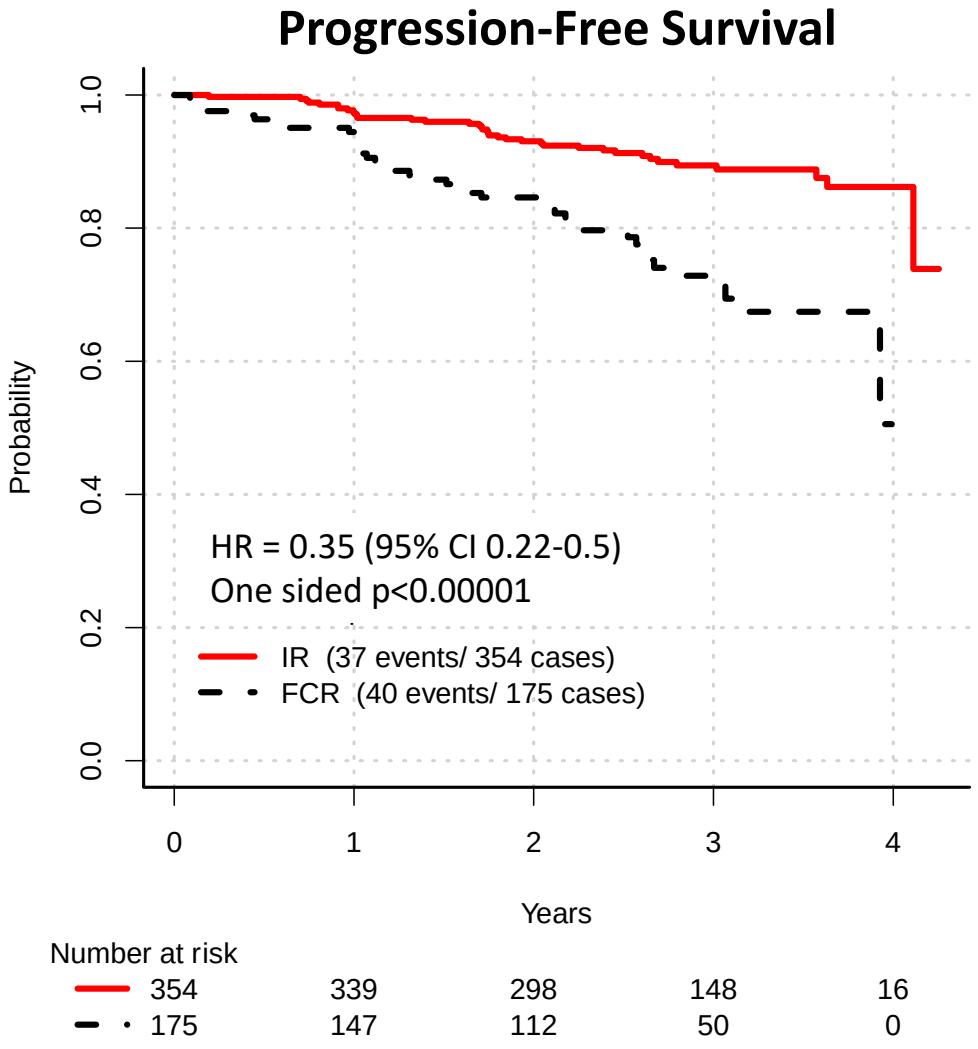
Study design

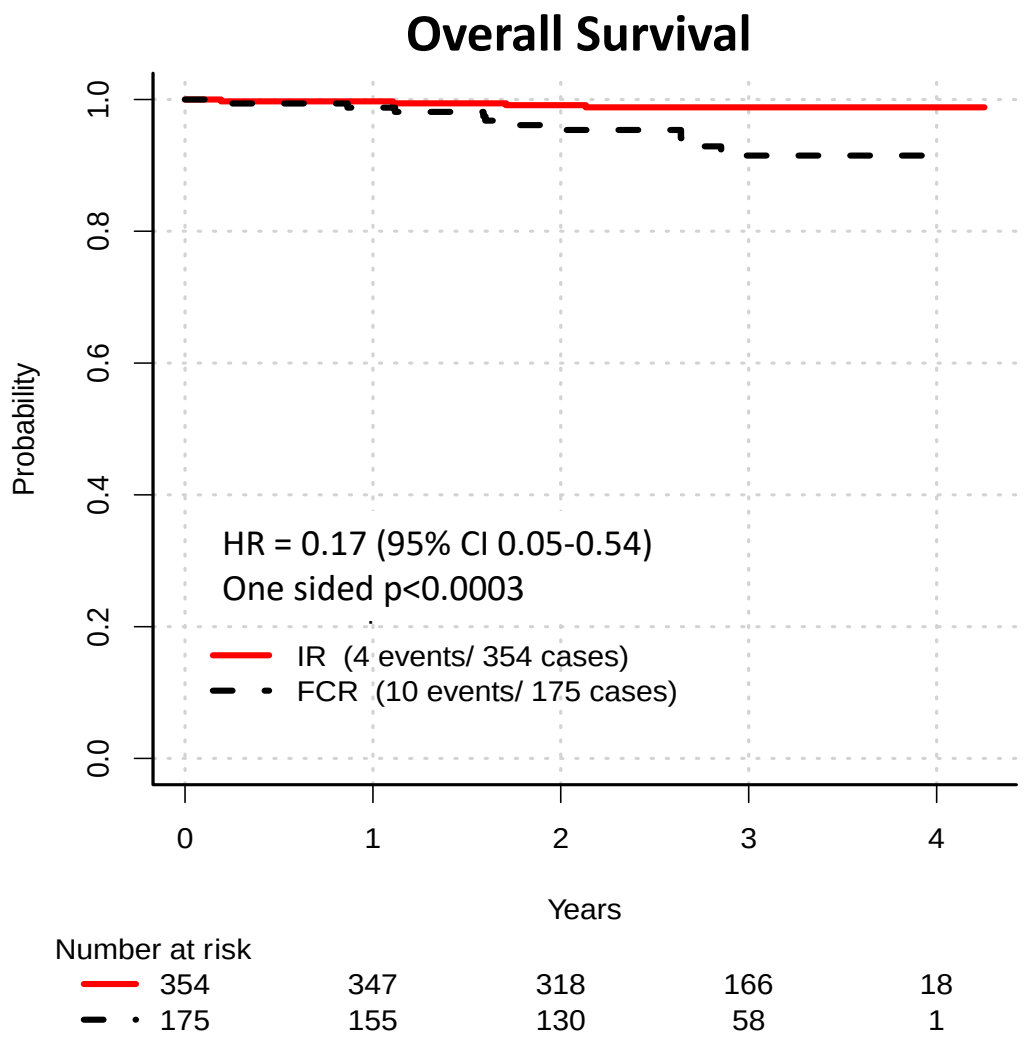


ECOG-ACRIN cancer research group | Reshaping the future of patient care

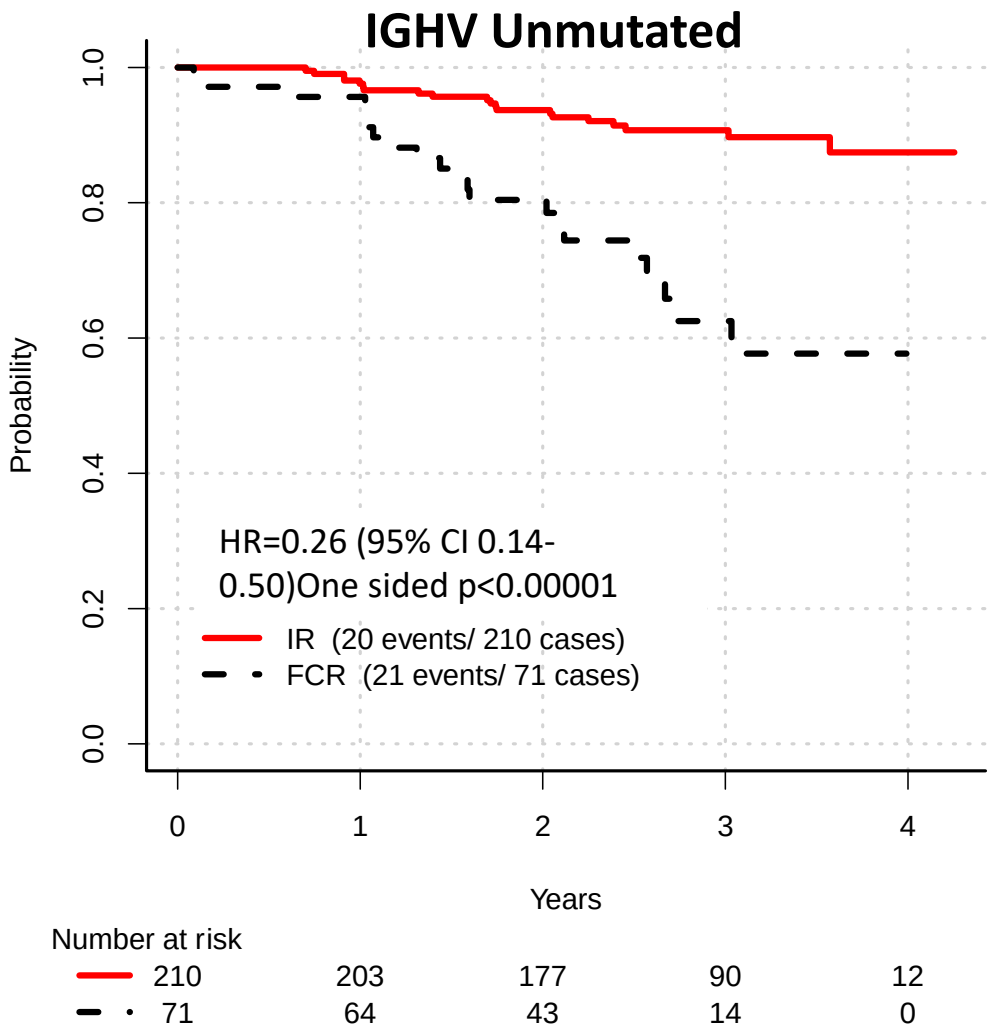
Shanafelt. ASH 2018. Abstr LBA-4. NCT02048813.

