UNIKLINIK KÖLN

DEUTSCHE STUDIENGRUPPE

BENDAMUSTINE + RITUXIMAB IN CLL

Barbara Eichhorst

Bologna 13. November 2017

CONFLICT OF INTERESTS

1. **Advisory Boards**

   Janssen, Gilead, Roche, Abbvie, GSK

2. **Honoraria**

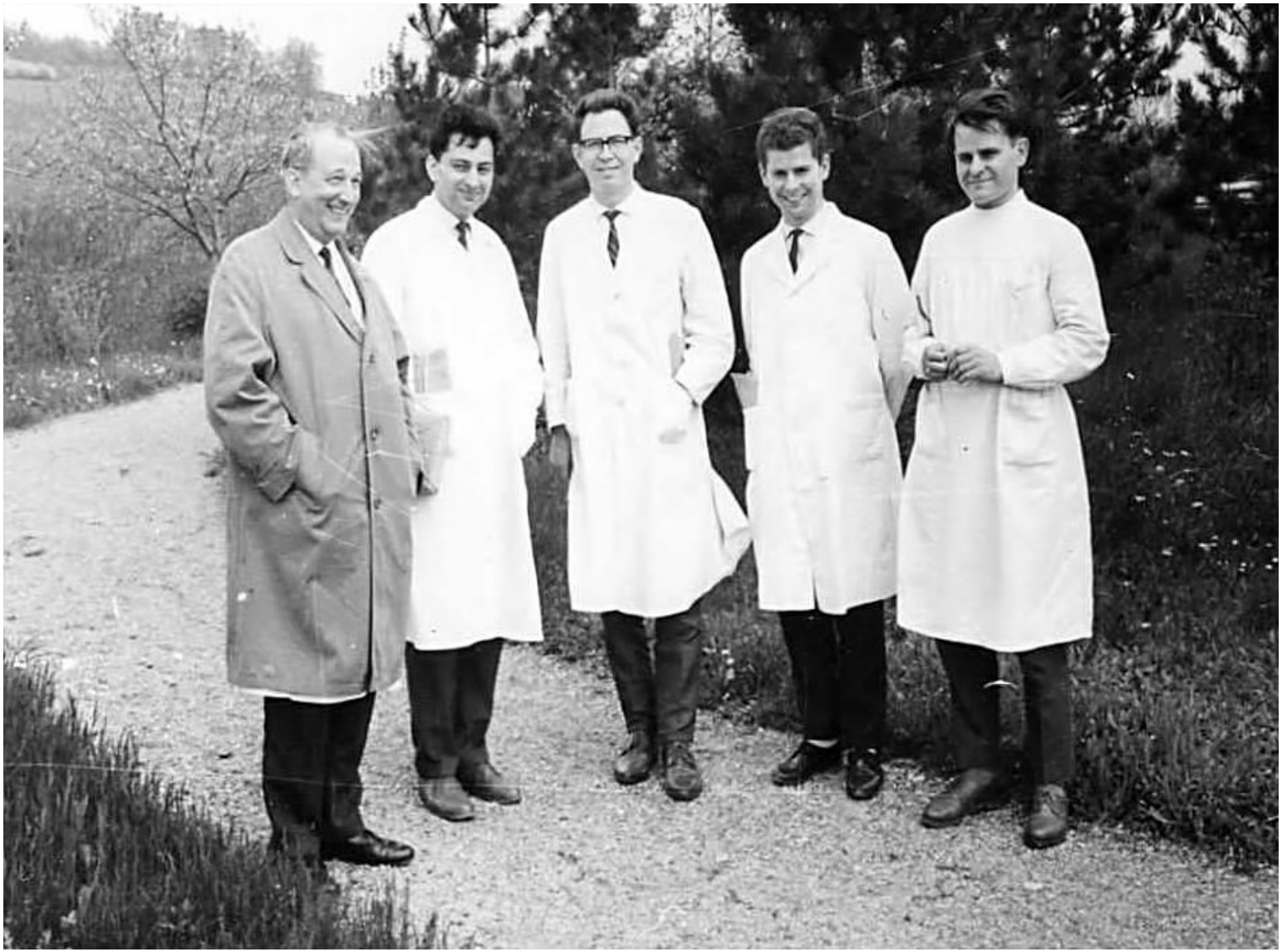
   Roche, GSK, Gilead, Janssen, Abbvie, Celgene

3. **Resarch support**

   Roche, Jannse, Abbvie, Gilead,

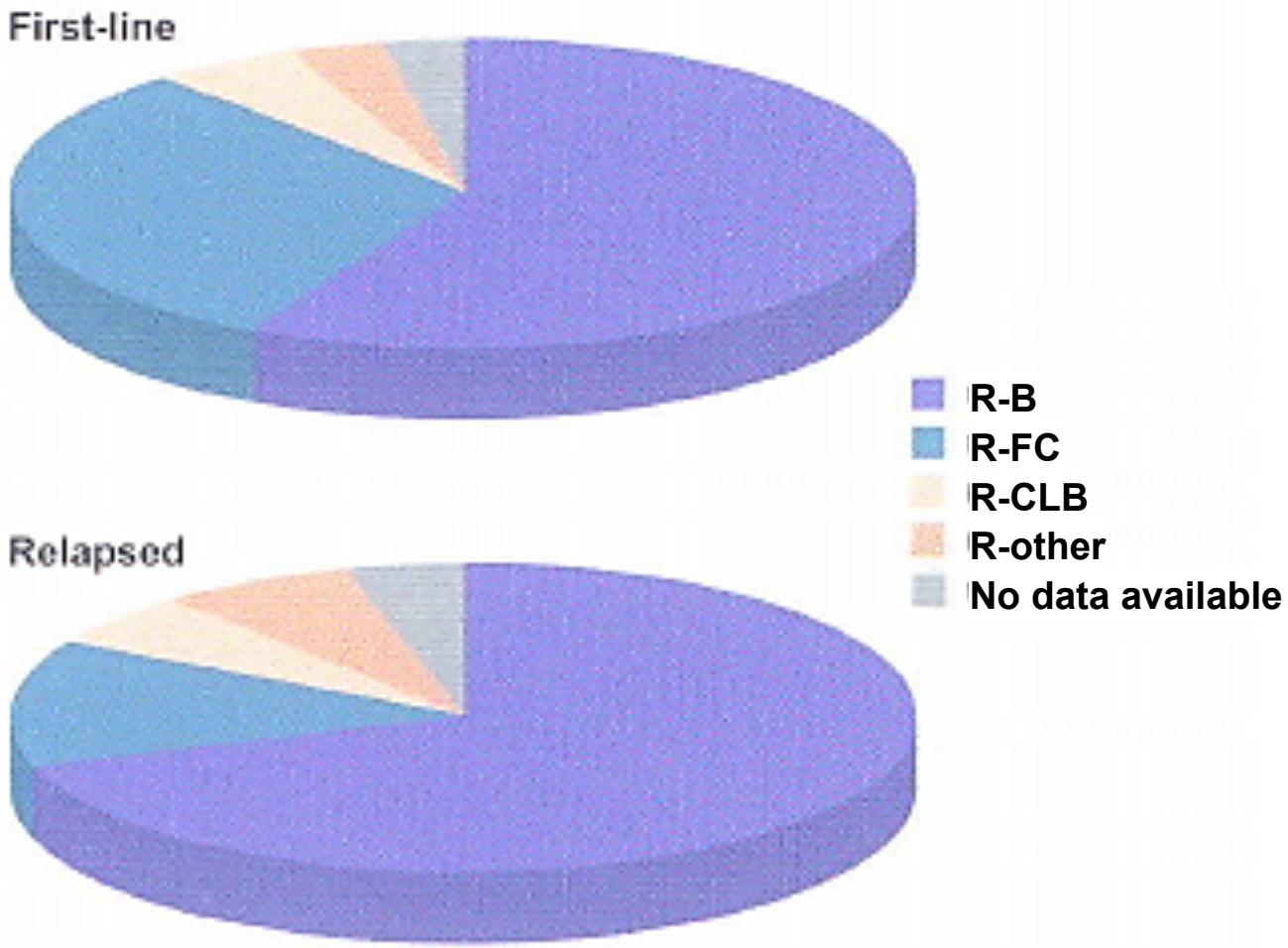
BENDAMUSTINE

W.Ozegowski, D.Krebs, Institute of Microbiology and Experimental Therapy, Jena (1962)



