FORUM IN EMATOLOGIA VERSO IL 2020

Bari, Villa Romanazzi-Carducci, 21-22 ottobre 2019

Una terapia chemo-free: quando e a chi?

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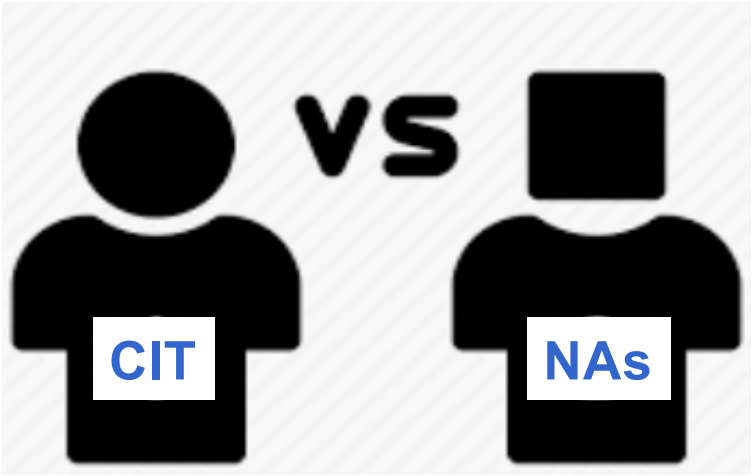
Una terapia chemo-free: quando e a chi?



Chemoimmunotherapy

Novel agents

TN patients

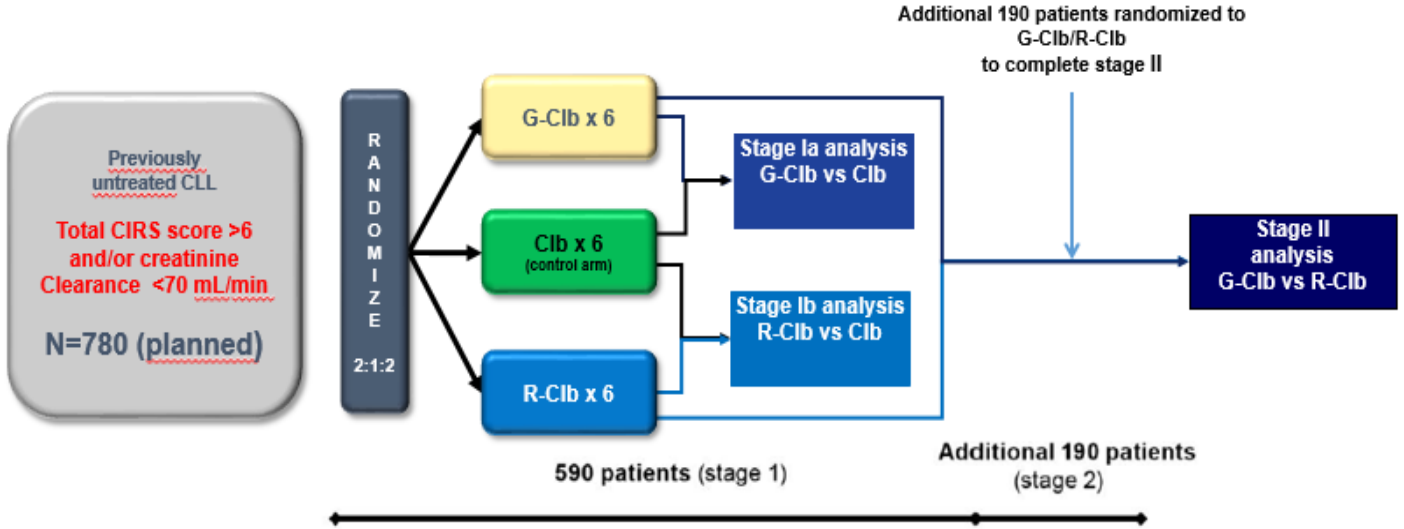
R/R patients

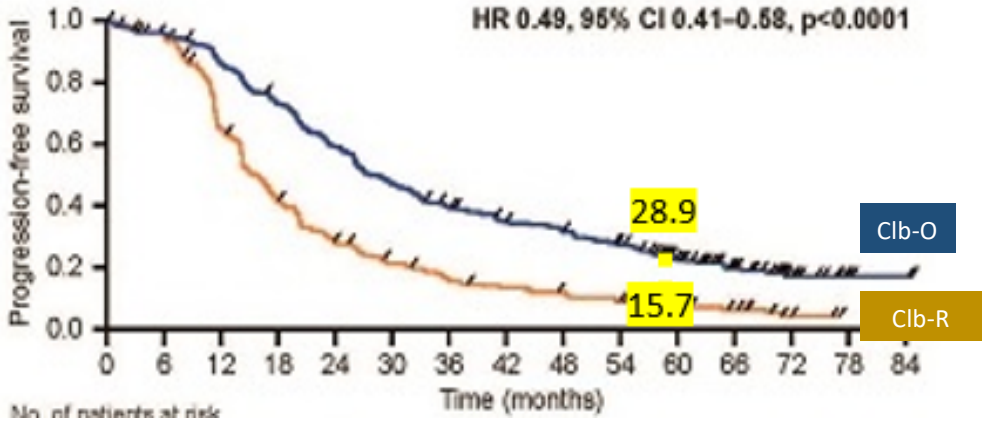
*TP*53 disrupted patients

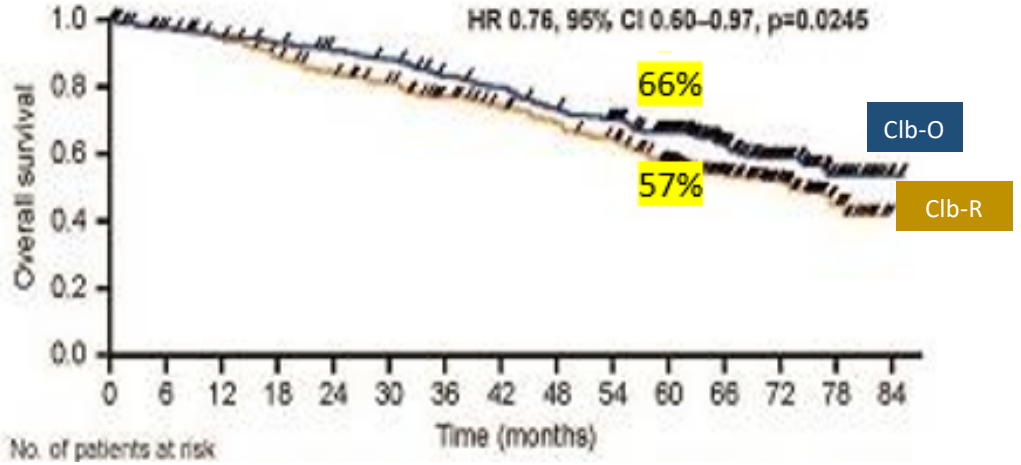
Front-line therapy: CIT vs NAs

	CIT	NAs
ELDERLY/UNFIT	CHLORAMBUCIL+ OBINUTUZUMAB	IBRUTINIB (RESONATE-2) IBRUTINIB+OBINUTUZUMAB (ILLUMINATE TRIAL) VENETOCLAX+OBINUTUZUMAB (CLL14)
OLDER/FIT	BENDAMUSTINE+ RITUXIMAB	IBRUTINIB/IBRUTINIB+RITUXIMAB
YOUNGER/FIT	FCR	IBRUTINIB

CLL11 Trial- CHL vs R-CHL vs GA101-CHL







Goede V, et al. EHA 2018

5-year update of the RESONATE-2 study: Ibrutinib vs CHL in older patients with CLL

PCYC-1115
N=269

Key eligibility criteria
- Previously untreated CLL/SLL requiring therapy
- Age ≥65 years
- For patients 65–69 years of age, comorbidity that may preclude FCR
- del(17p) excluded

Stratification factors
- ECOG PS status (0-1 vs 2)
- Rai stage (III-IV vs ≤II)

RANDOMIZE 1:1

Ibrutinib 420 mg once daily until disease progression (PD) or unacceptable toxicity
n=136

Chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) days 1 + 15 of 28-day cycle, up to 12 cycles
n=133

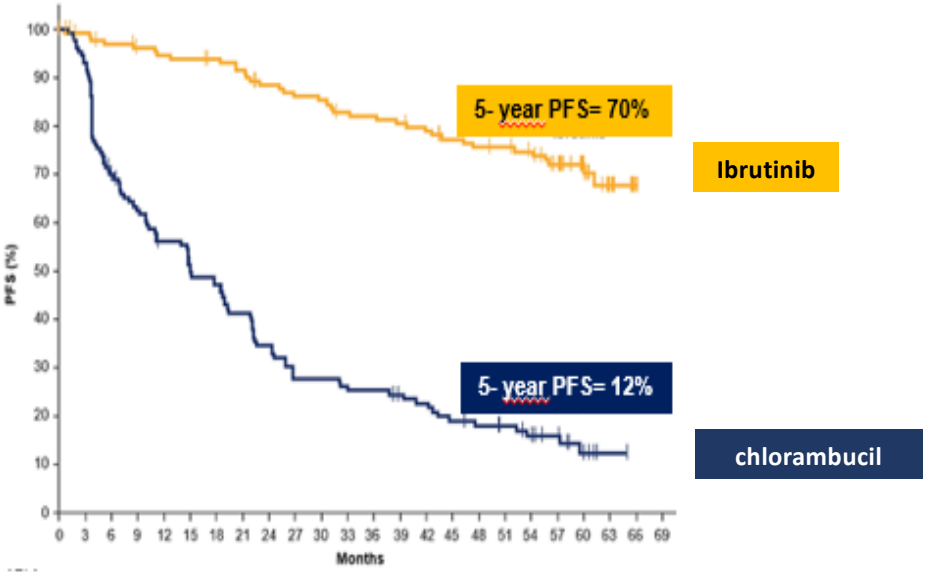
PCYC-1116 Extension Study

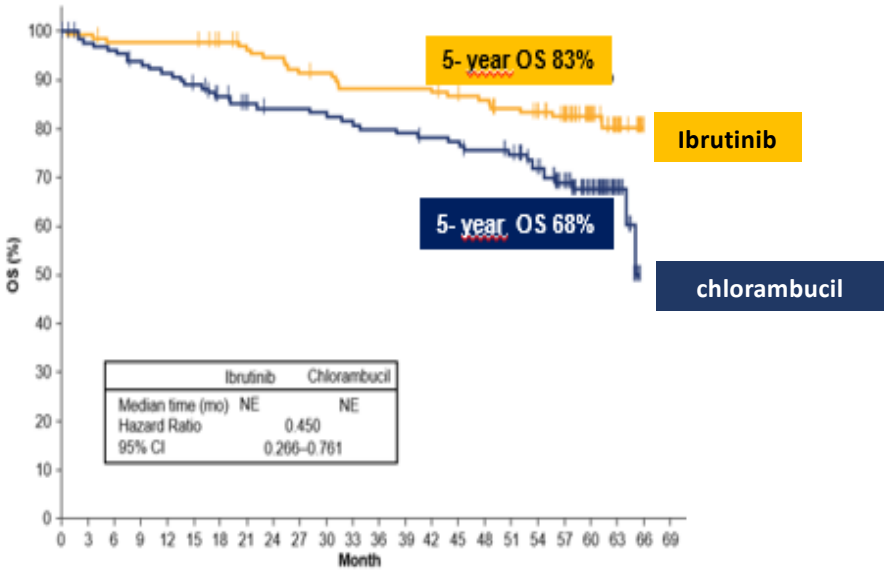
Patients could enroll in PCYC-1116 after IRC-confirmed PD or at PCYC-1115 closure

In chlorambucil arm, n=76 (57% of ITT population) crossed over to ibrutinib following PD

Primary end point
- PFS

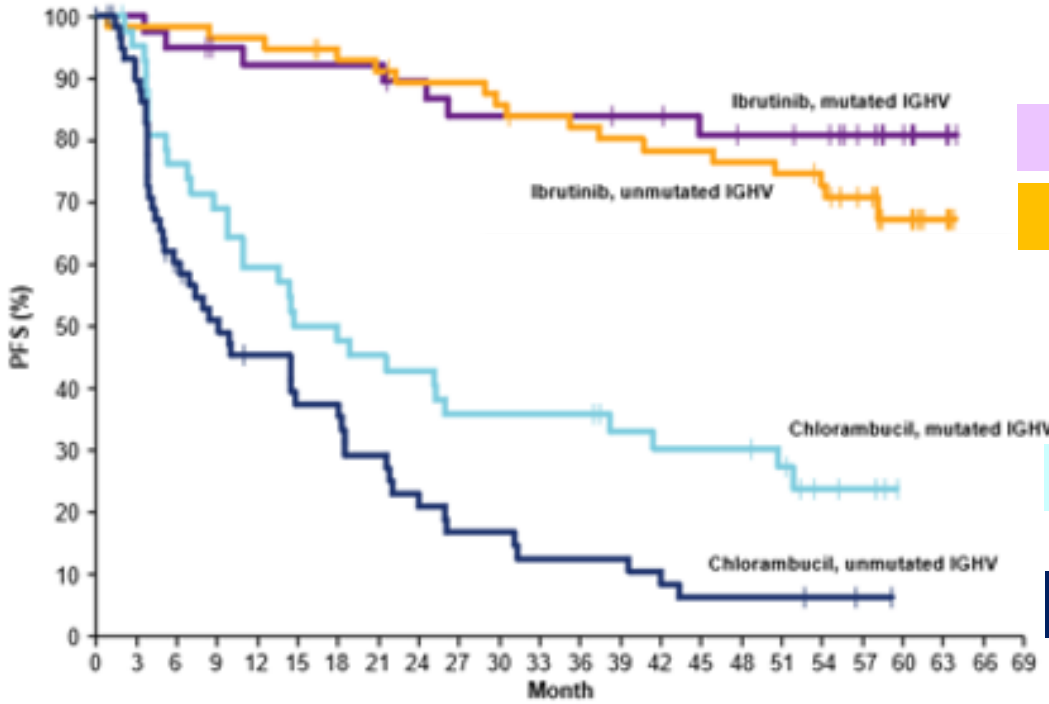
Secondary end points
- OS
- Overall response rate (ORR)
- Sustained hematologic improvement
- Safety





