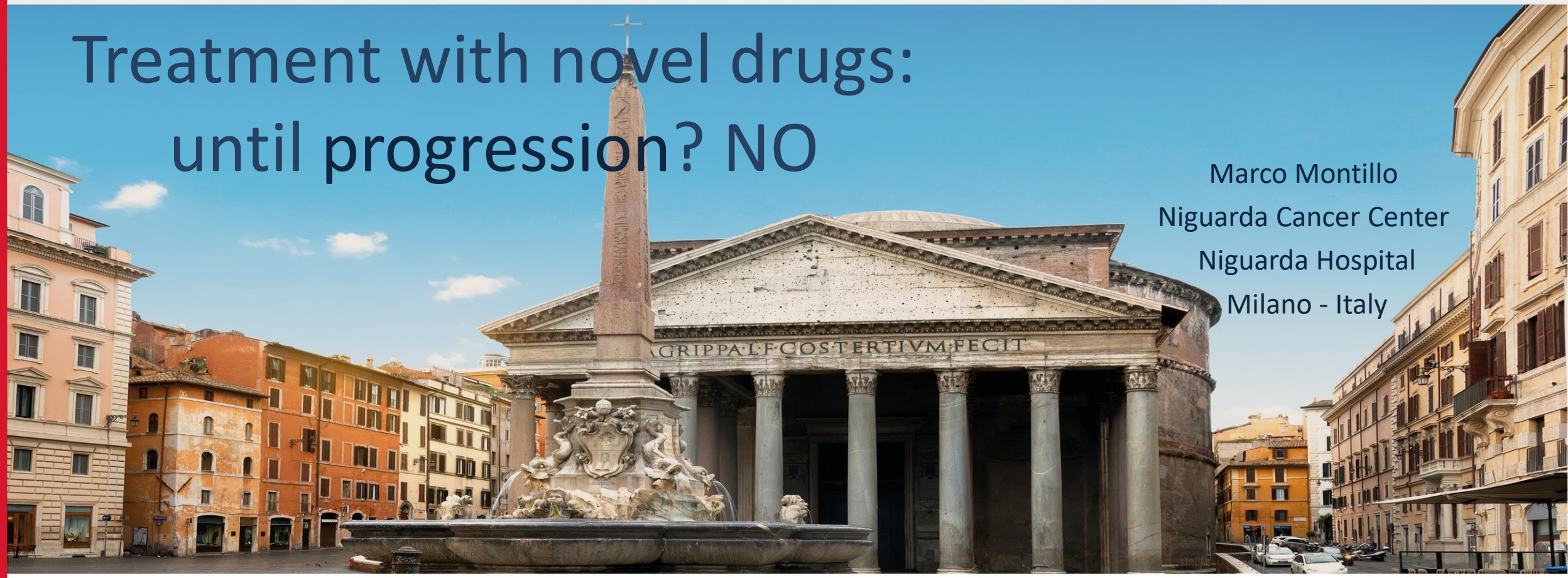
LEUKEMIA2020-2021

April 26-27, 2021

Coordinator: A.M. Carella
AIL President: S. Amadori

ASSOCIAZIONE ITALIANA CONTRO LE LEUCEMIE-LINFOMI E MIELOMA ONLUS

Treatment with novel drugs: until progression? NO



Marco Montillo
Niguarda Cancer Center
Niguarda Hospital
Milano - Italy

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

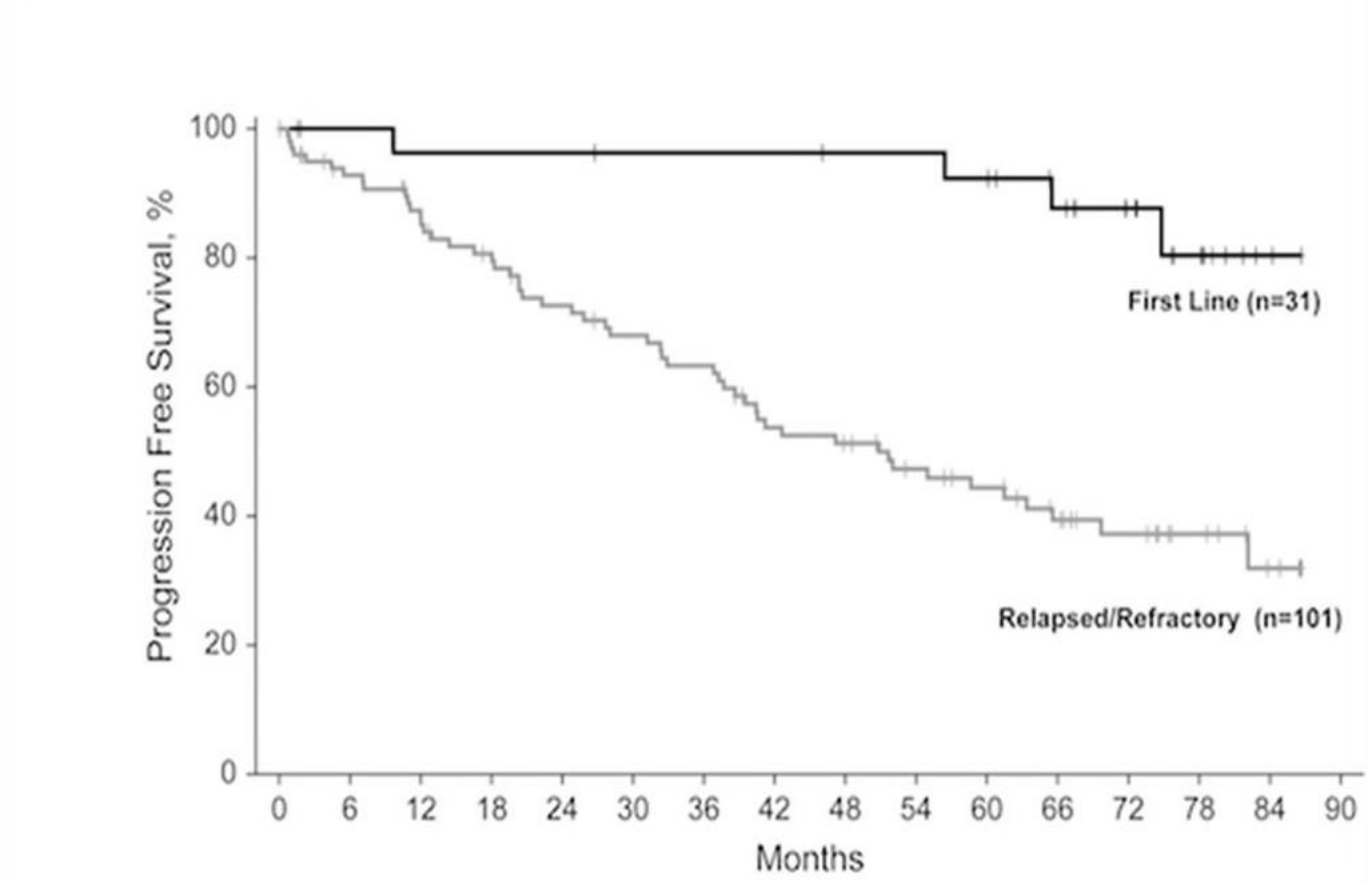
GITMO
GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

SIES Società Italiana Ematologia Sperimentale

SIE - Società Italiana di Ematologia

Frontline Ibrutinib monotherapy can lead to very durable responses but requires continous drug dosing

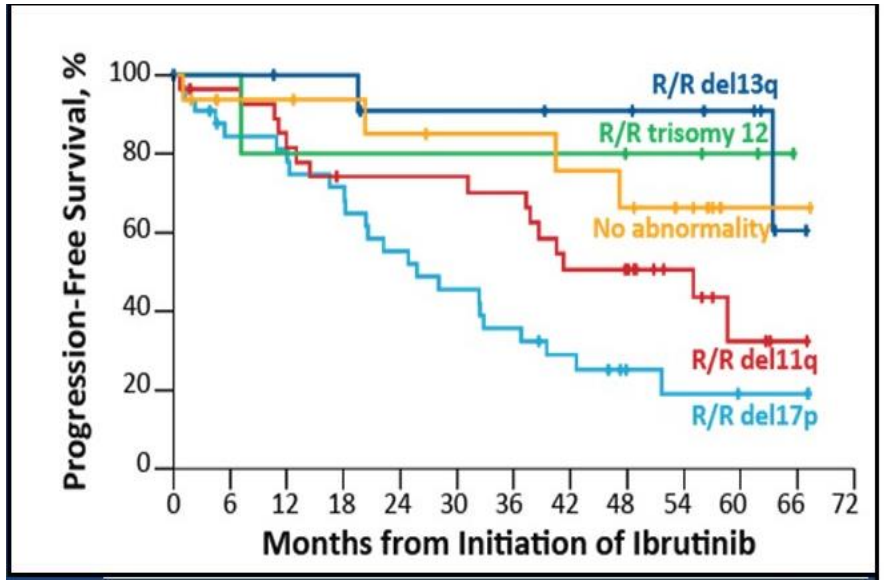
Figure 1. PFS for All-Treated First Line and Relapsed/Refractory Patients with CLL

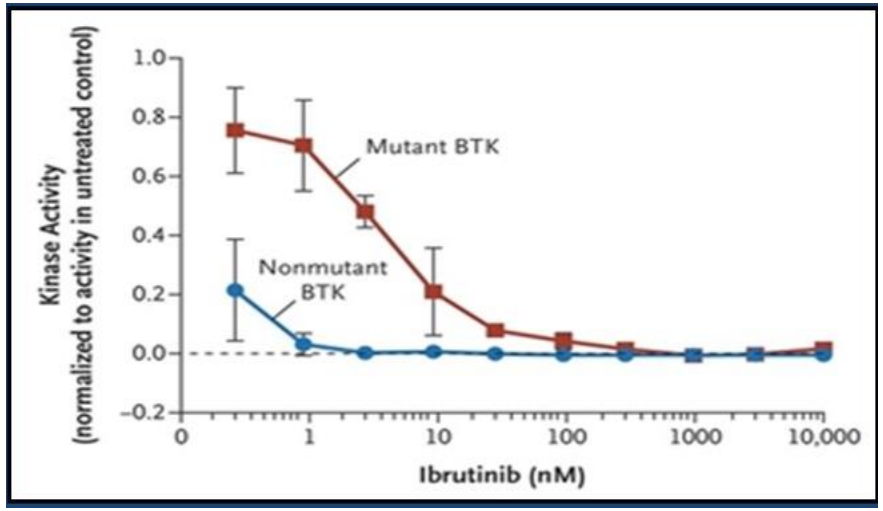


Byrd et al, ASH Annual Meeting 2018

Why not use indefinite novel agent monotherapy ?

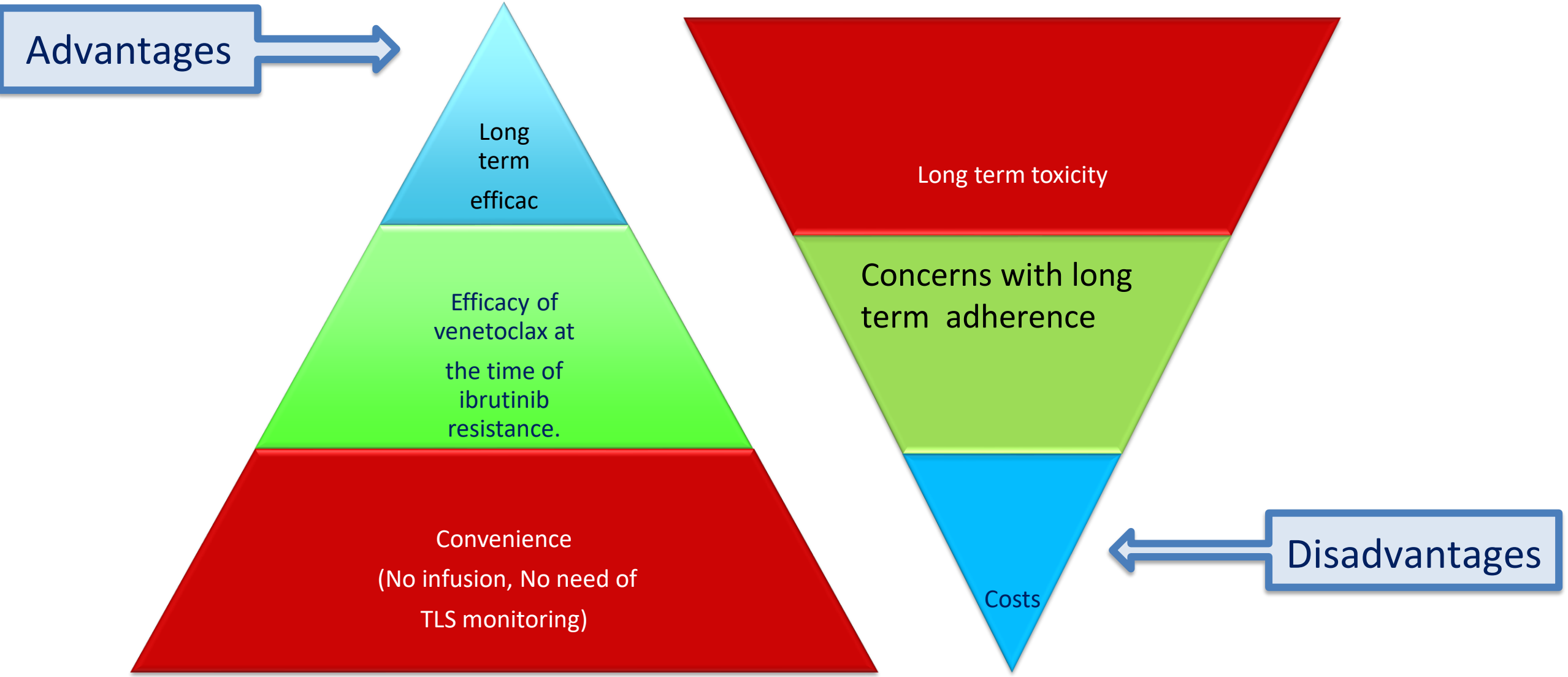
- Achievement of uMRD is rare
- Duration of response in del(17p)/complex karyotype is relatively short
- Resistance mutations described
- Potential for ongoing toxicities
- Long term adherence issues
- Cost





