Evolving Therapy In CLL

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ORIGINAL REPORT

Early Results of a Chemoimmunotherapy Regimen of Fludarabine, Cyclophosphamide, and Rituximab As Initial Therapy for Chronic Lymphocytic Leukemia

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ABSTRACT

Purpose

Fludarabine and cyclophosphamide (FC), which are active in treatment of chronic lymphocytic leukemia (CLL), are synergistic with the monoclonal antibody rituximab in vitro in lymphoma cell lines. A chemoimmunotherapy program consisting of fludarabine, cyclophosphamide, and rituximab (FCR) was developed with the goal of increasing the complete remission (CR) rate in previously untreated CLL patients to ≥ 50%.

Response to FC + Rituximab (NCI-WG: 300 Patients)

Response*	# Pts.	(%)	
CR	217	(72)	95%
Nodular PR	31	(10)	
PR	37	(12)	
No Response	13	(4)	
Early Death	2	(1)	

* Evaluated 6 months after last course

CLL10 Study: FCR VS BR in Front-Line

Design **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

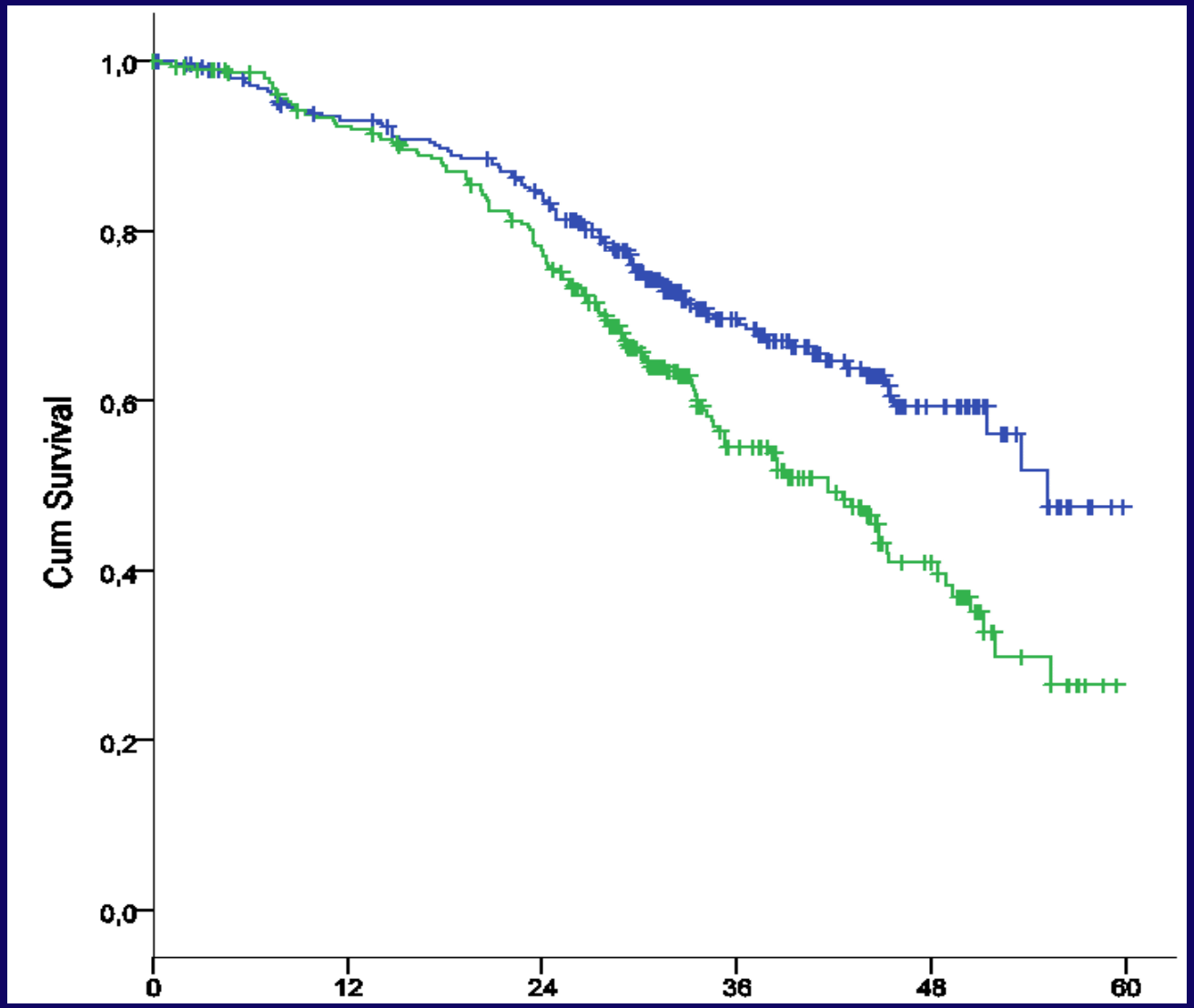
Non-Inferiority of BR in comparison to FCR for PFS:

HR (λ BR/FCR) less than 1.388

Eichhorst et al ASH 2014

CLL10 Study: FCR VS BR in Front-Line

ITT Progression-free Survival = Primary Endpoint



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

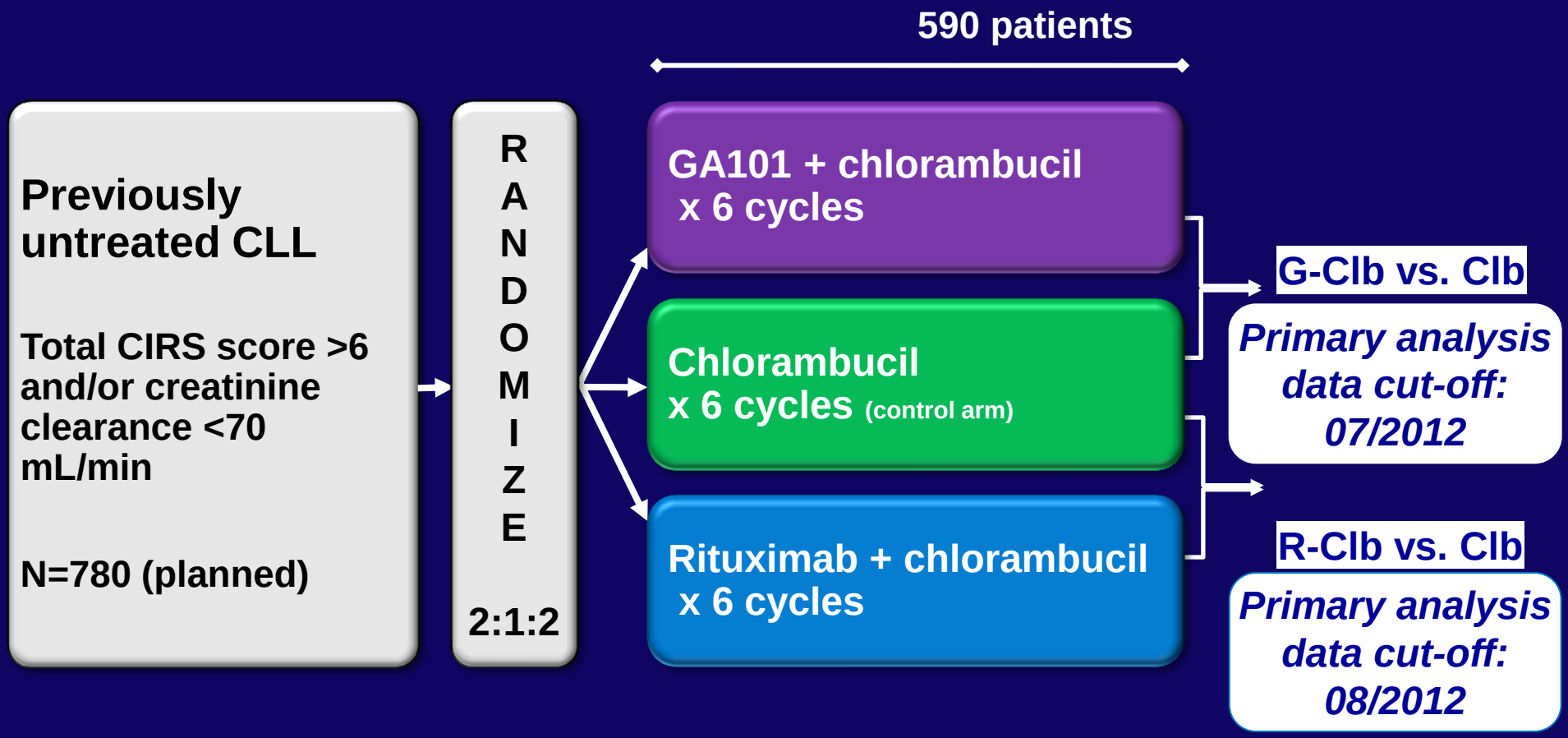
Adverse Events CTC °3-4 (1st cycle until end of study)

Adverse event	FCR (%) N= 279	BR (%) N=278	p value
Neutropenia	84.2	59.0	<0.001
Anemia	13.6	10.4	0.20
Thrombocytopenia	21.5	14.4	0.03
Infection	39.1	26.8	<0.001
Sec Neoplasm*	6.1	3.6	0.244

***sAML/MDS: FCR=6, BR = 1**

TRM	**4.6**	**2.1**	**0.107**
Infections	2.5	2.1	-
Sec Neoplasm	1.1	0	-
Other	1.0		

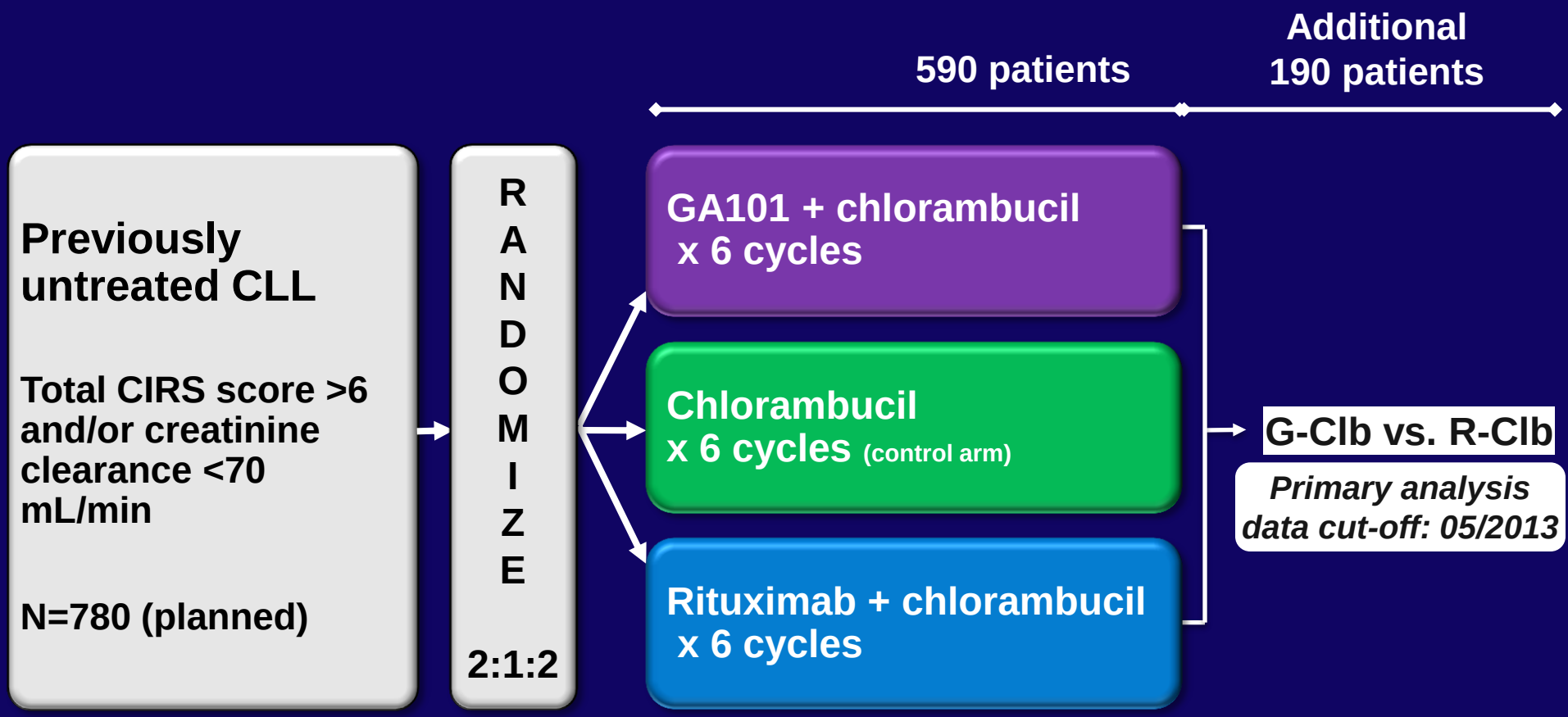
CLL11 Study Design



- GA101: 1000 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

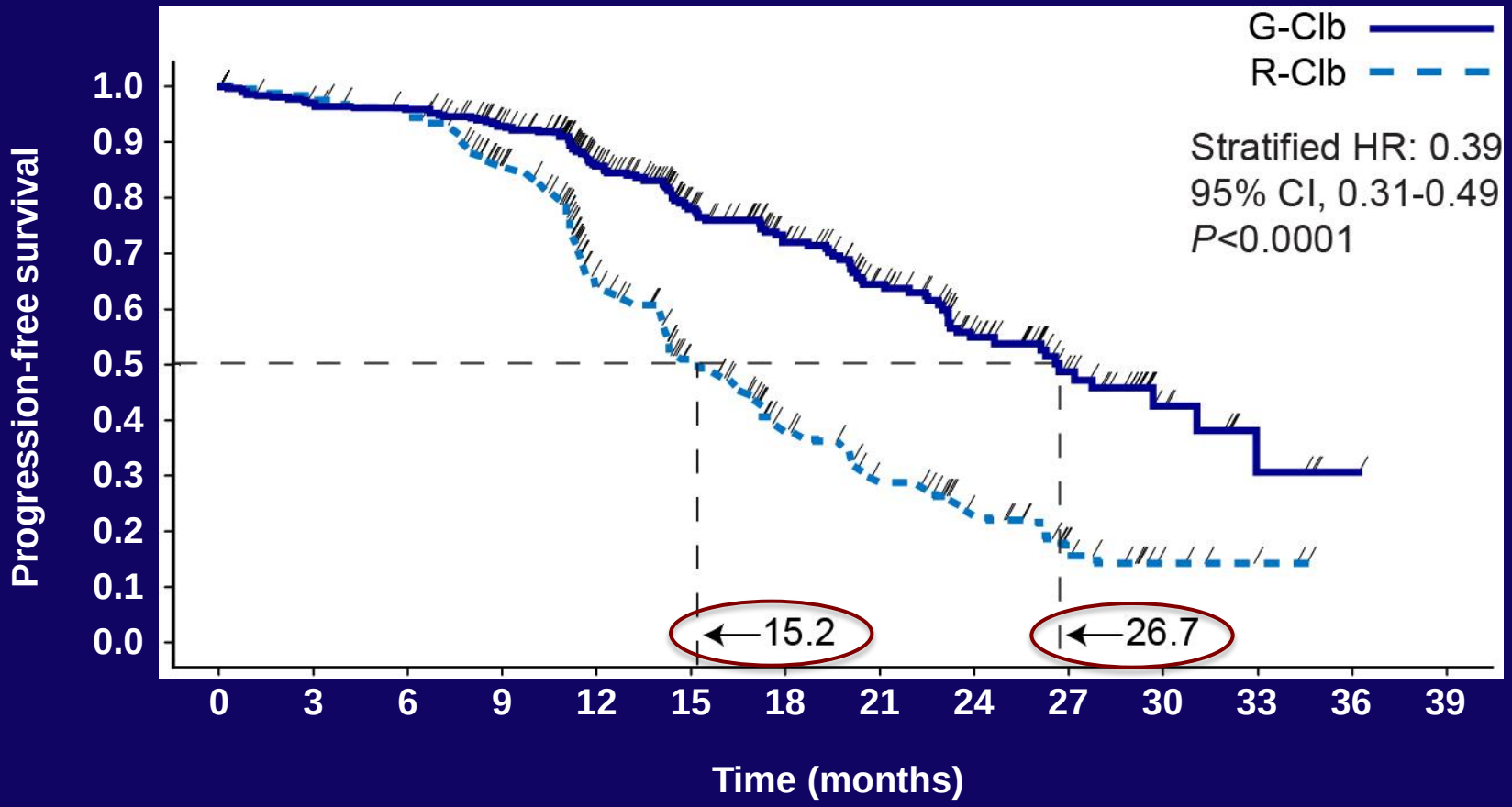
Goede et al N Engl J Med 2014 March 2015, 370 (12): 1101-10.

