UNIKLINIK KÖLN

ERIC european research initiative on CLL

DEUTSCHE STUDIENGRUPPE CLL

Chemoimmuntherapy in the R/R setting: Still useful?

Amsterdam

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Conflicts of interests

1. Advisory Boards

   Janssen, Gilead, Roche, Abbvie, Novartis, Celgene, AstraZeneca

2. Honoraria

   Roche, Novartis, Gilead, Janssen, Abbvie, Celgene

3. Resarch support

   Roche, Janssen, Abbvie, Gilead, Beigene

EMA-approved treatment options in RR CLL

FCR	BR	CLB + R
Ab alone	Ibrutinib	Idelalisib + R
BR + kinase inhibitor	Venetoclax +/- R	Allogeneic SCTX

Relevant factors for treatment decision in RR setting

- Prior remission duration
- Prior tolerance of treatment
- Genetic aberrations:
  - TP53 del/mut
  - Complex karyotype
- Comorbidities/Comedication

EMA-approved treatment options in RR CLL

FCR	BR	CLB + R
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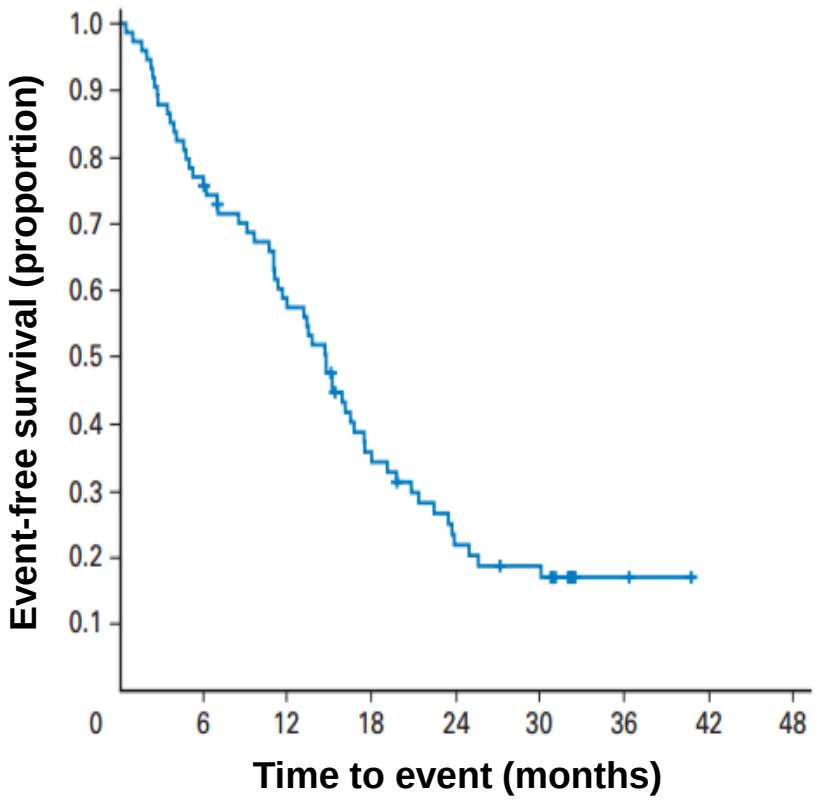
Efficacy of chemoimmunotherapies in R/R CLL