USE OF BR FOR TREATMENT OF CLL IN GERMANY

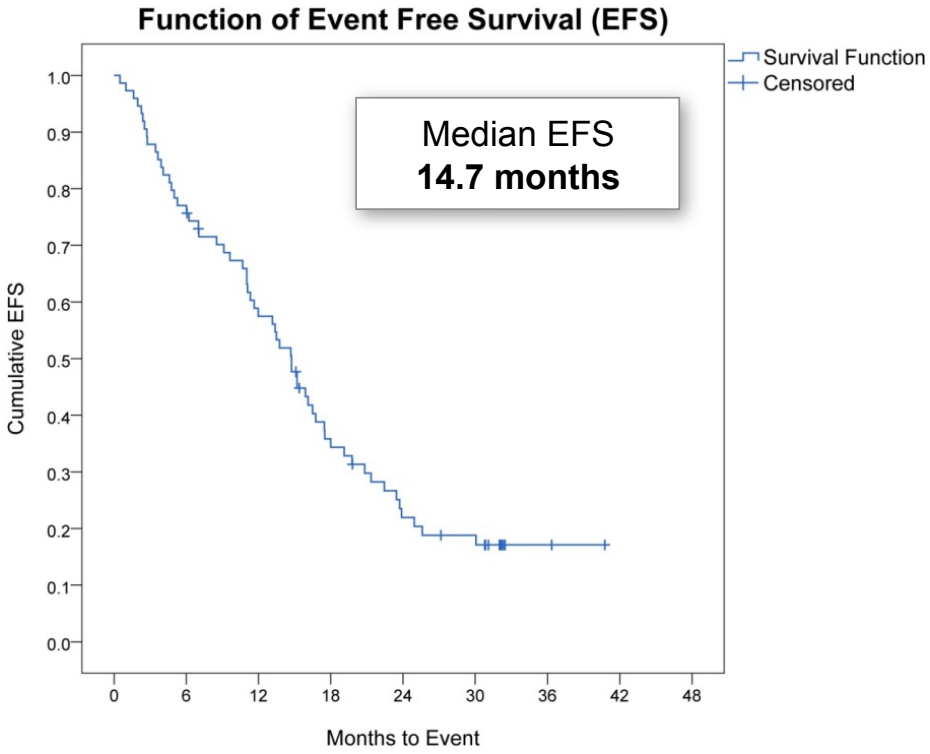
Data of the registry of private hematologists in Germany

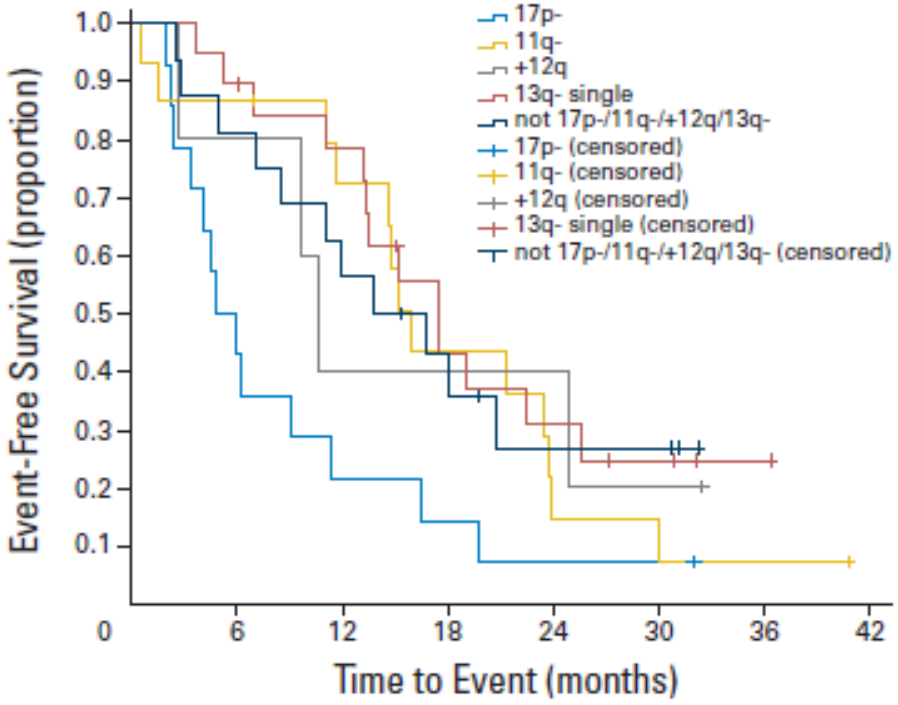


Reiser et al., Poster Presentation at DGHO Annual Meeting 2012

BR IN RELAPSE THERAPY OF CLL

Event free survival (EFS) after 24 months median observation time





Fischer et al., J Clin Oncol. 2011 Sep10;29(26):3559-66

BR IN FIRST LINE THERAPY OF CLL
PHASE II TRIAL IN 117 PATIENTS

Treatment efficacy ITT

Response	N = 117	%
ORR	103	88
CR	27	23

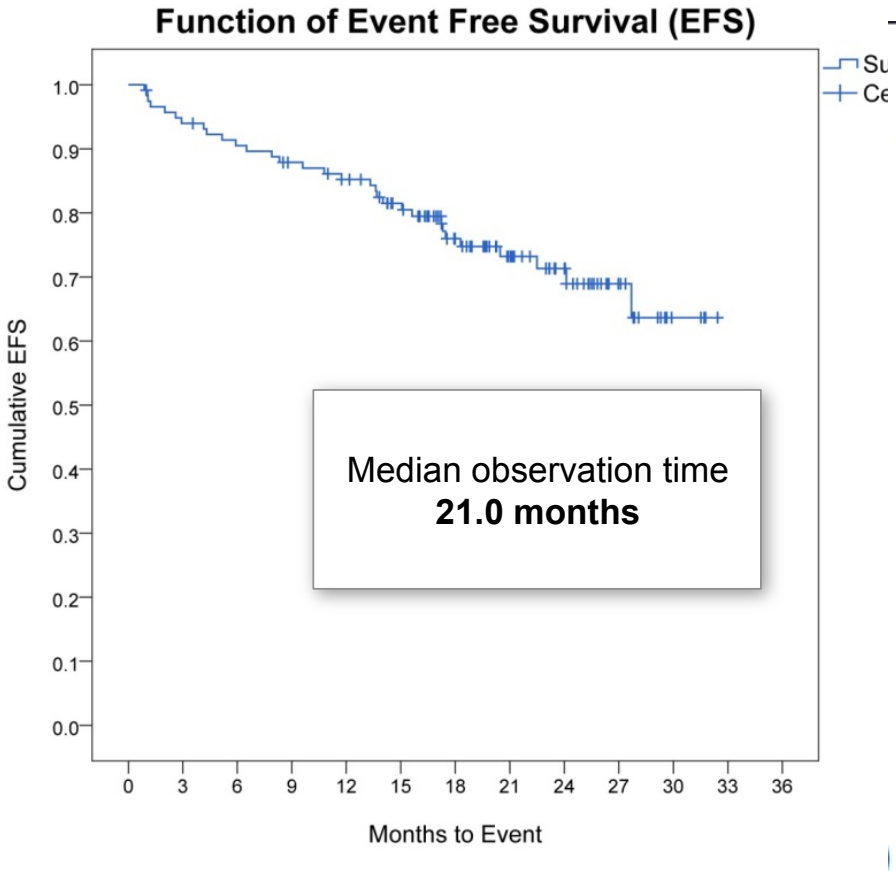
Treatment efficacy in prognostic subgroups

