NCCN 11th Annual Congress:
Hematologic Malignancies™

Debate—Examining Controversies in the Front-line Management of CLL: Chemo-immunotherapy vs. Continuous TKI Therapy

Steven Coutre, MD
Stanford Cancer Institute

William G. Wierda, MD, PhD
The University of Texas MD Anderson Cancer Center

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Continuous TKI Therapy for Chronic Lymphocytic Leukemia

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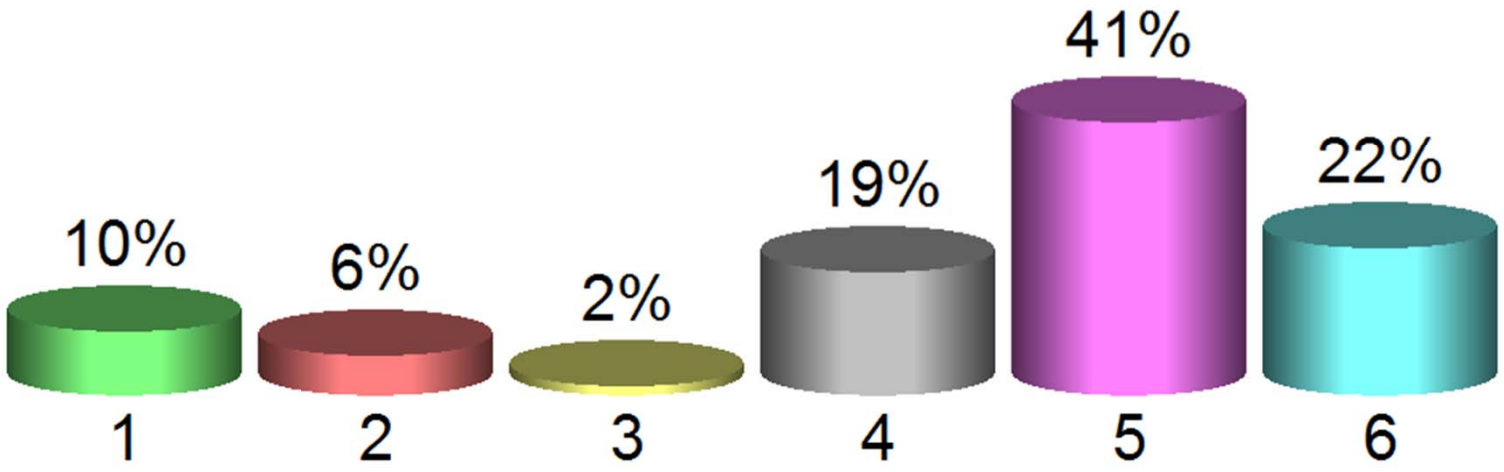
Audience Polling Results

Ibrutinib is approved for initial treatment for CLL based on the following:

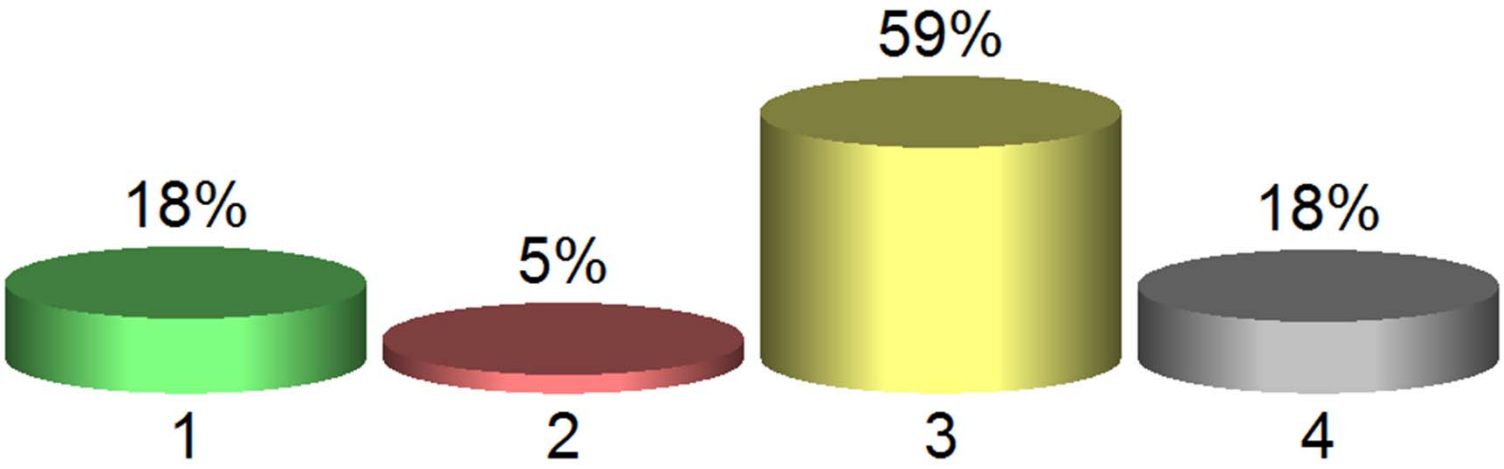
1. **OS advantage versus chlorambucil**
2. **PFS advantage versus BR**
3. **Long term safety data**
4. **Improved PFS in del17p CLL**
5. **All of the above**
6. **Option 1 + Option 3**



Audience Polling Results

For previously untreated CLL patients:

1. **FCR treatment demonstrated superior OS compared to BR treatment**
2. **PFS with Rituximab/chlorambucil is equivalent to obinutuzumab/chlorambucil**
3. **PFS and OS with Ibrutinib is superior to chlorambucil**
4. **With continued therapy, 50% of the responses with ibrutinib are CRs**



FRONT-LINE, OLDER PATIENT

Front-Line, Older Patient

- Your new patient is a 75 year old man who was diagnosed with CLL 10 years ago and has developed progressive adenopathy, splenomegaly, and anemia. He also has a history of CAD and stroke.

Front-line therapy of CLL in older patients

- Chlorambucil alone
- Rituximab alone
- Chlorambucil + Rituximab

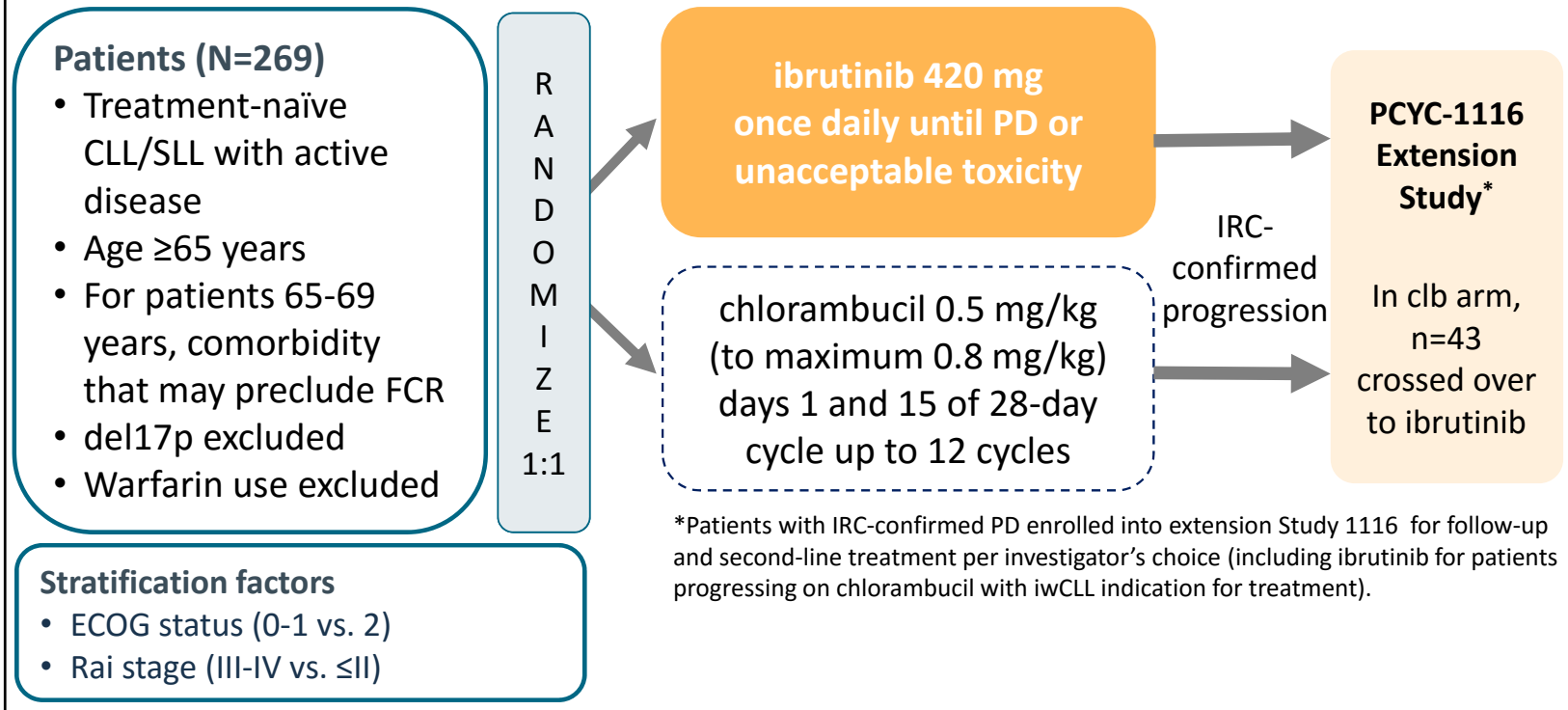
- Chlorambucil + Ofatumumab
- Chlorambucil + Obinutuzumab
- Bendamustine + Rituximab
- Ibrutinib

Results from the International, Randomized Phase 3 Study of Ibrutinib Versus Chlorambucil in Patients 65 Years and Older with Treatment-Naïve CLL/SLL (RESONATE-2™)

Alessandra Tedeschi, MD*, Paul M. Barr, MD, Tadeusz Robak, MD, PhD, Carolyn Owen, MD, Paolo Ghia, MD, PhD, Osnat Bairey, MD, Peter Hillmen, MB, ChB, PhD, Nancy L. Bartlett, MD, Jianyong Li, MD, David Simpson, MBBS, Sebastian Grosicki, MD, PhD, Stephen Devereux, FRCP, FRCPath, PhD, Helen McCarthy, FRCP, FRCPath, PhD, Steven Coutre, MD, Hang Quach, MBBS, Gianluca Gaidano, MD, PhD, Zvenyslava Maslyak, MD, Don A. Stevens, MD, Ann Janssens, MD, Fritz Offner, MD, PhD, Jiří Mayer, MD, Michael O'Dwyer, MD, Andrzej Hellmann, MD, PhD, Anna Schuh, MD, PhD, Tanya Siddiqi, MD, Aaron Polliack, MD, Constantine S. Tam, MBBS, Michael Keating, MBBS, Deepali Suri, MS, Cathy Zhou, MS, Fong Clow, ScD, Lori Styles, MD, Danelle F. James, MD, MAS, Thomas J. Kipps, MD, PhD, and Jan A. Burger, MD, PhD

Azienda Ospedaliera Niguarda Cà Granda, Milano, Italy

RESONATE™-2 (PCYC-1115) Study Design



*Patients with IRC-confirmed PD enrolled into extension Study 1116 for follow-up and second-line treatment per investigator's choice (including ibrutinib for patients progressing on chlorambucil with iwCLL indication for treatment).

- Phase 3, open-label, multicenter, international study
- **Primary endpoint**: PFS as evaluated by IRC (2008 iwCLL criteria)[1,2]
- **Secondary endpoints**: OS, ORR, hematologic improvement, safety

1. Hallek et al. *Blood*. 2008;111:5446-5456; 2. Hallek et al, *Blood.* 2012; e-letter, June 04, 2012.

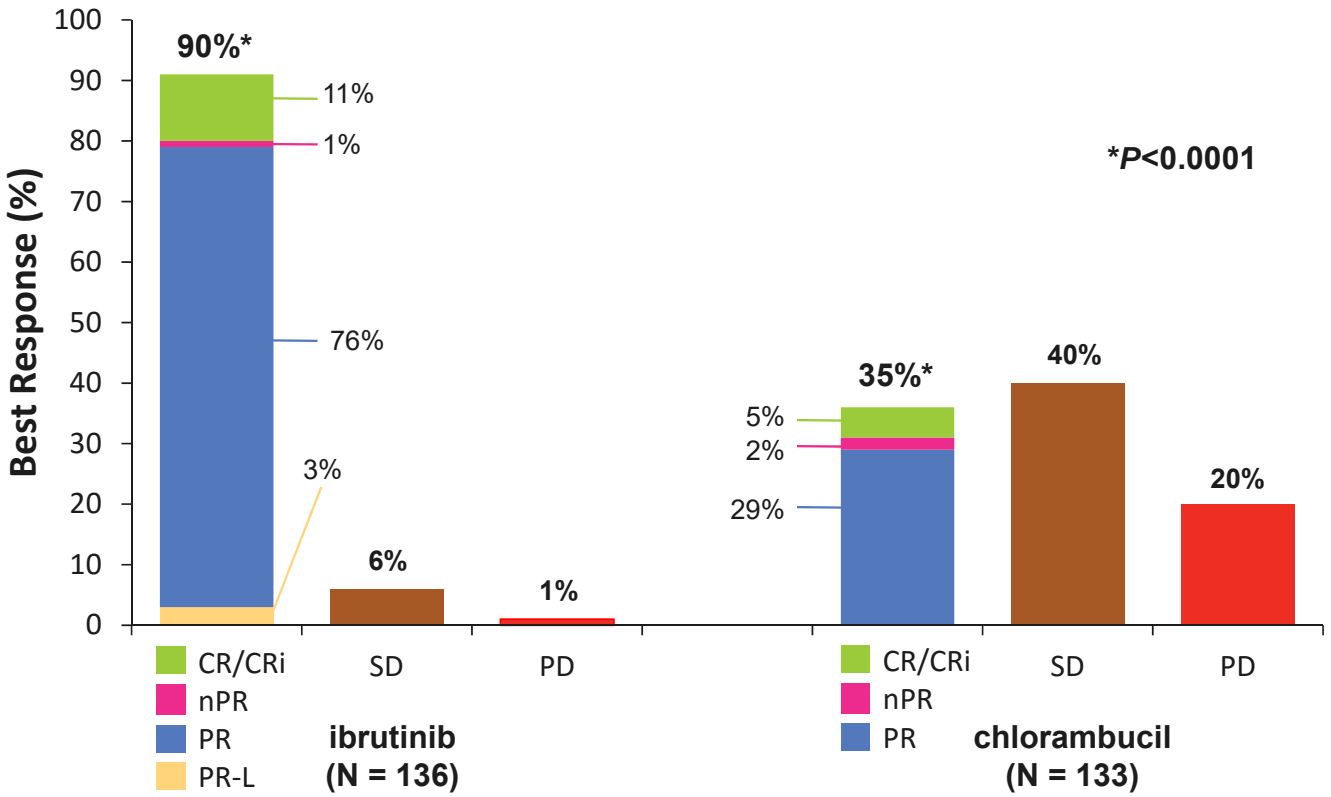
ASH 2015, PCYC-1115, Tedeschi A et al. Abstract 798.

Patient Characteristics

Characteristic	ibrutinib (n = 136)	chlorambucil (n = 133)
Median age, years (range) ≥70 years, %	73 (65–89) 71	72 (65–90) 70
ECOG status 2, %	8	9
Rai stage III or IV, %	44	47
CIRS score >6, %	31	33
Creatinine clearance <60 ml/min, %	44	50
Bulky disease ≥5 cm, %	40	30
β2-microglobulin >3.5 mg/L, %	63	67
Hemoglobin ≤11 g/dL, %	38	41
Platelet count ≤100,000 per mm^3, %	26	21
Del11q, %	21	19
Unmutated *IGHV,* %	43	45

ASH 2015, PCYC-1115, Tedeschi A et al. Abstract 798.

