NCCN 10th Annual Congress:
Hematologic Malignancies™

Optimizing Small Molecular Inhibitor Therapy for Chronic Lymphocytic Leukemia

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NCCN National Comprehensive Cancer Network®

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IWCLL-NCI: Indications to Initiate Treatment for CLL

- Constitutional symptoms referable to CLL
- Progressive marrow failure
- Autoimmune anemia +/- thrombocytopenia poorly responsive to steroids or other
- Massive (>6 cm) or progressive splenomegaly
- Massive (>10 cm) or progressive lymphadenopathy
- Progressive lymphocytosis, >50% increase over 2 months or LDT < 6 months
- **NO EARLY TREATMENT, EVEN FOR HIGH-RISK**

Hallek et al. (IWCLL) Blood 2008;111:5446-5456

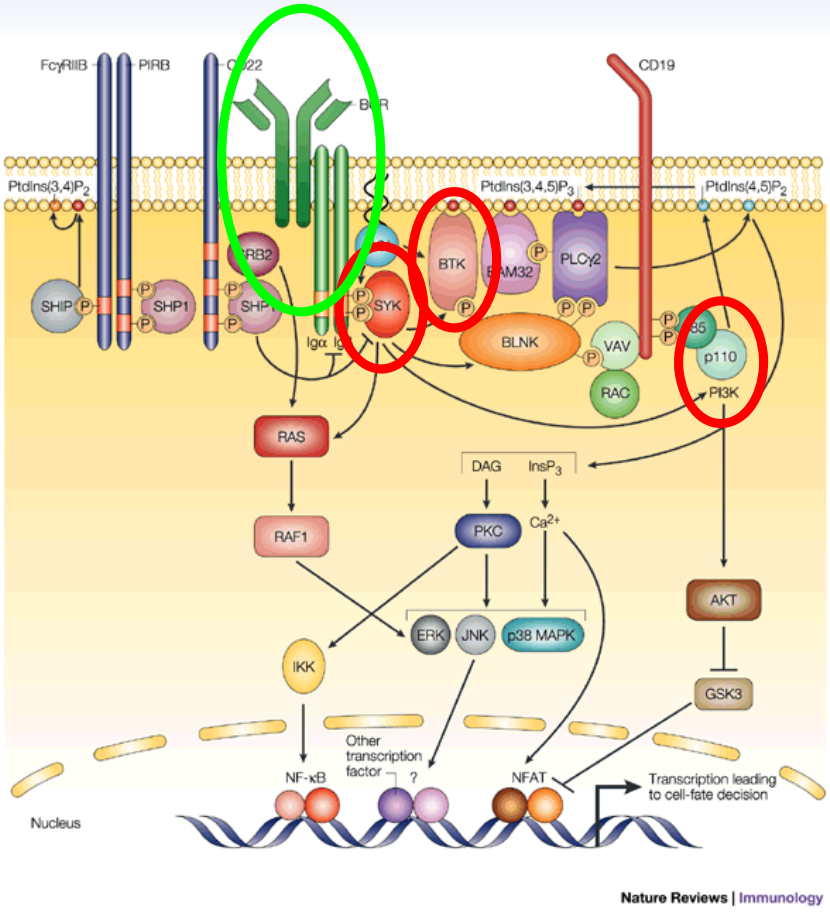
CLL Patient Populations and "Standards of Care"

- Untreated, high-risk - watch and wait
- First-line therapy (consider age and FISH)
  - Fit CIT-eligible – FCR
  - Elderly – chlorambucil+CD20 mAb → ibrutinib
  - Del(17p) - ibrutinib
- Salvage treatments for active disease
  - BTK-inhibitor (ibrutinib)
  - PI3-K-inhibitor (idelalisib) + rituximab
- Richter's transformation – intensive CIT, SCT

New Agents Changing Treatment for Patients with CLL

Agent	Development Phase
BTK inhibitors	
Ibrutinib	**Approved**
ONO-4059	**Phase I**
ACP-196	**Phase III**
PI3KY/δ inhibitors	
Idelalisib	**Approved**
GS-9820	Phase I
Duvelisib (IPI-145)	**Registration Phase III**
AMG/ACP-319	**Phase I**
TGR-1202	**Phase III**
SAR245408 (XL147)	Phase I
Syk inhibitors	
GS-9973	Phase II
Fostamatinib	Phase I/II
PRT-2070	Phase I
BCL-2 inhibitor	
Venetoclax (ABT-199)	Phase III

Targeting of BCR Signaling in CLL

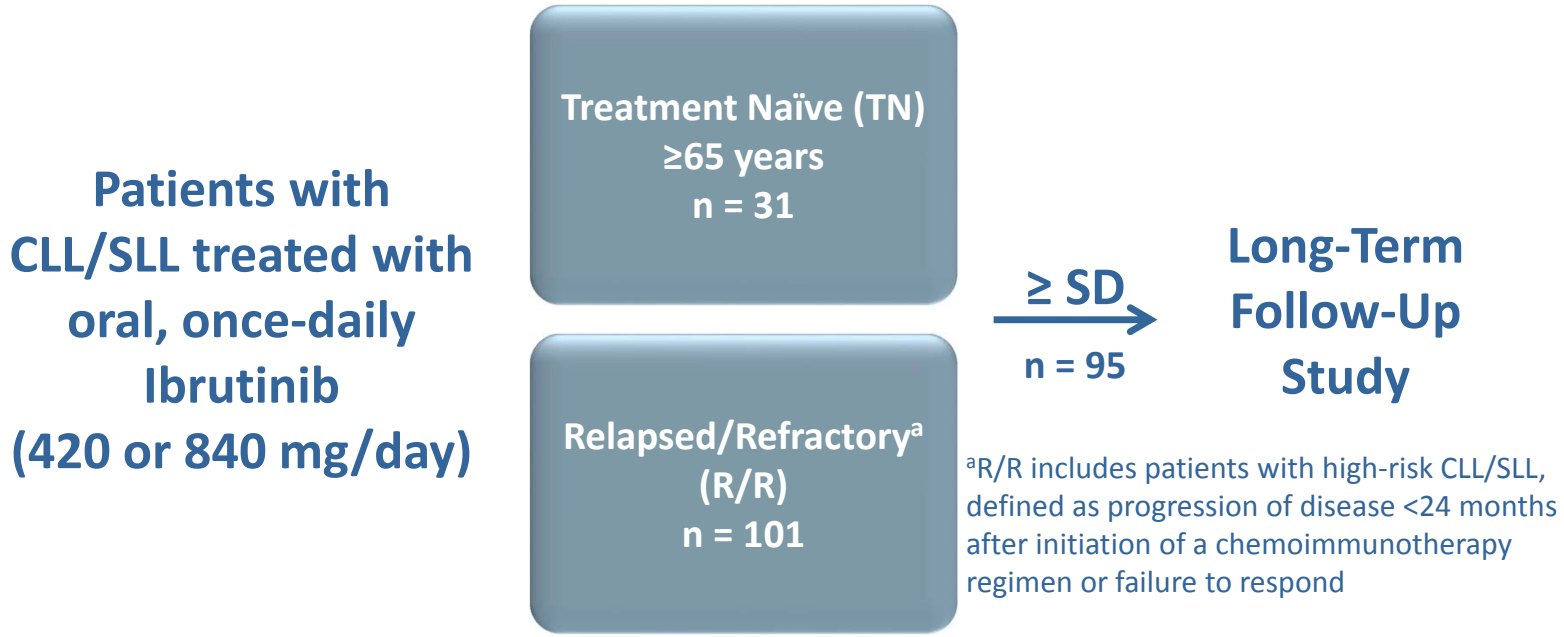


From: Nat Rev Immunol 2:945

- **BCR-associated kinases are targets of new drugs in clinical development**
- **Btk (Bruton's tyrosine kinase) inhibitors: Ibrutinib, ACP-196, CC-292**
- **PI3 kinase inhibitors: Isoform-Selective Inhibitor of PI3-Kinases[1], Idelalisib, Duvelisib (IPI-145), TGR-1202**
- **Syk (spleen tyrosine kinase) inhibitors: GS-9973, Fostamatinib, PRT-2070[2]**

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

PCYC-1102/1103 Phase 2 Study Design

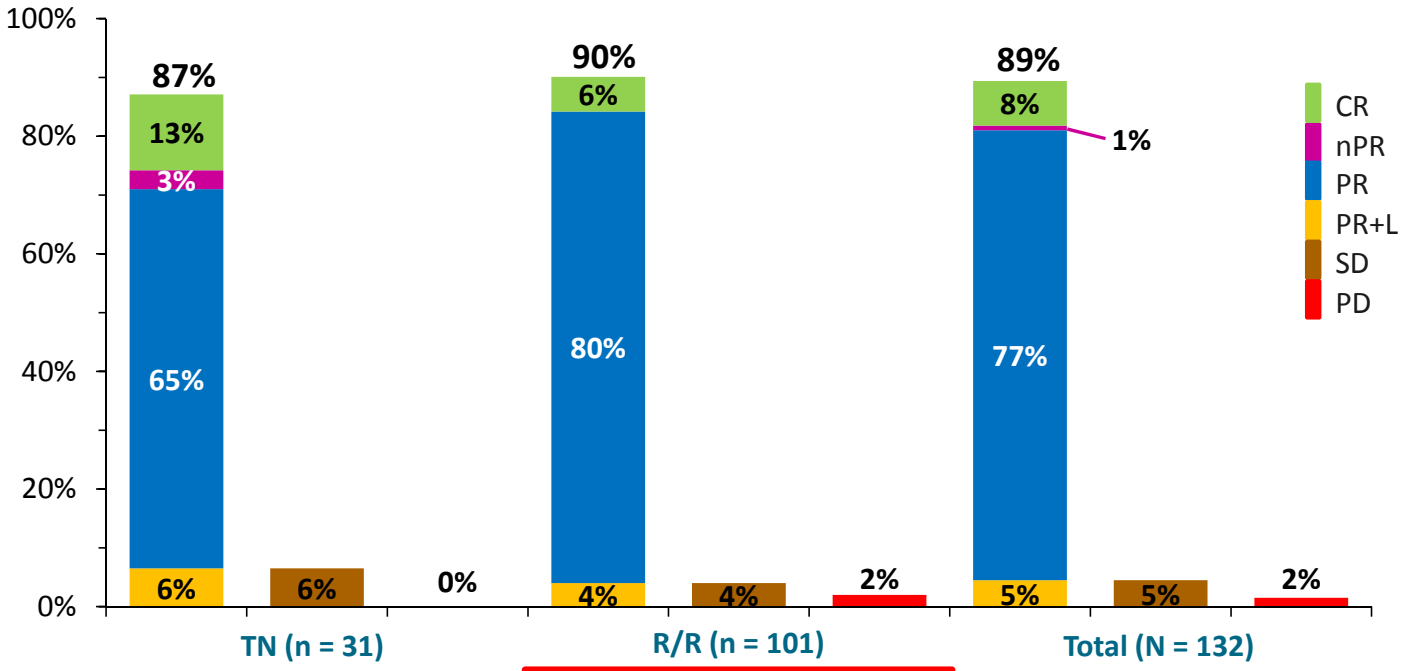


[a]R/R includes patients with high-risk CLL/SLL, defined as progression of disease <24 months after initiation of a chemoimmunotherapy regimen or failure to respond

- Phase 2 (PCYC-1102) and extension (PCYC-1103) study
  - 132 patients with treatment-naïve (TN) or relapsed/refractory (R/R) CLL/SLL
  - efficacy and safety
  - 3 years follow-up

American Society of Clinical Oncology 2014, PCYC 1102/1103, O'Brien et al.