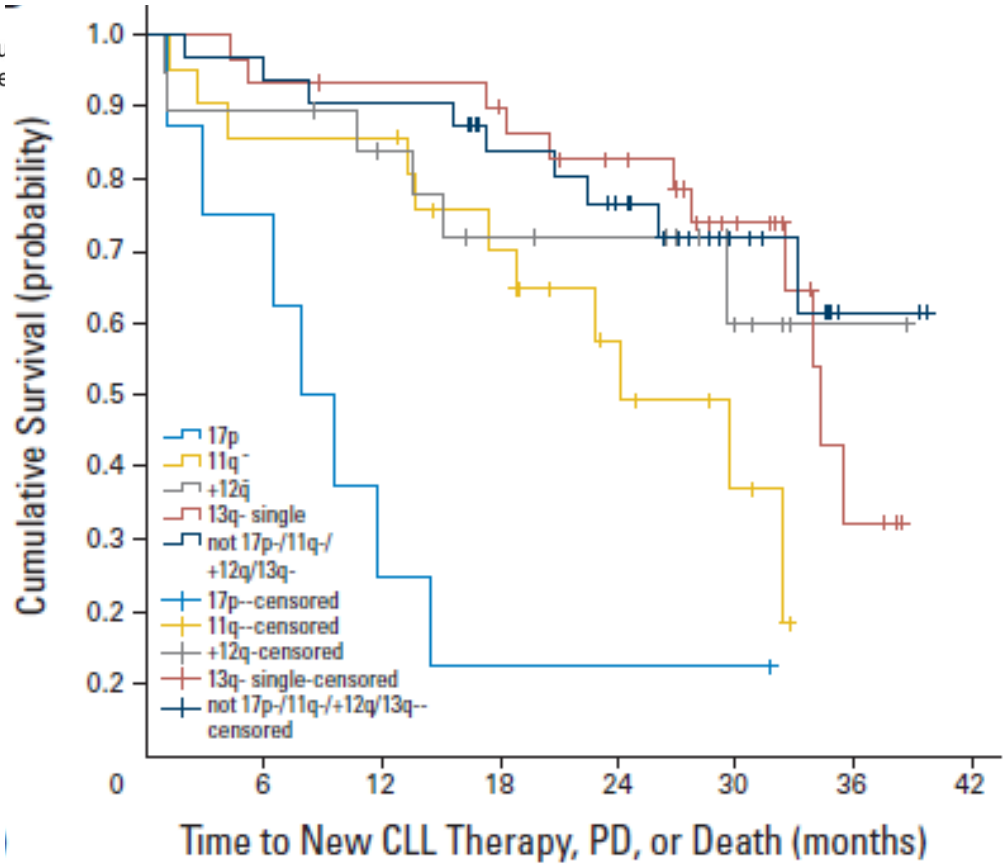
Genetic subgroups*	N	ORR (%)	CR (%)
+12	19	18 (95)	4 (21)
11q-	20	18 (90)	8 (40)
17p-	8	3 (37)	- (-)
IGHV unmutated	66	59 (89)	18 (27)

Fischer et al., JCO 2012

BR IN FIRST LINE THERAPY OF CLL

Event free survival (EFS)





Fischer et al., JCO 2012

BR IN FIRST LINE THERAPY OF CLL

Adverse events

Adverse Events (CTC Version 3.0)	**Grade 3/4/5** (n)	**Grade 3/4/5** (%)
Leukopenia	35	30
Neutropenia	24	20
Thrombocytopenia	27	23
Anemia	24	20
Tumor lysis syndrome	3	3
Hemolysis (before start of therapy)	2	2
Allergic reactions	11	9
Infections	12	10
TRM: 3.4% (3 infections, 1 liver failure)		

Fischer et al., JCO 2012

CLL10 STUDY: FCR VS BR IN FRONT-LINE

Design: Phase III non-inferiority trial

Patients with untreated, active CLL **without del(17p)** and good physical fitness
(CIRS ≤ 6, creatinine clearance ≥ 70 ml/min)

Randomization

FCR

Fludarabine 25 mg/m² i.v., days 1-3
Cyclophosphamide 250 mg/m², days 1-3,
Rituximab 375 mg/ m² i.v. day 0, cycle 1
Rituximab 500 mg/m² i.v. day 1, cycle 2-6

BR

Bendamustine 90mg/m² day 1-2
Rituximab 375 mg/m² day 0, cycle 1
Rituximab 500 mg/m² day 1, cycle 2-6

Eichhorst B et al. Lancet Oncology 2016

CLL10 STUDY: FCR VS BR IN FRONTLINE

ITT Best Response according to IWCLL & MRD

Response	FCR (%) n=282	BR (%) n=279	p value
CR (CR + CRi)	39.7	30.8	0.034
ORR	95.4	95.7	1.0
MRD negativity	**FCR %(N) n=282**	**BR %(N) n=279**	
BM at FR	26.6% (75/282)	11.1% (31/279)	
PB at FR	48.6% (137/282)	38.4% (107/279)	