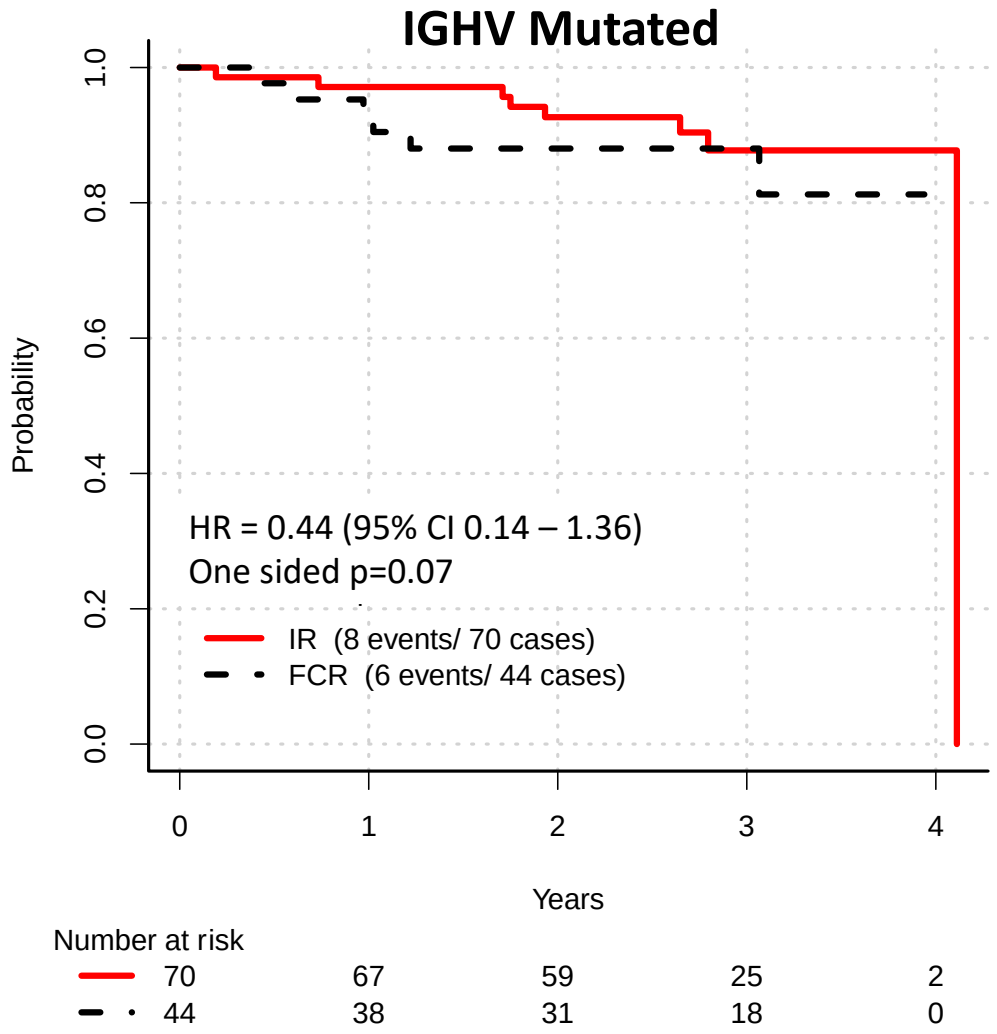
E1912: Results





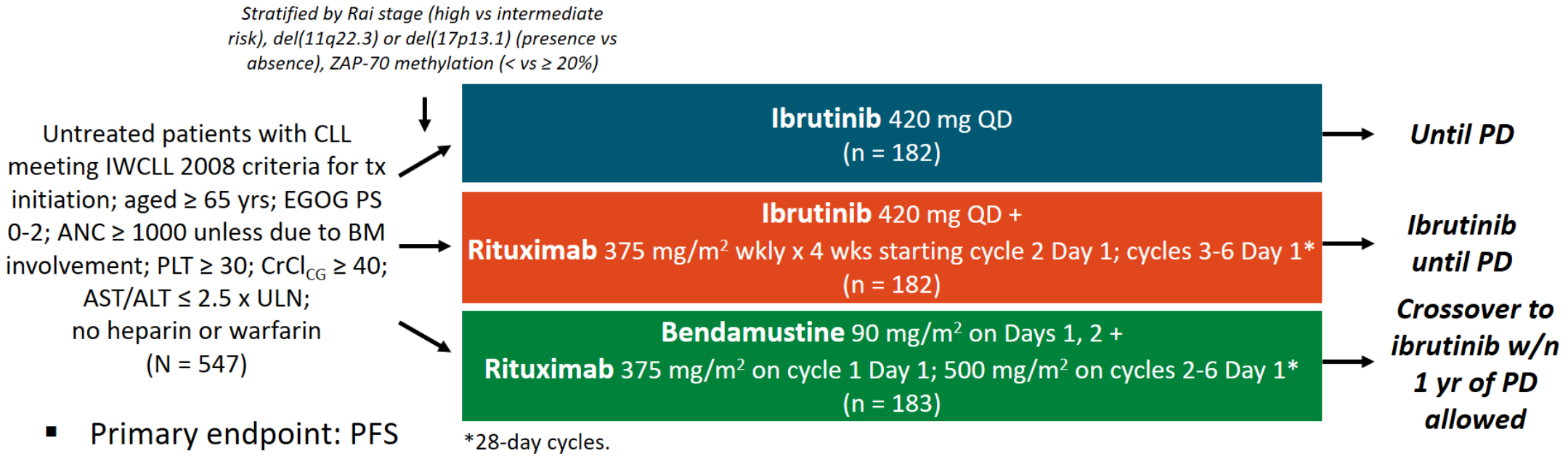
Progression-Free Survival: IGHV Status





A041202: Study Design

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

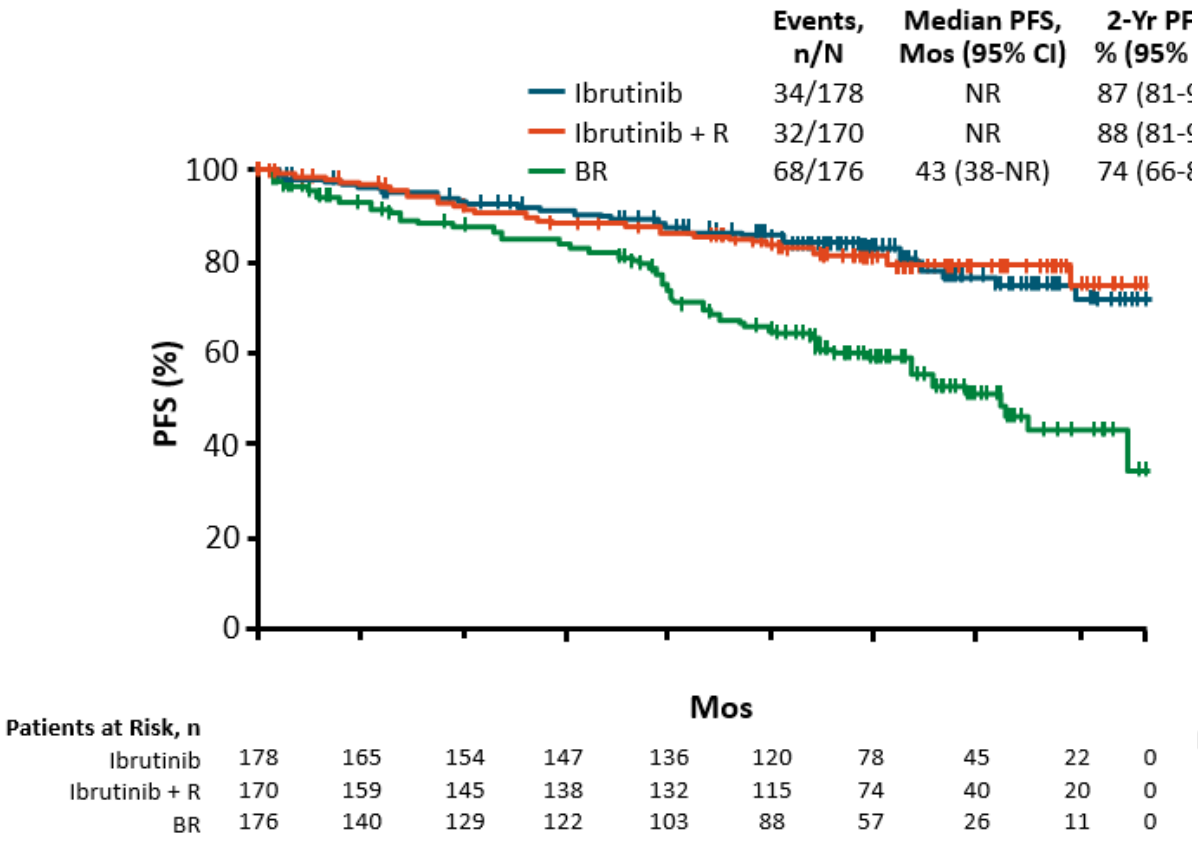


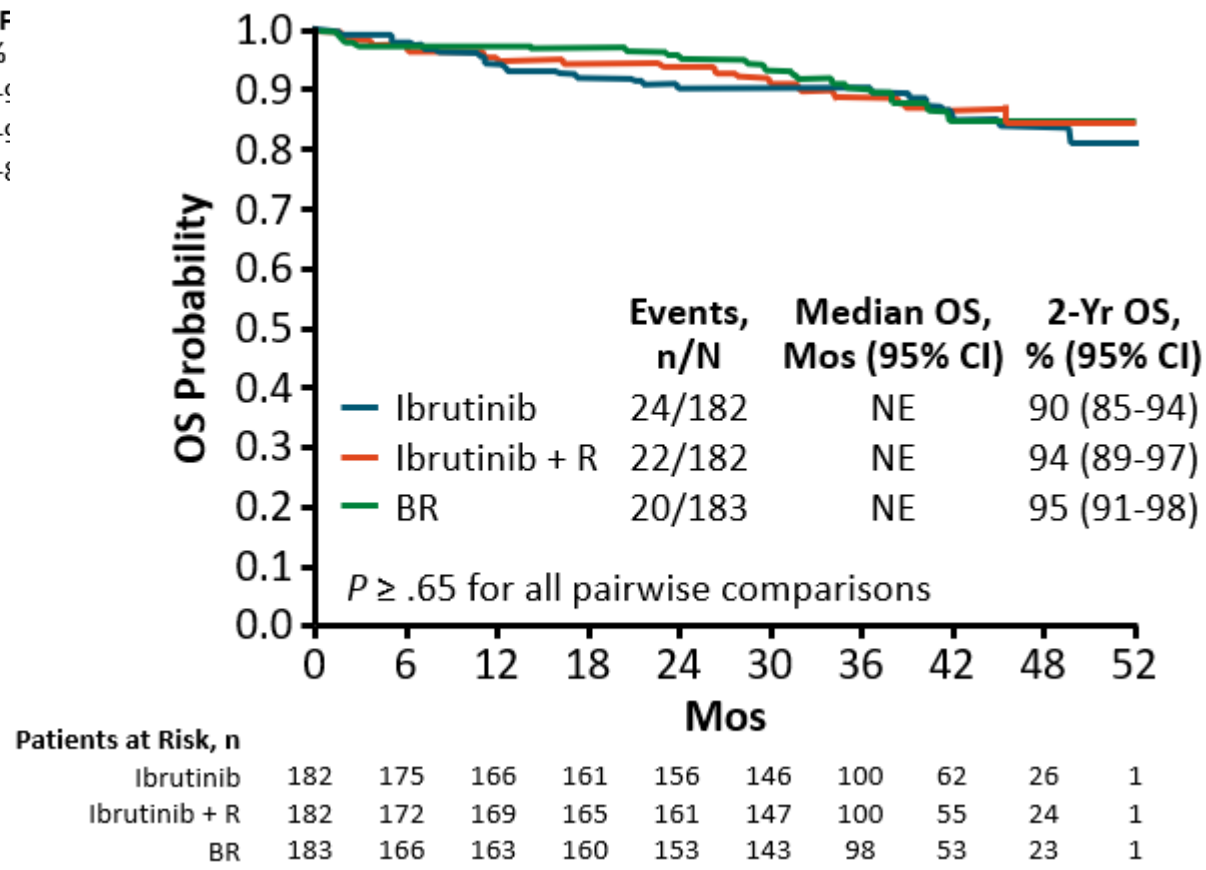
*28-day cycles.

- Primary endpoint: PFS
  - 2 primary comparisons of ibrutinib vs BR and ibrutinib + R vs BR with 90% power to detect HR of 0.586 (estimated 2-yr PFS rates: ibrutinib, 75%; BR, 61%) and overall 1-sided α = 0.025 for each comparison