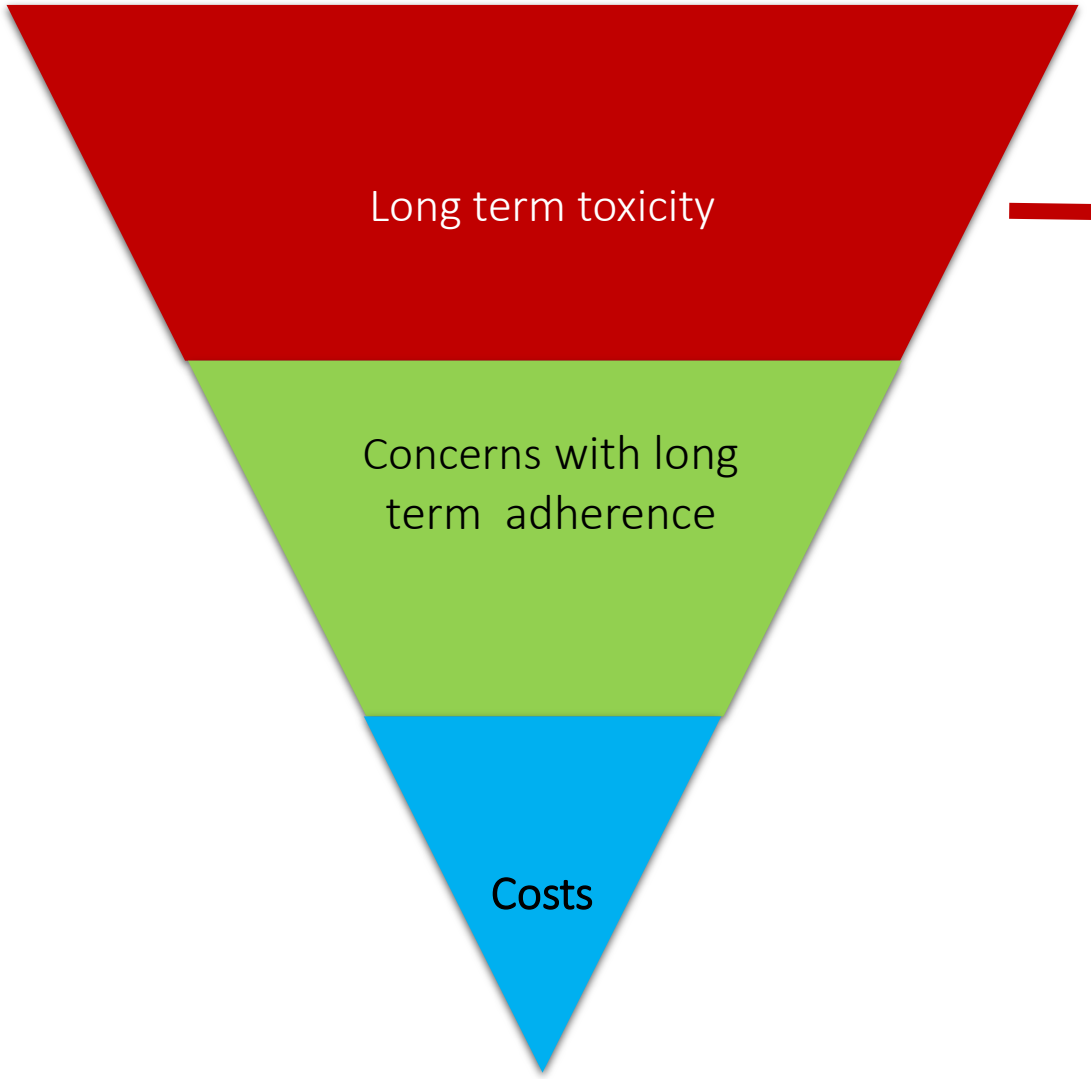
O'Brien S et al. Blood ,2018; Woyach J et al. NEJM , 2014

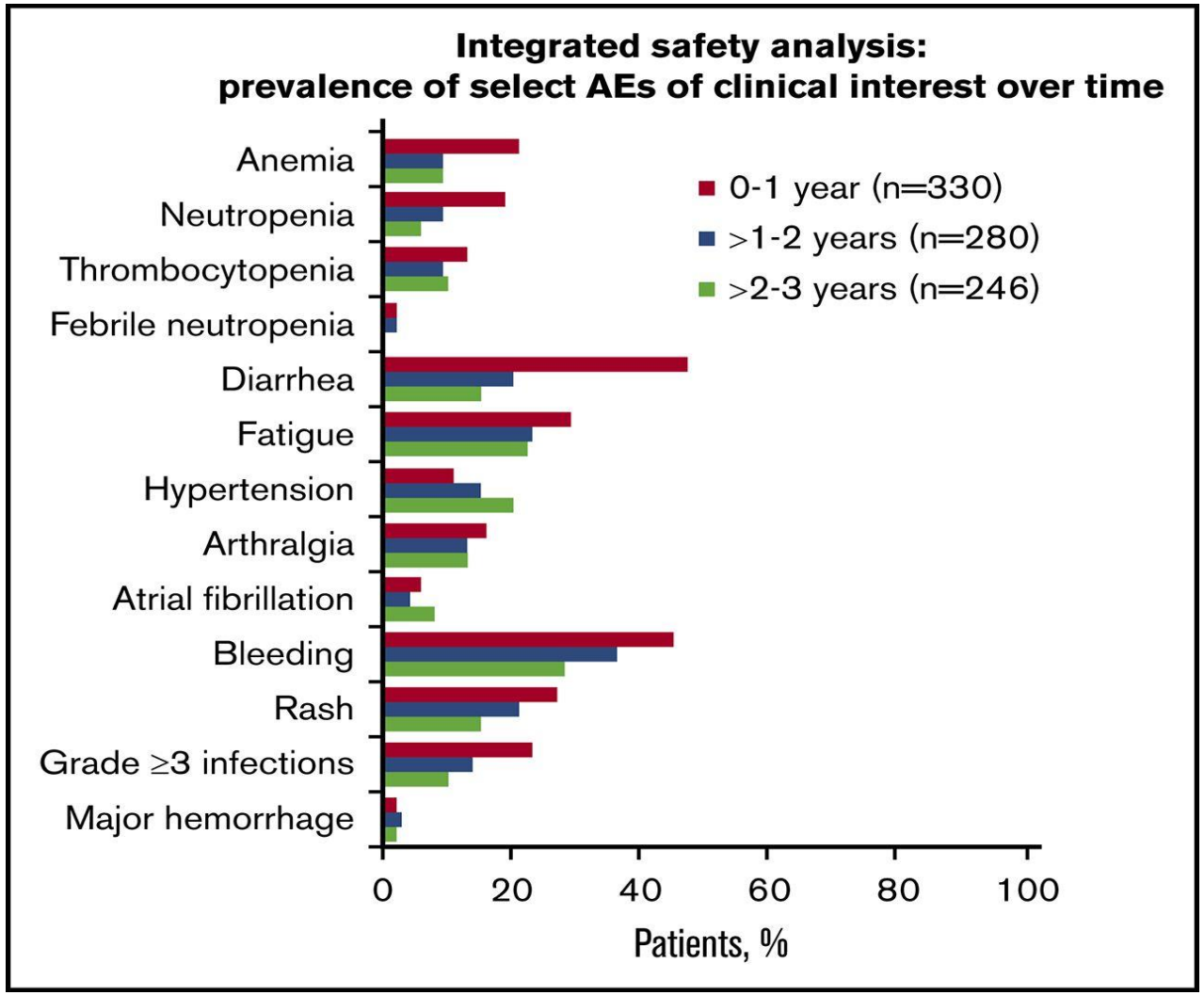
Ibrutinib : Factors to consider



Long-term safety of single-agent ibrutinib in patients with CLL in 3 pivotal studies (RESONATE,RESONATE2, PCYC-1102/1103)

Disadvantages



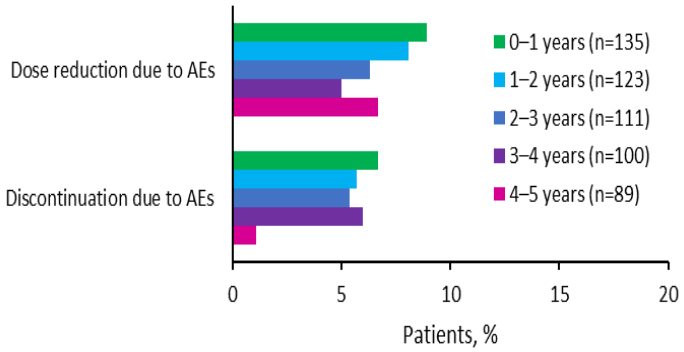


Coutre et al, Blood Advances 2019

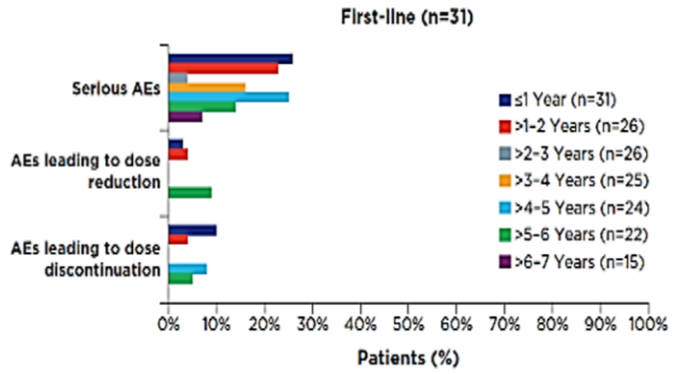
Dose Reductions and Discontinuations due to AEs by year of treatment

Treatment Naïve

Resonate-2[a]



PCYC-1102[b]



[a]Burger et al., 2019

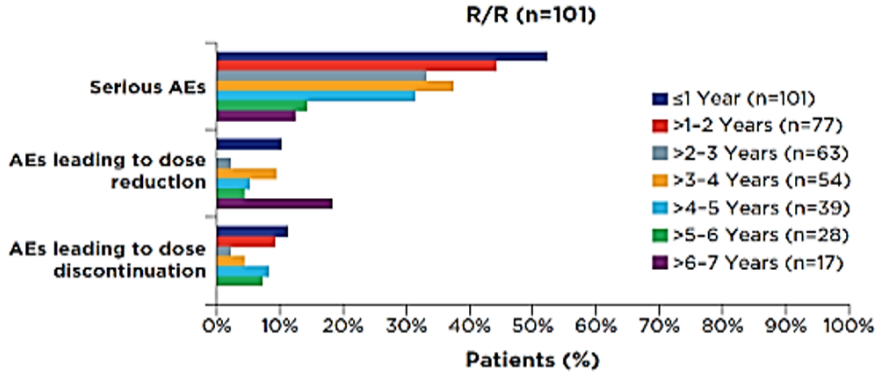
[b]Byrd et al., 2018

Relapsed Refractory

Resonate[c]

Discontinuations due to AE	
0-1 y	6%
1-2 y	3%
2-3 y	4%
3-4 y	4%
4-5 y	6%
5-6 y	4%

PCYC-1102[d]



