CORSO TEORICO-PRATICO PER LA GESTIONE OTTIMALE DEI PAZIENTI AFFETTI DA LINFOMA MANTELLARE, LINFOMA FOLLICOLARE E LEUCEMIA LINFATICA CRONICA

Torino, 21-23 Maggio 2018

LEUCEMIA LINFATICA CRONICA: TERAPIA DEL PAZIENTE IN RECIDIVA

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Guidelines for Diagnosis, Indications for Treatment, Response Assessment and Supportive Management of Chronic Lymphocytic Leukemia (NCI/IWCLL 2018 update)

- **Refractory** disease is defined as treatment failure (i.e. response <PR) or as progression within 6 months from the last dose of therapy
- **Relapse** is defined as evidence of disease progression in a patient who has previously achieved the criteria of a CR or PR for a period of 6 or more months
- **Disease relapse is not a criterion** to re-start therapy unless the disease is progressive and symptomatic
- Second-line treatment decisions should follow the **same indications** as those used **for first-line treatment**

Hallek M. et al., Blood 2018

Response evaluation

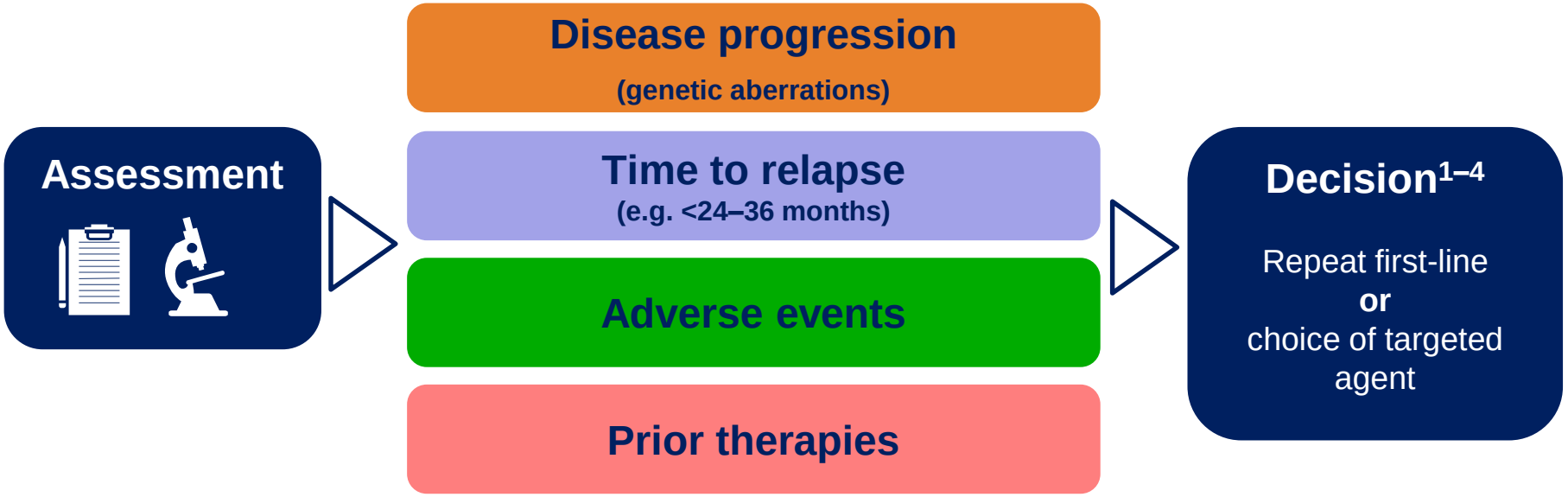
GROUP	PARAMETER	CR	PR	PD	SD
A	Lymph nodes	None ≥ 1,5 cm	Decrease ≥ 50% (from baseline) [1)]	Increase ≥ 50% from baseline or from response	Change of -49% to +49%
	Liver and/or spleen size*	Spleen size < 13 cm; liver size normal	Decrease ≥ 50% (from baseline)	Increase ≥ 50% from baseline or from response	Change of -49% to +49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline	Change of -49% to +49%
B	Platelet count	≥ 100.000/µl	≥ 100.000/µl or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL	Change of -49 to +49%
	Hemoglobin	≥ 11,0 g/dl (untransfused and without erythropoietin)	≥ 11 g/dl or increase ≥ 50% over baseline	Decrease of ≥ 2 g/dl from baseline secondary to CLL	Increase < 11,0 g/dl or < 50% over baseline, or decrease < 2 g/dl
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules.	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥ 50% on successive biopsies	No change in marrow infiltrate
		All	**1A + 1 B**	**Only 1**	**All**

When to treat?
The concept of active disease

1. Evidence of progressive **marrow failure** (anemia and/or thrombocytopenia)
2. Massive or progressive or symptomatic **splenomegaly**
3. **Massive nodes** (i.e., 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
4. **Progressive lymphocytosis** (increase of more than 50% over a 2-month period or LDT of less than 6 months
5. **Autoimmune anemia and/or thrombocytopenia** poorly responsive to corticosteroids or other standard therapy
6. Disease-related **symptoms** (weight loss, significant fatigue, fever, night sweats)

Hallek M. et al., Blood 2018

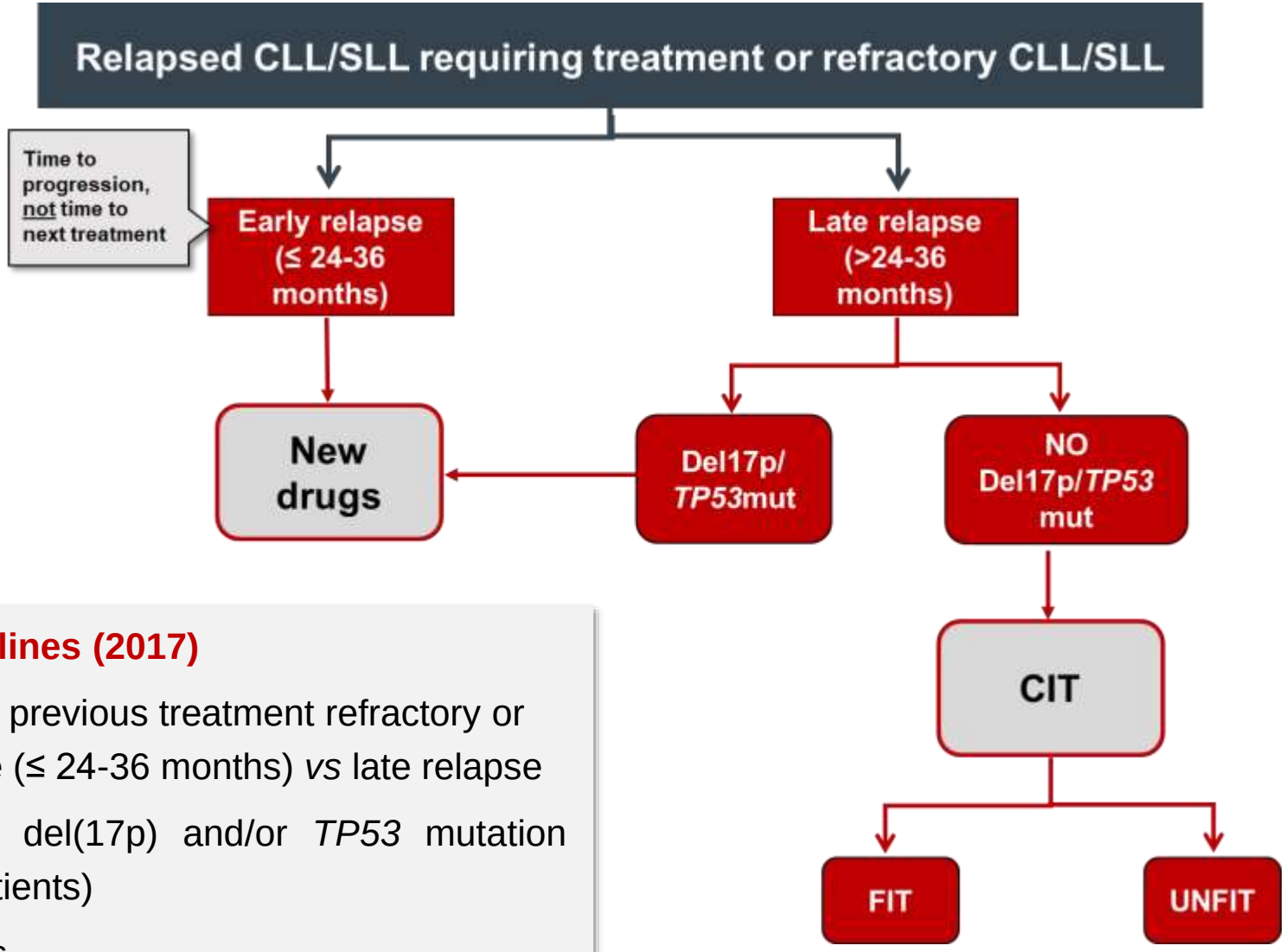
Second-line treatment decisions



Choice of subsequent treatments is strongly influenced by the response to first-line treatment

1. Hallek M, *et al. Blood*. 2008;111:5446–5456.
2. Hallek M, *et al.* iwCLL 2017 (Oral).
3. Eichhorst B, *et al. Ann Oncol* 2015; 26(Suppl 5):v78–v84. 4. ESMO eUpdate (Jun 2017; available at: http://www.esmo.org/Guidelines/Haematological-Malignancies/Chronic-Lymphocytic-Leukaemia/eUpdate-Treatment-Recommendations).

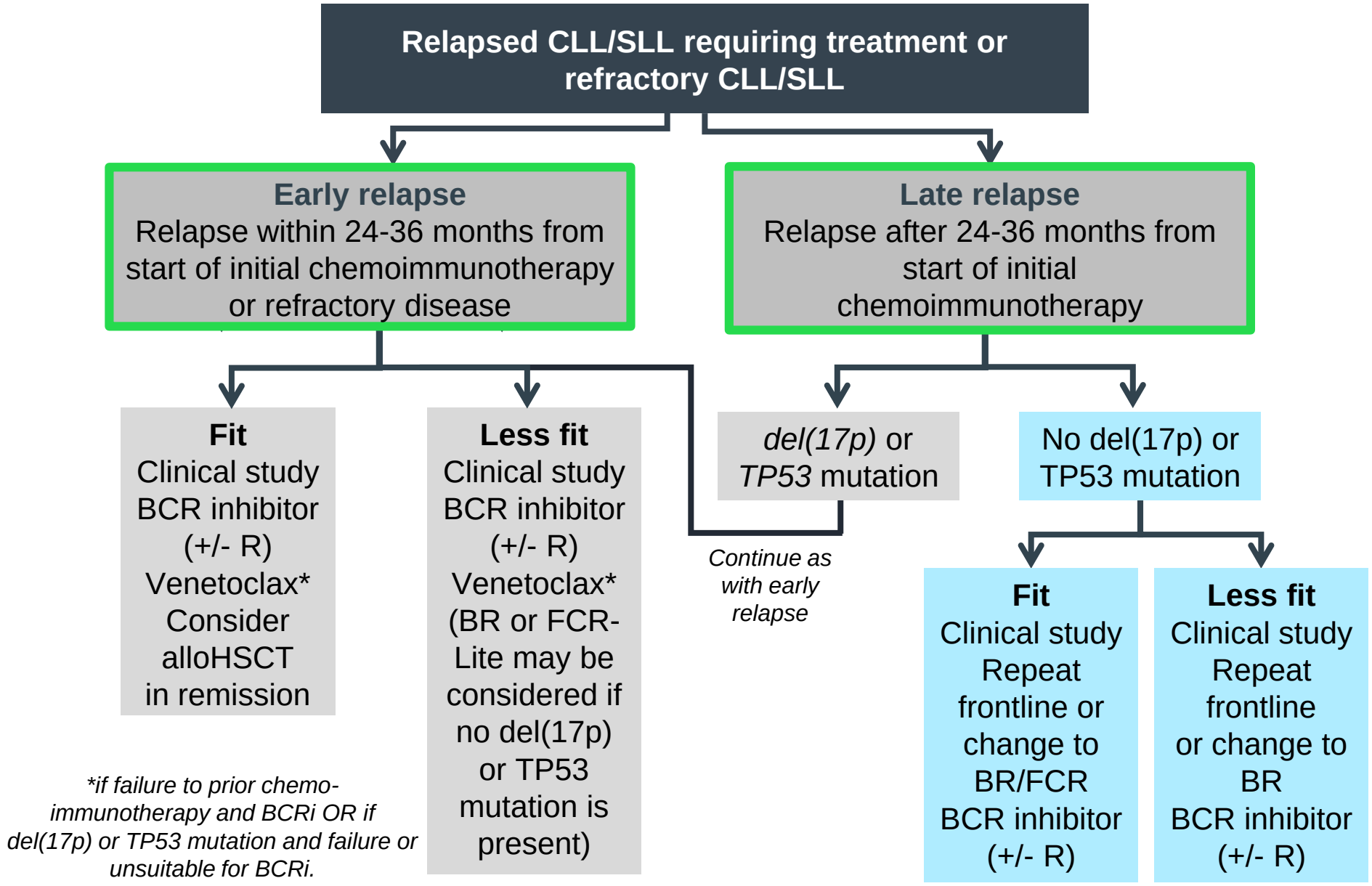
How to treat?
Criteria for treatment choice in R/R CLL



ESMO Guidelines (2017)

- Response to previous treatment refractory or early relapse (≤ 24-36 months) *vs* late relapse
- presence of del(17p) and/or *TP53* mutation (high risk patients)
- fitness status

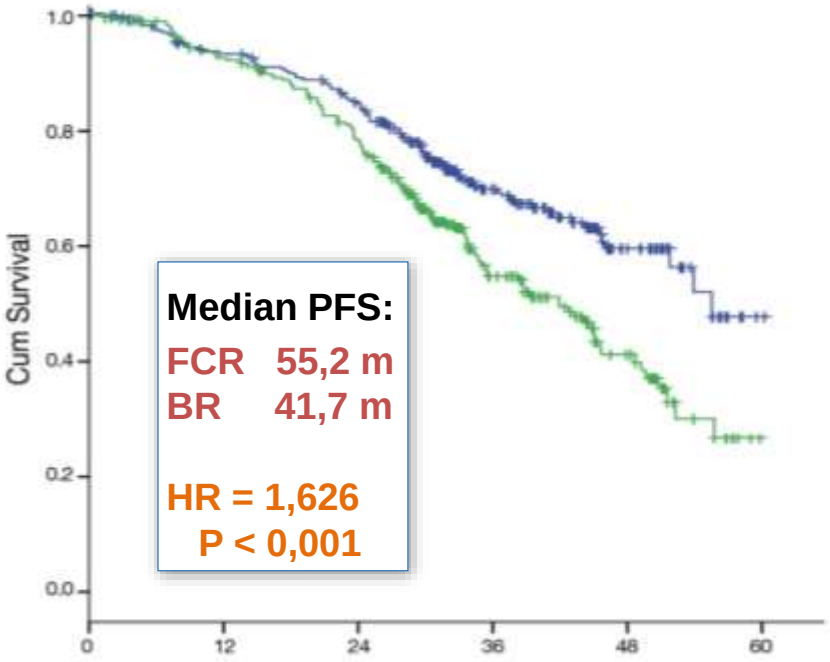
ESMO guidelines 2017 – R/R CLL



**if failure to prior chemo-immunotherapy and BCRi OR if del(17p) or TP53 mutation and failure or unsuitable for BCRi.*

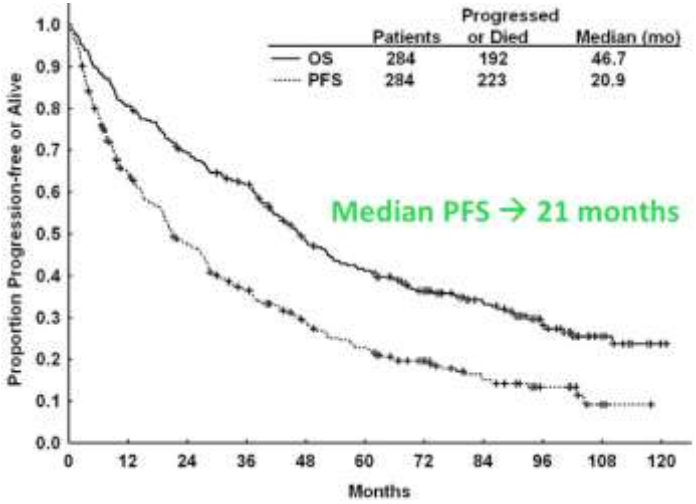
CIT at relapse

CLL10 - FCR vs BR in TN CLL



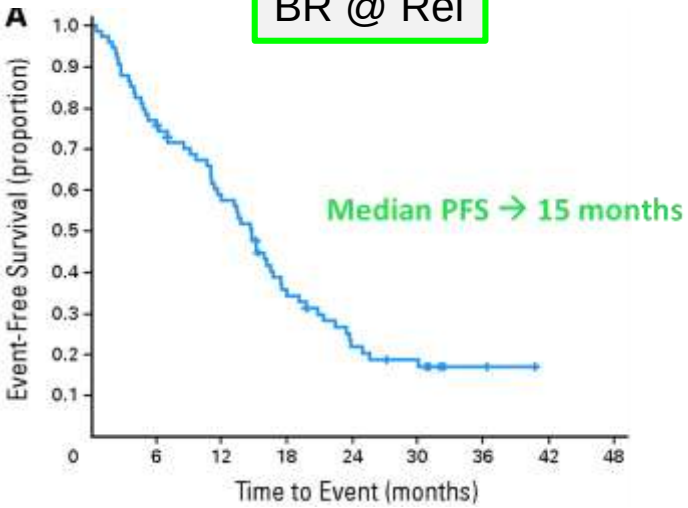
Eichhorst B. et al, Abstract #19 & oral presentation, ASH 2014