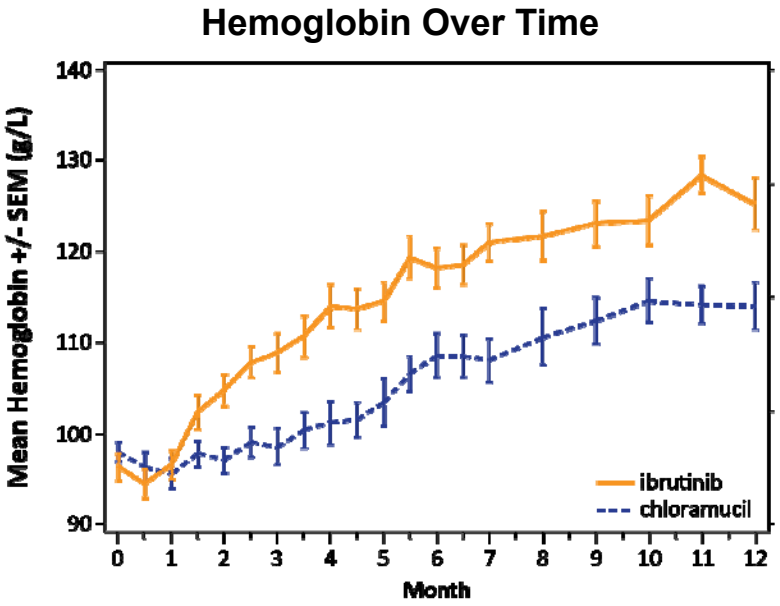
Best Response by Investigator Assessment

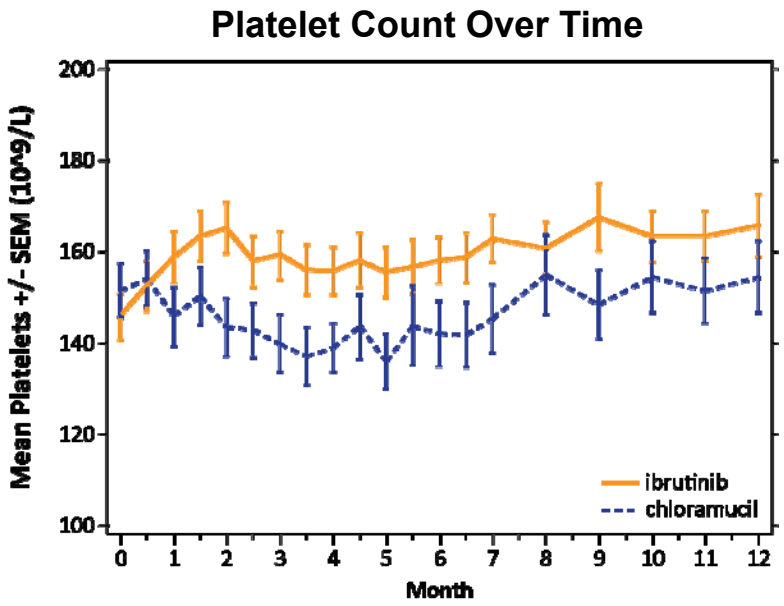


- ORR at 8 months: 82% with ibrutinib vs. 30% with chlorambucil
- ORR with ibrutinib higher than with chlorambucil at all time points

ASH 2015, PCYC-1115, Tedeschi A et al. Abstract 798.

Improvement in Hematologic Function

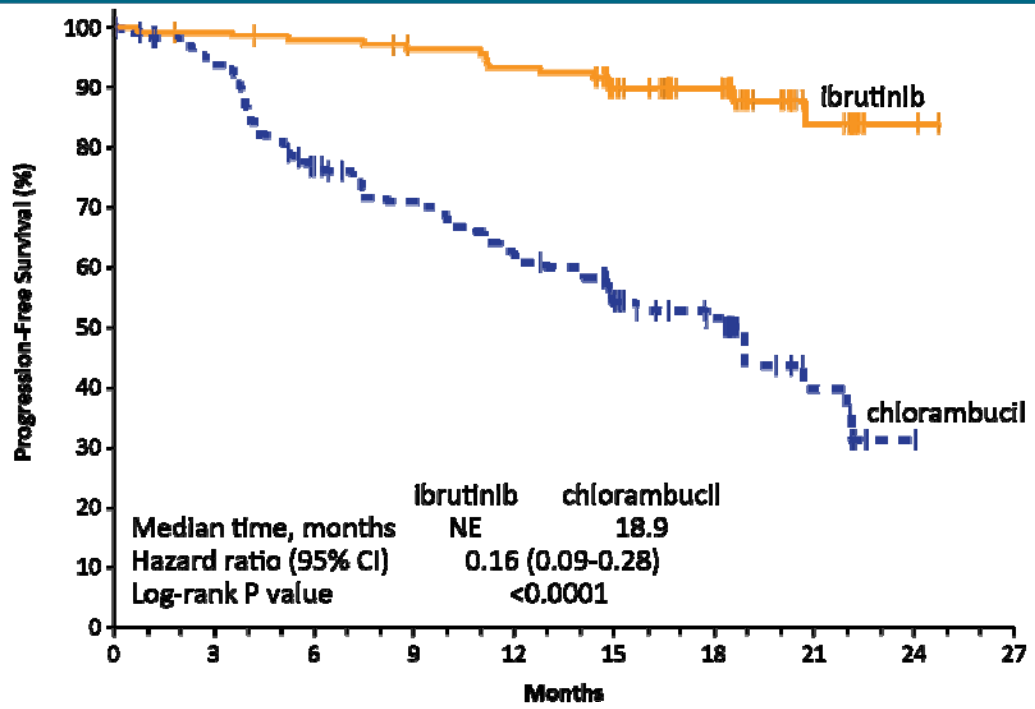




- Sustained improvement in hemoglobin in patients with anemia: 84% with ibrutinib vs. 45% with chlorambucil (*P*<0.0001)
- Sustained improvement in platelet count in patients with thrombocytopenia: 77% with ibrutinib vs. 43% with chlorambucil (*P*=0.0054)

ASH 2015, PCYC-1115, Tedeschi A et al. Abstract 798.

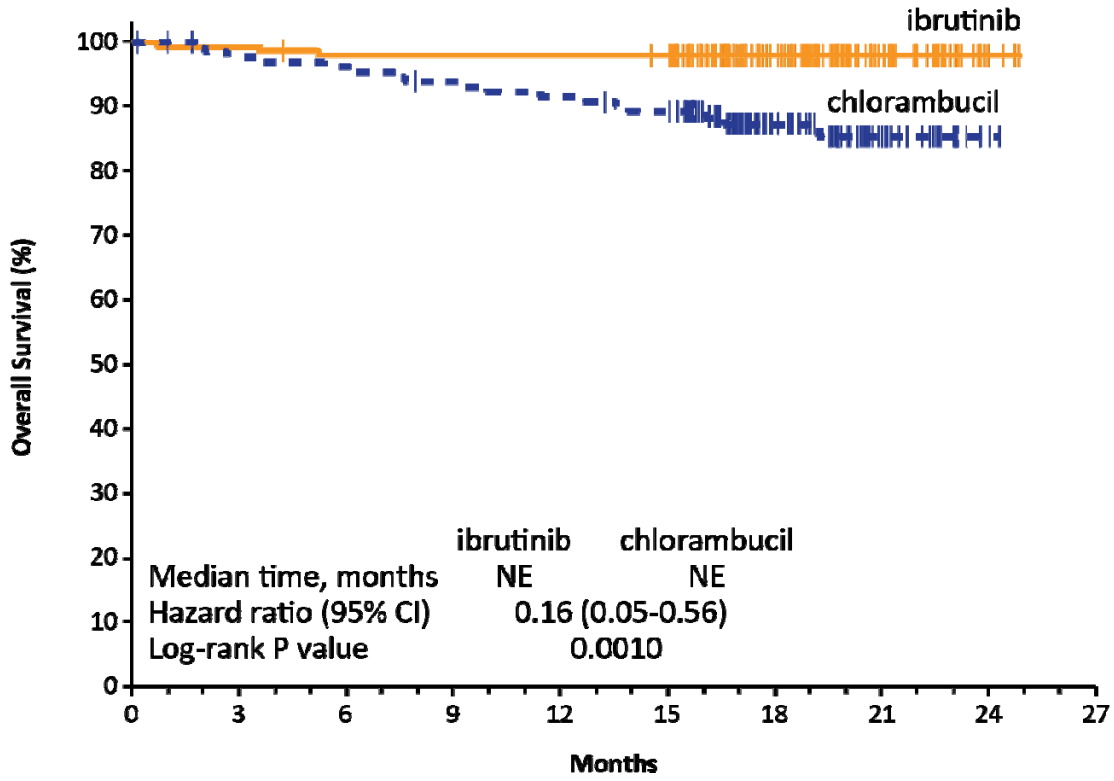
PFS by Independent Assessment



- 84% reduction in risk of progression or death with ibrutinib
- 18-month PFS rate: 90% with ibrutinib vs. 52% with chlorambucil
- Median follow-up: 18.4 months

ASH 2015, PCYC-1115, Tedeschi A et al. Abstract 798.

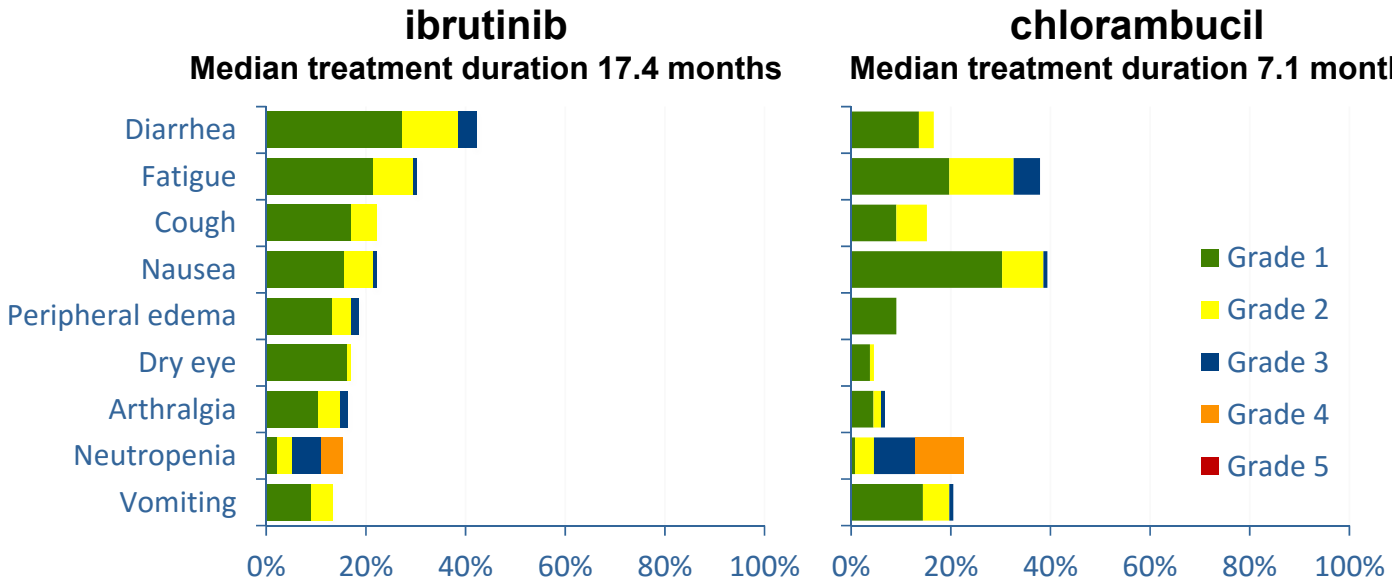
Overall Survival



- 84% reduction in risk of death with ibrutinib
- 24-month OS rate: 98% with ibrutinib and 85% with chlorambucil
- 3 deaths on ibrutinib arm vs. 17 deaths on chlorambucil arm

ASH 2015, PCYC-1115, Tedeschi A et al. Abstract 798.

Most Common Adverse Events*



*Adverse event that occurred in ≥15% of patients in either treatment arm, and that were imbalanced between treatment arms by a difference in frequency of ≥5%.

- Majority of the common AEs on ibrutinib arm were grade 1 and did not result in treatment discontinuation
- On the chlorambucil arm, fatigue, nausea, vomiting, and cytopenias occurred more frequently vs. ibrutinib
- Grade 3 maculopapular rash (no grade 4) in 3% for ibrutinib vs. 2% for chlorambucil

ASH 2015, PCYC-1115, Tedeschi A et al. Abstract 798.

Outcomes After Ibrutinib Discontinuation or Progression

- 12 patients discontinued ibrutinib due to AEs
  - 11 of these patients are alive
    - 3 progressed 2, 4, and 6 months after discontinuation; 1 started BR 8 months after PD and 2 with no subsequent therapy
    - 3 started subsequent therapy (2 FCR, 1 chlorambucil) 2, 3, and 8 months after discontinuation
    - 5 were progression-free without subsequent therapy
  - 1 died of pneumonia 1 month after discontinuation
- 2 patients discontinued primarily due to progression, alive without subsequent therapy
- 1 patient initially progressed by investigator (not IRC confirmed), remained on ibrutinib, subsequently achieved CR, and continues ibrutinib

ASH 2015, PCYC-1115, Tedeschi A et al. Abstract 798.

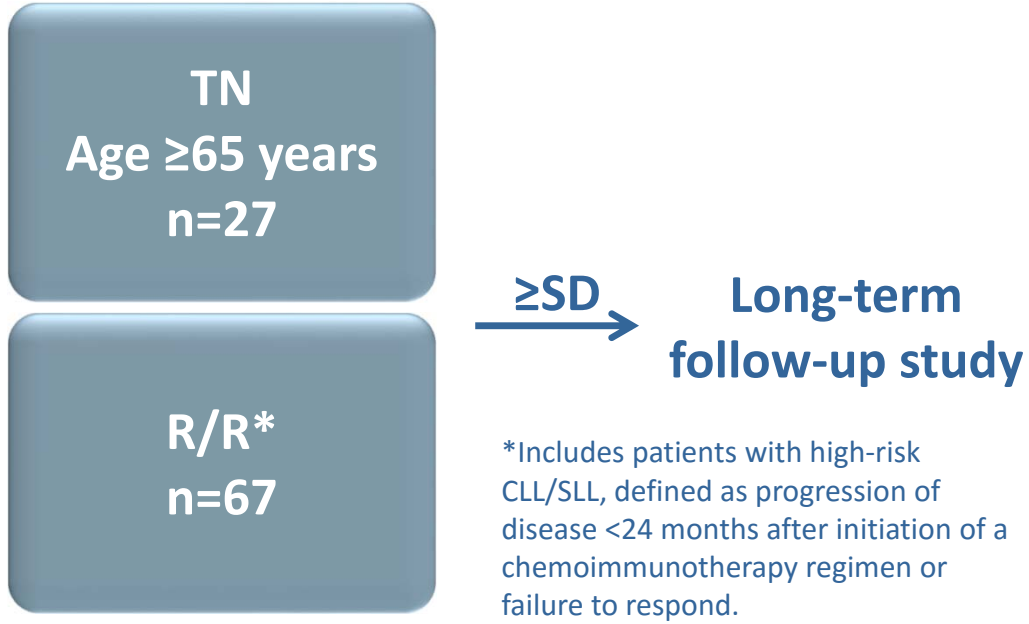
Single-Agent Ibrutinib 420 mg Induces Durable Responses Including Complete Responses in Patients With CLL Following Long Term Treatment

*Coutre S[1], O'Brien S[2], Furman R[3], Flinn I[4], Burger J[2], Blum K[5], Sharman J[6], Jones J[5], Wierda W[2], Zhao W[5], Heerema N[5], Johnson A[5], Tran A[7], Zhou C[7], Bilotti E[7], James D[7], Byrd J[5]

[1]Stanford Cancer Center, Stanford University School of Medicine, Stanford, CA; [2]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX; [3]Department of Medicine, Weill Cornell Medical College, New York, NY; [4]Sarah Cannon Research Institute, Nashville, TN; [5]The Ohio State University, Columbus, OH; [6]Willamette Valley Cancer Institute and Research Center, Springfield, OR; [7]Pharmacyclics LLC, an AbbVie Company, Sunnyvale, CA

Study Cohort

PCYC-1102/1103: patients with CLL/SLL treated with oral, once-daily ibrutinib (420 mg/day)

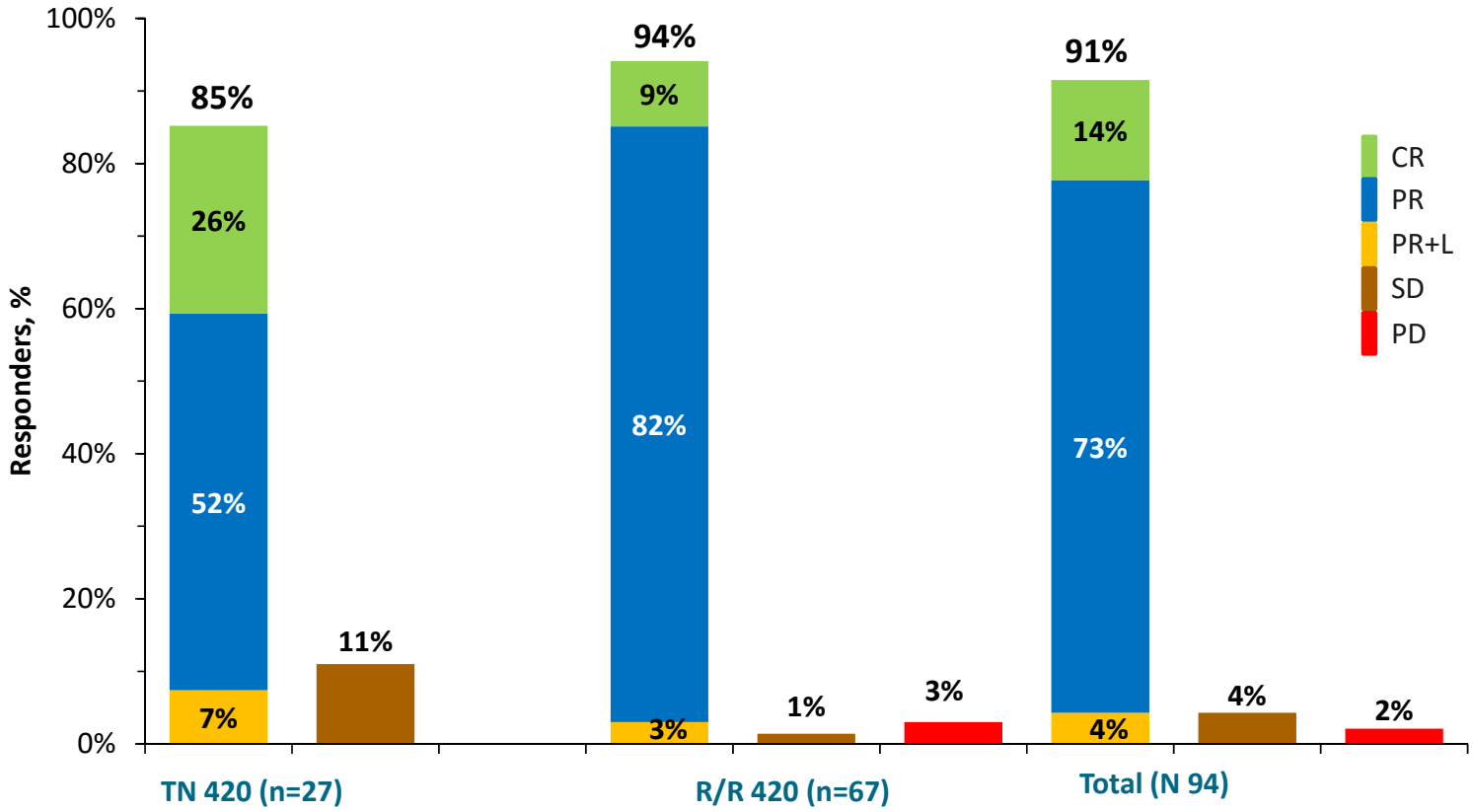


*Includes patients with high-risk CLL/SLL, defined as progression of disease <24 months after initiation of a chemoimmunotherapy regimen or failure to respond.