[c]Byrd et al., 2018

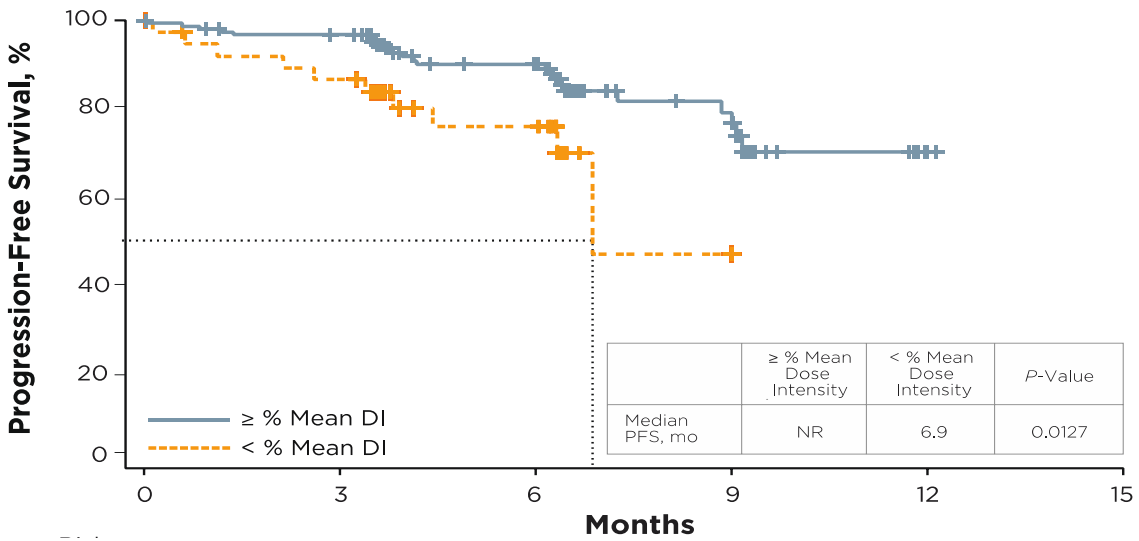
[D]Munir et al., 2019

Ibrutinib discontinuation

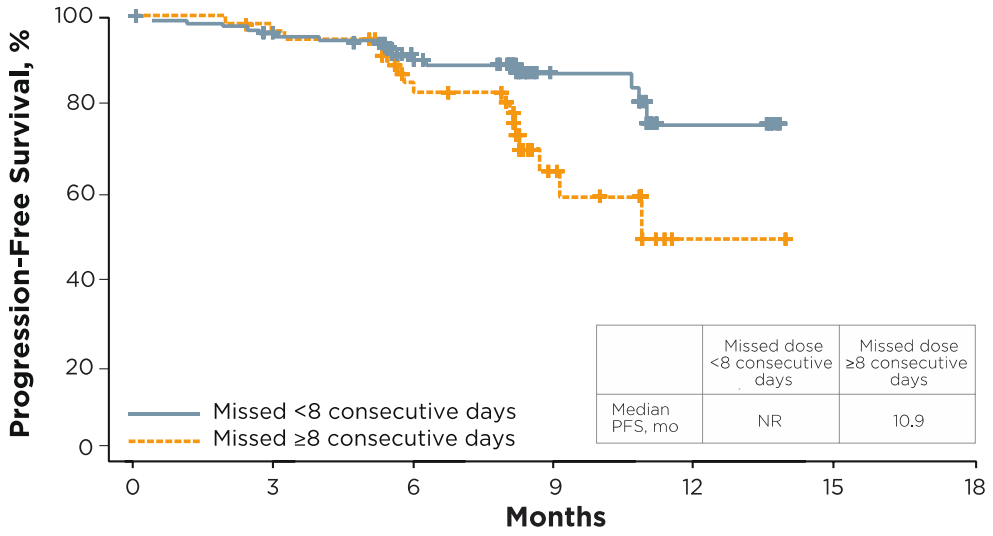
Impact of ibrutinib dose adherence on therapeutic efficacy in patients with previously treated CLL/SLL

Paul M. Barr,[1] Jennifer R. Brown,[2] Peter Hillmen,[3] Susan O'Brien,[4] Jacqueline C. Barrientos,[5] Nishitha M. Reddy,[6] Steven Coutre,[7] Stephen P. Mulligan,[8] Ulrich Jaeger,[9] Richard R. Furman,[10] Florence Cymbalista,[11] Marco Montillo,[12] Claire Dearden,[13] Tadeusz Robak,[14] Carol Moreno,[15] John M. Pagel,[16] Jan A. Burger,[4] Samuel Suzuki,[17] Juthamas Sukbuntherng,[17] George Cole,[17] Danelle F. James,[17] and John C. Byrd[18]

PFS by Mean Dose Intensity



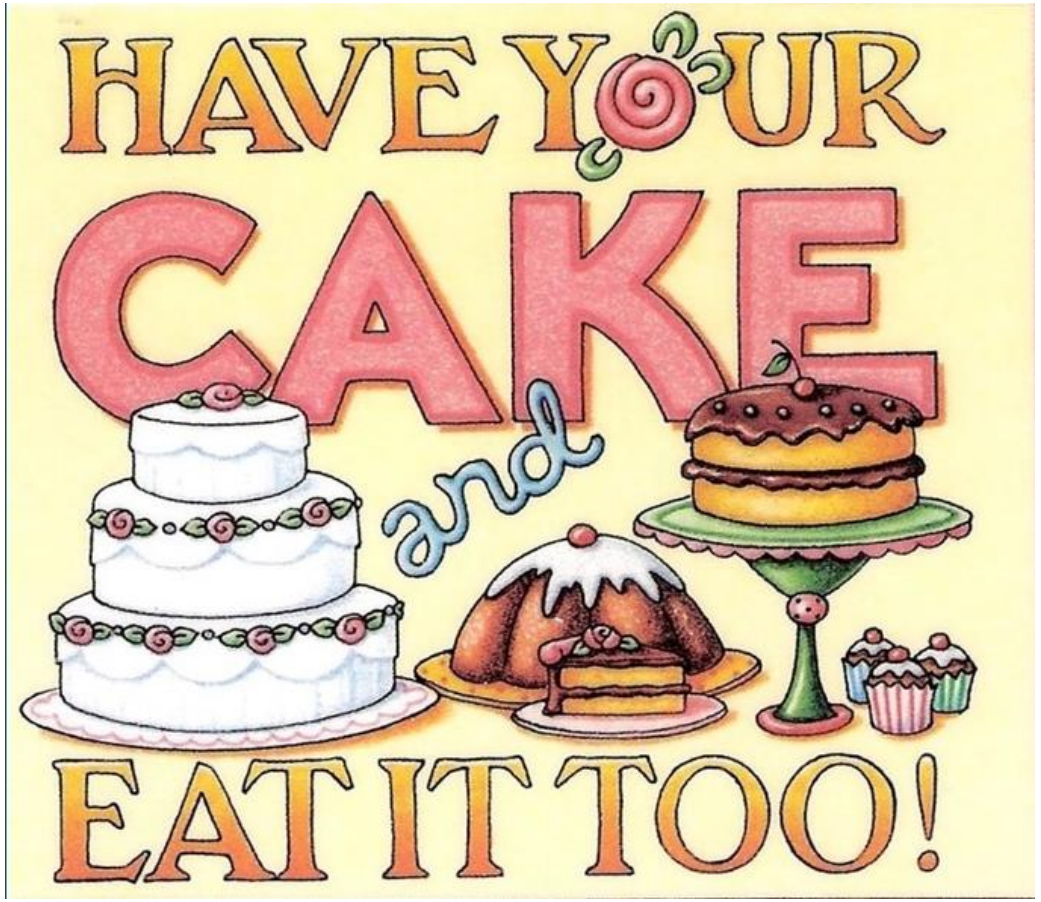
PFS by Missed Dose ≥8 Consecutive Days



DI: proportion of administered vs. planned doses of the full 420 mg ibrutinib dose.

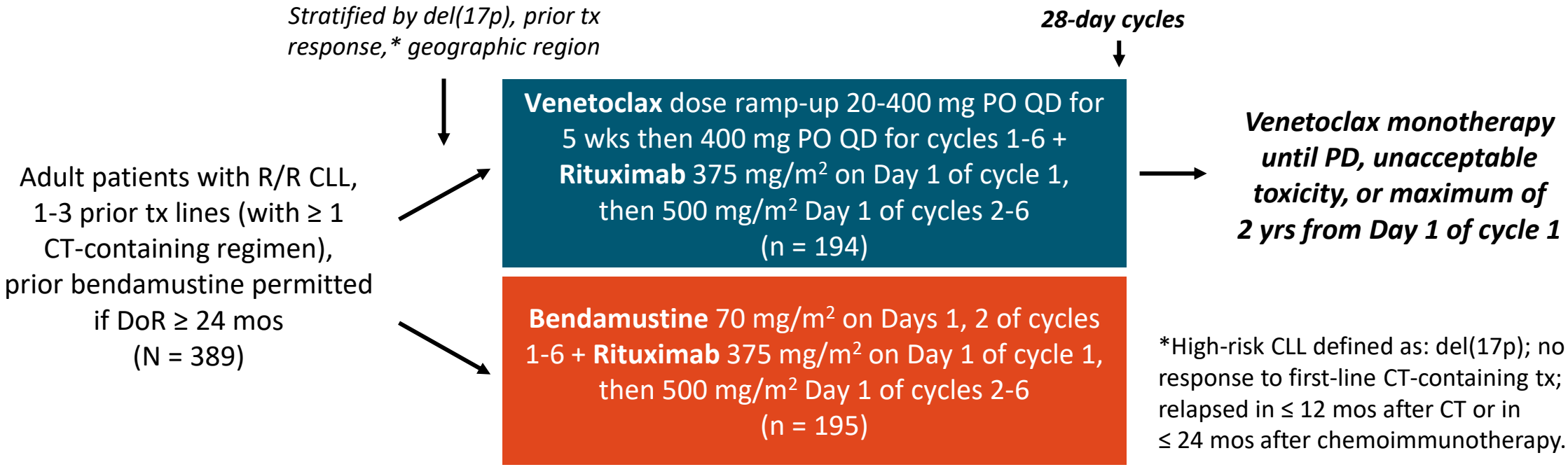
Barr et al. Blood 2017

It is possible to have a highly effective, time limited, novel agent only regimen for a diverse array of CLL patients?



Phase III Trial of Venetoclax + Rituximab vs BR in Previously Treated CLL/SLL (MURANO): Study Design

- Multicenter, randomized, open-label phase III trial



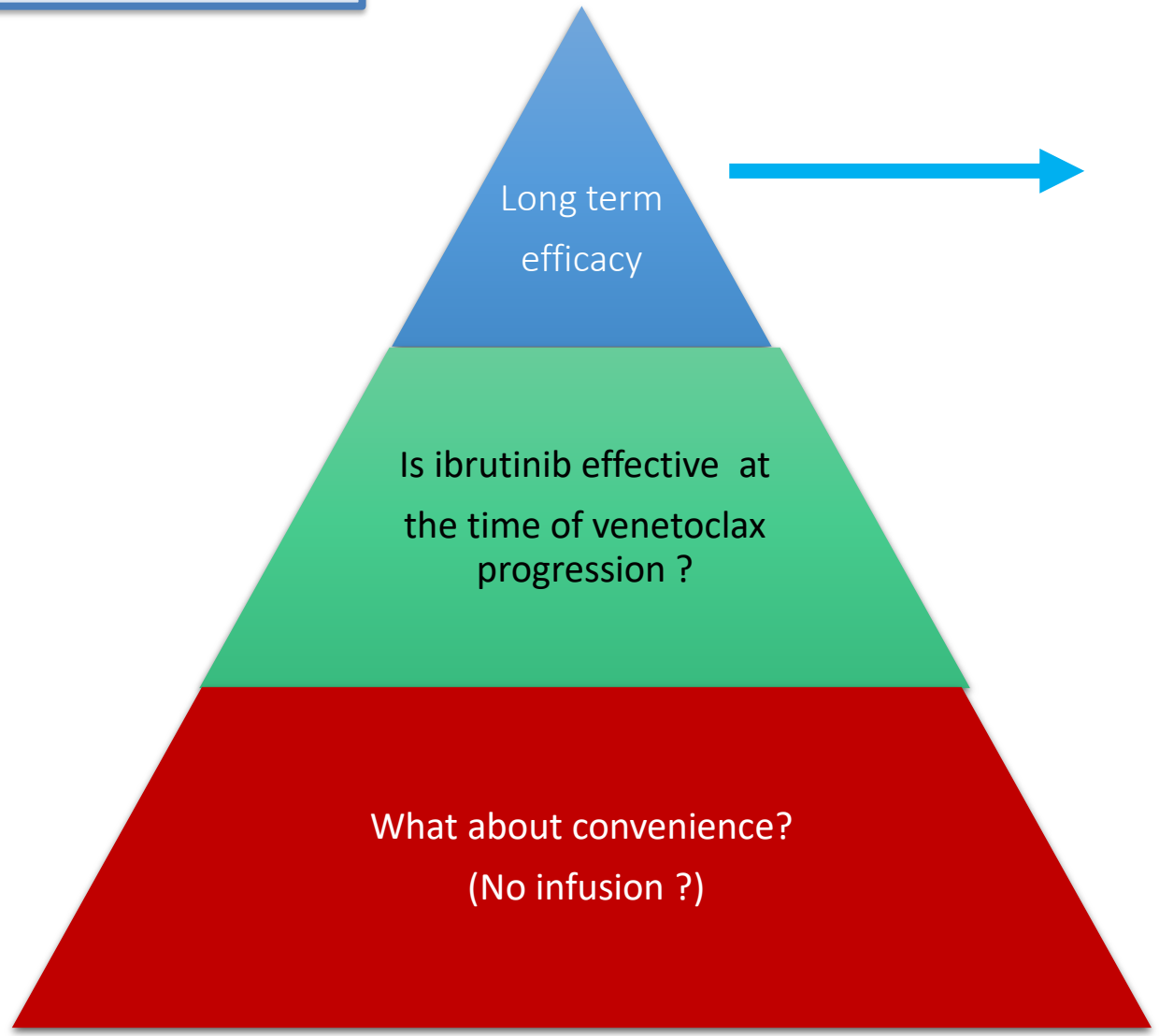
*High-risk CLL defined as: del(17p); no response to first-line CT-containing tx; or relapsed in ≤ 12 mos after CT or in ≤ 24 mos after chemoimmunotherapy.