Tedeschi et al. EHA 2019

5-year update of the RESONATE-2 study: Ibrutinib vs CHL in older patients with CLL



Ibr-M 5 yrs PFS: 81%

Ibr-UM 5 yrs PFS: 67%

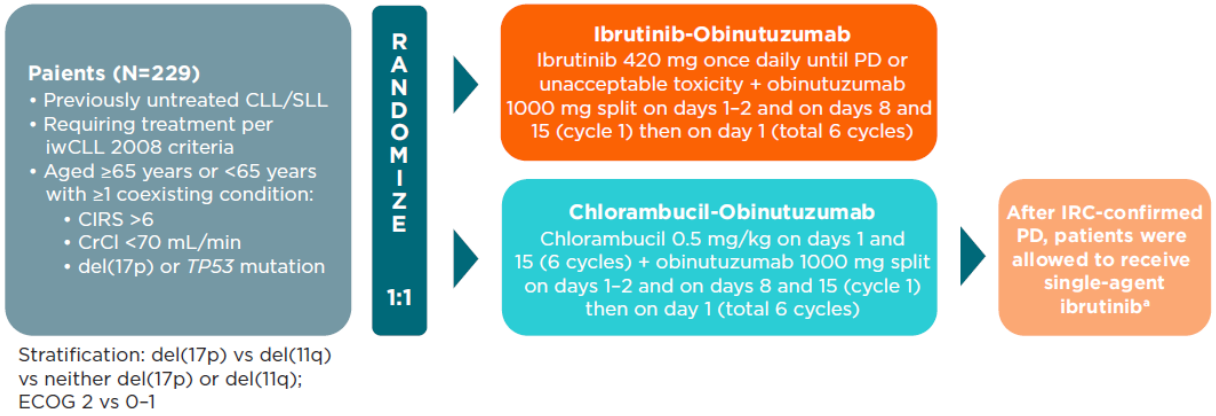
Clb-M 5 yrs PFS: 24%

Chl-UM 5 yrs PFS: 6%

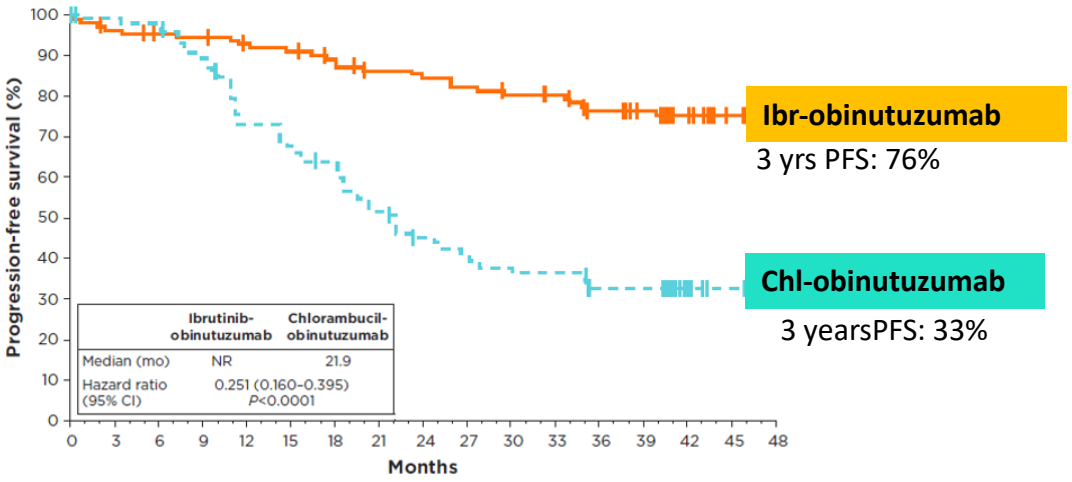
	Ibrutinib	
	Unmutated IGHV	Mutated IGHV
5 year PFS	67%	81%
Median PFS, mo	NE	NE
HR (95% CI)	0.632 (0.262–1.525)	

Tedeschi et al. EHA 2019

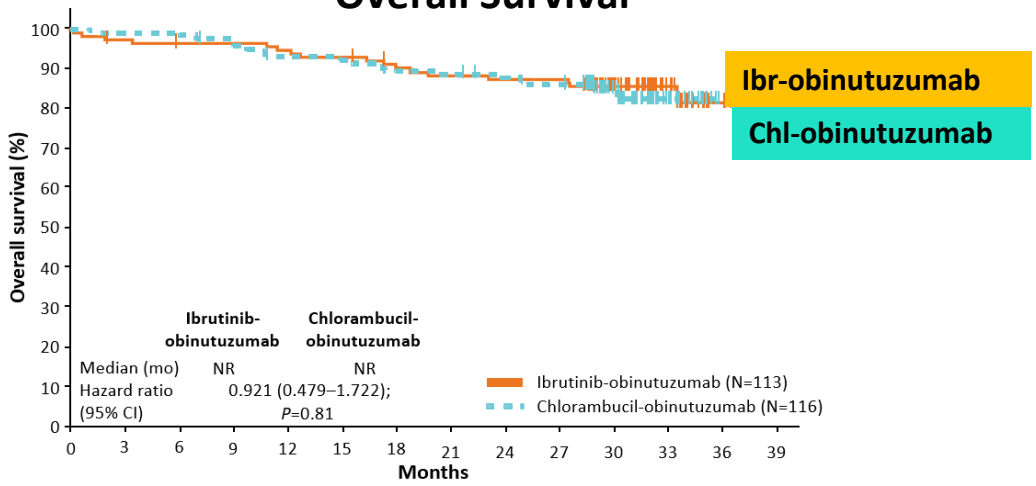
iLLUMINATE (PCYC-1130) TRIAL: Ibr+Obi vs Chl+Obi



Progression-free survival

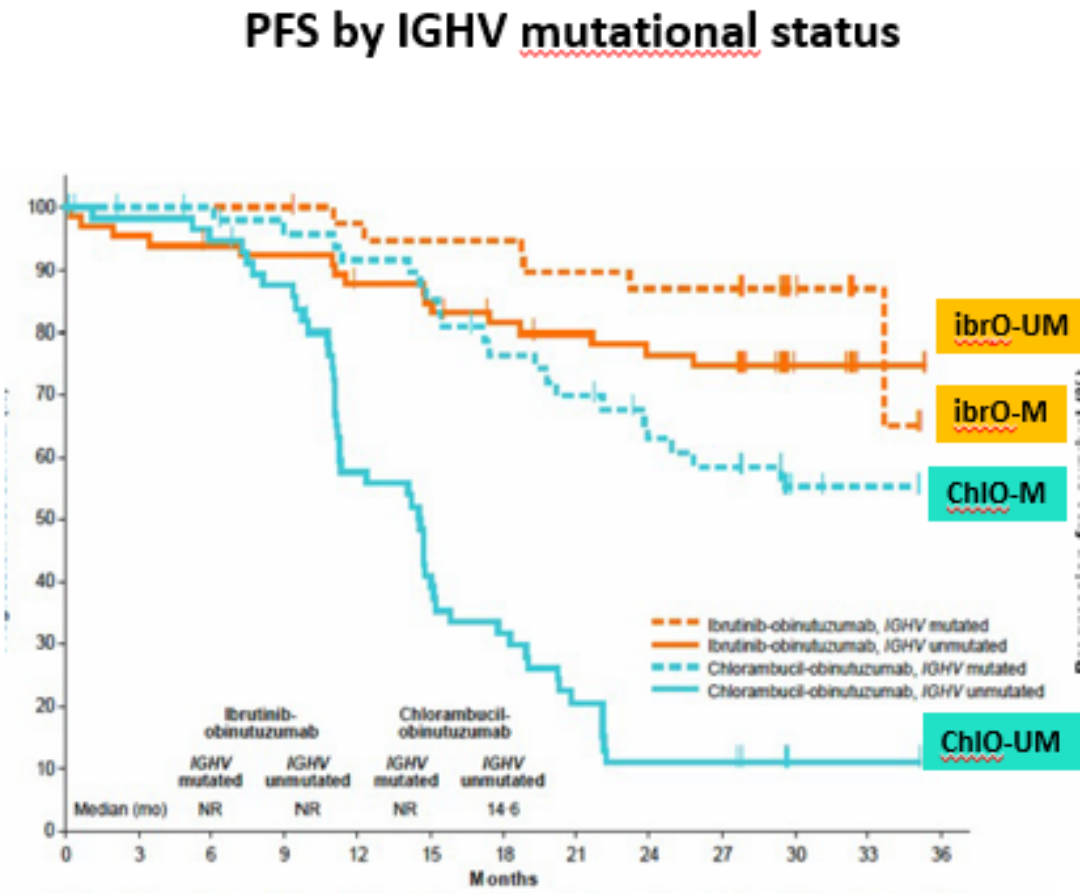


Overall Survival



Moreno et al. iWCLL 2019

iLLUMINATE (PCYC-1130) TRIAL: Ibr+Obi vs ChI+Obi



Moreno et al. iWCLL 2019;

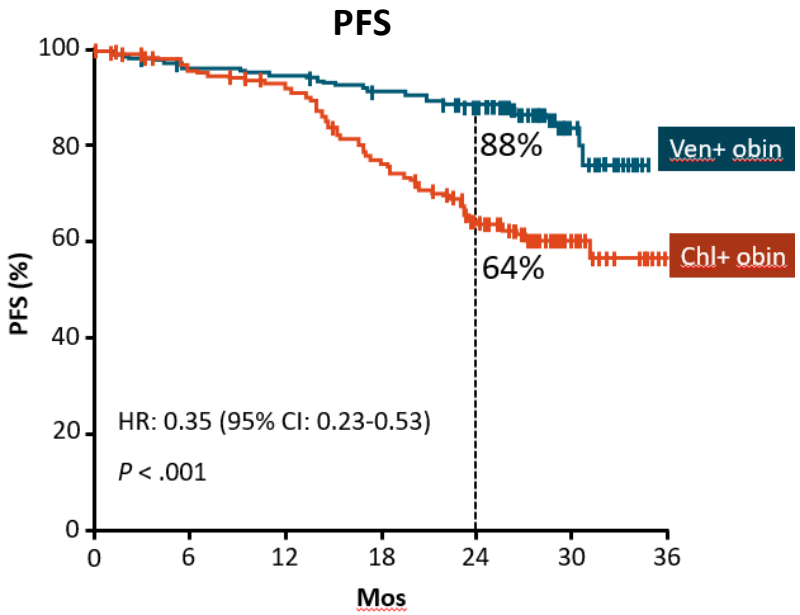
Obinutuzumab and Venetoclax vs Obinutuzumab and Chlorambucil in TN Patients With CLL and Coexisting Medical Conditions (CLL14 trial)

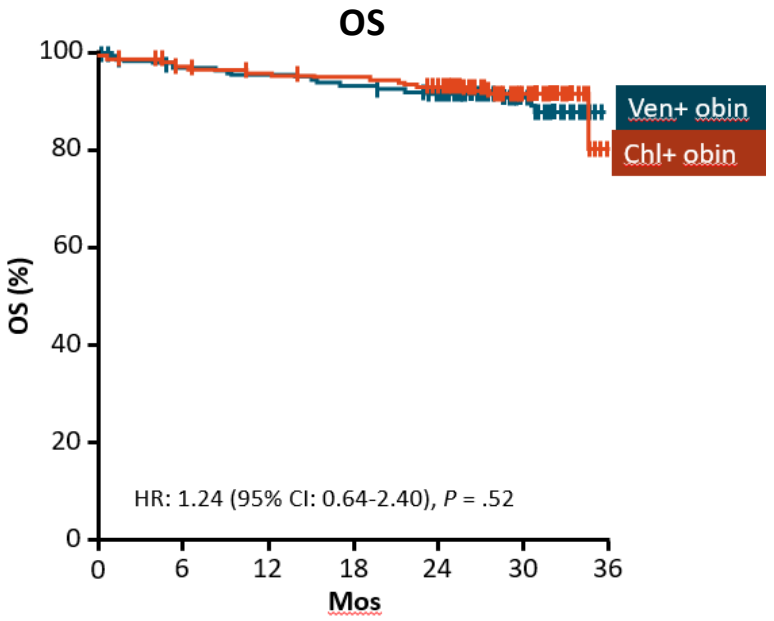
Patients with previously untreated CLL and coexisting medical conditions (CIRS > 6 and/or CrCl < 70 mL/min) (N = 432)

→ **Venetoclax** PO 5-wk ramp up from 20 to 400 mg/day starting on Day 22 of cycle 1, then 400 mg/day until end of cycle 12 **+ Obinutuzumab** IV 1000 mg Days 1, 8, 15 of cycle 1, then 1000 mg Day 1 of cycles 2-6 (n = 216)