Best Response (Investigator-Assessed)

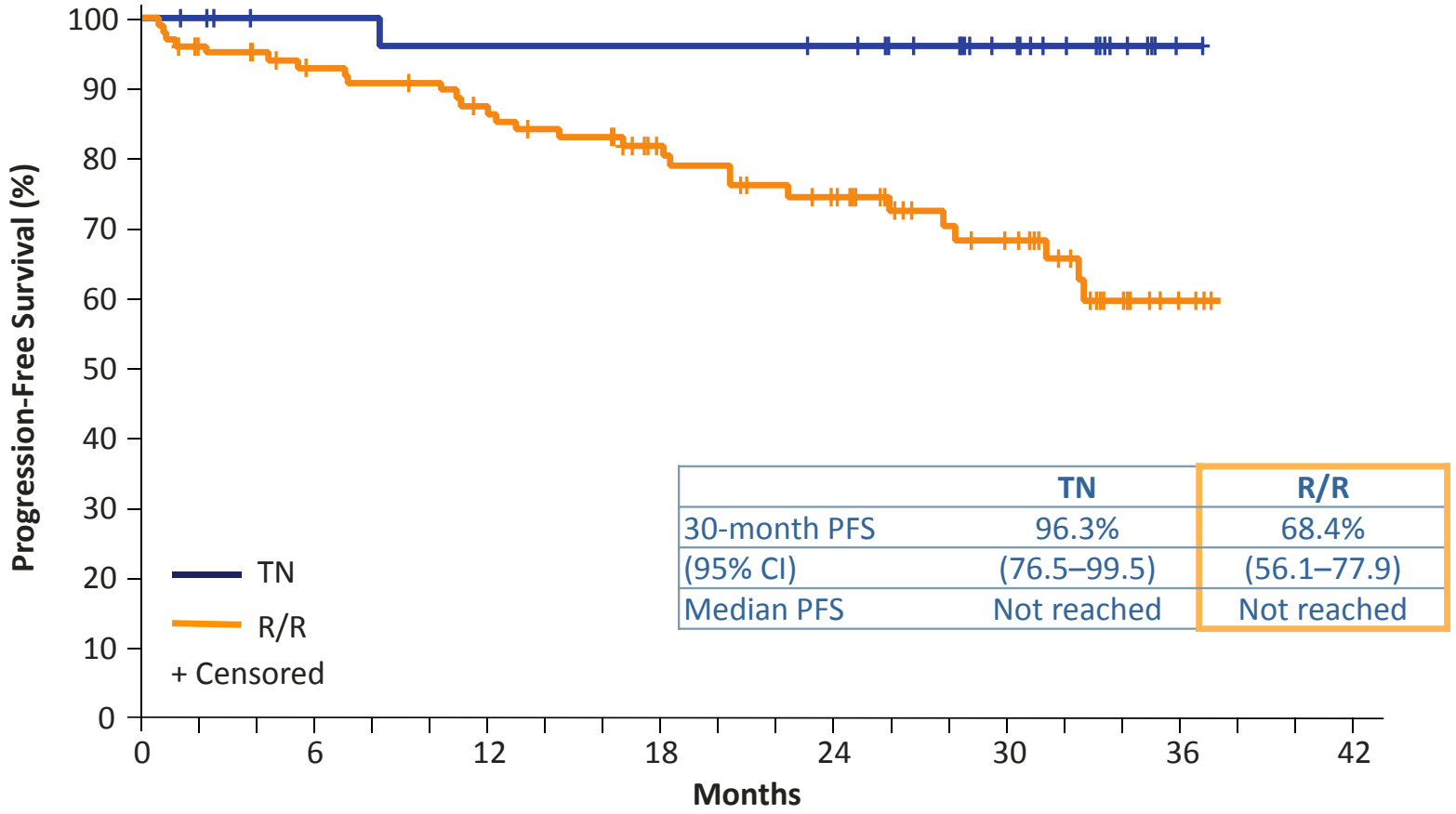


	TN (n = 31)	R/R (n = 101)	Total (N = 132)
Median DOR in months (range)	NR (0 to 35.0+)	NR (0 to 35.2+)	NR (0 to 35.2+)
Month 30 (95% CI)	100.0% (NE)	79.1% (64.2 to 88.4)	85.3 (74.4 to 91.8)

- 5/6 patients who received prior idelalisib responded to ibrutinib (4PR, 1 PR+L)
- 2/5 responders continue treatment with one additional patient moving on to SCT

American Society of Clinical Oncology 2014, PCYC 1102/1103, O'Brien et al.

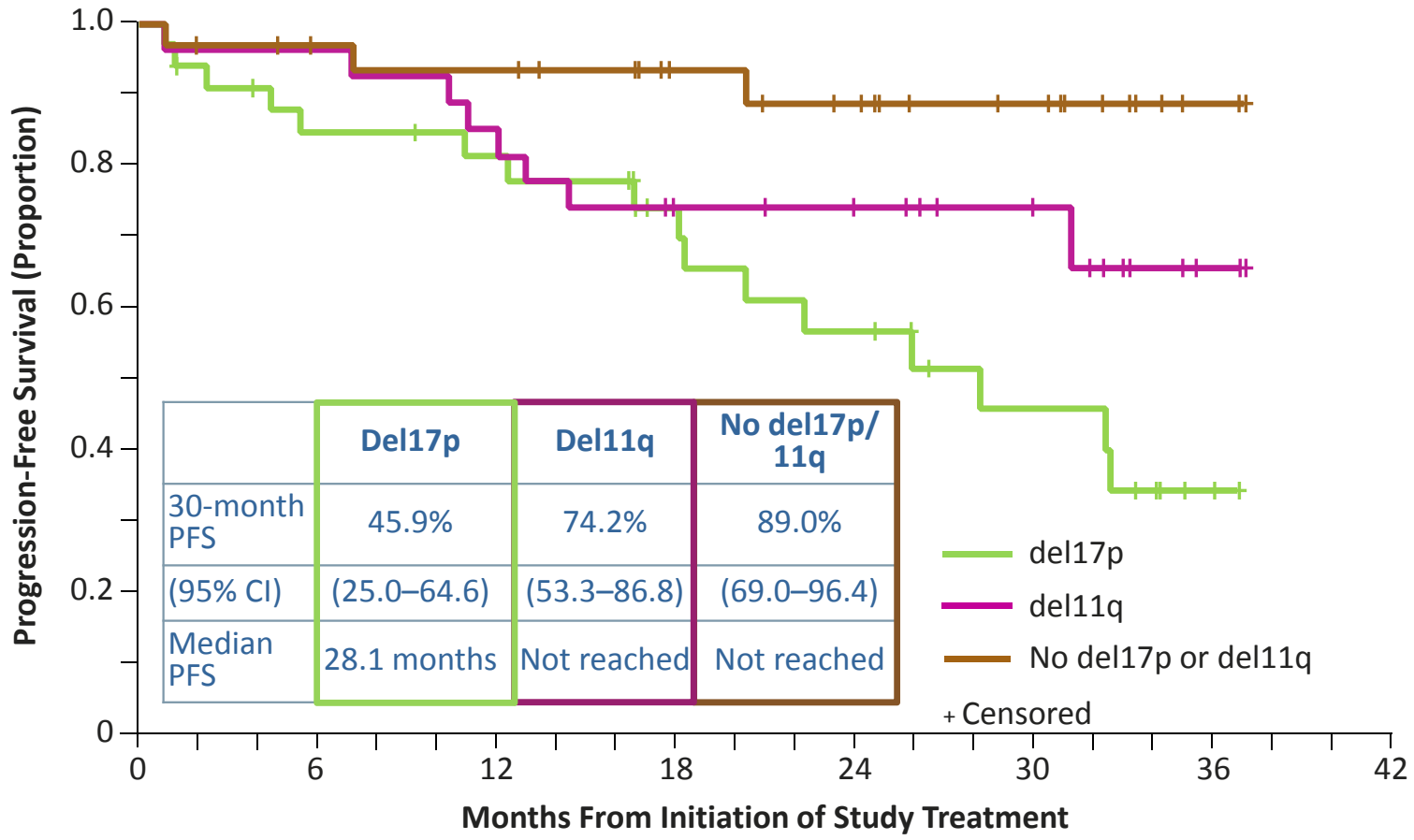
Progression-Free Survival



	TN	R/R
30-month PFS	96.3%	68.4%
(95% CI)	(76.5–99.5)	(56.1–77.9)
Median PFS	Not reached	Not reached

American Society of Clinical Oncology 2014, PCYC 1102/1103, O'Brien et al.

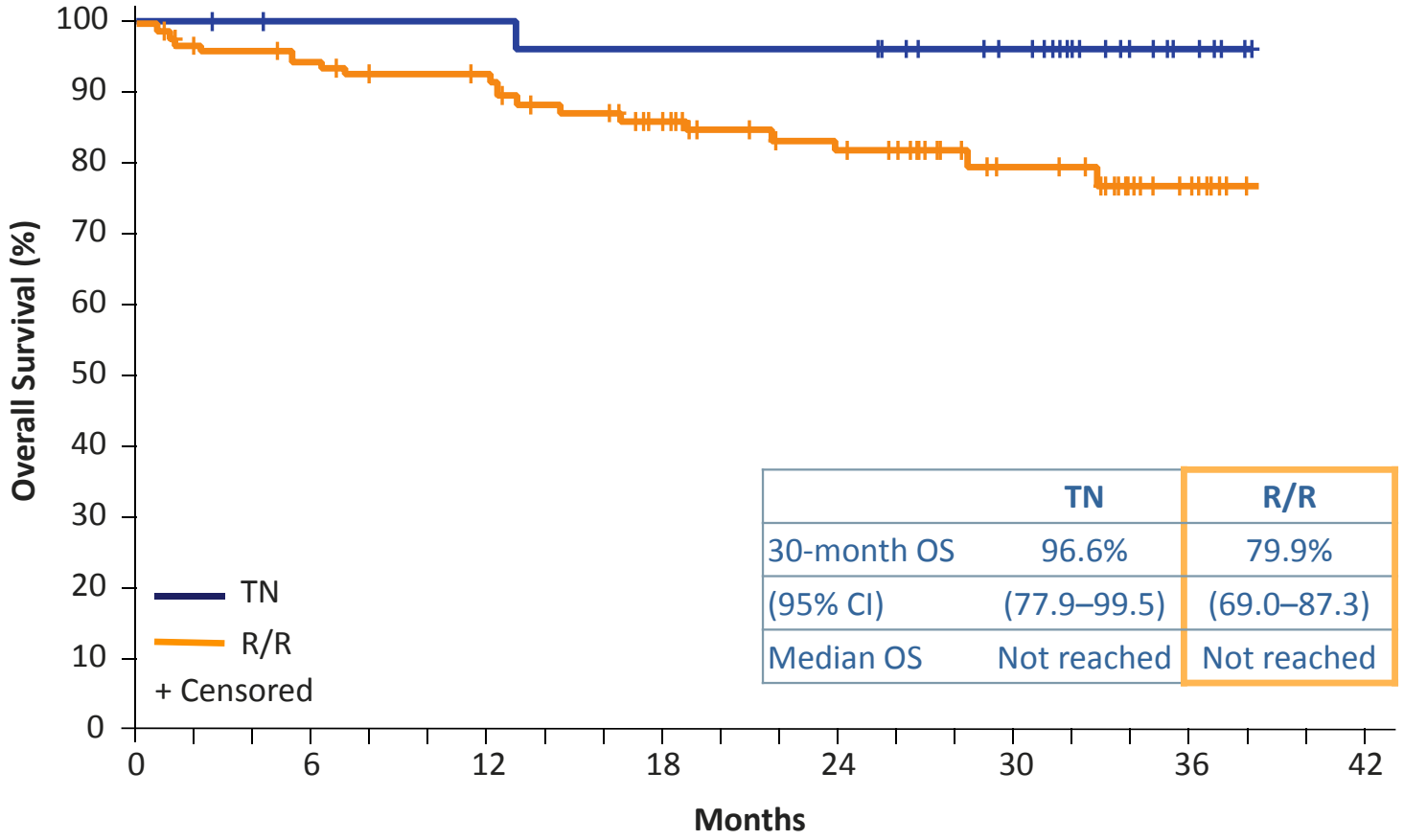
Progression-Free Survival by Cytogenetics (FISH) in Relapsed/Refractory CLL



	Del17p	Del11q	No del17p/ 11q
30-month PFS	45.9%	74.2%	89.0%
(95% CI)	(25.0–64.6)	(53.3–86.8)	(69.0–96.4)
Median PFS	28.1 months	Not reached	Not reached

American Society of Clinical Oncology 2014, PCYC 1102/1103, O'Brien et al.