- Primary endpoint: investigator-assessed PFS
- Secondary endpoints: IRC-assessed PFS and MRD negativity, IRC-assessed CR → ORR → OS (hierarchical testing), safety

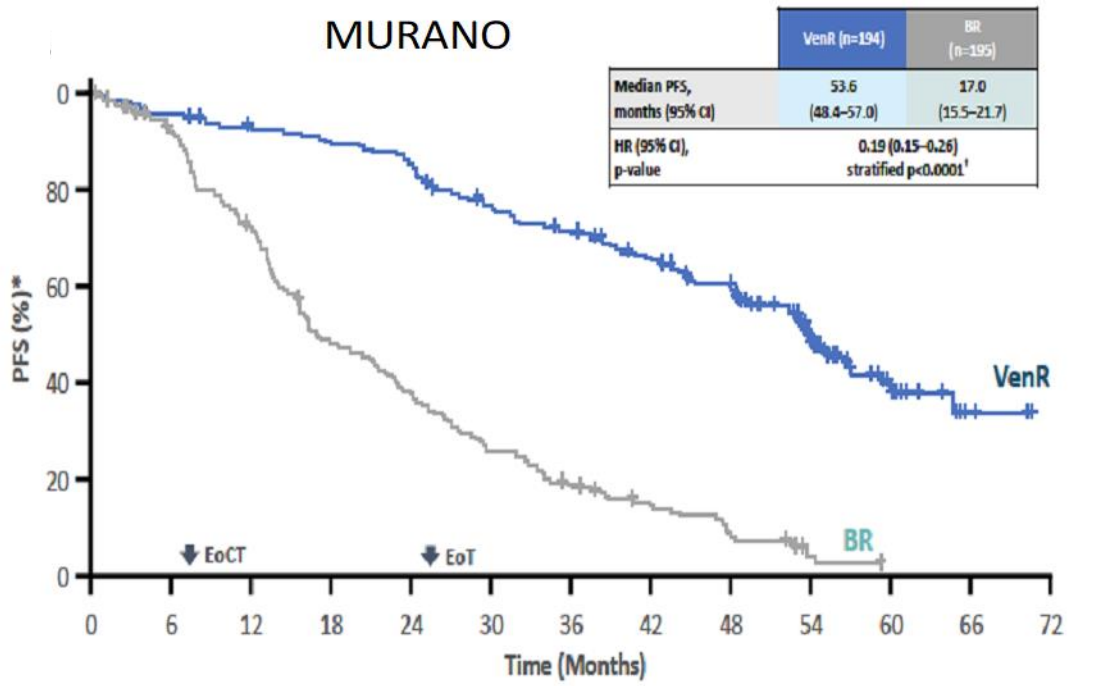
Seymour. NEJM. 2018;378:1107. NCT02005471.

Venetoclax : Factors to consider

Advantages



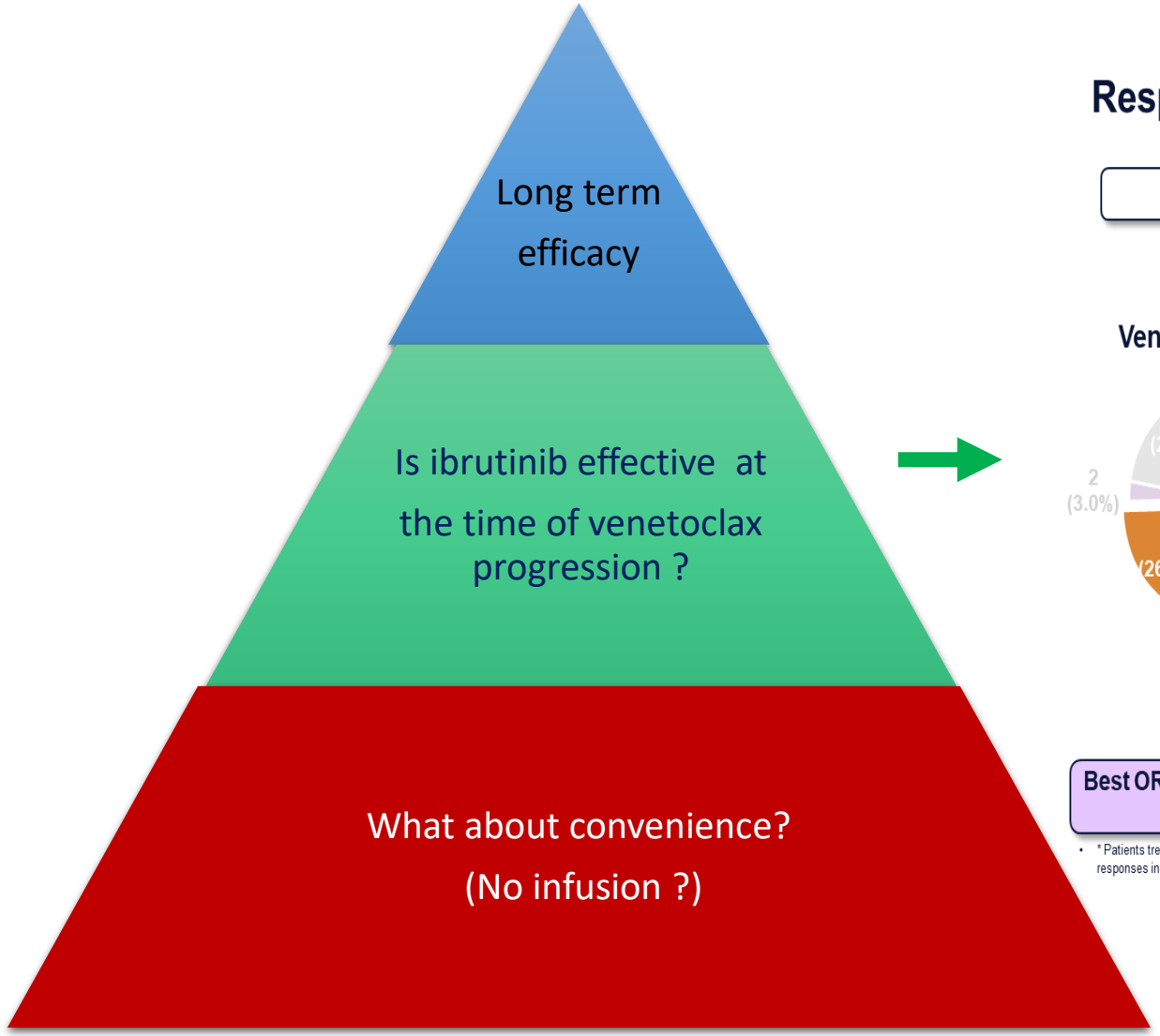
PFS - 5-year Follow up



At the 5-year analysis (median follow-up 59 months), the risk of progression or death was decreased by 81% with VenR vs BR

Kater et al. ASH 2020

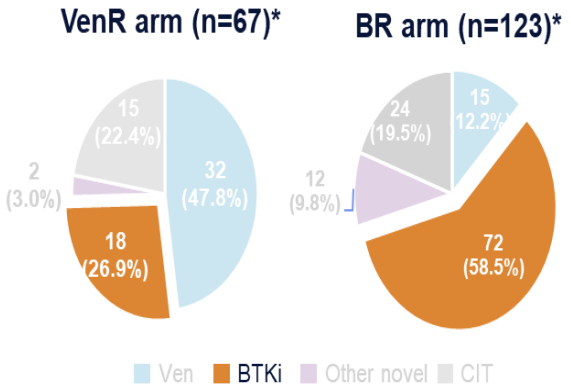
Venetoclax : Factors to consider



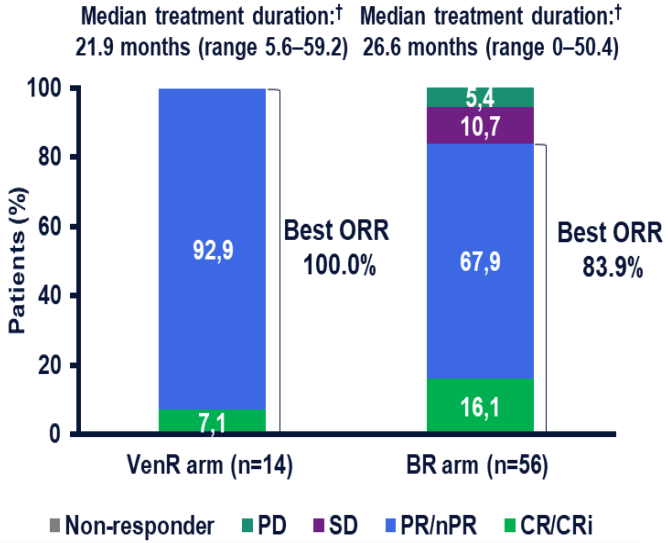
MURANO Study

Response Rates to Subsequent BTKi-Based Therapy Were High

Subsequent Therapy



Best ORR to Subsequent BTKi-Based Therapy†

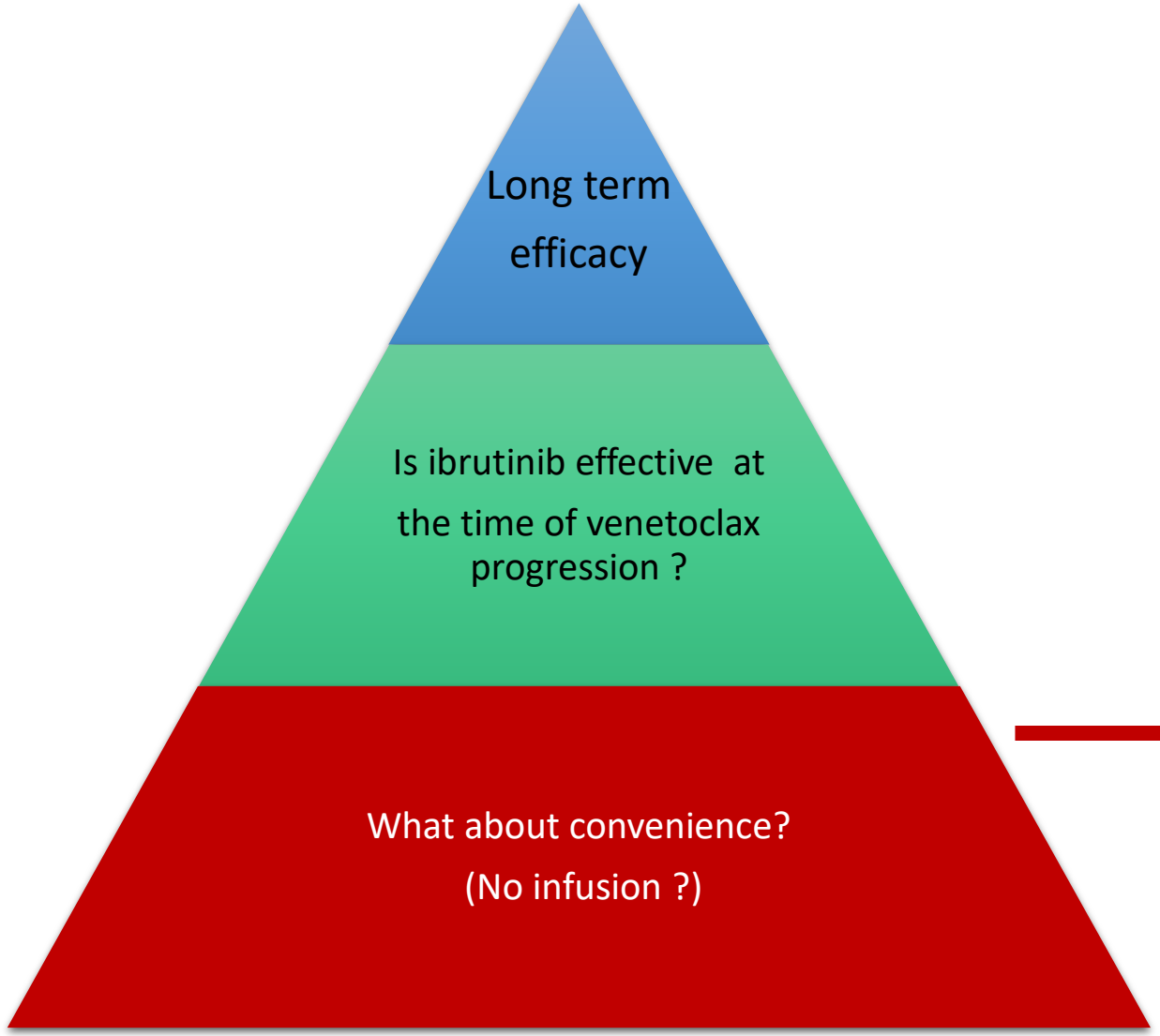


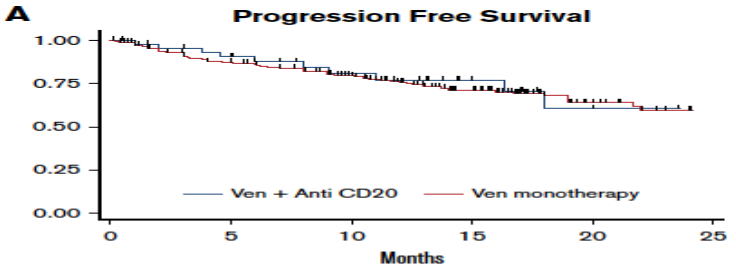
Best ORR to BTKi-based regimen as next therapy after PD was 100.0% and 83.9% in patients previously treated with VenR or BR, respectively

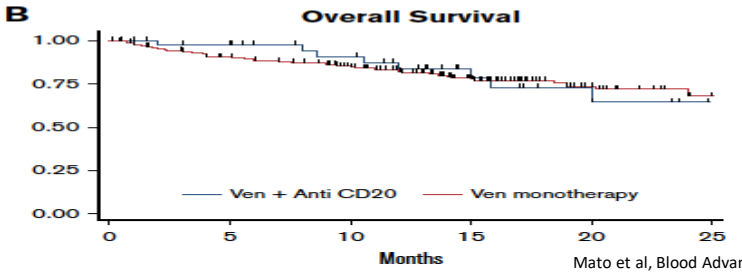
- * Patients treated; † Calculated among patients with evaluable responses (i.e. reported by the investigators prior to discontinuation/initiation of subsequent line of therapy; responses in patients who were treated for insufficient time to have their response assessed, or those who had no response assessments, were considered unevaluable).