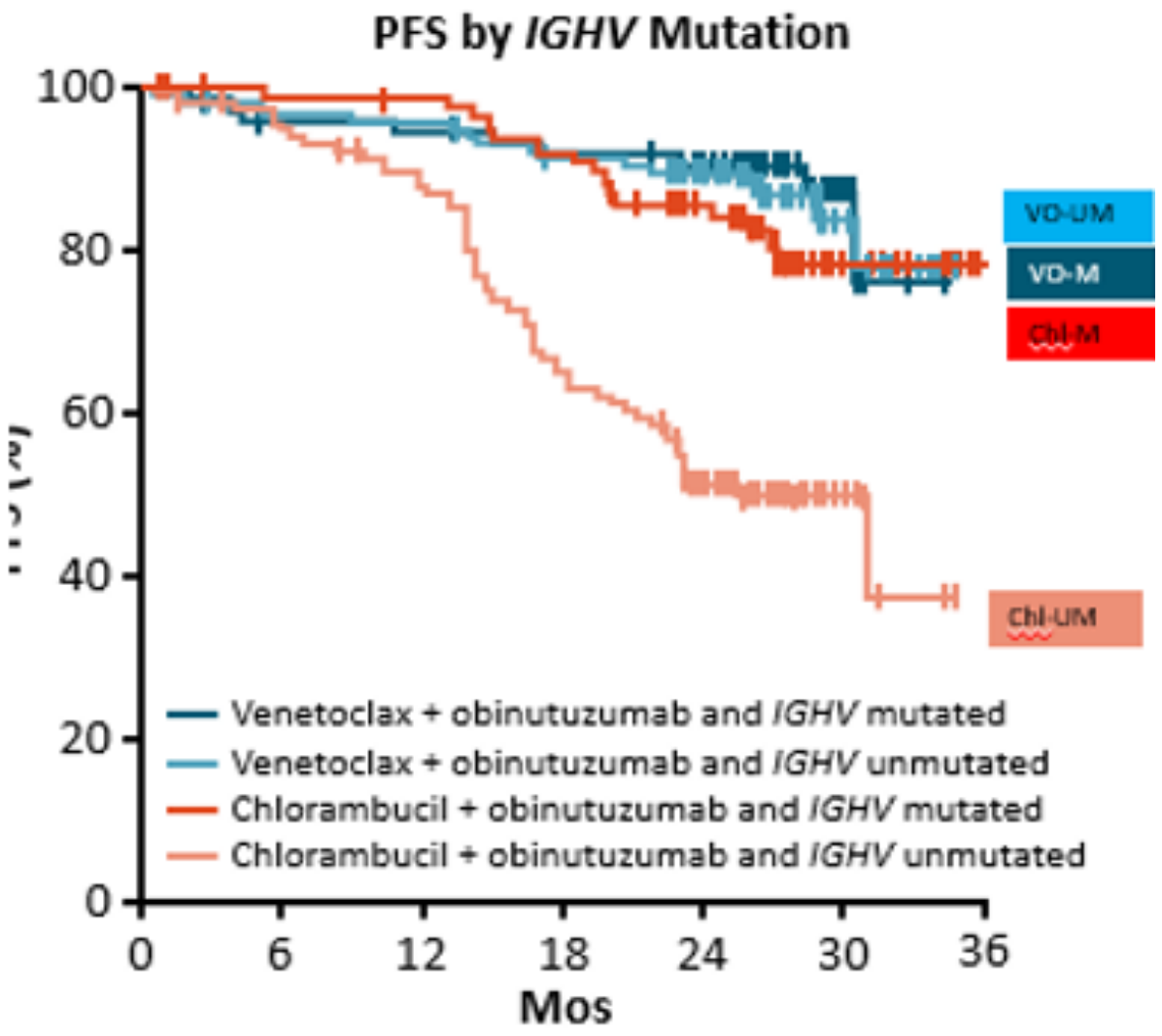
→ **Chlorambucil** PO 0.5 mg/kg Days 1, 15 of cycles 1-12 **+ Obinutuzumab** IV 1000 mg Days 1-2, 8, 15 of cycle 1, then 1000 mg Day 1 in cycles 2-6 (n = 216)

- Primary endpoint: investigator-assessed PFS



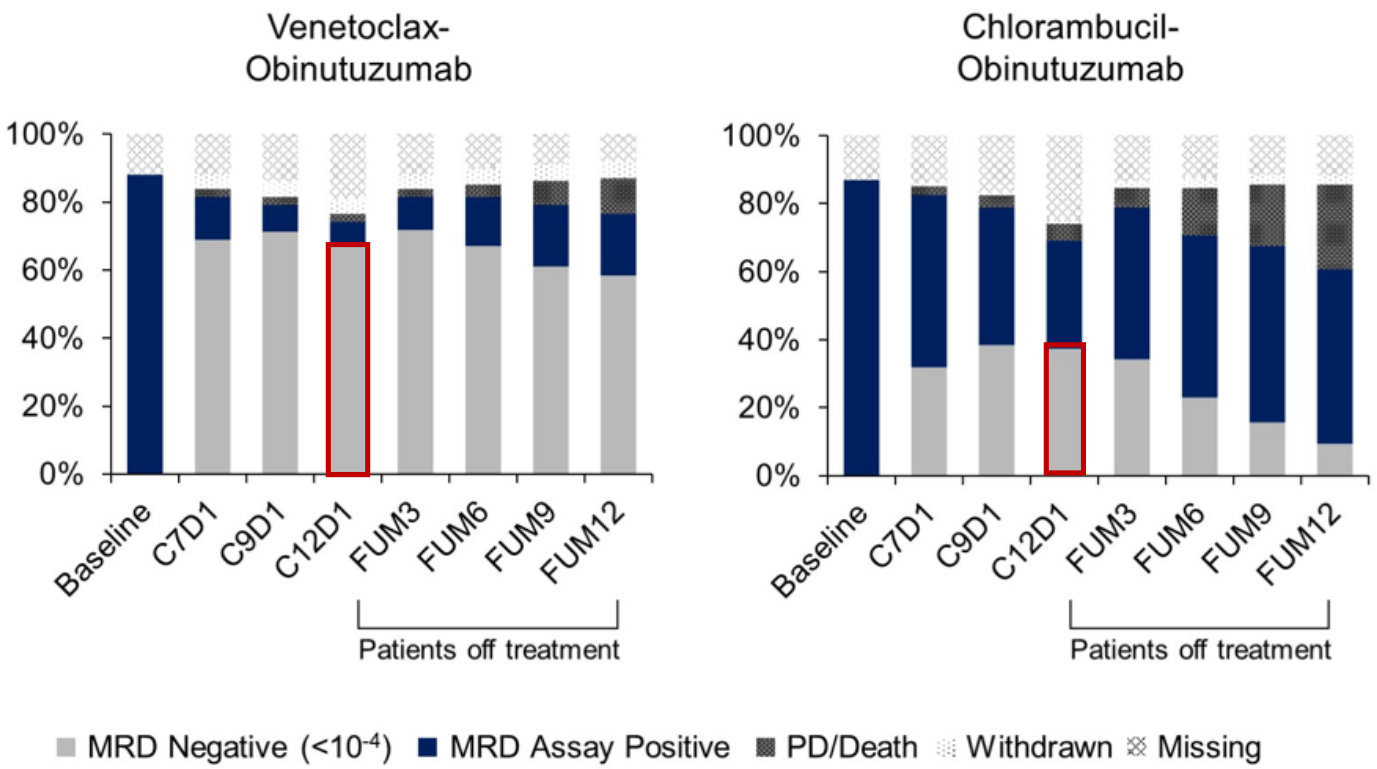


Fischer at 2019 ASCO & EHA Annual Meeting



Fischer at 2019 ASCO & EHA Annual Meeting

CLL 14 trial: MRD RATES



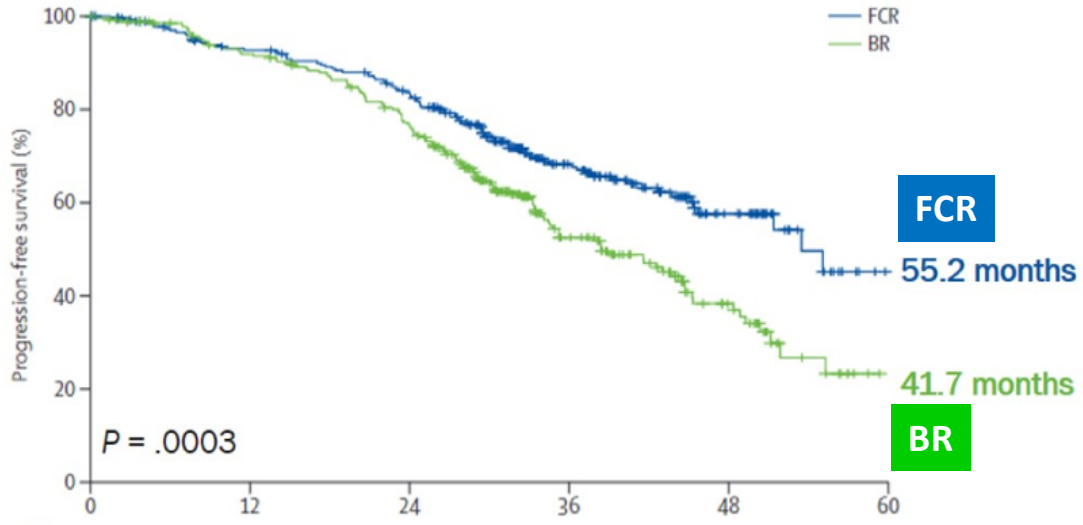
MRD Status,* %	Venetoclax + Obinutuzumab (n = 216)	Chlorambucil + Obinutuzumab (n = 216)	P Value
Peripheral blood			
▪ Negative ($< 10^{-4}$)	**76**	**35**	< .001
▪ Negative ($< 10^{-4}$) in CR	42	14	< .001
Bone marrow			
▪ Negative ($< 10^{-4}$)	**57**	**17**	< .001
▪ Negative ($< 10^{-4}$) in CR	34	11	< .001

Fischer at 2019 ASCO & EHA Annual Meeting

Front-line therapy: CIT vs NAs

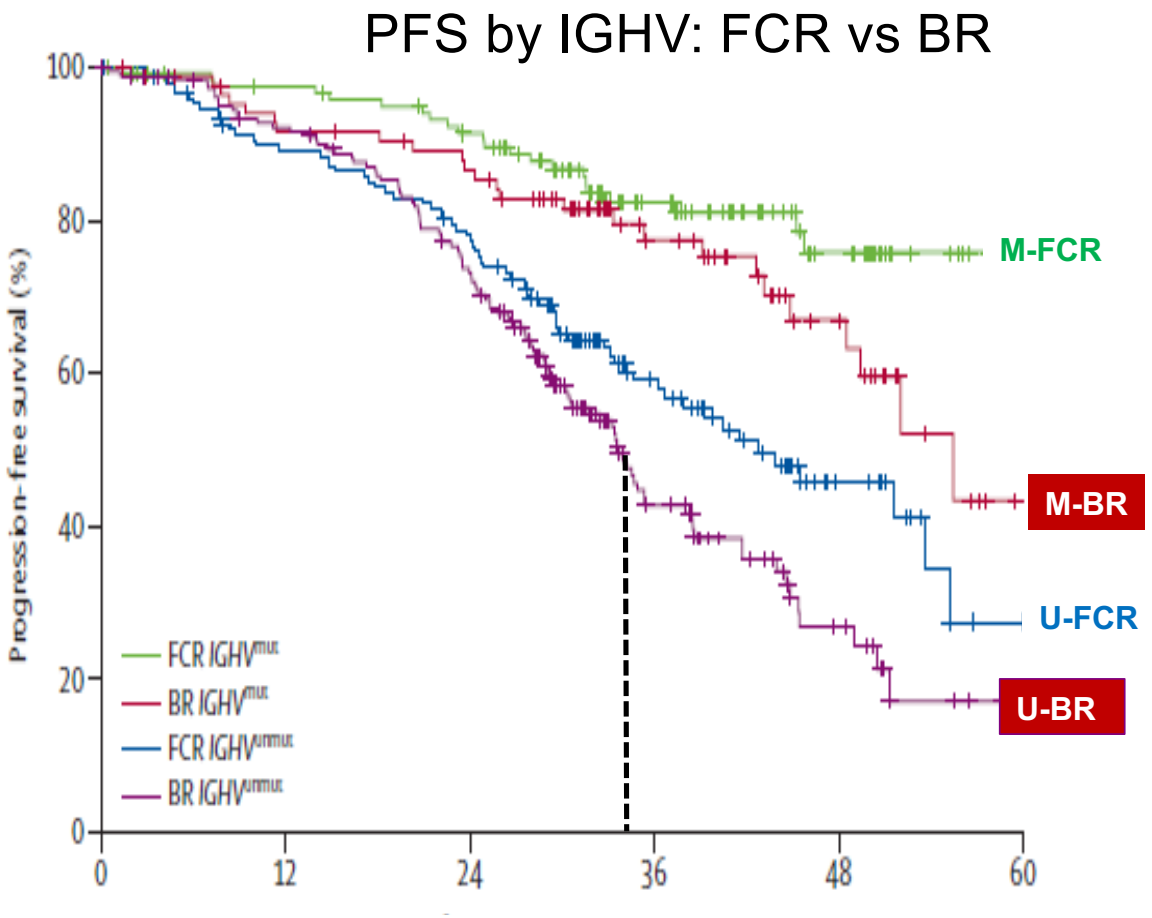
	CIT	NAs
ELDERLY/UNFIT	CHLORAMBUCIL+ OBINUTUZUMAB	IBRUTINIB (RESONATE- RESONATE-2) IBUTINIB+ OBINUTUZUMAB(ILLUMINATE TRIAL) VENETOCLAX+ OBINUTUZUMAB (CLL14)
OLDER/FIT	BENDAMUSTINE+ RITUXIMAB	IBRUTINIB/IBRUTINIB+RITUXIMAB
YOUNGER/FIT	FCR	IBRUTINIB

German CLL10 Study: FCR vs BR



Eichhorst et al., Lancet Oncology 2016

PFS: FCR vs BR study (CLL10 trial)



Eichhorst et al., Lancet Oncology 2016

ALLIANCE TRIAL: Ibrutinib±rituximab vs bendamustine+rituximab in untreated older patients with CLL (Study A041202)