  - If both primary comparisons significant, third planned comparison of ibrutinib + R vs ibrutinib

Woyach. ASH 2018. Abstr 6. Woyach. NEJM. 2018;[Epub].

A041202 (BR vs. IB vs. IB+R): Results





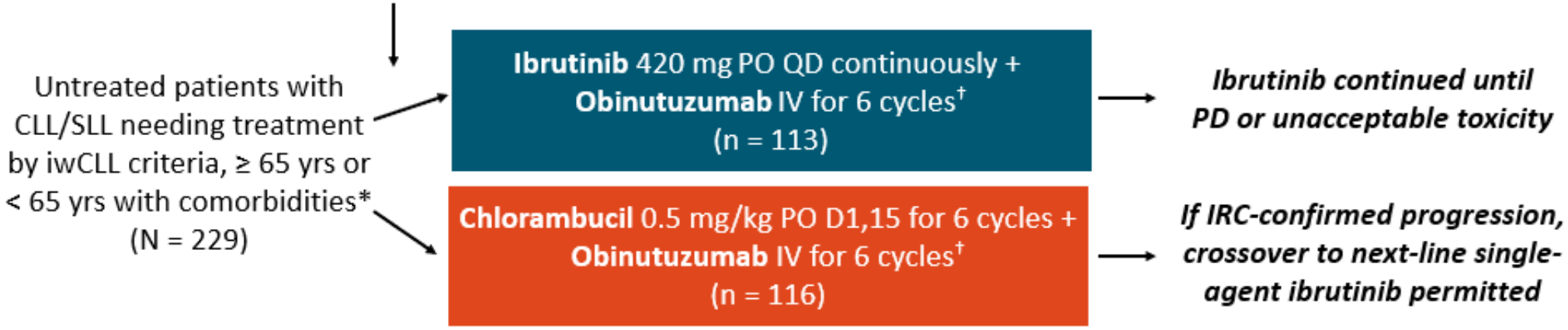
E1912 vs. A041202 Adverse Events

Grade 3-5 Treatment-Related AE	E1912: Ibrutinib + R[3] (n = 352)	041202: Ibrutinib + R[1,2] (n = 181)
Median age, yrs (range)	57 (31-70)	71 (65-86)
Infection, %	5	20