- Harrup RA, *et al.* ASH 2020; Poster 3139.

Venetoclax : Factors to consider

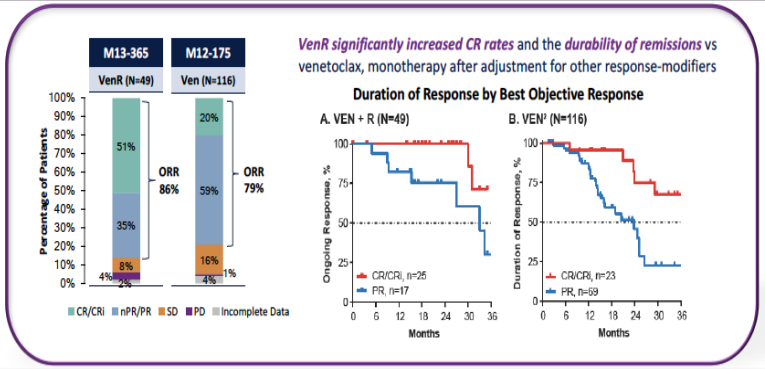






Mato et al, Blood Advances 2019

Indirect cross-study comparison[3]



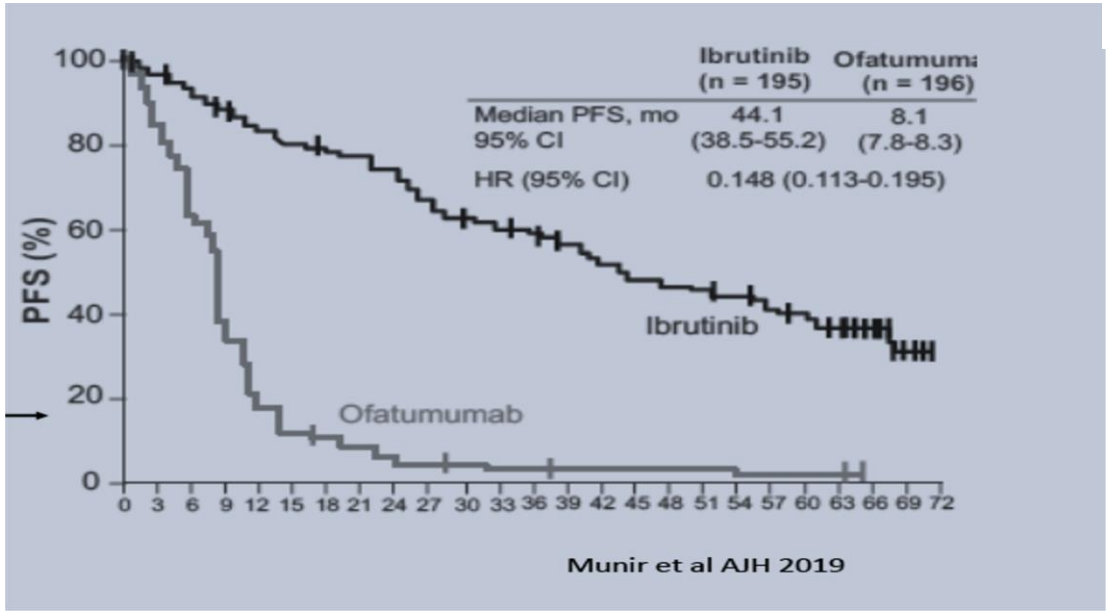
Currently, there are no direct comparative clinical data for combination vs monotherapy. However, the VenR efficacy results from MURANO give strong rationale for VenR and this level of efficacy (deep responses and PFS) has not been reported with venetoclax monotherapy.

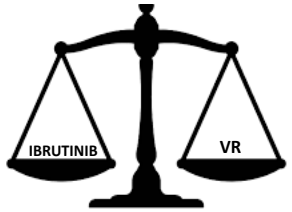
*si specifica che si fa riferimento ad una indicazione terapeutica approvata da EMA in data 29/10/2018. Tale indicazione non è ancora rimborsata dal Servizio Sanitario Nazionale

Roberts AW, et al. Poster #P209. 21st EHA Annual Meeting; June 9-12, 2016; Copenhagen, Denmark.

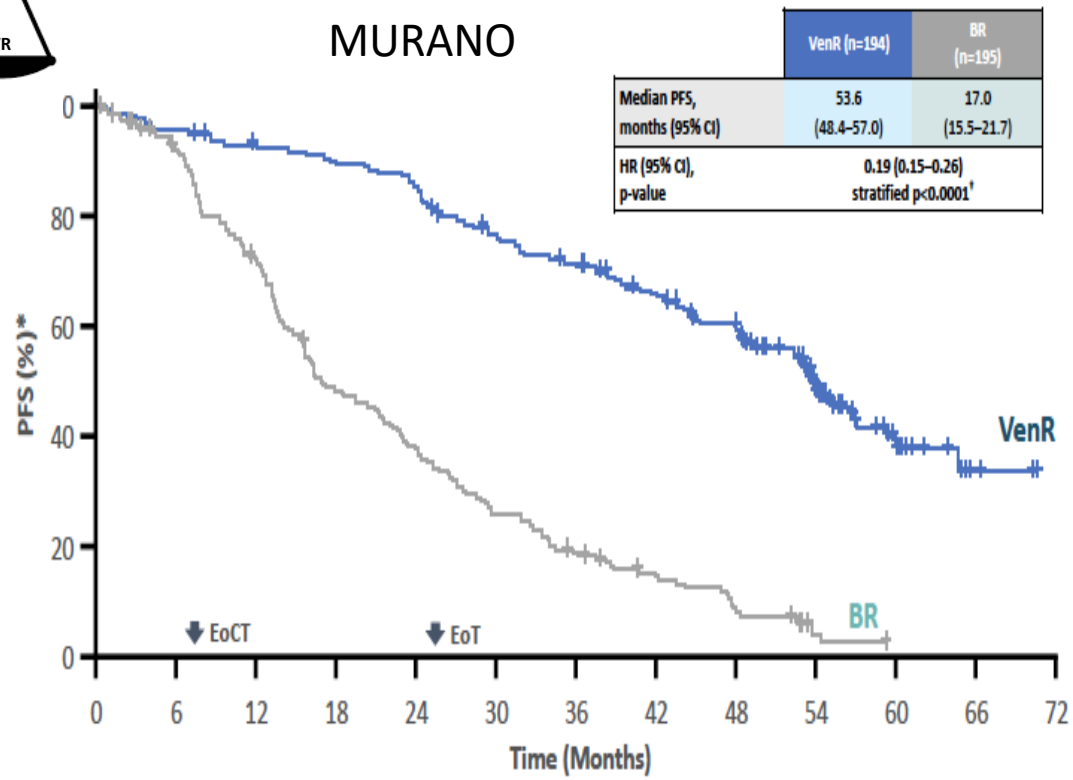
PFS of R/R CLL pts treated with Ibrutinib
(RESONATE-6 year FU or VR MURANO – 5 Year FU)

RESONATE





MURANO



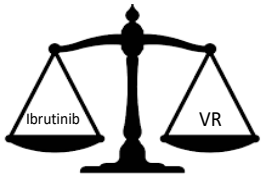
At the 6-year analysis (median follow-up 65.3 months), the risk of progression or death was decreased by 85% with Ibrutinib vs Ofatumumab

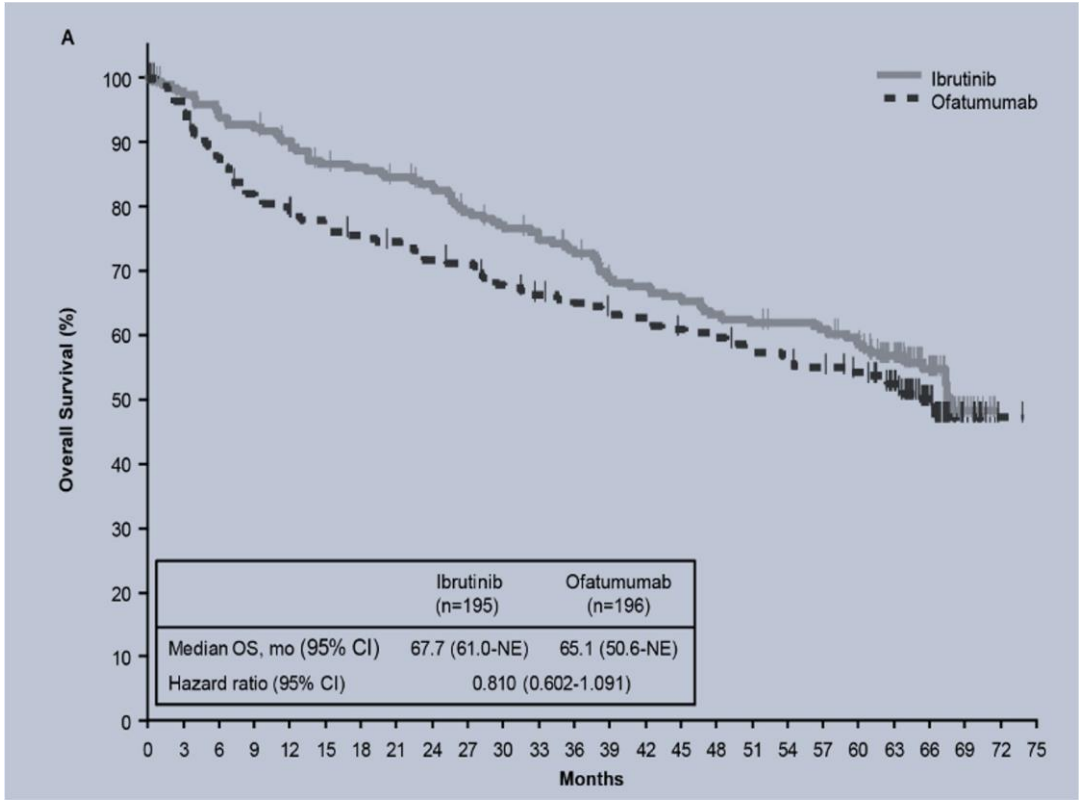
Munir et al AJH 2019

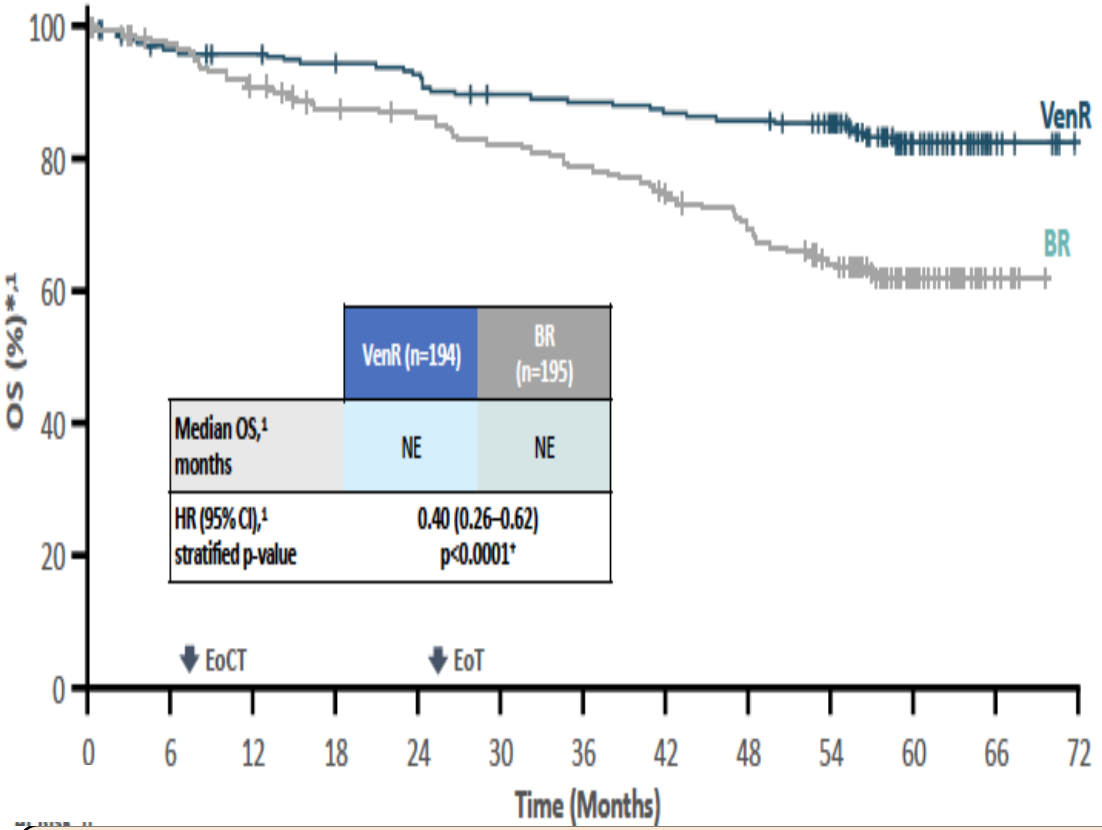
At the 5-year analysis (median follow-up 59 months), the risk of progression or death was decreased by 81% with VenR vs BR