Untreated pts
age ≥ 65
ECOG 0-2
CrCL≥40

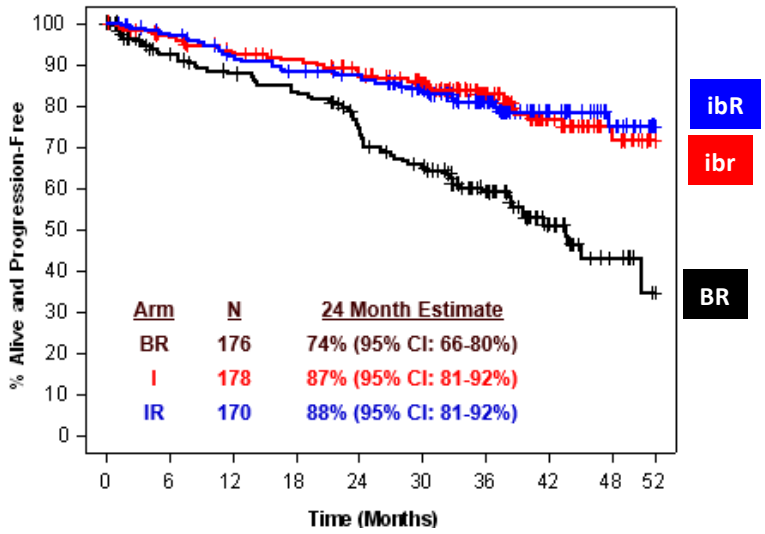
RANDOMIZE

BR
Bendamustine 90mg/m2 days 1&2 of each 28 day cycle +
Rituximab 375 mg/m2 day 0 cycle 1,
then 500 mg/m2 day 1 cycles 2-6

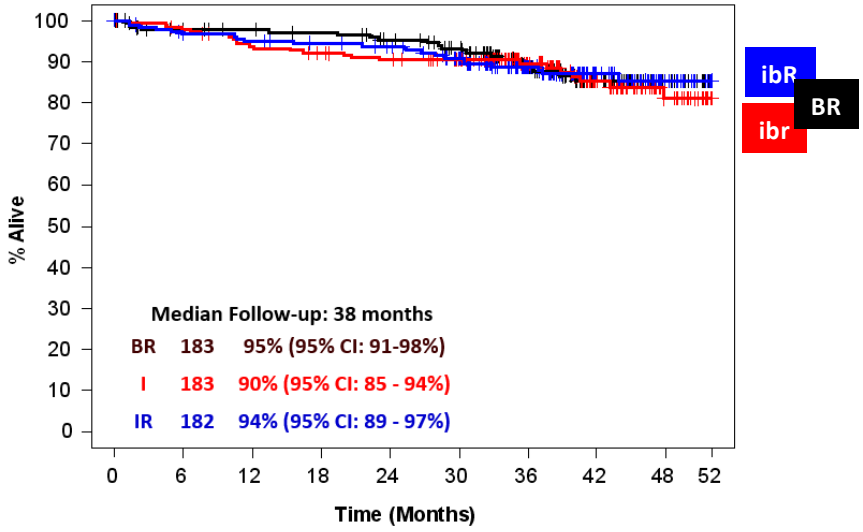
Ibrutinib
420mg daily until disease progression

IR
Ibrutinib 420mg daily until disease progression +
Rituximab 375 mg/m2 weekly for 4 weeks starting cycle 2 day 1, then day 1 of cycles 3-6

PFS: Eligible Patient Population

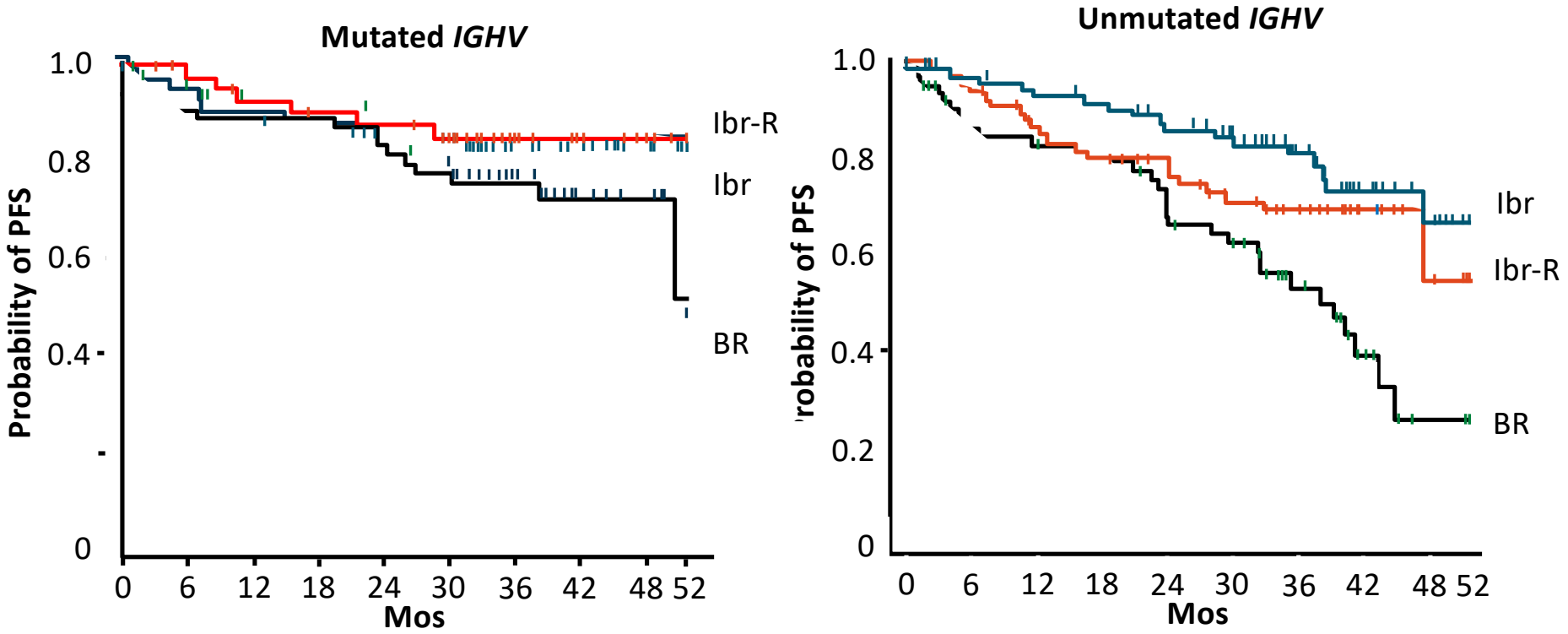


Overall survival



Woyach et al. NEJM. 2018

ALLIANCE TRIAL: Ibrutinib±rituximab vs bendamustine+rituximab in untreated older patients with CLL (Study A041202)

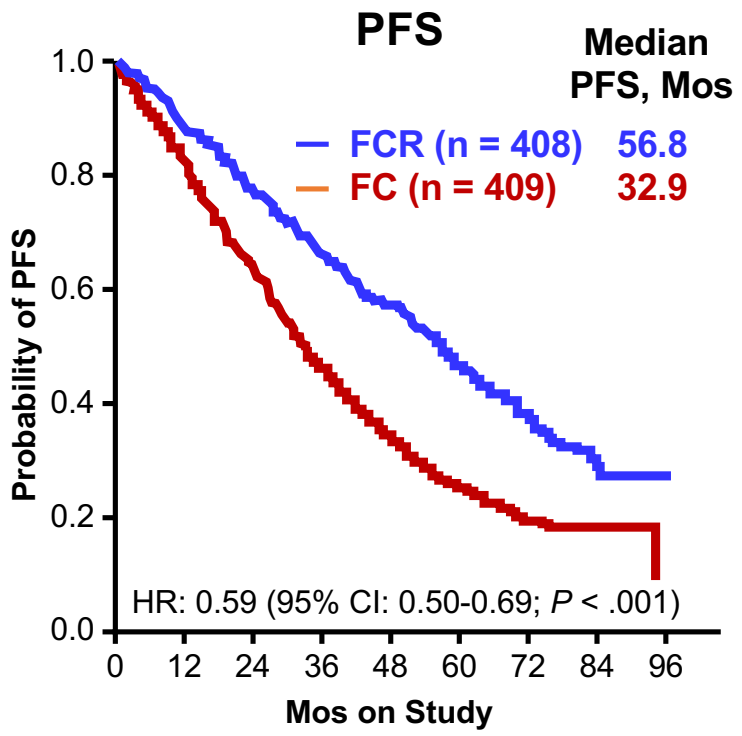


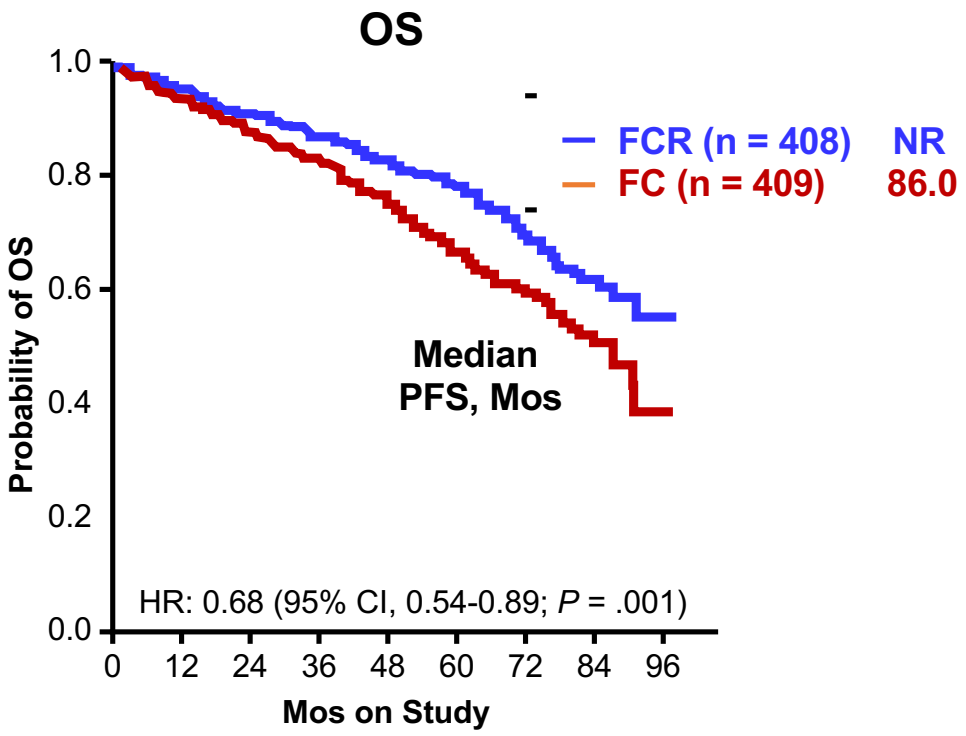
Woyach et al. NEJM. 2018

Front-line CIT vs NAs

	CIT	NAs
ELDERLY/UNFIT	CHLORAMBUCIL+ OBINUTUZUMAB	IBRUTINIB (RESONATE- RESONATE-2) IBUTINIB+ OBINUTUZUMAB(ILLUMINATE TRIAL) VENETOCLAX+ OBINUTUZUMAB (CLL14)
OLDER/FIT	BENDAMUSTINE+ RITUXIMAB	IBRUTINIB/IBRUTINIB+RITUXIMAB
YOUNGER/FIT	FCR	IBRUTINIB

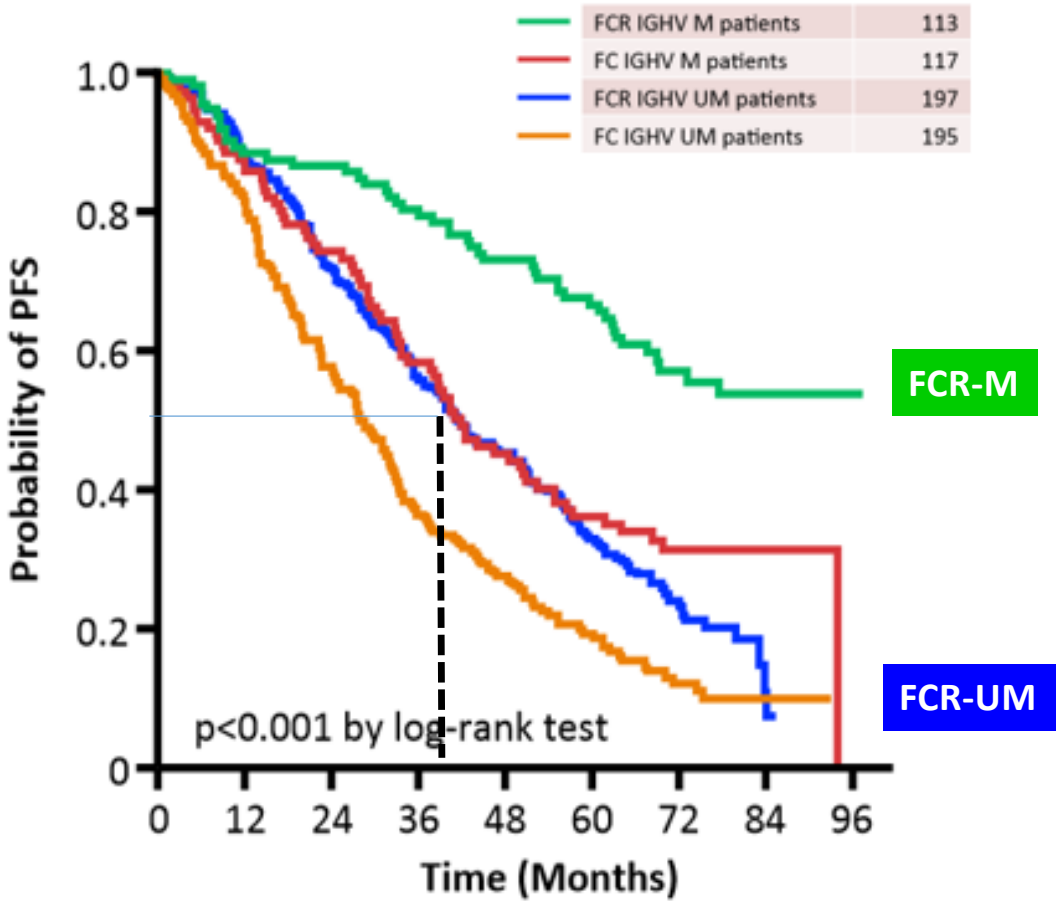
CLL8: Efficacy of FC vs FCR in fit Pts With Active CLL