- Phase 1/2b (PCYC-1102) and extension (PCYC-1103) studies
  - 94 TN and R/R CLL/SLL patients received ibrutinib 420 mg/day.
  - Median time on study 32 months (range, 0-44)

L&M 2015, PCYC-1102-1103, Coutre et al.

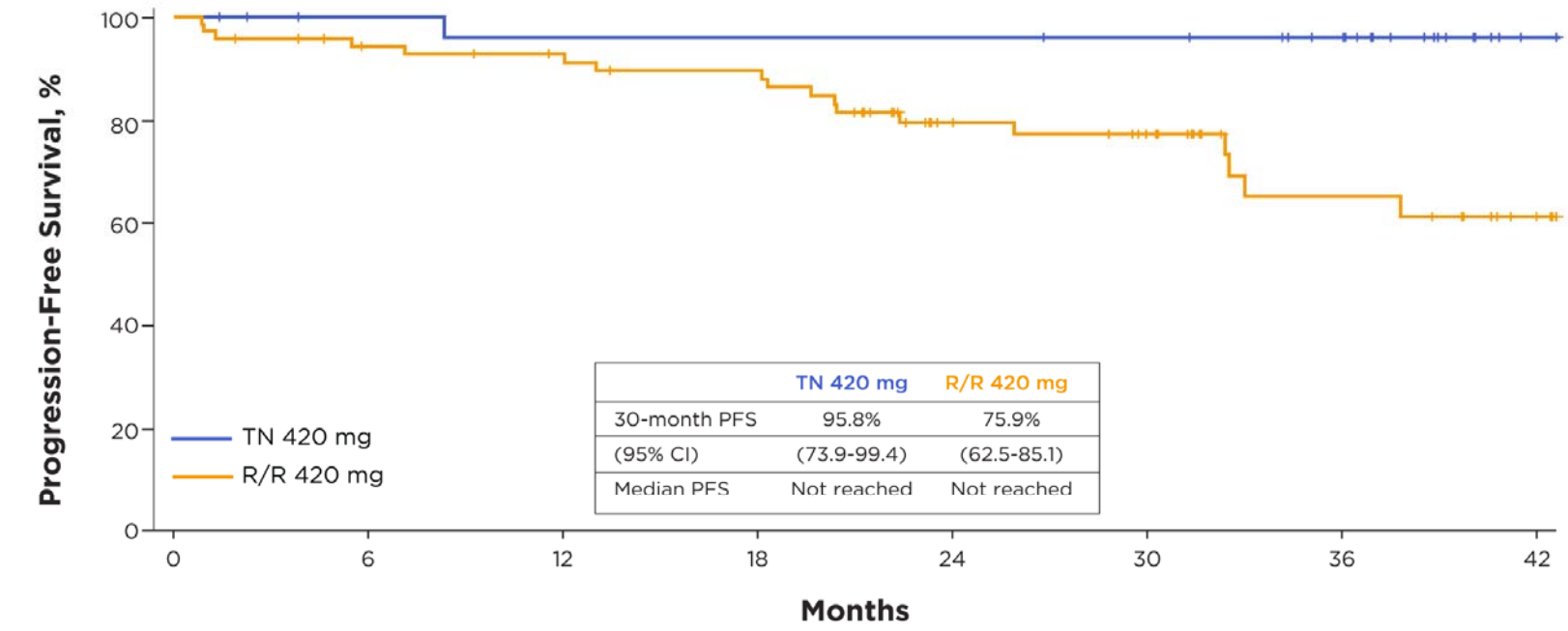
Best Response (Investigator-Assessed)



- Median time to best response was 7.4 months for TN and R/R cohorts.

L&M 2015, PCYC-1102-1103, Coutre et al.

Progression-Free Survival

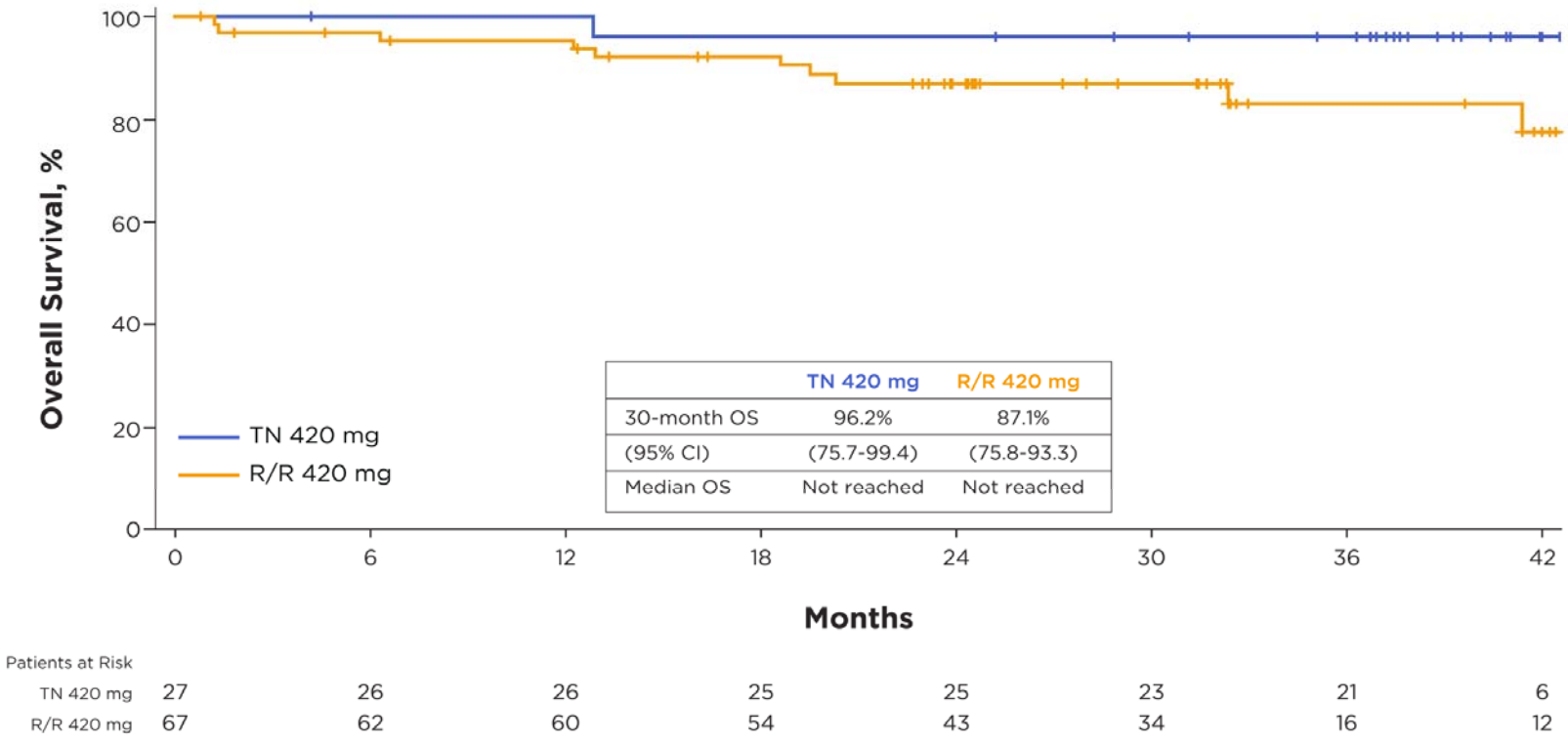


	TN 420 mg	R/R 420 mg
30-month PFS	95.8%	75.9%
(95% CI)	(73.9-99.4)	(62.5-85.1)
Median PFS	Not reached	Not reached

Patients at Risk								
TN 420 mg	27	24	23	23	23	22	17	2
R/R 420 mg	67	58	53	52	52	26	15	7

L&M 2015, PCYC-1102-1103, Coutre et al.

Overall Survival



	TN 420 mg	R/R 420 mg
30-month OS	96.2%	87.1%
(95% CI)	(75.7-99.4)	(75.8-93.3)
Median OS	Not reached	Not reached

Patients at Risk								
TN 420 mg	27	26	26	25	25	23	21	6
R/R 420 mg	67	62	60	54	43	34	16	12

L&M 2015, PCYC-1102-1103, Coutre et al.

Additional Safety Results

	ibrutinib (n = 135)			chlorambucil (n = 132)		
Median exposure, months (range)	17.4 (0.7-24.7)			7.1 (0.5-11.7)		
Adverse event	**Any**	**G3**	**G4**	**Any**	**G3**	**G4**
Hypertension	14%	4%	0	0	0	0
Atrial fibrillation	6%	1%	0	1%	0	0
Major hemorrhage	4%	3%	1%	2%	2%	0

- On ibrutinib arm
  - The 6 patients (4%) with grade 3 hypertension were managed with anti-hypertensive medication and did not require dose modification of ibrutinib
    - 4 of 6 patients: history of hypertension
  - Among 8 patients (6%) with atrial fibrillation, 2 discontinued ibrutinib
    - 7 of 8 patients: history of hypertension, CAD, and/or myocardial ischemia
  - Among 6 patients (4%) with major bleeding, 3 discontinued ibrutinib
    - 3 of 6 patients: concomitant LMWH, aspirin, or vitamin E at time of event
  - Overall, 19% of patients on the ibrutinib arm received anticoagulants and 47% received antiplatelet agents

ASH 2015, PCYC-1115, Tedeschi A et al. Abstract 798.

Summary

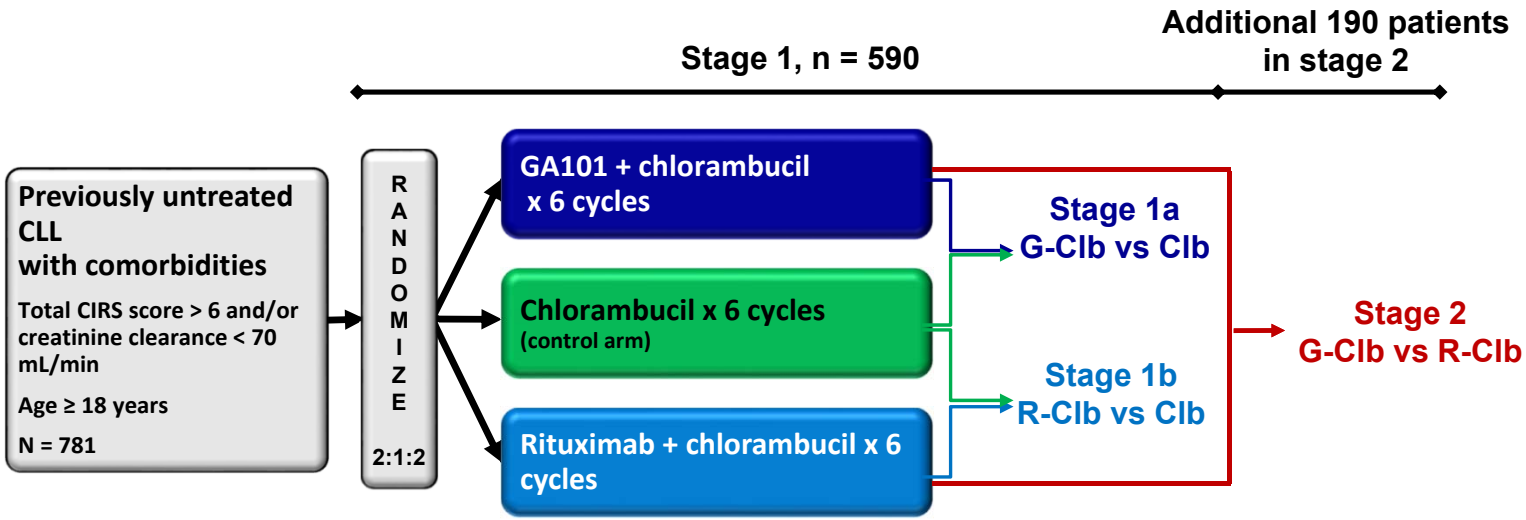
- Why use a less convenient therapy?
- Why not use a better tolerated therapy?
- Why not use in both fit and unfit patients?

FRONT-LINE, UNFIT PATIENT

Front-Line, Unfit Patient

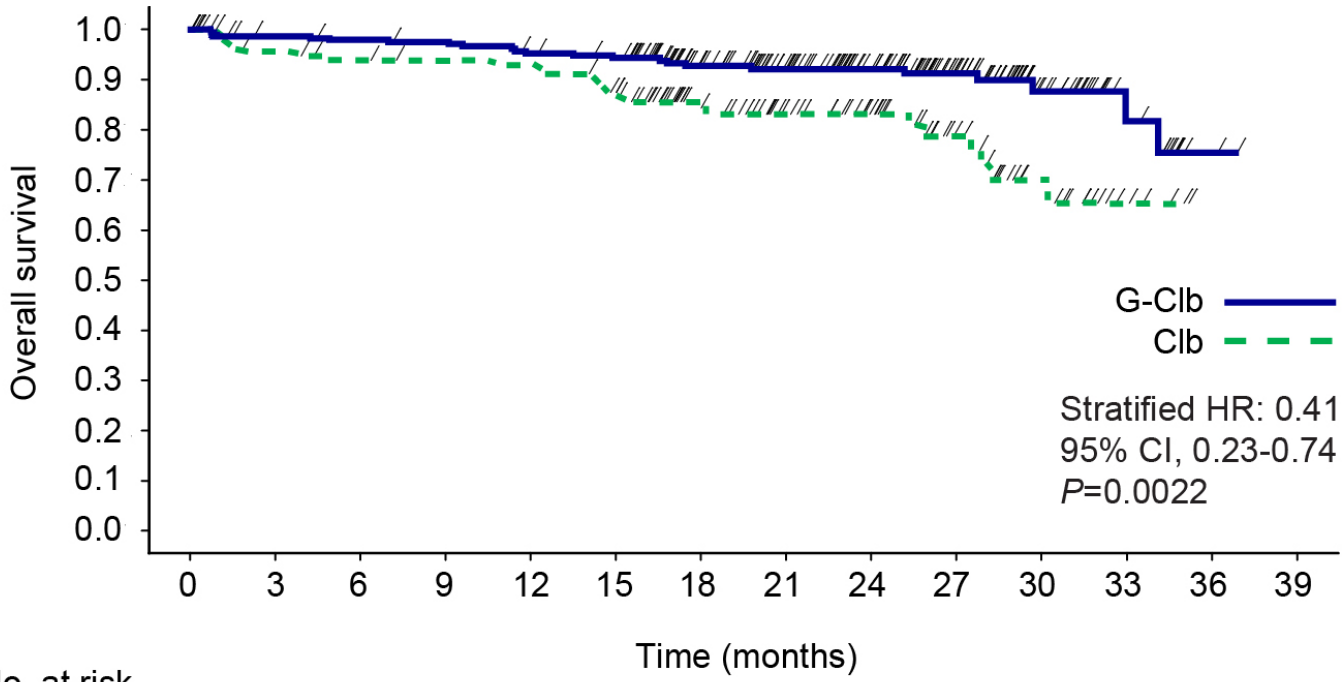
- Your new patient is a 74 year old woman who was diagnosed with CLL 5 years ago and has developed progressive adenopathy. She has fatigue and her cervical lymph nodes are uncomfortable. She does not want chemotherapy and is concerned about losing her hair with treatment. She has diabetes, HTN, and CKD with a GFR of 40.