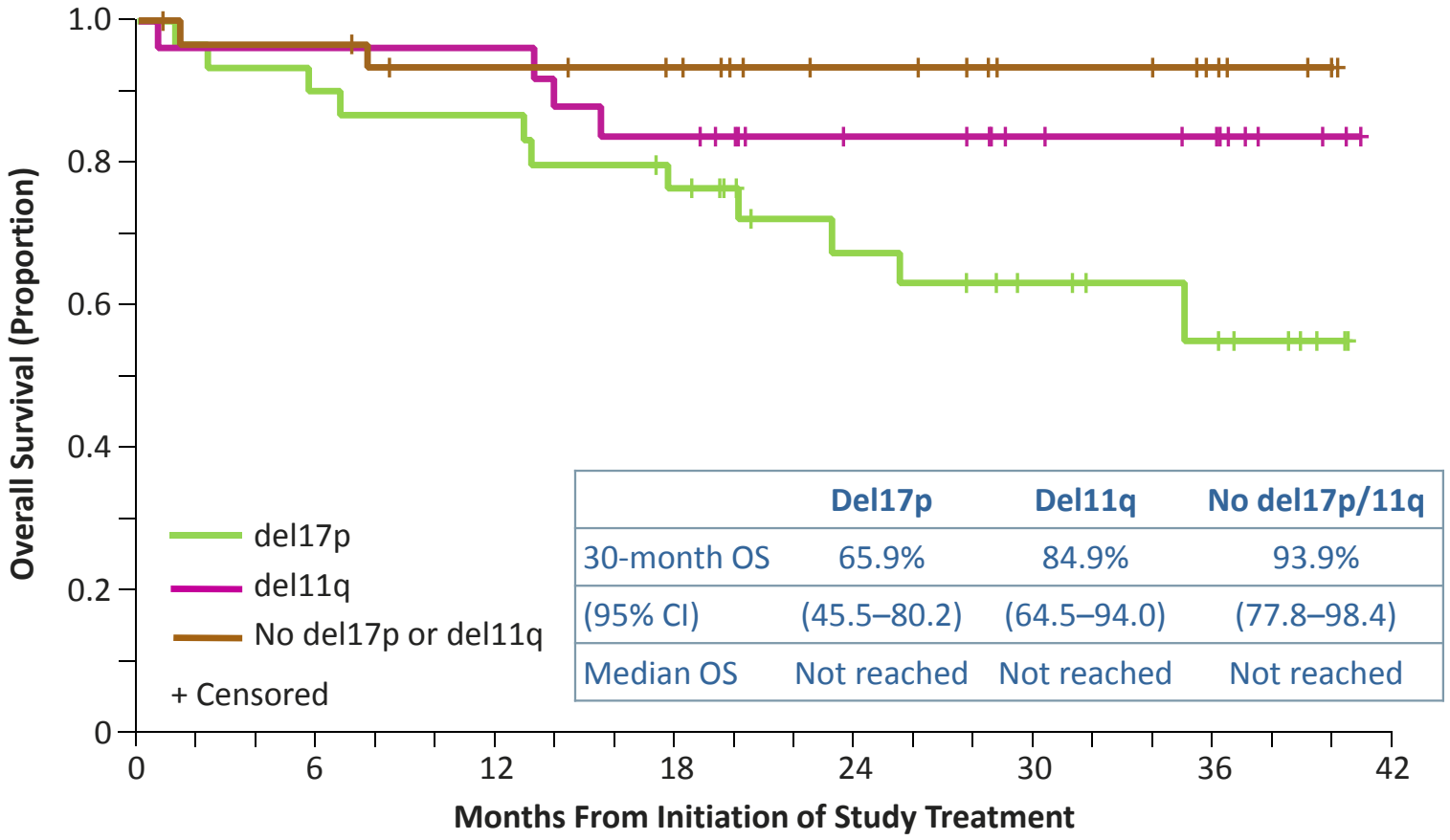
Overall Survival



	TN	R/R
30-month OS	96.6%	79.9%
(95% CI)	(77.9–99.5)	(69.0–87.3)
Median OS	Not reached	Not reached

American Society of Clinical Oncology 2014, PCYC 1102/1103, O'Brien et al.

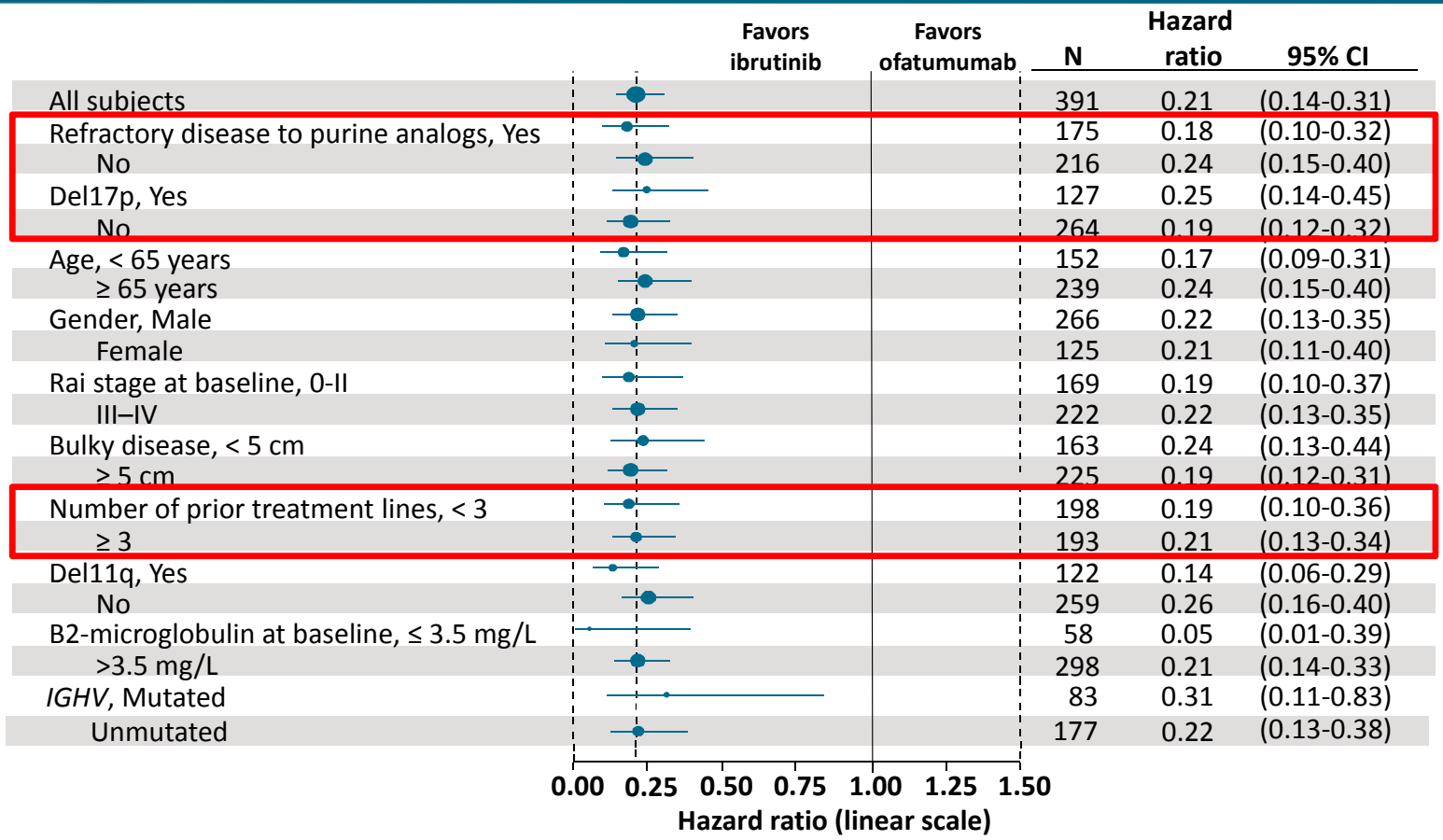
Overall Survival by Cytogenetics (FISH) in Relapsed/Refractory CLL



	Del17p	Del11q	No del17p/11q
30-month OS	65.9%	84.9%	93.9%
(95% CI)	(45.5–80.2)	(64.5–94.0)	(77.8–98.4)
Median OS	Not reached	Not reached	Not reached

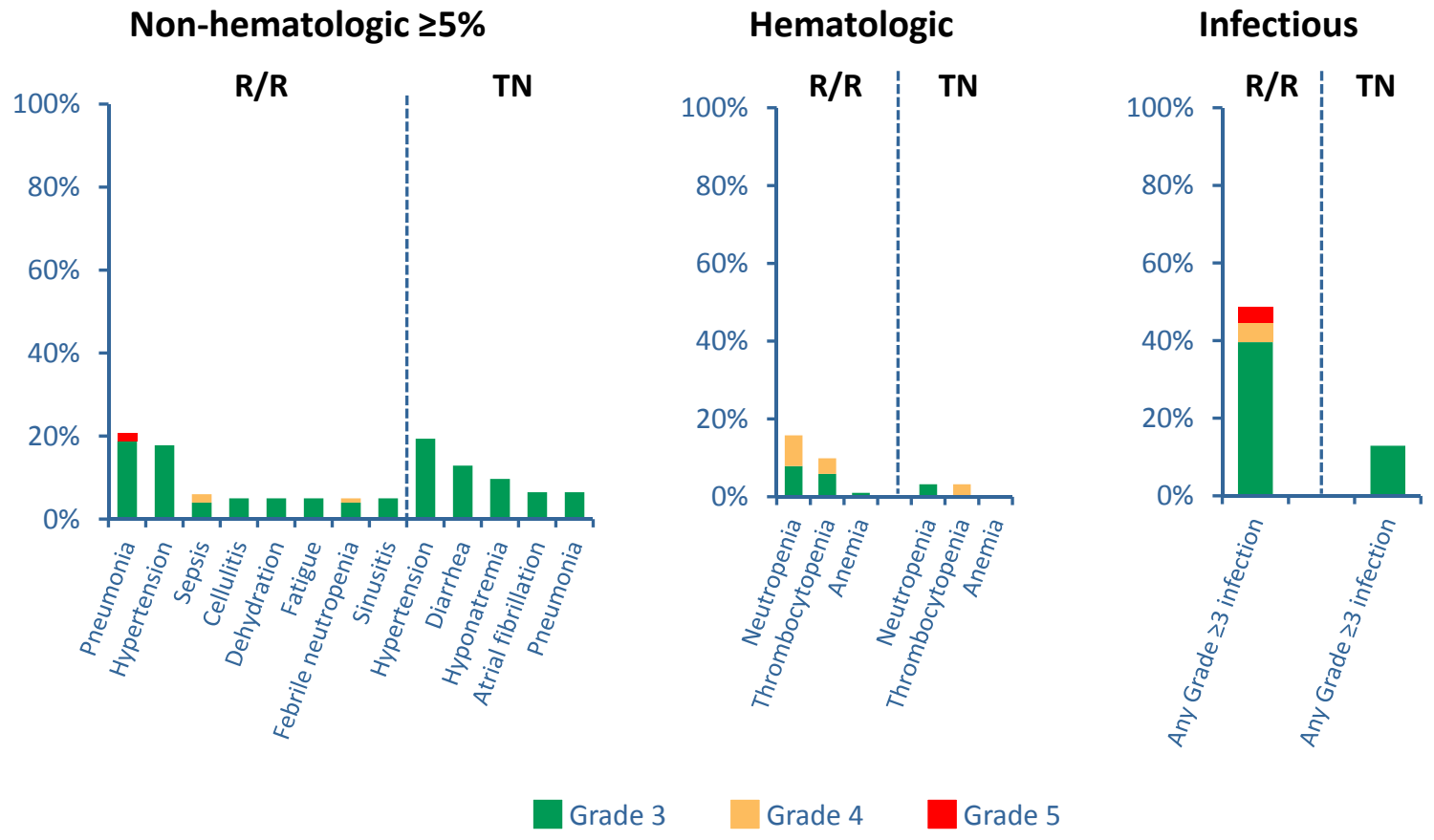
American Society of Clinical Oncology 2014, PCYC 1102/1103, O'Brien et al.