FCR @ Rel



Badoux XC et al., Blood 2011

BR @ Rel

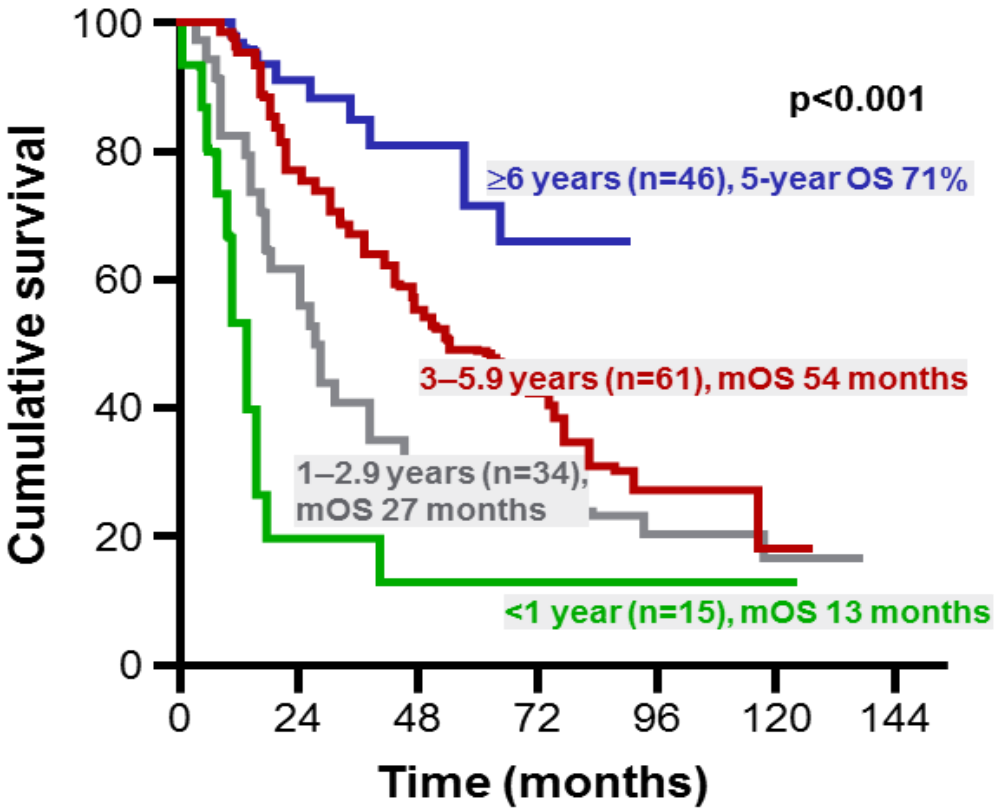


Fischer K. et al., J Clin Oncol 2011

Early relapse after FCR

Survival is short in patients with CLL who relapse early after FCR

(treated with conventional salvage regimens)

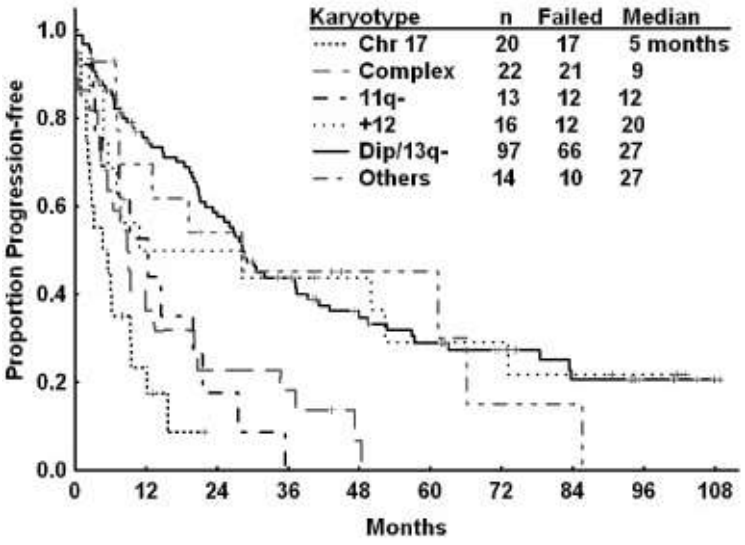


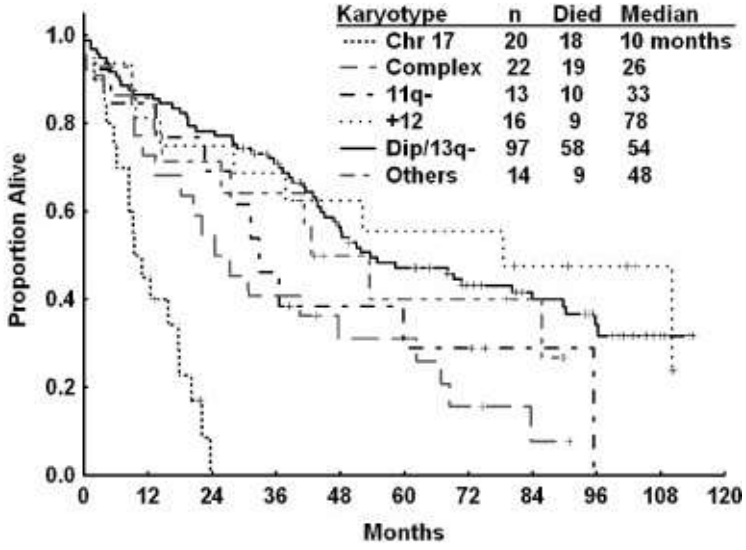
- 32% of patients relapse <3 years after 1st line FCR (REM1) → median OS 2.5 y
- In multivariate analysis a REM1 <3 y is a strong predictor for a short post-progression survival

Tam CS, et al. Blood 2014; 124:3059–3064

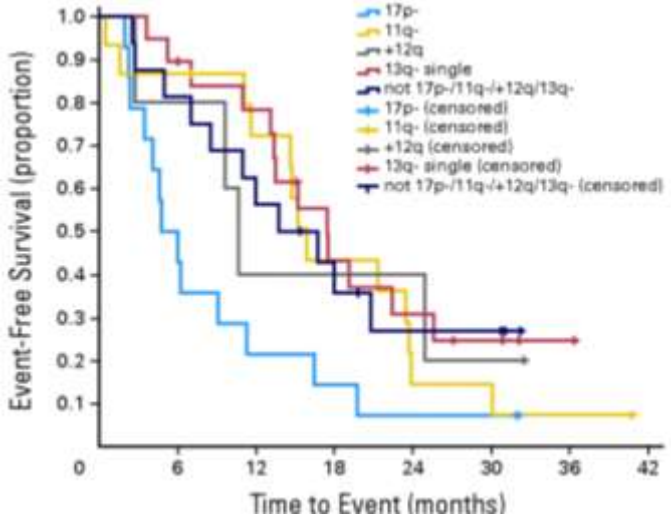
CIT at relapse – subgroup analysis

FCR @ Rel



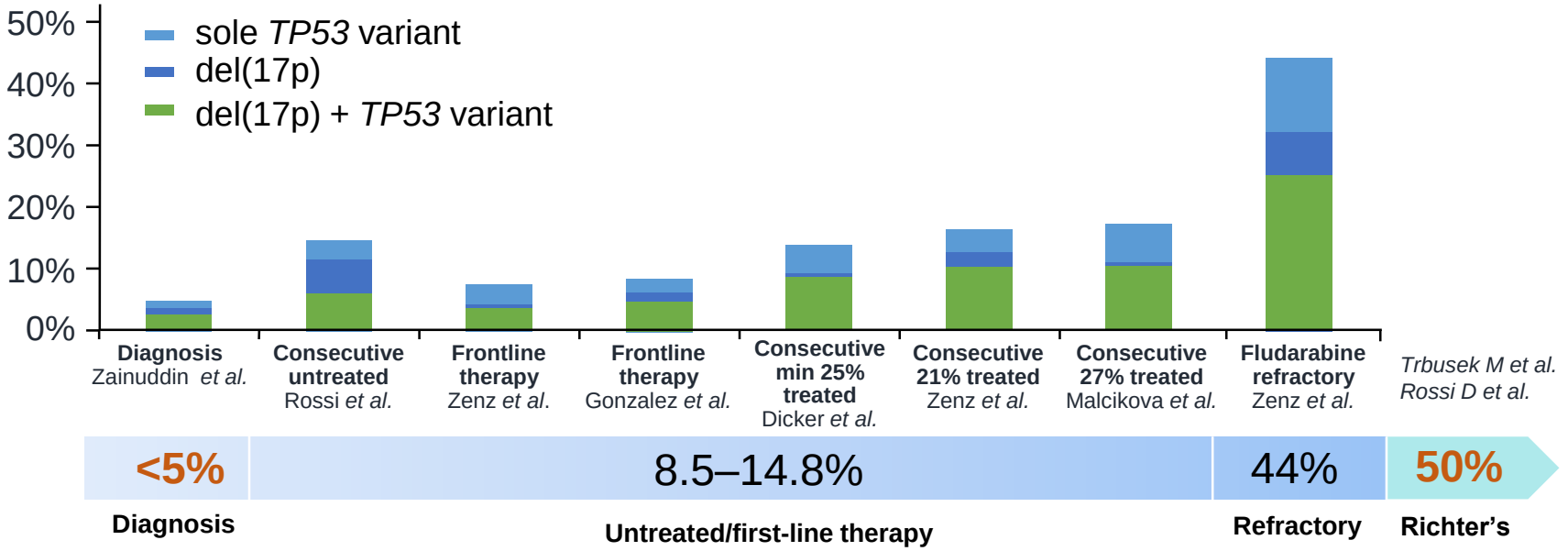


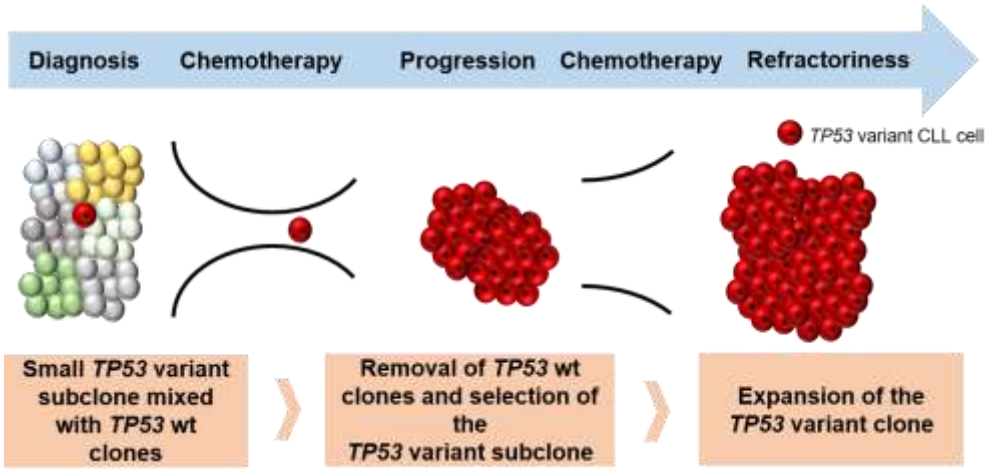
BR @ Rel



PFS <6 months in R/R del(17p) CLL patients treated with FCR or BR

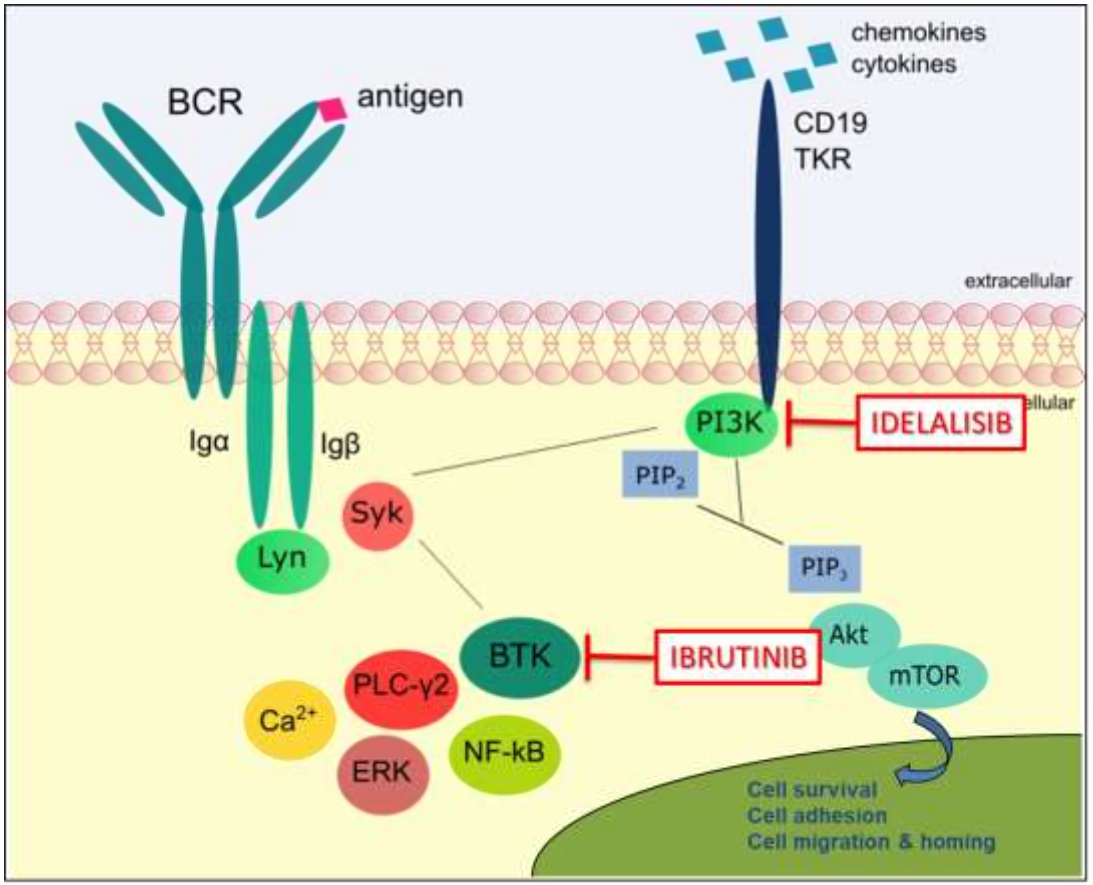
Incidence of TP53 aberrations increases with disease progression and lines of treatment

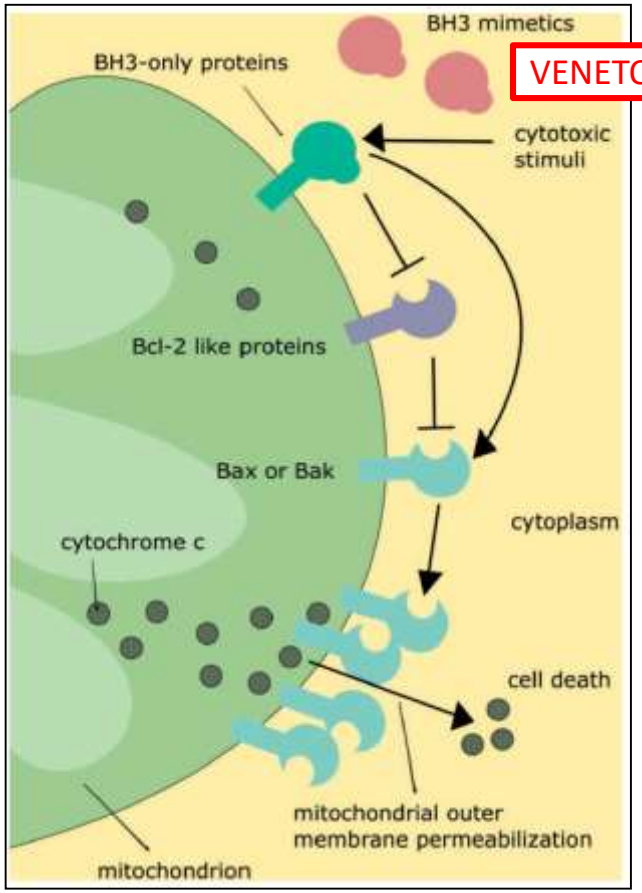




Rossi D, *et al. Blood* 2014;123:2139–47

New drugs for CLL treatment – BCR inhibitors and Bcl-2 inhibitors





Modified from Vitale C et al., Expert Opin Pharmacother 2017

NCCN guidelines 2018 – R/R CLL

del(17p)/*TP53* mutation

NO

Relapsed/Refractory Therapy

- Age <65 y without significant comorbidities
  - Preferred regimens
    - ◊ Ibrutinib[c] (category 1)
    - ◊ Idelalisib + rituximab[c,j] (category 1)
    - ◊ Venetoclax[c,k] + rituximab (category 1)
  - Other recommended regimens
    - ◊ Acalabrutinib[c,l]
    - ◊ Alemtuzumab[n] ± rituximab
    - ◊ Bendamustine + rituximab
    - ◊ FC + ofatumumab
    - ◊ FCR[f,g,h]
    - ◊ HDMP + rituximab
    - ◊ Idelalisib[c]
    - ◊ Lenalidomide[m] ± rituximab
    - ◊ Obinutuzumab
    - ◊ Ofatumumab
    - ◊ PCR
    - ◊ Venetoclax[c,k]
    - ◊ Bendamustine, rituximab + ibrutinib[c] (category 2B)
    - ◊ Bendamustine, rituximab + idelalisib[c] (category 2B)

Relapsed/Refractory Therapy

- Frail patient with significant comorbidity or age ≥65 y and younger patients with significant comorbidities
  - Preferred regimens
    - ◊ Ibrutinib[c] (category 1)
    - ◊ Idelalisib + rituximab[c,j] (category 1)
    - ◊ Venetoclax[c,k] + rituximab (category 1
  - Other recommended regimens
    - ◊ Acalabrutinib[c,l]
    - ◊ Alemtuzumab[n] ± rituximab
    - ◊ Chlorambucil + rituximab
    - ◊ Reduced-dose FCR[f,g,h]
    - ◊ HDMP + rituximab
    - ◊ Idelalisib[c]
    - ◊ Lenalidomide[m] ± rituximab
    - ◊ Obinutuzumab
    - ◊ Ofatumumab
    - ◊ Reduced-dose PCR
    - ◊ Venetoclax[c,k]
    - ◊ Dose-dense rituximab (category 2B)
    - ◊ Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated), rituximab ± ibrutinib[c] or idelalisib[c] (category 2B for BR and BR + ibrutinib; category 3 for BR + idelalisib)

YES

Relapsed/Refractory Therapy

- Preferred regimens
  - Ibrutinib[c] (category 1)
  - Venetoclax[c,k] + rituximab (category 1
  - Idelalisib + rituximab[c,j]
  - Venetoclax[c,k]
- Other recommended regimens
  - Acalabrutinib[c,l]
  - Alemtuzumab[n] ± rituximab
  - HDMP + rituximab
  - Idelalisib[c]
  - Lenalidomide[m] ± rituximab
  - Ofatumumab[o]