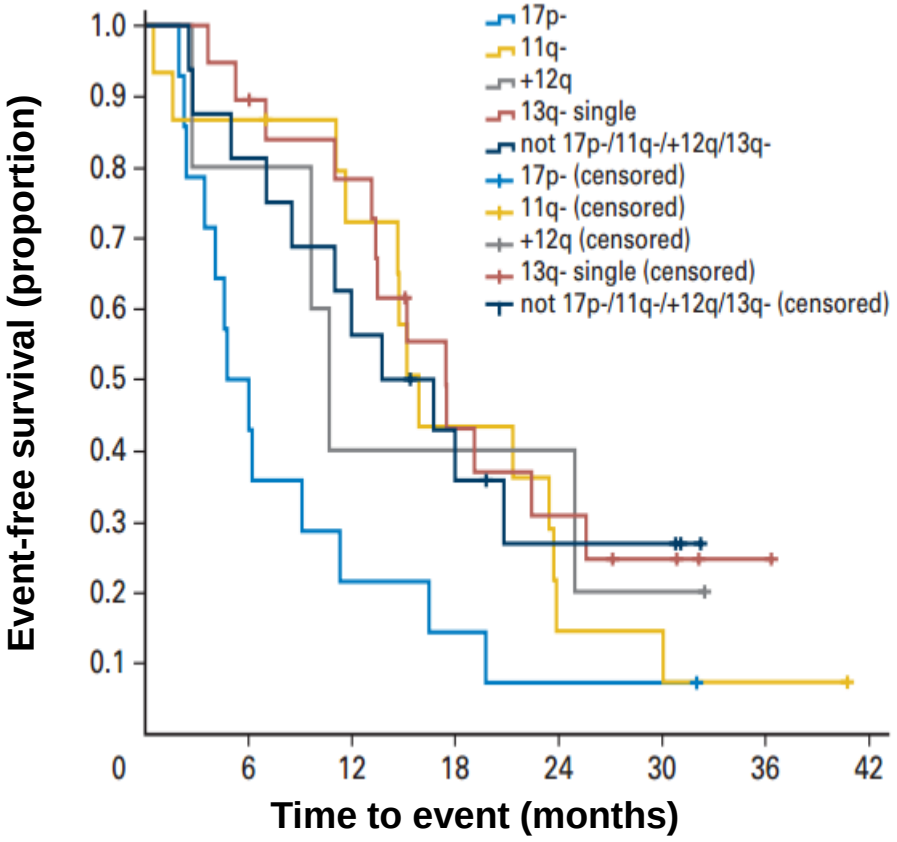
	FCR Wierda et al., JCO 2005	FCR Robak et al., JCO 2010	BR Fischer et al., JCO 2011	BR Michallet et al., Haematol. 2018	CLB+R Michallet et al., Haematol. 2018
n pts	177	276	78	57	59
ORR	73%	70%	59%	54%	53%
CR	25%	24%	9%	16%	2%
uMRD ITT	n.e.	13%	2%	16%	13%
PFS (med. mo.)	28	30.6	14.7*	26.0	16.0
OS	42	NR	33.9	NR	40.3

Bendamustine + rituximab in RR CLL (CLL2M, Phase 2): poor prognosis for del(17p)