RESONATE: Progression-Free Survival by Baseline Characteristics and Molecular Features



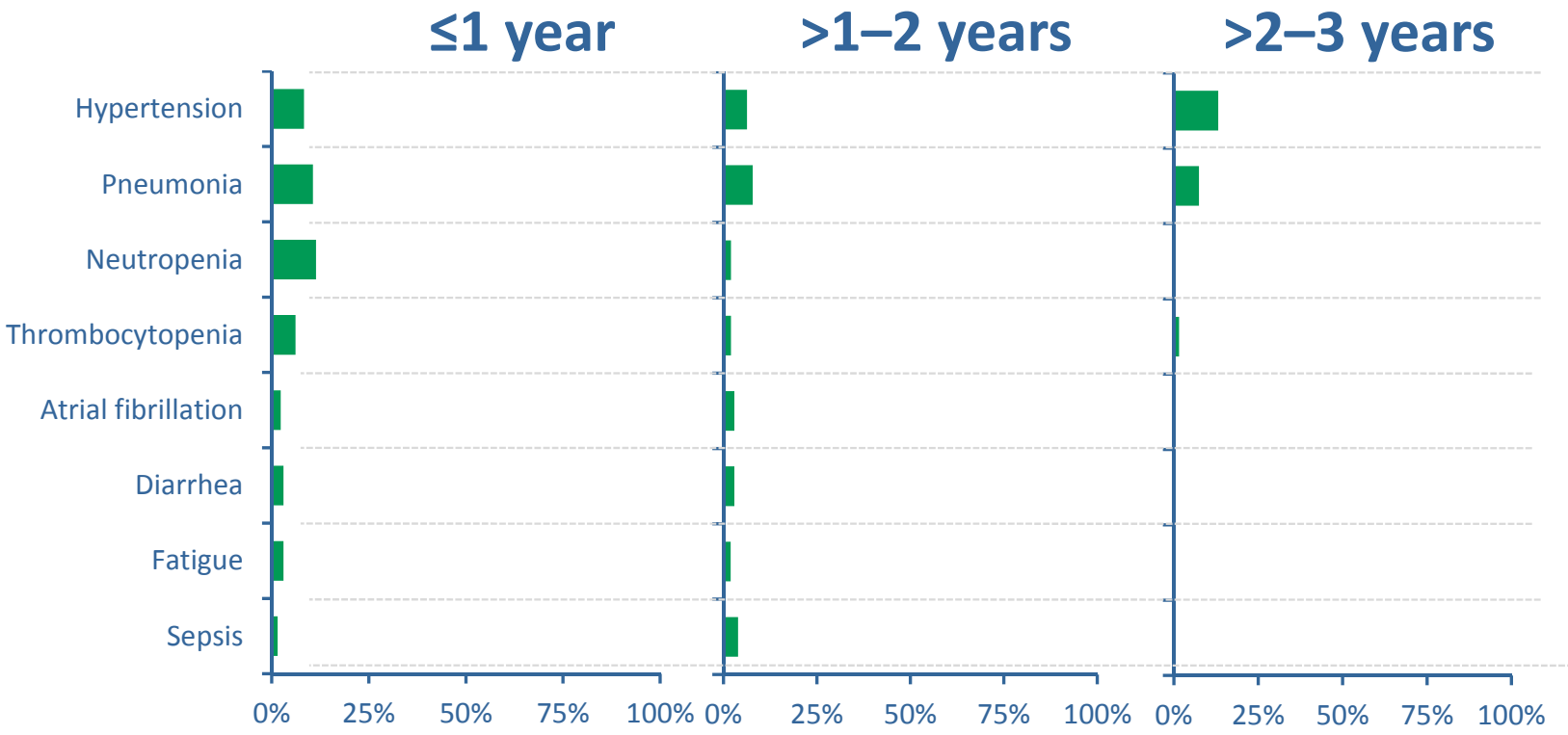
Byrd et al. ASCO 2014, Abstract LBA7008

Safety: Frequency of Grade ≥3 Adverse Events



American Society of Clinical Oncology 2014, PCYC 1102/1103, O'Brien et al.

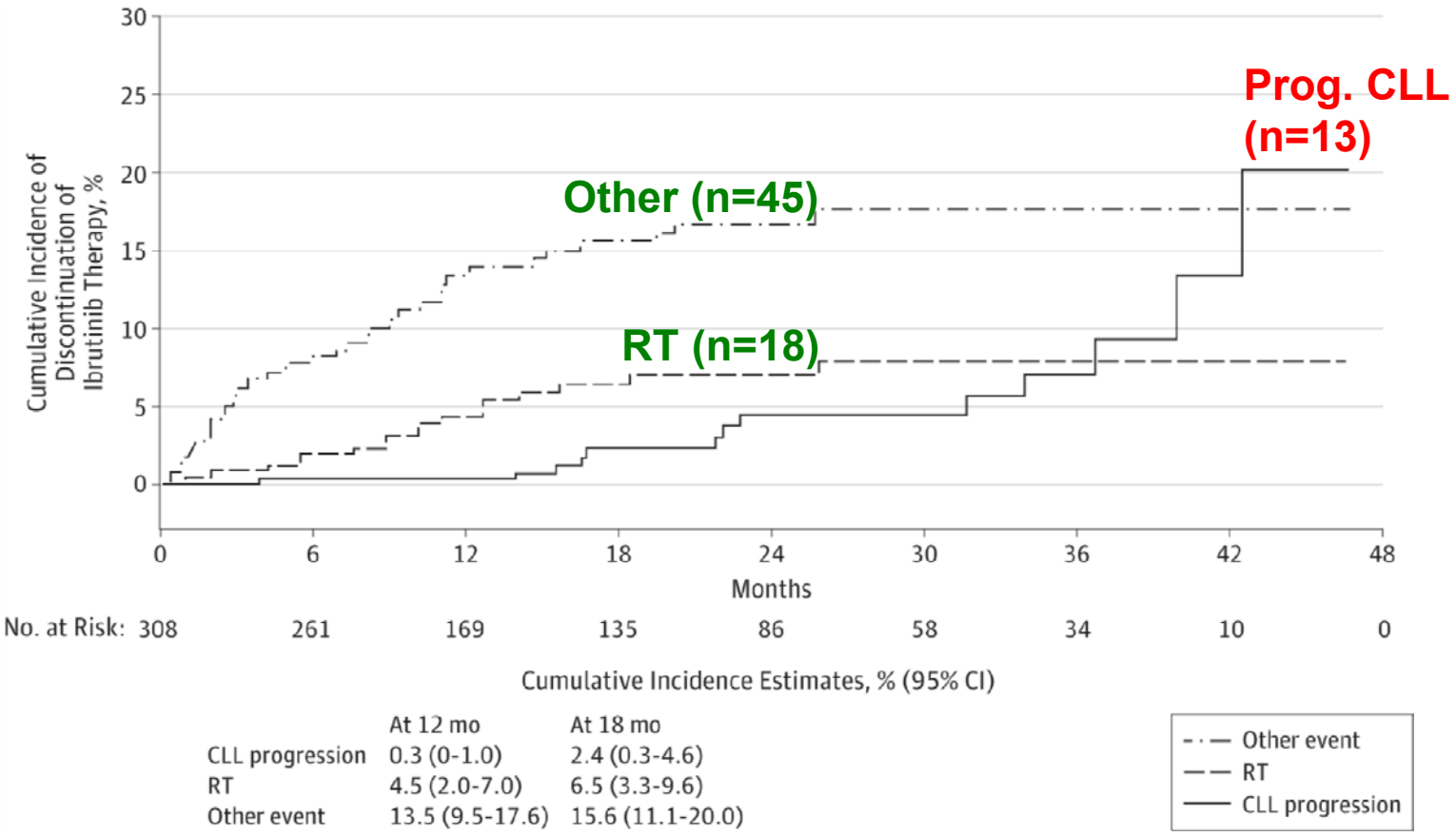
Safety: Grade ≥3 Adverse Events by Time to Event Onset*



*Listed adverse events include those that occurred in ≥5% of patients in all-treated population; denominator for each term and time period can vary based on those at risk

American Society of Clinical Oncology 2014, PCYC 1102/1103, O'Brien et al.

Reasons for Ibrutinib Discontinuation



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

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

Deep Sequencing of 13 Patients Who Relapsed on Ibrutinib

					Baseline		Relapse	
Patient No.	Type of Relapse	Chromosome	Gene	AA Change	Coverage	Variant Frequency, %	Coverage	Variant Frequency, %
1	CLL	16	*PLCG2*	R665W	870	0	9977	5.5
		16	*PLCG2*	S707P	2940	0	9980	5.3
		16	*PLCG2*	S707F	2937	0	9996	3.3
		16	*PLCG2*	R742P	1623	0	9987	6.1
		16	*PLCG2*	L845fs	1200	0	5436	14.9
2	CLL	16	*PLCG2*	R665W	3230	0	9252	45.0
3	CLL	X	*BTK*	C481F	1837	0	6687	84.0
4	CLL	X	*BTK*	C481S	2730	0	4417	16.9
5	CLL	16	*PLCG2*	R665W	3465	0	2781	2.0
		16	*PLCG2*	S707Y	8456	0	2346	6.6
		16	*PLCG2*	L845F	3431	0	1025	23.8
		X	*BTK*	C481S	875	0	7429	6.8
6	CLL	X	*BTK*	C481S	2086	0	5903	37.8
7	CLL	X	*BTK*	C481S	4453	0	490	47.5
8	CLL	X	*BTK*	C481S	1210	0	2689	74.7
9	CLL	X	*BTK*	C481S	2260	0	8699	6.0
10	CLL	16	*PLCG2*	D1140G	1372	0	5974	13.5
		X	*BTK*	C481S	3109	0	6941	13.0
11	CLL	X	*BTK*	C481S	1119	0	4638	5.4/3.4[b]
12	RT	X	*BTK*	C481S	1622	0	497	51.9
		X	*BTK*	T474I	264	0	112	4.0
		X	*BTK*	T474S	264	0	112	4.0
13	RT	16	*PLCG2*	D334H	629	0	27622	5.7
		X	*BTK*	C481Y	487	0	16800	28.7
		X	*BTK*	C481R	488	0	17699	24.2
		X	*BTK*	L528W	310	0	9994	7.9