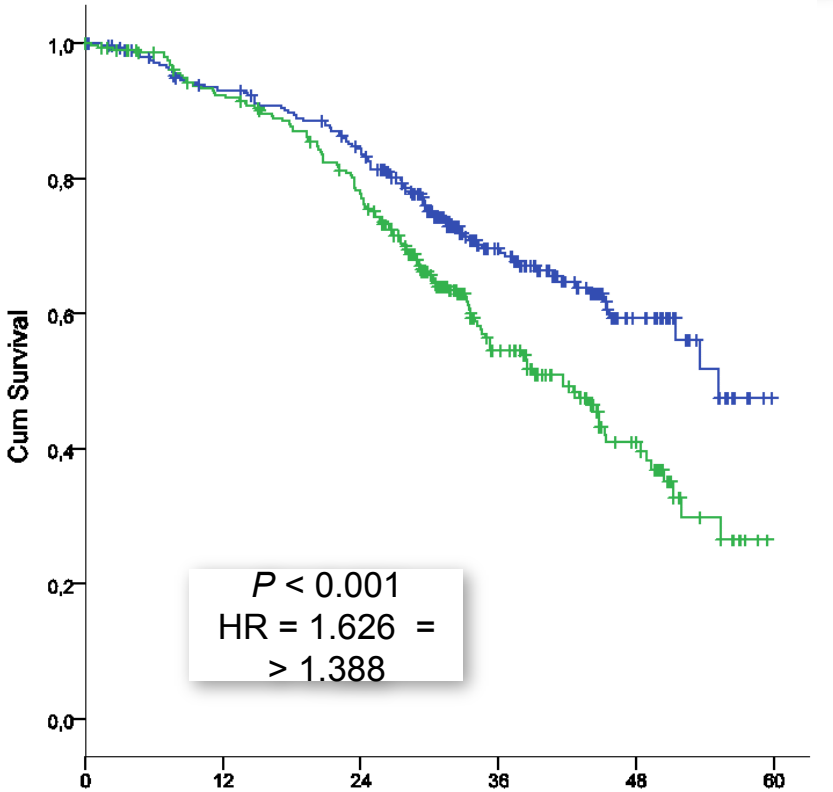
Eichhorst B et al. Lancet Oncology 2016

CLL10 STUDY: FCR VS BR IN FRONT-LINE

ITT Progression-free survival = Primary endpoint

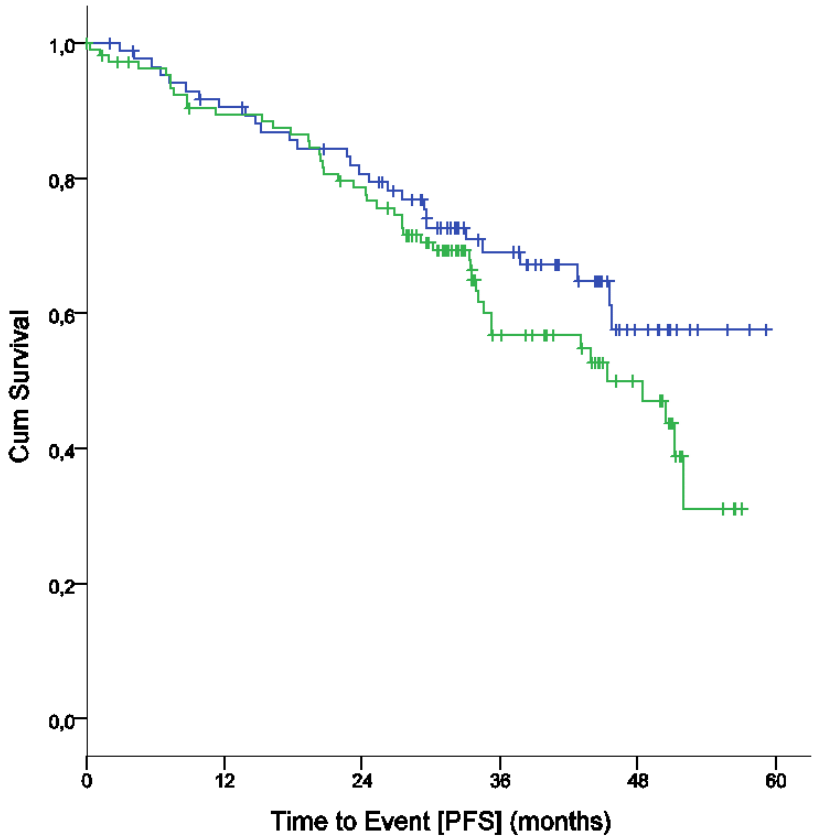
Median PFS all patients

FCR 55.2 months BR 41.7 months



Patients > 65 years: *P = 0.170*

FCR not reached BR 48.5 months



Eichhorst B et al. Lancet Oncology 2016

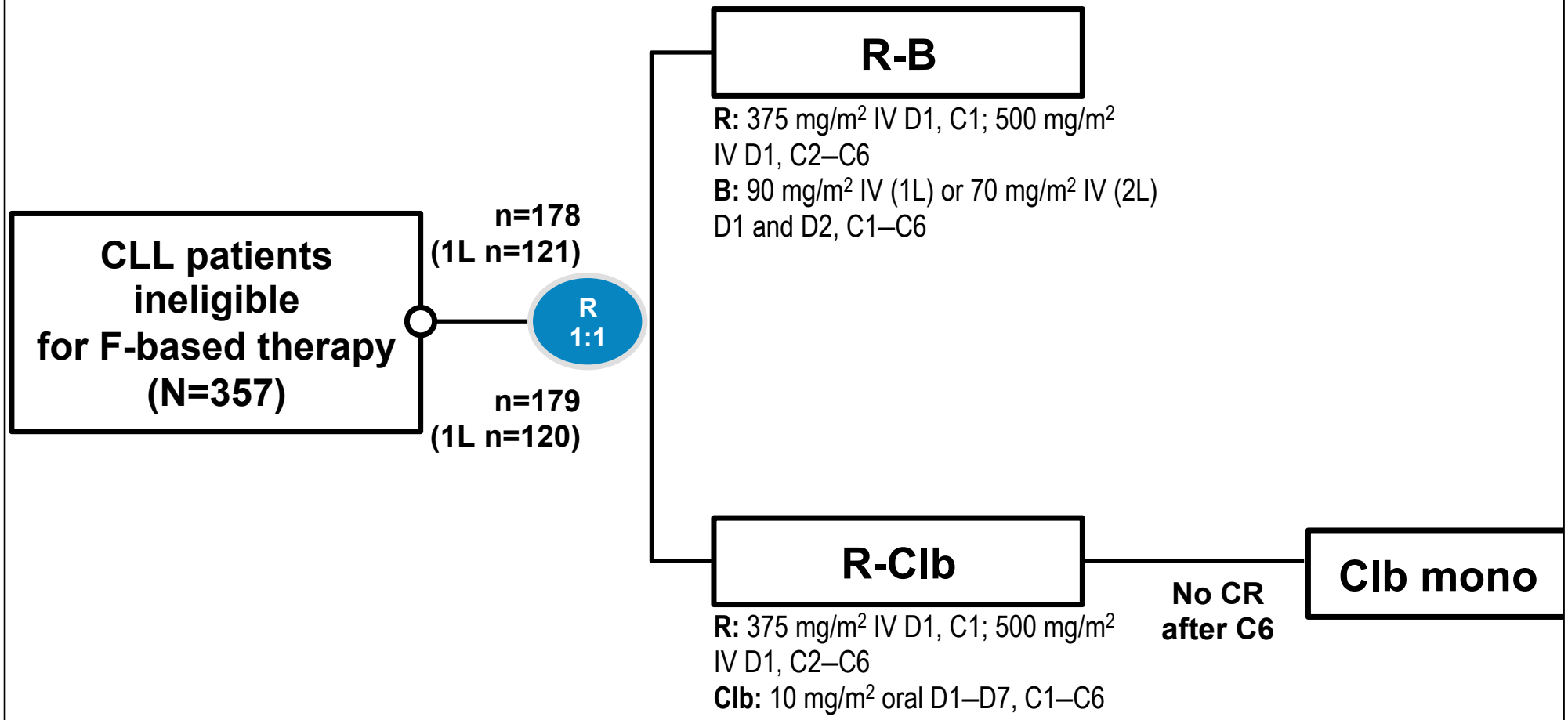
CLL10 TRIAL: TOXICITY

		FCR (n=279)	BR (n=278)
Severe infections	all	35.2	27.5
	> 65 only	47.7	20.6
SPM		49 (18%)	35 (12%)
Solid tumor		28 (10%)	25 (9%)
Skin tumor		9 (3%)	8 (3%)
AML/MDS	all	12 (4%)	2 (1%)
	> 65 only	6 (7%)	1 (1%)
RT		5 (2%)	8 (3%)