CLL11: Study design



- GA101: 1,000 mg days 1, 8, and 15 cycle 1; day 1 cycles 2–6, every 28 days
- Rituximab: 375 mg/m^2 day 1 cycle 1, 500 mg/m^2 day 1 cycles 2–6, every 28 days
- Chlorambucil: 0.5 mg/kg day 1 and day 15 cycle 1–6, every 28 days
- Patients with progressive disease in the Clb arm were allowed to cross over to G-Clb

G-Clb vs Clb: Overall survival



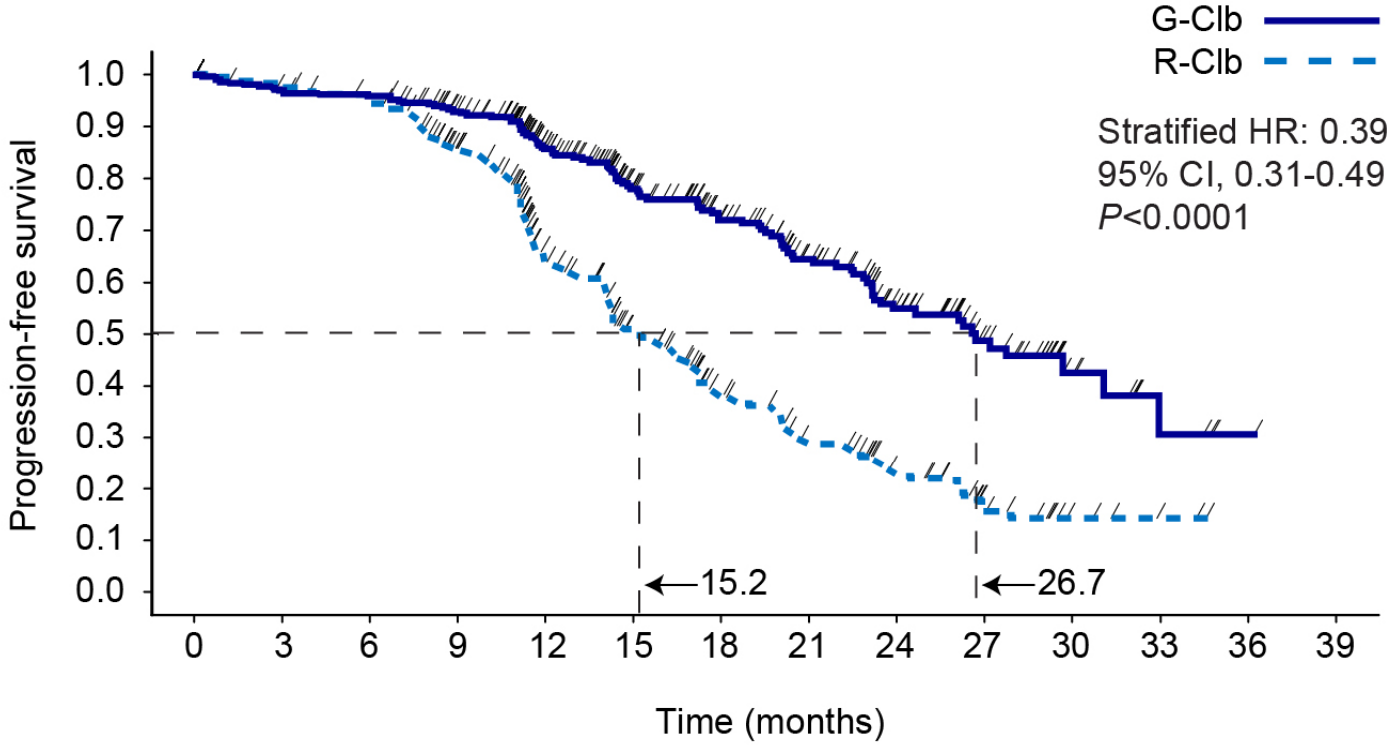
No. at risk

G-Clb:	238	226	223	221	215	211	170	144	115	71	34	14	2	0
Clb:	118	109	105	103	102	94	70	56	44	29	15	5	0	0

Total number of deaths: G-Clb, 22 (9%); Clb, 24 (20%)

Median observation time: G-Clb, 23.2 months; Clb, 20.4 months.
No multiplicity adjustment was done for secondary endpoints.

G-Clb vs R-Clb: Progression-free survival

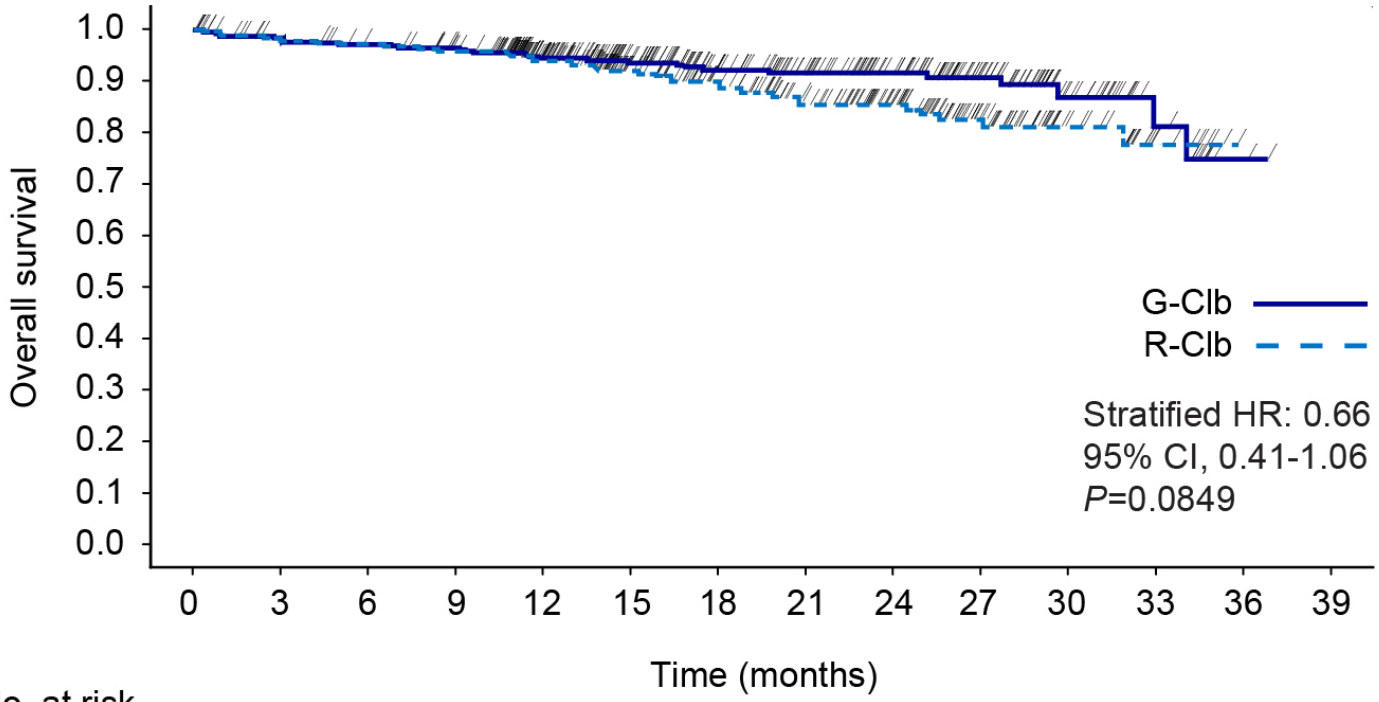


No. at risk

G-Clb:	333	307	302	278	213	156	122	93	60	34	12	4	1	0
R-Clb:	330	317	309	259	163	114	72	49	31	14	5	2	0	0

Median observation time: G-Clb, 18.8 months; R-Clb, 18.6 months.
Type 1 error controlled through closed test procedure; p-value of the global test was <.0001.
Independent Review Committee (IRC) - assessed PFS was consistent with investigator-assessed PFS.

G-Clb vs R-Clb: Overall survival



No. at risk

G-Clb:	333	316	310	303	261	214	170	144	115	71	34	14	2	0
R-Clb:	330	320	314	305	255	203	169	138	105	61	27	8	0	0

Total number of deaths: G-Clb, 28 (8%); R-Clb, 41 (12%)

Median observation time: G-Clb, 18.8 months; R-Clb, 18.6 months.
No multiplicity adjustment was done for secondary endpoints.

Summary

- Physicians familiar with single agent rituximab
- Time-limited, well-tolerated therapy
- Goals of treatment accomplished
- Little or no financial cost to patient
- What about ibrutinib?

FRONT-LINE, YOUNG PATIENT

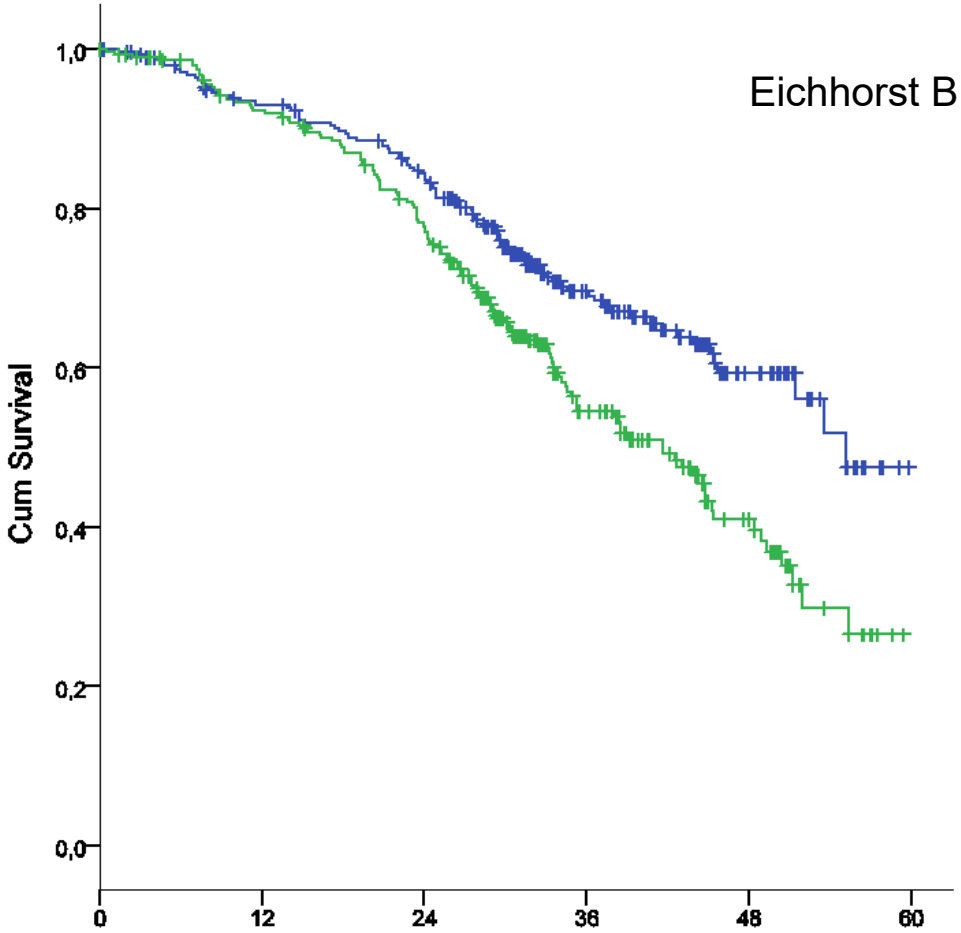
Case Study

- Your new patient is a 60 year old man who was diagnosed with CLL 5 years ago when asymptomatic lymphocytosis was noted along with modest cervical lymphadenopathy. Recently, he has developed progressive adenopathy and anemia. He has no significant medical co-morbidities. His doctor told him that treatment is indicated and he presents for your opinion.

CLL10 STUDY: FCR VS BR IN FRONT-LINE

DEUTSCHE STUDIENGRUPPE CLL

ITT Progression-free survival = Primary endpoint



Eichhorst B, et al. ASH 2014. Abstract 19.

Median PFS

FCR 55.2 months

BR 41.7 months

***P* < 0.001**
HR = 1.626 =
> 1.388

CLL10 STUDY: FCR VS BR IN FRONT-LINE

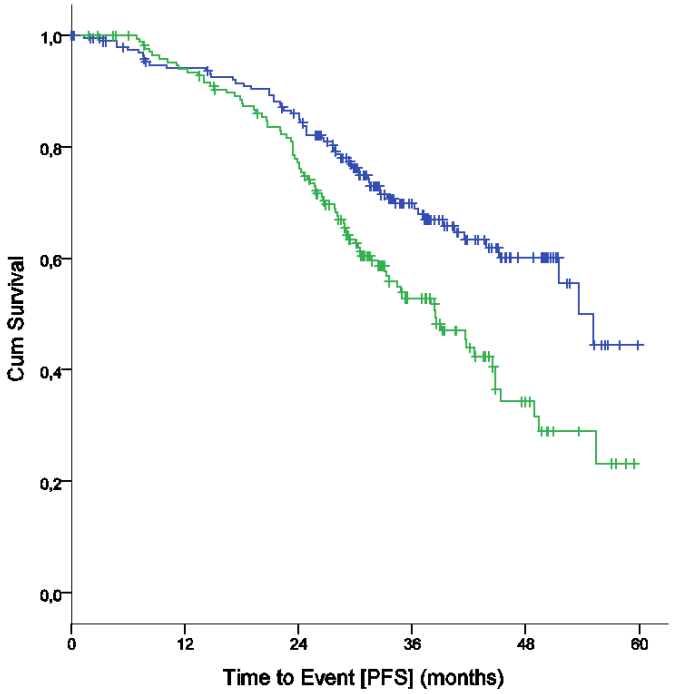
DEUTSCHE STUDIENGRUPPE CLL

Progression-free survival by age group

Eichhorst B, et al. ASH 2014. Abstract 19.

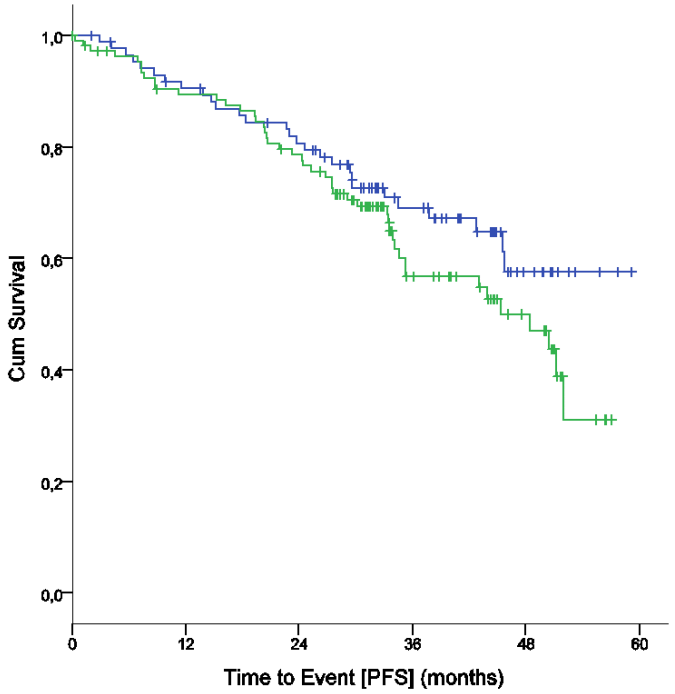
Patients ≤ 65 years: ***P < 0.001***

FCR 53.6 months BR 38.5 months

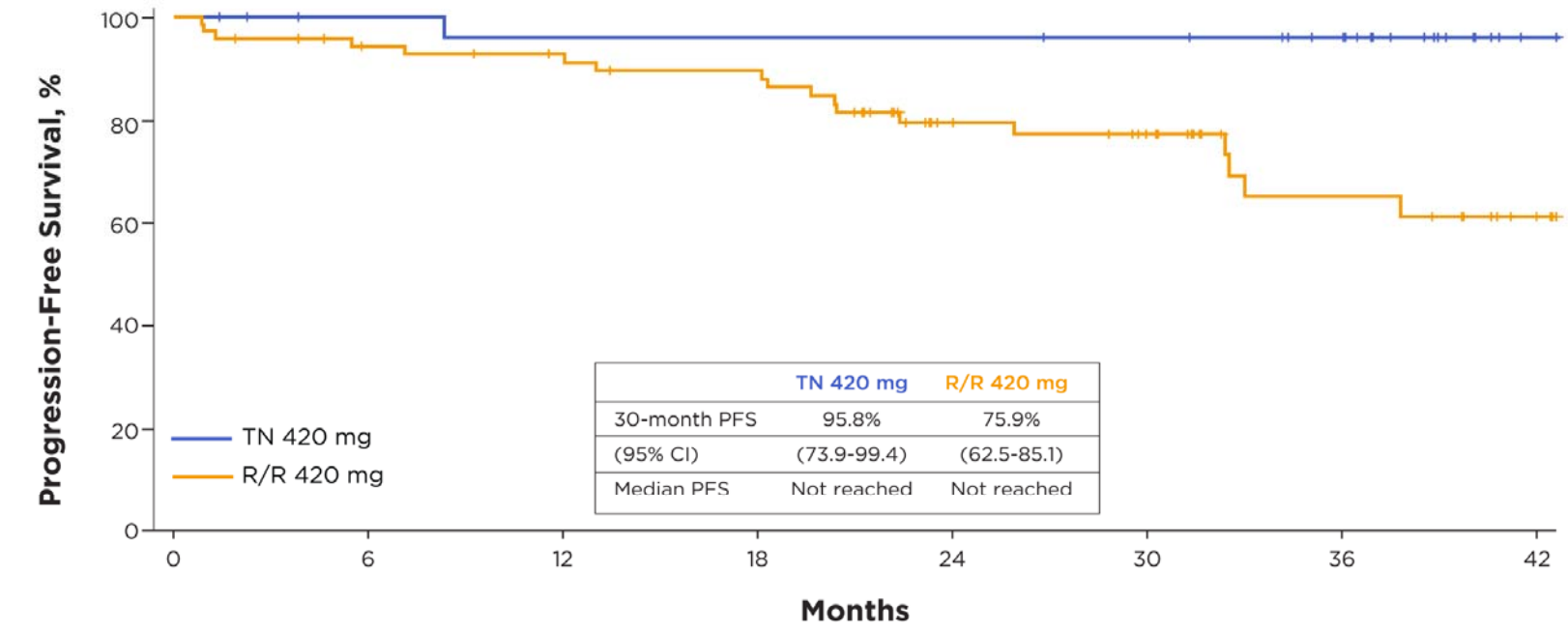


Patients > 65 years: ***P = 0.170***

FCR not reached BR 48.5 months



Progression-Free Survival



	TN 420 mg	R/R 420 mg
30-month PFS	95.8%	75.9%
(95% CI)	(73.9-99.4)	(62.5-85.1)
Median PFS	Not reached	Not reached