Atrial fibrillation, %	3	6
Bleeding, %	1	3
Hypertension, %	7	34
Deaths during active treatment + 30 days. %	1	7

iLLUMINATE: Study Design

- Randomized, open-label, multicenter phase III trial

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



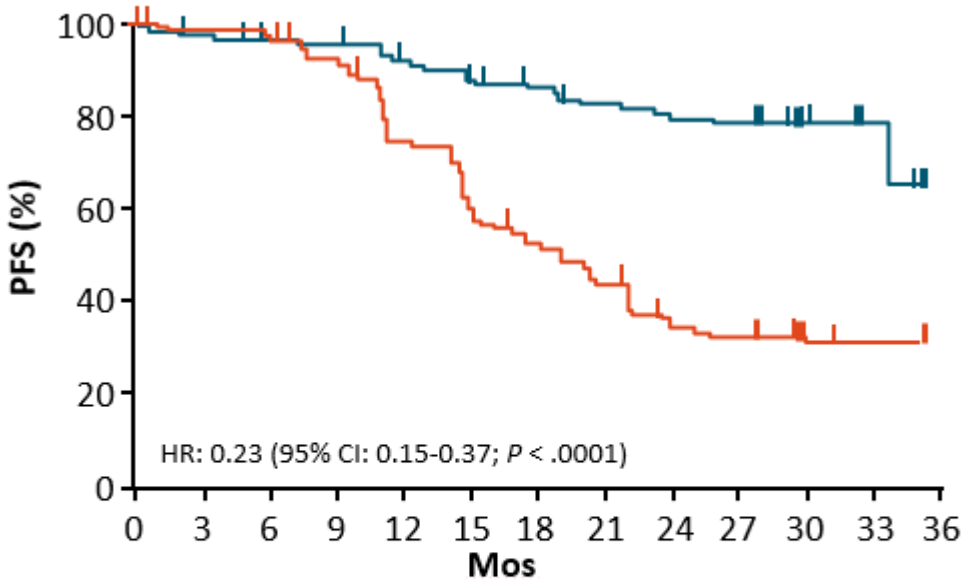
*Cumulative Illness Rating Score > 6, creatinine clearance < 70 mL/min, and/or del(17p)/*TP53* mutation.
†Cycle 1: 100 mg, Days 1; 900 mg, Day 2; 1000 mg, Days 8, 15. Cycle 2-6: 1000 mg, Day 1.