CLL11 Study Design



Goede et al N Engl J Med 2014 March 2015, 370 (12): 1101-10.

Progression-Free Survival *(Head-to-Head)*

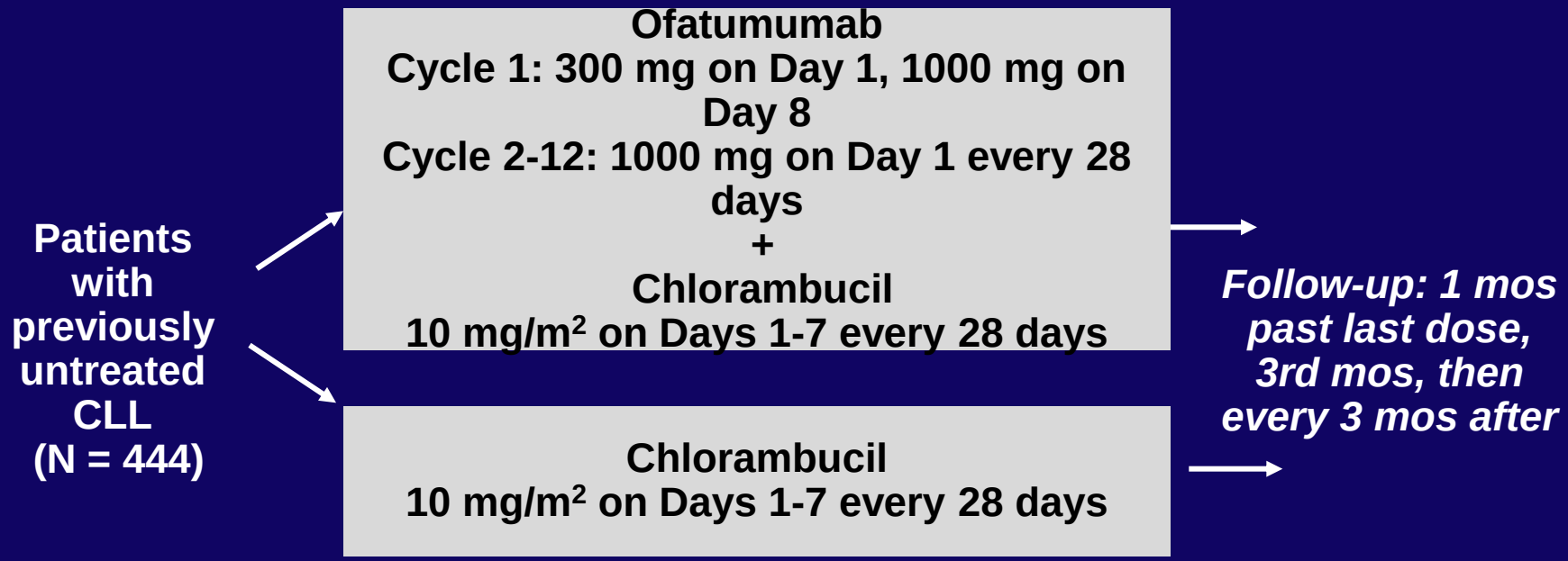


No. at risk

G-Clb:	330	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 <0.0001
Independent Review Committee-assessed progression-free survival (PFS) was consistent with investigator-assessed PFS

Phase III COMPLEMENT1: Ofatumumab + Chlorambucil vs Chlorambucil Alone

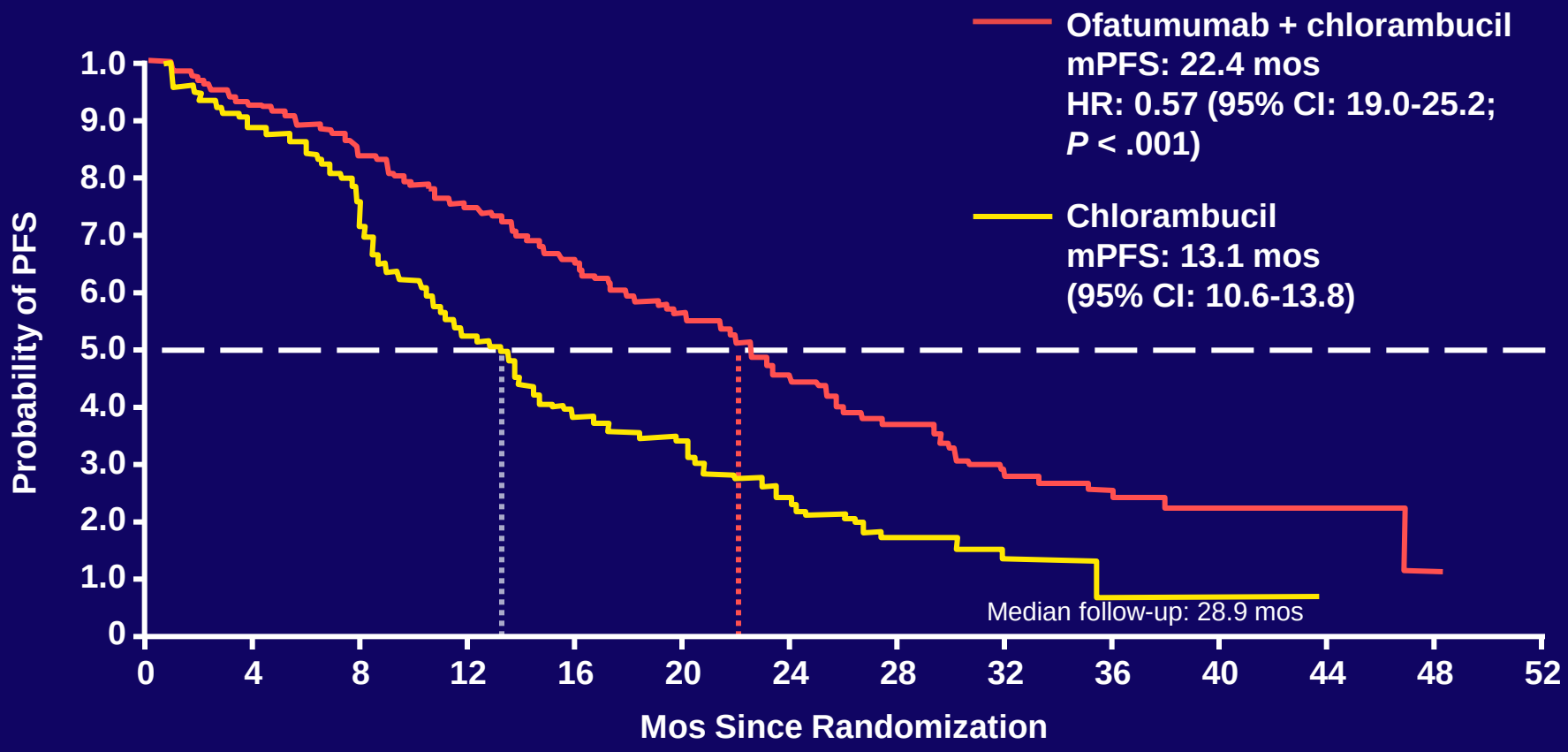


***Minimum 3 cycles or until best response or PD; maximum 12 cycles; no crossover allowed.**

Dose rationale: highest PFS and ORR with the lowest toxicity compared with any other chlorambucil treatment

Hillmen P, et al. ASH 2013. Abstract 528.

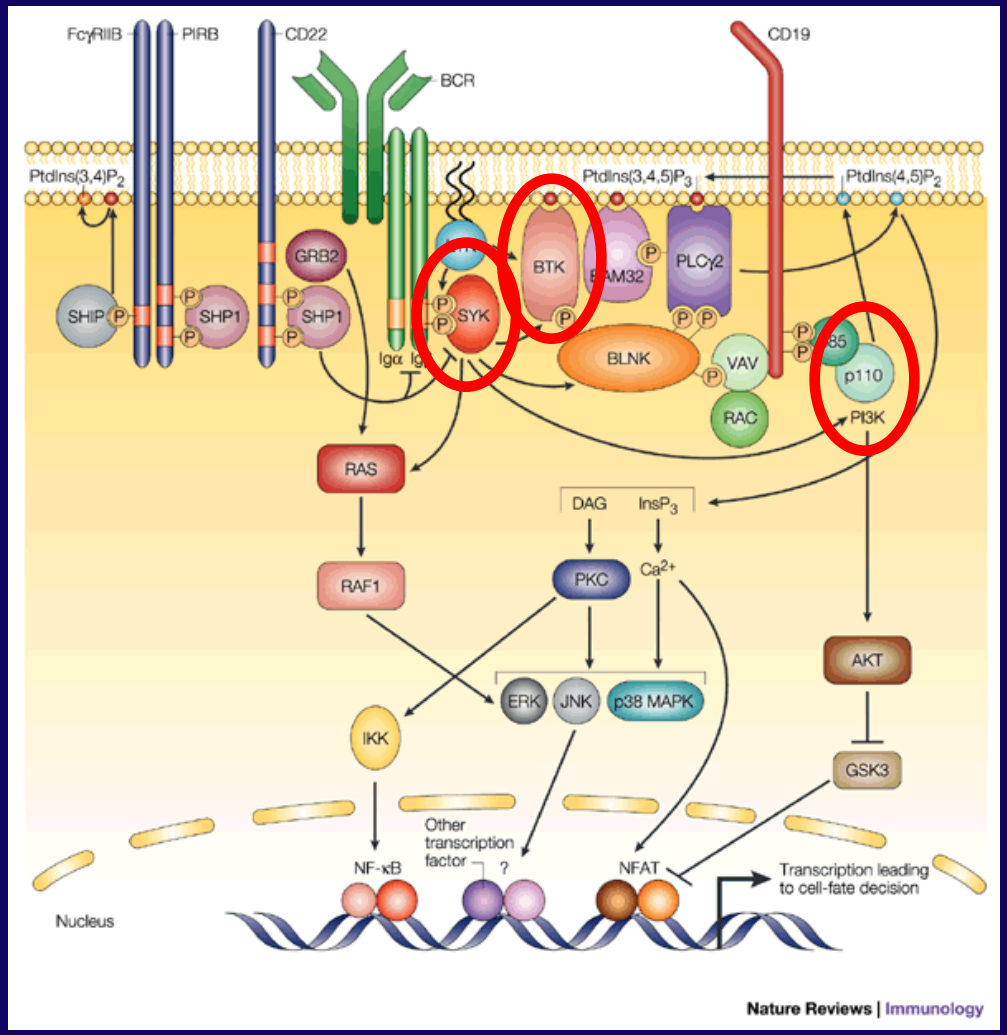
Ofatumumab + Chlorambucil vs Chlorambucil Alone: PFS*



*As assessed by an Independent Review Committee,

Hillmen P, et al. ASH 2013. Abstract 528.

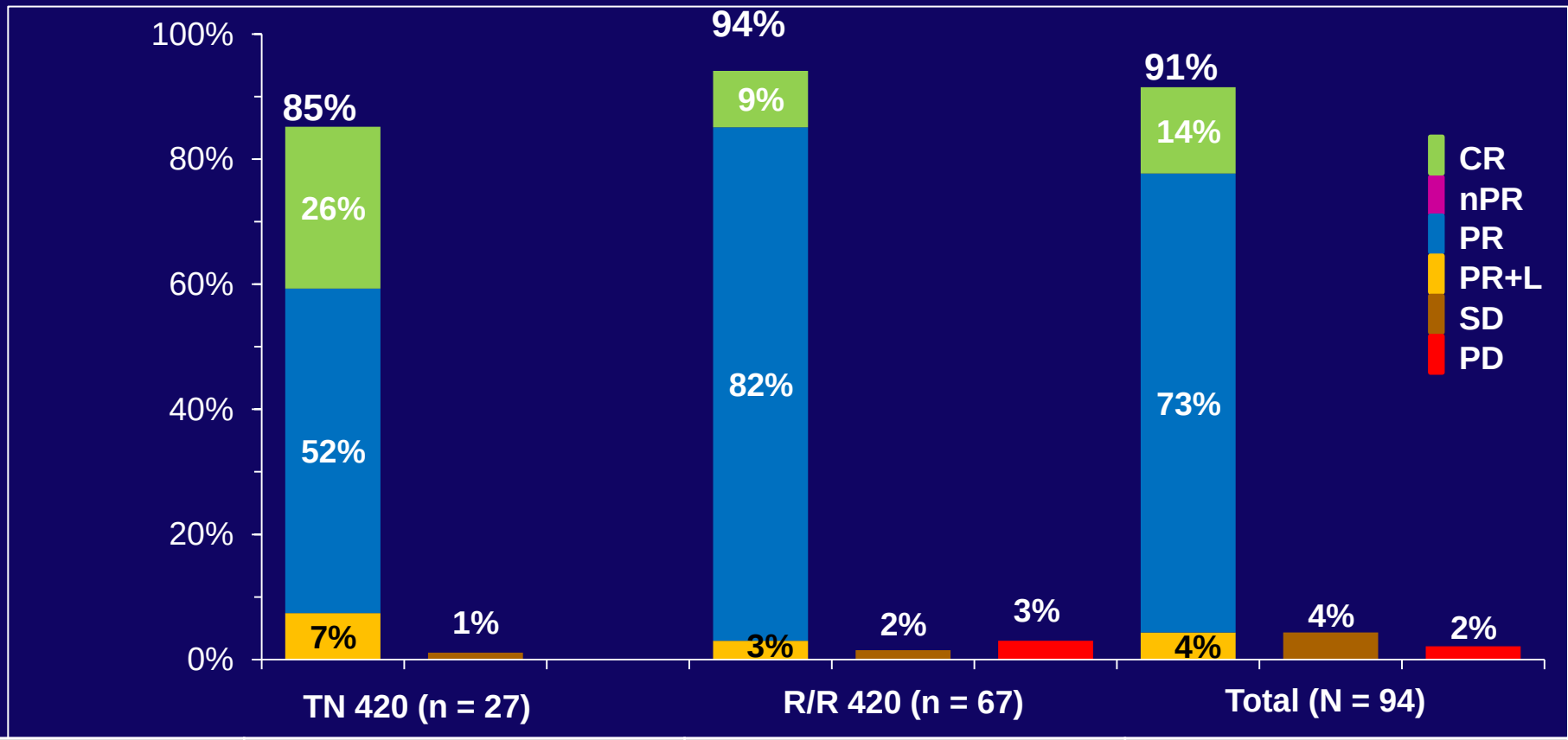
Targeting of BCR Signaling in CLL



- BCR-associated kinases are targets of new drugs in preclinical and clinical development
- Syk (spleen tyrosine kinase) inhibitors: R406, Portola's Syk inhibitors[1]
- Btk (Bruton's tyrosine kinase) inhibitors: ibrutinib, CC-292, ONO-4059, ACP196
- PI3 kinases: Isoform-Selective Inhibitor of PI 3-Kinases[2], idelalisib, IPI-145, TGR-1202