Patients at Risk								
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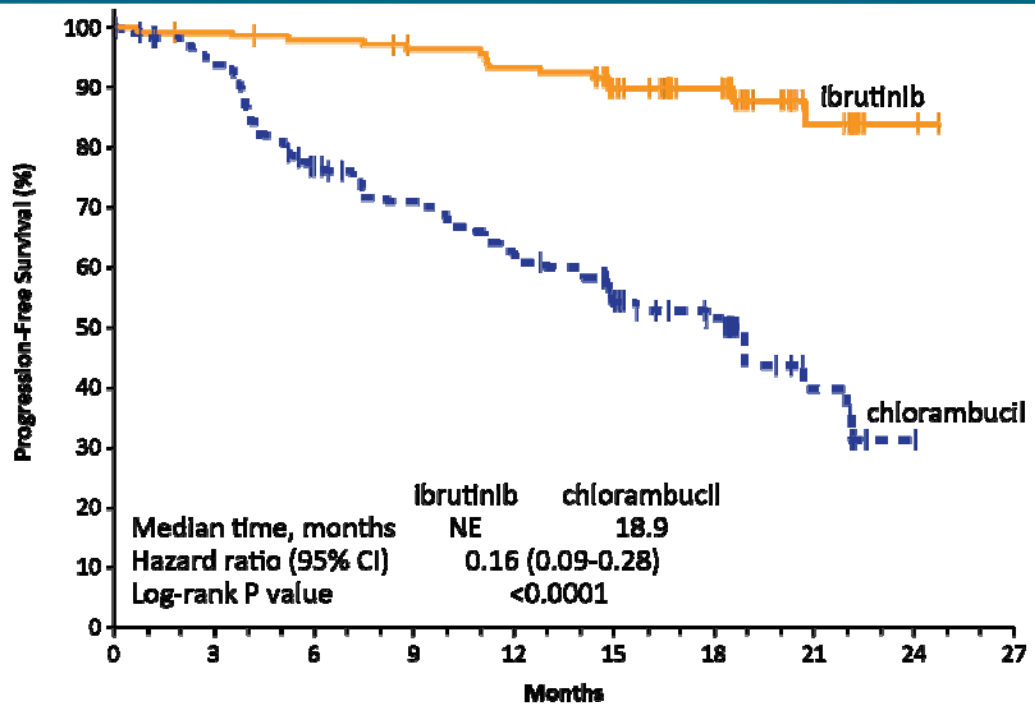
L&M 2015, PCYC-1102-1103, Coutre et al.

PFS by Independent Assessment



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- 18-month PFS rate: 90% with ibrutinib vs. 52% with chlorambucil
- Median follow-up: 18.4 months

ASH 2015, PCYC-1115, Tedeschi A et al. Abstract 798.

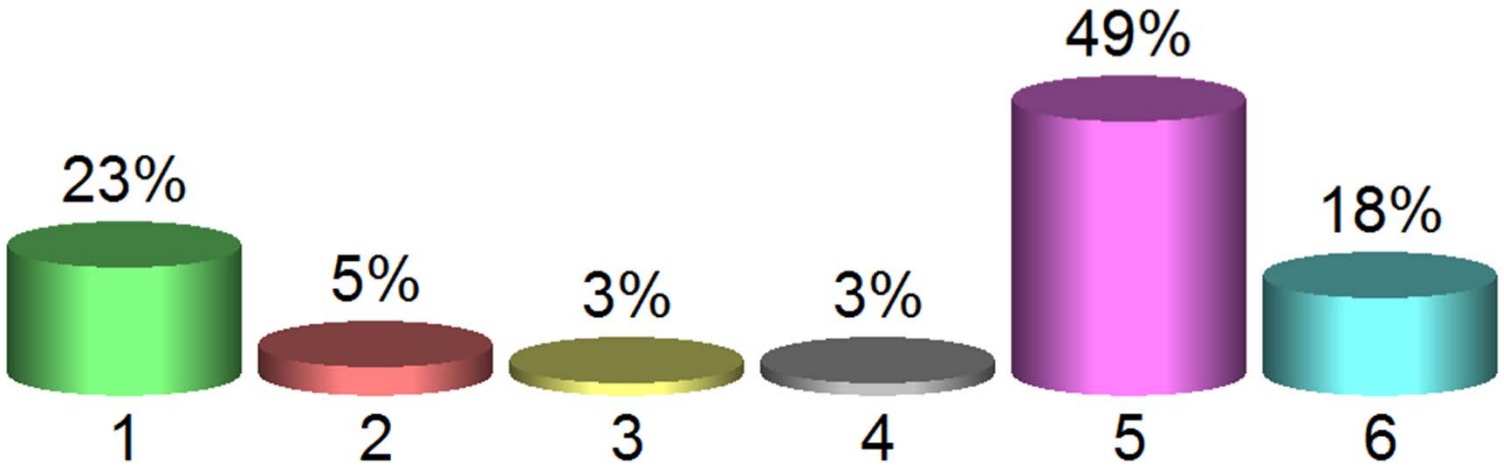
Summary

- Well-tolerated oral therapies are not just for unfit patients.
- Only longer follow up of large studies will provide definitive data on continued efficacy and safety with ibrutinib.
- Randomized trial of FCR versus ibrutinib/rituximab fully enrolled.

Audience Polling Results

Ibrutinib is approved for initial treatment for CLL based on the following:

1. **OS advantage versus chlorambucil**
2. **PFS advantage versus BR**
3. **Long term safety data**
4. **Improved PFS in del17p CLL**
5. **All of the above**
6. **Option 1 + Option 3**



Audience Polling Results

For previously untreated CLL patients:

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2. **PFS with Rituximab/chlorambucil is equivalent to obinutuzumab/chlorambucil**
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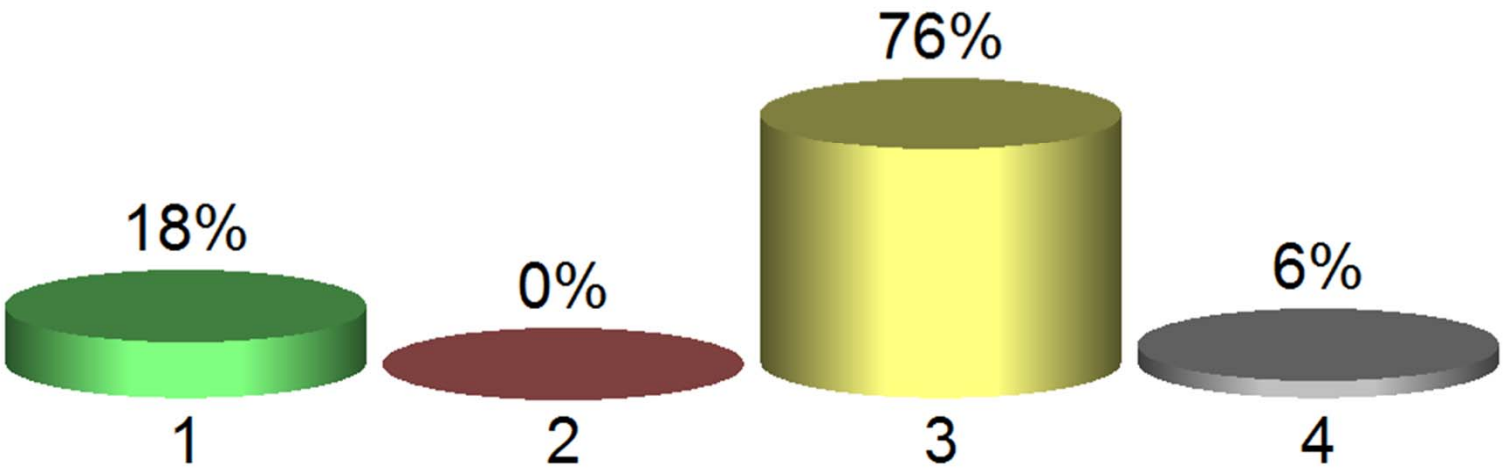

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

SUGGESTED TREATMENT REGIMENS
(in order of preference)

CLL/SLL without del(17p)/TP53 mutation

First line therapy

- **Frail patient with significant comorbidity (not able to tolerate purine analogs)**
  - Obinutuzumab + chlorambucil (category 1)
  - Ibrutinib (category 1)
  - Ofatumumab + chlorambucil
  - Rituximab + chlorambucil
  - Obinutuzumab (category 2B)
  - Rituximab (category 3)
  - Chlorambucil (category 3)
- **Age ≥65 y and younger patients with significant comorbidities**
  - Obinutuzumab + chlorambucil (category 1)
  - Ibrutinib (category 1)
  - Ofatumumab + chlorambucil
  - Rituximab + chlorambucil
  - Bendamustine (70 mg/m^2 in cycle 1 with escalation to 90 mg/m^2 if tolerated) ± rituximab
  - Obinutuzumab (category 2B)
  - Chlorambucil (category 3)
  - Rituximab (category 3)
- **Age <65 y without significant comorbidities**
  - Chemoimmunotherapy
    - FCR (fludarabine, cyclophosphamide, rituximab) (category 1)
    - FR (fludarabine, rituximab)
    - PCR (pentostatin, cyclophosphamide, rituximab)
    - Bendamustine ± rituximab
  - Ibrutinib

CSLL-D

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

SUGGESTED TREATMENT REGIMENS
(in order of preference)

CLL/SLL with del(17p)/TP53 mutation

First-line therapy
- Ibrutinib
- HDMP + rituximab
- Obinutuzumab + chlorambucil (category 3)
- Alemtuzumab ± rituximab

Relapsed/Refractory therapy
- Ibrutinib
- Venetoclax
- Idelalisib + rituximab
- Idelalisib
- HDMP + rituximab
- Lenalidomide ± rituximab
- Alemtuzumab ± rituximab
- Ofatumumab
- OFAR

Second-line Extended Dosing
- Ofatumumab maintenance (for complete or partial response after relapsed or refractory therapy) (category 2B)

CSLL-D

NCCN 11th Annual Congress:
Hematologic Malignancies™

First-line Chemo-immunotherapy for Chronic Lymphocytic Leukemia

William G. Wierda, MD, PhD

The University of Texas
MD Anderson Cancer Center

National Comprehensive Cancer Network®

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Question

Ibrutinib is approved for initial treatment for CLL based on the following:

1. OS advantage versus chlorambucil
2. PFS advantage versus BR
3. Long term safety data
4. Improved PFS in del17p CLL
5. All of the above
6. Option 1 + Option 3

Weaknesses of RESONATE-2 and Challenges with First-line Ibrutinib

- Chlorambucil is an unreasonable comparator as standard of care
- Follow up time is short
- Population limited to age >65yrs
- Ibrutinib approved for relapsed / refractory CLL

- Challenges with first-line ibrutinib therapy
  - Ibrutinib therapy is continuous and costly
  - Associated toxicities, increased in elderly
  - Long-term side-effects unknown
  - Compliance issue

Multivariable Models for Cumulative Incidence of Ibrutinib Failure: Disease Progression and Toxicity

	Event			
	Progression		Toxicity	
Variable	HR (95% CI)[a]	*P* Value	HR (95% CI)[a]	*P* Value
Age, 10-y increase	NA	NA	1.87 (1.33-2.64)	<.001
No. of prior treatments, 1 unit increase	NA	NA	1.09 (1.00-1.19)	.054
BCL6 abnormality, yes vs no	2.70 (1.25-5.85)	.01	NA	NA
Complex karyotype, yes vs no	4.47 (1.50-13.34)	.007	NA	NA

Abbreviations: HR, hazard ratio; NA, not applicable.

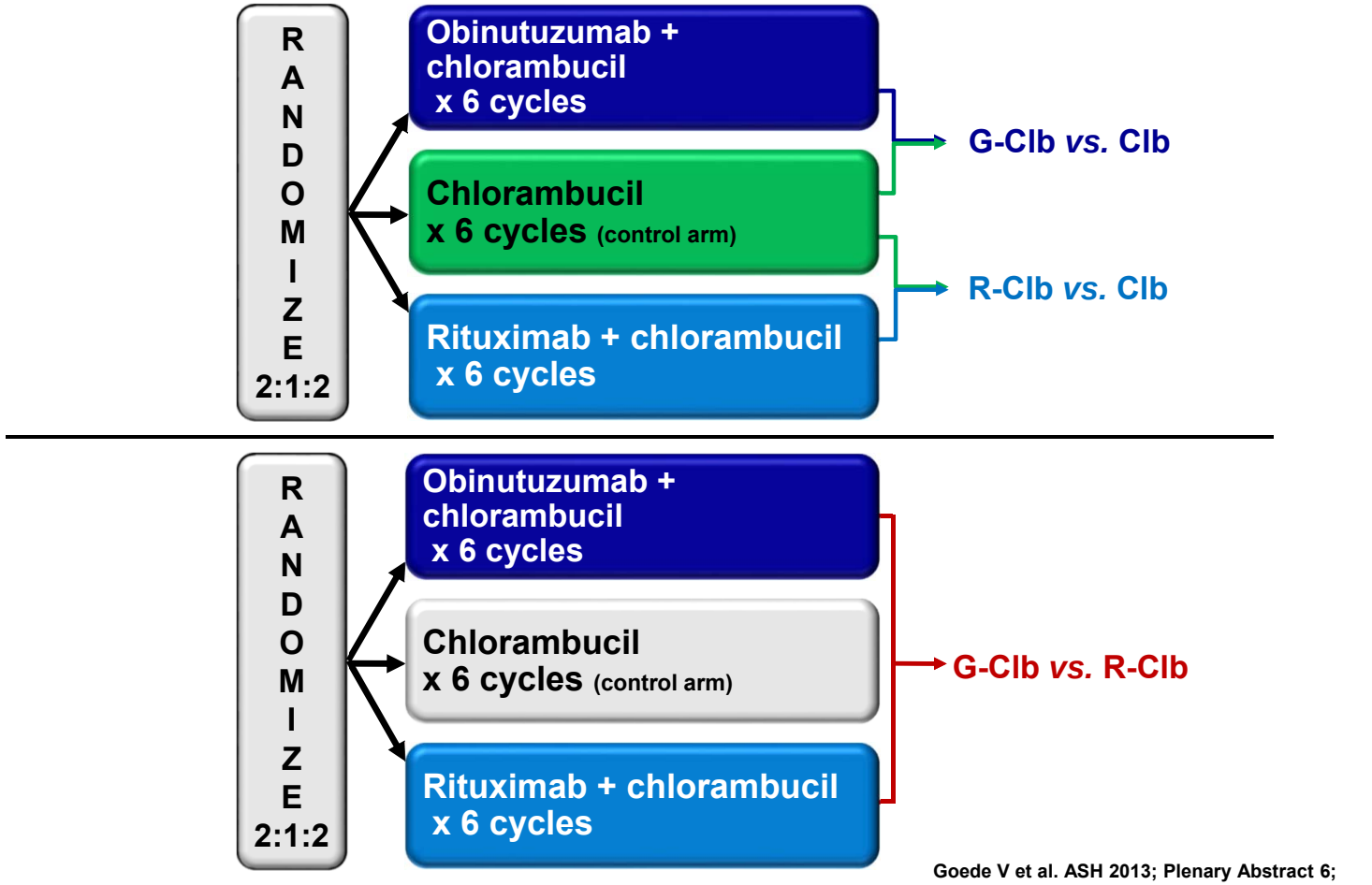
[a] An HR greater than 1 (lower than 1) indicates a higher (lower) risk of an event for the first category listed for dichotomous variables or increasing values of continuous variables.