Event-free survival



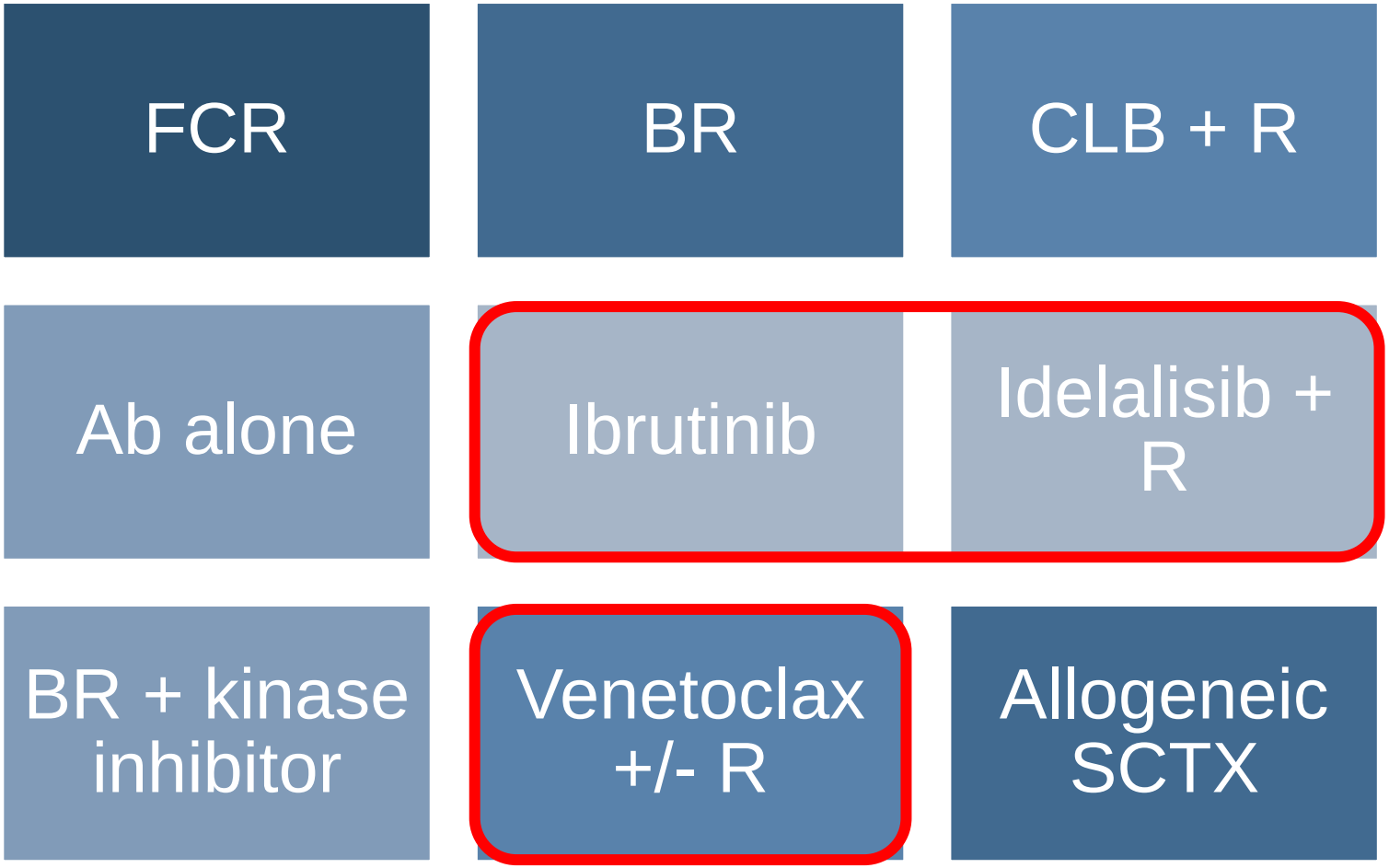
Event-free survival



Severe Toxicity of chemoimmunotherapies in R/R CLL

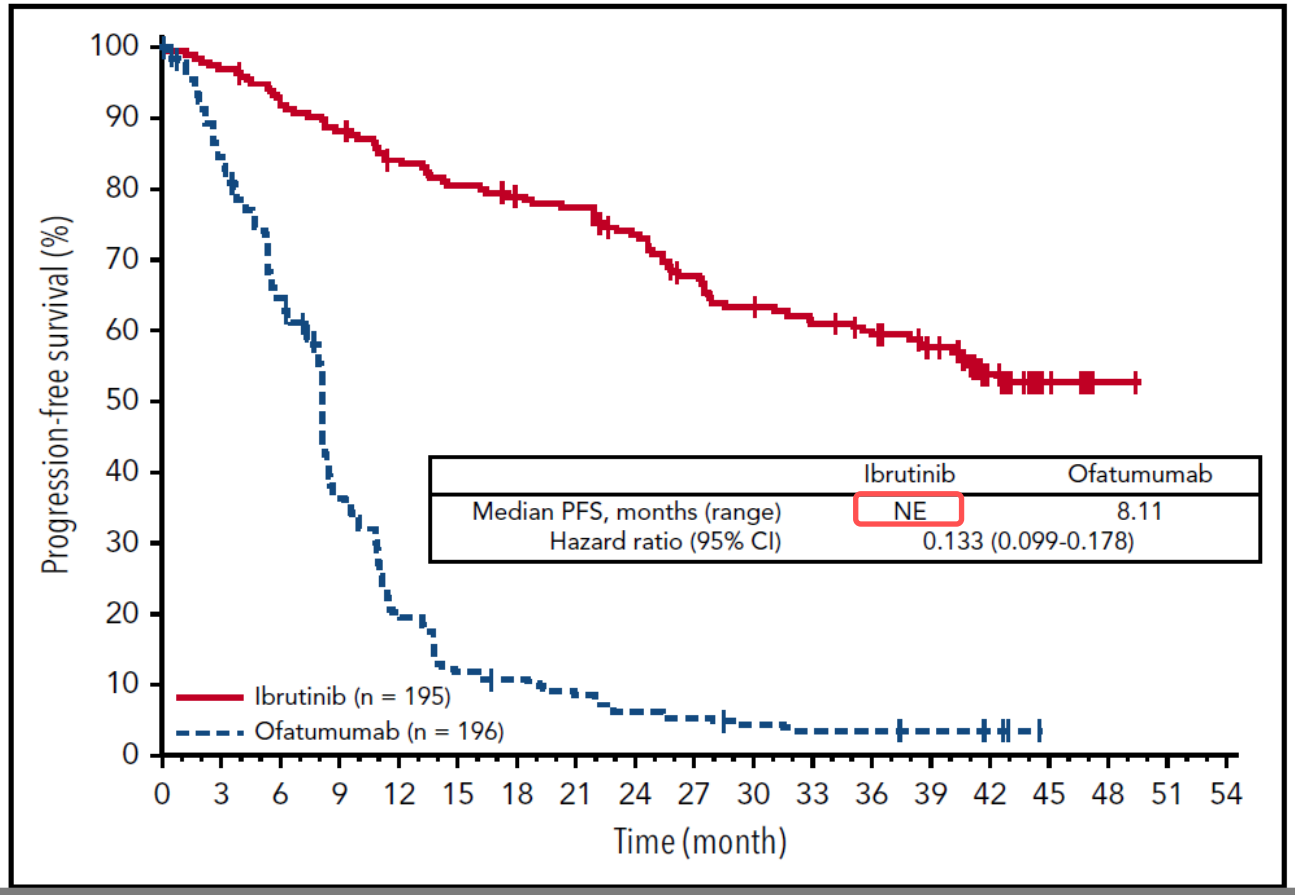
	FCR Wierda et al., JCO 2005	FCR Robak et al., JCO 2010	BR Fischer et al., JCO 2011
n patients	177	276	78
Neutropenia	81%	42%	23%
Thrombopenia	34%	11%	28%
Anemia	24%	12%	17%
Infections	16%	17%	13%