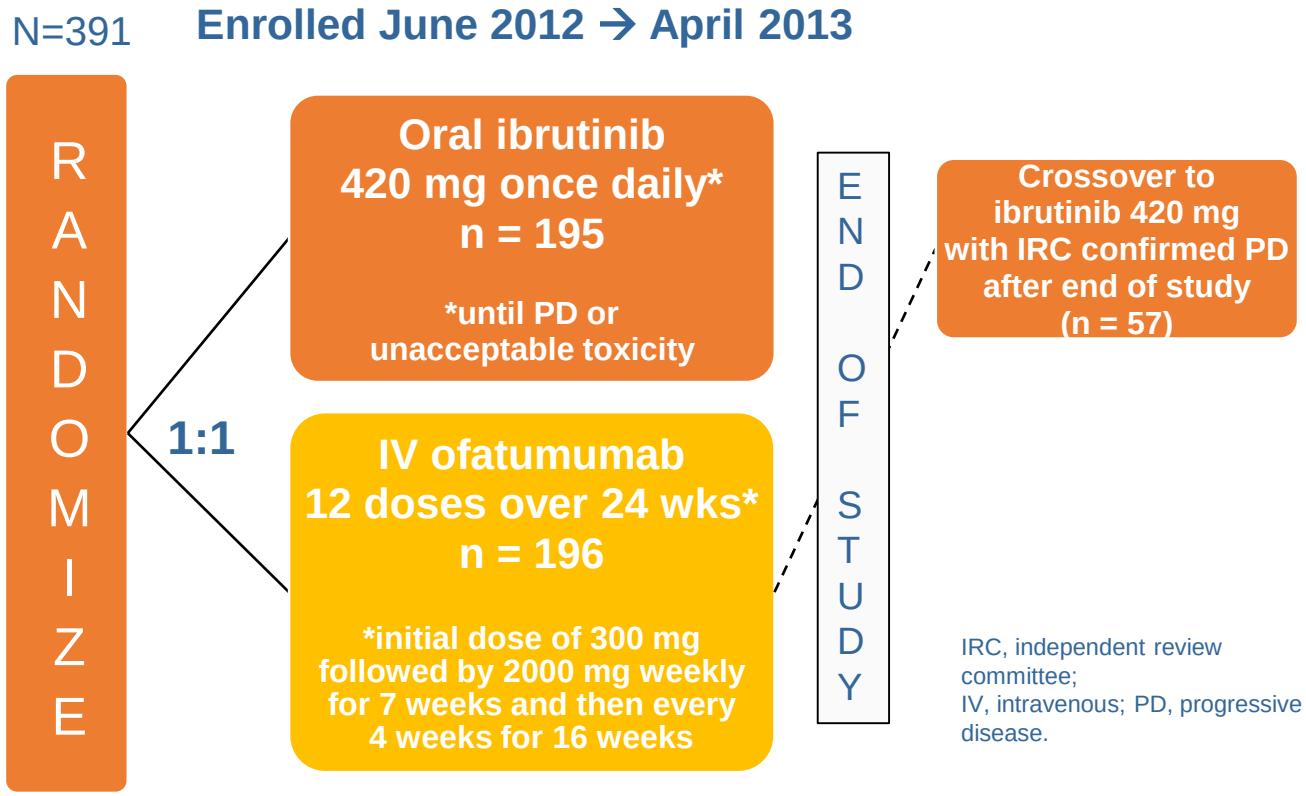
NCCN Guidelines (2018)

- presence of del(17p) and/or *TP53*mut
- age (<65 yo vs ≥65 yo) & fitness status/comorbidities

Ibrutinib monotherapy in R/R CLL

RESONATE (PCYC-1112) Study Design

- **Phase 3, open-label, randomized, multicenter study**
- **Patients with previously treated CLL or SLL, not appropriate for purine analogue treatment**



Stratification according to:

- Disease refractory to purine analogue chemoimmunotherapy (no response or relapsed within 12 months)
- Presence or absence of the 17p13.1 deletion (del17p)

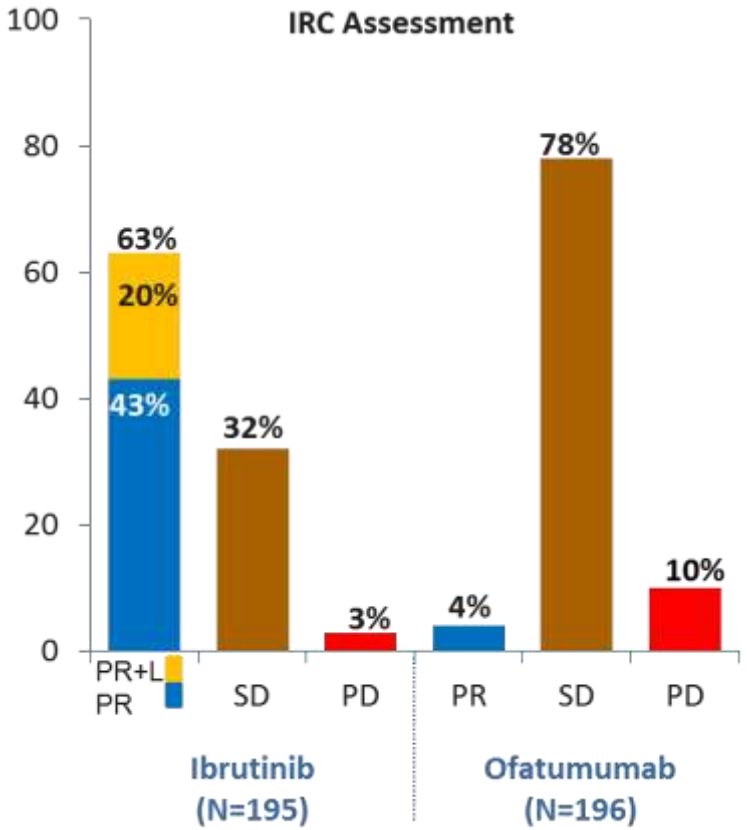
Byrd JC, et al. *N Engl J Med*. 2014;371(3):213-223

Ibrutinib monotherapy in R/R CLL

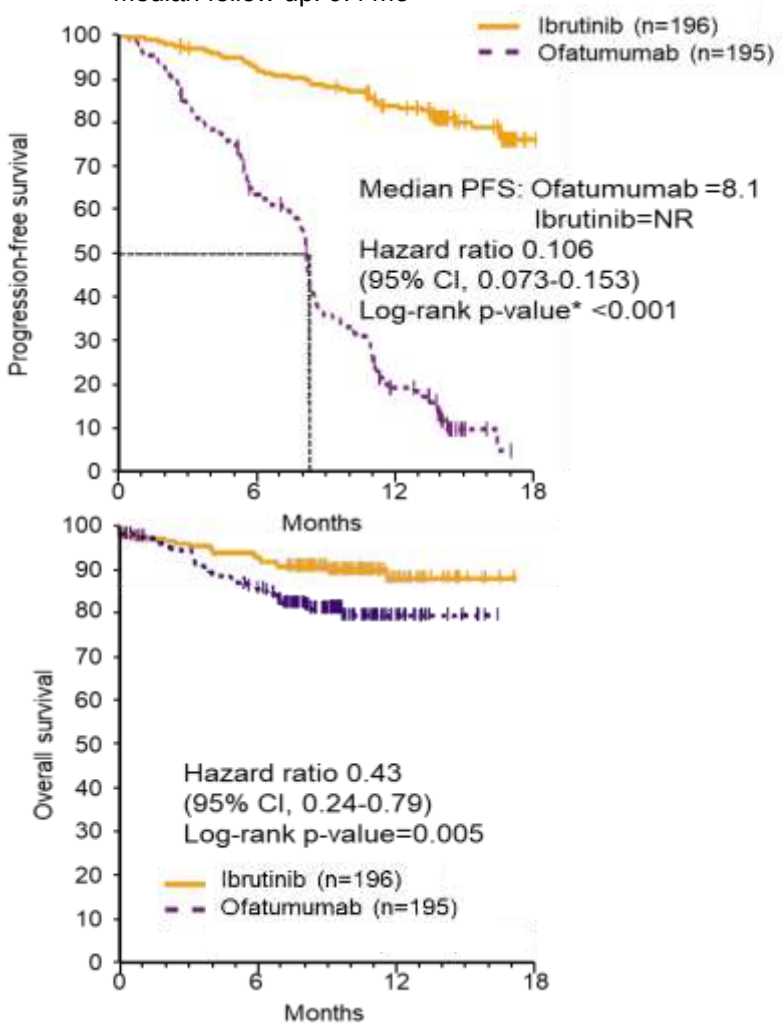
Phase III RESONATE study – ibrutinib vs ofatumumab

Highly unfavourable features

Not suitable for F-based Tx [short PFS after CIT, age≥70 And comorbidities, del(17p)]



Median follow-up: 9.4 mo



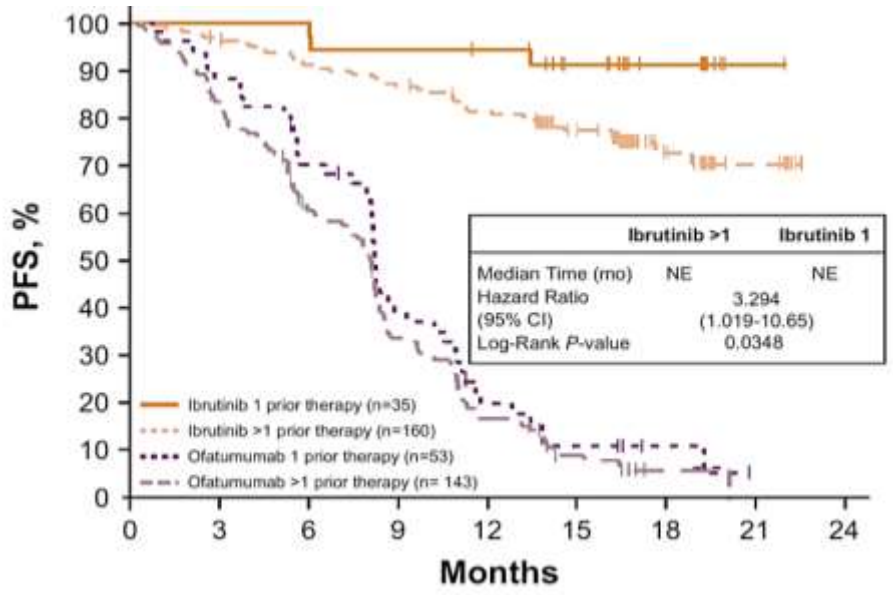
Brown *et al*, *Blood* 2014 124:3331 (Poster presented at ASH meeting 2014)

Byrd *et al. New Engl J Med.* 2014 Jul 17;371(3):213-2

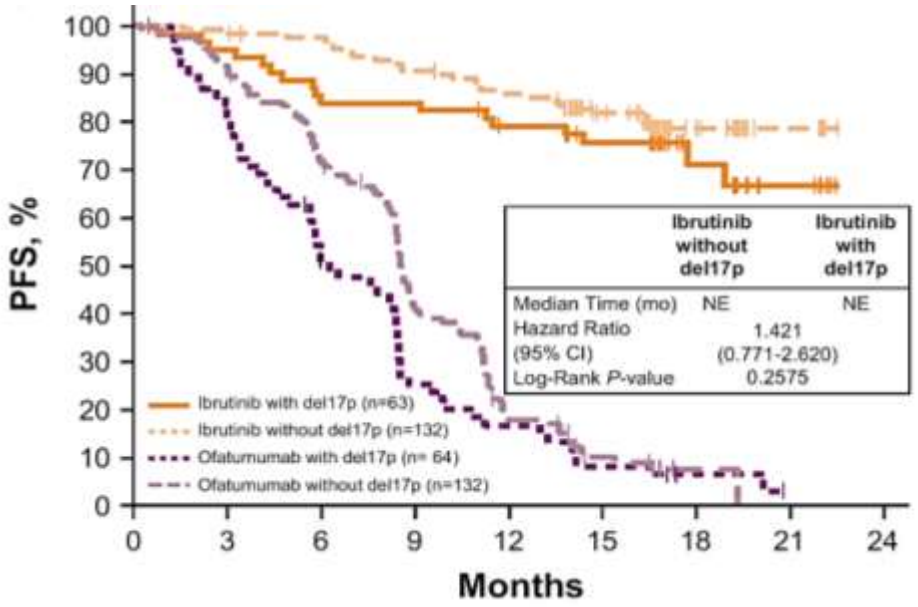
Ibrutinib monotherapy in R/R CLL

PFS in Patient Subgroups at 19-month follow-up

1 vs > 1 prior therapy



Del17p

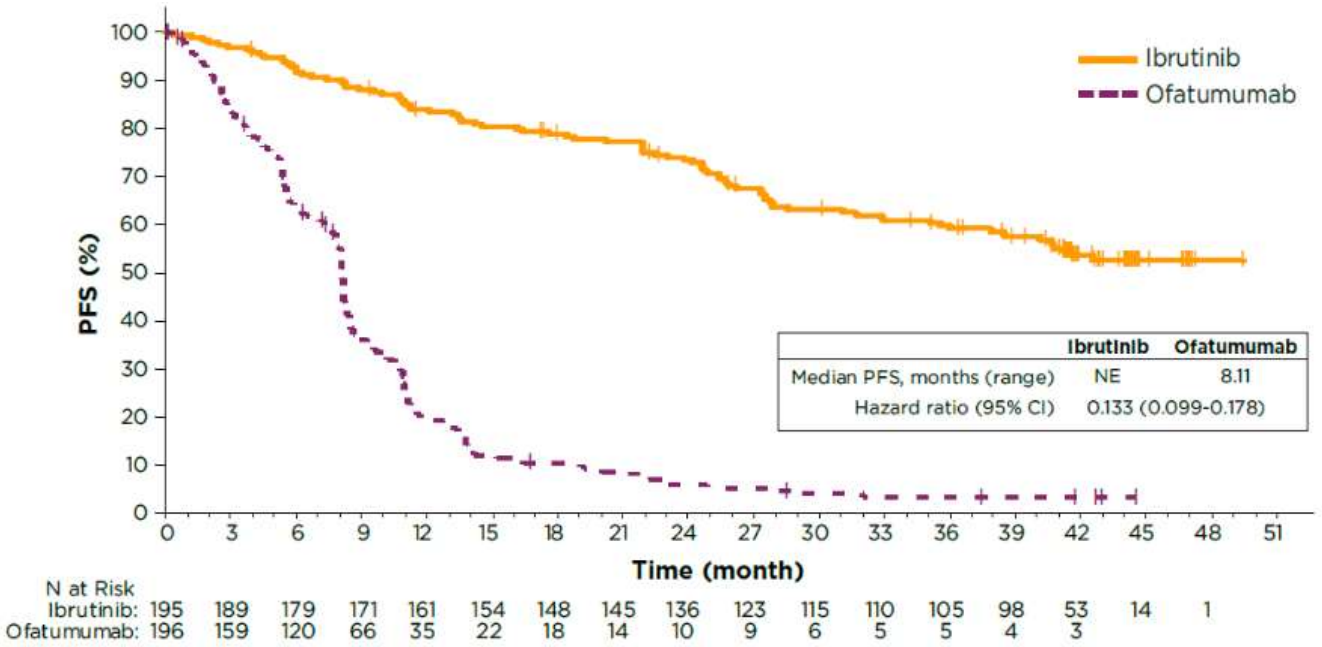


- 24-month PFS rate 74% ibrutinib arm
- Second-line ibrutinib PFS outcomes significantly improved compared with those in later lines of therapy (P=0.0348)

Ibrutinib monotherapy in R/R CLL – long term follow-up

RESONATE study long-term follow up

Median follow-up for the ibrutinib arm: 44 mo



At a **median follow-up of 44 months** (range, 0.33-53 months) for ibrutinib, PFS was significantly longer for ibrutinib vs. ofatumumab with hazard ratio (HR) of 0.133

- ✓ Median PFS was not reached with ibrutinib vs 8.1 months for ofatumumab.
- ✓ The 3-year PFS rate was 59% with ibrutinib vs 3% with ofatumumab.

John C. Byrd et al. ASCO 2017 Poster 272 - RESONATE 4 Year Follow-Up PCYC

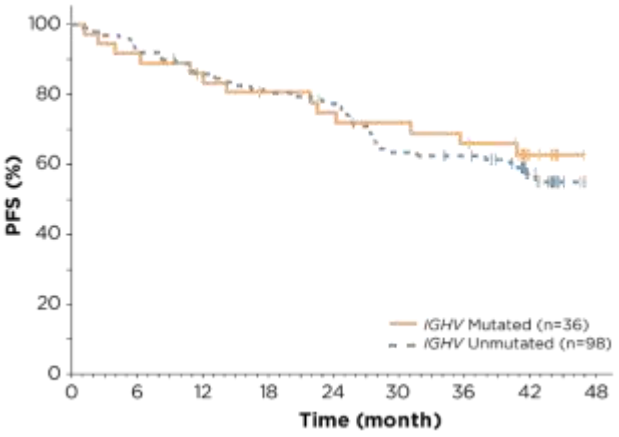
Ibrutinib monotherapy in R/R CLL – long term follow-up

RESONATE study long-term follow up

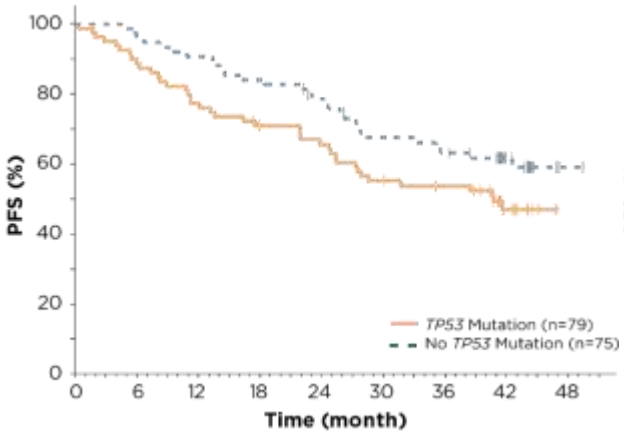
Ibrutinib - PFS Subgroup Analysis

Median follow-up for the ibrutinib arm: 44 mo

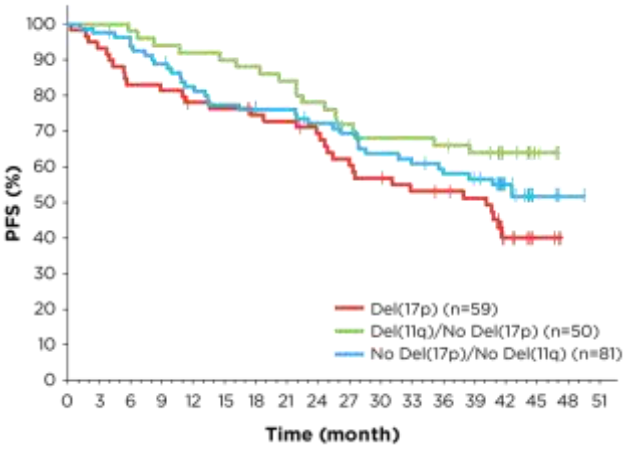
IGHV Mutation Status



TP53 Mutation Status



FISH abnormalities



- No significant differences in median PFS by IGHV mutation status (NR in either subgroup)
- Trend for more favorable PFS in patients without TP53 mutations vs with TP53 mutations (median NR vs 40.7 months)
- 3-year PFS rates: 53% for del(17p); 66% for del(11q)/no del(17p); 58% for no del(17p)/no del(11q) (NS)

Montillo et al, ICML 2017

Ibrutinib monotherapy in R/R CLL – long term follow-up

blood

Single-Agent Ibrutinib in Treatment-Naïve and Relapsed/Refractory Chronic Lymphocytic Leukemia: A 5-Year Experience

Susan O'Brien,[1,2] Richard R. Furman,[3] Steven Coutre,[4] Ian W. Flinn,[5] Jan A. Burger,[1] Kristie Blum,[6] Jeff Sharman,[7] William Wierda,[1] Jeffrey Jones,[6] Weiqiang Zhao,[6] Nyla A. Heerema,[6] Amy J. Johnson,[6] Ying Luan,[8] Danelle F. James,[8] Alvina D. Chu,[8] John C. Byrd[6]

Blood First Edition Paper, prepublished online February 8, 2018; DOI 10.1182/blood-2017-10-810044

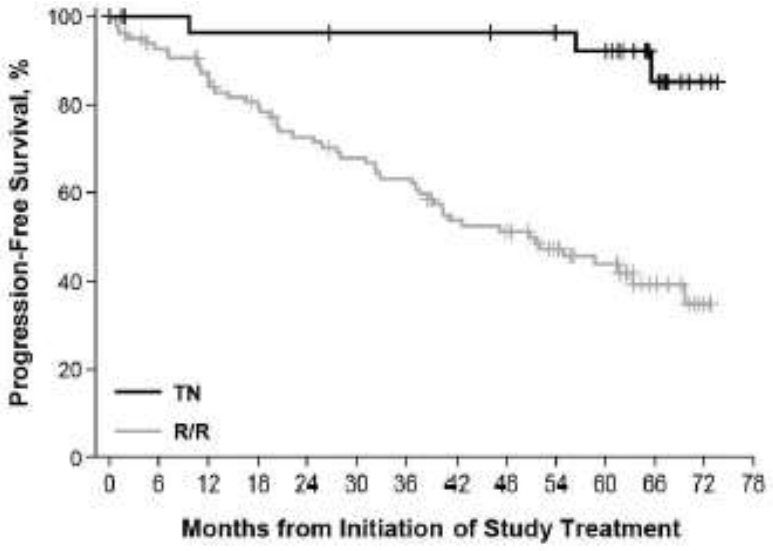
Disposition	TN (n=31)	R/R (n=101)
Median time on study, months (range)	62 (1–67)	49 (1–67)
Duration of study treatment, n (%)		
≤1 year	5 (16%)	24 (24%)
>1–2 years	0	14 (14%)
>2–3 years	1 (3%)	9 (9%)
>3–4 years	1 (3%)	19 (19%)
≥4 years	24 (77%)	35 (35%)
Patients remaining on ibrutinib therapy, n (%)	**20 (65%)**	**30 (30%)**
Primary reason for discontinuation, n (%)		
Progressive disease	1 (3%)	33 (33%)
Adverse event	6 (19%)	21 (21%)
Consent withdrawal	3 (10%)	5 (5%)
Investigator decision	0	11 (11%)
Lost to follow-up	1 (3%)	1 (1%)

After ~5 years of follow-up, 65% of TN and 30% of R/R patients continue treatment on study.