Fischer et al. Blood. 2016

PFS by IGHV after front-line FCR: FCR300 trial



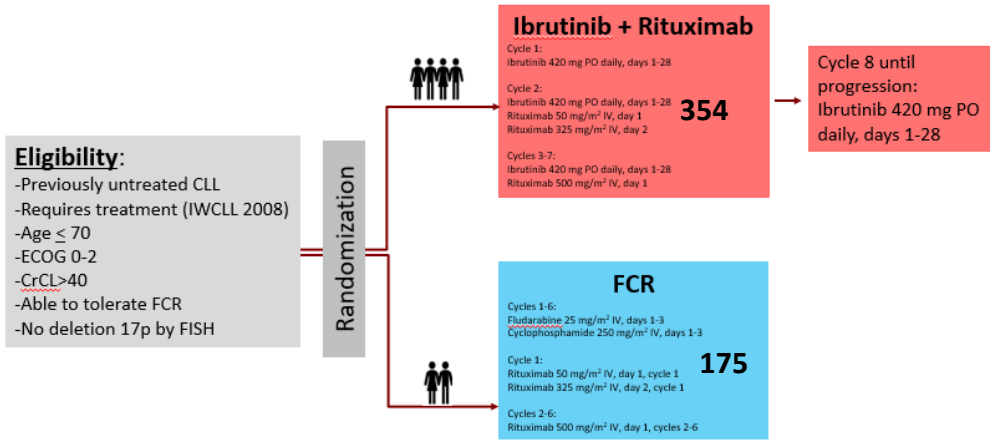
IGVH mutated

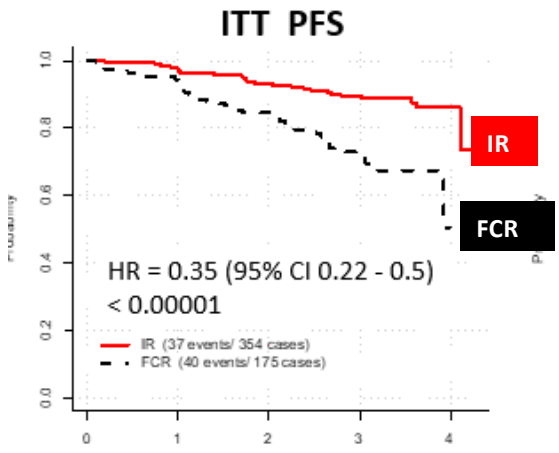
Prog-free @ 13 yrs=54%

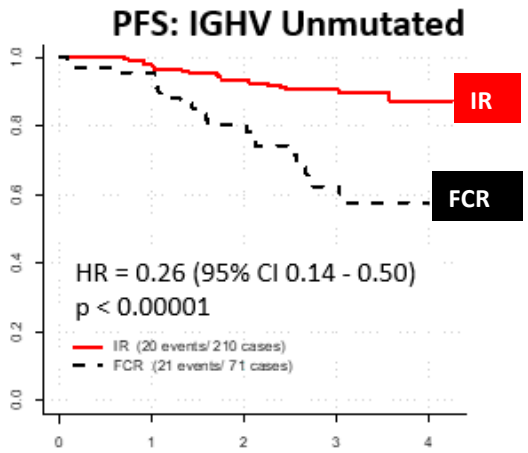
curve plateaued beyond 10.4 yrs

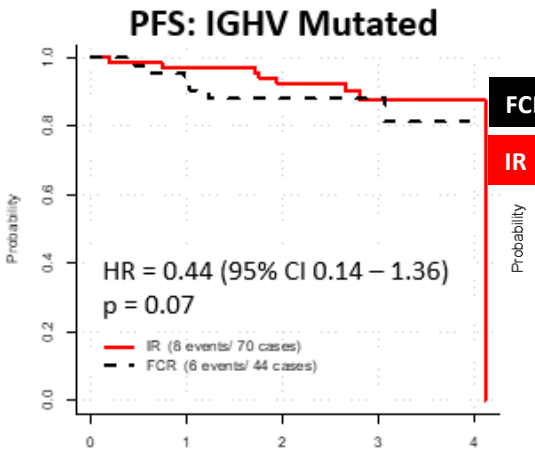
Thomson et al., Blood 2015

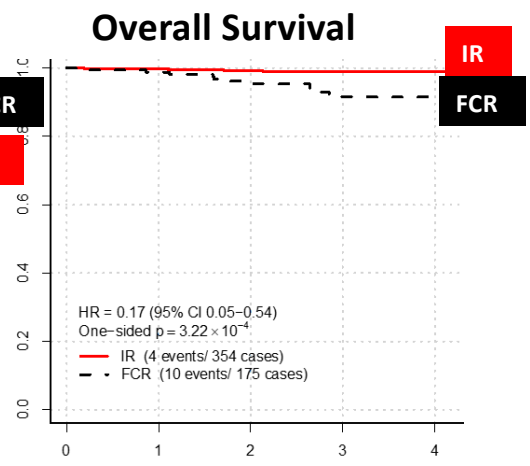
Ibrutinib+rituximab vs FCR in TN young CLL with no del 17p ECOG-E1912 trial











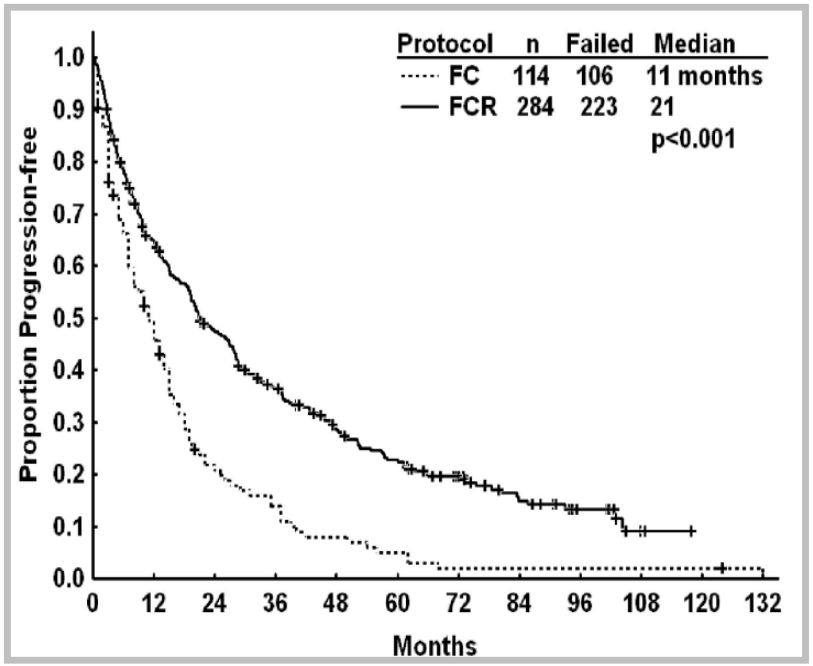
Shanafelt T, LBA-4 – ASH 2018

Salvage therapy in R/R patients with CLL: CIT vs NAs

CIT	NAs
FCR BR	IBRUTINIB (RESONATE trial) VENETOCLAX VENETOCLAX+ RITUXIMAB

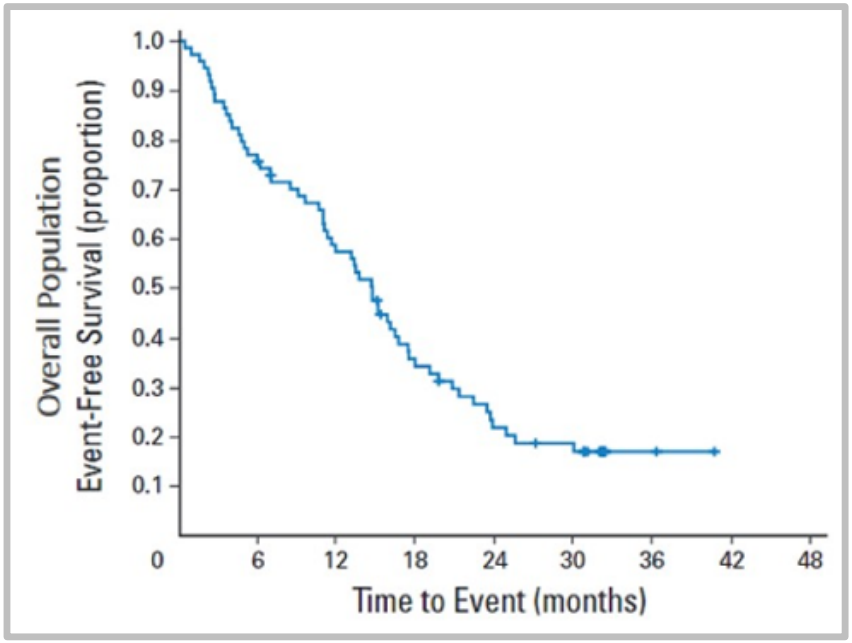
Outcome of R/R patients treated with CIT

FCR (MDACC)



Median PFS= 21 months

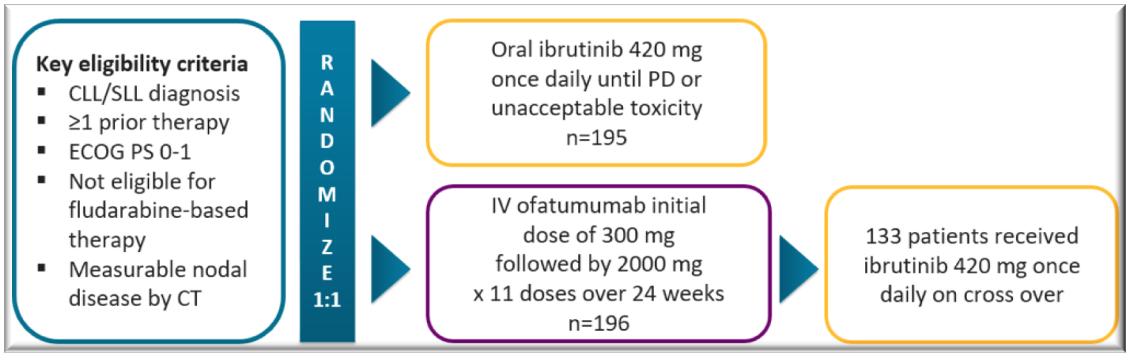
Bendamustine+Rituximab

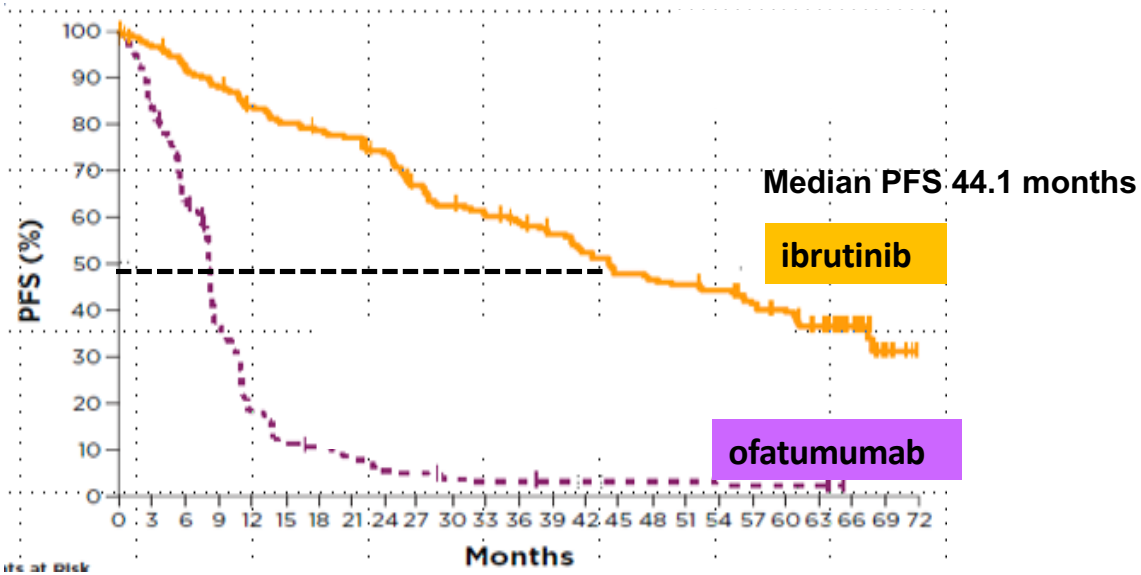


Median PFS= 15 months

Badoux et al. 2011, Fischer et al. 2011, Robak et al. 2010

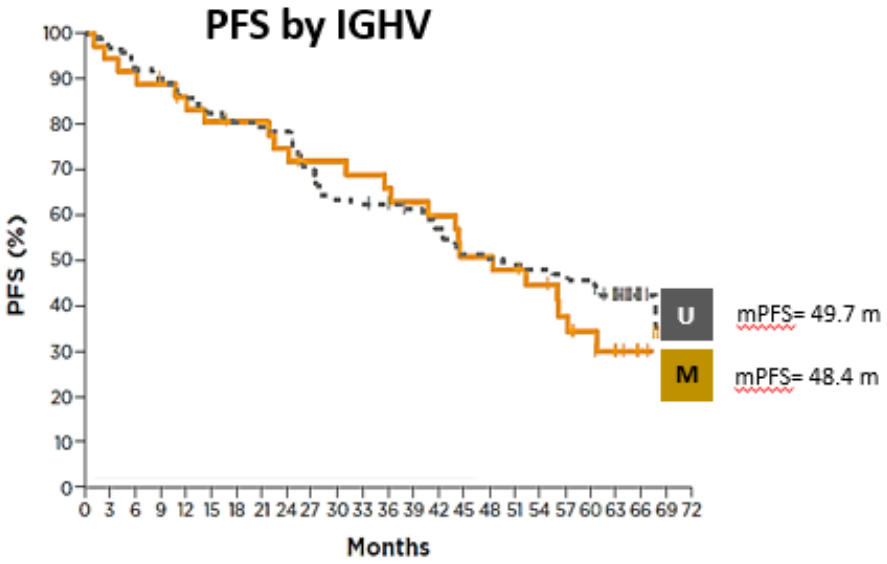
Resonate Trial: ibrutinib vs ofatumumab in R/R patients with CLL: 6 years follow-up