[1] Quiroga MP, et al. Blood 114(5):1029-37, 07/2009
[2] Niedermeier M, et al. Blood 113(22):5549-57, 5/2009

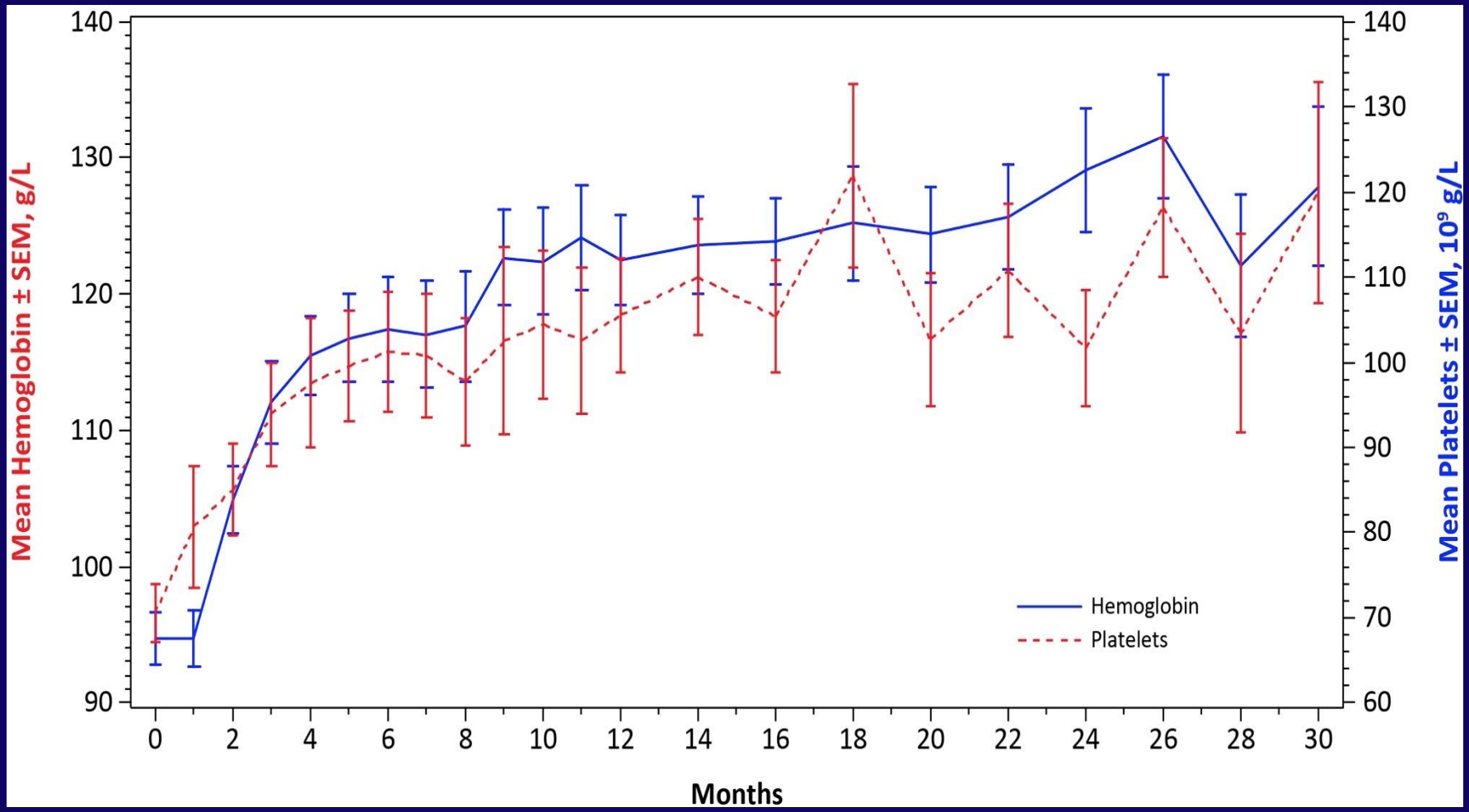
Ibrutinib Phase 2 Best Response (Investigator-Assessed)



Median DOR, months (95% CI)*	NR (NE to NE)	NR (35.9 to NE)	NR (NE to NE)
Month 30 (95% CI)*	100% (100 to 100)	82.2% (68.5 to 90.4)	87.3% (77 to 93.2)

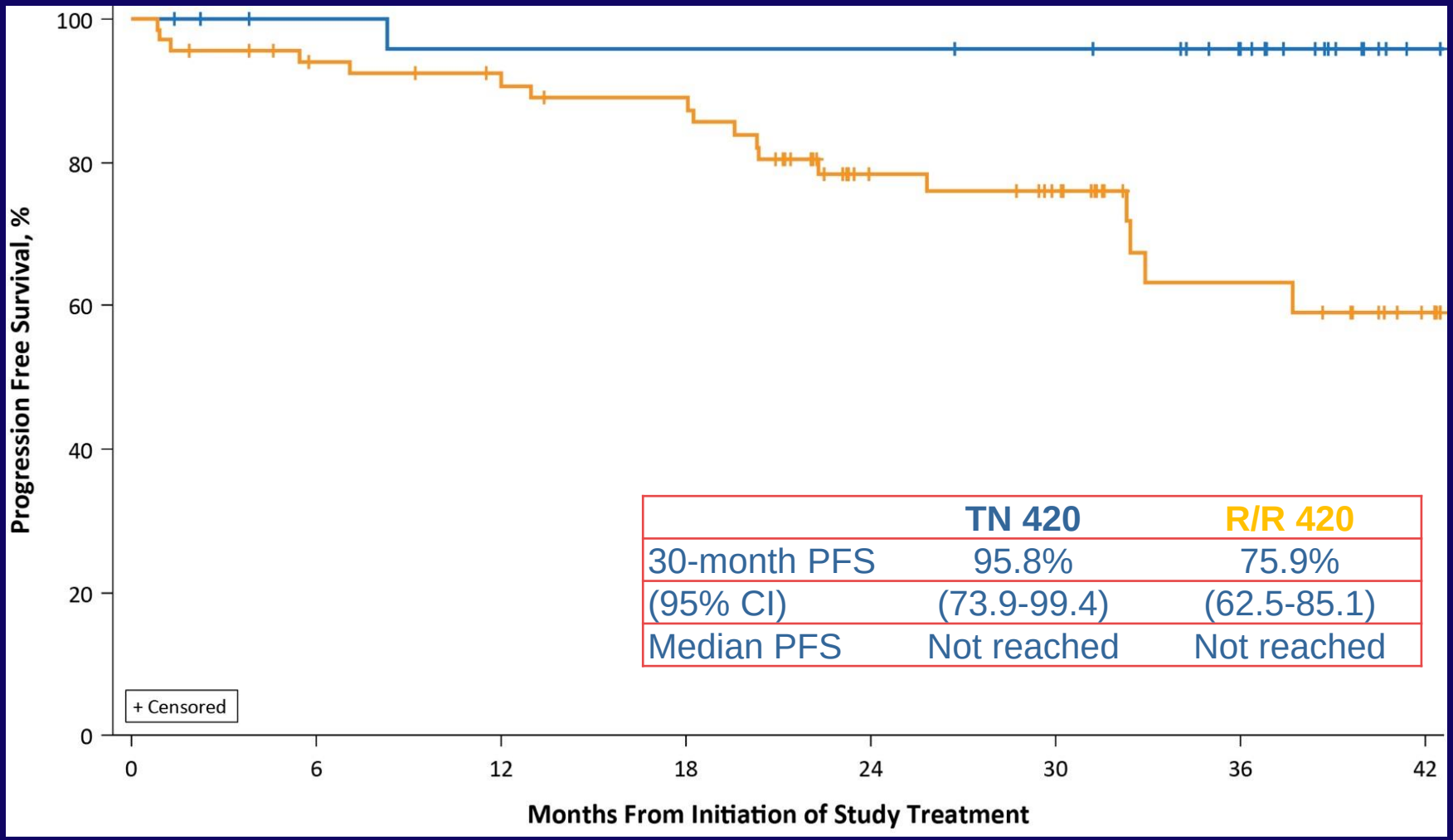
*TN: n = 21, R/R: n = 61, total: N = 82.

Platelet Counts and Hemoglobin Levels



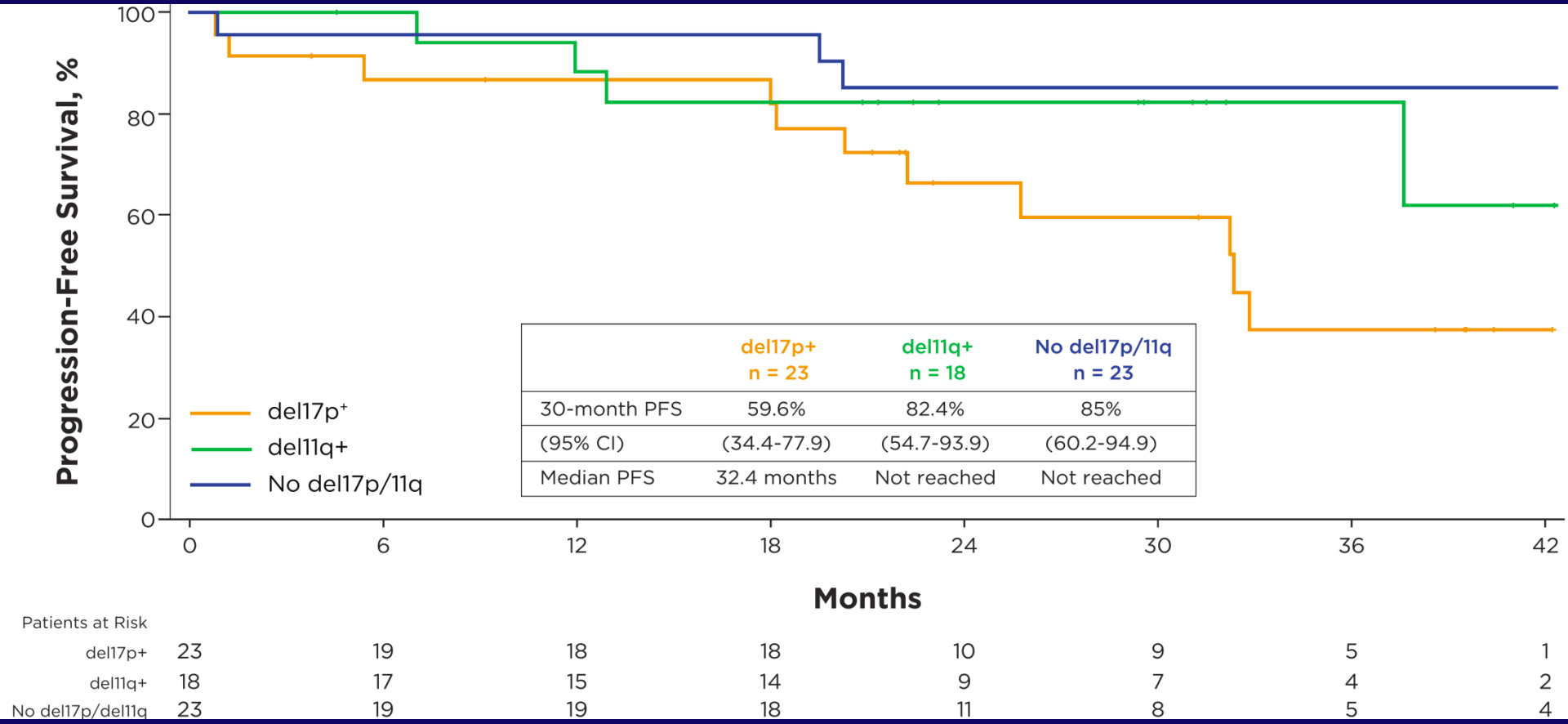
Population: all patients receiving 420 mg/day with baseline anemia or thrombocytopenia.

Progression-Free Survival



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

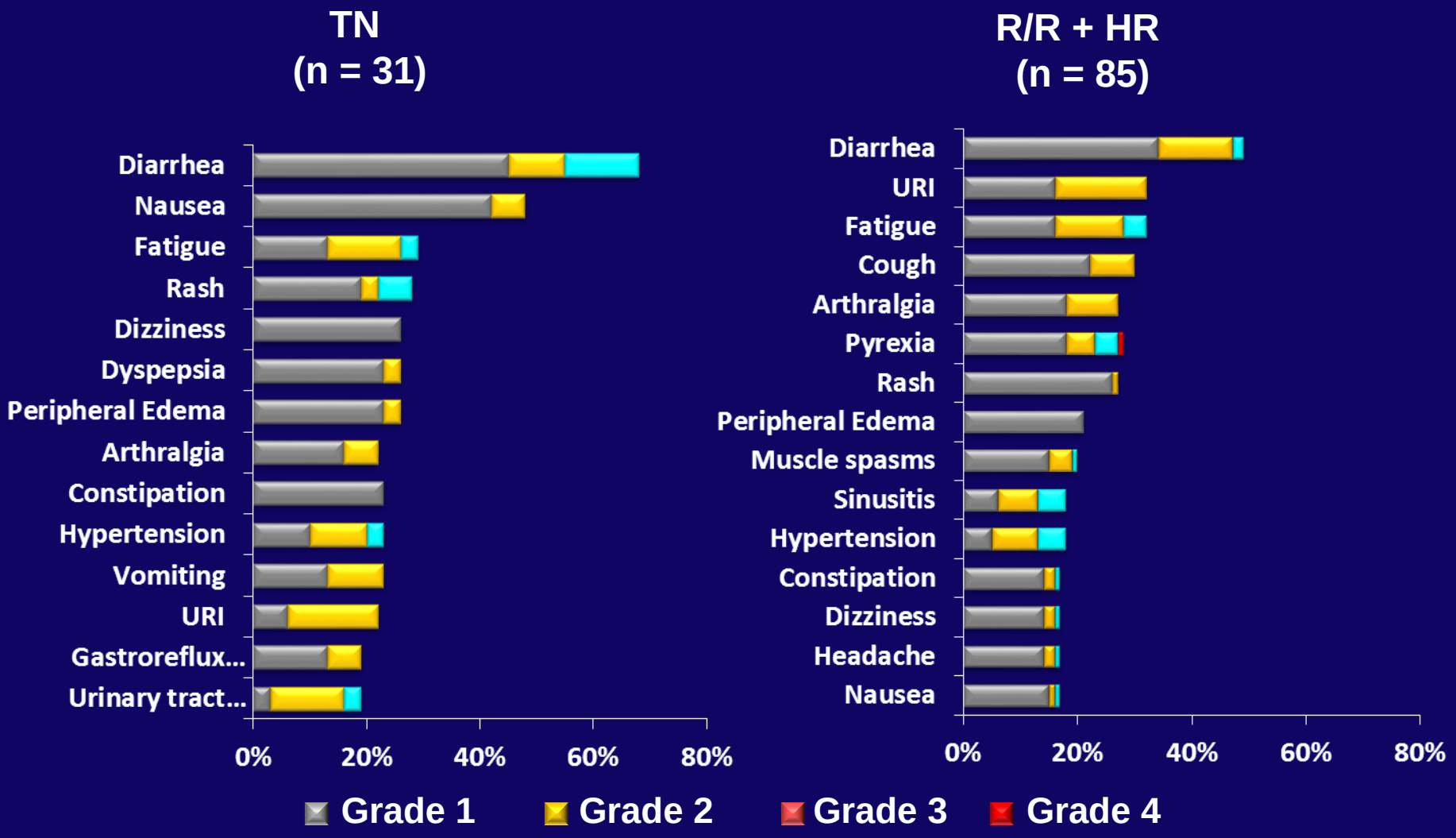
PFS Outcomes by Cytogenetics (FISH) in Relapsed/Refractory Population



	del17p+ n = 23	del11q+ n = 18	No del17p/11q n = 23
30-month PFS	59.6%	82.4%	85%
(95% CI)	(34.4-77.9)	(54.7-93.9)	(60.2-94.9)
Median PFS	32.4 months	Not reached	Not reached