Ibrutinib monotherapy in R/R CLL – long term follow-up

Survival Outcomes: Overall Population

Progression-Free Survival



Overall Survival

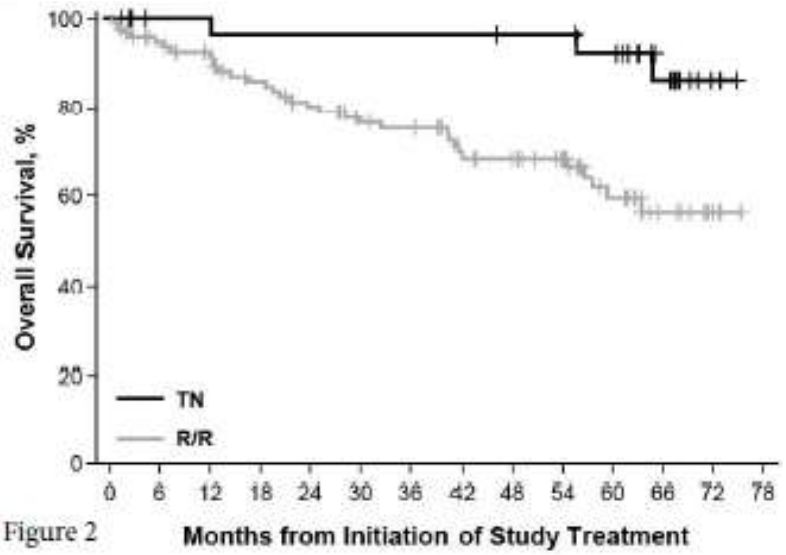


Figure 2

	Median PFS	5-year PFS
TN (n=31)	NR	92%
R/R (n=101)	51 mo	43%

	Median OS	5-year OS
TN (n=31)	NR	92%
R/R (n=101)	NR	57%

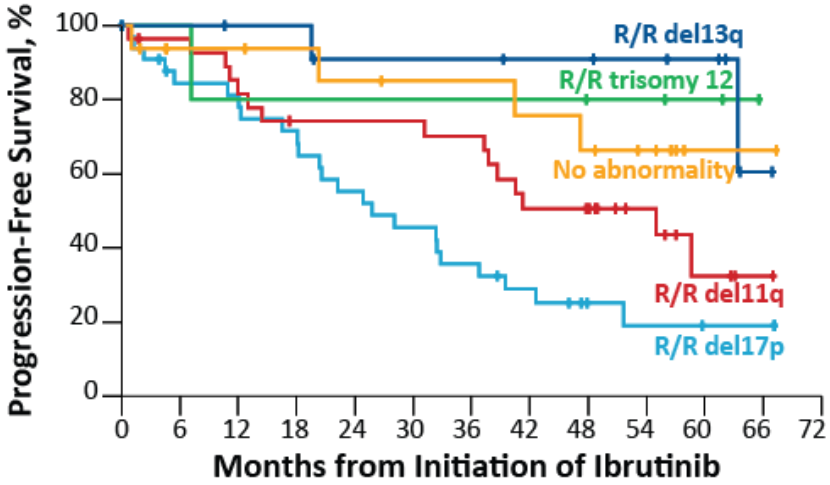
At 5-years of follow-up for RR patients median PFS is 51 mo, median OS has not been reached

O'Brien et al., Blood 2018

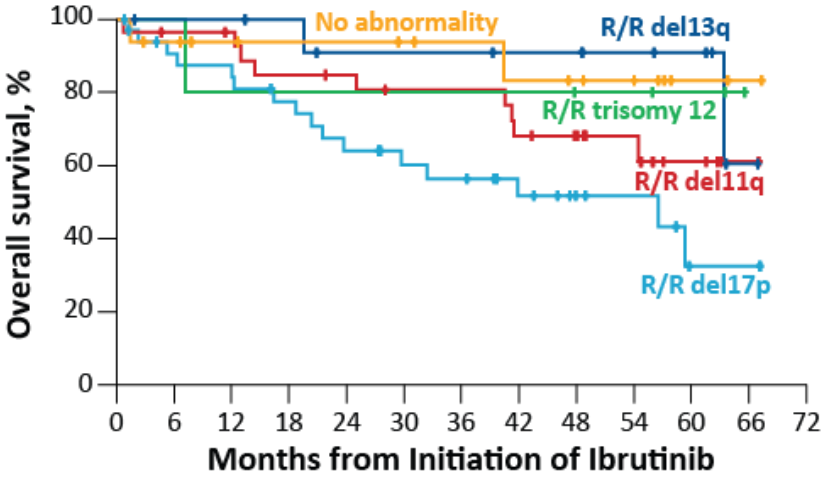
Ibrutinib monotherapy in R/R CLL – long term follow-up

Survival Outcomes by Chromosomal Abnormalities Detected by FISH in R/R Patients

Progression-Free Survival



Overall Survival



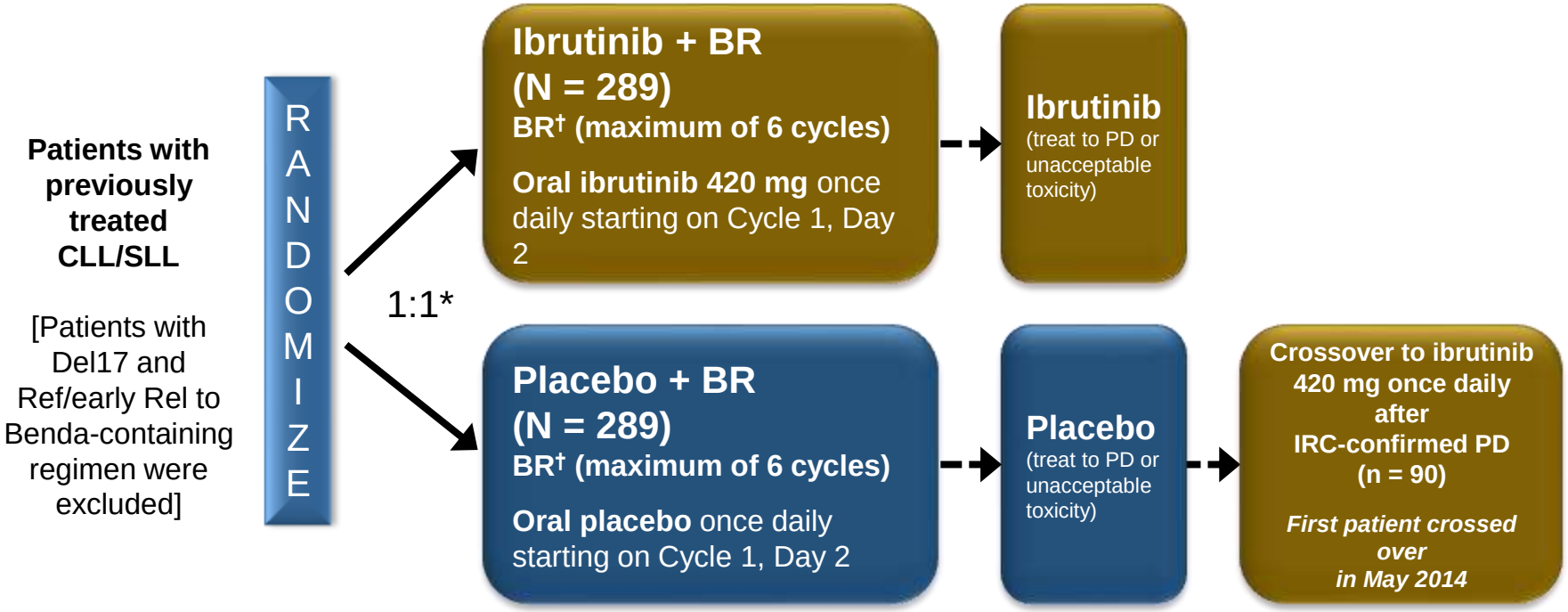
	Median PFS	5-year PFS
Del17p (n=34)	26 mo	19%
Del11q (n=28)	55 mo	33%
Trisomy 12 (n=5)	NR	80%
Del13q (n=13)	NR	91%
No abnormality** (n=16)	NR	66%

	Median OS	5-year OS
Del17p (n=34)	57 mo	32%
Del11q (n=28)	NR	61%
Trisomy 12 (n=5)	NR	80%
Del13q (n=13)	NR	91%
No abnormality** (n=16)	NR	83%

O'Brien et al., ASH 2016, 1102-03 5-year Update

Ibrutinib + BR in R/R CLL

HELIOS: Phase 3 Study Design



*Stratified by disease refractory to purine analog chemoimmunotherapy (failure to respond or relapse within 12 months) and the number of prior lines of therapy (1 line vs > 1 line).

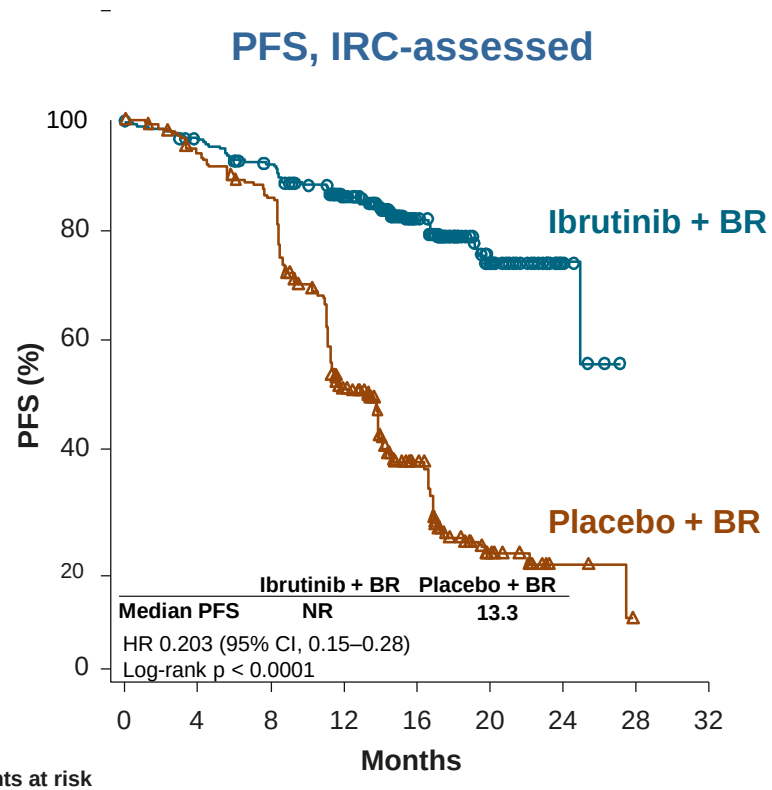
†BR= bendamustine: 70 mg/m^2 IV on Cycle 1, Days 2-3 and Cycles 2-6, Days 1-2; rituximab: 375 mg/m^2 on Cycle 1, Day 1, and 500 mg/m^2 on Cycles 2-6, Day 1.

Chanan-Khan et al. Lancet Oncol 2016; 17: 200-211

Ibrutinib + BR in R/R CLL

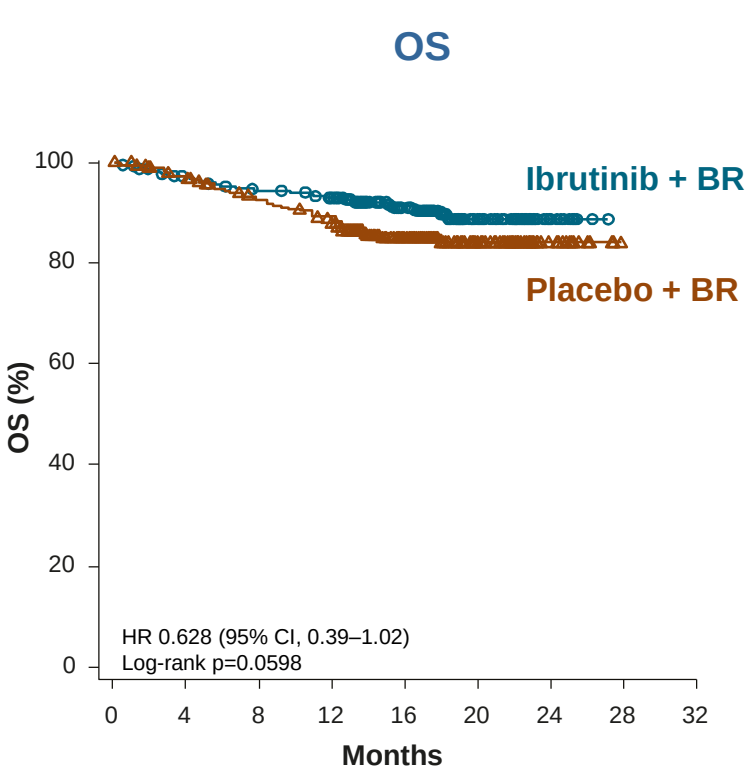
PFS & OS in the Intent-to-Treat Population

Median follow-up: 17 mo



Patients at risk

Ibrutinib + BR	289	264	247	200	127	52	5	0	0
Placebo + BR	289	259	234	117	59	17	3	0	0



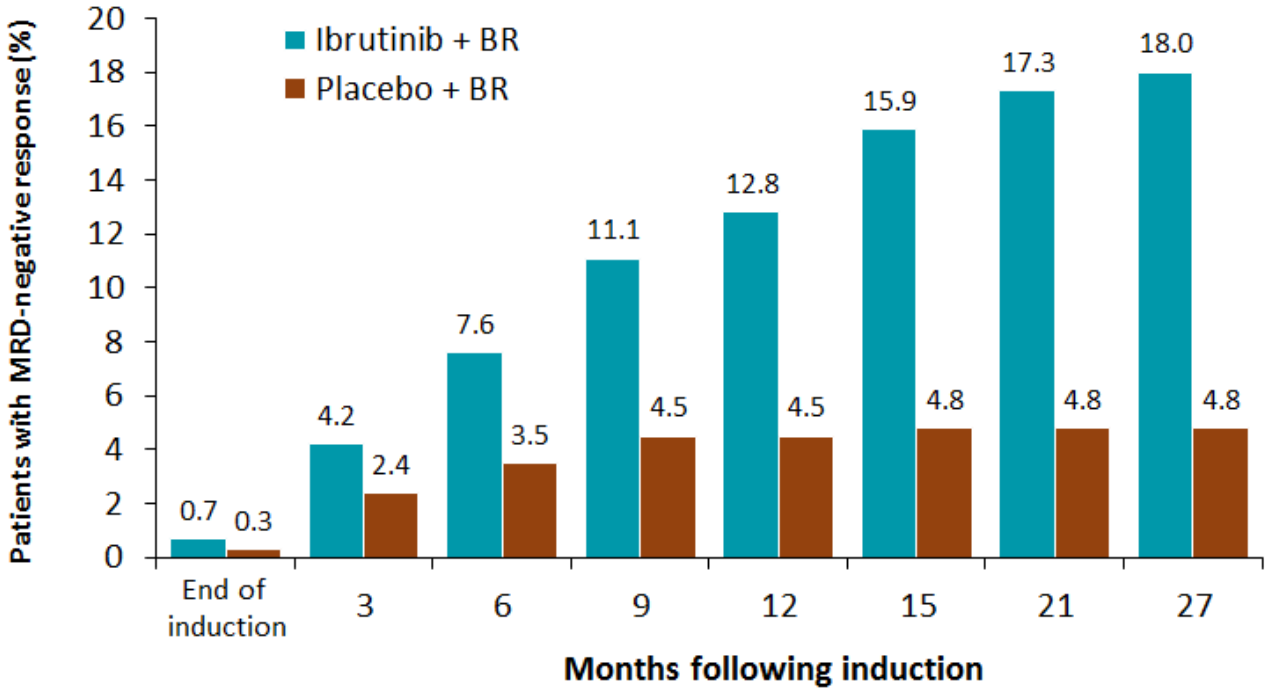
Patients at risk

Ibrutinib + BR	289	273	261	250	147	73	8	0	0
Placebo + BR	289	273	255	237	138	70	16	0	0

Chanan-Khan A, et al. *Lancet Oncol*. 2016;17:200-211

Ibrutinib + BR in R/R CLL

MRD-Negative Response Over Time



- MRD-negative response continues to increase over time for patients treated with ibrutinib + BR
- As of Mar 2016, 60 patients (20.7%) demonstrated an MRD-negative response