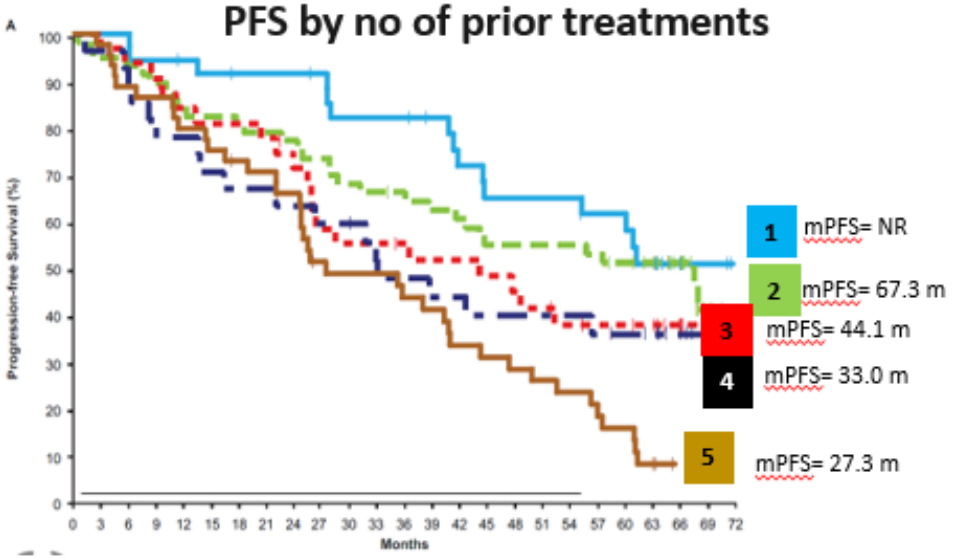




Munir et al. – AJH 2019

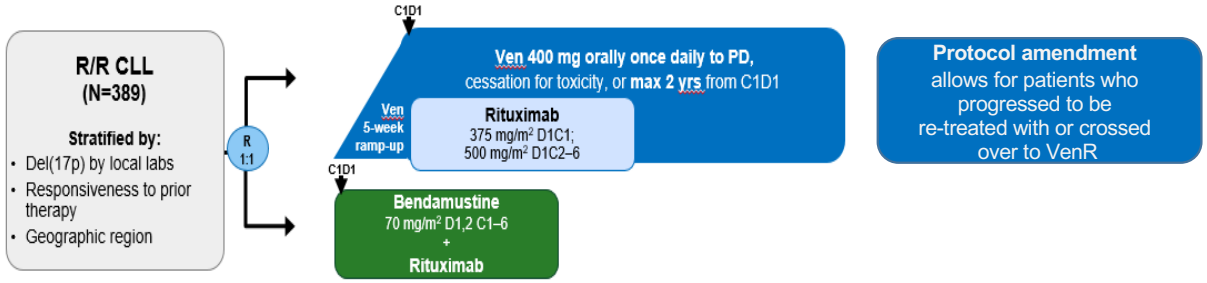
Resonate Phase 3 Trial in R/R patients with CLL: 6 years follow-up



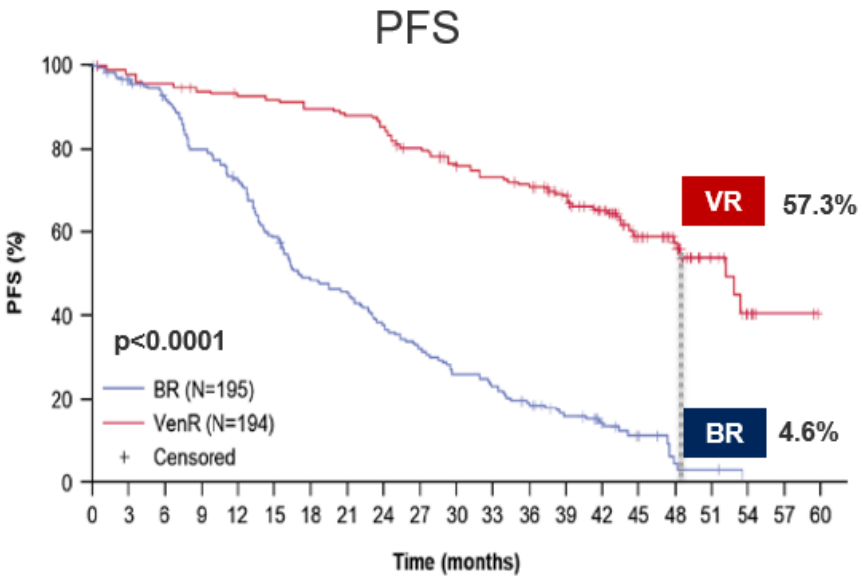


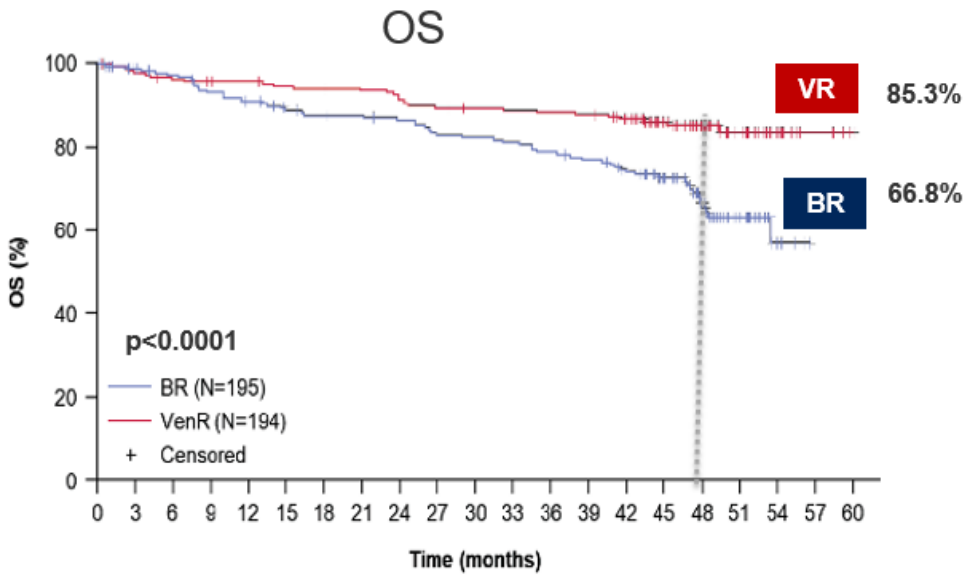
Munir et al. – AJH 2019

Venetoclax-R vs BR in Patients With R/R CLL: 4 years Follow-up of the MURANO Study



Characteristics	VenR (n=194)	BR (n=195)
Median age, yrs (range)	64.5 (28–83)	66 (22–85)
del(17p) and/or *TP53* mut, n/N (%)*†‡	72/178 (40.4)	75/170 (44.1)
Unmutated *IGHV*, n/N (%)*	123/180 (68.3)	123/180 (68.3)
Number of prior therapies, n (%)		
1	111 (57.2)	117 (60.0)
2	58 (29.9)	43 (22.1)
3	23 (11.9)	35 (17.9)
>3	2 (1.0)	0 (0)

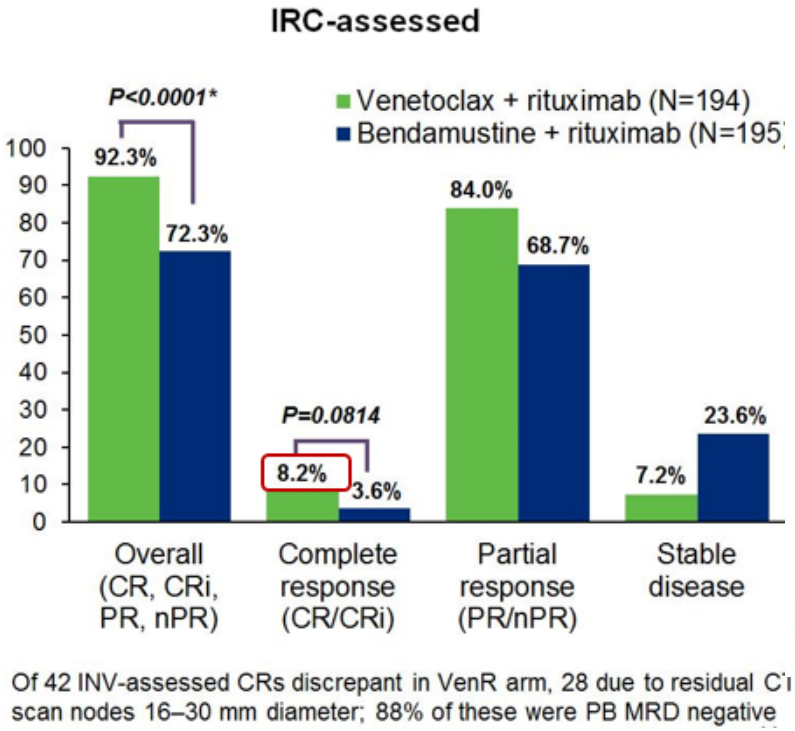




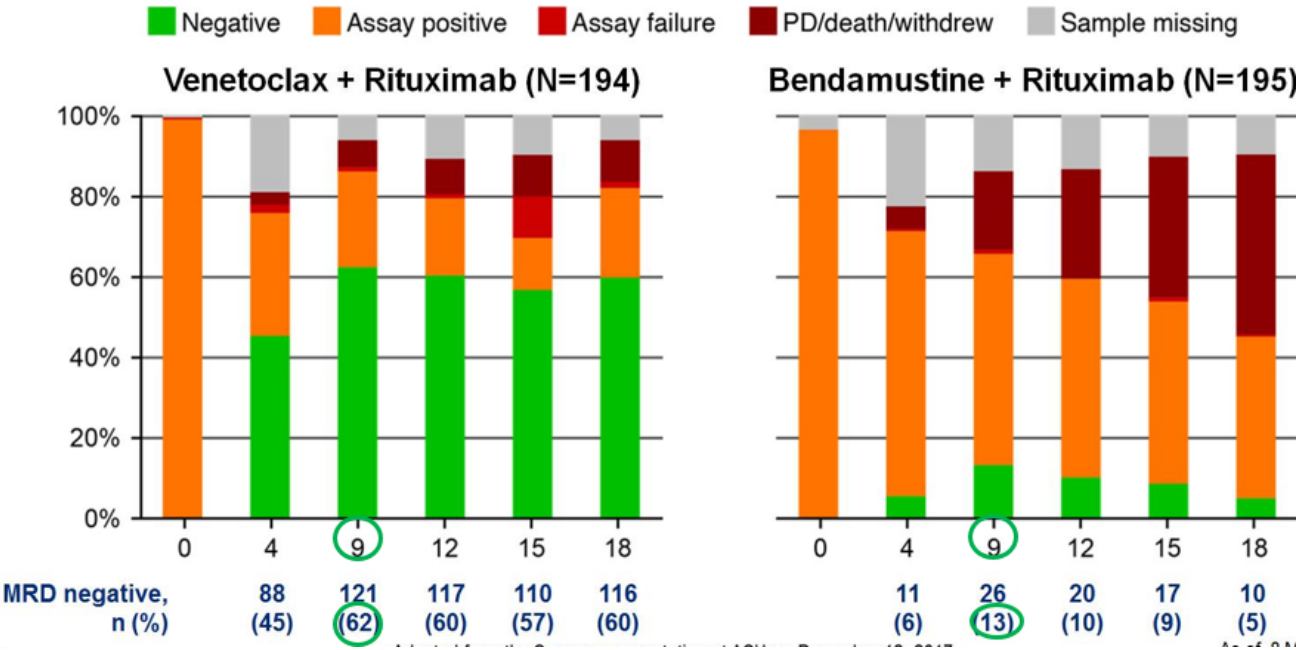
BR patients receiving a novel targeted anti-CLL agent after PD (BTK inhibitors [n=60], PI3K inhibitors [n=9], Ven [n=1O] or investigational medicina! products [n=2]).