GCLLSG CLL10 updated analysis 2016 unpublished

MABLE STUDY: CLBR VS BR IN PTS NOT SUITABLE FOR FCR

Design: Primary endpoint = confirmed CR rate at 6 months

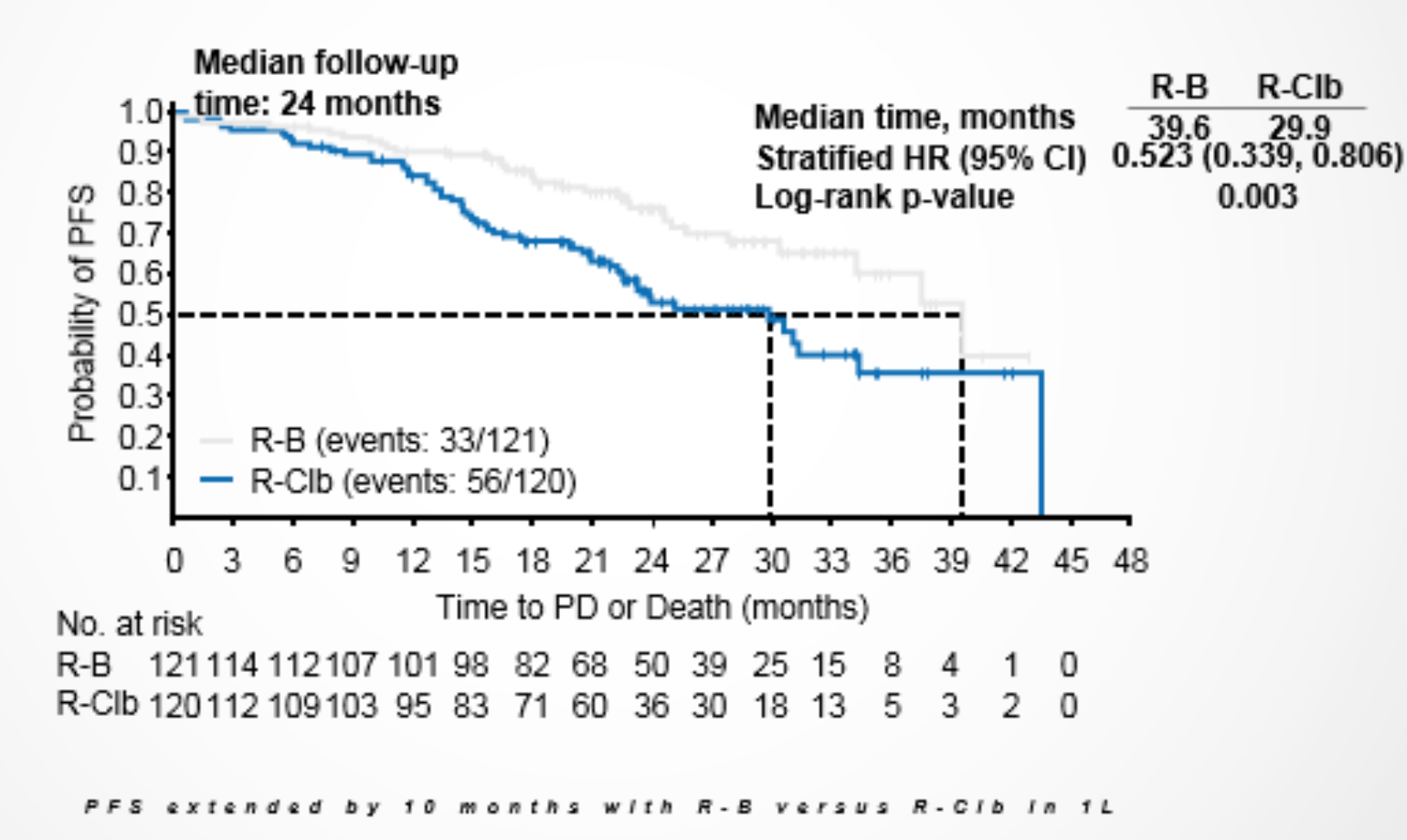


A-S Michallet, IWCLL 2015

MABLE STUDY: CR RATE & PFS

Primary endpoint:

CR rate at C6 was higher with R-B (24%) versus R-Clb (9%; p=0.002)

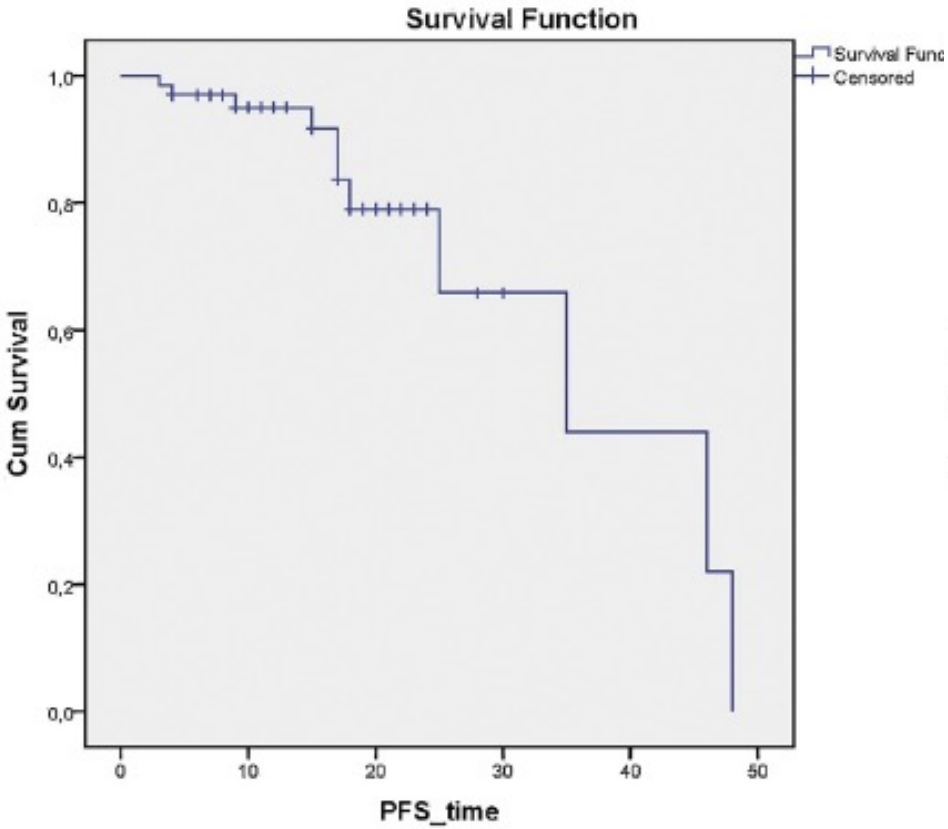


A-S Michallet, IWCLL 2015

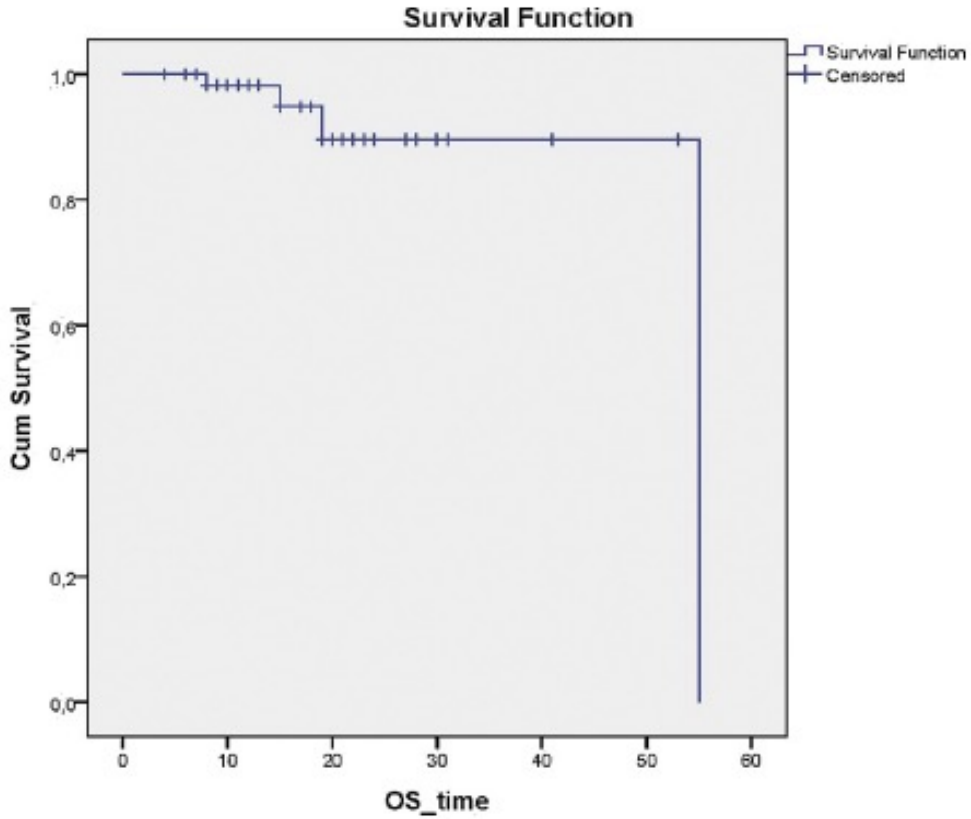
BR IN FRONTLINE OF ELDERLY PATIENTS: REAL WORLD