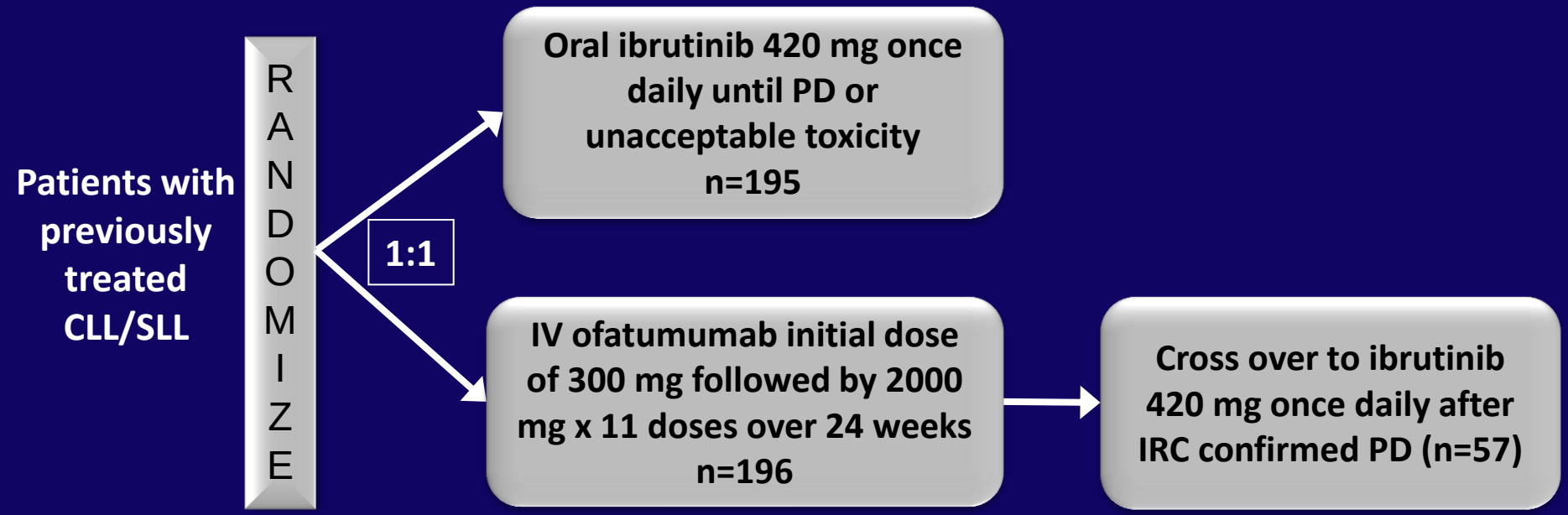
Patients at Risk								
del17p+	23	19	18	18	10	9	5	1
del11q+	18	17	15	14	9	7	4	2
No del17p/del11q	23	19	19	18	11	8	5	4

Ibrutinib: Common AEs (All Grades, Regardless of Causality)



IWCLL 2013, PCYC 1102, Furman et al.

RESONATE™ Phase 3 Study Design

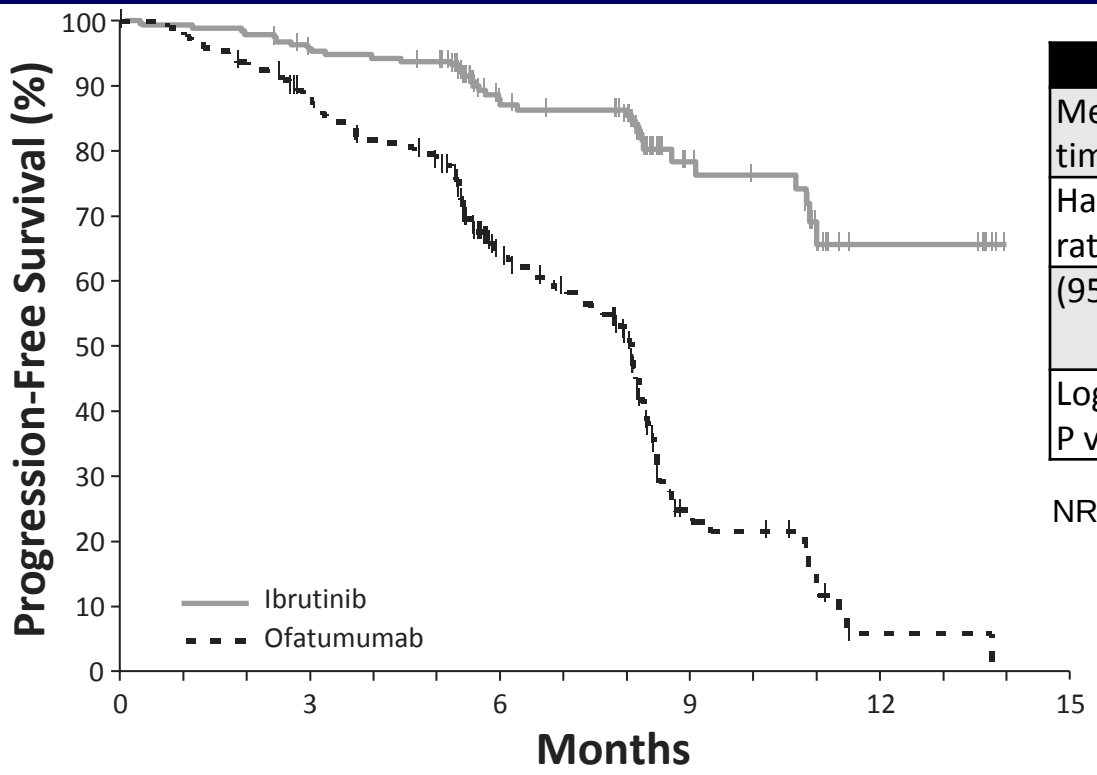


- Primary Endpoint: PFS
- Stratification according to:
  - Disease refractory to purine analog chemoimmunotherapy (no response or <12 months)
  - Presence or absence of 17p13.1 (17p del)
- At time of interim analysis, median time on study was 9.4 months

Protocol amended for cross over with support of Data Monitoring Committee and discussion with health authorities.
PD, progressive disease.

Byrd et al N Engl J Med 2014, Jul 17: 371 (3); 213-23

Progression-Free Survival



	Ofatumumab	Ibrutinib
Median time (mo)	8.08	NR
Hazard ratio	0.215	
(95% CI)	(0.146-0.317)	
Log-rank P value	< 0.0001	

NR, not reached

- This represent s a 78% reduction in the risk of PD or death with ibrutinib compared with ofatumumab
- Richter's transformation was confirmed in 2 patients on each arm.
- Another patient on the ibrutinib arm had transformation to prolymphocytic leukemia

Safety: Atrial Fibrillation and Bleeding-Related Adverse Events

- Atrial fibrillation any grade: ibrutinib n=10, ofatumumab n=1
  - Discontinuation of ibrutinib in only 1 patient

    Patients were ≥60 years old (median age 73)

    Most had predisposing risk factors (a prior history of atrial fibrillation or in the setting of a pulmonary infection)

- Bleeding-related AEs of any grade:
  most commonly petechiae and ecchymoses
  ibrutinib 44%, ofatumumab 12%
  - No difference in severe/major bleeding events:

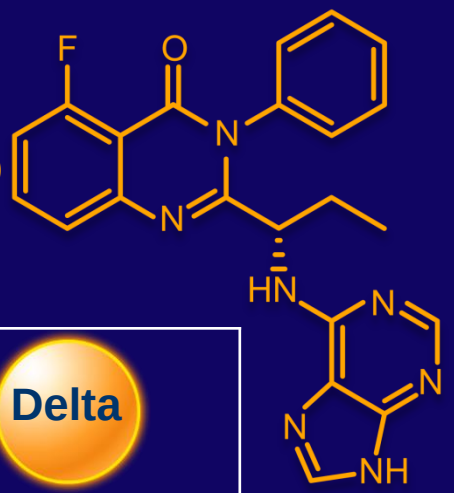
    ibrutinib n=2, ofatumumab n=3, 1 SDH with ibrutinib
  - One patient discontinued ibrutinib due to a bleeding AE
  - Concomitant anti-platelets or anticoagulants

    50% ibrutinib and 39% ofatumumab

Byrd et al N Engl J Med 2014, Jul 17: 371 (3); 213-23

Idelalisib is an Orally Bioavailable Small Molecule that Inhibits PI3K Delta Potently and Selectively

Idelalisib



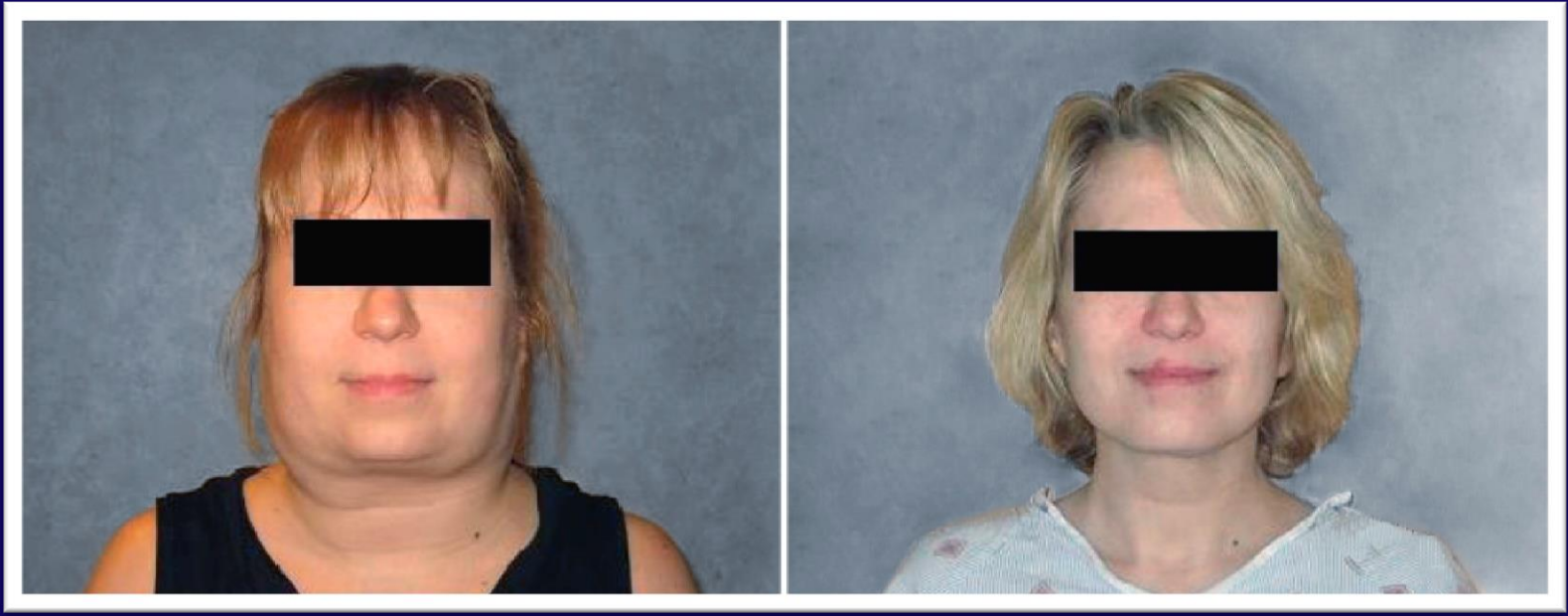
Class I PI3K Isoform	Alpha	Beta	Gamma	Delta
Cell-Based Activity	PDGF-induced pAKT	LPA-induced pAKT	fMLP-induced CD63+	FcεR1-induced CD63+
EC_{50} (nM)	>20,000	1,900	3,000	8

- Selectivity relative to Class I PI3K isoforms involved in insulin signaling and other physiological functions
- No off-target activity against Class II or III PI3K, mTOR, or DNA-PK
- No off-target activity seen in screen of >350 protein kinases (Ambit KINOMEscan™)

Lannutti, Blood, 2011

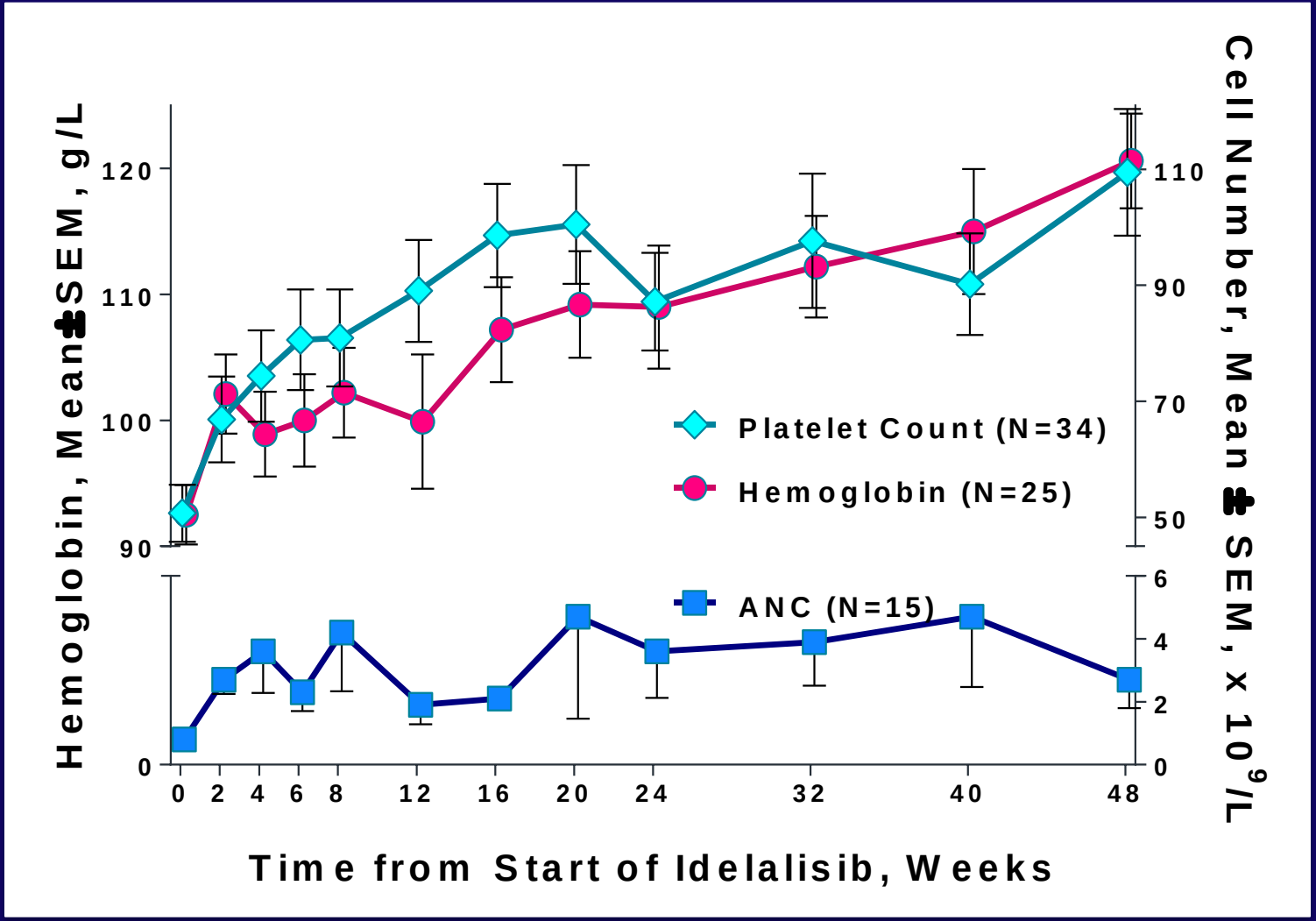
Marked Reductions in Peripheral Lymphadenopathy Were Observed