Kater et al. ASH 2020

OS of R/R CLL pts treated with Ibrutinib
(RESONATE-6 year FU or VR (MURANO – 5 Year FU)







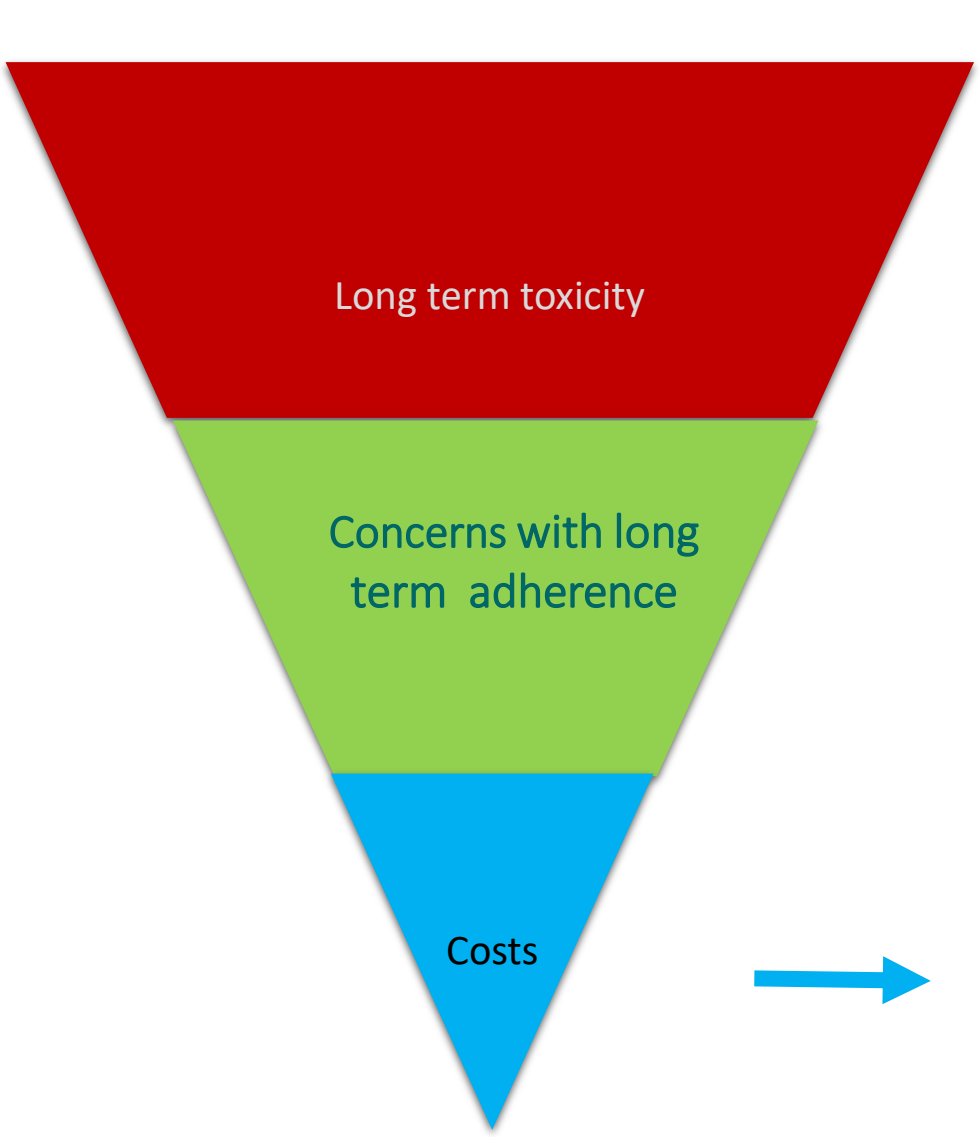
At the 6-year analysis (median follow-up 65.3 months), the risk of progression or death was decreased by 19% with Ibrutinib vs Ofatumumab

At the 5-year analysis, the risk of death was decreased by 60% with VenR vs BR,[1] despite a high proportion of patients with PD in the BR arm receiving novel targeted agents as their first follow-up therapy (99/123; 80.5%)[2]

Munir et al AJH 2019

Kater et al. ASH 2020

Comparison between costs of ibrutinib and veneteoclax treatment



Disadvantages

€ 166.057,6

Venetoclax

€ 6.919 /mo. x 24

(months of therapy) +

€ 1.600 (ramp up)

€ 266.904

Ibrutinib

€ 6.066,1/mo. x 44

(median PFS in months of RESONATE with a median follow-up of 65 mo.)

Time-Limited versus continuous therapy in R/R CLL Patients

- Long-term efficacy (FU, @ 5 years)
- No cardiac or bleeding risks
- Less concern with adherence.
- Potential for cost-saving

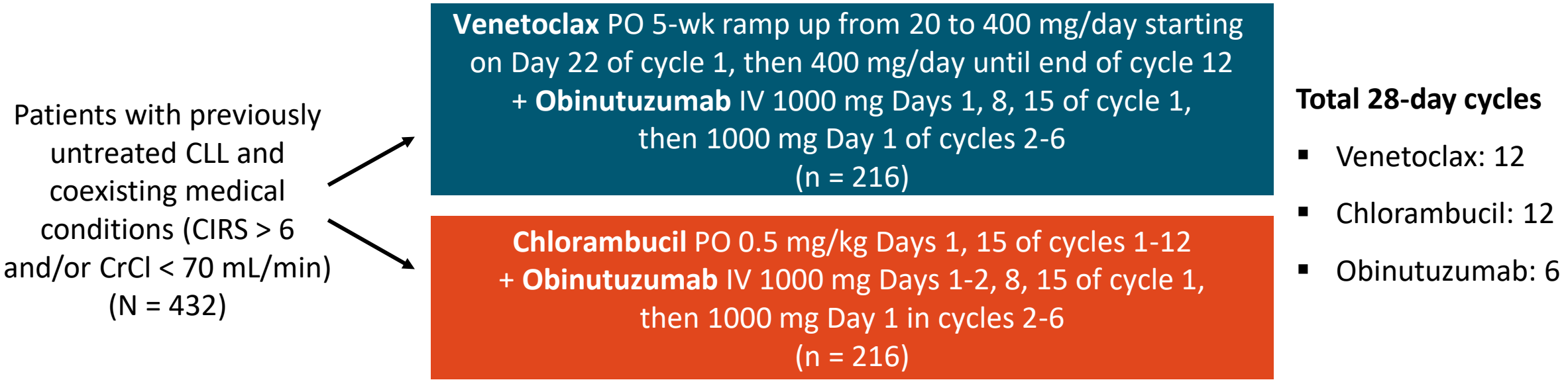
Time limited

Continuous

- Long-term efficacy (FU, @ 6 years)
- No infusions, TLS monitoring.
- More data on efficacy of ven after ibrutinib

CLL14: First-line Obinutuzumab + Venetoclax or Chlorambucil in CLL

- Open-label, multicenter, randomized phase III trial

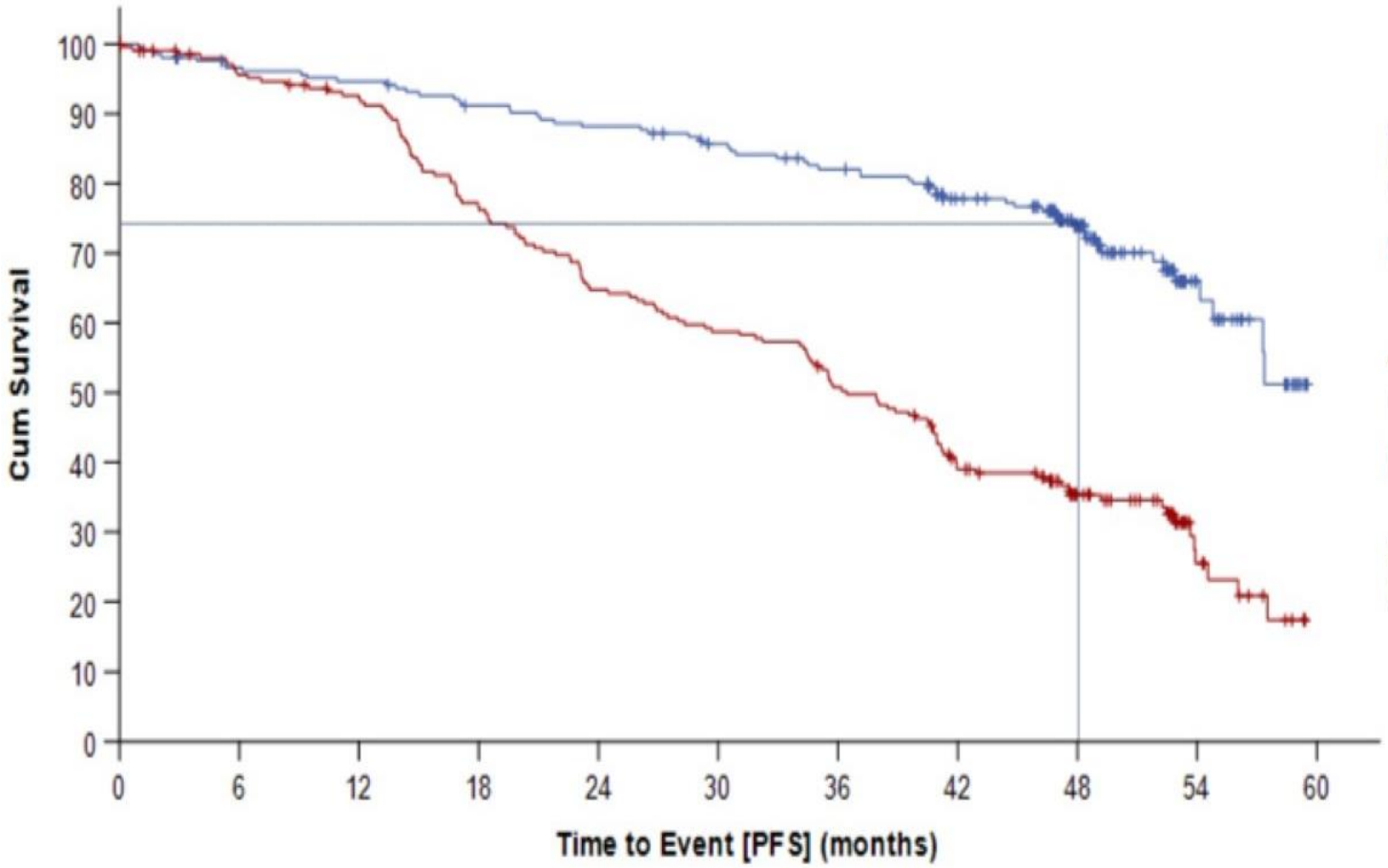


- Primary endpoint: investigator-assessed PFS
- Secondary endpoints: IRC-assessed PFS, ORR, MRD negativity, OS, safety

Fischer. ASCO 2019. Abstr 7502. Fischer. NEJM. 2019;380:2225. Al-Sawaf. Lancet Oncol. 2020;21:1188. NCT02242942.