Retrospective analysis of 70 patients ≥ 65 years in 12 Italian centers

PFS: 79% at 2 years



OS: 89% at 2 years



Laurenti et al, Leuk reserach 2015

Other chemoimmunotherapies based on bendamustin

BENDAMUSTINE PLUS OFATUMUMAB OR OBINUTUZUMAB

BENDAMUSTINE PLUS OFATUMUMAB: PHASE II STUDY

44 patients with previously untreated CLL

Response, n (%)	Response without CT scan (n=44)	Response with CT scan (n=44)
Overall response	42 (95)	37 (84%)
Complete response	19 (43%)	12 (27%)

Flinn et al, Am J Hematol 2017

GREEN-STUDY: RESPONSE ASSESSMENT

Phase IV study in 158 patients receiving bendamustine plus obinutuzuamb

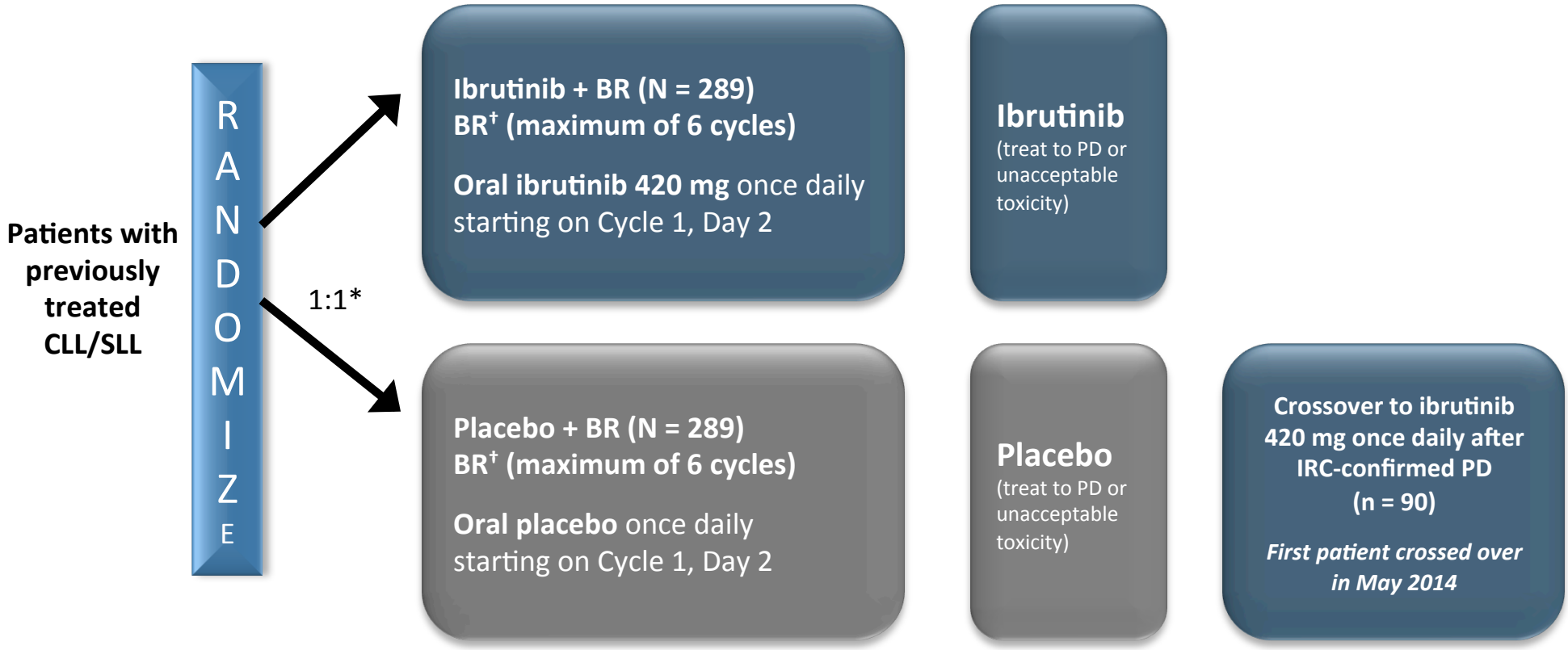
Response, n (%)	G-B cohort, N=158	Fit patients, n=74	Unfit patients, n=84
Overall response	124 (78.5%)	60 (81.1%)	64 (76.2%)
Complete response	51 (32.3%)	22 (29.7%)	29 (34.5%)

Analysis population	Blood	Bone marrow
ITT	93/158 (58.9%)	45/158 (28.5%)
MRD evaluable	93/102 (91.2%)	45/64 (70.3%)