Maddocks, et al., JAMA Oncology 2015;1:80-87

First-line Chemoimmunotherapy (CIT) for CLL

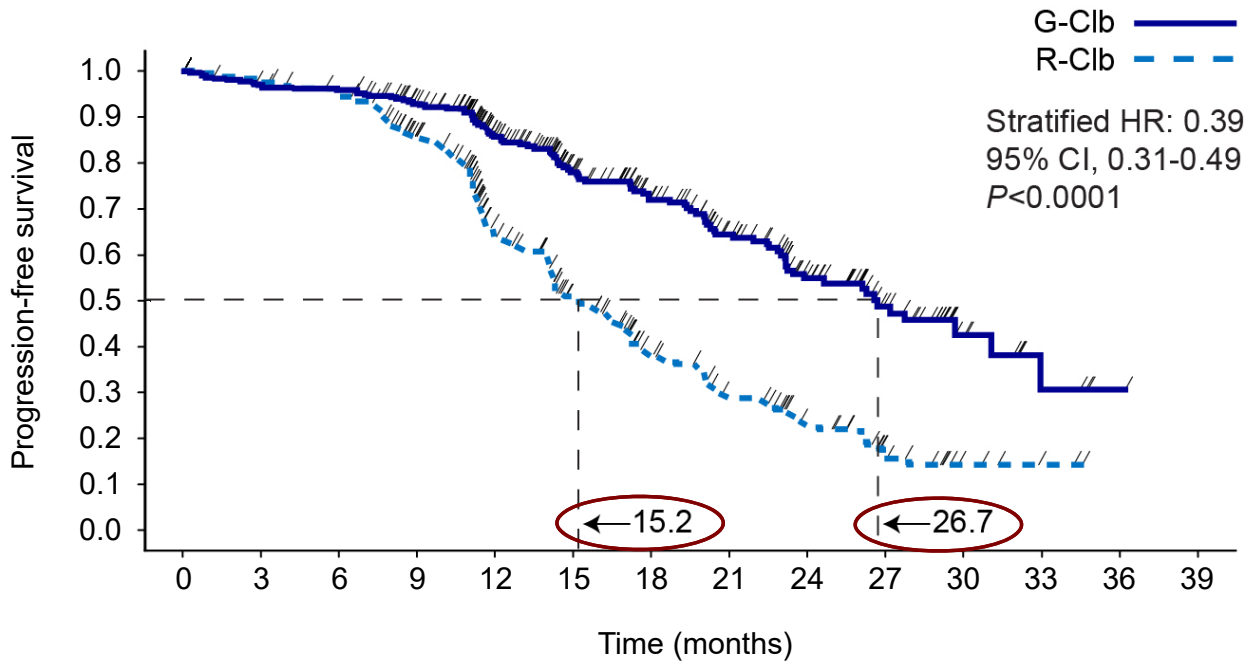
- Defined treatment period to achieve remission allowing for treatment-free period
- Intent of treatment
  - Prolong time-to-event endpoints; cure for subgroups?
- MRD-negative remission as treatment endpoint
  - Correlated with longer PFS and OS
  - Correlated with HR for PFS in randomized trials
  - Reflects “deeper” remission
  - Tool to help develop curative strategies

CLL11: Treatment comparisons



Goede V et al. ASH 2013; Plenary Abstract 6;
Goede V et al. N Engl J Med 2014;370:1101-1111

CLL11: Progression-free survival *(Head-to-Head)*



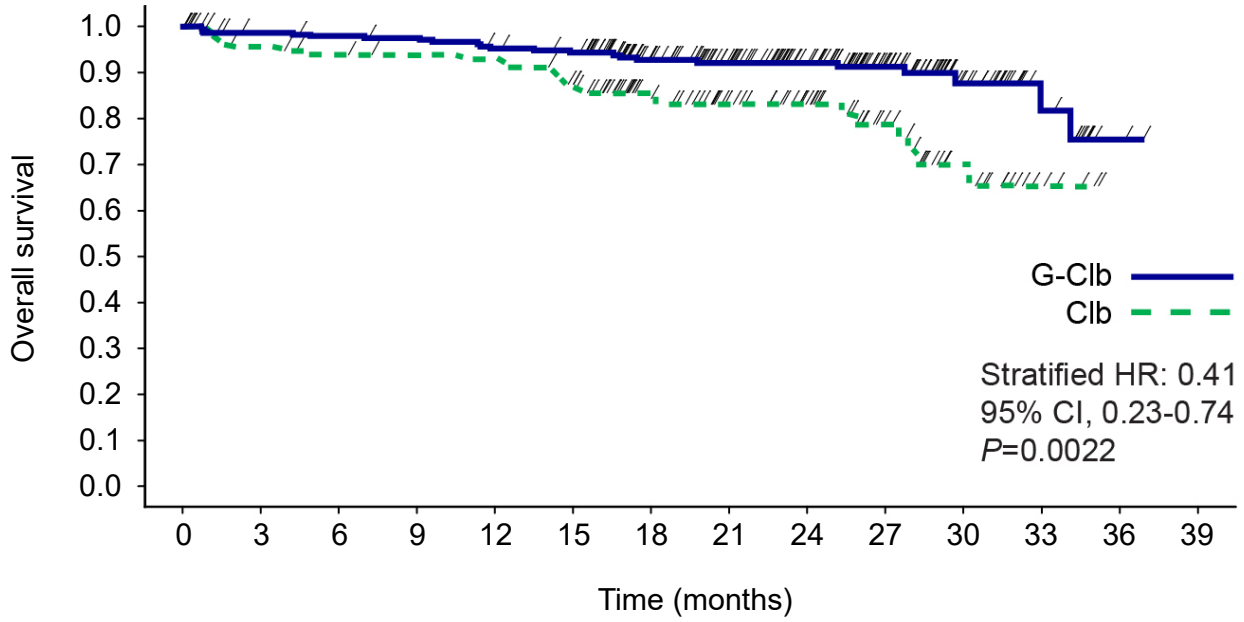
No. at risk

Currently no significant difference in overall survival

Median observation time: G-Clb, 18.8 months; R-Clb, 18.6 months
Type 1 error controlled through closed test procedure; *P* value of the global test was <0.0001
Independent Review Committee-assessed progression-free survival (PFS) was consistent with investigator-assessed PFS

Goede V et al. ASH 2013; Plenary Abstract 6; Goede V et al. N Engl J Med 2014;370:1101-1111

CLL11: Overall survival *(Obinutuzumab)*



No. at risk

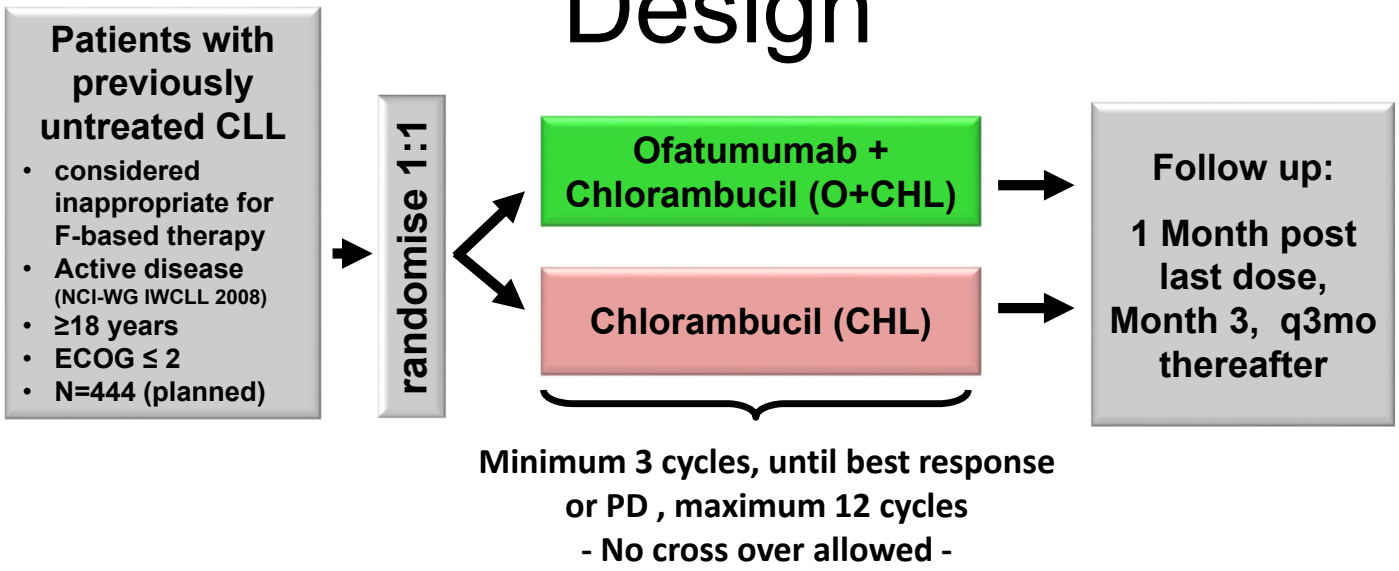
G-Clb:	238	226	223	221	215	211	170	144	115	71	34	14	2	0
Clb:	118	109	105	103	102	94	70	56	44	29	15	5	0	0

Total number of deaths: G-Clb, 22 (9%); Clb, 24 (20%)

Median observation time: G-Clb, 23.2 months; Clb, 20.4 months
No multiplicity adjustment was done for secondary endpoints

Goede V et al. ASH 2013; Plenary Abstract 6; Goede V et al. N Engl J Med 2014;370:1101-1111

COMPLEMENT 1: Study Design



O: cycle 1 d1 300 mg, d8 1000 mg, Cycle 2-12 d1 1000 mg every 28 days

CHL: 10 mg/m^2 d1-7 every 28 days

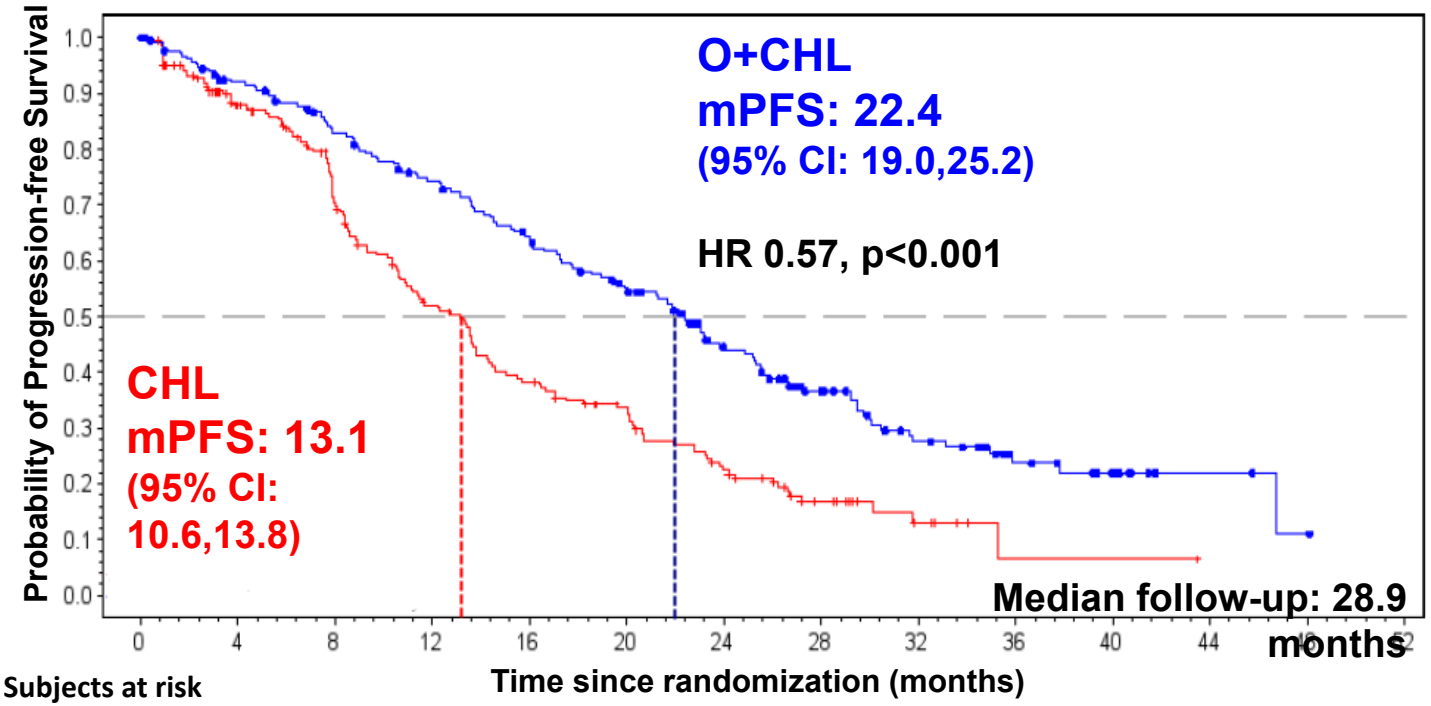
Dose rationale: evidence of highest ORR and longest PFS with low toxicity compared to any other CHL monotherapy regimen

Hillmen et al. ASH 2013, Abstract 528.

Progression-free Survival

as assessed by an Independent Review Committee

(median [months])



Subjects at risk													
C	226	173	130	92	67	52	33	17	6	1	1		
O+CHL	221	192	169	148	125	104	70	46	28	15	9	3	1

Hillmen et al. ASH 2013, Abstract 528.

Currently no difference in overall survival

Bendamustine/Obinutuzumab for First-line CLL GREEN study: Baseline characteristics

Characteristic		*G-B cohort, N=158*
Age, years	Median	69.0
CIRS	Median	3.0
CrCl, mL/min	Median	71.5
Fitness status, n (%)	Fit* Unfit†	74 (46.8%) 84 (53.2%)
Binet stage, n (%)	A B C	50 (31.6%) 60 (38.0%) 48 (30.4%)
ALC baseline, n (%)	≥50 x 10**9/L	89 (56.3%)
Tumor bulk, n (%)	≥5cm	99 (62.7%)

*CIRS ≤6 and CrCl ≥70 mL/min; †CIRS >6 and/or CrCl <70mL/min

Stilgenbauer et al. ASH 2015, Abstract 493.

Bendamustine/Obinutuzumab for First-line CLL GREEN study: Response assessment

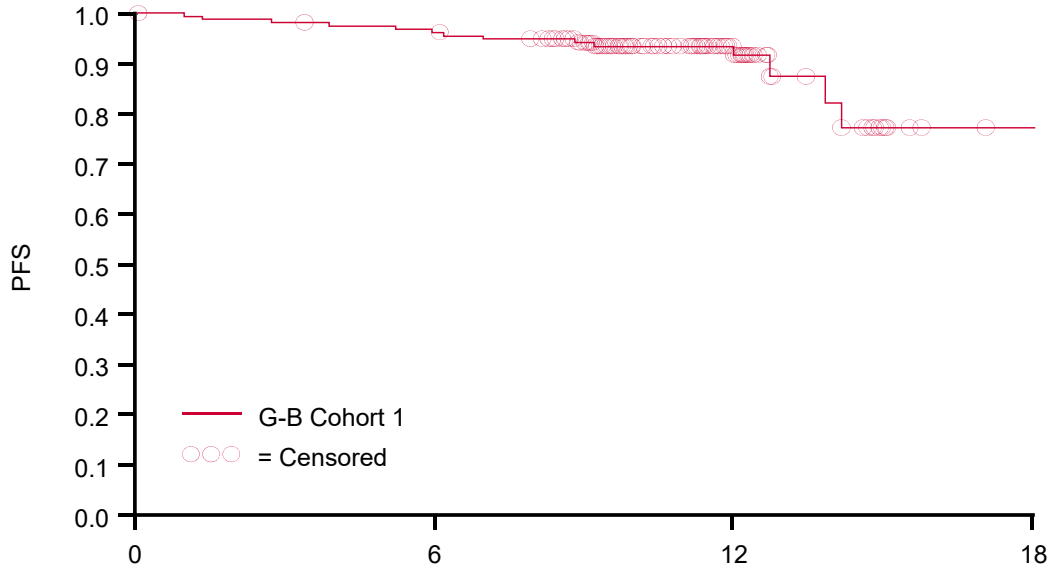
Response, n (%)	*G-B cohort, N=158*	*Fit patients*, n=74*	*Unfit patients†, n=84*
Overall response	124 (78.5%)	60 (81.1%)	64 (76.2%)
Complete response‡	51 (32.3%)	22 (29.7%)	29 (34.5%)
Partial response	73 (46.2%)	38 (51.4%)	35 (41.7%)
Stable disease	17 (10.8%)	8 (10.8%)	9 (10.7%)
Progressive disease	1 (0.6%)	0	1 (1.2%)
Missing	16 (10.1%)	6 (8.1%)	10 (11.9%)

*CIRS ≤6 and CrCl ≥70mL/min; †CIRS >6 and/or CrCl <70mL/min; ‡including CRi (CR with incomplete marrow recovery)

Stilgenbauer et al. ASH 2015, Abstract 493.

Bendamustine/Obinutuzumab for First-line CLL GREEN study: PFS

Median observation time 11.2 months (N=158)



No. of patients				
G-B Cohort 1	158	149	44	0

Stilgenbauer et al. ASH 2015, Abstract 493.