CLL14: Progression-Free Survival (4 Year Follow-up)

Median observation time 52.4 months



Median PFS

Ven-Obi: not reached

Clb-Obi: 36.4 months

4-year PFS rate

Ven-Obi: 74.0%

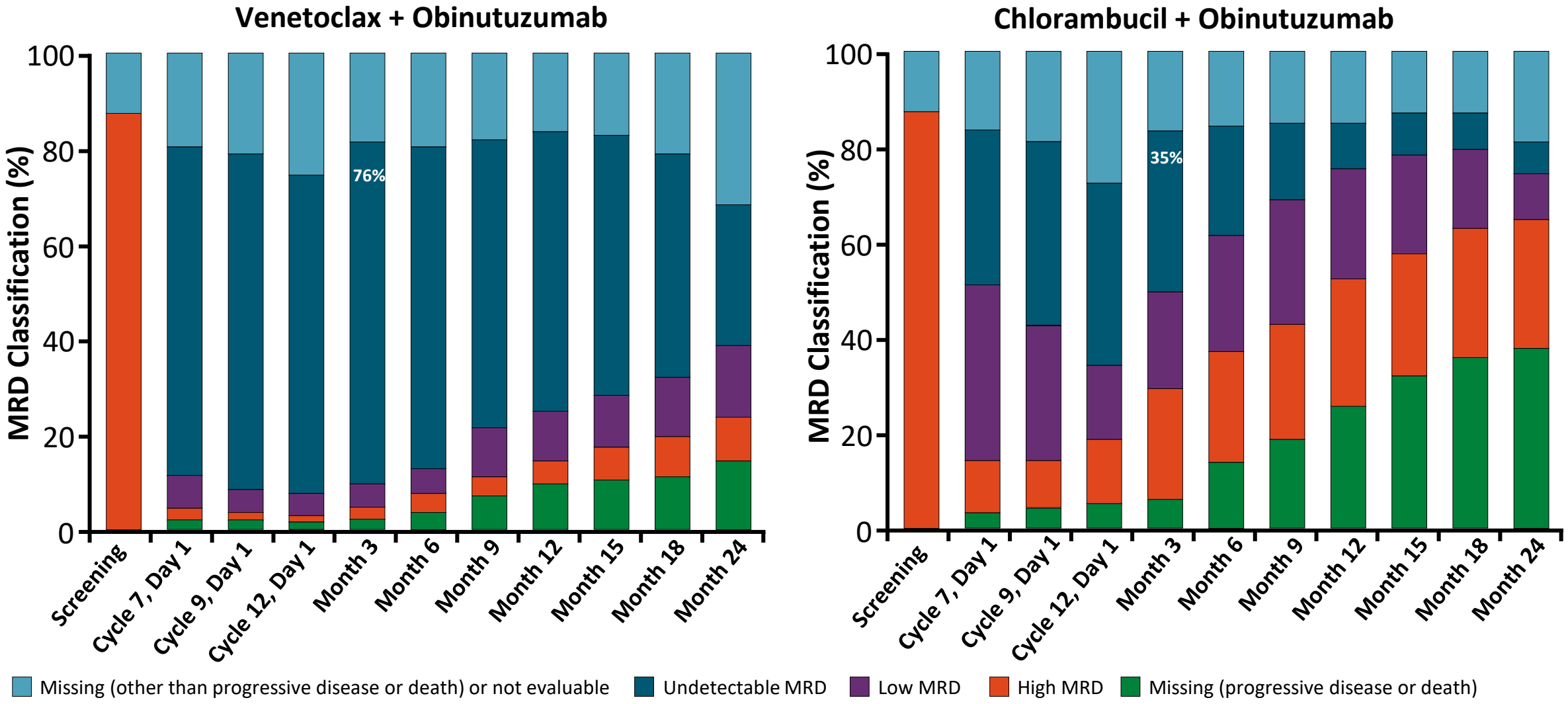
Clb-Obi: 35.4%

HR 0.33, 95% CI [0.25-0.45]

P<0.0001

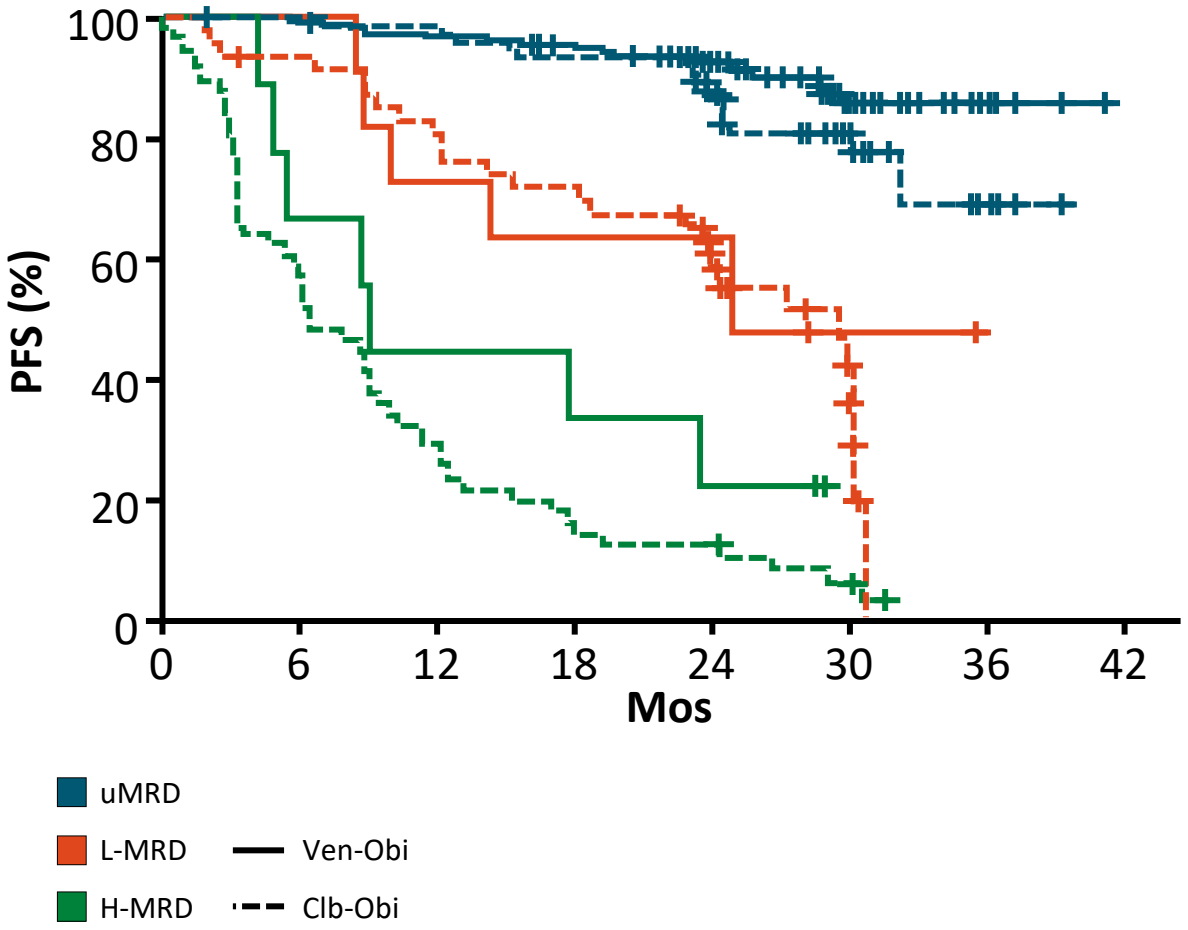
Al-Sawaf O et al. . ASH Annual meeting 2020

CLL14: MRD Negativity



Al-Sawaf. Lancet Oncol. 2020;21:1188.

CLL14: Landmark Analysis for PFS by MRD Status



- Should venetoclax + obinutuzumab be continued after 12 mos in certain subsets?
  - TP53 deleted/mutated
  - Detectable MRD

  or
- Should MRD be monitored after discontinuation and venetoclax resumed at re-emergence of MRD?

Al-Sawaf. Lancet Oncol. 2020;21:1188.

CLL14: Safety

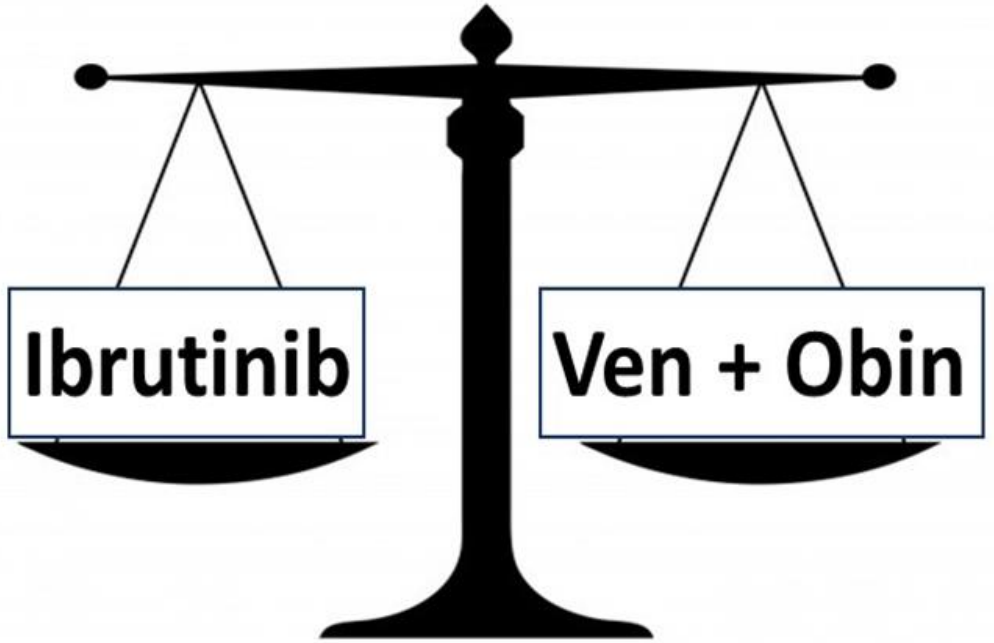
Grade 3/4 AE During Treatment, %	Venetoclax + Obinutuzumab (n = 212)	Chlorambucil + Obinutuzumab (n = 214)
Hematologic AEs	59	55
▪ Neutropenia	52	47
▪ Thrombocytopenia	14	15
▪ Anemia	8	6
▪ Febrile neutropenia	4	3
Injury, poisoning, procedural complications	11	12
▪ Infusion-related reaction	9	10
Infections and infestations	12	12
▪ Pneumonia	3	3
Metabolism, nutrition disorders*	10	8

*P = .02

Grade 5 AE, n (%)	Venetoclax + Obinutuzumab (n = 212)	Chlorambucil + Obinutuzumab (n = 214)
Total events	19 (9)	11 (5)
Events during therapy	4 (2)	5 (2)
▪ Infections and infestations	3 (1)	3 (1)
▪ Neoplasms	1 (< 1)	2 (< 1)
Events after therapy completion	16 (8)	6 (3)
▪ Cardiac disorders	3 (1)	1 (< 1)
▪ Infections and infestations	7 (3)	1 (< 1)
▪ Neoplasms	2 (< 1)	3 (1)
▪ Other reasons	2 (< 1)	1 (< 1)

Fischer. ASCO 2019. Abstr 7502. Fischer. NEJM. 2019;380:2225. Al-Sawaf. Lancet Oncol. 2020;21:1188.