EMA-approved treatment options in RR CLL



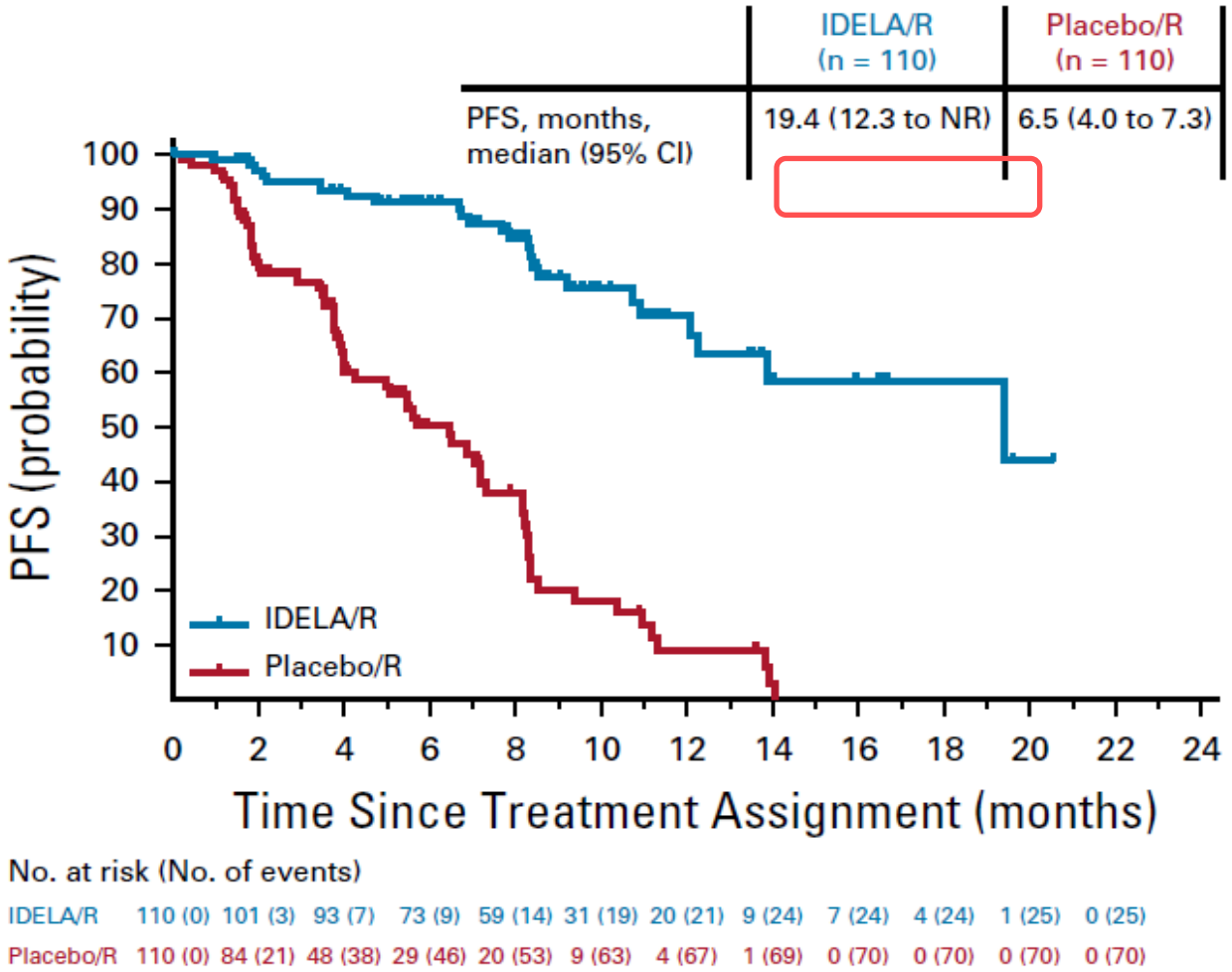
Phase III RESONATE I trial: PFS Ibrutinib vs Ofatumumab