Fraser et al. EHA 2016: Abstract S430 (Oral Presentation)

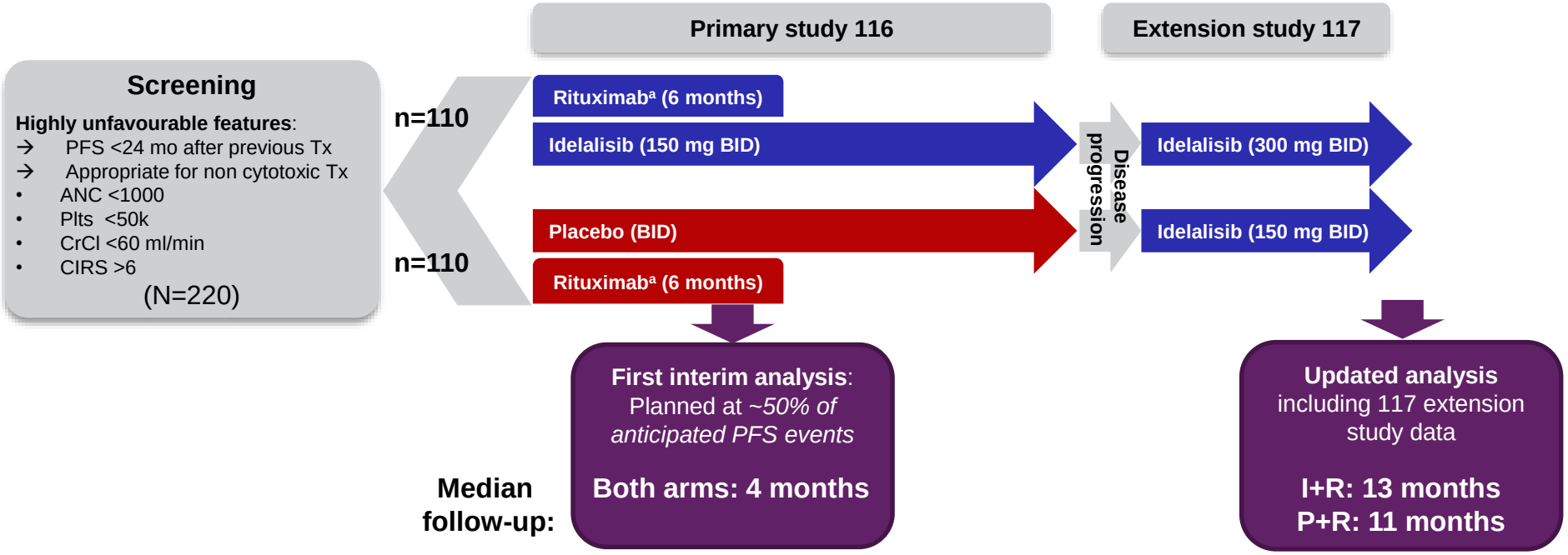
IBRUTINIB → EMA approved indications in CLL

- **Imbruvica®** as a single agent is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see section 5.1)

- **Imbruvica®** as a single agent or in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.

Idelalisib + rituximab in R/R CLL

GS-US-312-0116 and 117 Study Design



[a] 375 mg/m^2, then 500 mg/m^2 every two weeks x 4, then 500 mg/m^2 every 4 weeks x 3

Study 116 was stopped due to significant efficacy of idelalisib + R

Furman RR, *et al. N Engl J Med* 2014; 370:997–1007.
Sharman JP, *et al.* ASH 2014 (Abstract 330; oral).

Idelalisib + rituximab in R/R CLL

Phase III study – Rituximab + idelalisib vs Rituximab + placebo

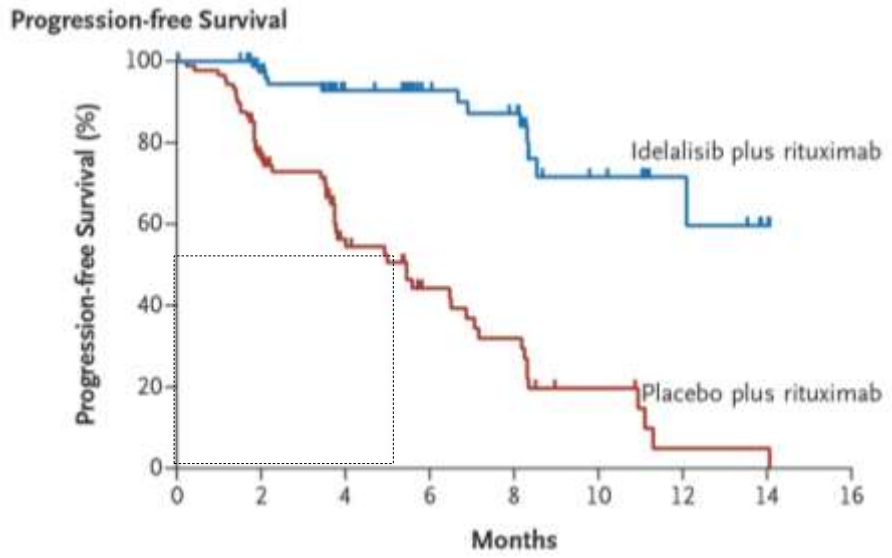
Highly unfavourable features:

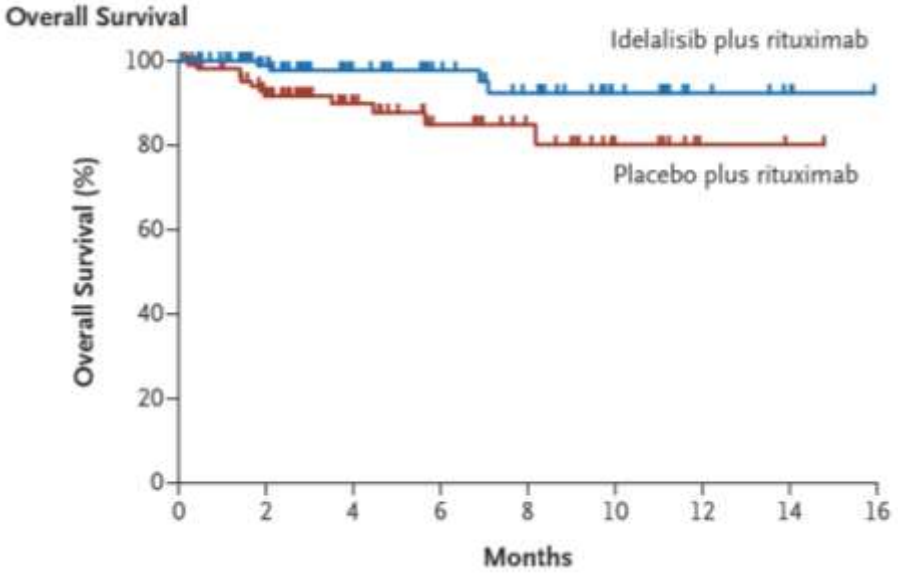
→ PFS <24 months after previous Tx

Appropriate for non cytotoxic treatment

- ANC <1000
- Plt <50
- CrCl <60 ml/min
- CIRS >6

	Idelalisib + R	Placebo + R
ORR	81%	13%
CR	0	0
PR	81%	13%
Median PFS	NR	5.5 months

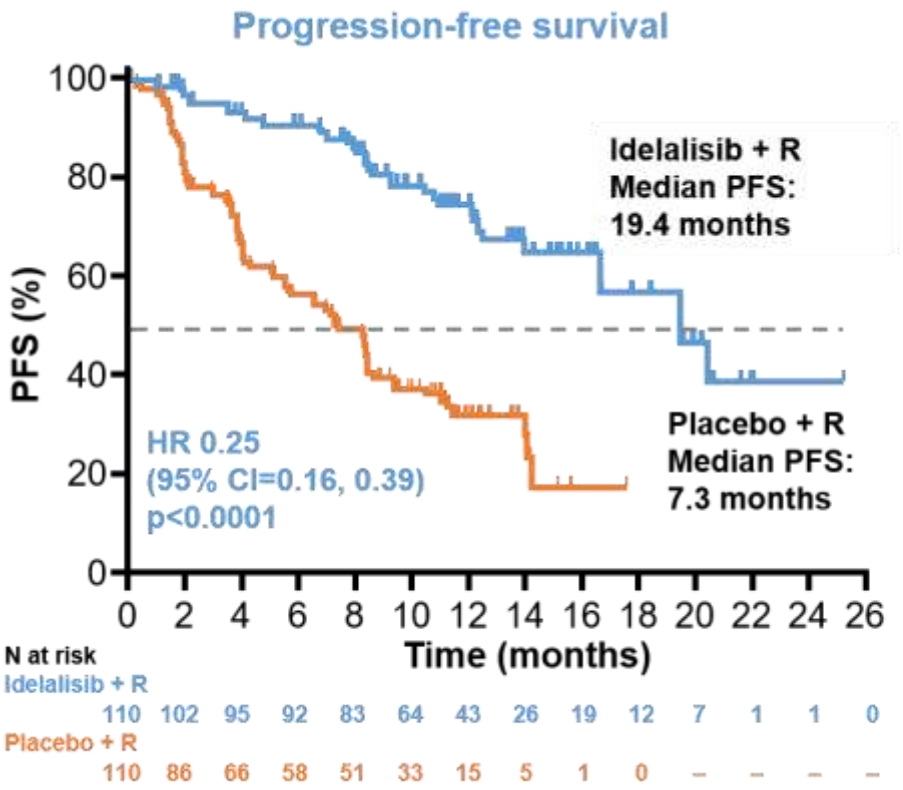


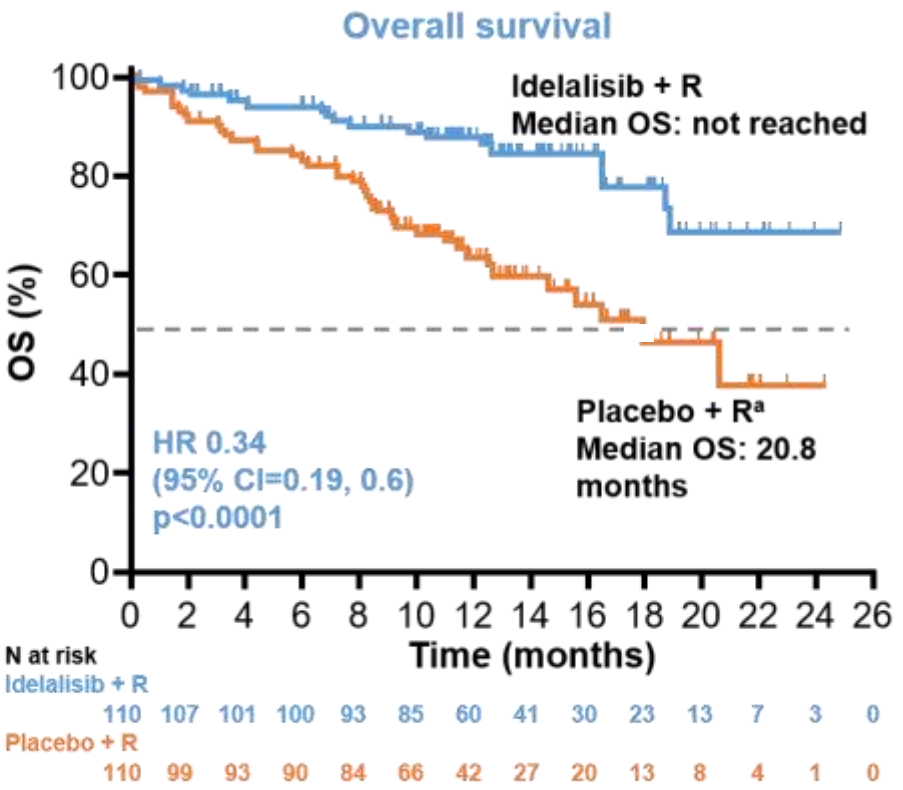


Furman RR et al. N Engl J Med 2014

Idelalisib + rituximab in R/R CLL

Median (range) exposure:
IDELA+R 5 (0-17) mo
PBO+R 4 (0-15) mo





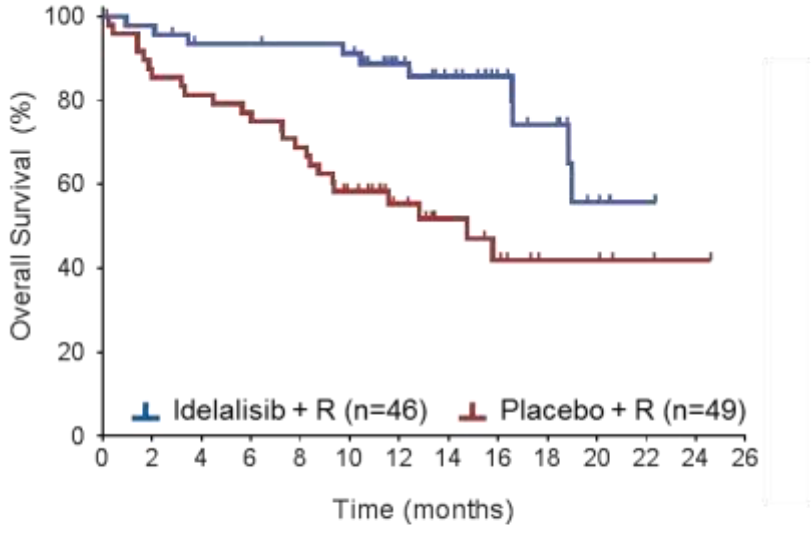
Updated analysis including 117 extension study
Patients represented as randomized, including cross-over

Furman RR et al. N Engl J Med 2014; 1. Sharman JP, *et al.* ASH 2014 (Abstract 330; oral presentation).

Idelalisib + rituximab in R/R CLL

Overall Survival Subgroup Analysis
Idelalisib + R *vs* Placebo + R

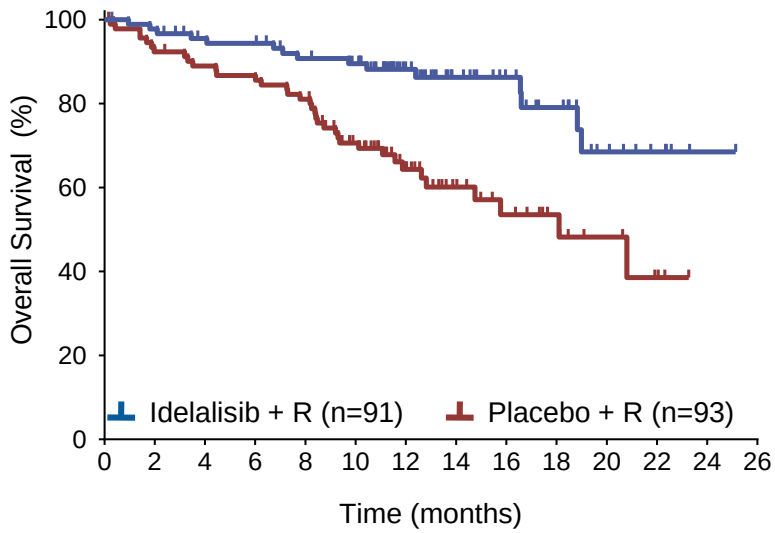
Del17p/TP53 Mutation (Either)



N at risk													
IDELA + R	46	45	41	41	40	39	30	23	16	12	5	2	0
PBO + R	49	41	39	37	33	25	17	11	8	4	4	2	1	0

	Median OS (95% CI)	HR (95% CI)	p-value
IDELA + R	NR (18.8, –)	0.31 (0.15, 0.65)	0.001
PBO + R	14.8 mo (8.4, –)		

IGHV Unmutated



91	88	82	81	75	70	48	33	25	19	10	6	2	0
93	83	79	77	72	55	35	22	15	10	6	3	0	

Median OS (95% CI)	HR (95% CI)	p-value
NR (19.0, –)	0.35 (0.19, 0.6)	0.0003
18.1 mo (14.8, –)		

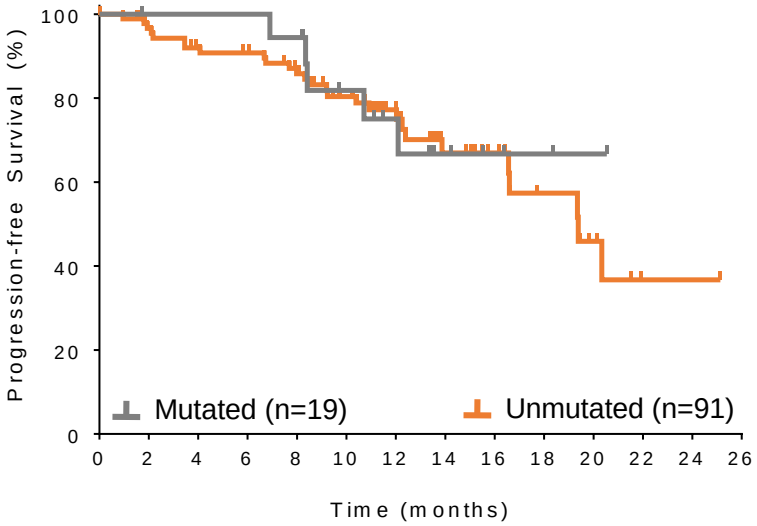
Updated analysis including 117 extension study
Patients represented as randomized, including cross-over

Sharman, ASH, 2014, Abstract 330

Idelalisib + rituximab in R/R CLL

PFS Subgroup Analysis
Idelalisib + R arm

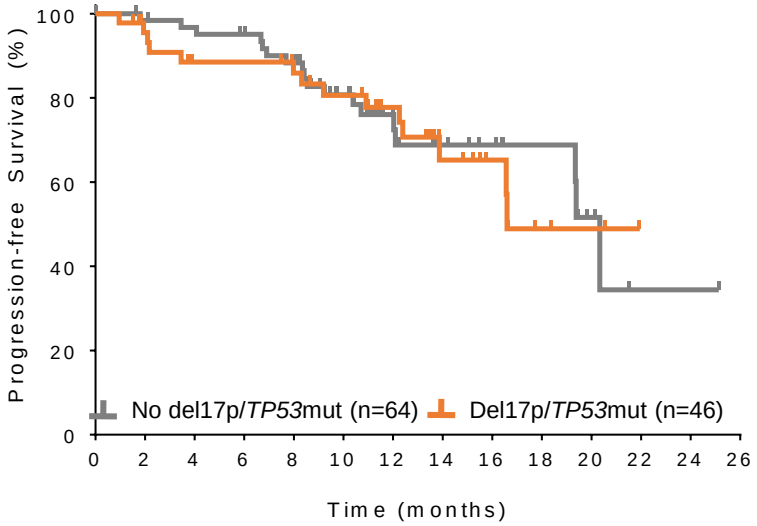
IGHV: Unmutated vs Mutated



N at risk													
Mutated	19	18	18	18	17	12	9	5	3	2	1	0	
Unmut	91	84	77	75	68	54	34	21	16	10	6	1	1	0