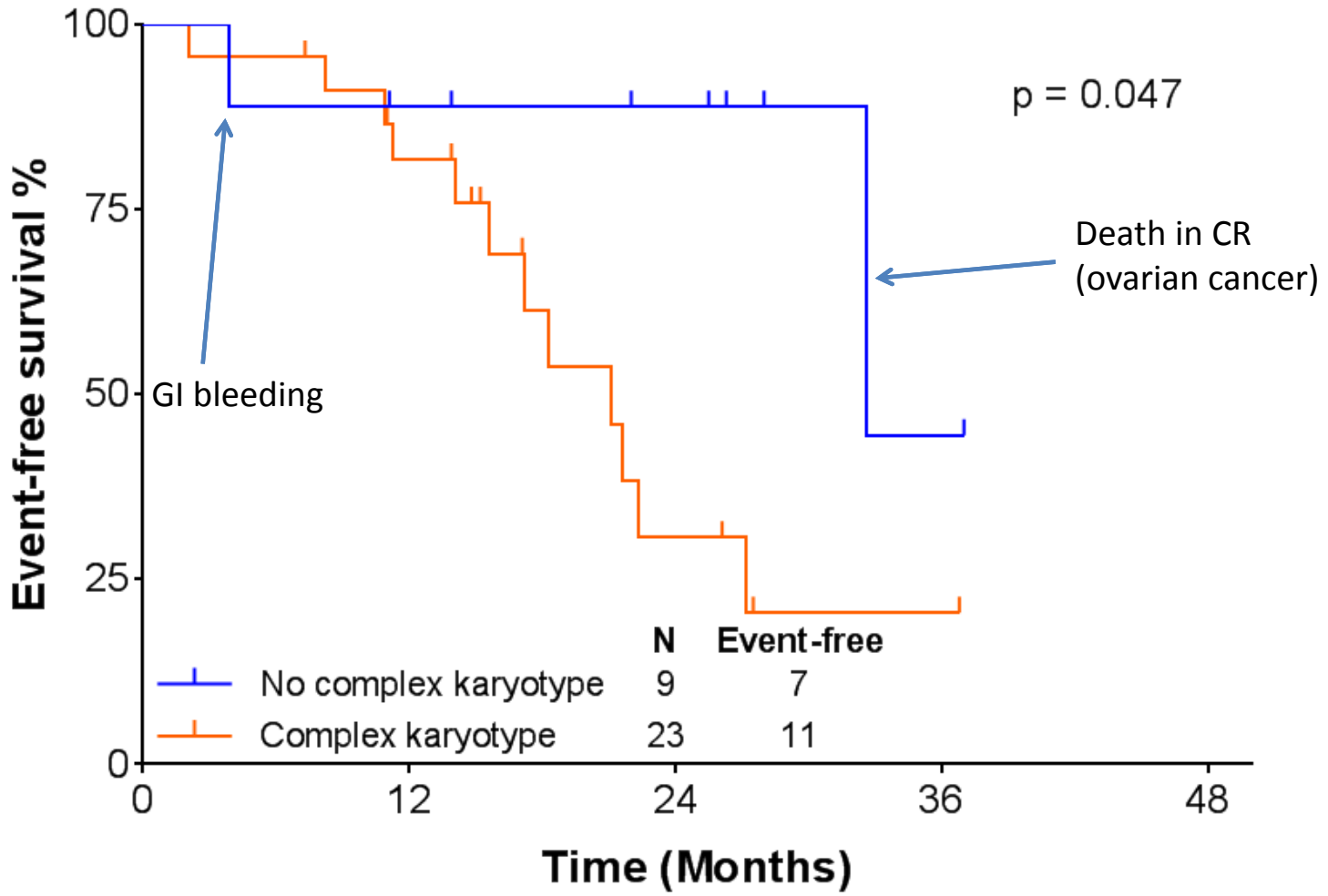
Abbreviation: CLL, chronic lymphocytic leukemia; RT, Richter's transformation.

[a] Seven patients with RT did not have mutations identified in *BTK* or *PLCG2* with similarly deep coverage and are not included.

[b] Patient with 2 different mutations that both resulted in C481S change.

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

EFS in Patients with del(17p) by Karyotype Complexity



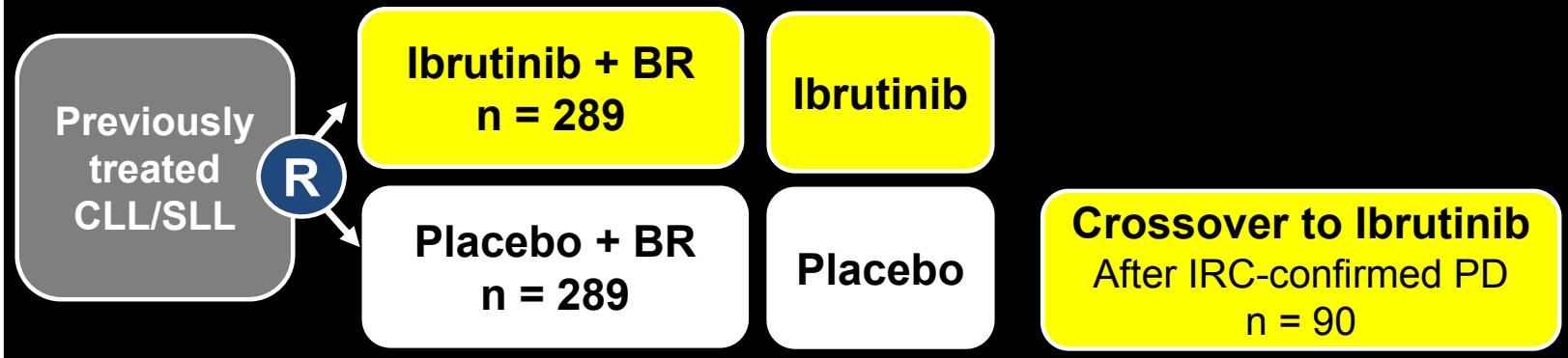
Thompson et al., ASH 2014, Abstract 22

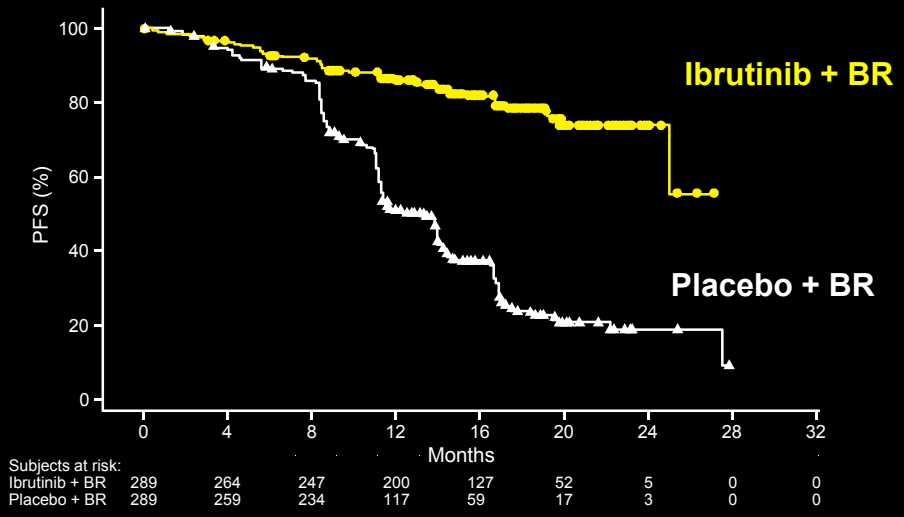
Multivariable Survival Analysis

Variable	HR (95% CI)	p Value
Fludarabine-refractory disease	6.4 (1.8-22.8)	0.004
Complex karyotype	5.7 (1.5-22.2)	0.011
β_2-microglobulin ≥4.0	3.0 (0.9-9.8)	0.076
Del(17p) by FISH	0.9 (0.3-3.2)	0.981

Thompson et al., ASH 2014, Abstract 22

Ibrutinib + BR vs Placebo + BR
HELIOS, PFS





- **PFS benefit with ibrutinib + BR in all subgroups analyzed**
- **Median OS, not yet reached in either arm**
- **No significant difference in OS**

Chanan-Khan A, et al. *ASCO Annual Meeting*. 2015. Abstract LBA 7005.

Ibrutinib

- Approved: relapsed CLL; first-line del(17p)
- Monotherapy @ 420 mg once daily-continuous
- Lymphocytosis on start, resolves with Tx
- Potent LN shrinkage, most responses partial, residual disease in blood and marrow
- GI toxicity most common; <5% a. fib. / bleeding
- 90% prog-free @30 mo (non-del(17p)-del(11q)
- Median PFS for relapsed CLL with del(17p) is 28 months
- Improved OS *vs*. ofatumumab in relapsed CLL

Ongoing Studies with Ibrutinib

Agent	Combination or Comparator	Phase – Trial #
Ibrutinib	+ Lenalidomide	I – NCT01886859
	+ Lenalidomide + Rituximab	I – NCT02200848
	+ TGR-1202 (PI3K-I)	I – NCT02268851
	+ TGR-1202 (PI3K-I) + Ublituximab	I – NCT02006485
	+ Selenexor	I – NCT02303392
	+ CC-122 + Rituximab / Obinutuzumab	I/II – NCT02406742
	+ IPH2201 (NKG2A mAb)	I/II – NCT02557516
	+ Fludarabine	II – NCT02514083
	+ FCR	II – NCT02251548
	Benda ➤ Ibrutinib + Obinutuzumab (CLL2-BIG)	II – NCT02345863
	+ Nivolumab (PD-1)	II – NCT02420912
	+ Obinutuzumab (CD20 mAb)	II – NCT02315768
	vs. IR	II – NCT02007044
	+ Venetoclax + Obinutuzumab	II – NCT02427451
	+ Rituximab *vs.* FCR	III – NCT02048813
	vs. Ibrutinib + Rituximab *vs.* BR	III – NCT01886875
	vs. Ibrutinib + Ublituximab	III – NCT02301156
	+ Obinutuzumab *vs.* Chlor + Obinutuzumab	III – NCT02264574

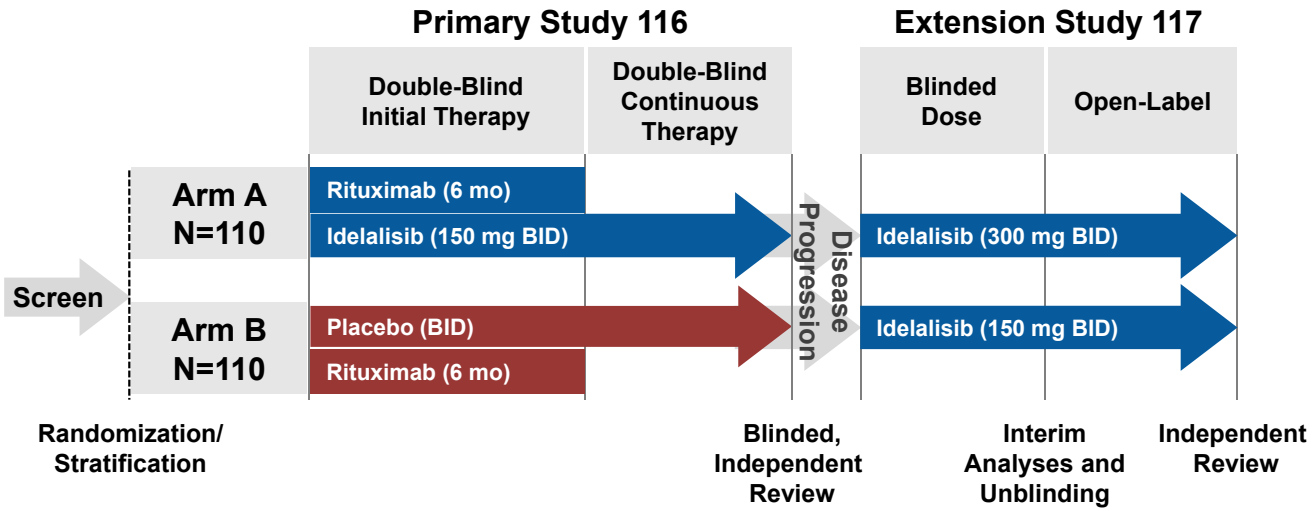
Ongoing Studies with BTK-inhibitors in CLL

Agent	Combination or Comparator	Phase – Trial #
Ibrutinib	Multiple	Multiple
ACP-196	+ Obinutuzumab (CD20 mAb)	I – NCT02296918
	+ ACP-319 (PI3K-Inhibitor)	I/II – NCT02328014
	+ Pembrolizumab (PD-1 mAb)	II – NCT02351739
	vs. Ibrutinib (BTK-Inhibitor)	III – NCT02477696
	vs. ACP-196 + Obinutuzumab *vs.* Chlor + Obin	III – NCT02475681
BGB-3111	Monotherapy	I – NCT02343120
ONO-4059	+ Idelalisib (PI3K-I)	I – NCT02457598