Seymour et al. –Poster 2266 - iwCLL 2019

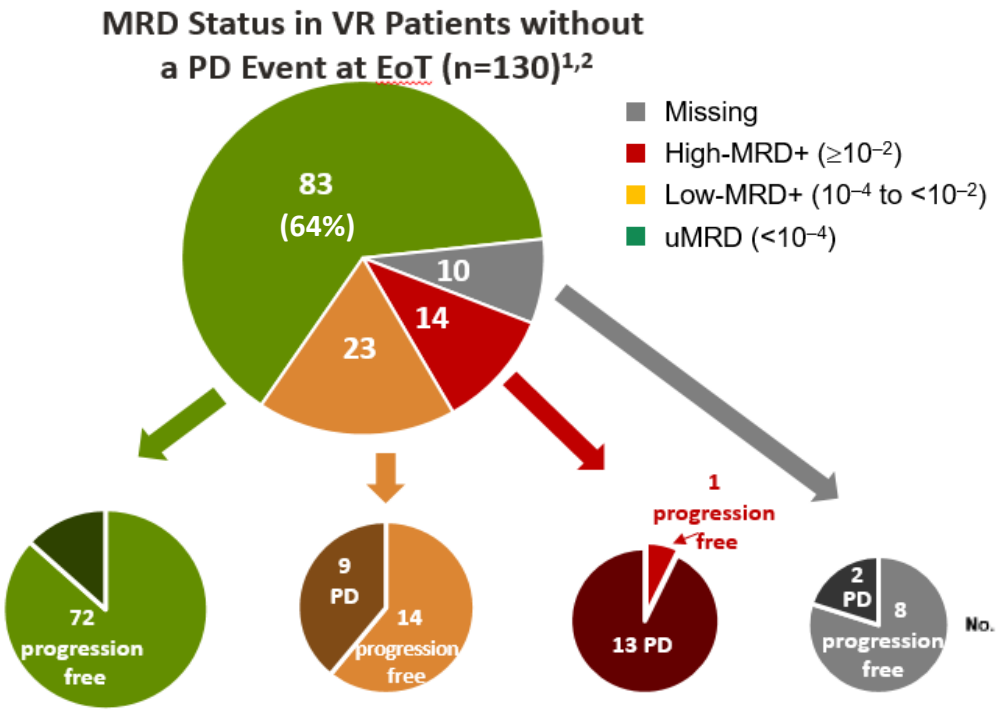
Venetoclax-R vs BR in Patients With R/R CLL: Longer-Term Follow-up of the MURANO Study

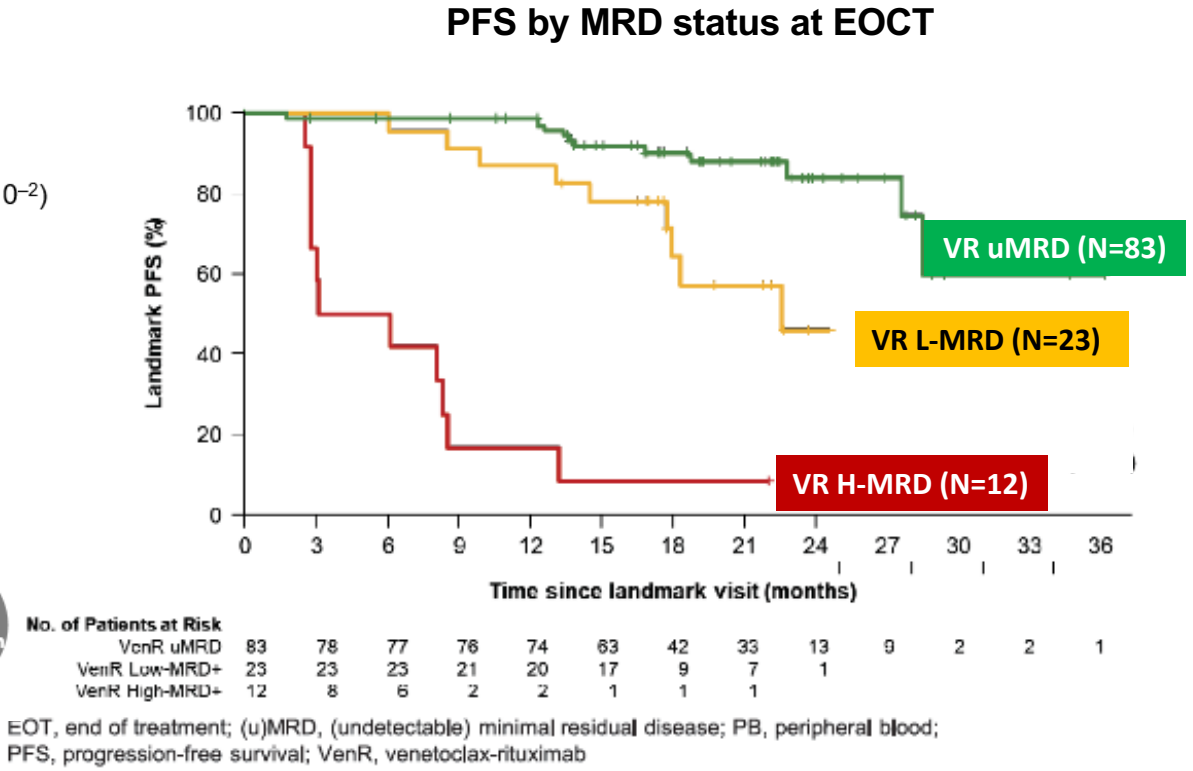


Of 42 INV-assessed CRs discrepant in VenR arm, 28 due to residual CT scan nodes 16–30 mm diameter; 88% of these were PB MRD negative



Venetoclax-R vs BR in Patients With R/R CLL: 4 years Follow-up of the MURANO Study

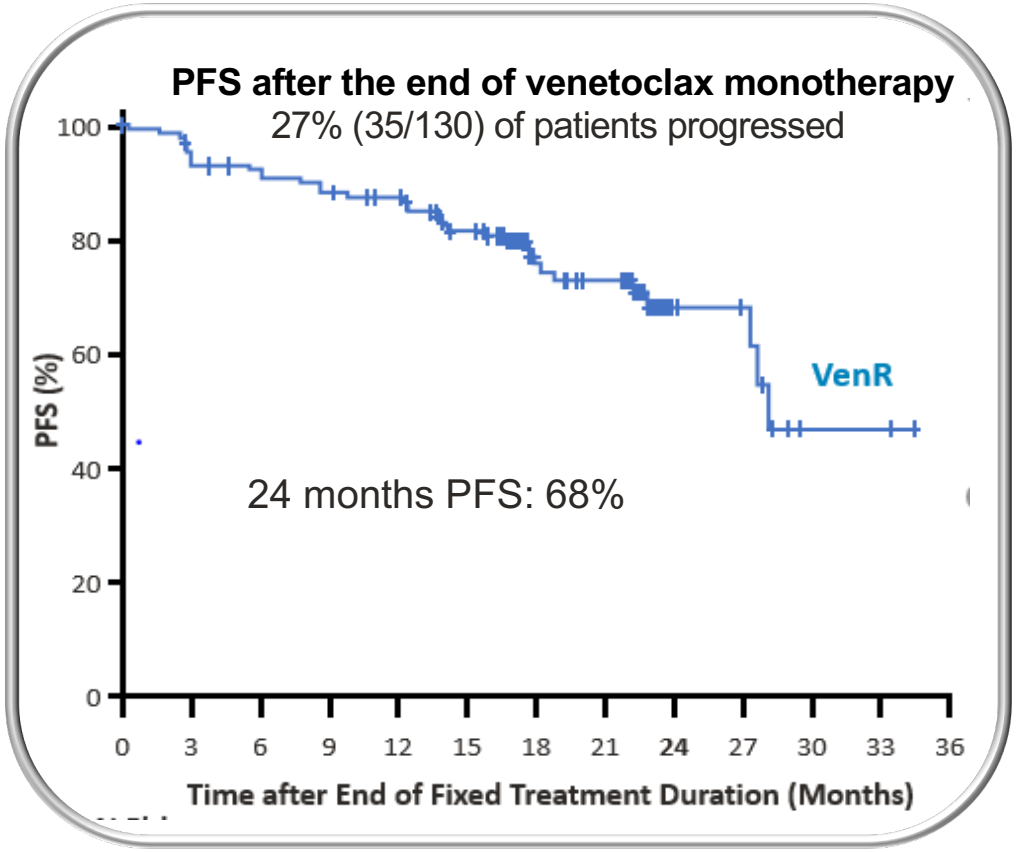




EOT, end of treatment; (u)MRD, (undetectable) minimal residual disease; PB, peripheral blood; PFS, progression-free survival; VenR, venetoclax-rituximab

1. Seymour JF, *et al.* iwCLL 2019; Abstract #2266; 2. Seymour JF, *et al.* iwCLL 2019; Poster #2266.

Venetoclax-R vs BR in Patients With R/R CLL: 4 years Follow-up of the MURANO Study



Predictors of DP after venetoclax cessation

- MRD status (p<0.0001)
- Del(17p)/*TP*53 mutation

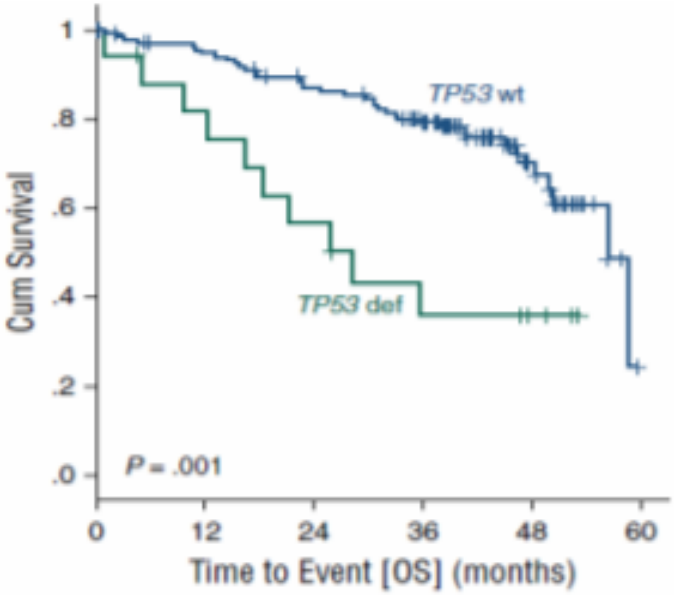
1. Kater AP, *et al. J Clin Oncol* 2019; **37:**269–277; 2. Seymour JF, *et al.* iwCLL 2019; Abstract #2266. Wu et al., iwCLL 2019

CIT vs Nas in patients with *TP*53 disruptions

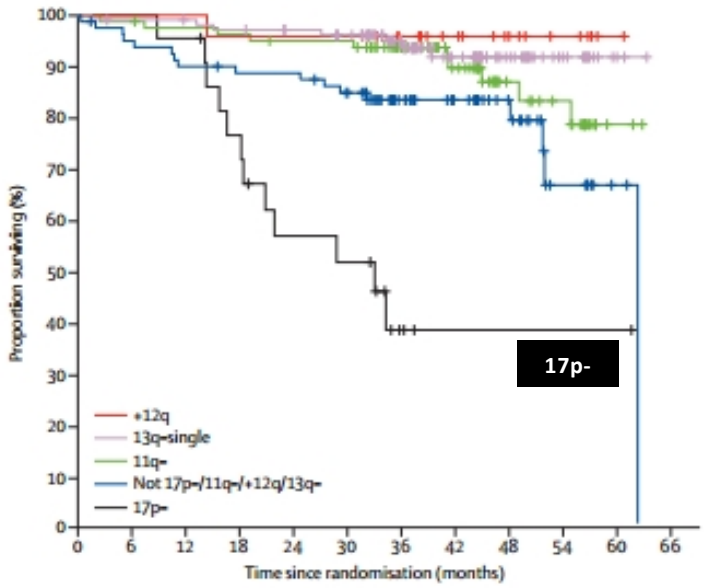
	CIT	NAs
TREATMENT NAIVE PATIENTS	CLL11 TRIAL CLL8 TRIAL	IBRUTINIB (RESONATE) IBUTINIB+ OBINUTUZUMAB(ILLUMINATE TRIAL) VENETOCLAX+ OBINUTUZUMAB (CLL14)
RELAPSED/ REFRACTORY PATIENTS	FCR BR	IBRUTINIB/IBRUTINIB+RITUXIMAB VENETOCLAX +RITUXIMAB

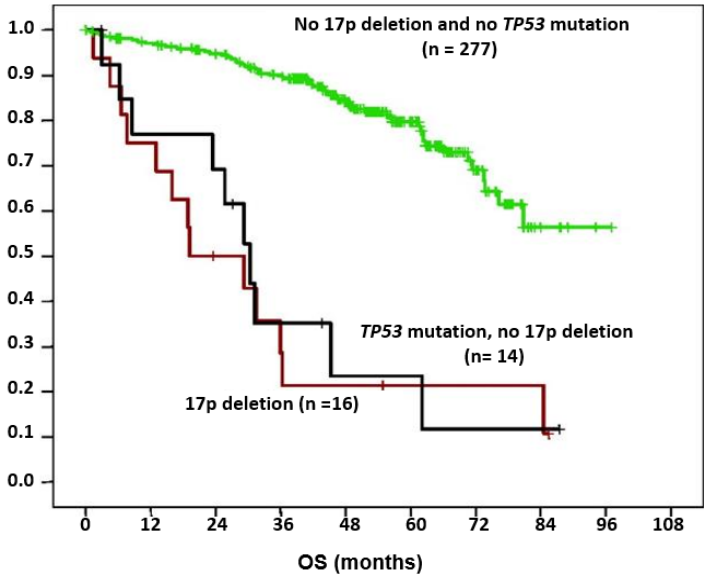
Impact of *TP53* aberrations on OS of patients with CLL treated front-line with CIT

CLL11 trial



CLL8 trial

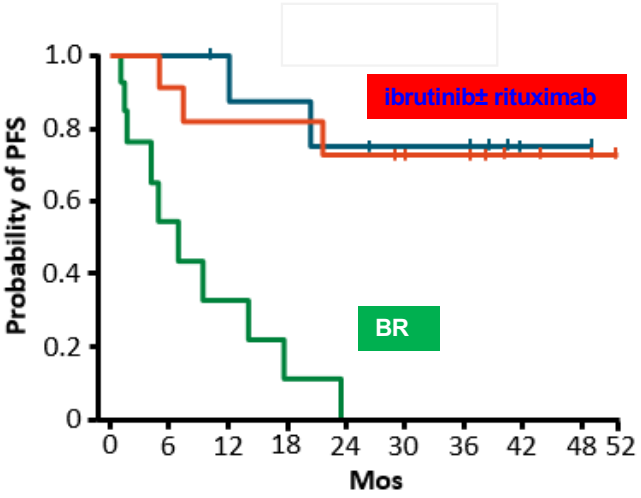




Herling et al., Blood 2016; Hallek et al., Lancet 2010; Stilgenbauer et al. Blood. 2014