- Primary endpoint: PFS by IRC in ITT population
- Secondary endpoints: PFS in high-risk patients (positive for del(17p) or *TP53* mutation, del(11q), or unmutated *IGHV*), MRD, ORR, OS, IRRs, safety

Moreno. ASH 2018. Abstr 691. Moreno. Lancet Oncol. 2018;[Epub].

iLLUMINATE: Results

Progression-Free Survival



	Patients, n	Median PFS, Mos	30-Mo PFS, % (95% CI)
Ibrutinib + obinutuzumab	113	NR	79 (70-85)
Chlorambucil + obinutuzumab	116	19.0	31 (23-40)

No Overall Survival Benefit

Venetoclax + obinu vs. CHL + obinu German CLL14 Study

Media Release

Basel, 01 November 2018

Phase III data showed that Venclexta/Venclyxto plus Gazyva/Gazyvaro reduced the risk of disease worsening or death in people with previously untreated chronic lymphocytic leukaemia with co-morbidities

- **The phase III CLL14 study compared Venclexta/Venclyxto in combination with Gazyva/Gazyvaro to standard-of-care Gazyva/Gazyvaro plus chlorambucil**
- **Data will be submitted to health authorities and presented at an upcoming medical meeting**

Summary of Frontline CLL Studies for First Line ASH 2018

- Ibrutinib is standard of care for first line.
- There is no benefit in adding rituximab to ibrutinib.
- Benefit not clear in patients with a mutated IGHV gene.
- The only patients in whom FCR may not be the wrong answer:
  - young (<65) and fit (no-comorbidities);
  - mutated IGHV;
  - without del17p or TP53 mutation;
  - without del11q.
- Important to remember: ibrutinib> BR but no OS benefit.

Waiting to see the CLL14 study results – May change the current standard.

Relapsed CLL

Relapsed CLL

	Ibrutinib	Venetoclax	Idelalisib/Duvelisib
Target	BTK	BCL-2	PI3K delta / Delta+Gamma
Regimen	Single agent	With R	With Rituximab (idela)
Dose	420 mg po daily	Ramp-up ➔ 2 years!	150 mg po BID (idela) 25 mg po BID (develisib)
Addition of Anti CD20 Ab	No major benefit Faster “response”	Recommended R/R label	R/R label
Major side effect (concern)	Bleeding (anticoagulation) - rare	TLS (initially)	Colitis (diarrhea) Infections (FDA alert)
Other side effects	• Body pain • Fatigue • Hypertension • A fib	• Neutropenia	• Pneumonitis • Transaminitis • PJP • CMV
FDA label for CLL	• Everybody	• del 17 p after 1 line • R/R	• R/R (after 2 lines)

Ibrutinib vs. Venetoclax for Relapsed CLL

- No head-to-head studies.
- Both reasonable options.
- Both superior to idelalisib (based on toxicity profile).

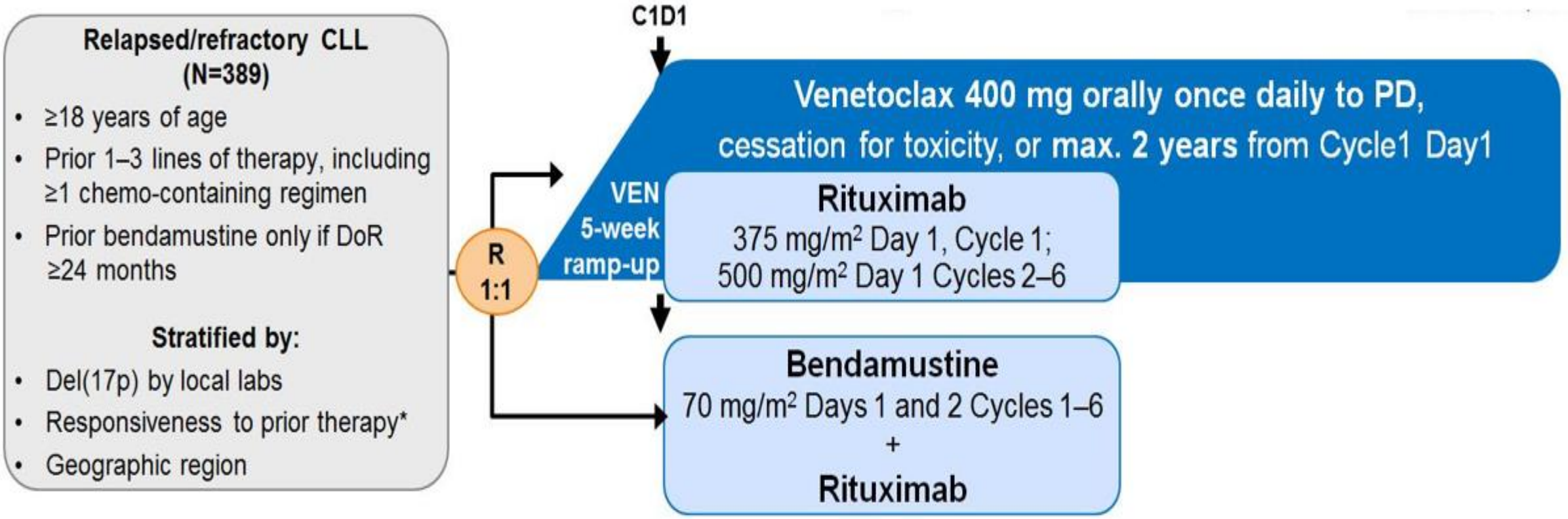
In favor of Venetoclax

- **Fixed treatment duration**.
- **After the first 4-5 weeks, seems to be better tolerated**.
- Higher rate of CR and MRD negativity.
- **Treatment holiday/hold is expected (not proven yet)**.
- Preferred in patients with A fib, bleeding issues, HTN.