RESONATE 1-Study: N = 391 – FU 44 months



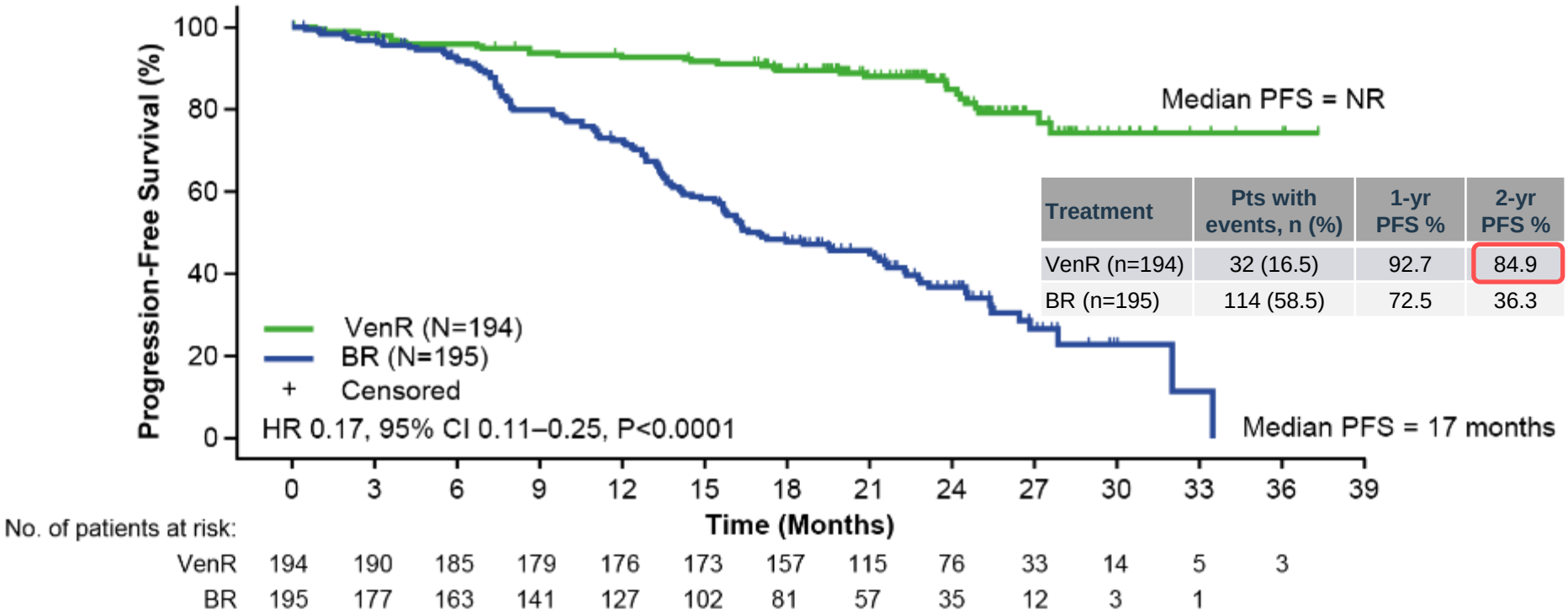
Phase III Study in elderly patients with R/R CLL: Idelalisib + R vs Placebo + R

PFS for 220 patients after longterm FU



Sharman J et al. JCO 2019

MURANO-trial:
Bcl2-Inhibitor Venetoclax+R for 24 months vs BR



Treatment	Pts with events, n (%)	1-yr PFS %	2-yr PFS %
VenR (n=194)	32 (16.5)	92.7	84.9
BR (n=195)	114 (58.5)	72.5	36.3

Seymour J at al. NEJM 2018

- Median (range) duration of follow-up, 23.8 (0.0–37.4) months:
- Venetoclax + rituximab, 24.8 months; bendamustine + rituximab, 22.1 months

Chemoimmuntherapy in the R/R setting: Still useful?