Pretreatment **With IdelalisibTreatment**



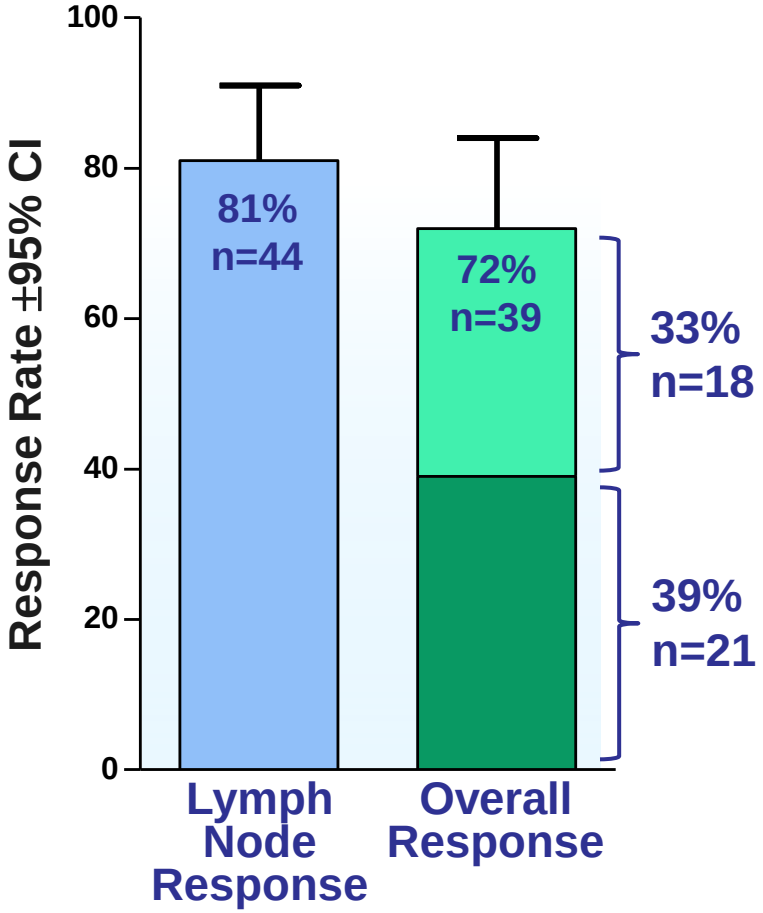
38-year-old patient with refractory CLL and 5 prior therapies

Idelalisib: Idelalisib Improvement of Baseline Cytopenias



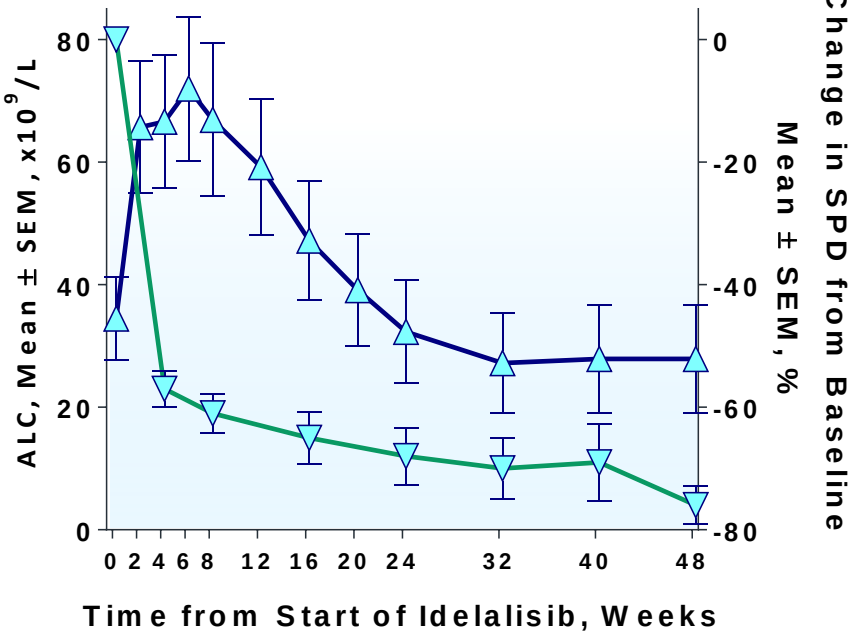
Brown et al. Blood. 2014 May 29; 123 (22): 3390-7

Idelalisib: Nodal and Overall Response Rate



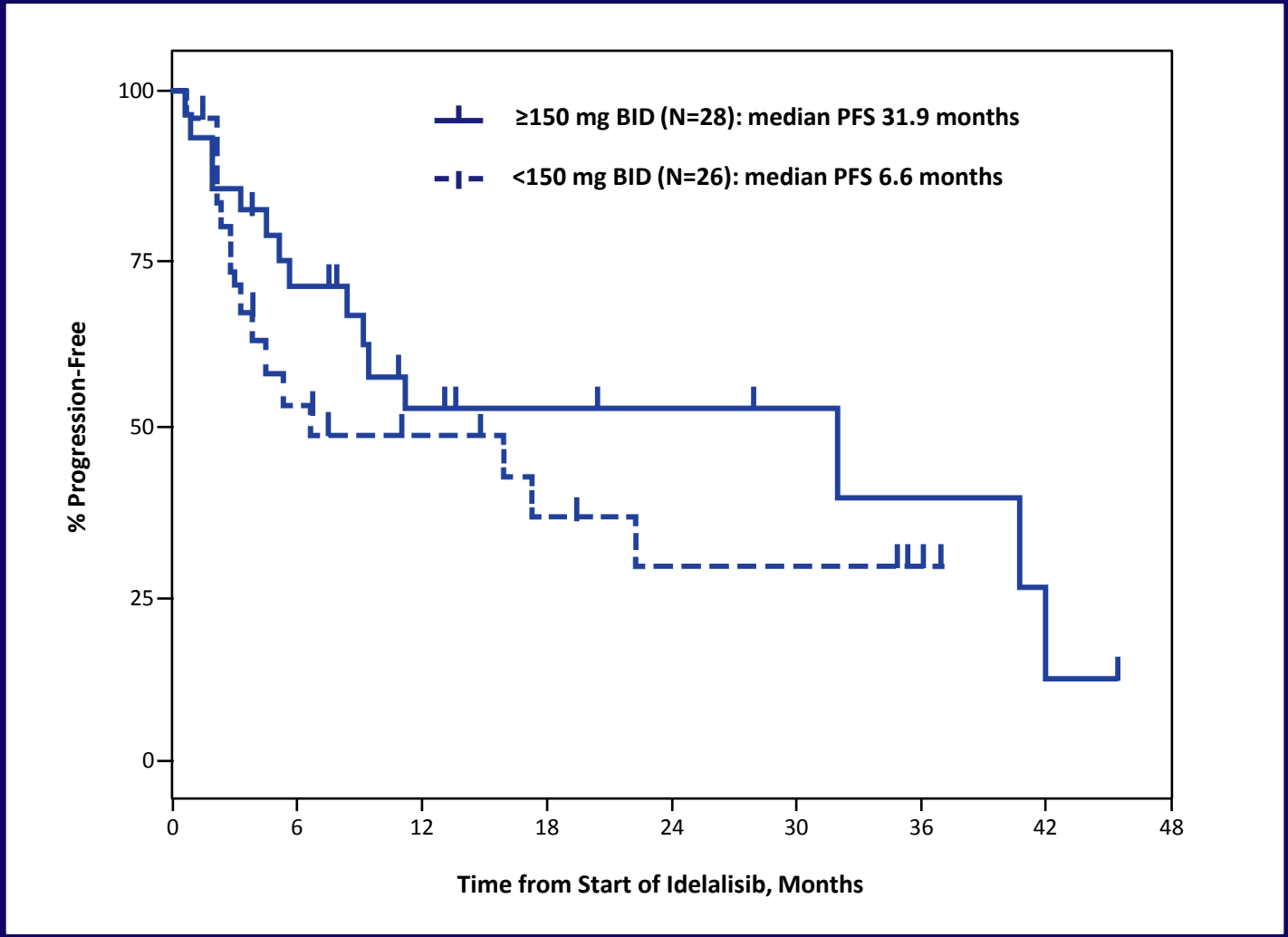
Decrease by ≥50% of nodal SPD
PR with lymphocytosis (Cheson 2012)
PR by IWCLL criteria (Hallek 2008)

ALC and Tumor Burden Over Time



ALC (N=54)
SPD (N=51)

Idelalisib: Progression-Free Survival by Dose



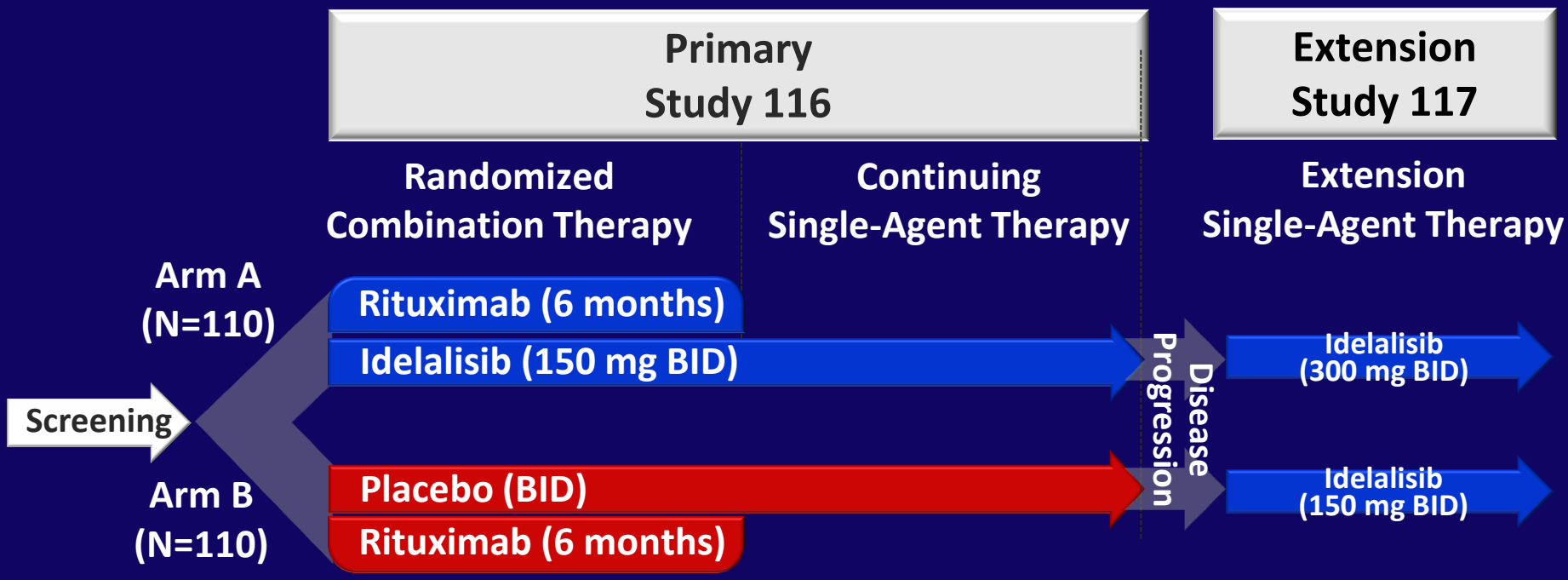
Brown et al. Blood. 2014 May 29; 123 (22): 3390-7

Idelalisib: Adverse Events (≥ 15%) and Selected Lab Abnormalities (N = 54)

AE, n (%)	Any Grade, (%)	Grade ≥ 3, (%)
Fatigue	17 (32)	1 (2)
Diarrhea	16 (30)	3 (6)
Pyrexia	16 (30)	2 (4)
Cough	13 (24)	2 (4)
Back pain	12 (22)	0
Rash	12 (22)	0
URI	12 (22)	0
Pneumonia	11 (20)	10 (19)
Night sweats	10 (19)	0
Chills	9 (17)	0
Laboratory abnormality, n (%)		
AST, increased*	13 (24)	1 (2)
ALT, increased*	10 (19)	1 (2)
*15 subjects total with transaminase elevations		

Brown et al. Blood. 2014 May 29; 123 (22): 3390-7

Study 116: Randomized, Double-Blind, Placebo-Controlled



Rituximab administration

- 375 mg/m^2, then 500 mg/m^2 Q2W x 4, then 500 mg/m^2 Q4W x 3

Clinical Endpoints

- Primary: PFS as assessed by IRC
- Events: Disease progression or death
- Secondary: ORR, LNR, OS

Planned interim analyses at 50% and 75% of events

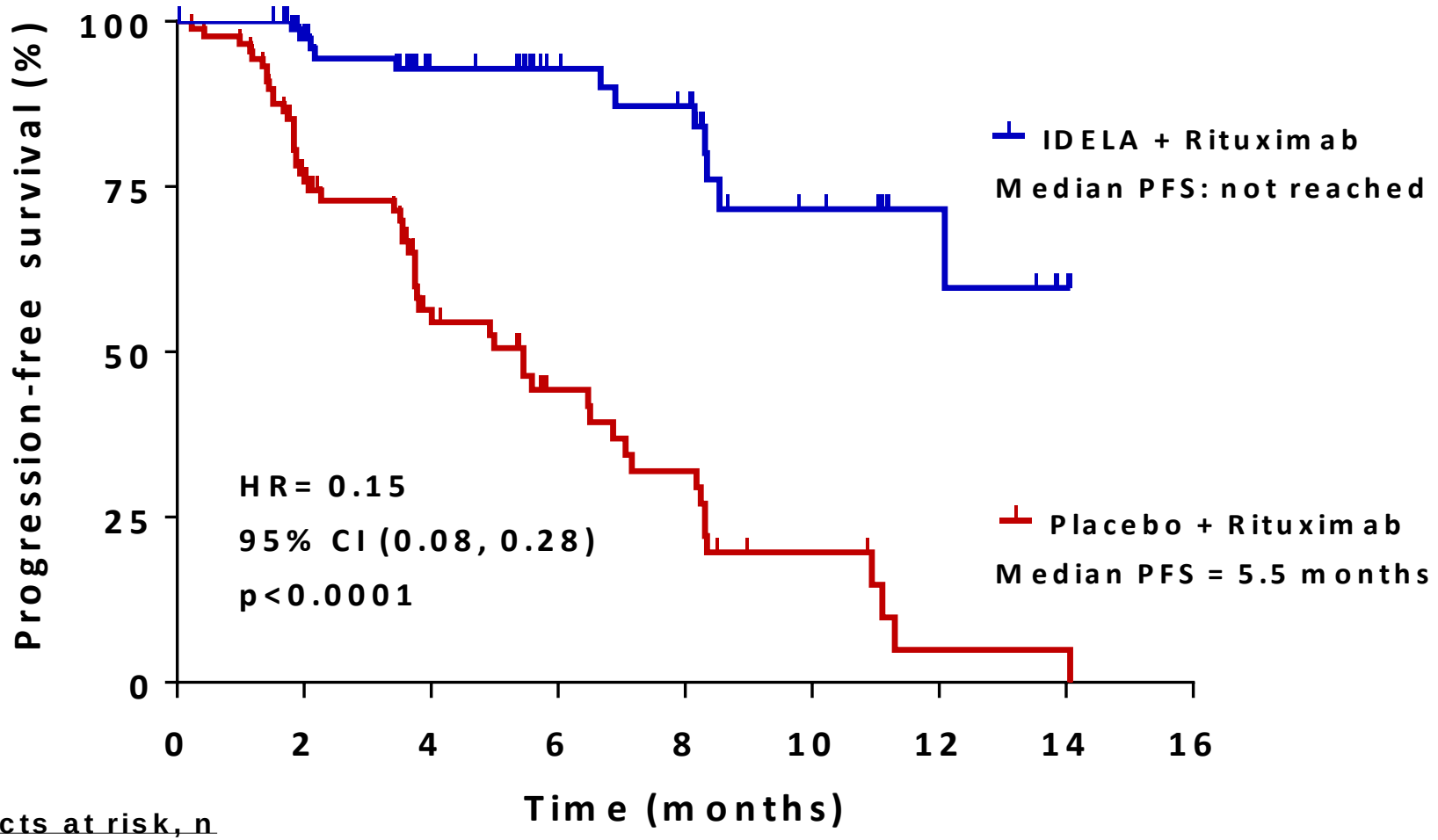
Furman et al N Engl J Med 2014, Mar 13, 370 (11): 997-1007