In favor of Ibrutinib

- Longer track record.
- Easier to start.
- **More information about salvage options if stops working**.

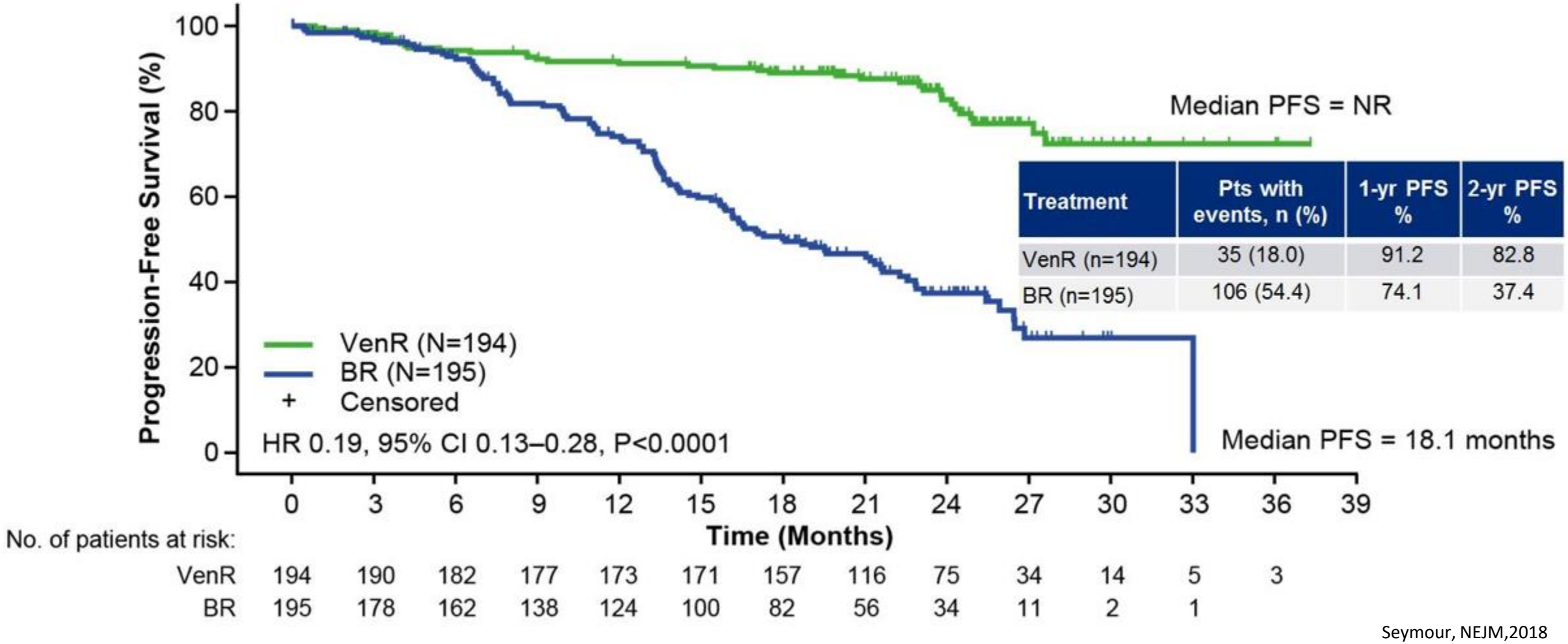
Ven-R vs. BR in relapsed CLL (MURANO Study)



Primary Endpoint	INV-assessed PFS

Seymour, NEJM,2018

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

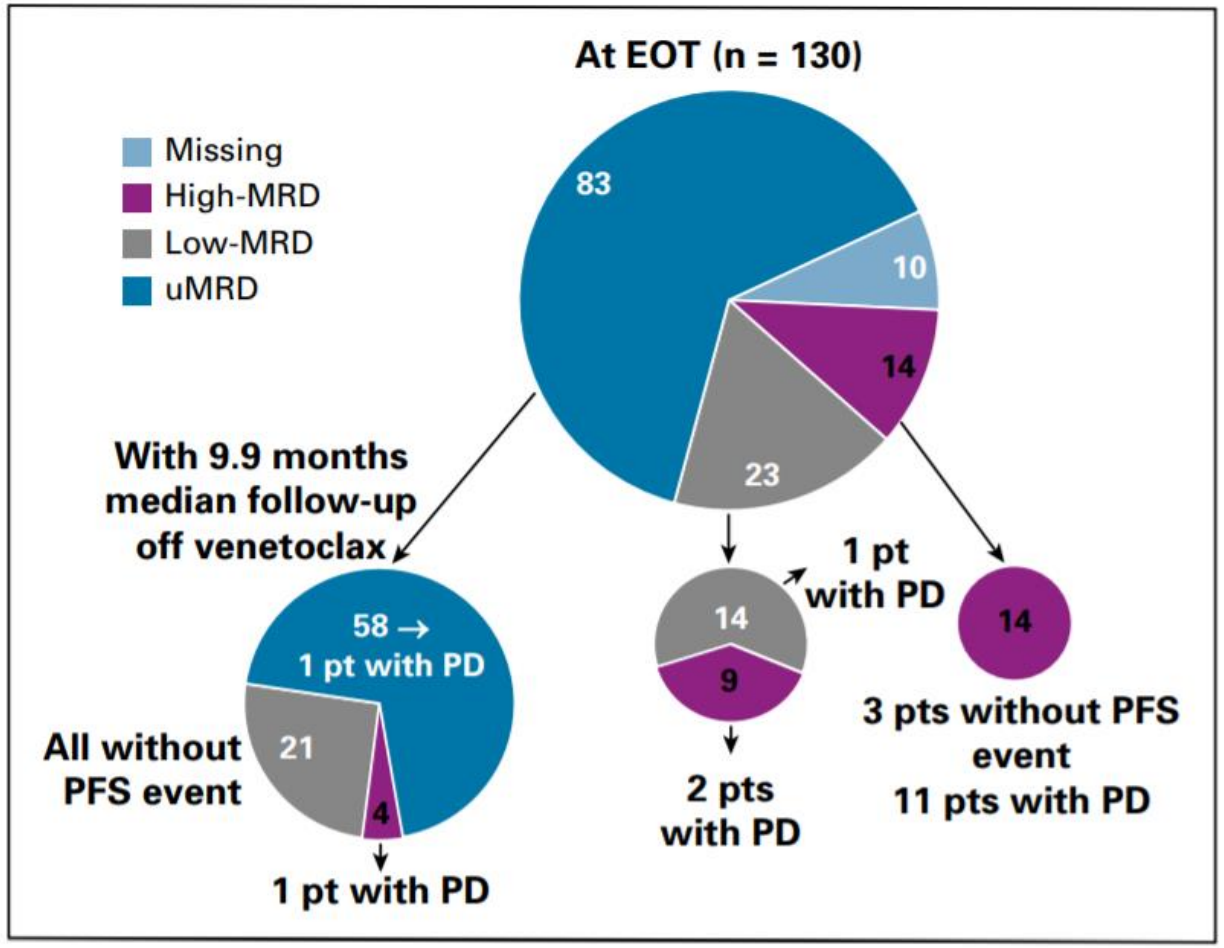


Treatment	Pts with events, n (%)	1-yr PFS %	2-yr PFS %
VenR (n=194)	35 (18.0)	91.2	82.8
BR (n=195)	106 (54.4)	74.1	37.4

Seymour, NEJM,2018

What Happens After Stopping Venetoclax?