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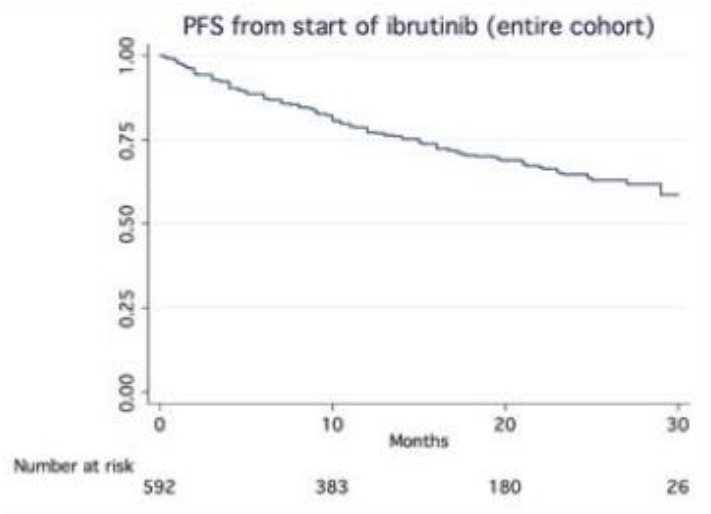
Chemoimmuntherapy in the R/R setting: Still useful?