Study 116: Key Eligibility

Criteria	Requirement
Relapsed CLL	• CLL progression <24 months since last therapy • Treatment warranted according to IWCLL criteria
Lymphadenopathy	• Presence of ≥1 measurable nodal lesion
Prior therapies	• ≥ 1 anti-CD20 antibody containing therapy or ≥ 2 prior cytotoxic therapies
Appropriate for non-cytotoxic therapy	• CIRS score >6 or creatinine clearance <60 ml/min (≥30 mL/min) or Grade 3/4 neutropenia or thrombocytopenia due to prior myelotoxicity
Bone marrow function	• Any grade anemia, neutropenia or thrombocytopenia allowed
Karnofsky score	• ≥40

Furman et al N Engl J Med 2014, Mar 13, 370 (11): 997-1007

Primary Endpoint: Progression-Free Survival



Subjects at risk, n

IDELA + R:	110	69	44	34	30	14	6	2	0
Placebo + R:	110	62	30	18	13	6	1	1	0

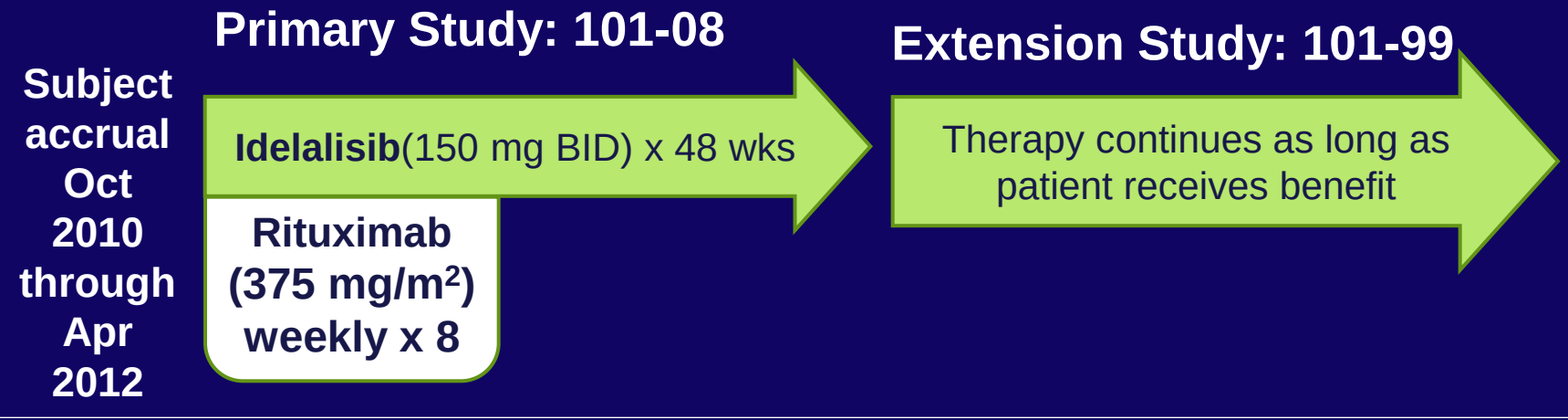
Adverse Events ≥10% In Either Study Arm

AE, n (%)	IDELA + R (N=110)		Placebo + R (N=107)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Patients with any AE	100 (91)	62 (56)	101 (94)	51 (48)
Pyrexia	32 (29)	3 (3)	17 (16)	1 (1)
Fatigue	26 (24)	3 (3)	29 (27)	2 (2)
Nausea	26 (24)	0	23 (22)	0
Chills	24 (22)	2 (2)	17 (16)	0
Diarrhea	21 (19)	4 (4)	15 (14)	0
Infusion-related reaction	17 (16)	0	30 (28)	4 (4)
Cough	16 (15)	0	27 (25)	2 (2)
Decreased appetite	13 (12)	0	9 (8)	1 (1)
Constipation	13 (12)	0	12 (11)	0
Vomiting	13 (12)	0	8 (8)	0
Dyspnea	12 (11)	2 (2)	20 (19)	3 (3)
Rash	11 (10)	2 (2)	6 (6)	0
Night sweats	11 (10)	0	8 (8)	0

Furman et al N Engl J Med 2014, Mar 13, 370 (11): 997-1007

Phase 2 Single Arm, Open Label Study of Idelalisib + Rituximab in Frontline CLL

Study Schema



Eligibility	• Age ≥ 65 years • Treatment naive CLL requiring therapy (IWCLL 2008) • No exclusions for cytopenias
Disease assessment	• Investigator determined • Weeks 0, 8, 16, 24, 36, 48 and per SOC thereafter
Endpoints	• Primary: ORR • Secondary: DOR, PFS, Safety

O'Brien et al Blood E published October 15, 2015

Idelalisib + Rituximab: Response

	All Patients		Del(17p) and/or TP53 mutation	
	N = 64	(%)	N = 9	(%)
Complete Response	12	(19)	3	(33)
Partial Response	50	(78)	6	(67)
Stable Disease	0		0	
Progressive Disease	0		0	
Not Evaluable	2	(3)	0	
Overall Response	62	(97)	9	(100)

- Median Time to Response 1.9 months
- 24/26 patients with B symptoms resolved by week 16

No on-study progression

O'Brien et al Blood E Published October 15, 2015

Idelalisib + Rituximab: In Frontline CLL

Adverse Events Leading to Discontinuation

Patients, n (%)*	Treatment Duration			Total n=23
	<24 wk n=10	24-48 wk n=6	>48 wk n=11	
Diarrhea/colitis	0	4	8	12 (19)
Respiratory disorders	6	0	1	7 (11)
Rash	3	0	0	3 (5)
Infection	1	2	0	3 (5)
Anemia	1	1	0	2 (3)
ALT/AST	1	0	0	1 (2)
Other	2	4	2	8 (13)

*Patients may have >1 AE.

Deaths

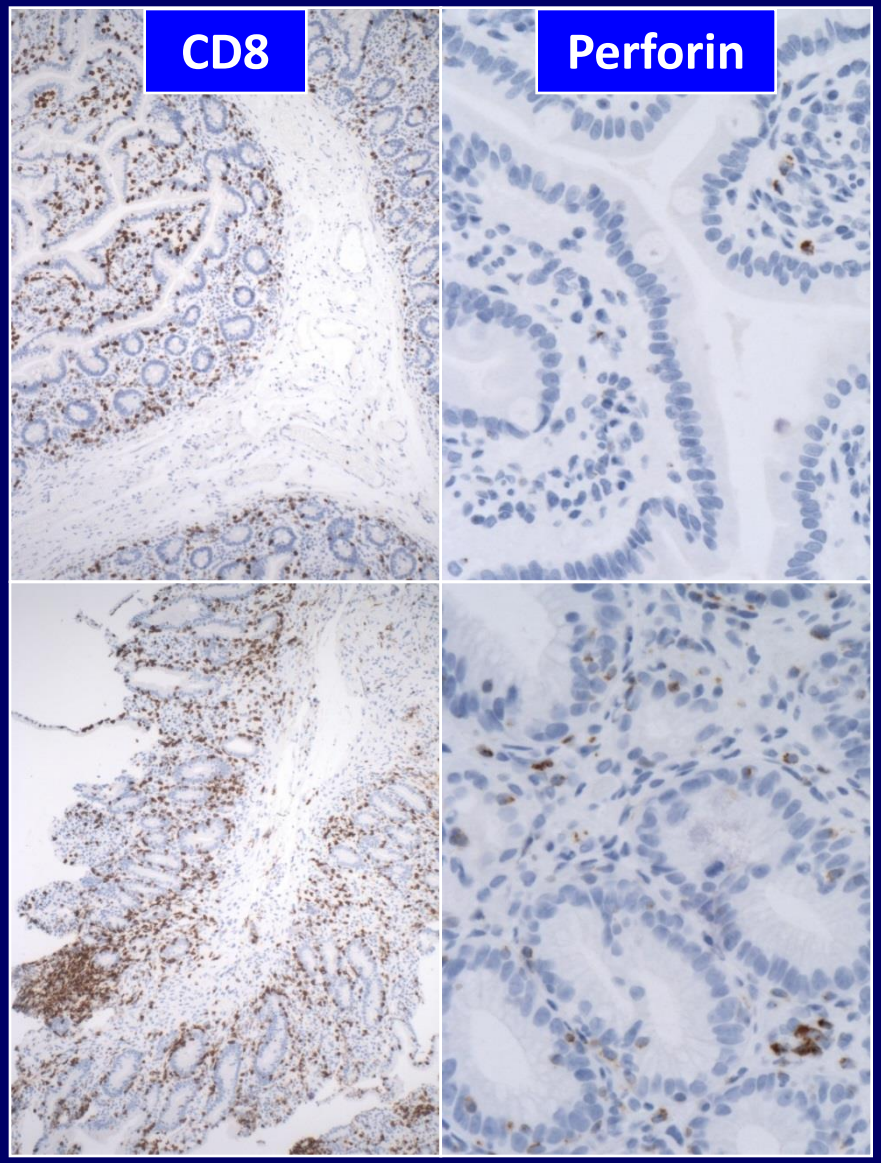
- **5 deaths**
  - **Pneumonia/sepsis (n=1); pneumonia/metastatic melanoma (n=1); pneumonitis (n=2); myocardial infarction (n=1)**

O'Brien et al Blood E published October 15, 2015

Diarrhea/Colitis

- 27 patients (42%) developed Grade ≥3 diarrhea/colitis
  - Onset at median 9.5 months (range 3–29)
  - Dosing interrupted or discontinued in 21 patients
  - 11 patients received a corticosteroid (budesonide or prednisone)
- 21 patients rechallenged following idelalisib dose interruption or had dose reduced to 100 mg BID
  - 12 patients (44% of 27 affected) were subsequently able to maintain dosing for minimum of 120 days

Immune Infiltrate in Subjects with Colitis



- **Intestinal biopsies from patients with idelalisib-related colitis show intraepithelial CD8+ lymphocytosis and crypt cell apoptosis**

Weidner *Am J Surg Path* 2015

Louie *Am J Surg Path* 2015

The Connection Between p110δ and Tregs

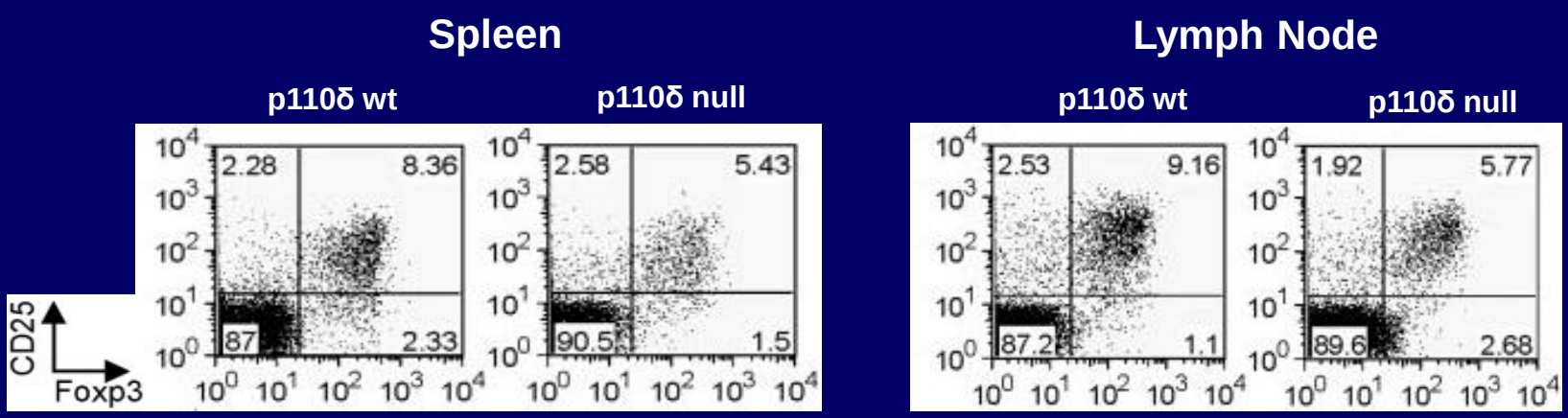
- Mice with genetic inactivation of p110δ develop an autoimmune colitis

  Okkenhaug *Nature* 2002

- Mutations that disrupt Treg function in mice and humans lead to autoimmune syndromes with hepatitis, enteritis, and pneumonitis