	Median PFS (95% CI)	p-value
Mut	NR (10.7, –)	0.75
Unmut	19.4 mo (16.6, –)	

Del17p/TP53mut: Present vs Not Present



No del	64	61	59	59	52	37	21	14	11	8	4	1	1	1
Del	46	41	36	36	33	30	22	12	8	4	3	0		

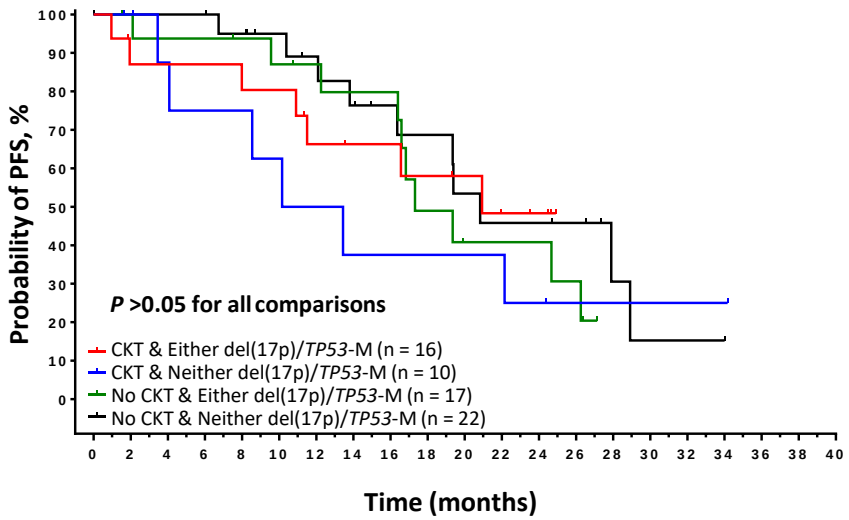
	Median PFS (95% CI)	p-value
No del	20.3 mo (19.4, –)	0.94
Del	16.6 mo (13.9, –)	

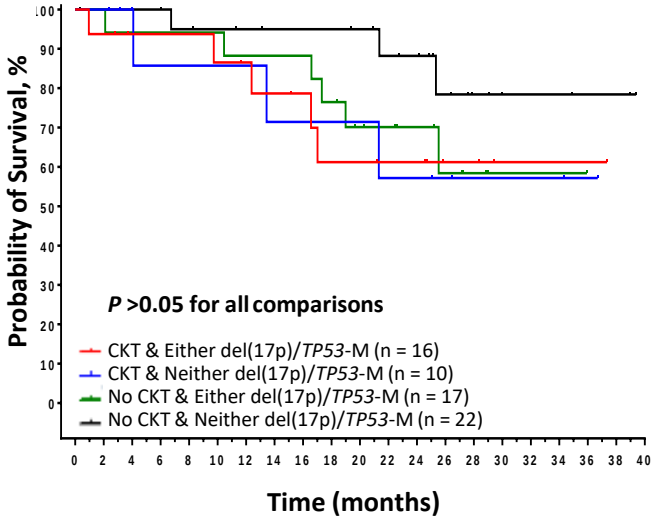
*Including extension study

Sharman, ASH, 2014, Abstract 330

Idelalisib + rituximab in R/R CLL

PFS Subgroup Analysis
Idelalisib + R arm (N=110)





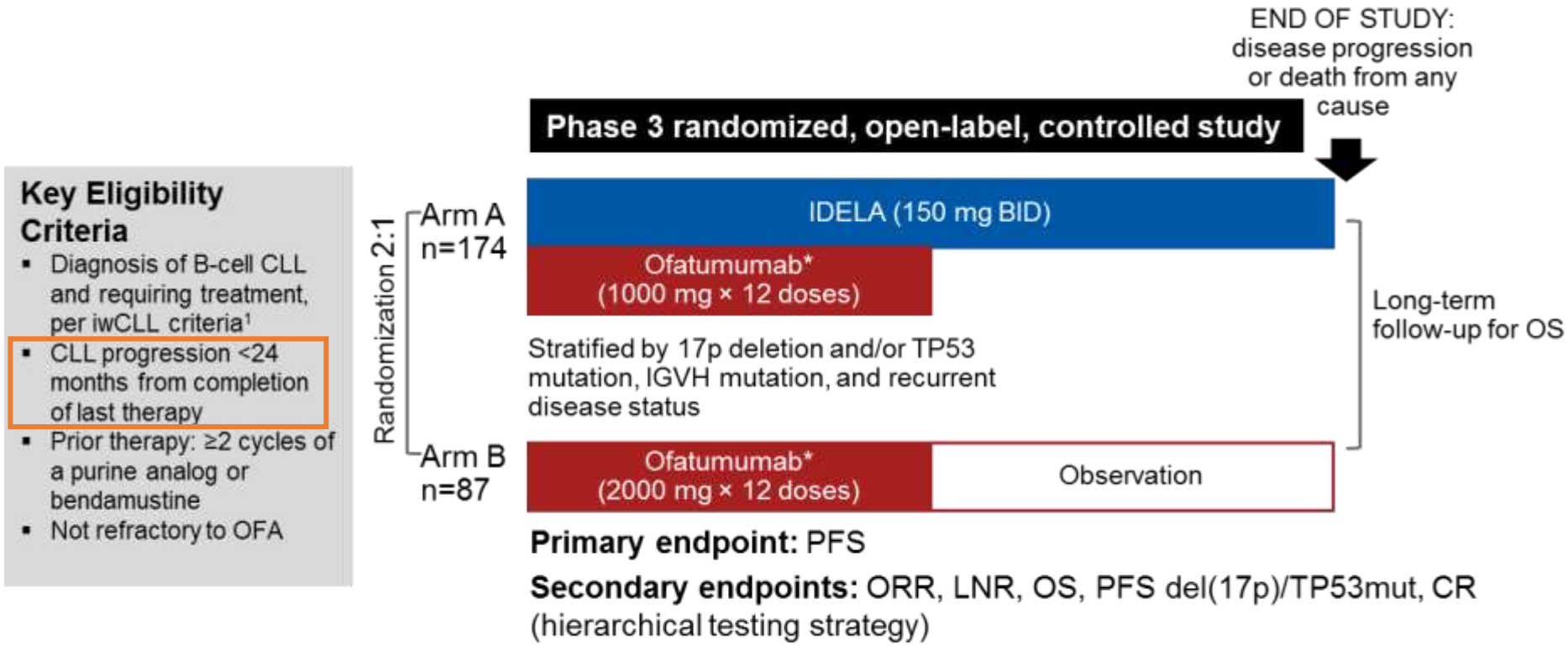
median follow-up: 21.4 mo

- **Pateients treated with IDELA+R demonstrated similar ORR, PFS, and OS, irrespective of CKT status**
- **No significant interaction was observed for CKT and other risk factors with respect to PFS and OS**

Adapted from Kreuzer, et al. Abstract #192, ASH 2016

Idelalisib + ofatumumab in R/R CLL

GS-US-312-0119 Study Design



[1]Hallek, et al. Blood 2008
*300 mg Week 1; then 1000 mg (Arm A) or 2000 mg (Arm B) weekly x 7 and then every 4 weeks x 4 (total 12 doses; finishing Week 24).
CLL, chronic lymphocytic leukemia; CR, complete response; IDELA, idelalisib; IVGH, immunoglobulin heavy chain variable region gene; iwCLL: International Workshop on Chronic Lymphocytic Leukemia; LNR, lymph node response; ORR, objective response rate; OFA, ofatumumab; PFS, progression-free survival; OS, overall survival; PI3K, phosphoinositide kinase-3.

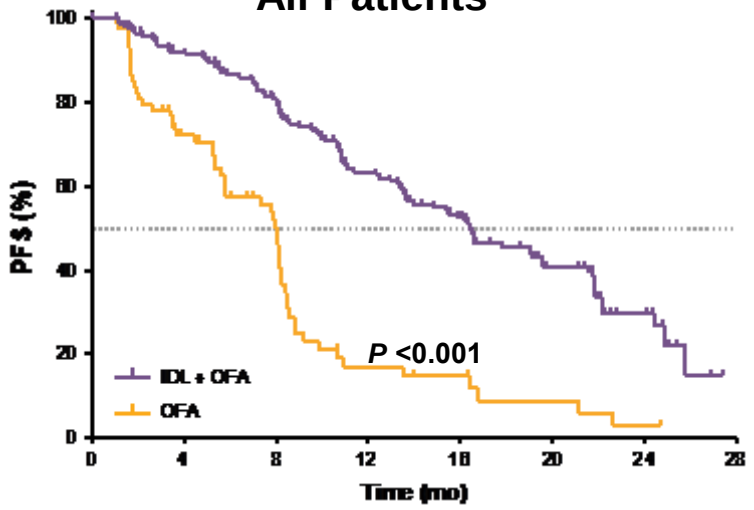
Jones, ASCO 2015, 7023
Robak. EHA 2015, LB598

Jones, ASCO, 2016, 7515
Robak, EHA, 2016, P213
Jones JA et al, Lancet Haematol. 2017

Idelalisib + ofatumumab in R/R CLL

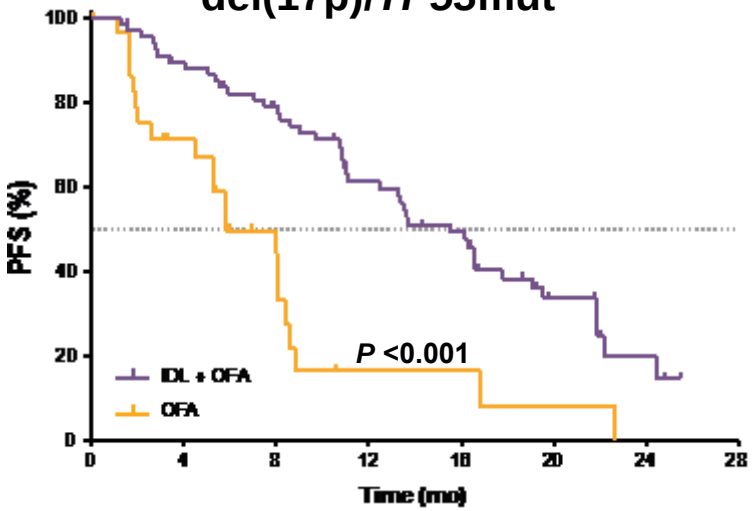
Progression-Free Survival

All Patients



	IDL+OFA n=174	OFA n=87
Events, n (%)	97 (56)	59 (64)
Median PFS, mo (95% CI)	16.4 (13.6, 19.5)	8.0 (5.7, 8.2)
Adjusted HR (95% CI)	0.26 (0.18, 0.37)	—
P-value	<0.001	
Median observation, mo	13.3	5.3

del(17p)/*TP53*mut



	IDL+OFA n=174	OFA n=87
Events, n (%)	45 (64)	21 (64)
Median PFS, mo (95% CI)	15.5 (11.1, 19.1)	5.8 (4.5, 8.4)
Adjusted HR (95% CI)	0.32 (0.18, 0.55)	—
P-value	<0.001	
Median observation, mo	12.9	4.5

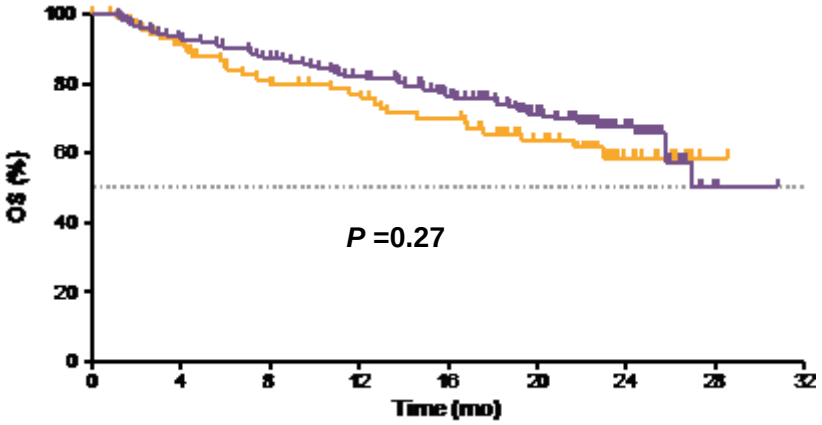
IDL+OFA yielded superior PFS compared with OFA alone in patients with previously treated CLL, including patients with del(17p)/*TP53* mut

Jones, ASCO, 2016, 7515
Robak, EHA, 2016, P213
Jones JA et al, Lancet Haematol. 2017

Idelalisib + ofatumumab in R/R CLL

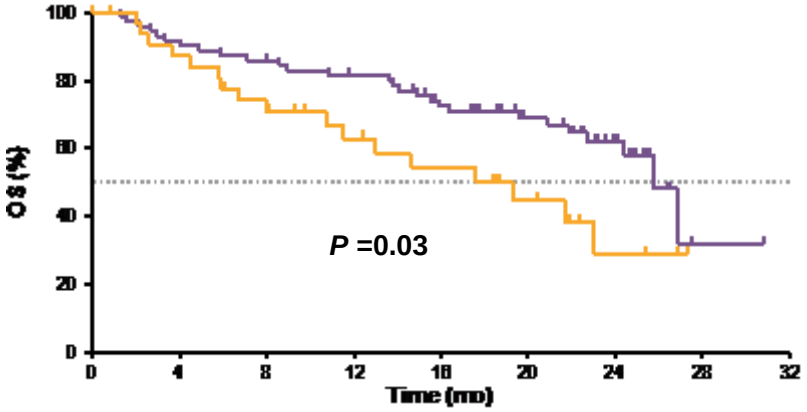
Overall Survival

All Patients



	IDL+OFA n=174	OFA n=87
Deaths, n (%)	55 (32)	29 (33)
Median OS, mo (95% CI)*	NR (25.8, NR)	NR (21.7, NR)
Q1	18.2 (12.3, 22.7)	12.7 (6.0, 19.3)
Q3	NR (NR, NR)	NR (NR, NR)
Adjusted HR (95% CI)†	0.75 (0.48, 1.18)	—
P-value‡	0.27	
Median observation, mo	20.2	17.5

del(17p)/*TP53*mut



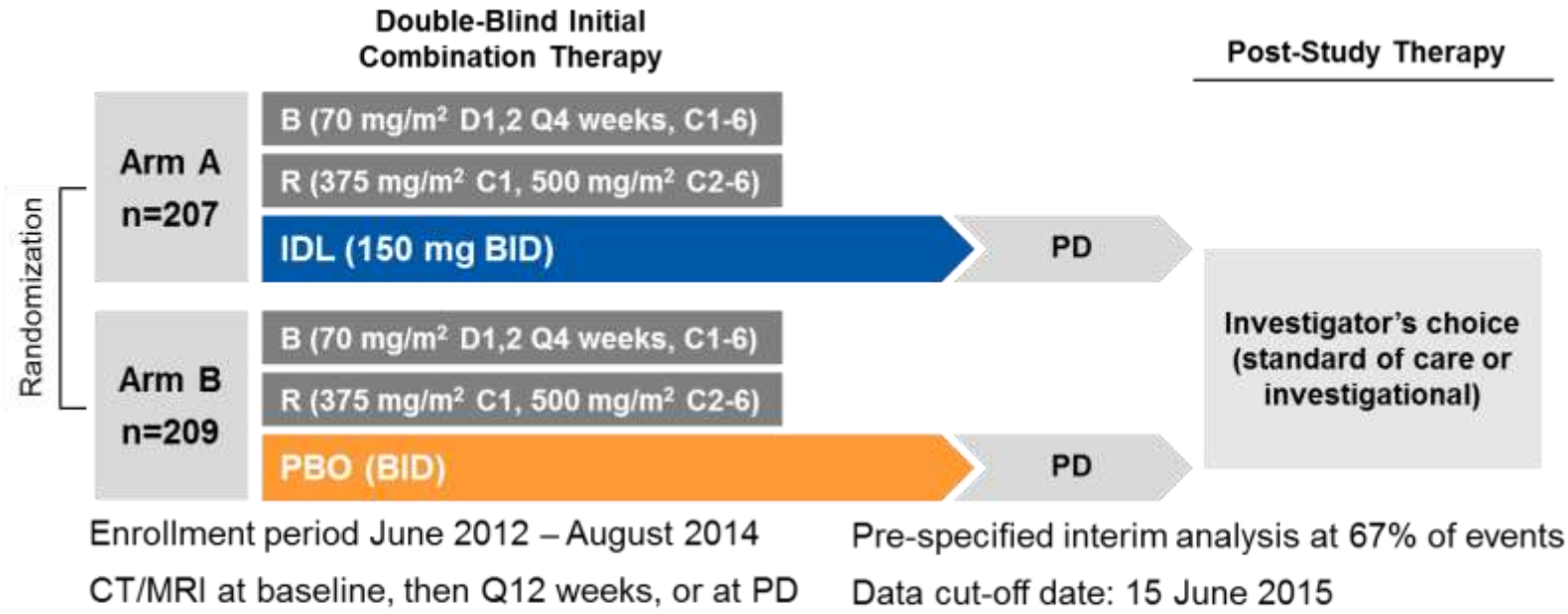
	IDL+OFA n=70	OFA n=33
Deaths, n (%)	27 (39)	17 (52)
Median OS, mo (95% CI)*	25.8 (22.7, NR)	19.3 (10.7, NR)
Unadjusted HR (95% CI)†	0.52 (0.28, 0.96)	—
P-value‡	0.03	
Median observation, mo	19.7	11.5

In an exploratory sub-analysis of patients with del(17p)/TP53-M, the unadjusted hazard ratio for OS was 0.59, which favored IDL+OFA compared to OFA (p =0.03)

Jones, ASCO, 2016, 7515
Robak, EHA, 2016, P213
Jones JA et al, Lancet Haematol. 2017

Idelalisib + BR in R/R CLL

GS-US-312-0115 Study Design



Key Eligibility Criteria

- CLL progression <36 mo from last therapy, requiring treatment
- No history of CLL transformation
- Not refractory to bendamustine
- No prior inhibitors of BTK, PI3Kδ, SYK