…but maybe in subgroups

Efficacy of ibrutinib outside clinical trials appears to be lower

Registry data of 621 pts including 536 at relapse receiving ibrutinib

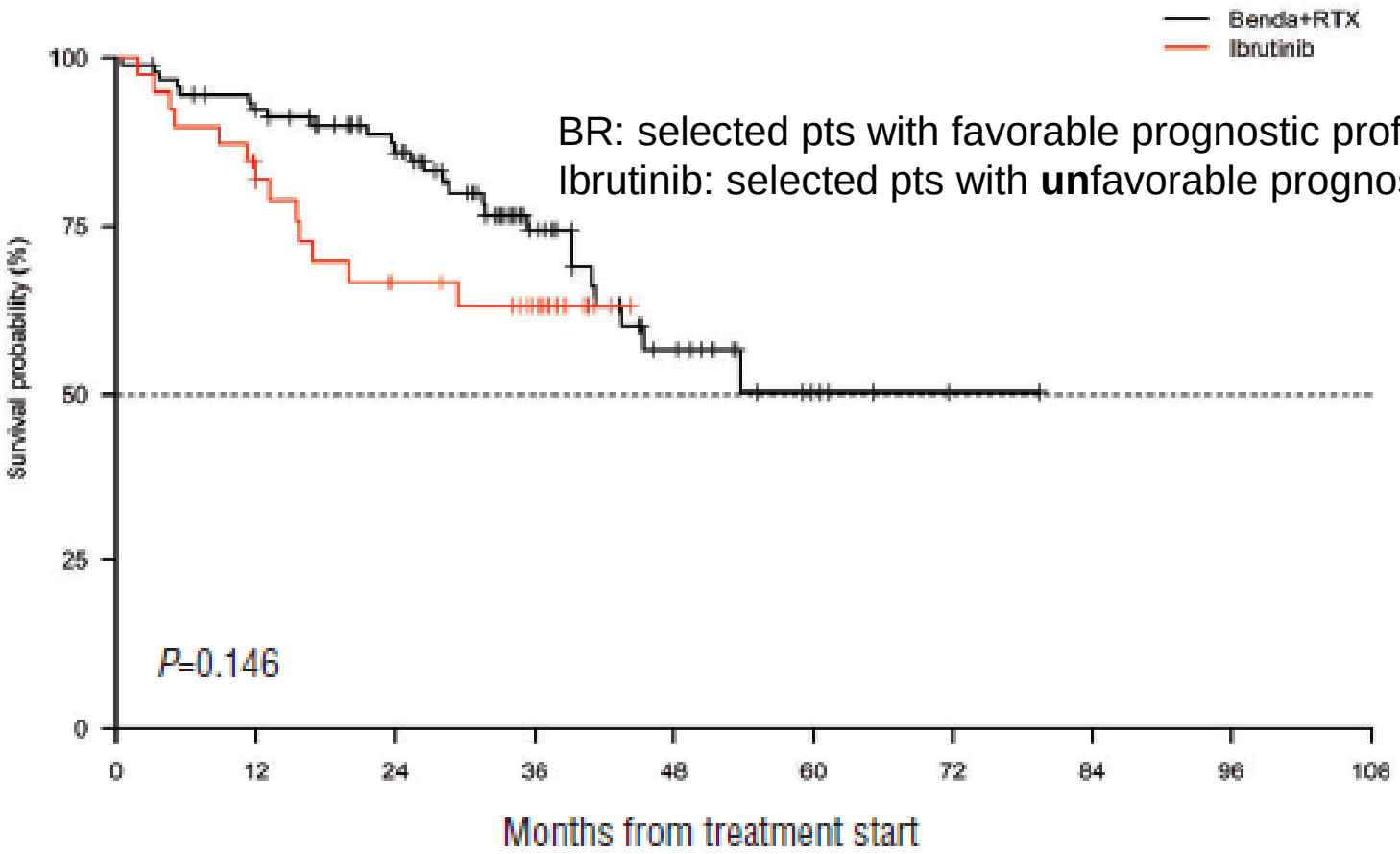


Mato et al., Haematologica 2018

Reason for ibrutinib discontinuation	Ibrutinib in front-line n=19	Ibrutinib in relapse n=231
Toxicity	63.1% (n=12)	50.2% (n=116)
CLL progression	15.8% (n=3)	20.9% (n=49)
Other/unrelated death	5.3% (n=1)	12.1% (n=28)
Physician or patient preference	10.5% (n=2)	6.7% (n=15)
RT DLBCL	5.3% (n=1)	4.6% (n=10)
Stem cell transplantation/CAR T-cell	0	3.3% (n=8)
Financial concerns	0	0.8% (n=2)
Secondary malignancy	0	0.8% (n=2)
RT Hodgkin Lymphoma	0	0.4% (n=1)

Observational trial of ERIC for BR in 1st relapsed CLL

137 pts from an observational trial for BR wihtout TP53 dysfunction :
Indirect comparison with 71 patients receiving Ibrutinib within a NPP

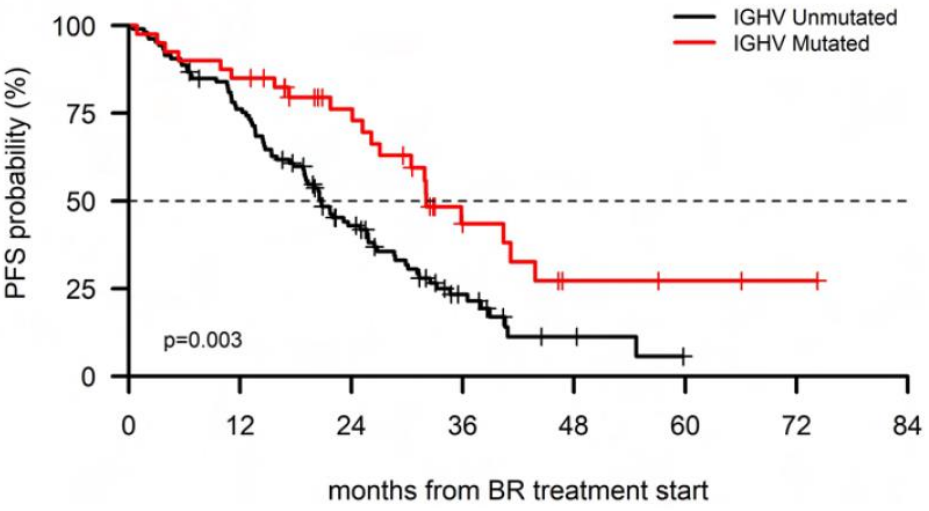


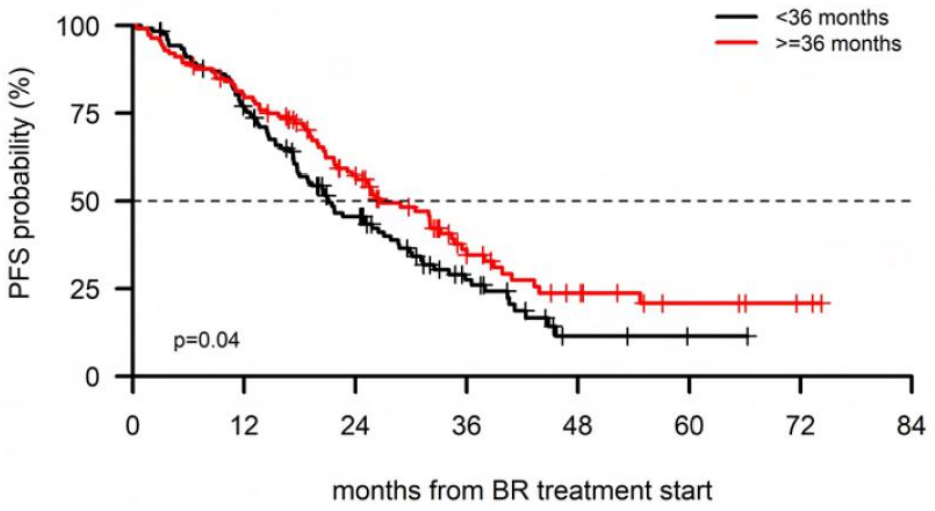
BR: selected pts with favorable prognostic profile
Ibrutinib: selected pts with **un**favorable prognostic profile