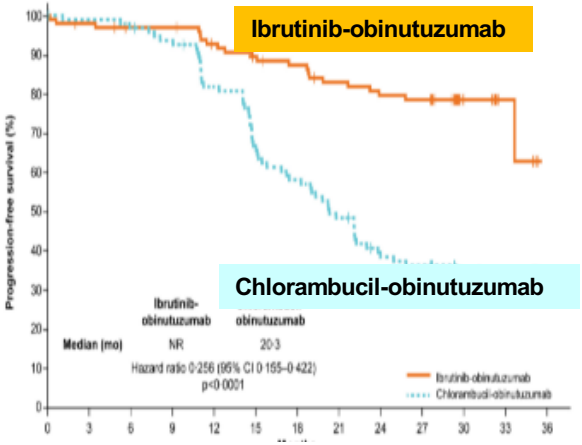
Outcomes of TN patients with *TP53* aberrations treated front-line with NAs

ALLIANCE



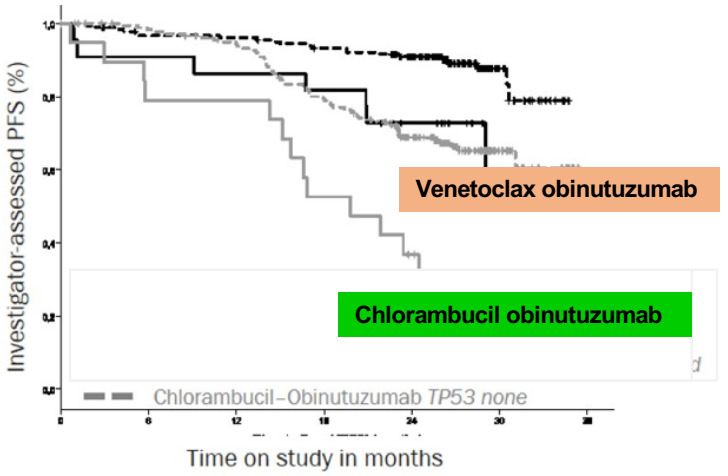
Woyach. Et al. NEJM. 2018.

iLLUMINATE



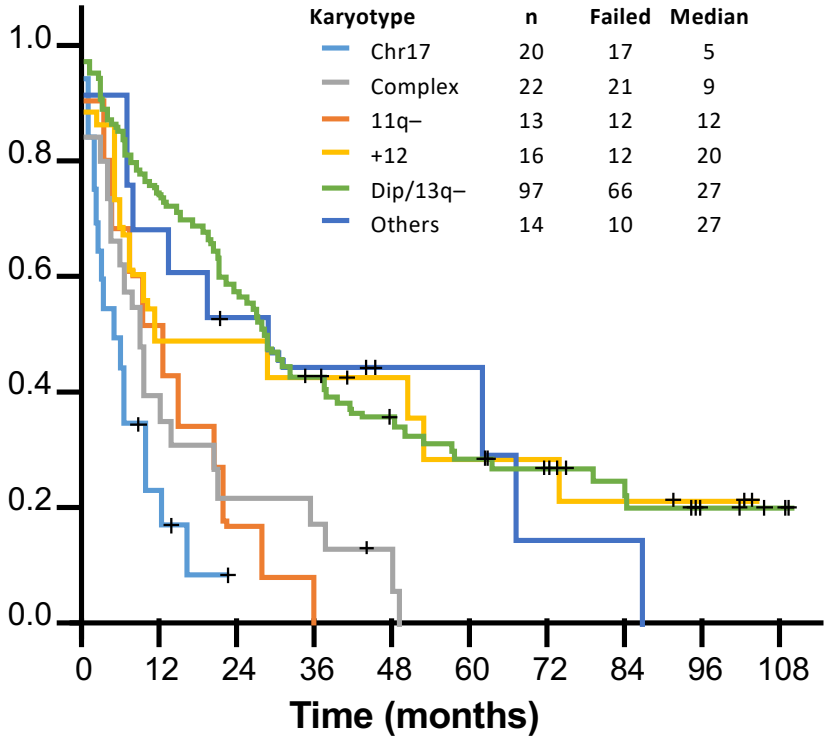
Moreno et al. Lancet Oncol 2018

CLL14

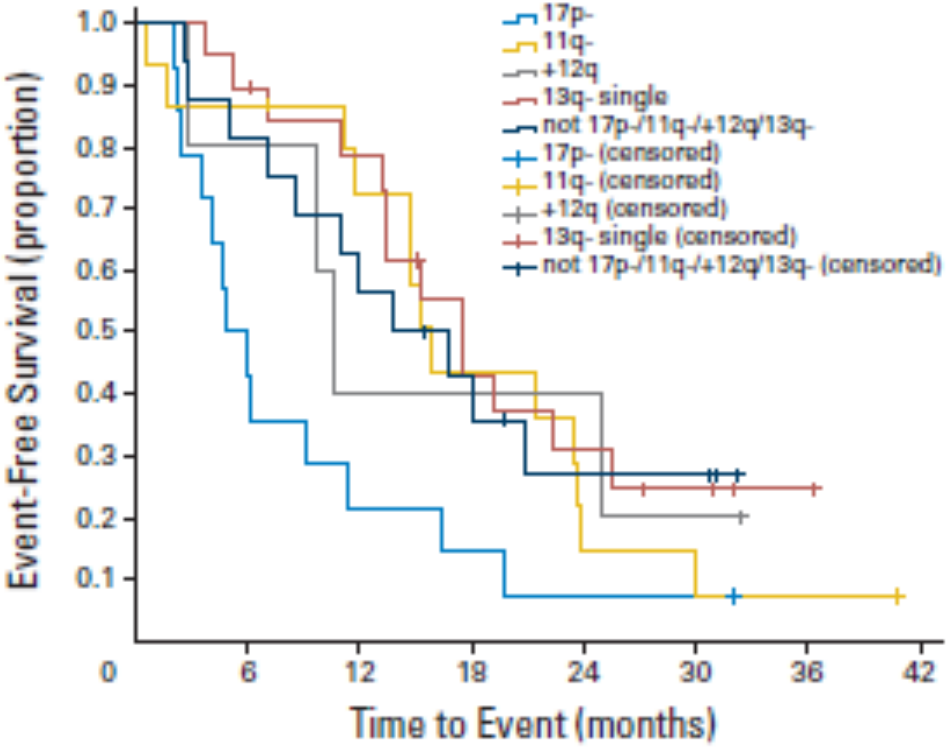


Fischer et al. NEJM 2019

CIT in R/R patients with del17p



FCR: Median PFS= 5 months

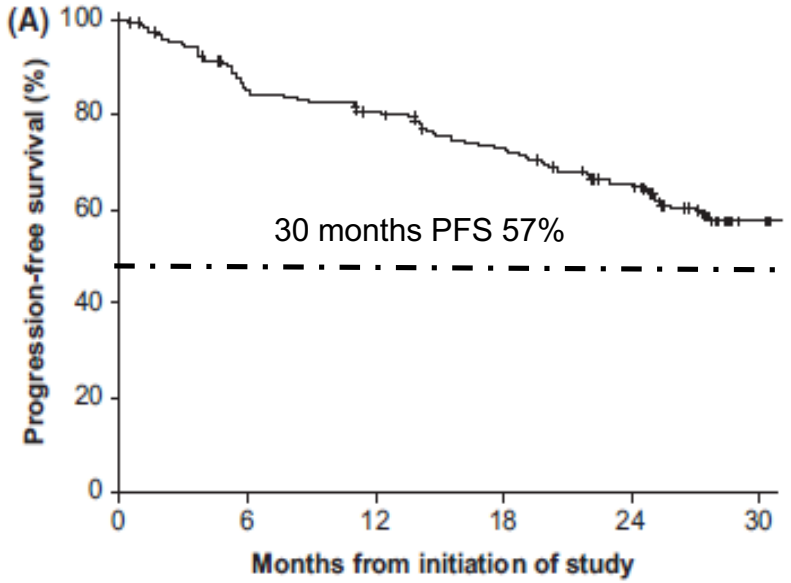


BR: Median EFS= 6.8 months

(1)Badoux et al., JCO 2011; (2) Fisher et al, JCO 2011

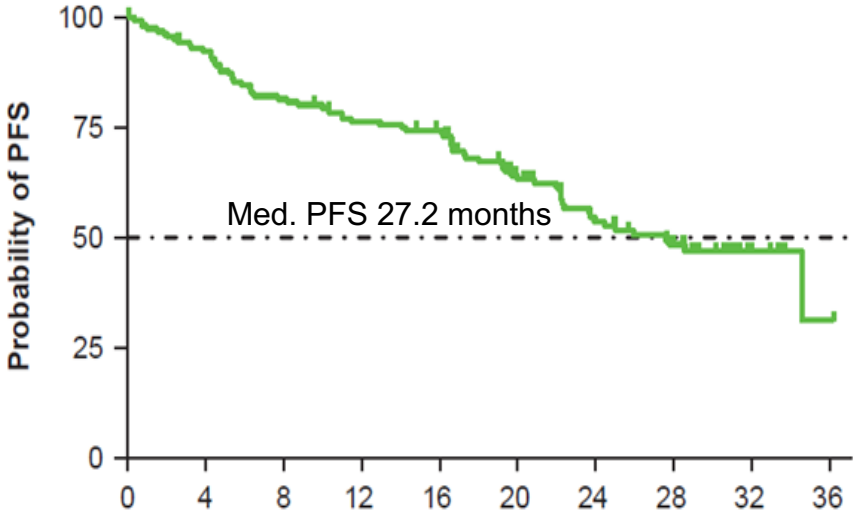
Outcomes of R/R patients with *TP53* aberrations treated with NAs

ibrutinib



Jones et al. BJH 2018

venetoclax



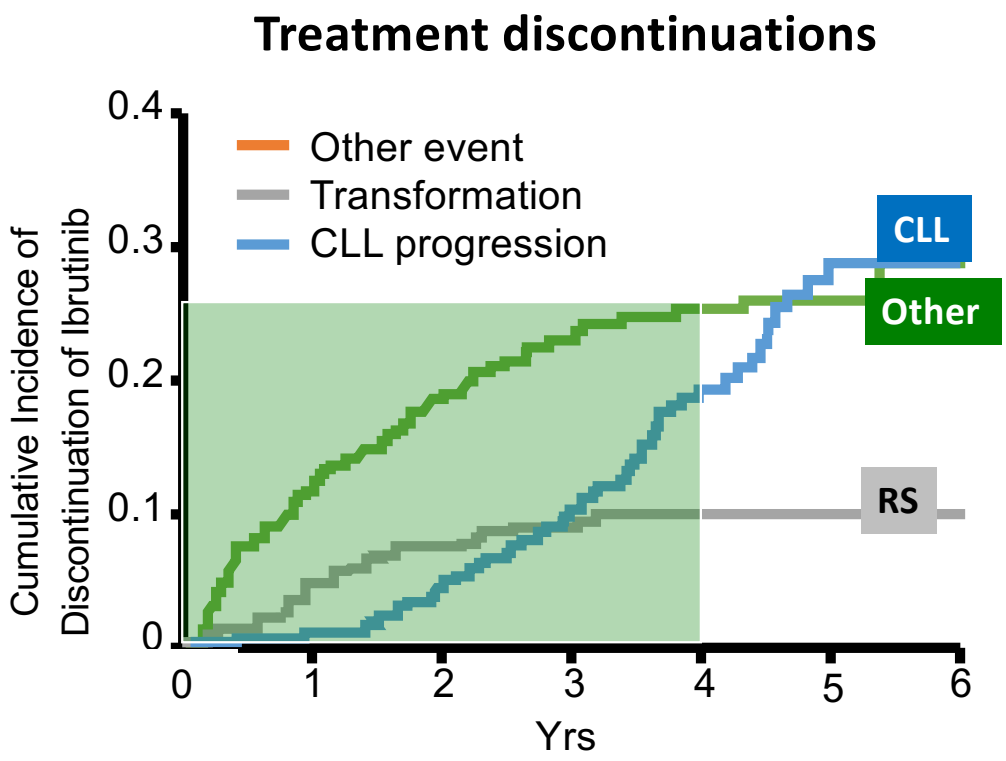
Stilgenbauer et al., iwCLL 2017, abstract 420

Safety profile: NAs

Outcome of 308 patients treated with ibrutinib at the Ohio State University

Cumulative Incidence Estimates, % (95% CI)	At 2 Yrs	At 3 Yrs	At 4 Yrs
CLL progression	5.0 (2.5-7.5)	10.8 (7.1-14.4)	19.1 (13.9-24.3)
Transformation	7.3 (4.3-10.2)	9.1 (5.8-12.4)	9.6 (6.2-13.0)
Other events	18.7 (14.3-23.1)	23.9 (19.0-28.8)	**25.0 (20.0-30.1)**

N = 158/308



Woyach, et al. J Clin Oncol. 2017

CIT and NAs: expected adverse events

CIT	Ibrutinib	Idelalisib	Venetoclax
Granulocytopenia	Bleeding risk	Transaminitis	TLS
Thrombocytopenia	Atrial fibrillation	Colitis	Granulocytopenia
Infections	Hypertension	Pneumonitis	
MDS	Myalgias	Infections	

Treatment choice in CLL patients: decision making process

CLL biology

- IGHV
- Del17p/*TP*53 mutation

Patient characteristics

- Age
- Fitness
- Co-morbidities
- Co-treatment
- Patient preferences

Treatment options

- Treatment toxicity
- Interaction with co-treatment
- Individual risk of treatment discontinuation

CLL-related life expectancy

Normal life expectancy

Goal of treatment

Disease control

Deep response with treatment discontinuation

Conclusions

Chemo-free treatment is eclipsing chemoimmunotherapy in R/R and TN patients with CLL:

- no role of CIT in patients with *TP*53 disruption
- no/very limited role of CIT in R/R patients
- chemo-free treatment more effective in IGHV unmutated patients

The optimal treatment choice of CLL patients should consider:

- the biologic profile of CLL
- the clinical characteristics of patients
- the treatment goal