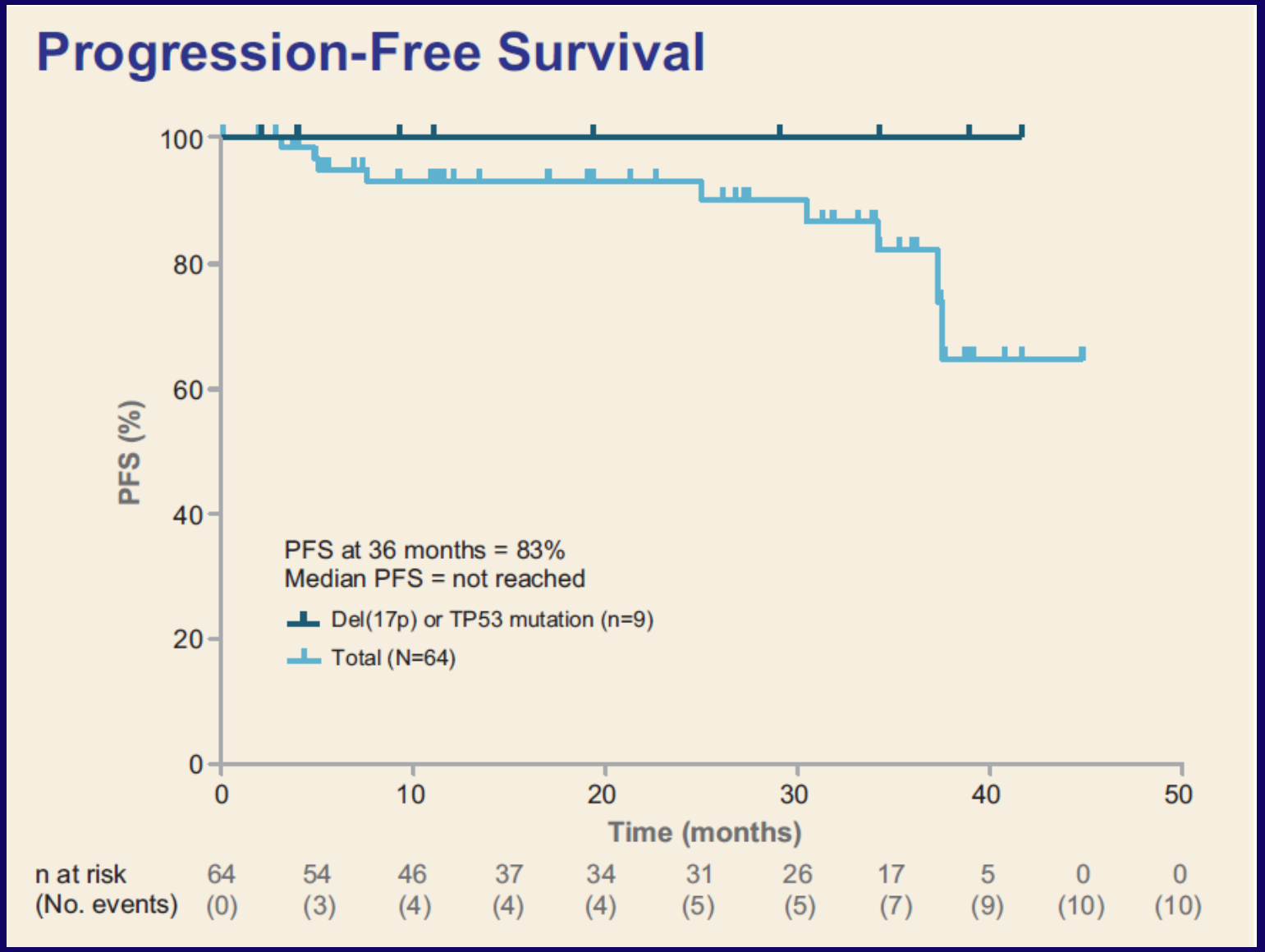
  Torgerson *J Allergy Clin Immunol* 2007
  Godfrey *Am J Path* 1991

- Mice with genetic inactivation of p110δ have decreased numbers and function of regulatory T cells



Patton *J Immunol* 2006

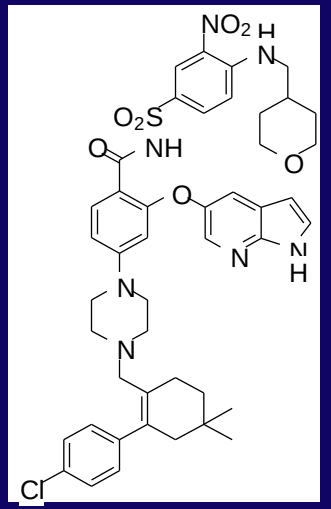
Results: PFS



O'Brien et al Blood E published October 15, 2015

Venetoclax: Potent and Selective Bcl-2 Inhibition

- Small molecule, orally bioavailable
- High affinity for Bcl-2, lower affinity for BCL-xL, Mcl-1
- >100-fold improved functional selectivity for Bcl-2 over Bcl-x_L in assays with tumor cell lines



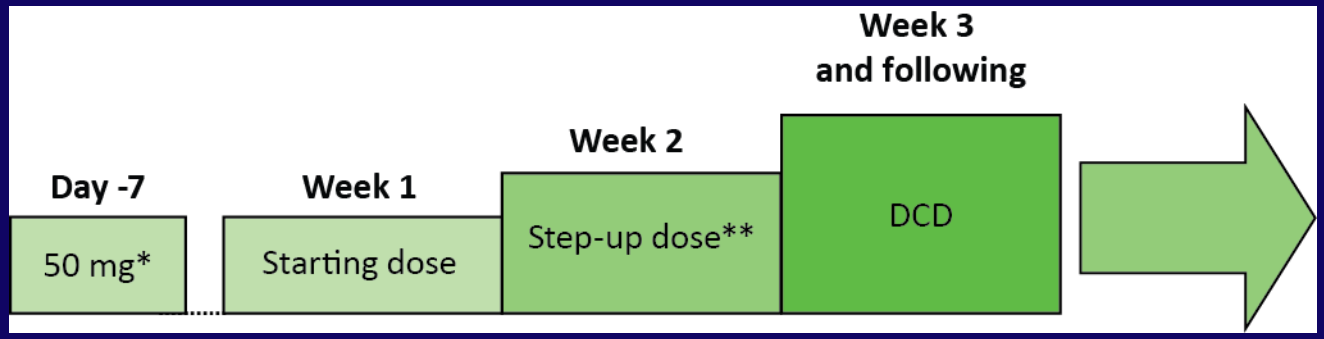
ABT-199

	Affinity				Cellular Efficacy, EC_{50}, nM				
	TR FRET K_i, nM				FL5.12, 3% FBS			Human tumor cell lines, 10% HS	
Agents	Bcl-2	Bcl-x_L	Bcl-w	Mcl-1	Bcl-2	Bcl-x_L	Functional Selectivity	RS4;11 (Bcl-2)	H146 (Bcl-x_L)
Navitoclax	0.04	0.05	7	>224	20	13	0.6	110	75
ABT-199	< 0.01	48	21	>440	4	261	65	12	3600

S. Jin, P. Kovar, P. Nimmer, M. Smith, Y. Xiao

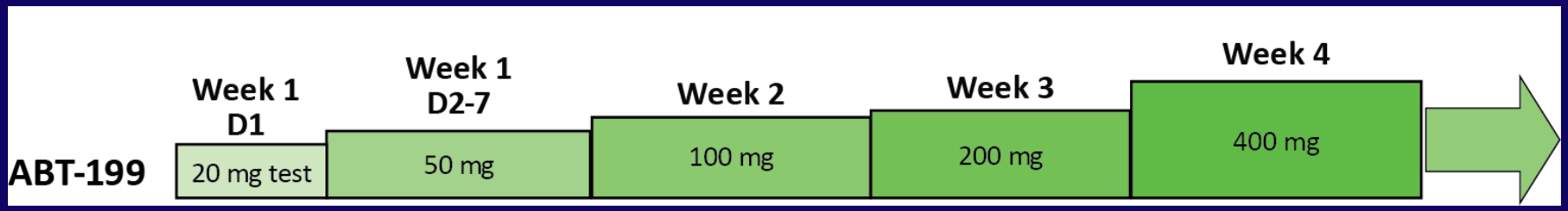
Dosing Schedule of Venetoclax: Dose Escalation Schematic

Dose Escalation Scheme



*3 patients (1 each in cohorts 2, 3, & 5) received ABT-199 20 mg as initial dose.
**Step-up doses range from 100 to 400 mg.
DCD = Designated Cohort Dose

Lead-in to Designated Cohort Dose - Expanded Safety Cohort



Median time on study 10.9 months

Seymour et al. EHA 2014

Objective Responses of Venetoclax Treated Patients

Responses	All n (%), n = 78	del (17p) n (%), n = 19	F-Refractory n (%), n = 41	Unmutated n (%), n = 24
Overall response	60 (77)	15 (79)	31 (76)	18 (75)
Complete response (CR/CRi)[#]	18 (23)	5 (26)	9 (22)	7 (29)
Partial response*	42 (54)	10 (53)	22 (54)	11 (46)
Stable disease	10 (13)	2 (11)	7 (17)	2 (8)
Disease progression	2 (3)	1 (5)	1 (3)	2 (8)
D/C Prior to assessment[+]	6 (8)	1 (5)	2 (5)	2 (8)

Some patients may have more than one high risk marker.
[#]4 patients have CRi; [+]D/C = discontinued, first assessment at 6 weeks
*3 patients had confirmatory CT imaging assessments at less than an 8 week interval (5, 6, and 7 weeks)

- As of April 9, 78 patients had 2 CT scans, performed approximately 8 weeks apart n=55 from dose escalation and n=23 from the safety expansion cohort
- A total of 26 patients are not yet evaluable in the SE cohort (12 patients had a PR at their first scan, 14 patients have not yet reached their first assessment)
- The median duration of response has not yet been reached

Minimal Residual Disease (MRD): Preliminary Analyses

- 11/18 patients with CR/CRi assessed for MRD
- Quantification by 4 color flow using local lab
- BM: MRD ⊖ = 6

  (3 suboptimal cell #)

  MRD +

  low level = 4 (0.17%, 0.7%, 0.75%, 1.5%)
- PB: MRD ⊖ = 1 (no BM)
- BM MRD ⊖ 1 F refractory, 17p-

  3 F refractory

  1 17p

Seymour et al EHA 2014

RESONATE™-2 (PCYC-1115) Study Design

Patients (N=269)
- Treatment-naïve CLL/SLL with active disease
- Age ≥65 years
- For patients 65-69 years, comorbidity that may preclude FCR
- del17p excluded
- Warfarin use excluded

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

RANDOMIZE 1:1

ibrutinib 420 mg once daily until PD or unacceptable toxicity

chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg) days 1 and 15 of 28-day cycle up to 12 cycles

IRC-confirmed progression

PCYC-1116 Extension Study*

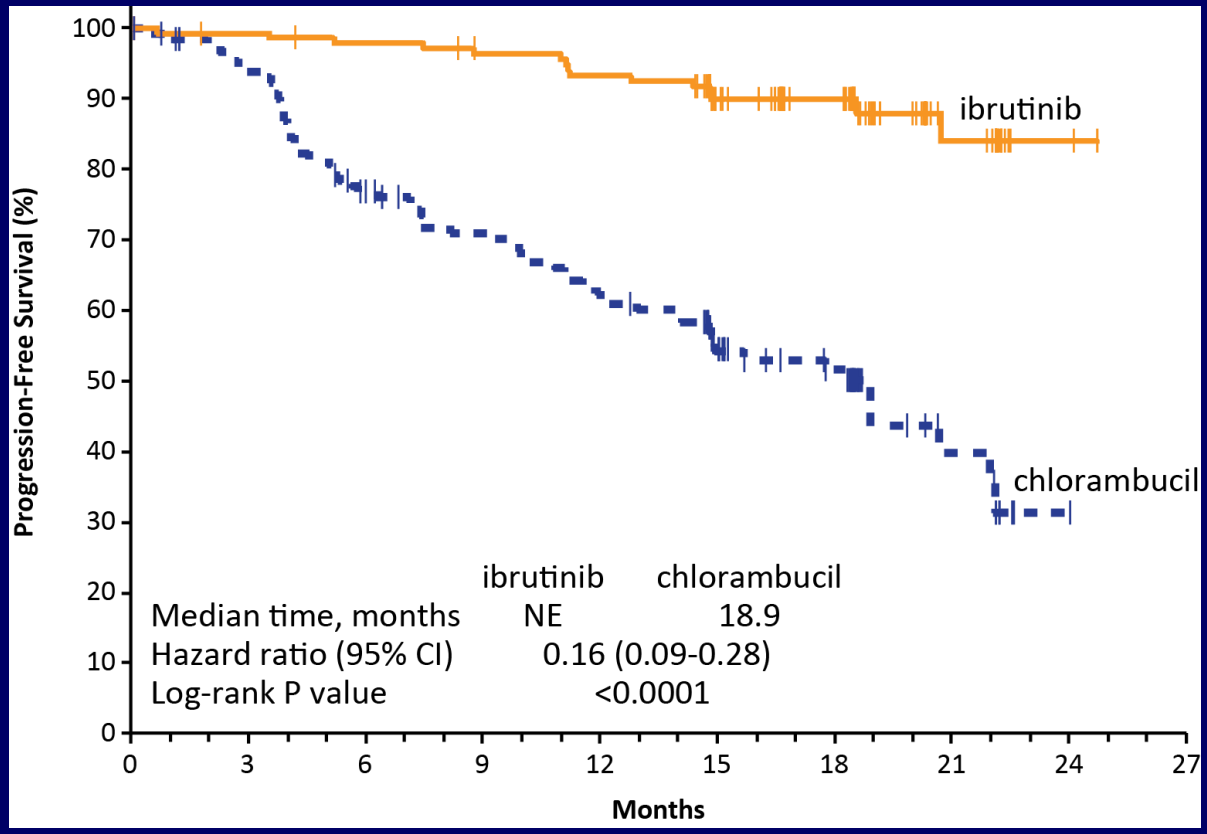
In clb arm, n=43 crossed over to ibrutinib

*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

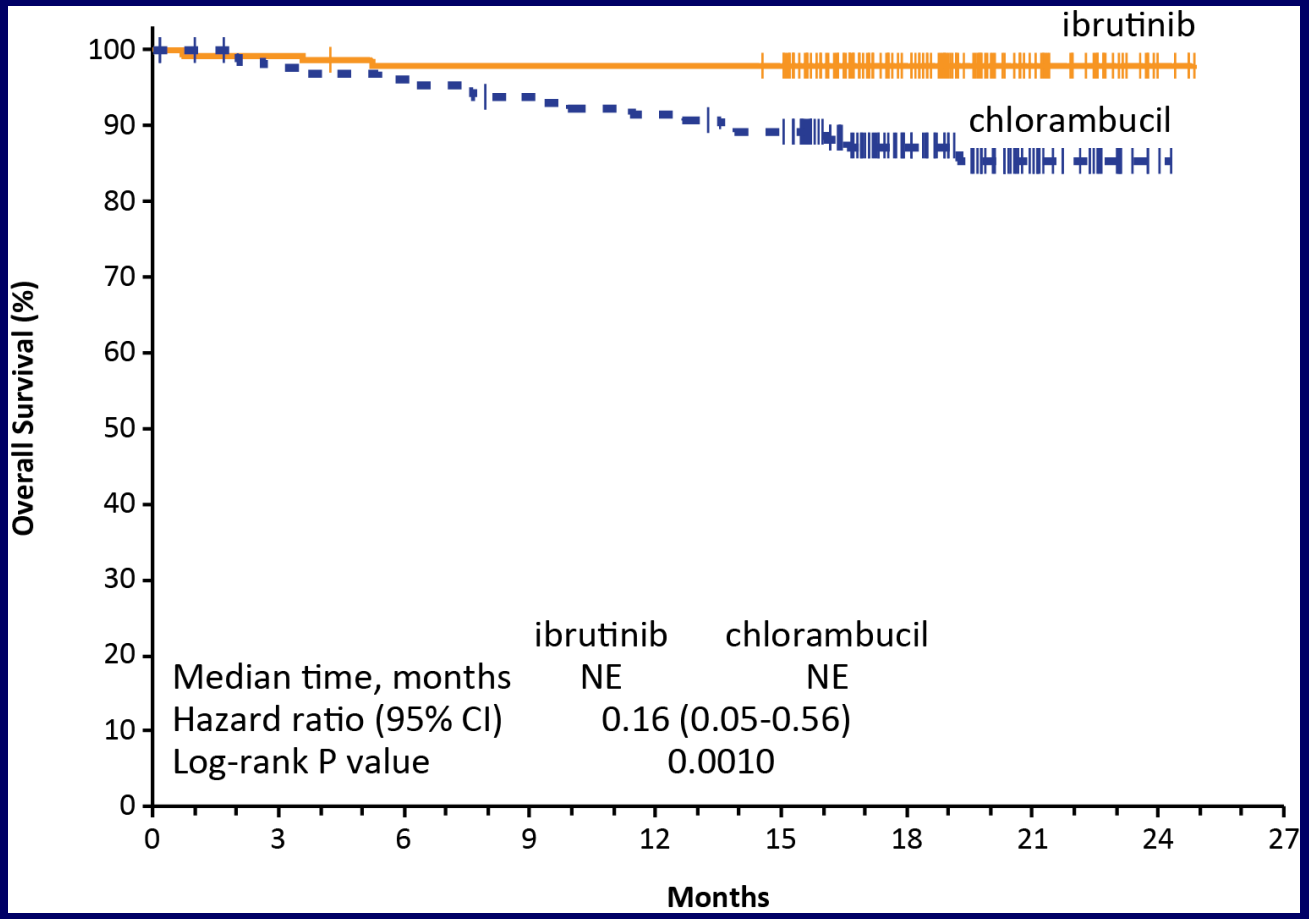
1. Hallek et al. *Blood*. 2008;111:5446-5456; 2. Hallek et al, *Blood.* 2012; e-letter, June 04, 2012.