Cuneo & Follows et al., Haematologica 2018

Observational trial of ERIC for BR in 1st relapsed CLL

137 pts from an observational trial for BR

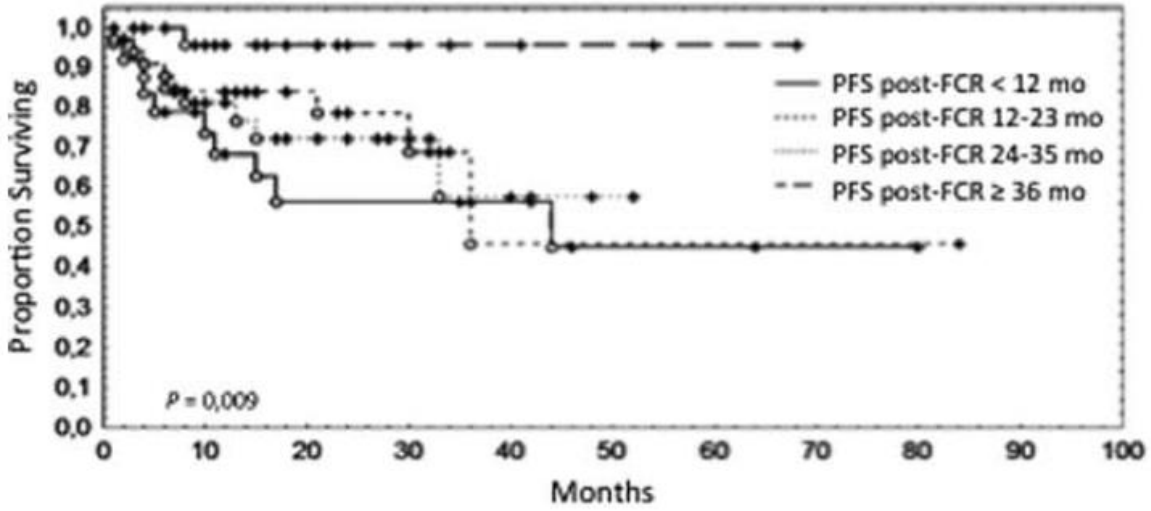




Cuneo and Follows et al., Haematologica 2018

Relapse > 36 months after FCR is associated with good prognosis

42 of 132 pts with late relapse and salvage treatment after 1st line FCR



Fornecker et al., Am J Hematol 2015

Selection of relapse treatment according to toxicity profile

	Ibrutinib	Idelalisib	Venetoclax
Test	EKG	CMV	GFR CT scan
Cave	• Anticoagulans • OP	• CMV • PJP prophylaxis	• High TLS risk
Relative Contra-indication	• Prior bleeing + Anticoag. • Atrial fib	• CMV infection • Transaminitis • Colitis	• Renal insufficiency

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Relative Contra-indication	• Prior bleeing + Anticoag. • Atrial fib • Impaired compliance	• CMV infection • Transaminitis • Colitis • Impaired compliance	• Renal insufficiency • Impaired compliance

Treatment sequence in CLL

Treatment sequence in CLL:
Is there are a role of CIT in pretreated, chemo-naive CLL ?

Use of chemoimmunotherapy in RT to DLBCL

Regimen	n	CR %	ORR%	PFS months	OS months	Ref.
O-CHOP+O-Maintenance	37	25	44	6	11	Eyre et al 2016
R-CHOP	15	7	67	11	27	Langerbeins et al. 2014
R-hyper-CVXD-R-MA	30	38	41	N/A	10	Tsimberidou et al. 2003
Hyper-CVXD	29	38	44	N/A	10	Dabaja et al. 2001
OFAR1	20	20	50	3	8	Tsimberidou et al. 2008
OFAR2	35	6	39	3	6	Tsimberidou et al. 2013
FACPGM	22	5	5	1.5	2.2	Tsimberidou et al. 2002

Still a role for chemoimmunotherapy ?

No, but with some exceptions:

- Long lasting (>36 months) remission to prior chemoimmunotherapy AND no TP53 dysfunction
- No compliance to oral drug intake
- Possibly after failure of several lines of targeted agents in chemo-naive patients
- Richter transformation