New Agents Changing Treatment for Patients with CLL

Agent	Development Phase
BTK inhibitors	
Ibrutinib	**Approved**
ONO-4059	Phase I
ACP-196	Phase I
PI3KY/δ inhibitors	
Idelalisib	**Approved**
GS-9820	Phase I
Duvelisib (IPI-145)	Registration Phase III
AMG 319	Phase I
TGR-1202	Phase I
SAR245408 (XL147)	Phase I
Syk inhibitors	
GS-9973	Phase II
Fostamatinib	Phase I/II
PRT-2070	Phase I
BCL-2 inhibitor	
ABT/GDC-199	Phase III

Phase 3 Trial of Idelalisib + Rituximab in Relapsed CLL: Subgroup Analysis of High-Risk Groups

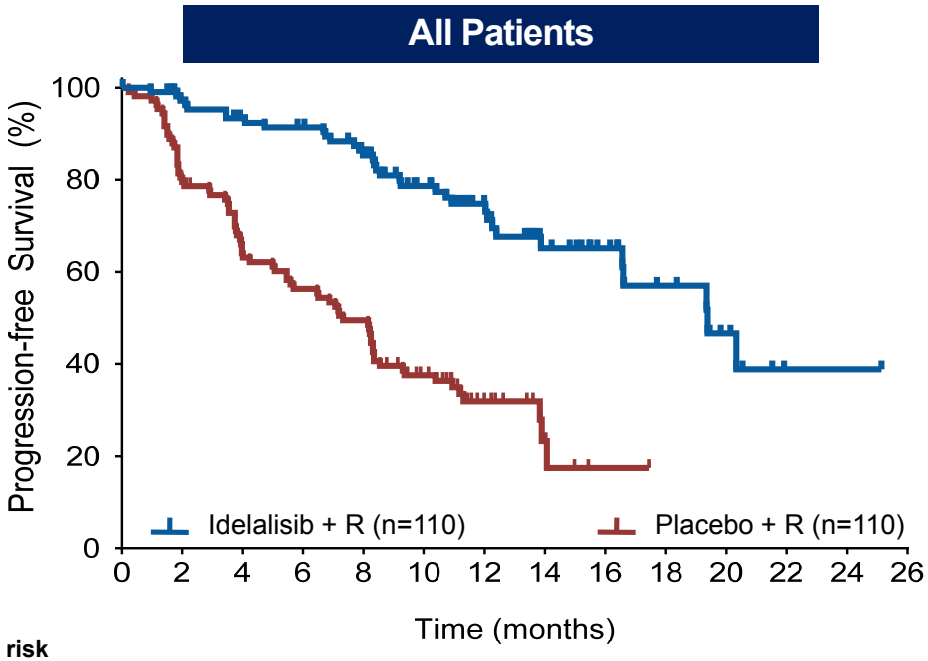


	Median Follow-up, months		
	IDELA + R	PBO + R	
1st Interim Analysis	4	4	DMC halted trial (Furman NEJM 2014)
2nd Interim Analysis	6	5	Blind ended (Coutre ASCO 2013) • Arm A continues • Arm B crosses over
Update	13	11	PFS, OS by subgroup analysis

Sharman et al., ASH 2014, Abstract 330

PFS, Including Extension Study*

Idelalisib + R vs Placebo + R



N at risk														
IDELA + R	110	102	95	92	83	64	43	26	19	12	7	1	1	0
PBO + R	110	86	66	58	51	33	15	5	1	0	-	-	-	-

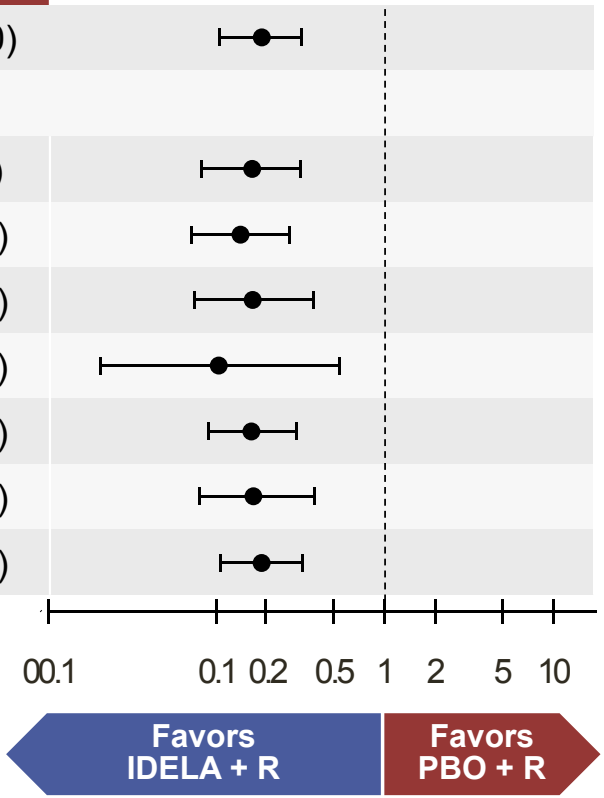
	Median PFS (95% CI)	HR (95% CI)	p-value
IDELA + R	19.4 mo (16.6, –)	0.25 (0.16, 0.39)	<0.0001
PBO + R	7.3 mo (5.5, 8.5)		

*Placebo + R includes those patients who received open-label idelalisib after unblinding without prior progression (n=42).

Sharman et al., ASH 2014, Abstract 330

Progression-Free Survival, 2nd Interim Analysis

	IDELA + R PFS (n)	Placebo + R PFS (n)
All patients	NR (110)	5.5 (110)
Subgroup		
Rai Stage III/IV	NR (70)	13 (72)
Unmutated *IGHV*	NR (91)	5.5 (93)
Del(17p)/*TP53* mutation	NR (46)	4.0 (49)
Del(11q)	10.7 (25)	6.9 (23)
ZAP70+	NR (98)	5.5 (93)
CD38+	NR (62)	6.9 (51)
ß2-microglobulin: >4 mg/L	NR (94)	5.0 (83)

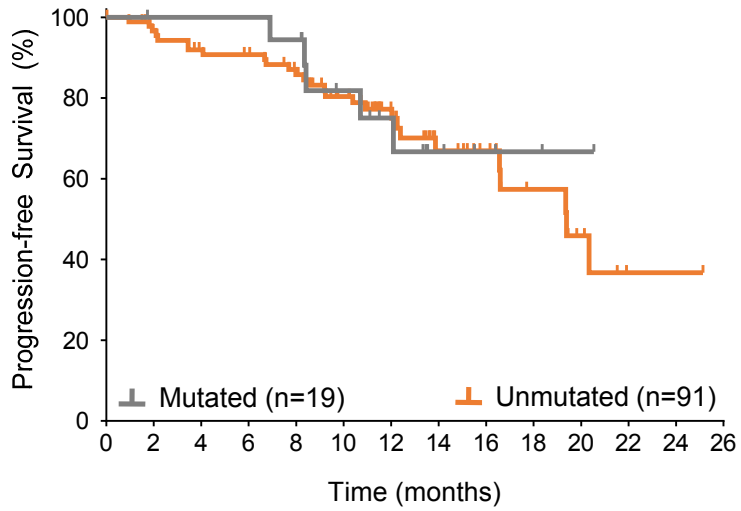


Sharman et al., ASH 2014, Abstract 330

PFS Subgroup Analysis*

Idelalisib + R (n=110)

IGHV: Unmutated vs Mutated

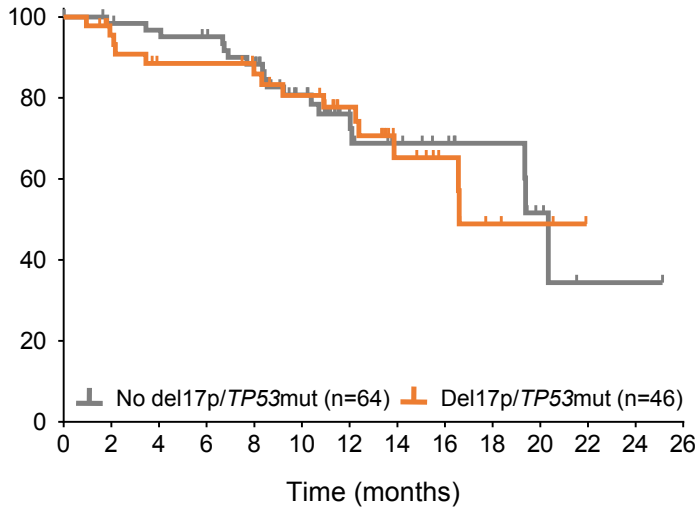


N at risk

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, –)	

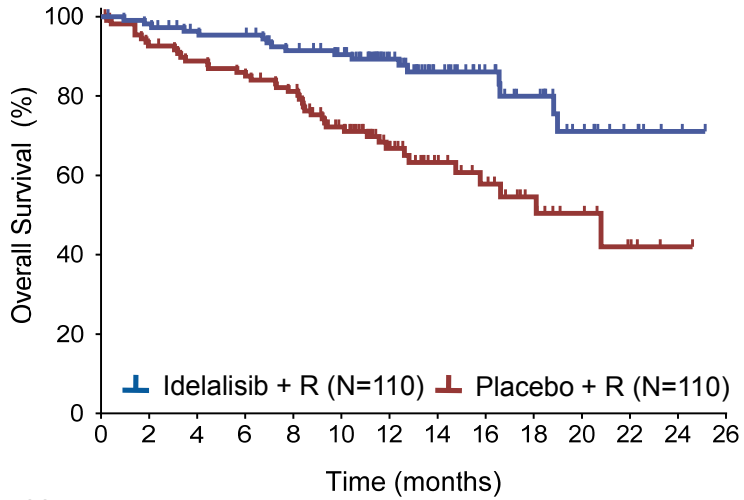
*Including extension study

Sharman et al., ASH 2014, Abstract 330

Overall Survival, Including Extension Study*

Idelalisib + R vs Placebo + R → Idelalisib

All Patients

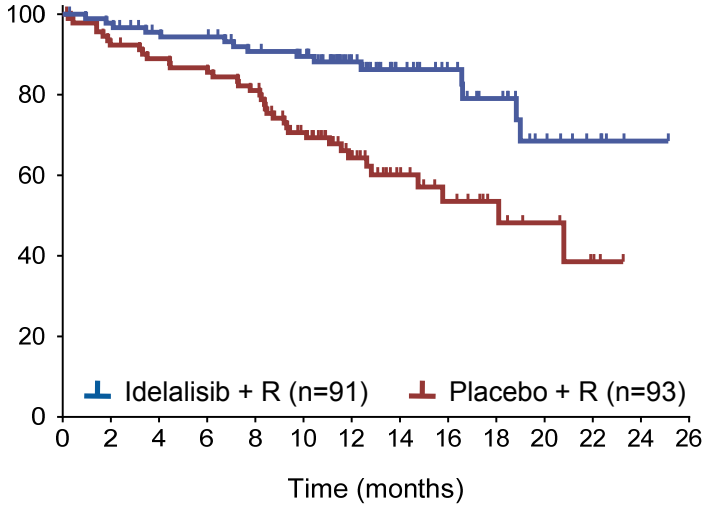


N at risk

IDELA + R	110	107	101	100	93	85	60	41	30	23	13	7	3	0
PBO + R	110	99	93	90	84	66	42	27	20	13	8	4	1	0

	Median OS (95% CI)	HR (95% CI)	p-value
IDELA + R	NR	0.34 (0.19, 0.6)	0.0001
PBO + R	20.8 mo (14.8, –)		