- 10 months follow-up after stopping venetoclax.
- Only 12% of patients relapsed.
- Some still don't need treatment.
- Relapse was less likely if there was minimal detectable disease at the end of 2 years.

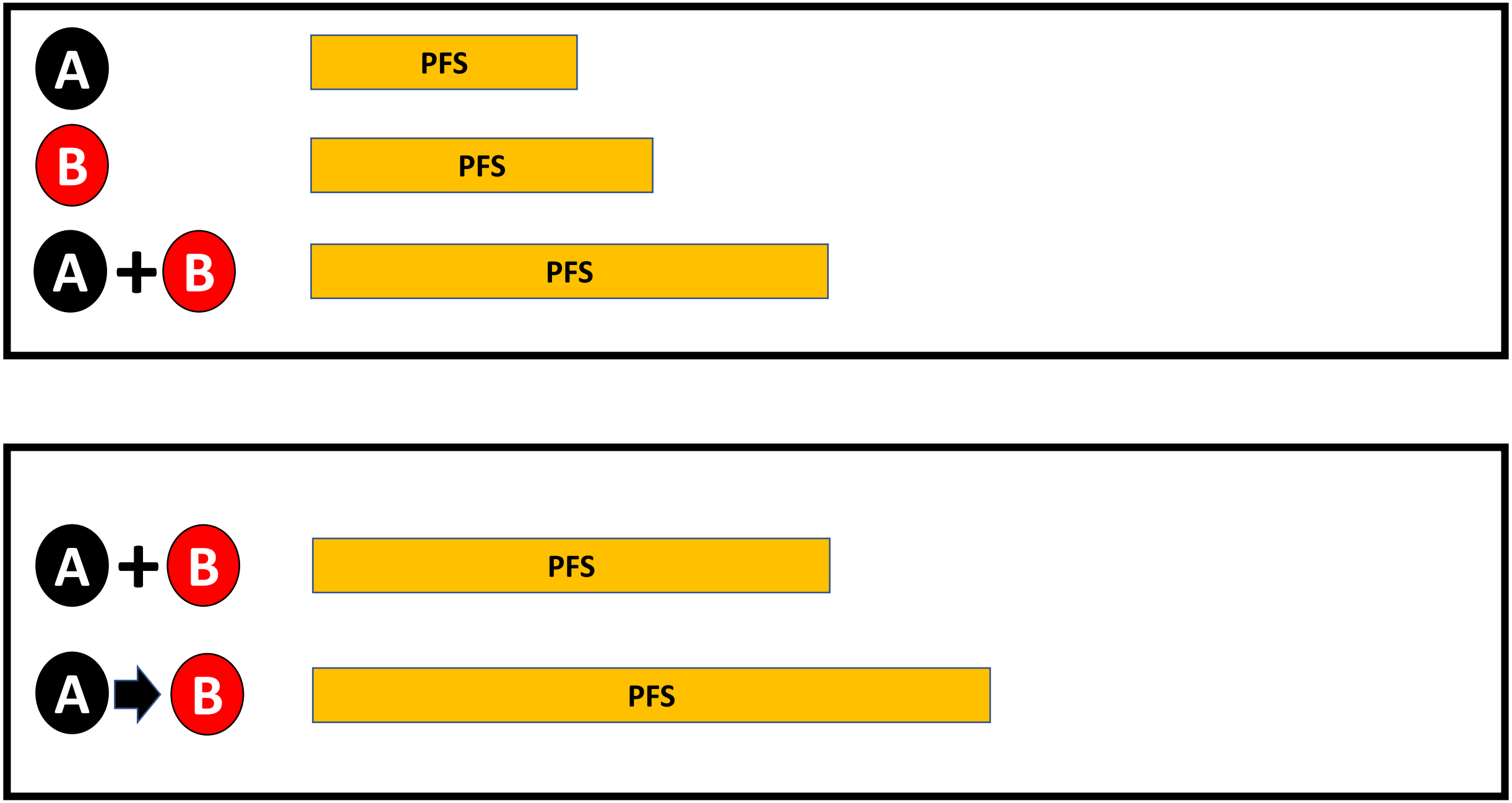


Kater, JCO,2019

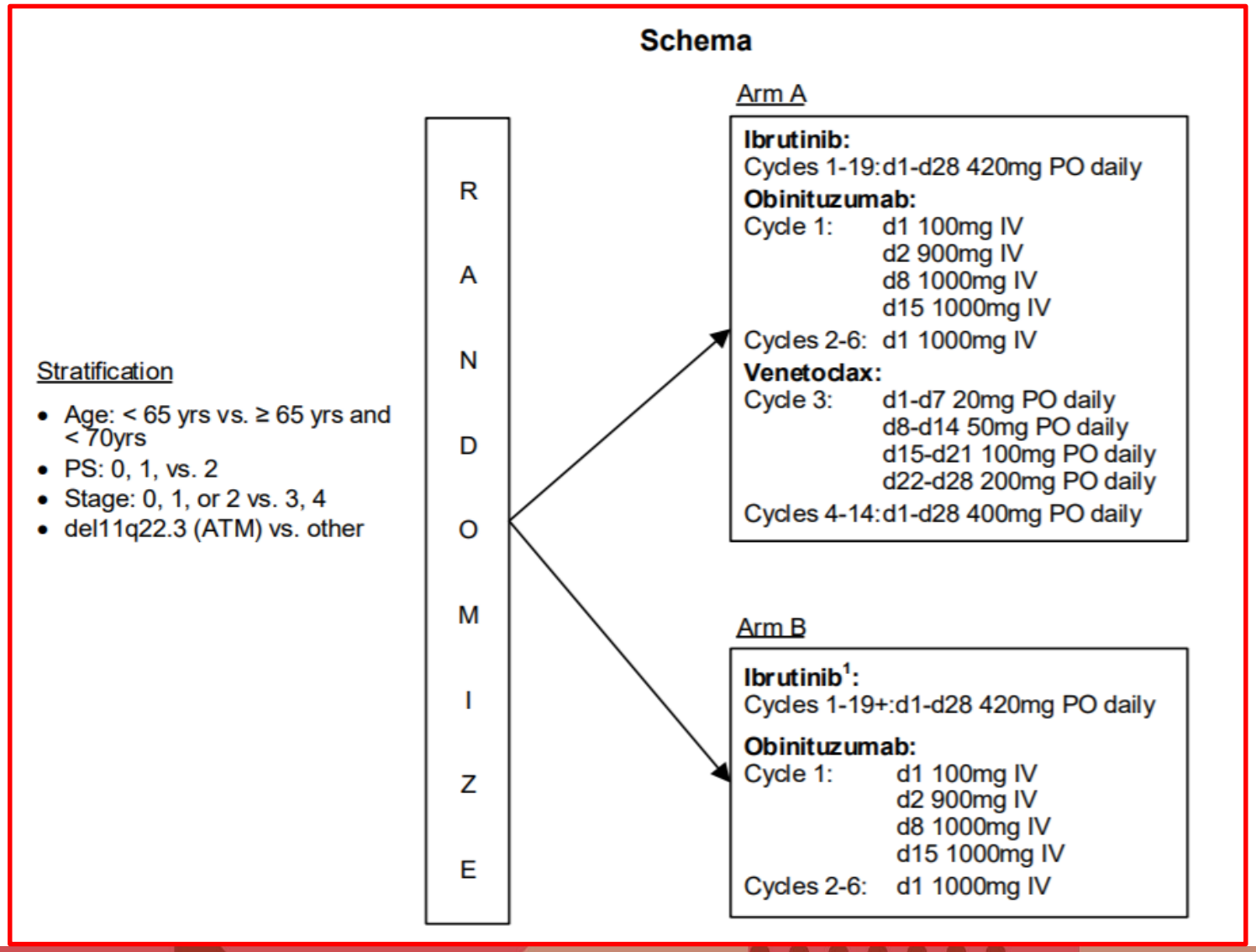
Combination Therapies

Ongoing Combination Studies

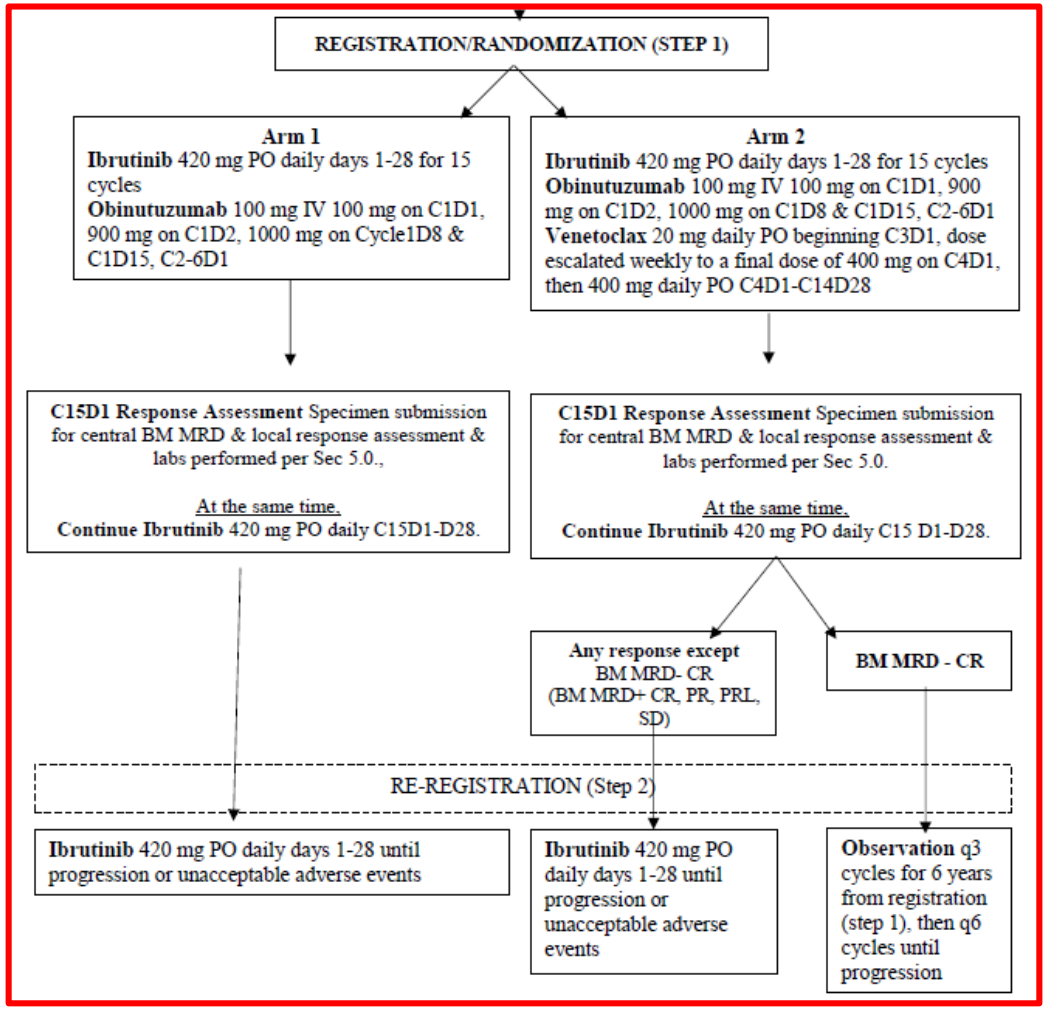
Study	Setting	Regimen	MRD neg	Referecne
MDACC	TN and R/R	Venetoclax + Ibrutinib	18 months: 69% (TN)	Jain, ASH18
The OSU	TN	Venetoclax + Ibrutinib +Obinutuzimab	EOT: 67% (TN); 50% (Relapsed)	Rogers,ASH18
TAP CLARITY	R/R	Venetoclax + Ibrutinib	6 cycles	Hillmen,ASH17
CAPTIVATE	TN	Venetoclax + Ibrutinib	12 cycles: 81%	Wierda, ASCO18,#1142


A
PFS
B
PFS
A + B
PFS
A + B
PFS
A → B
PFS

EA9161 Study



A041702 Study



Take-Home Points

1. Clinical trials are highly recommended until CLL is cured.
2. Treatment algorithms are for physicians, make your own algorithm.
3. We are officially in the “chemo-free” era for CLL but for selected patients, chemo may still be reasonable.
4. The goal is to cure CLL with a “chemo-free” regimen and with fixed-duration.
5. Combination therapy will most likely be the future – we will find out!

Thank You