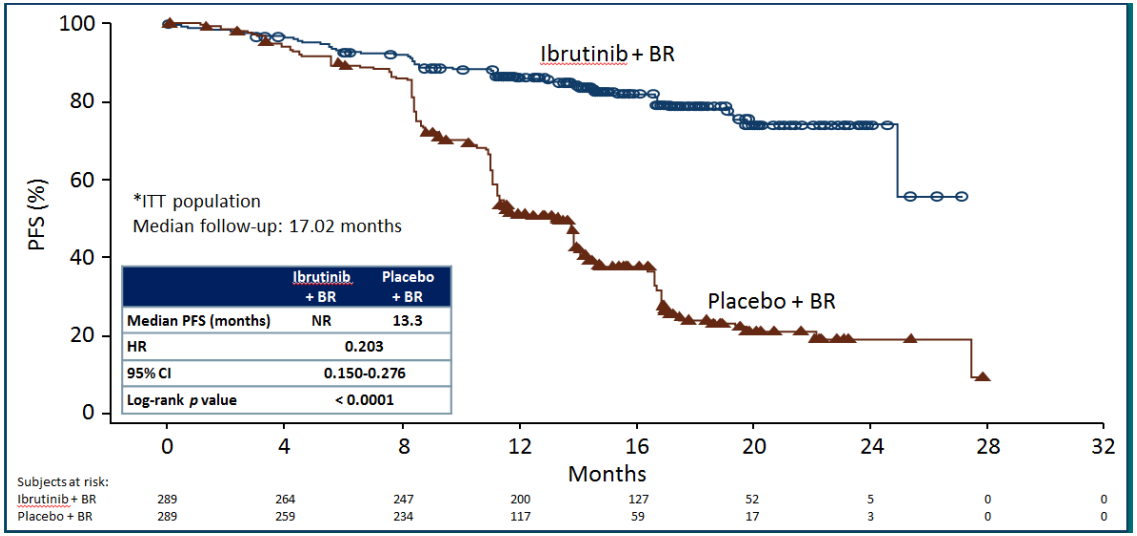
Stilgenbauer S et al. ASH 2017

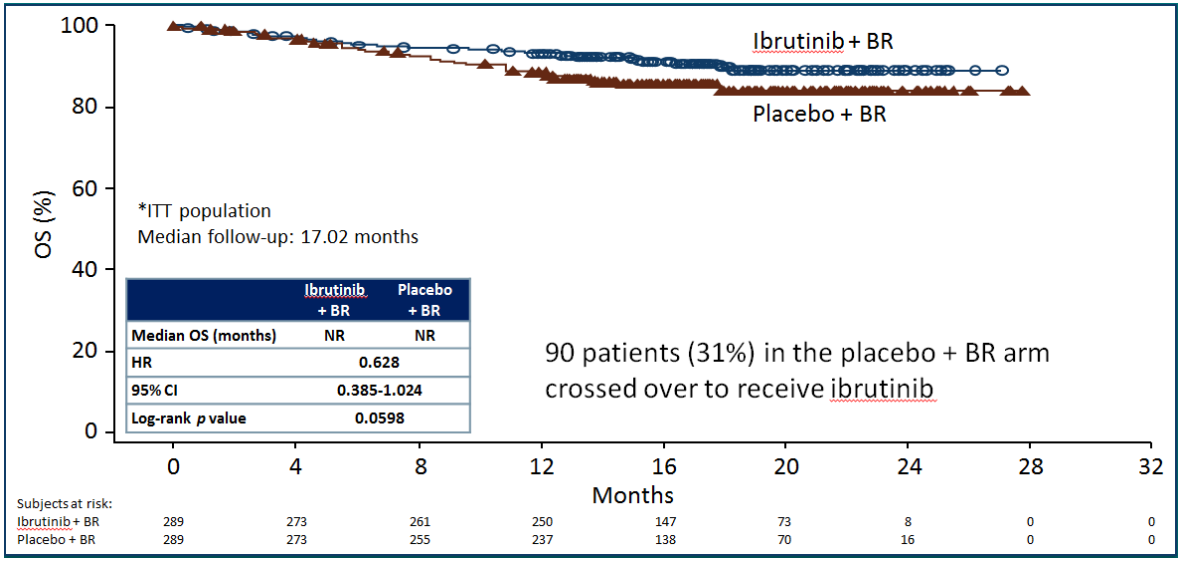
BR IN COMBINATION WITH NOVEL AGENTS

HELIOS: PHASE 3 STUDY DESIGN



BR + IBRUTINIB VS BR + PLACEBO: PFS & OS





Chanan-Khanet al. Lancet Oncol 2016

HELIOS-STUDY MRD NEGATIVITY IN THE IBRUTINIB ARM

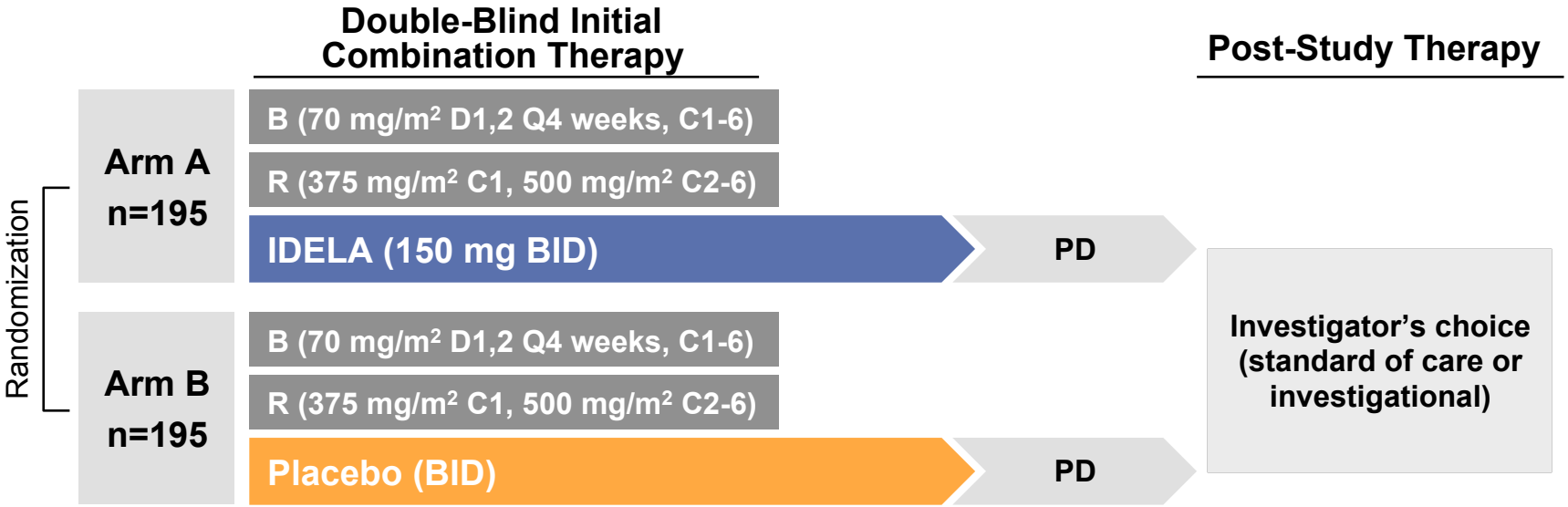
Median observation time of 25 months at 2nd analyses

	BR+Ibrutinib	BR + Placebo
1st analysis at 17 months observation	13%	5%
2nd analysis at 25 months observation	18%	5%

Chanan-Khan et al. EHA 2016

BR +/- IDELALISIB

STUDY 115 DESIGN



Pre-specified interim analysis at 67% of events

Stratification

- 17p deletion and/or TP53 mutation
- IGHV mutation status
- Refractory vs relapsed disease

Endpoints

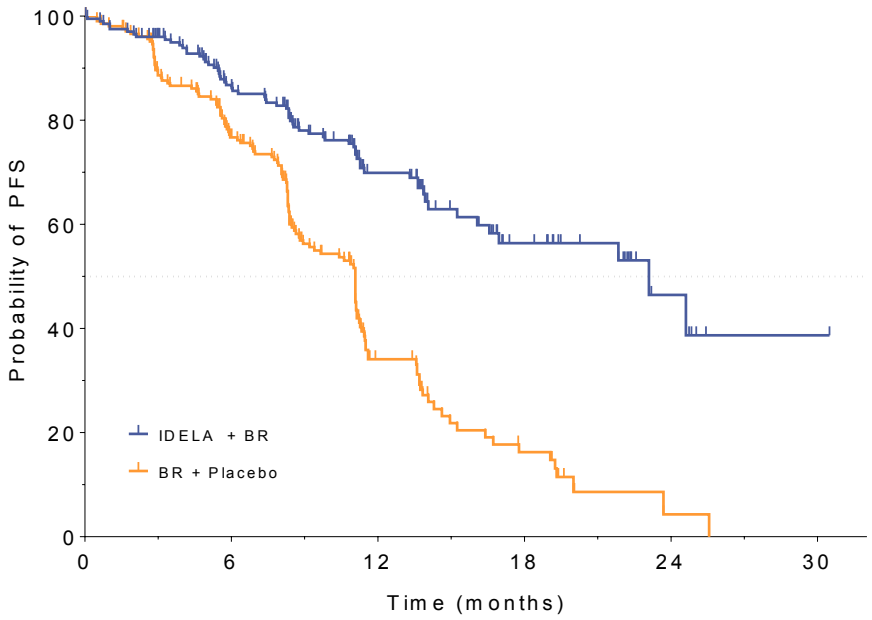
- Primary: PFS
- Secondary: ORR, nodal response, OS, CR