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	

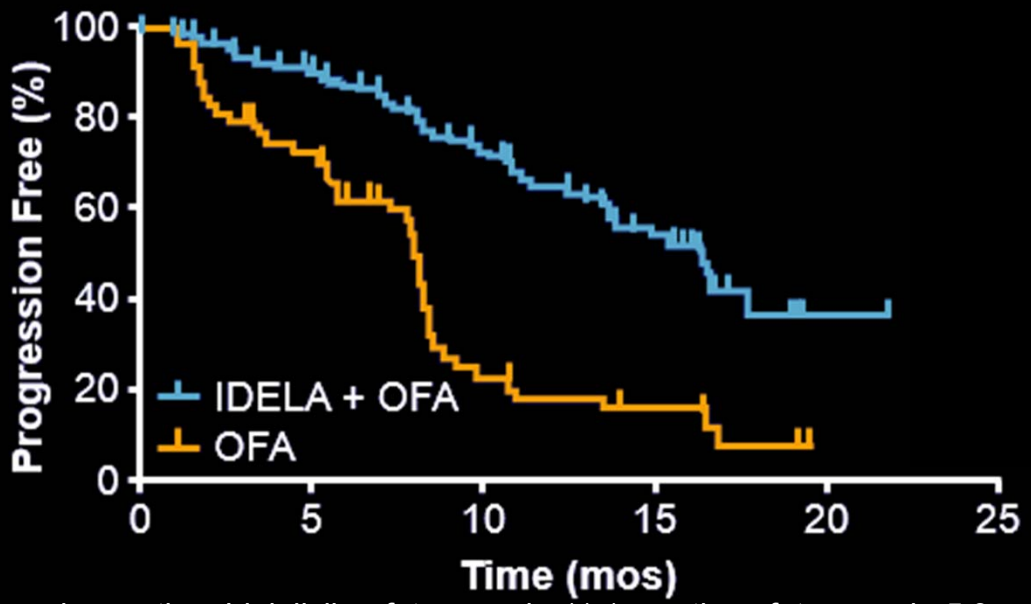
Median OS (95% CI)	HR (95% CI)	p-value
NR (19.0, –)	0.35 (0.19, 0.6)	0.0003
18.1 mo (14.8, –)		

*As randomized, including cross-over

Sharman et al., ASH 2014, Abstract 330

Idelalisib + Ofatumumab vs Ofatumumab

Progression-Free Survival



Median observation: Idelalisib+ofatumumab, 11.1 months; ofatumumab, 5.3 months.

	Idelalisib + ofatumumab	Ofatumumab	HR, *P*
Median PFS	16.3 months	8.0 months	0.27, < 0.0001
Median OS	20.9 months	19.4 months	0.74, 0.027

Jones J, et al. *ASCO Annual Meeting Abstracts*. 2015. Abstract 70023.

Idelalisib

- FDA approved for relapsed CLL appropriate for rituximab monotherapy
- Twice daily dosing, continuous + rituximab
- Toxicities: elevated LFTs, GI / diarrhea; less common colitis and pulmonary
- Most responses are partial, residual disease
- Median PFS was 19.4 months
- Efficacy in relapsed CLL with del(17p) & del(11q)
- Improved OS *vs*. rituximab + placebo

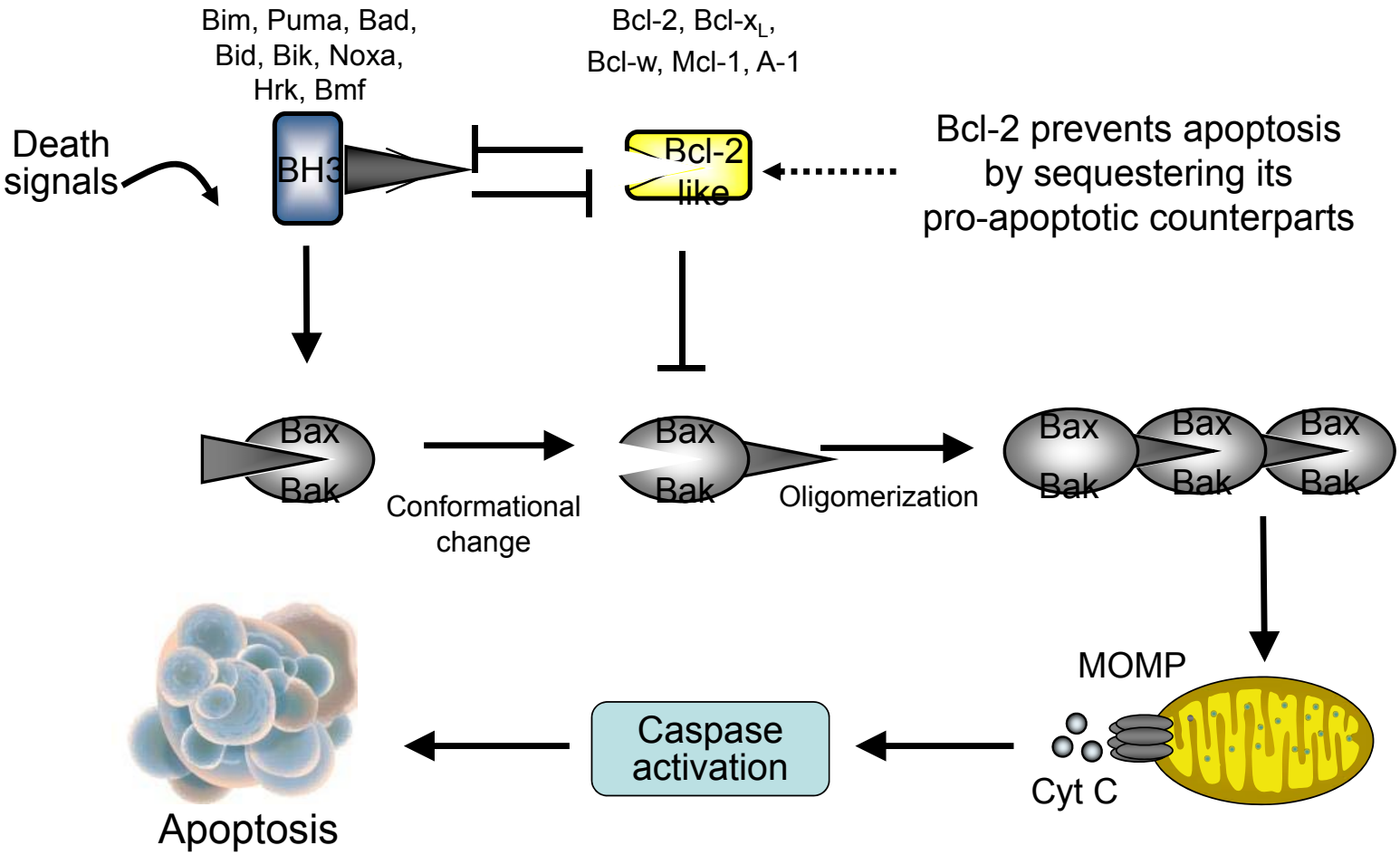
Ongoing Studies with PI3-kinase-inhibitors in CLL

Agent	Combination or Comparator	Phase – Trial #
Idelalisib	+ ONO-4059 (BTK-I)	I – NCT02457598
	+ BI836826 (CD37 mAb)	I/II – NCT02538614
	+ Ofatumumab	II – NCT02135133
	Benda ➤ Idelalisib + Obinutuzumab (CLL2-BCG)	II – NCT02445131
	+ Obinutuzumab *vs.* Chlor + Obinutuzumab	III – NCT01980875
Duvelisib (IPI-145)	+ BR/Rituximab	I – NCT01871675
	+ Obinutuzumab	I – NCT02292225
	+ FCR	I/II – NCT02158091
	vs. Ofatumumab	III – NCT02004522
TCR-1202	+ Ibrutinib + Ublituximab	I – NCT02006485
	+ Chlor + Obinutuzumab +/- Ibrutinib	I/Ib – NCT02100852
	+ Ublituximab (CD20 mAb) + Pembrolizumab	I/II – NCT02535286
ACP-319	+ ACP-196 (BTK-I)	I/II – NCT02157324

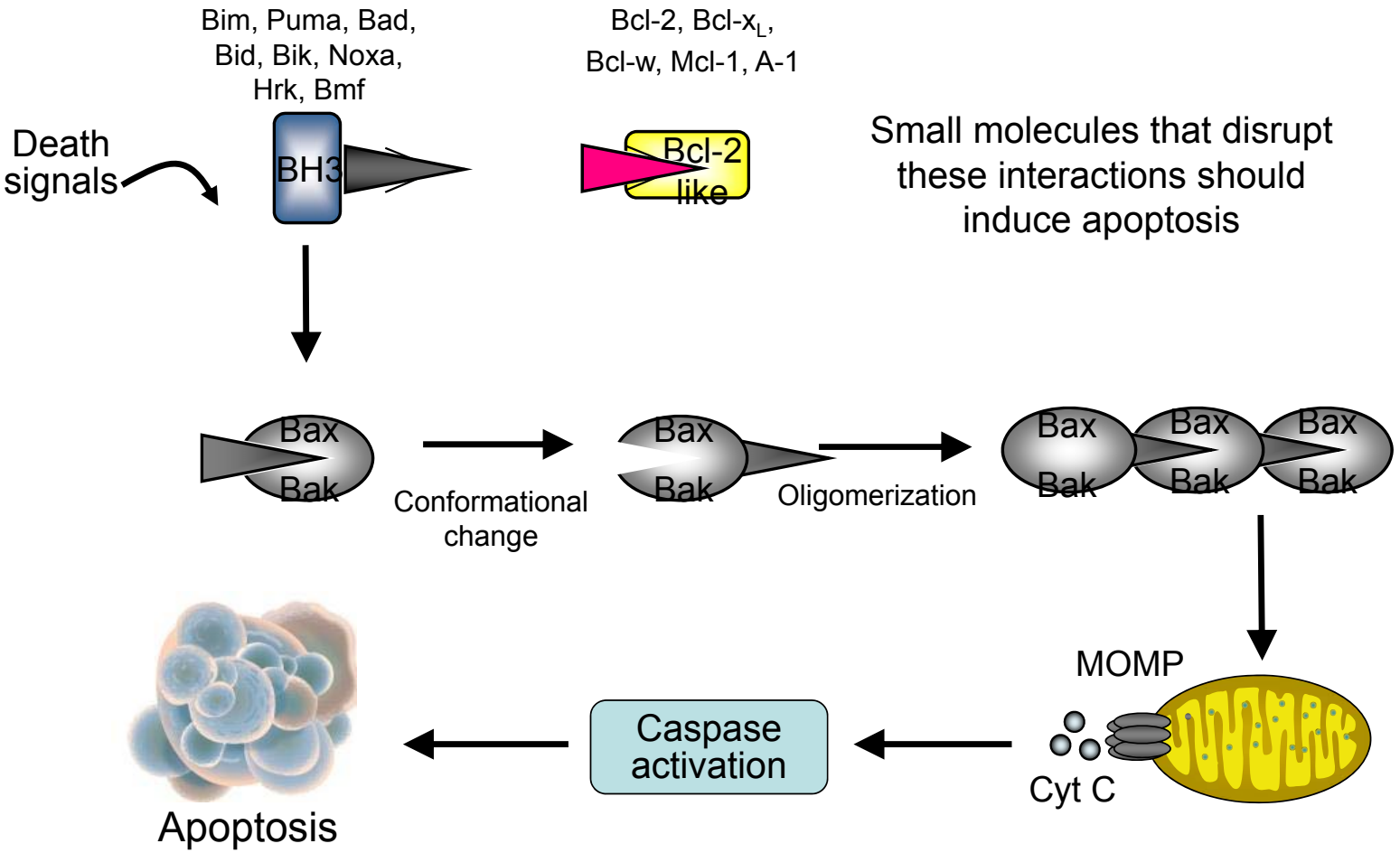
New Agents Changing Treatment for Patients with CLL