Time-Limited versus continuous therapy in naïve CLL Patients



- Long term efficacy data
- Convenience (No infusions, TLS monitoring)
- Phase 3 data compared to FCR and BR
- More data for efficacy of Ven at time of Ibrutinib progression

- Potential for-1-year time limited therapy
- Non known cardiac or bleeding risks
- Less concern for longterm adherence
- Potential for cost-savings if 1-year of therapy is durable

Long term follow-up: progression while on treatment

Patients disposition

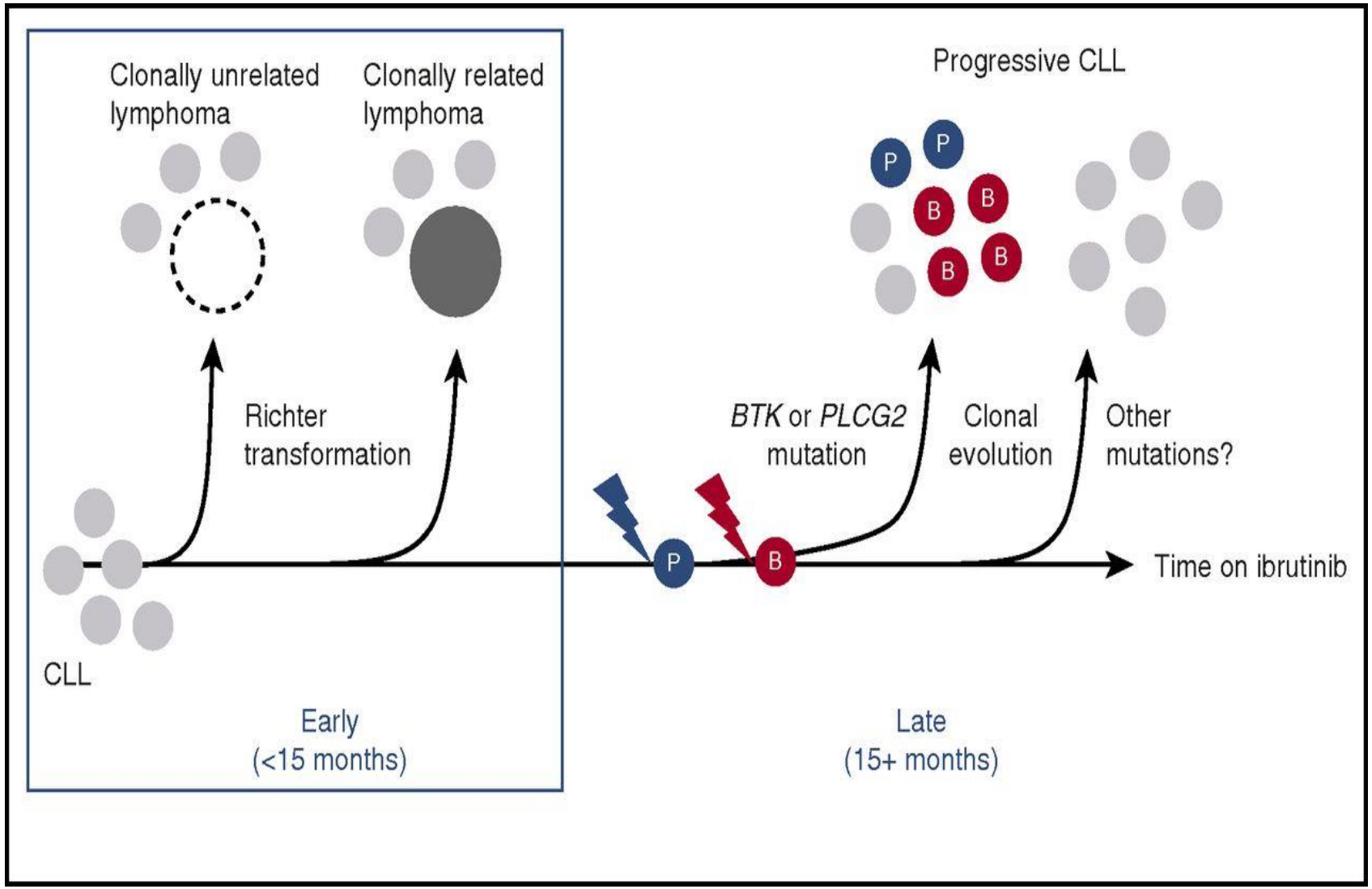
	Treatment Naïve			Relapse/Refractory	
	Resonate-2[a] Ib N=136	Illuminate[b] Ib Obi N= 113	ECOG[c] IR N=354	PCYC-1102[d] N=101	Resonate[e] N=195
Median duration of ibrutinib tx	57.1 m	40.7 m	43 m	82 m	41 m
Patients remaining on ibrutinib tx	79 (58%)	68 (60%)	73%	16 (16%)	0 (study closed)
Primary Reasons for discontinuation					
Progressive Disease while on tx	8 (6%)	7%*	23 (7%)	38 (38%)	72 (36.9%)
Adverse Event	29 (21%)	25 (22%)	48 (14%)	23 (23%)	32 (16.4%)
Consent withdrawal	7 (5%)	6 (5%)		8 (8%)	15 (7.7%)
Investigator Decision	4 (3%)	3 (3%)		15 (15%)	20 (10.3%)
Lost Follow-up/Other	-	3 (3%)	Others reasons 7%	1 (1%)	43 (22.1%)^
Death	8 (6%)	n*		-	13 (6.7%)

*PD plus Death: 7%

^ study terminated by sponsor

[a]*Burger et al., 2019*
[b]*Moreno et al., 2019*
[c] *Shanafelt et al., 2019*
[a]*Byrd et al., 2020*
[d]*Munir et al., 2019*

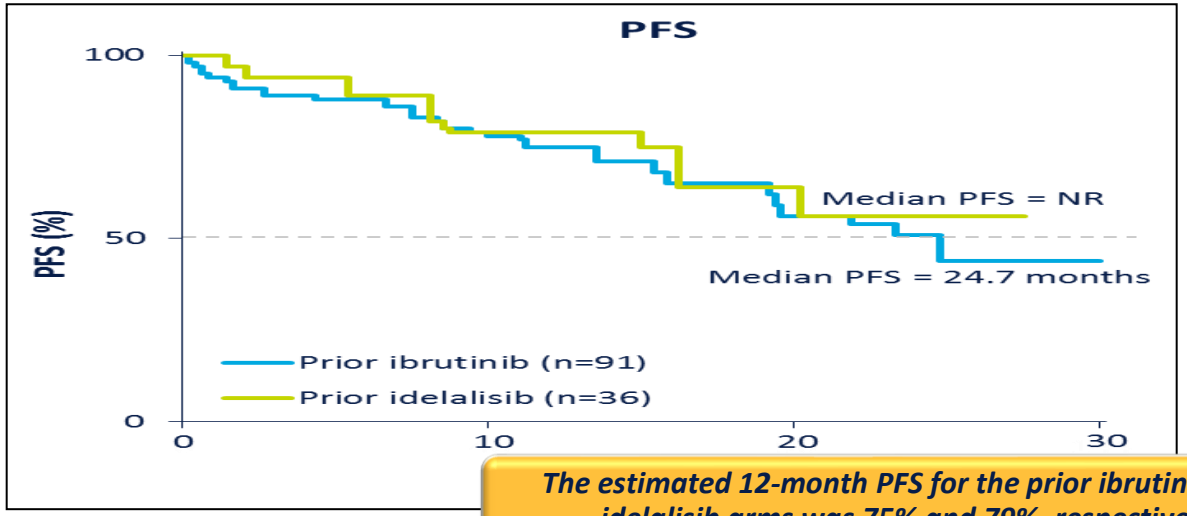
Ibrutinib-resistant CLL: unwanted and unwonted!



Mertens D, Stilgenbauer S Blood 2017

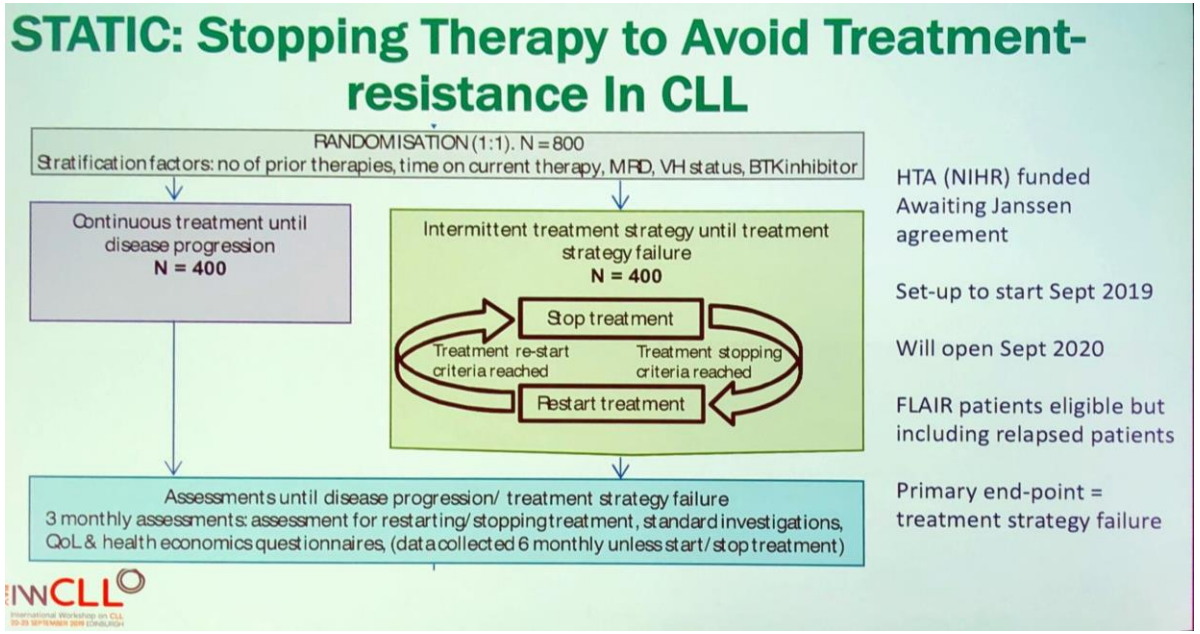
How can we overcome resistance to BTKi ?

- **Venetoclax**
- XP01 inhibitors
- BRD4 inhibitors
- ROR1 targeting agents
- CAR-T cells
- **Prevention ?**

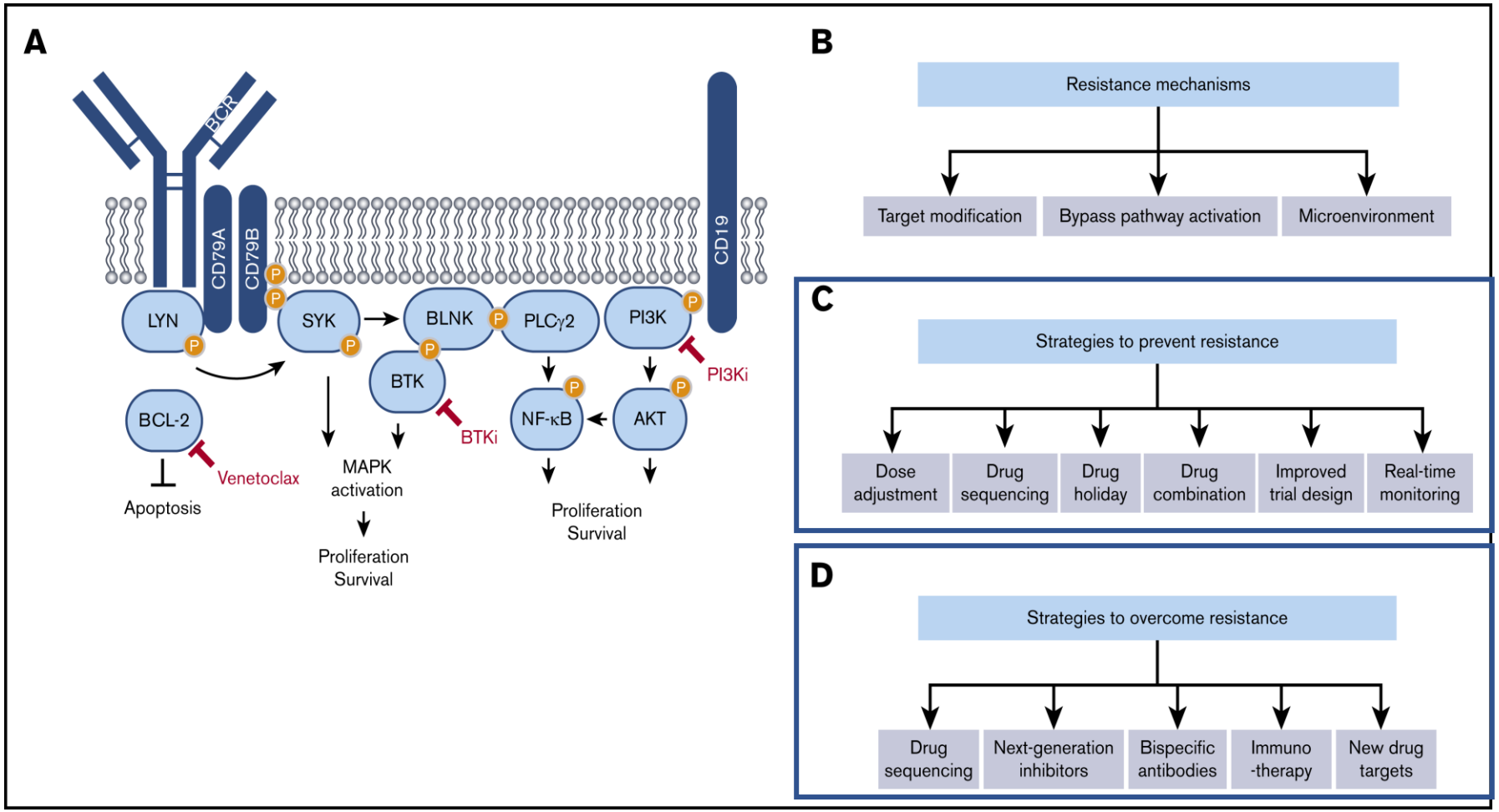


The estimated 12-month PFS for the prior ibrutinib and idelalisib arms was 75% and 79%, respectively

1. Jones JA, et al. Lancet Oncol. 2017 Dec 12. doi: 10.1016/S1470-2045(17)30909-9
2. Coutre S, et al. Blood. 2018 Jan 5. doi: 10.1182/blood-2017-06-788133



Overcoming resistance to targeted therapies in CLL



Skånland SS, Mato AR Blood Adv, 2021

My Key take-aways

- Novel agents have eclipsed chemoimmunotherapy as initial treatment for CLL in the vast majority of patients
- Safety profile of Venetoclax looks favorable and distinct from ibrutinib
- Rates of uMRD are promising, which in the R/R setting is associated with durability of response to venetoclax
- Ven+Obinutuzumab as a time-limited regimen and is an immediately practice-changing combination for frontline CLL treatment