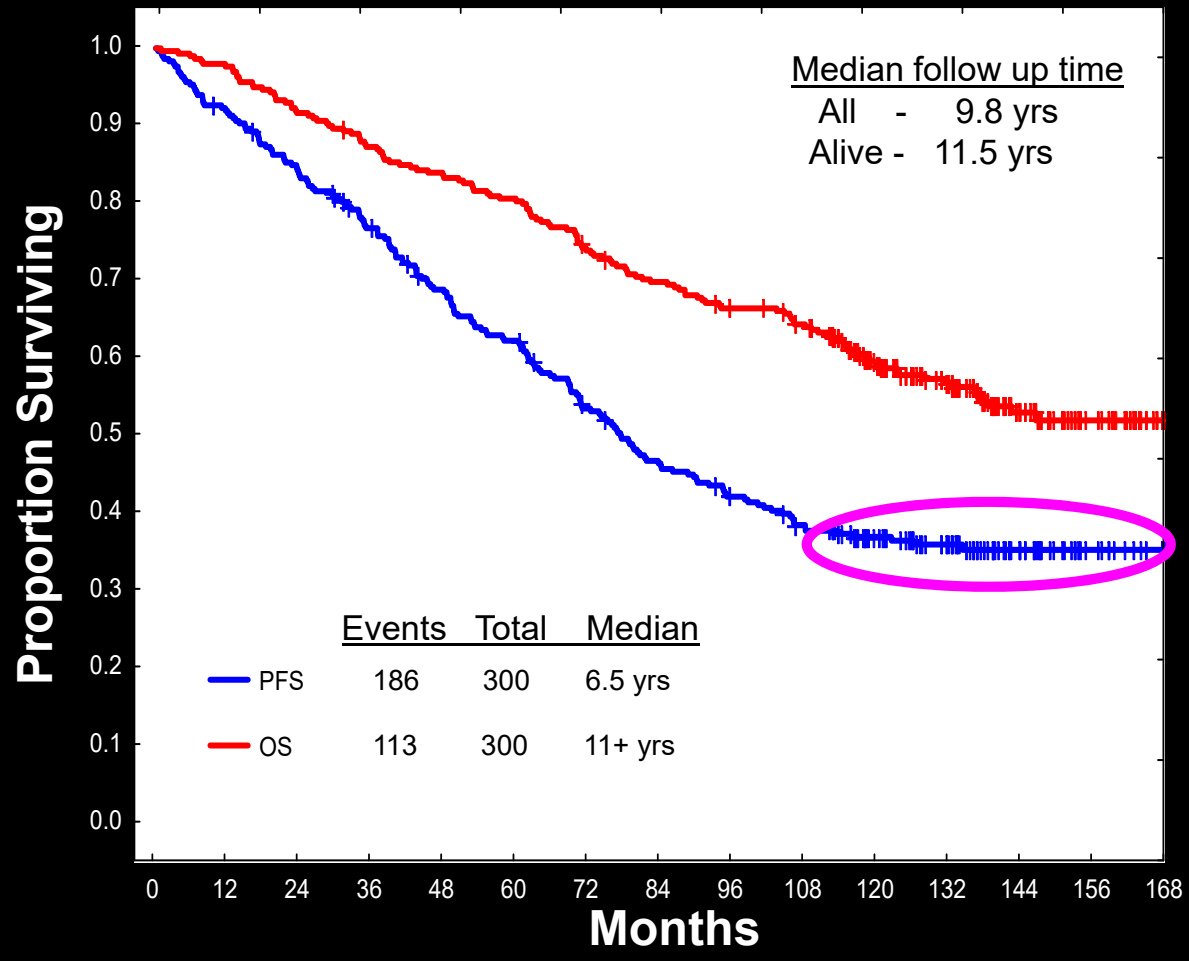
Bendamustine/Obinutuzumab for First-line CLL GREEN study: : MRD-negativity rates

Analysis population	*Blood*	*Bone marrow*
ITT*	93/158 (58.9%)	45/158 (28.5%)
Intent-to-ship†	93/140 (66.4%)	45/140 (32.1%)
MRD evaluable‡	93/102 (91.2%)	45/64 (70.3%)

*all patients at all sites
†all patients at sites that could perform timely shipment of samples to allow delivery to the central laboratory in Kiel, Germany within 48 hours of being taken (sites unable to ship within 48 hours included those in Brazil, Canada, Korea, Mexico and Thailand)
‡as above, but including only those patients with evaluable samples at the end-of-treatment assessment

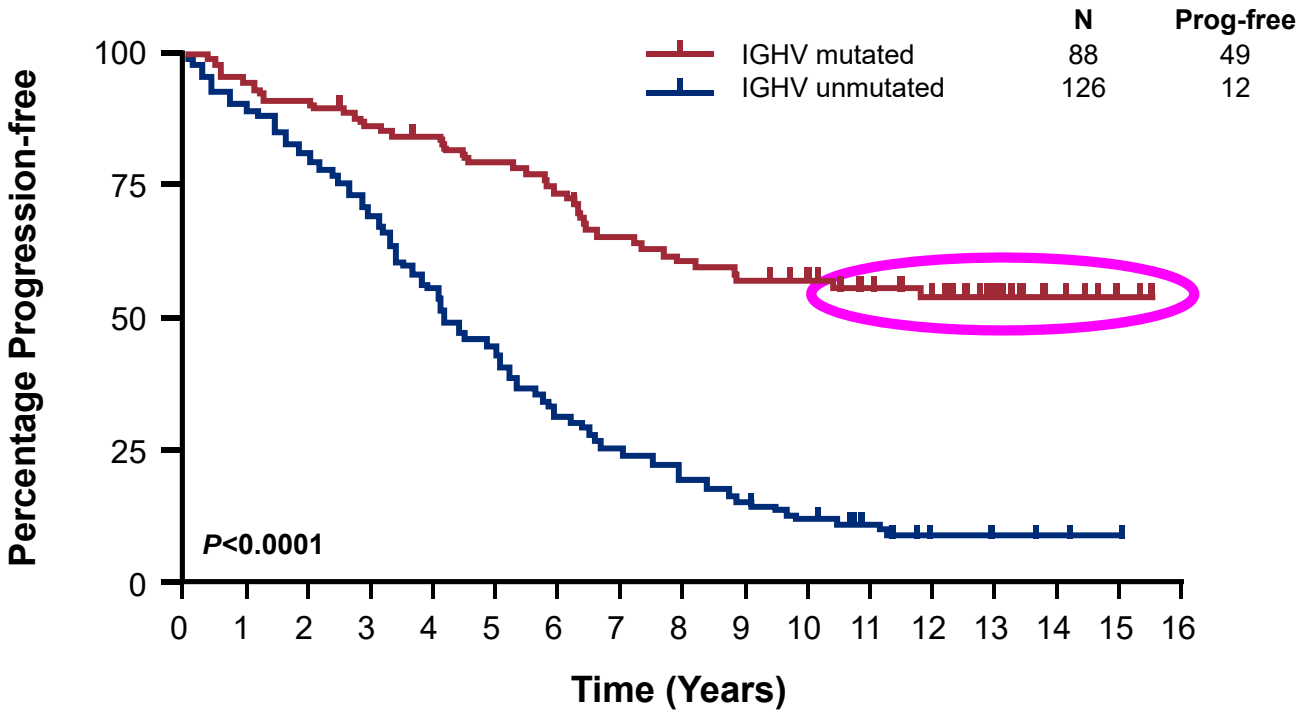
Stilgenbauer et al. ASH 2015, Abstract 493.

FCR300: Progression-free & Overall Survival



MDACC Data, IWCLL 2013, Cologne

FCR300: PFS by IGHV Mutation Status



Thompson PA, *et al. Blood* 2016;127:303–309

First-line FCR: Prospective Evaluation of Prognostic Factors and MRD

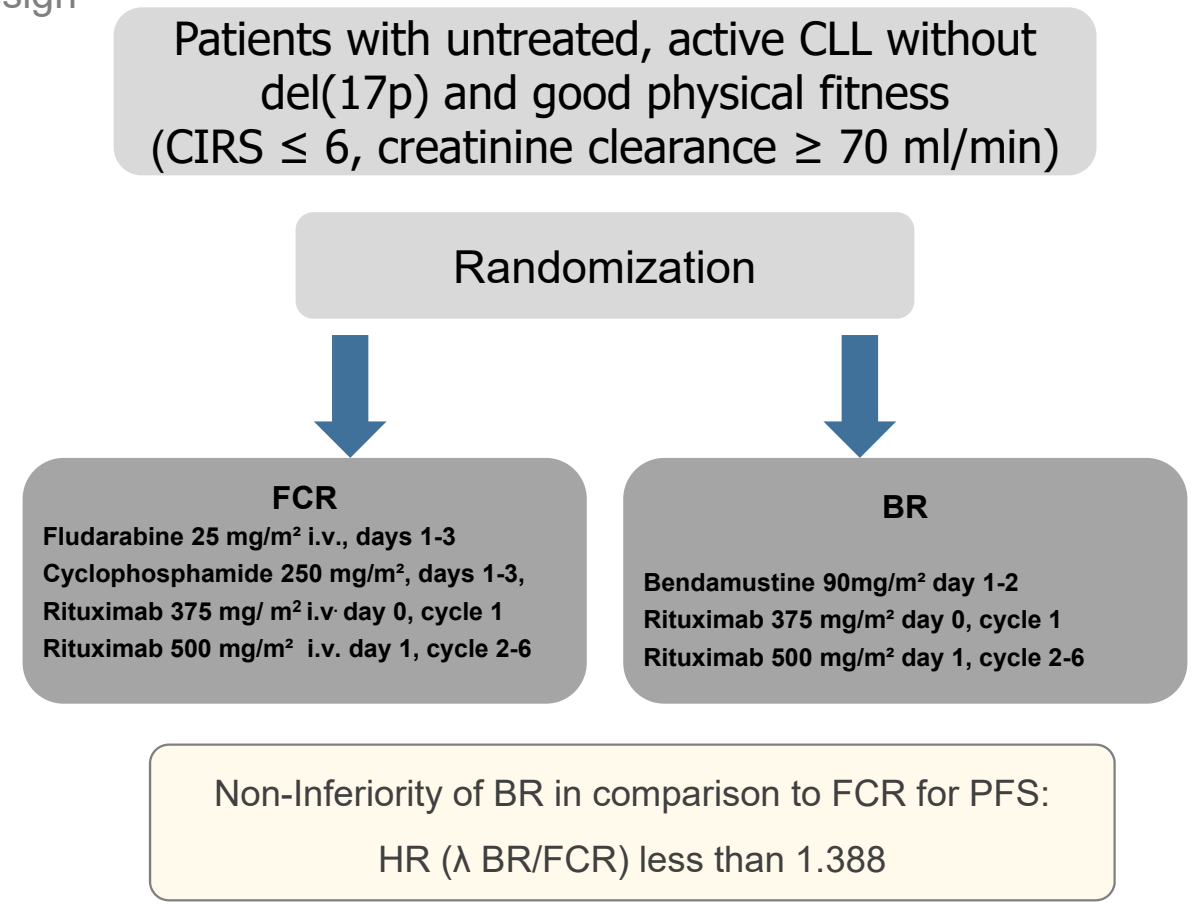
Pretreatment characteristic		N	MRD negative, %	p-value
IGHV	Unmutated	115	47	0.006
	Mutated	78	71	
ZAP-70 IHC	Positive	129	55	0.252
	Negative	71	63	
$CD38^{+}$	≥7%	134	57	0.51
	<7%	74	62	
FISH	del(17p)	15	27	0.04
	del(11q)	44	52	0.70
	+12	38	76	0.04
	None	41	70	0.12
	del(13q)	68	56	Ref

*Bone marrow evaluation by 4-color flow (sensitivity 0.01%).

Updated from: Strati P, *et al. Blood* 2014;123:3727–3732.

CLL10 STUDY: FCR VS BR IN FRONT-LINE

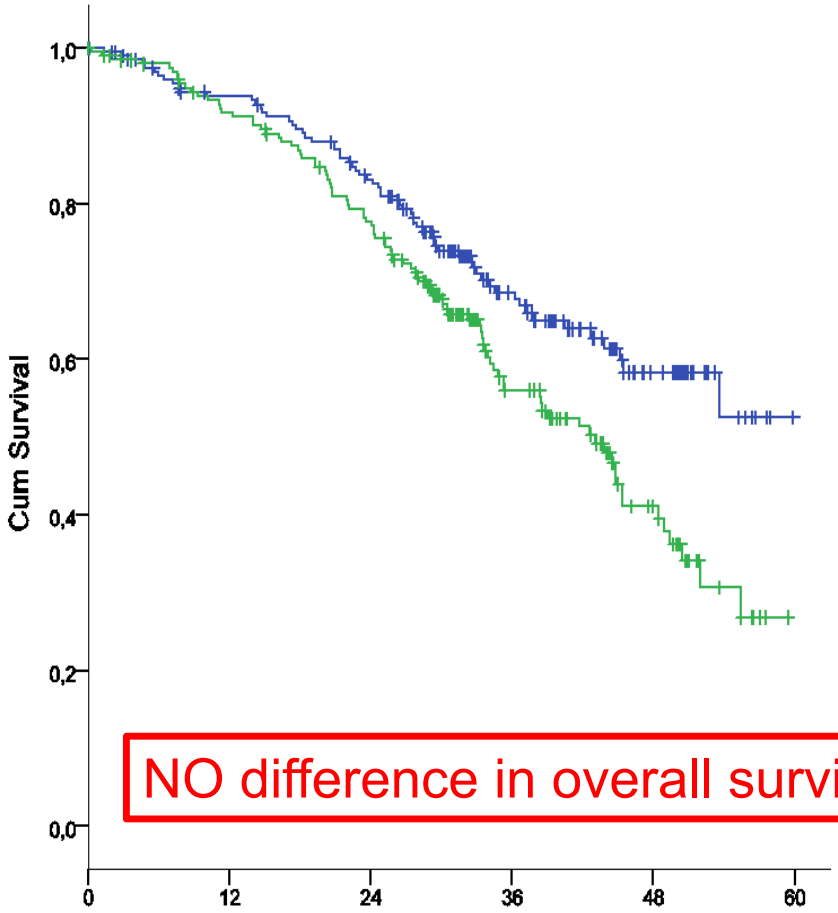
Design



Eichhorst et al., ASH 2014, Abstract 19

CLL10 STUDY: FCR VS BR IN FRONT-LINE

PFS in IGHV matched population (n=398: FCR= 201; BR =197)



Median PFS

FCR NR

BR 43.1 months

***P* = 0.005**
HR = 1.565 =
> 1.388

NO difference in overall survival

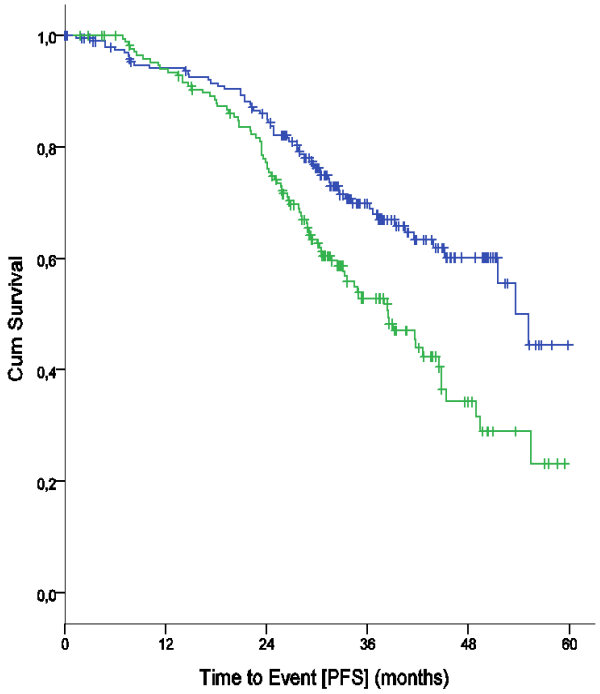
Eichhorst et al., ASH 2014, Abstract 19

CLL10 STUDY: FCR VS BR IN FRONT-LINE

Progression-free survival by age group

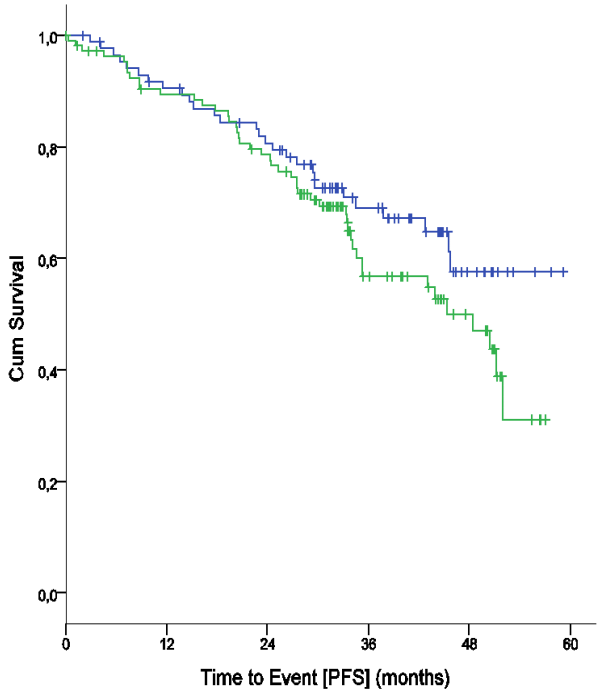
Patients ≤ 65 years: ***P < 0.001***

FCR 53.6 months **BR 38.5 months**



Patients > 65 years: ***P = 0.170***

FCR not reached **BR 48.5 months**



Eichhorst et al., ASH 2014, Abstract 19

CLL10 STUDY: FCR VS BR IN FRONT-LINE

Infections CTC 3-4 in detail

Adverse event	FCR (% of pt)	BR (% of pt)	p value
All Infections	**39.1**	**26.8**	**<0.001**
Infections during therapy only	22.6	17.3	0.1
Infections during first 5 months after therapy	11.8	3.6	<0.001
All infections in patients ≤ 65years	35.2	27.5	0.1
All infections in patients > 65years	47.7	20.6	<0.001