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**

Overall Survival



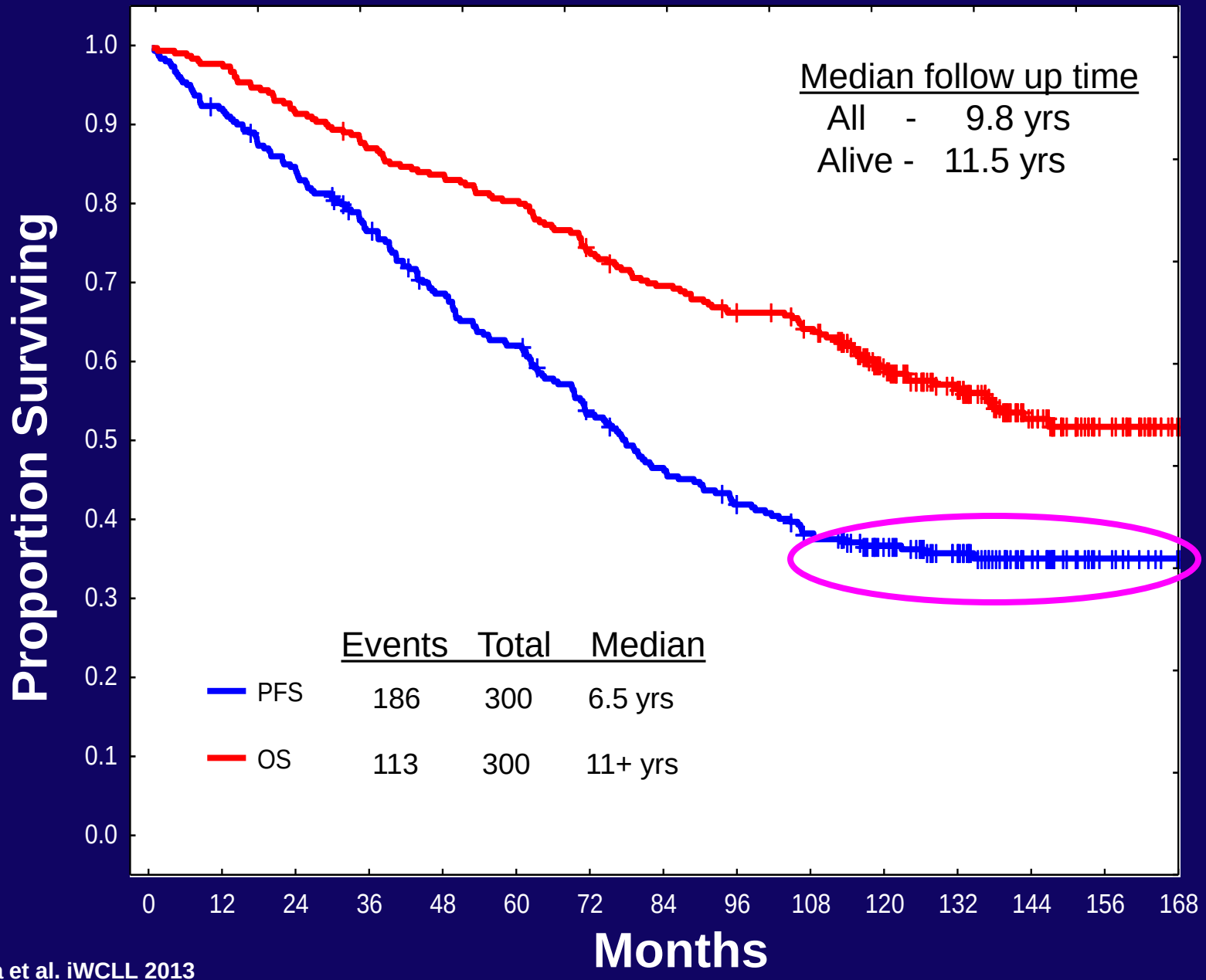
- **84% reduction in risk of death with ibrutinib**
- **24-month OS rate: 98% with ibrutinib and 85% with chlorambucil**
- **3 deaths on ibrutinib arm vs. 17 deaths on chlorambucil arm**

Response to FC + Rituximab (NCI-WG: 300 Patients)

Response*	# Pts.	(%)	
CR	217	(72)	95%
Nodular PR	31	(10)	
PR	37	(12)	
No Response	13	(4)	
Early Death	2	(1)	

* Evaluated 6 months after last course

FCR300: Progression-Free & Overall Survival



Wierda et al. iWCLL 2013

First-Line FCR: 2008 NCI-WG Response and Bone Marrow MRD Status

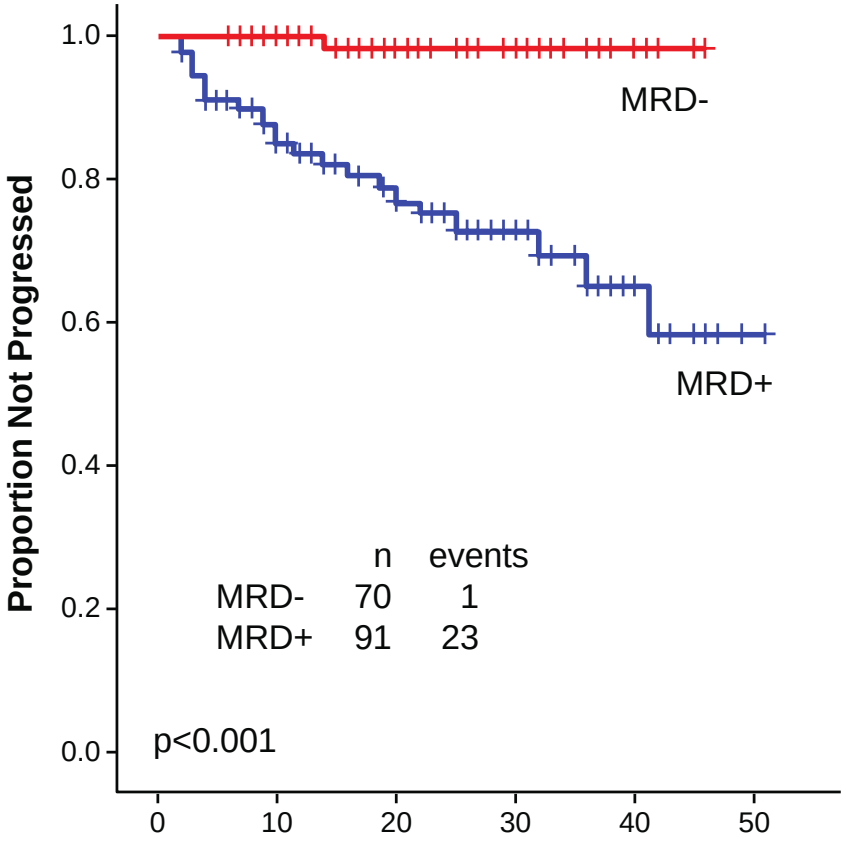
NCI-WG Response	n	% of Patients	% MRD-Negative*
CR	154	65	63
CRi	17	7	33
nPR	28	12	0
PR	31	13	17
NR	7	3	0
Overall MRD	161	68	43

*Bone marrow evaluation by 4-color flow cytometry (sensitivity .01%)

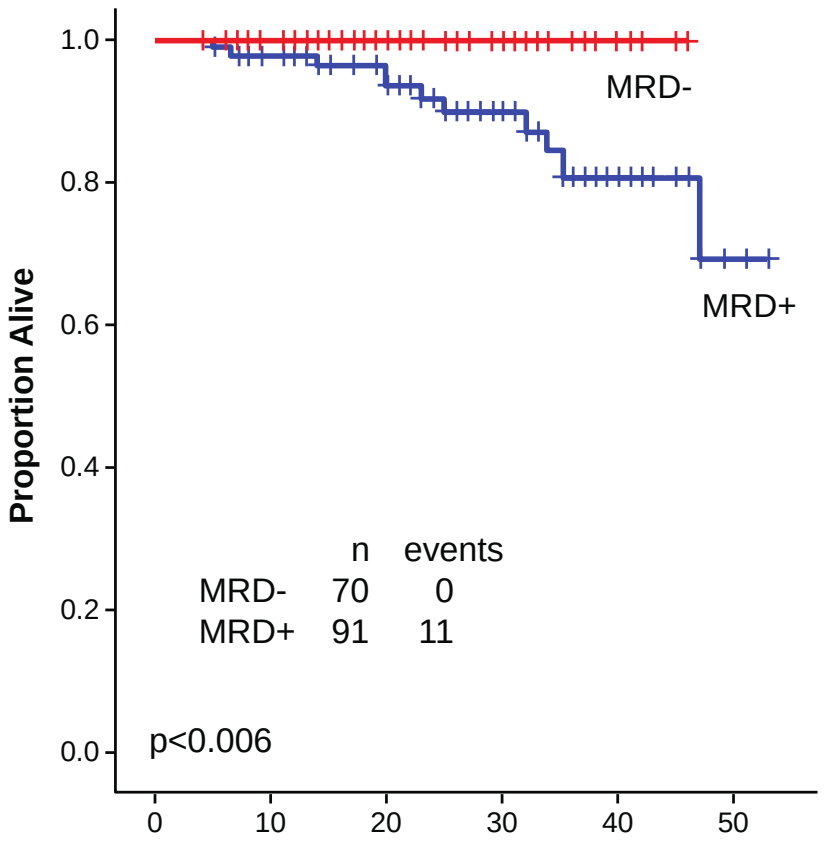
Strati et al. Blood. 2014; June 12; 123(24): 3797-802

First-Line FCR: PFS and OS Outcomes by MRD Status

Progression-free Survival



Overall Survival



Strati et al. Blood. 2014; June 12; 123(24): 3797-802

First-Line FCR: Multivariable Model for Progression-Free Survival

Characteristics	HR (95% CI)	*P*-value
Absence of 17p del	0.08 (0.02-0.3)	<.001
Complete remission	0.2 (0.05-0.6)	.007
Overall remission	0.1 (0.03-0.5)	.003
MRD-negative	0.1 (0.01-0.8)	.03

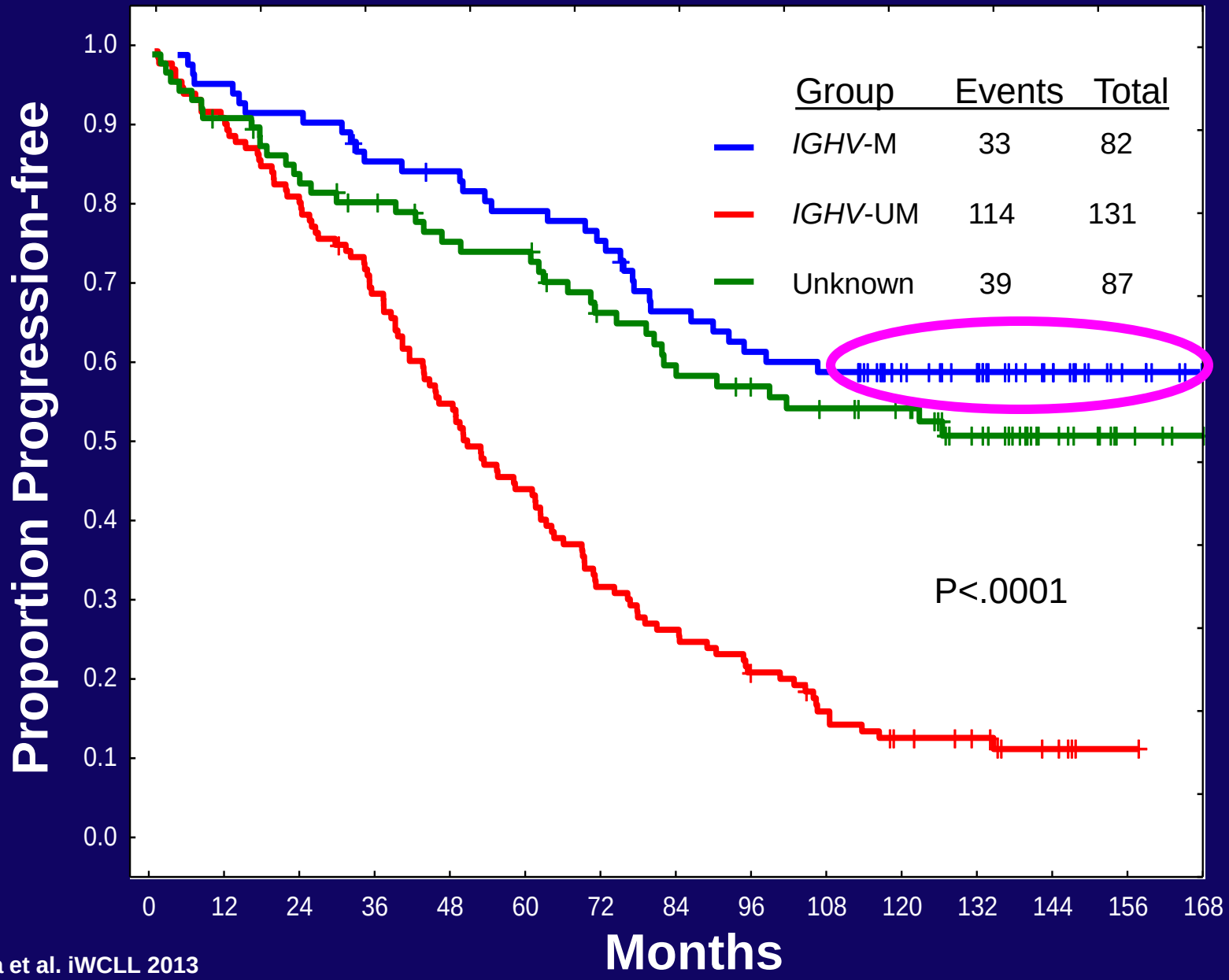
Strati et al. Blood. 2014; June 12; 123(24): 3797-802

First-Line FCR: Multivariable Model for Bone Marrow MRD-Negative Status

Pretreatment characteristic	OR (95% CI)	*P*-value
IGHV mutated	2.7 (1.1-6.3)	.02
Trisomy 12	2.7 (1.1-7.2)	.05

Strati et al. Blood. 2014; June 12; 123(24): 3797-802

FCR300: PFS by *IGHV* Mutation Status



Wierda et al. iWCLL 2013

Conclusions

- FCR best standard of care
  - Not in 17p deletion or older patients

- BCR inhibitors changing the CLL landscape
  - Ibrutinib now has a frontline indication
    For everyone?
  - Idelalisib, given with rituximab
    high response rates but increased side effects in previously untreated patients

- Venetoclax (BCL-2 inhibitor):
  high response rates in relapse
  approved 4/16 for relapsed 17p deletion

- 33% of FCR patients disease free 10+ yrs
  - Mutated, trisomy 12, no 17p or 11q
  - How do we best assure doing no harm while incorporating novel agents?