Stratification

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

Endpoints

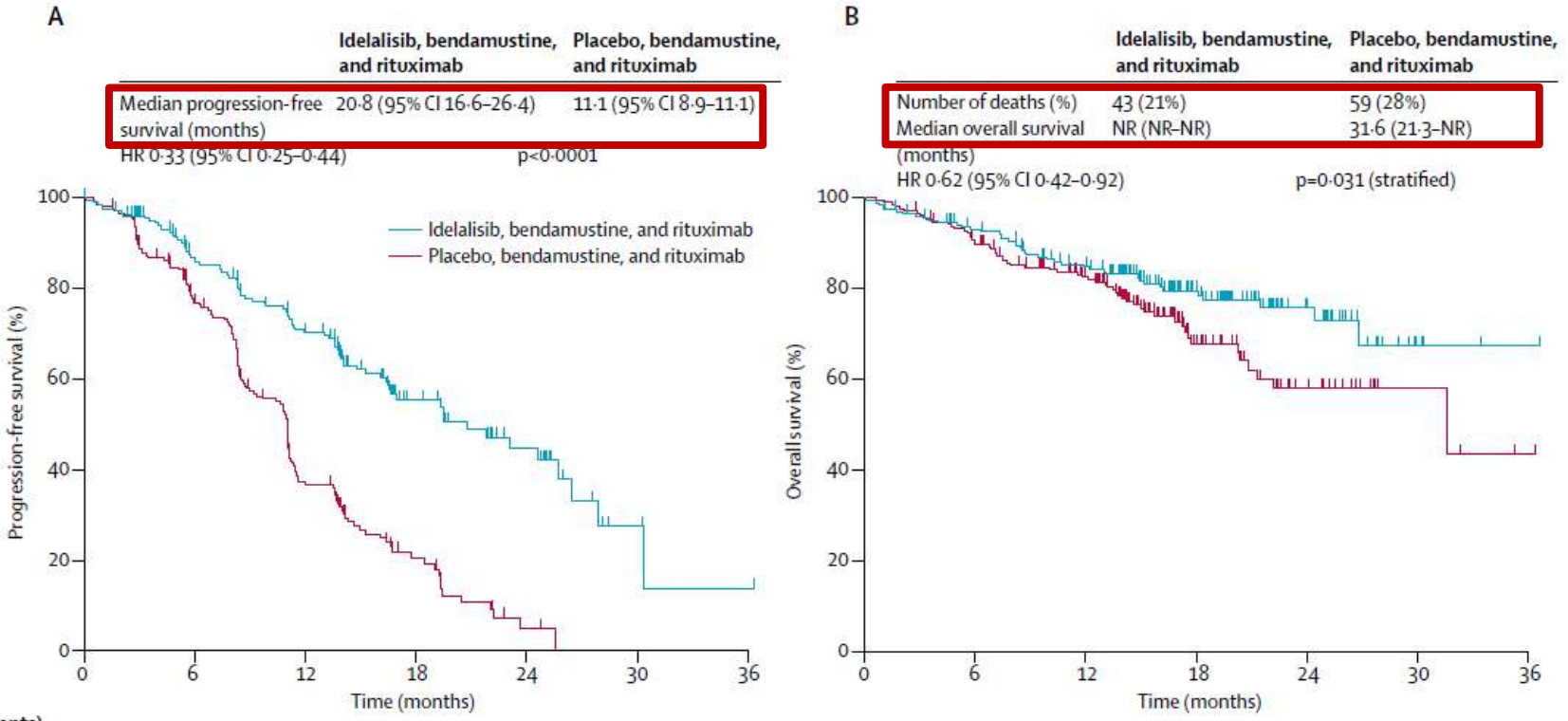
- Primary: PFS
- Secondary: ORR, nodal response, OS, CR

Zelenetz AD *et al., Lancet Oncol 2017; 18: 297–311*

Idelalisib + BR in R/R CLL

IRC-Assessed PFS and OS

Median follow-up: 14 mo (IQR 7-18)



Number at risk (events)														
Idelalisib, bendamustine, and rituximab	207 (0)	156 (25)	118 (54)	40 (73)	18 (79)	3 (83)	1 (84)	207 (0)	184 (14)	158 (30)	75 (38)	29 (41)	4 (43)	1 (43)
	209 (0)	146 (46)	63 (118)	16 (138)	2 (148)	0 (149)	0 (149)	209 (0)	182 (21)	149 (35)	51 (53)	19 (58)	4 (58)	1 (59)
Number of patients (censored)														
Placebo, bendamustine, and rituximab	0	26	35	94	110	121	122	0	9	19	94	137	160	163
	0	17	28	55	59	60	60	0	6	25	105	132	147	149

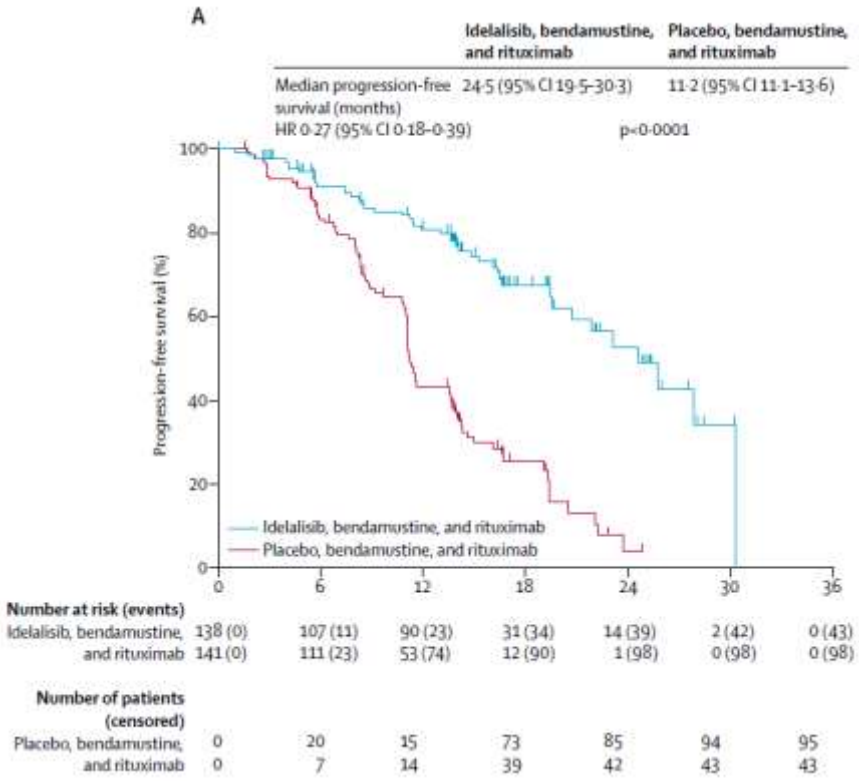
>30% of enrolled patients were TP53 disrupted
>80% of enrolled patients were IGHV UM

Zelenetz AD *et al., Lancet Oncol 2017; 18: 297–311*

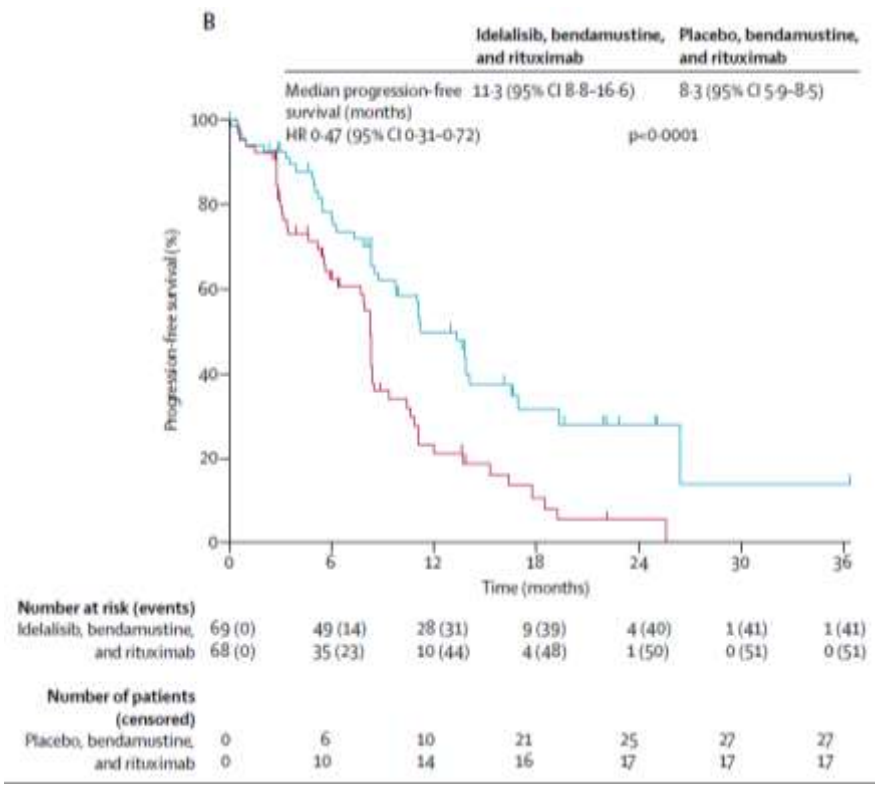
Idelalisib + BR in R/R CLL

Median follow-up: 14 mo (IQR 7-18)

Neither del(17p) nor TP53 mutation



Either del(17p) or TP53 mutation



Zelenetz AD *et al., Lancet Oncol 2017; 18: 297–311*

IDELALISIB → EMA approved indications in CLL

- **Zydelig®** is indicated in combination with an anti-CD20 monoclonal antibody (rituximab or ofatumumab) for the treatment of adult patients with chronic lymphocytic leukaemia (CLL):
  - who have received at least one prior therapy,
  - or as first line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies

Venetoclax in R/R CLL

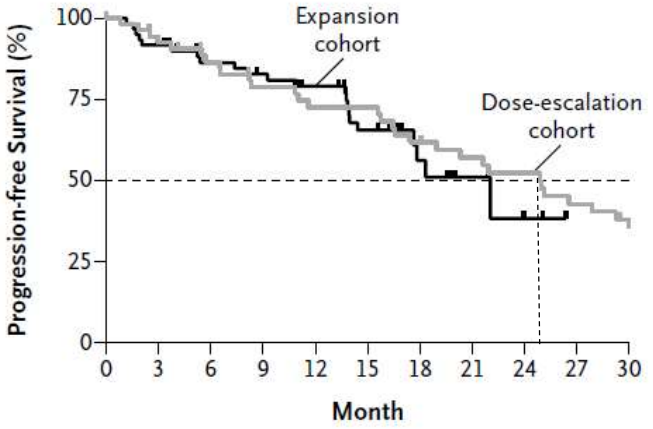
Phase I study

dose-escalation cohort n=56
expansion cohort n=60

Table 3. Complete and Overall Response Rates, According to Cohort and Subgroup.

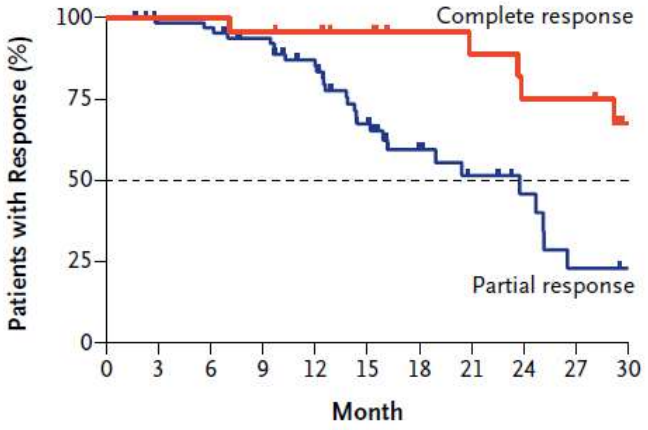
Variable	No. of Patients	Complete Response Rate*	Overall Response Rate
		percent of patients (95% CI)	
All patients	116	20 (13–28)	79 (71–86)
Dose-escalation cohort	56	30 (19–44)	77 (64–87)
Expansion cohort	60	10 (4–21)	82 (70–91)
Age			
≥70 yr	34	21 (9–38)	71 (53–85)
<70 yr	82	20 (12–30)	83 (73–90)
No. of previous therapies			
≥4	56	16 (8–28)	73 (60–84)
<4	60	23 (13–36)	85 (73–93)
Fludarabine resistance			
Yes	70	16 (8–26)	79 (67–88)
No	44	27 (15–43)	82 (67–92)
Bulky nodes of >5 cm			
Yes	67	8 (3–17)	78 (66–87)
No	48	38 (24–53)	83 (70–93)
Chromosome 17p deletion			
Yes	31	16 (6–34)	71 (52–86)
No	60	18 (10–30)	80 (68–89)
Chromosome 11q deletion			
Yes	28	11 (2–28)	82 (63–94)
No	62	21 (12–33)	76 (63–86)
IGHV status			
Unmutated	46	17 (8–31)	76 (61–87)
Mutated	17	29 (10–56)	94 (71–100)

* A complete response includes complete remission with incomplete count recovery.



No. at Risk

Expansion cohort	60	55	48	45	40	29	10	5	2		
Dose-escalation cohort	56	49	44	39	34	34	27	24	22	18	15



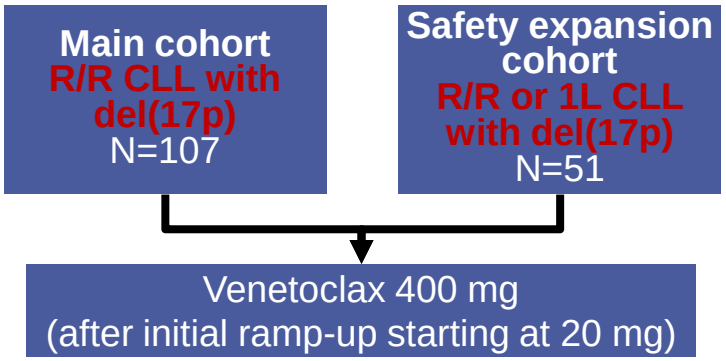
No. at Risk

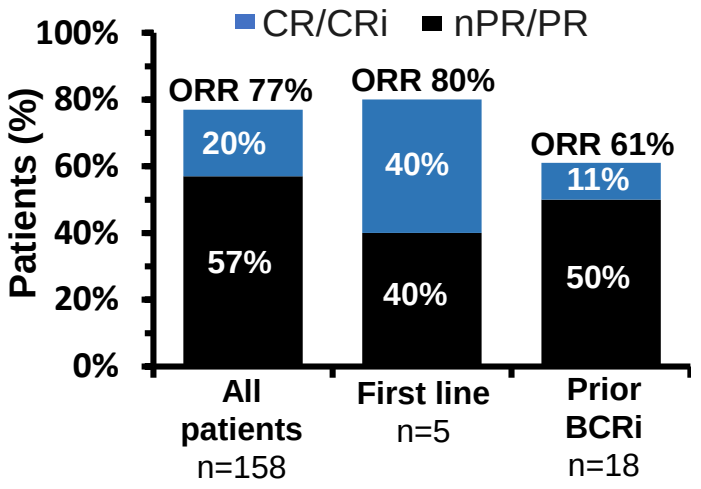
Complete response	23	23	23	22	21	18	14	13	11	11	6
Partial response	69	63	62	56	48	32	18	12	8	4	3

Roberts AW, NEJM 2016

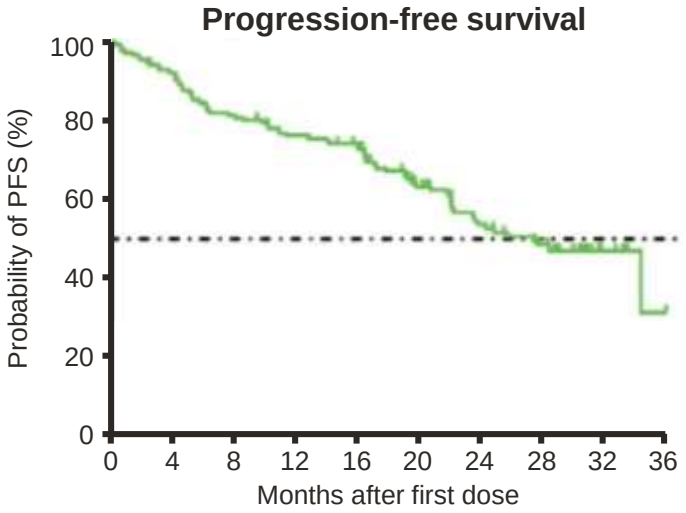
Venetoclax in R/R CLL

M13-982 Phase II study





Best MRD status by flow cytometry and/or NGS*	
PB, n=101	
MRD negative, n	48 (30% ITT)
MRD positive, n	53
BM, n=28/48	
MRD negative, n	20
MRD positive, n	8



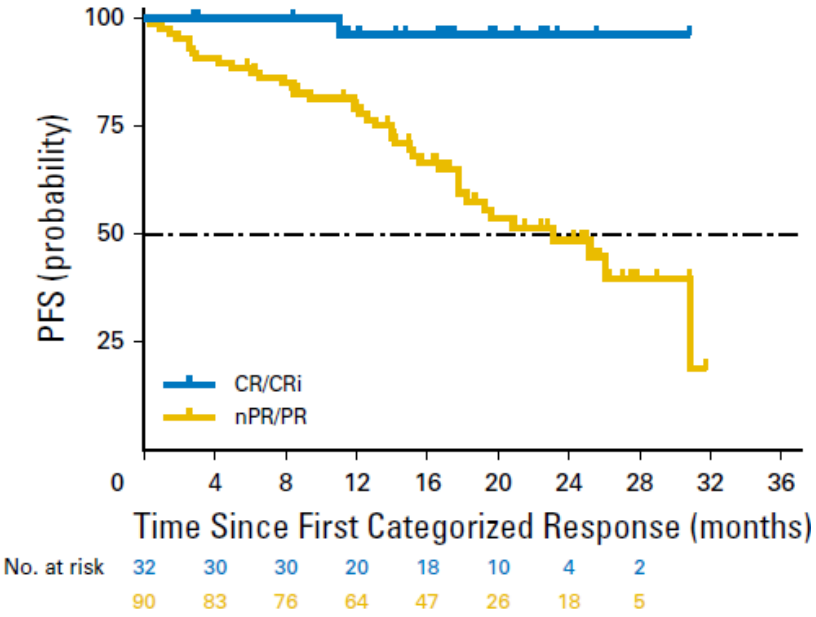
- **Median time to first response: 1 month (range 0.5–4.4)**
- **Median time to CR/CRi: 9.8 months (range 2.7–31.1)**

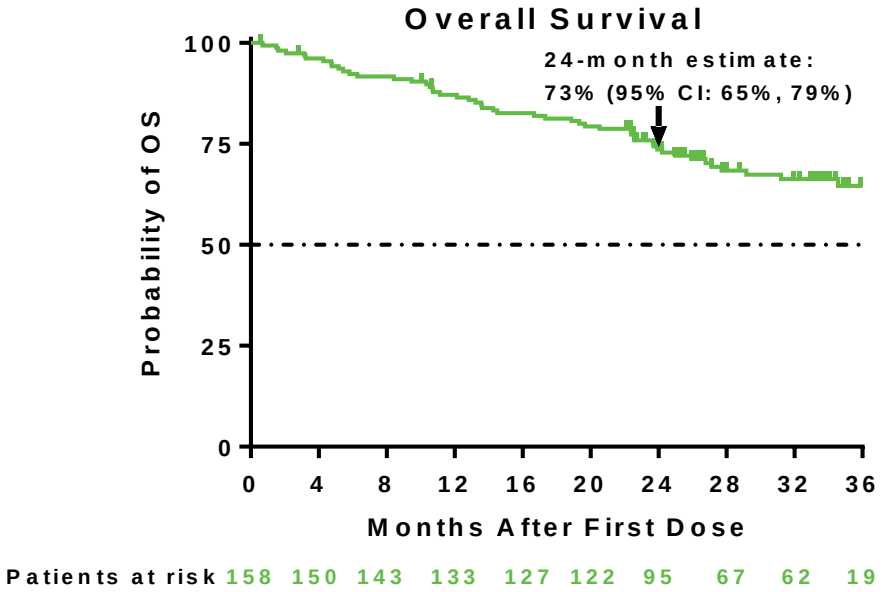
Median PFS = 27.2 months (95% CI = 21 – NR)
24-month estimate: 54% (95% CI = 45–62)