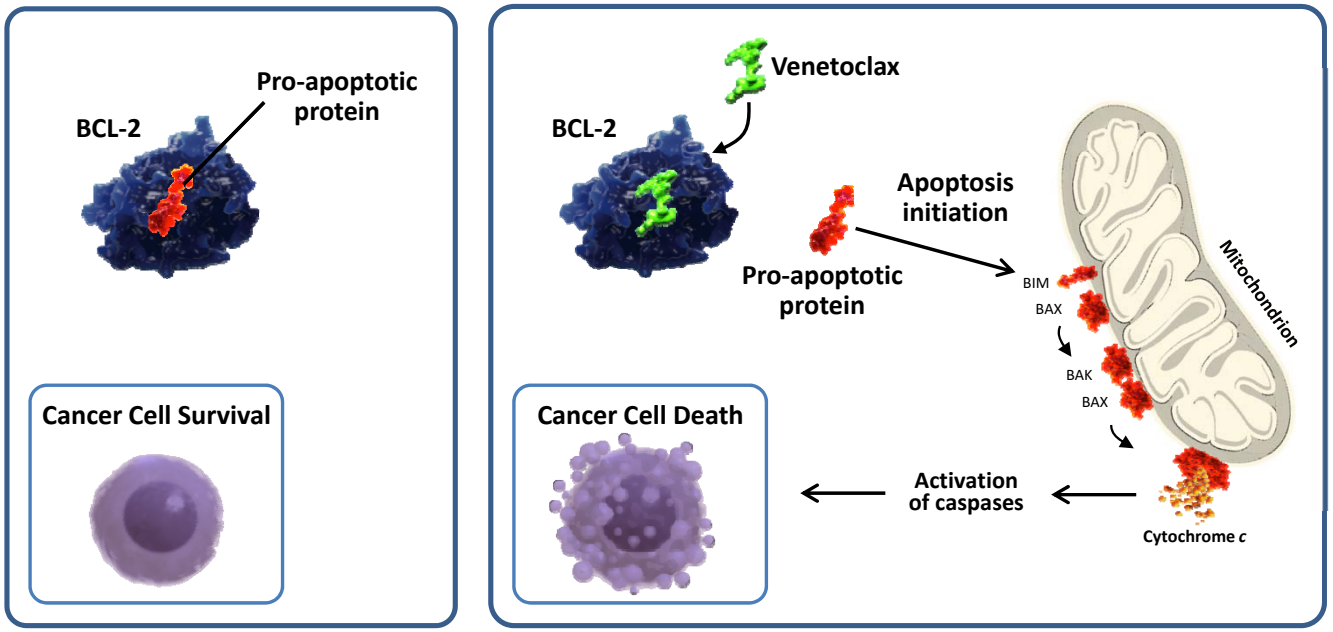
Eichhorst et al., ASH 2014, Abstract 19

Challenges with First-line CIT

- Myelosuppression and risk for infection
- Immune deficiency and risk for infection
- Risk for secondary MDS and AML
- Risk for Richter's transformation
- Potential selection of high-risk cytogenetics

Venetoclax is a BCL-2 Selective Inhibitor

Restoration of apoptosis through BCL-2 inhibition

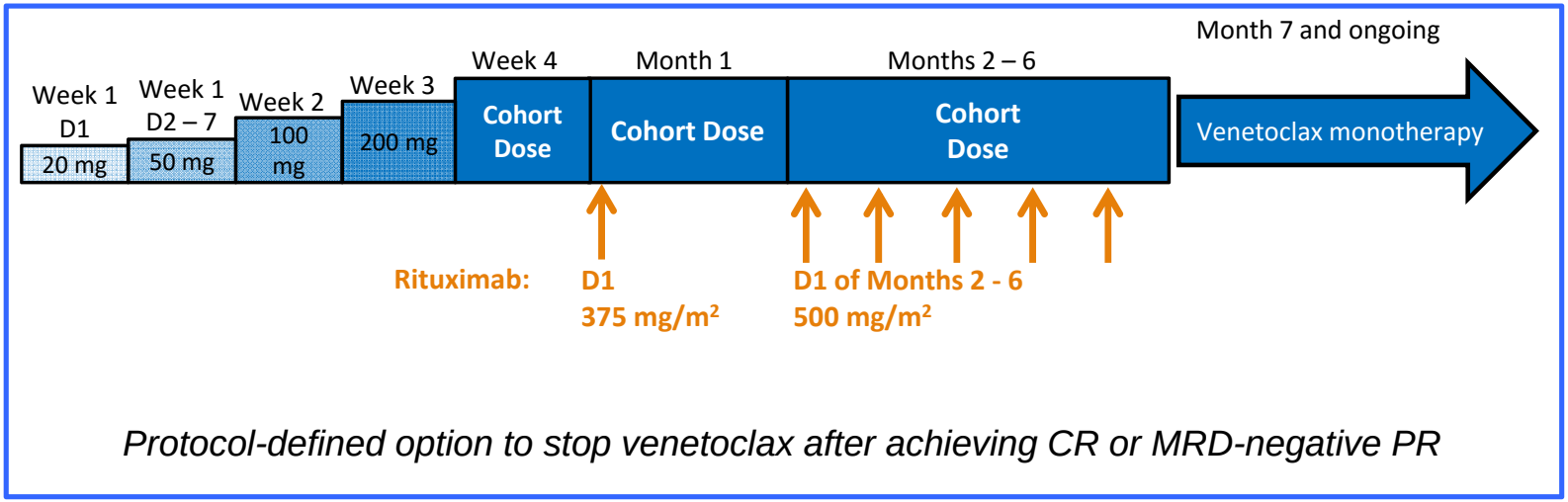


BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins

Venetoclax binds selectively to BCL-2, freeing pro-apoptotic proteins that initiate programmed cell death (apoptosis)

Dosing Schedule of Venetoclax and Rituximab

Final Escalation Strategy:



Protocol-defined option to stop venetoclax after achieving CR or MRD-negative PR

Dose escalation phase: 200, 300, 400, 500, 600mg/day cohorts (n = 41)

Safety expansion phase: 400mg/day cohort (n = 8)

Data pooled for these safety and efficacy analyses

Ma et al. ASH 2015; Abstract 830

Multivariate Analysis of R/R CLL/SLL in Phase 1 Studies of Venetoclax ± Rituximab – Outcomes

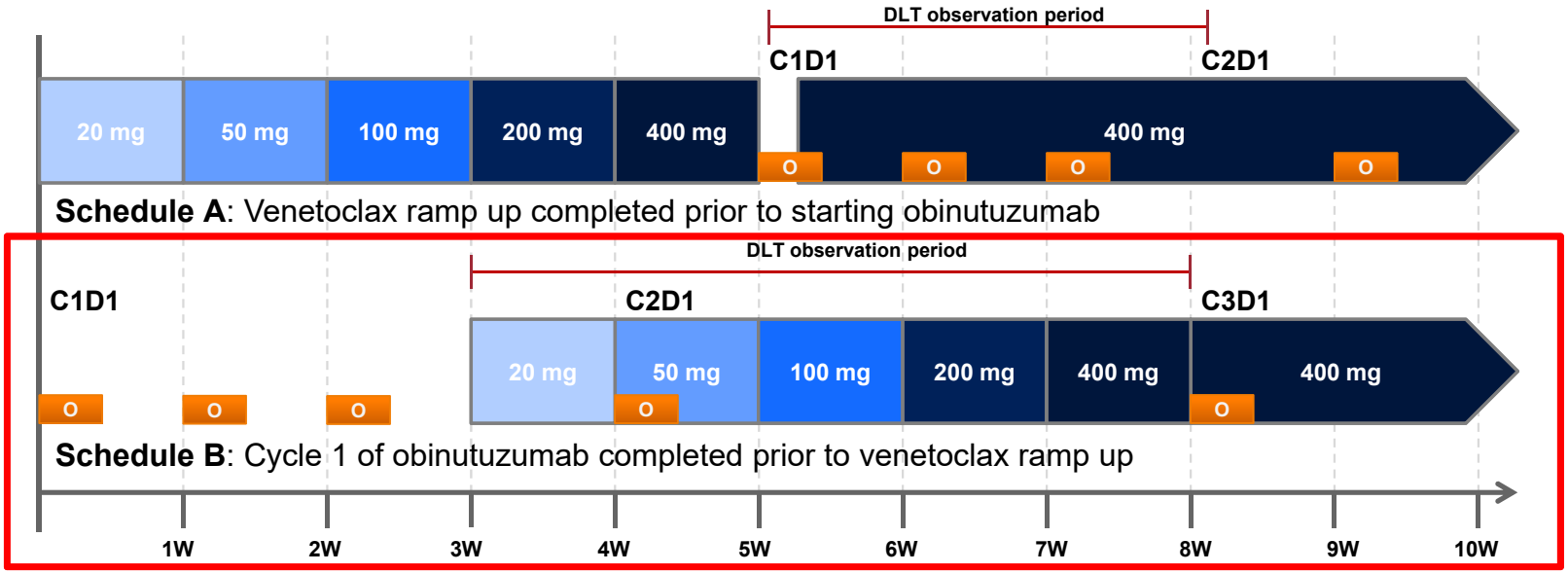
Response, n/N (%)	ORR		CR/CRi	
	Ven + R	Ven	Ven + R	Ven
Best objective response	42/49 (86)	92/116 (79)	**25/49 (51)**	**23/116 (20)**
Subgroups				
Prior therapies ≥3	16/21 (76)	52/72 (72)	9/21 (43)	13/72 (18)
Lymph node size >5 cm	18/22 (82)	52/67 (78)	9/22 (41)	5/70 (7)
Del17p	8/9 (89)	22/31 (77)	6/9 (67)	5/31 (16)
Del11q	17/20 (85)	23/28 (82)	5/20 (25)	3/28 (11)
Age ≥70 years	17/22 (77)	24/34 (71)	11/22 (50)	7/34 (21)
Dose ≥400 mg	28/33 (85)	72/87 (83)	18/33 (55)	18/87 (21)

Multivariate Analysis	ORR Odds Ratio* (95% CI); *P* Value (n=157)	CR Odds Ratio† (95% CI); *P* Value (n=129)	DOR HR for Relapse (95% CI); *P* Value (n=105)
Ven + R *vs.* Ven	1.14 (.43-3.02); .79	**6.13 (2.44-15.44); .0001**	**.37 (.15-.89); .03**
Prior therapies <3 vs ≥3	4.58 (1.62-12.91); .004	NS	NS
Lymph node size ≤5 cm vs >5 cm	NS	3.50 (1.39-8.84); .008	.36 (.15-.84); .02
11q, not deleted vs deleted	NS	2.96 (1.04-8.43); .04	NS
17p, not deleted vs deleted	NS	NS	.42 (.18-.95); .04
Age, continuous variable	NS	NS	NS
Dose of Ven, >400 mg vs 400 mg	NS	NS	1.72 (.62-4.76); .29

*Responders vs non-responders; †CR/CRi vs all other patients.

Roberts et al. EHA 2016. Abstract P209

Venetoclax + Obinutuzumab for CLL
Venetoclax Ramp-Up and Dosing Schedule



C, cycle; D, day; DLT, dose-limiting toxicity; O, obinutuzumab infusion; w, study week.

- Obinutuzumab dosing schedule: C1D1: 100 mg, C1D2: 900 mg, C1D8 and 15: 1000 mg, C2-6D1: 1000 mg
- Venetoclax and obinutuzumab administered in combination through the end of Cycle 6 followed by venetoclax monotherapy
- Continuous dosing of venetoclax until progression in R/R patients or <2 years in 1L patients

Flinn et al. ASH 2015, Abstract 494.

Venetoclax + Obinutuzumab for CLL
Preliminary Efficacy

n (%)	R/R patients (N=22)	1L patients (N=6)
Best ORR	21/22 (95.5)	6/6 (100)
CR/CRi	4/22 (18.2)	3/6 (50)
PR/nPR	17/22 (77.3)	3/6 (50)
SD/PD	0 (0)	0 (0)
Discontinued Prior to Assessment [a]	1/22 (4.5)	0 (0)
Peripheral blood MRD rates [b], n (%)	**R/R patients**	**1L patients**
MRD negative	9/22 (40.9)	1/6 (16.7)
MRD positive	5/22 (22.7)	3/6 (50)
Undetermined [c]	8/22 (36.4)	2/6 (33.3)

CR, complete remission; CRi, complete remission with incomplete marrow recovery; MRD, minimal residual disease; nPR, nodular partial remission; ORR, overall response rate; PD, progressive disease; PR, partial remission; R/R, relapsed/refractory; SD, stable disease.

[a] 1 patient discontinued study secondary to adverse event prior to starting combination therapy.
[b] MRD was assessed by four-color flow cytometry; in eight patients MRD was assessed in the marrow, two of whom were MRD negative.
[c] Undetermined indicates sensitivity of test not < 10^{-4} however, 9/10 of these patients had no CLL cells detected.

Flinn et al. ASH 2015, Abstract 494.

GCLLSG CLL14 DESIGN

Patients with untreated active CLL & with coexisting medical conditions*

Safety Run-In Phase: Obinutuzumab + Venetoclax

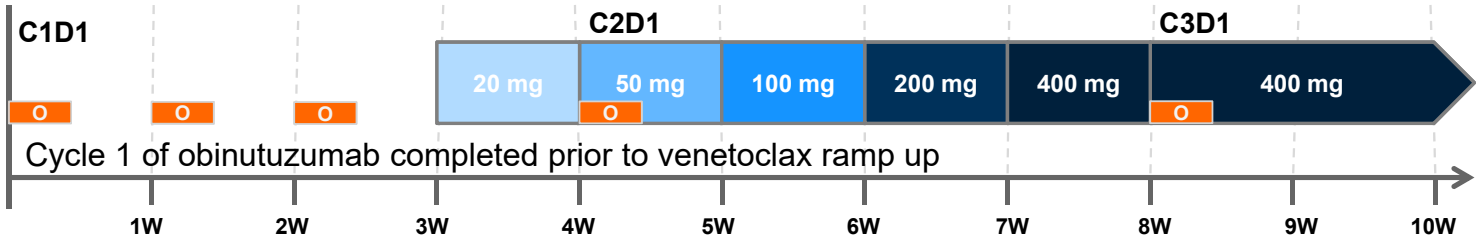
Independent Data Monitoring Commitee (iDMC)

Obinutuzumab + Chlorambucil
6 x Obinutuzumab + Chlorambucil
+ 6 x Chlorambucil

Obinutuzumab + Venetoclax
6 x Obinutuzumab + Venetoclax
+ 6 x Venetoclax

*CIRS > 6 and/ or CrCl < 70mL/min

Follow-up Phase



Fischer et al. ASH 2015, Abstract 496.

GCLLSG CLL14
CLINICAL RESPONSE ASSESSMENT

N=12

After 3 cycles	
ORR	**92%**
PR	92%
SD	8%

After 6 cycles	%
ORR	**100%**
PR	100%

Fischer et al. ASH 2015, Abstract 496.

NCCN 2017 Guidelines – First-line for non-del(17p) CLL

- **Age ≥ 65 yr and younger with comorbidities**
  - Obinutuzumab + chlor. (cat 1)
  - Ibrutinib (cat 1)
  - Ofatumumab + chlor. (cat 2A)
  - Rituximab + chlor. (cat 2A)
  - Bendamustine ± rituximab (2A)
  - Obinutuzumab (cat 2B)
  - Chlorambucil (cat 3)
  - Rituximab (cat 3)
- **Age < 65 yr**
  - Chemoimmunotherapy
    - FCR (cat 1)
    - FR (cat 2A)
    - PCR (cat 2A)
    - B ± R(cat 2A)
  - Ibrutinib (cat 2A)

Next Treatment Advances for CLL

- Effective chemotherapy-free treatment
- Effective “consolidation” strategy for patients on BTK-I that would allow treatment-free interval
- Effective “maintenance” strategy that doesn’t require daily treatment
- Cure with no/limited toxic effects
- Immune reconstitution
  - Eliminating CLL-related infectious complications
  - Eliminating CLL-related second cancers
  - Eliminating CLL-related autoimmune disorders

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