Zelenetz A et al. Lancet Oncol 2017

BR PLUS IDELALISIB VERSUS PLACEBO: PFS & OS

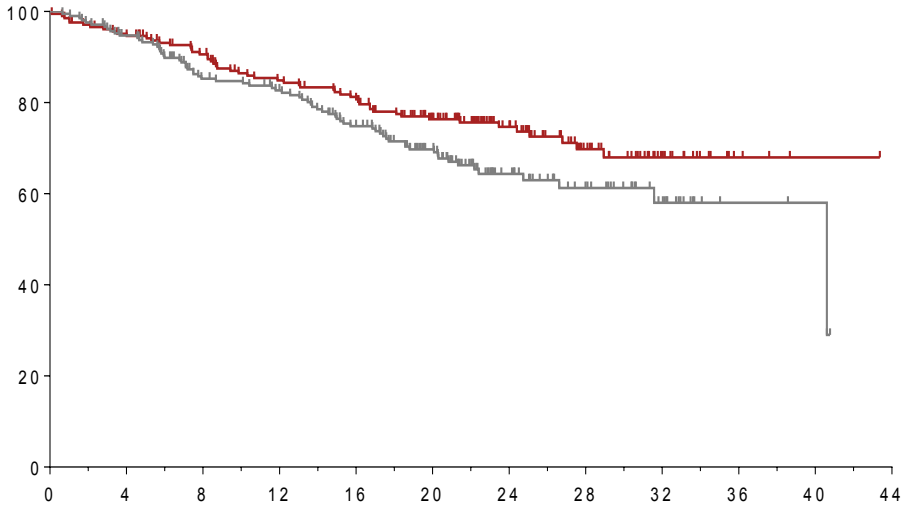
Median observation time 12 mo

	IDELA + BR	BR + Placebo
Median PFS (mo)	23.1	11.1
HR (95% CI)	0.33 (0.24, 0.45)	
p-value	<0.0001	



Median observation time 21 mo

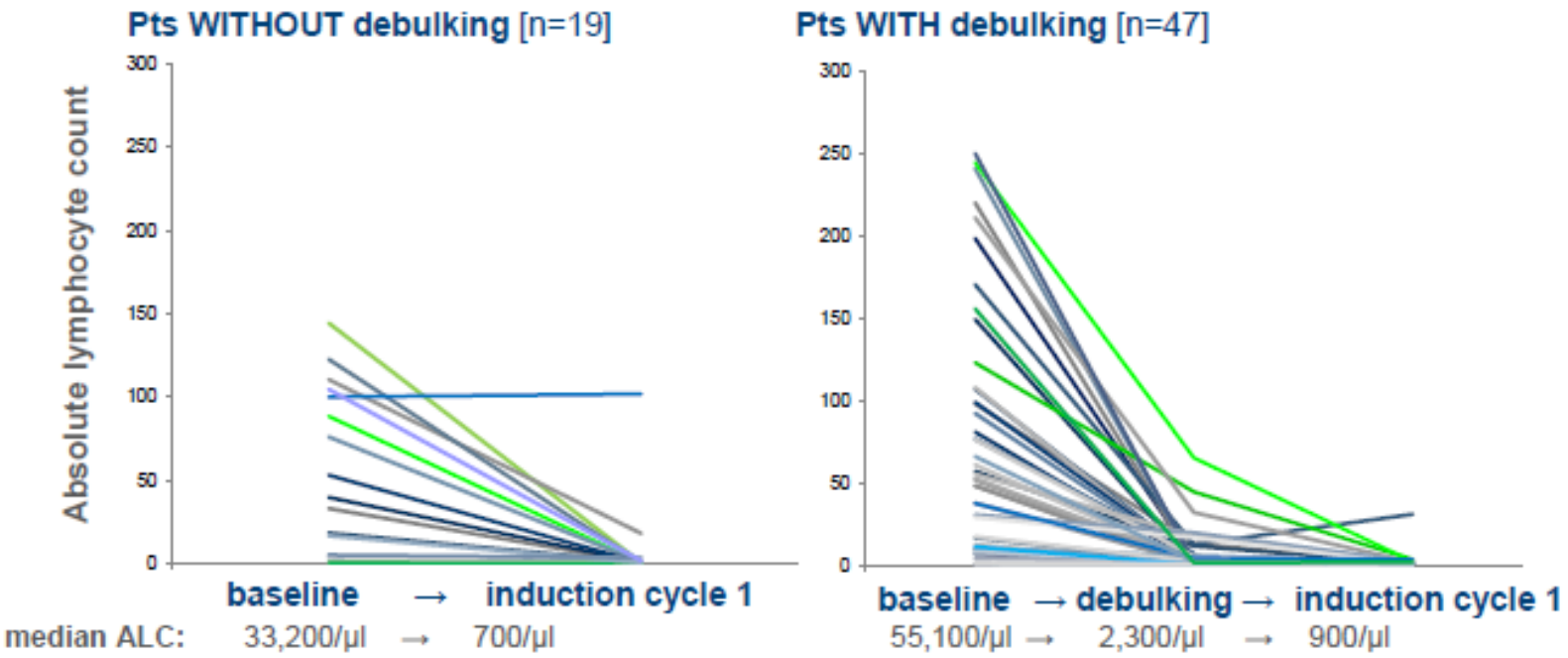
	IDELA+BR	PBO+BR
Median OS, mo	NR	40.6
Hazard Ratio, 95% CI	0.67 (0.47, 0.96)*	
P-value	0.04 (stratified)†	
Median follow-up, mo (range)	21 (0.1, 43.3)	



Zelenetz A et al. Lancet Oncol 2017/ Zelentz et al. ASH 2016

FUTURE POSSIBLE ROLE OF BENDAMUSTINE: DEBULKING ?

Debulking with 1 – 2 cycles Bendamustine bevor Venetoclax + Obinutuzumab:
Phase II including 66 treatment naive and relapsed CLL patients



Cramer et al. ASH 2016

SUMMARY

- BR is a feasible and effective 1st line therapy
  in elderly patients without TP53 mut/del
- No very long lasting remission duration observed with BR
- B + Ofa alternative combination, but less data availble
- B + Obi with higher rates of MRD negativity, but not approved
- The benefit of combinations of BR with kinase inhibitors
  in R/R CLL is unclear
- Possible benefit of BR in the future: debulking ?

DEUTSCHE STUDIENGRUPPE

For prevention of toxic epidermal necrolysis with bendamustine the following safety precautions should be undertaken:

- No Cotrimoxazole prophylaxis for PJP during treatment with bendamustine
- Low dose steroid administration (f.e. 20mg prednisolone daily) d1-d10 of cycle 1 with bendamustine
- Stop Allopurinol 48h before bendamustine adminsitration and restart 24h after day 2 administration.

The MRD negativity rate measured in peripheral blood at the end BR frontline treatment ranges between:

- > 70%
- 55-70%
- 40-54%
- 25-39%
- 10-24%

Which statement is NOT correct?

- BR has not been comapred to CLB+Obinnnutuzumab
- BR is superior to CLBR
- BR is not inferior to FCR
- There is no OS difference between BR and FCR
- There is no OS difference between CLBR and BR