Stilgenbauer S, *et al*. *Lancet Oncol* 2016; 17:768–7783; Stilgenbauer S, *et al. Haematologica* 2017; Stilgenbauer S, et al. Blood 2018

Venetoclax in R/R CLL

Venetoclax for Patients with Chronic Lymphocytic Leukemia With 17p Deletion: Results From the Full Population of a Phase II Pivotal Trial

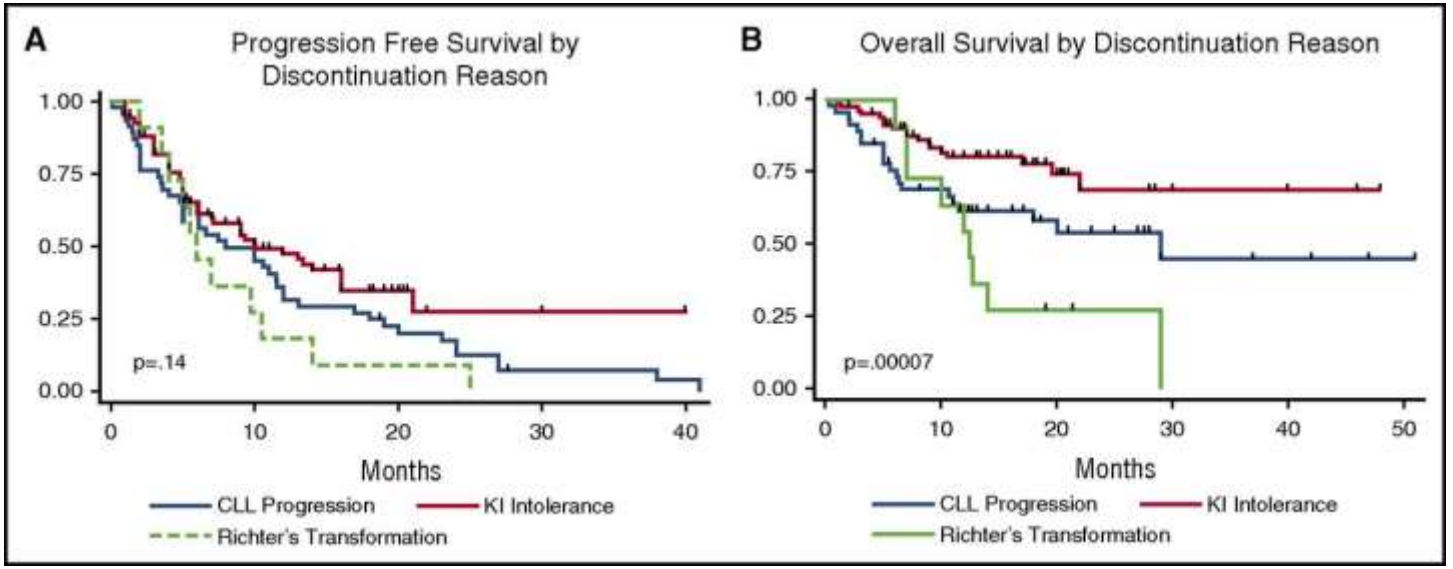


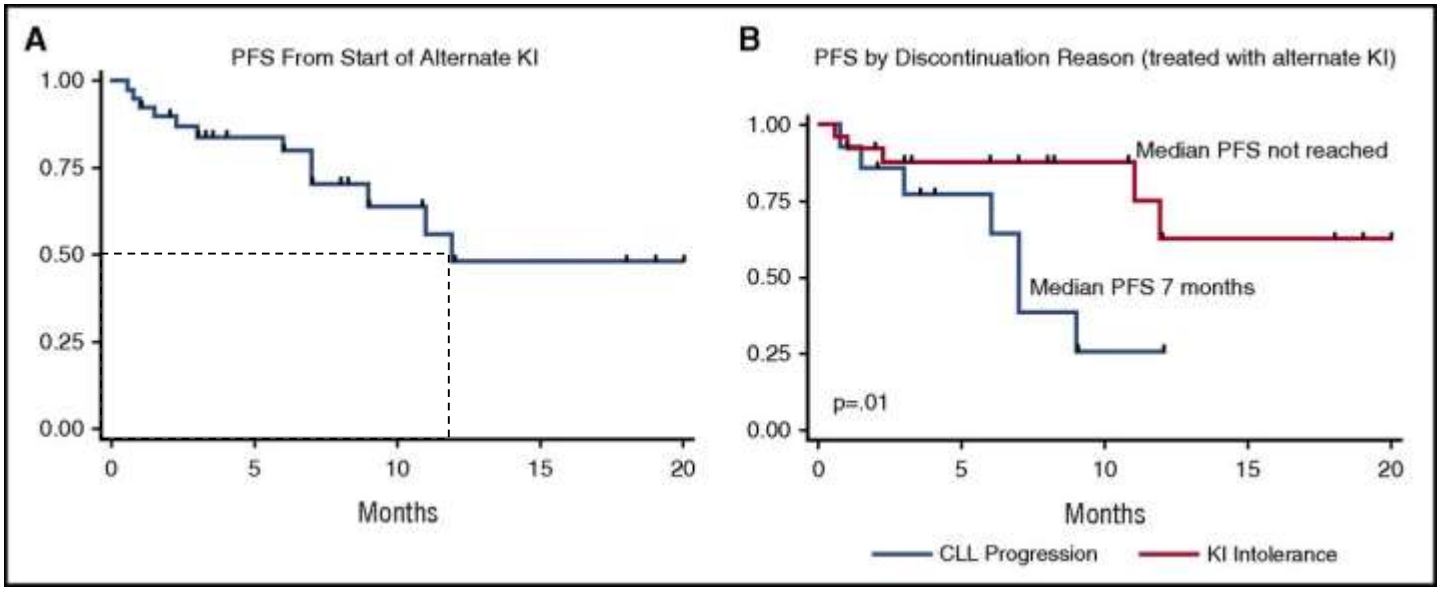


Median PFS = 27.2 months (95% CI = 21 – NR)

Stilgenbauer S, *et al*. *Lancet Oncol* 2016; 17:768–7783; Stilgenbauer S, *et al. Haematologica* 2017; Stilgenbauer S, et al. Blood 2018

Outcomes of CLL patients treated with sequential kinase inhibitor therapy





Anthony R. Mato et al. Blood 2016;128:2199-2205

Venetoclax in R/R CLL who previously received BCRi

M14-032 Phase II study (prior BCRi)

Venetoclax 400 mg/day until PD or unacceptable toxicity (up to 2 years)

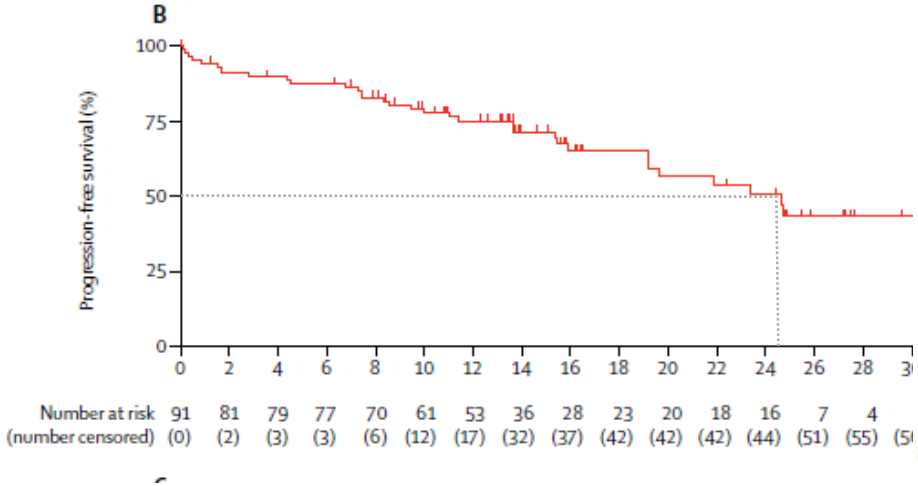
Main cohort
7-day whashout
Ramp up: 5 weeks

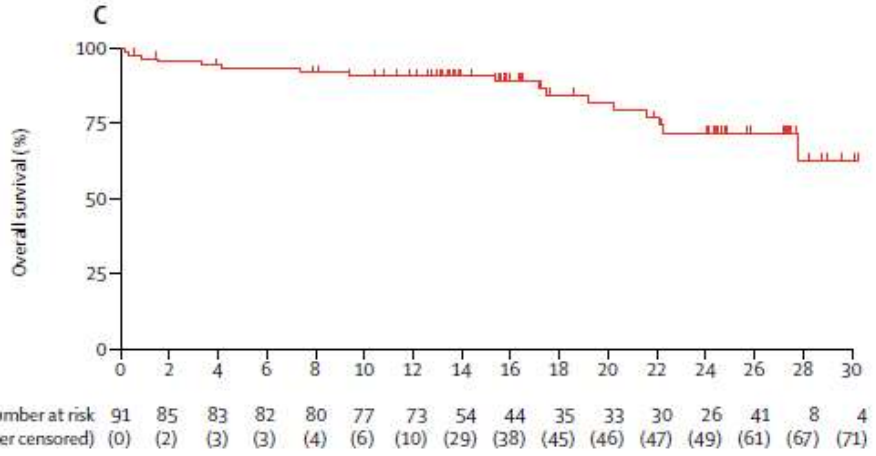
Espansion cohort
3-day whashout
Compressed dose ramp-up allowed: 3 weeks
Dose escalation to 600 mg allowed if SD at W12

Last BCRi ibrutinib N=91 (43+48)

OR 65% (95% CI, 53–74)
CR/CRi 8%, nPR 3%, PR 52%

24/57 (42%) MRDnegative in PB (26% ITT)





Median PFS 24,7 mo (95% CI 19,2-NR)
Estimated PFS @1y 75%

Median OS NR (27,8-NR)
Estimated OS @1y 91%

Median follow-up 14 months (IQR 8–18)

Jones JA, *Lancet Oncol* 2018

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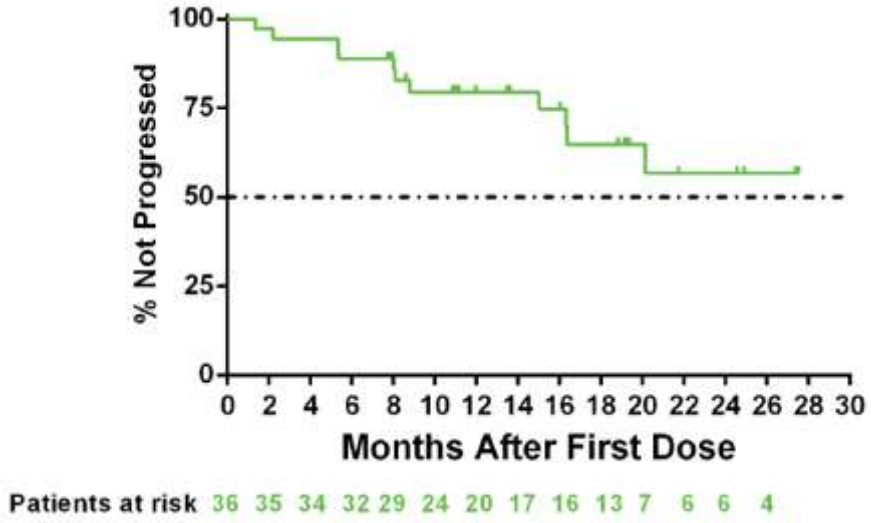
Last BCRi idelalisib N=36 (21+15)

OR 67%
CR/CRi 8%, PR 58%

8/17 (40%) MRDnegative in PB (22% ITT)



Median PFS NR
Estimated PFS @1y 79%

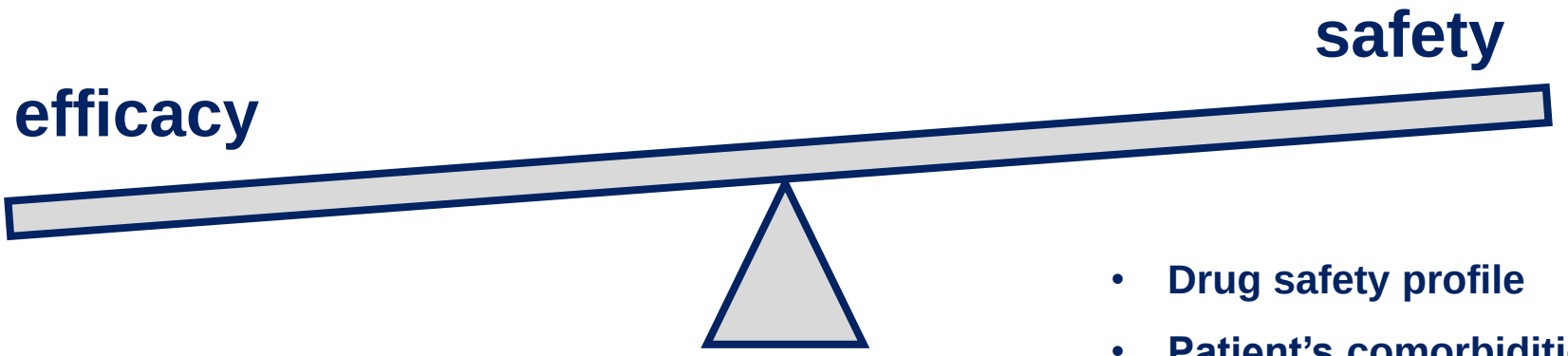
Median follow-up 14 months

Coutre S, *Blood* 2018

VENCLYXTO → EMA approved Indications in CLL

- **Venclyxto ®** monotherapy is indicated for the treatment of chronic lymphocytic leukaemia (CLL)
  - in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor.
  - in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

Treatment choice for R/R CLL



- Previous treatment
- Duration of response
- Molecular characteristics

- Drug safety profile
- Patient's comorbidities

Head-to-head comparisons of novel drugs are lacking

No clear guidelines exist to direct the optimal sequential use of new targeted agents

Further prospective data are required to determine the long-term efficacy in high-risk groups

Other options for R/R CLL

New targeted drugs dramatically changed the treatment landscape of CLL

… but:

- **curative potential is still lacking**
- **disease control in certain high-risk groups of R/R patients is limited** (→ need for a new common definition of high risk patients)
- **adverse prognosis of patients discontinuing new targeted drugs due to progression**

Allogeneic HSCT???

Other options for R/R CLL

Allogeneic HSCT

ESMO guidelines (2017)

Consider in patients achieving remission with kinase inhibitors or BCL2 antagonists after early relapse from chemoimmunotherapy and/or with del(17p) or TP53 mutation. In this situation, long-term treatment with inhibitors is an alternative option. The decision should be based on transplant- and disease-risk and the patient's preferences. In patients failing to several lines of therapy, allogeneic bone marrow transplantation should be considered [III, B].

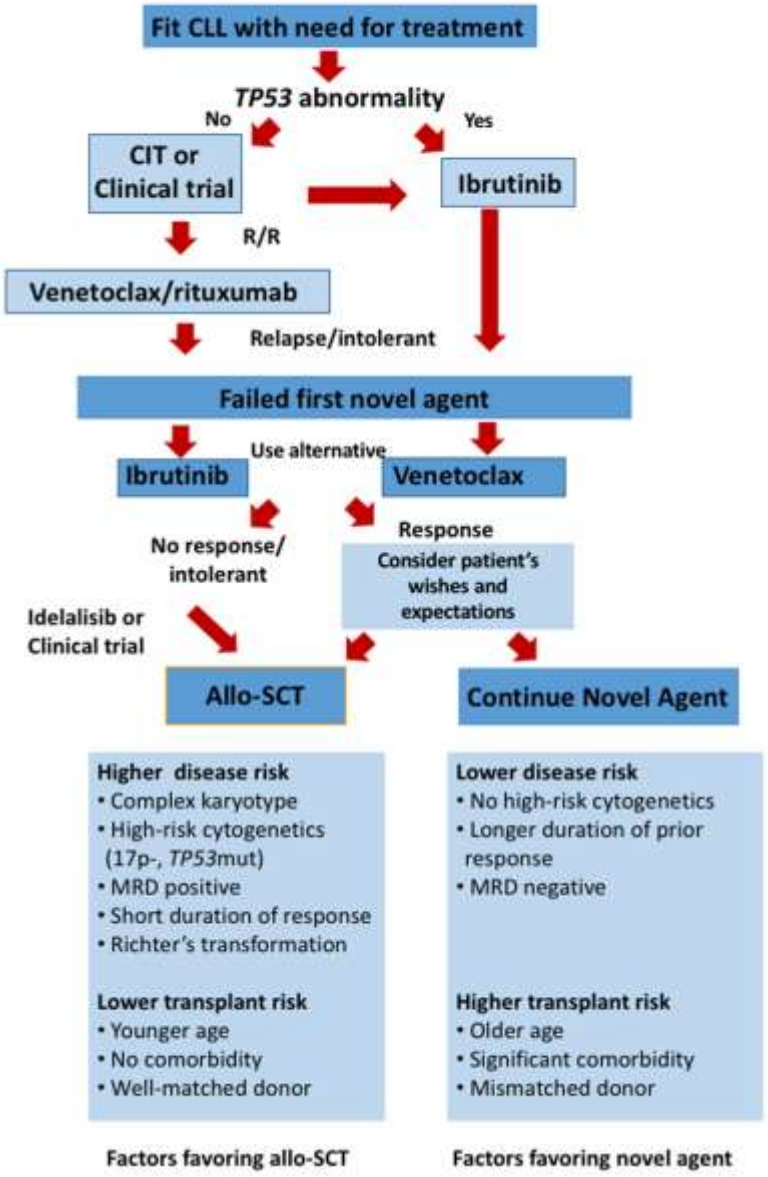
EBMT/ERIC guidelines awaited for 2018

NCCN Guidelines (2018)

HCT may be an effective treatment option for patients with high-risk CLL (disease that is refractory to purine analog-based chemoimmunotherapy or disease relapse within 2 years after treatment with purine analog-based chemoimmunotherapy and/or disease with del (17p) or TP53 mutation).

Other options for R/R CLL

Allogeneic HSCT



Gribben J, Blood 2018

Other options for R/R CLL

Additional targeted agents (alone or in combination)

- Alternative BTK inhibitors
- Alternative PI3K inhibitors
- SYK inhibitor
- Alternative Bcl2 inhibitors
- Checkpoint inhibitors (anti-PD-1)
- Monoclonal antibodies (anti-CD20)
- AKT inhibitors
- Cyclin-dependent kinase inhibitors