Agent	Development Phase
BTK inhibitors	
Ibrutinib	**Approved**
ONO-4059	Phase I
ACP-196	Phase I
PI3KY/δ inhibitors	
Idelalisib	**Approved**
GS-9820	Phase I
Duvelisib (IPI-145)	Registration Phase III
AMG 319	Phase I
TGR-1202	Phase I
SAR245408 (XL147)	Phase I
Syk inhibitors	
GS-9973	Phase II
Fostamatinib	Phase I/II
PRT-2070	Phase I
BCL-2 inhibitor	
Venetoclax	Phase III

Bcl-2 Family Regulates Apoptosis



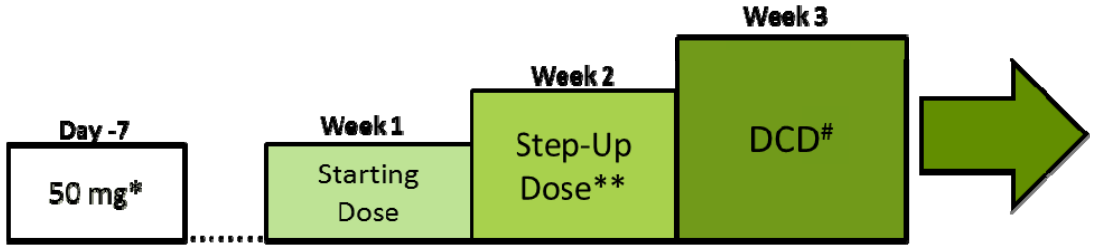
Bcl-2 Family Regulates Apoptosis



Venetoclax (ABT-199) Dosing Schema

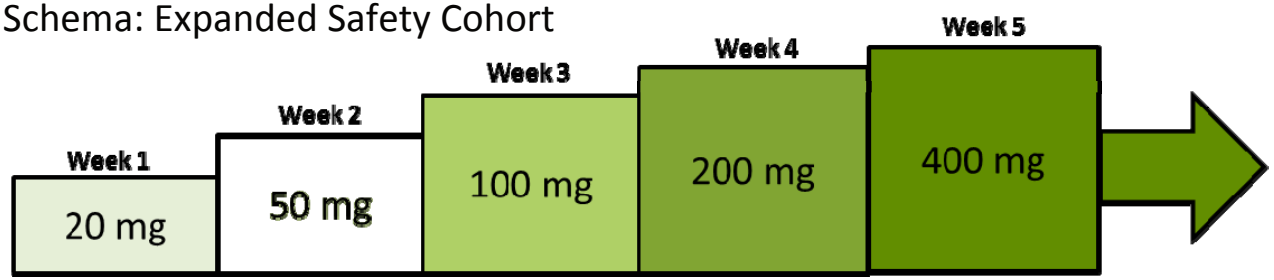
Daily Venetoclax doses increased weekly to the designated cohort dose (DCD)

Initial Ramp-Up Schema: Dose Escalation



* 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 ranges from 150 to 1200 mg

Ramp-Up Schema: Expanded Safety Cohort



Seymour et al. EHA 2014, Abstract S702

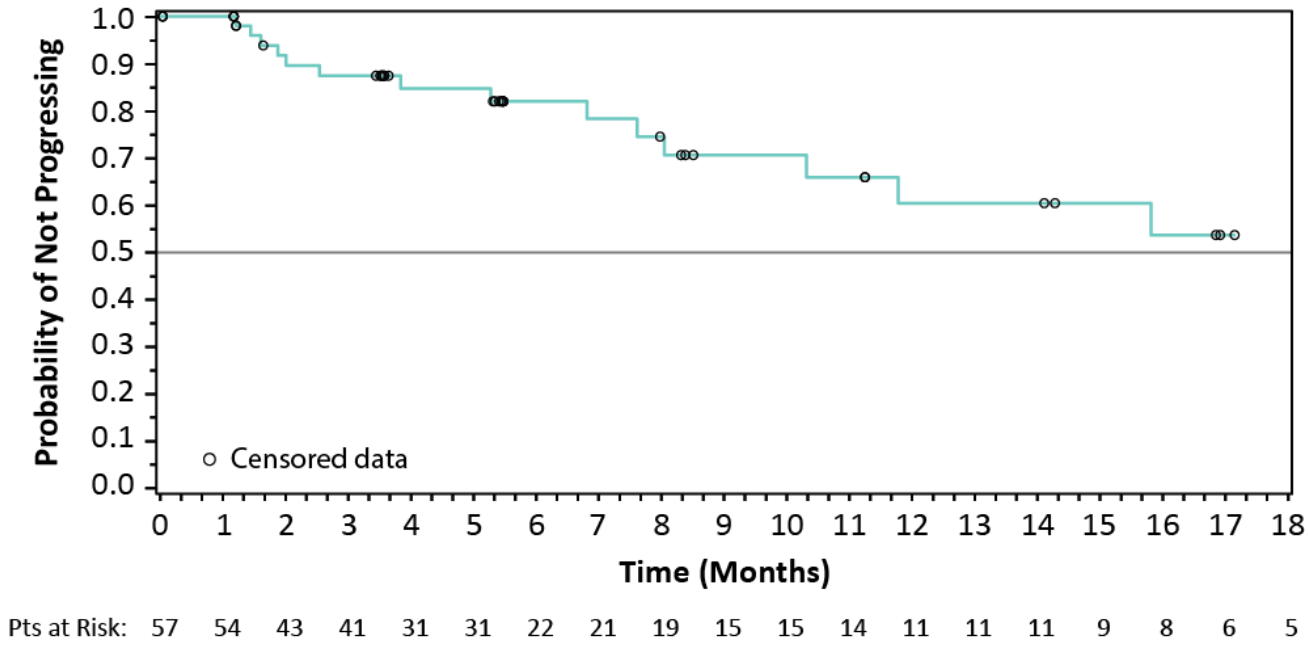
Objective Responses of Venetoclax (ABT-199) Treated Patients

Responses	All n (%), n = 78	del (17p) n (%), n = 19	F-Refractory n (%), n = 41	IGHV 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, evaluable patients (n=78) 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 based on current patient enrollment numbers.**

Progression Free Survival (PFS) at 400 mg or Higher in High Risk Patients



- Median PFS for fludarabine refractory and/or del(17p) patients treated at or above 400 mg has not yet been reached (median follow-up 5.3 months, range [0.03 – 22])

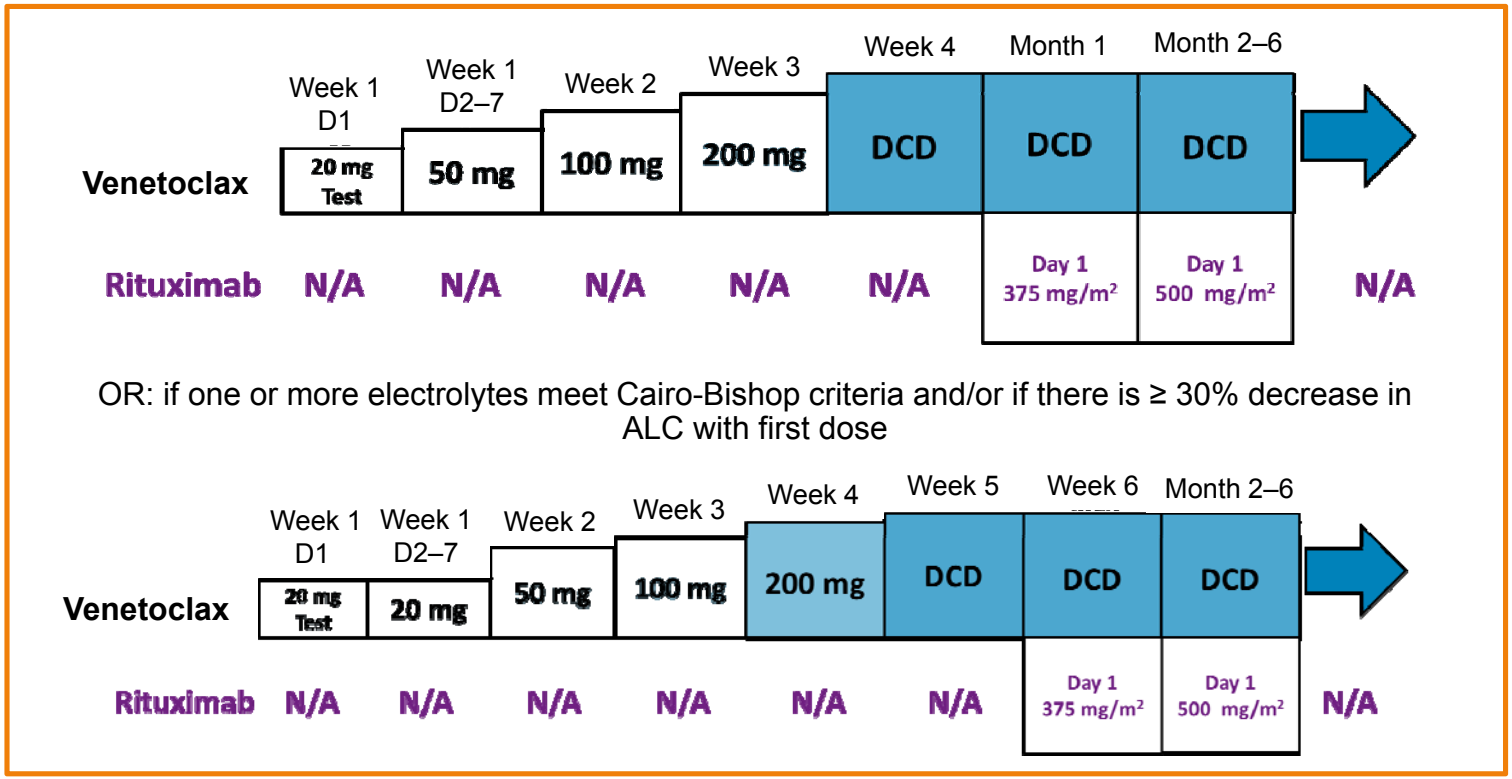
Venetoclax - Adverse Events

All Grades ≥20% of pts	N=105 n (%)
Diarrhea	42 (40)
Neutropenia	38 (36)
Nausea	37 (35)
Upper respiratory tract infection	35 (33)
Fatigue	27 (27)
Cough	21 (20)
Grades 3/4 ≥ 5% pts	**n (%)**
Neutropenia	35 (33)
Anemia	10 (10)
Febrile neutropenia	7 (7)
Thrombocytopenia	7 (7)
Hyperglycemia	7 (7)
Tumor lysis syndrome (TLS)	7 (7)
Hypokalemia	5 (5)

Seymour et al. EHA 2014, Abstract S702

Dosing Schedule of Venetoclax and Rituximab

Final Escalation Strategy:



D, day; DCD, designated cohort dose
Protocol amendment permits 20 mg for first week, as needed

Roberts et al., ASH 2014, Abstract 325

Venetoclax+Rituximab: Preliminary Efficacy Results

Best Response, n (%)	All Patients n=49	Evaluable Patients[a] n=44	17p del Patients n=9
Overall Response	43 (88)	39 (89)	7 (78)
Complete Response (CR)/CRi	15 (31)	15 (34)	2 (22)
Partial response (PR)	22 (45)	22 (50)	5 (56)
PR unconfirmed[b]	6 (12)	2 (5)	
Stable disease	2 (4)	2 (5)	1 (11)
Disease progression	3 (6)	3 (7)	0 (0)
Death (TLS)[c]	1 (2)		1 (11)

[a]Evaluable patients reached full bone marrow assessment at 7 months or discontinued
[b]PR unconfirmed = follow-up assessment not available at time of analysis (4 pending, 2 withdrew)
[c]No other fatal TLS events occurred after modification of the protocol
As of October 7, 2014

Roberts et al., ASH 2014, Abstract 325

Venetoclax+Rituximab: Bone Marrow Minimal Residual Disease (MRD) at 7 Months

MRD was assessed in 15 patients with CR/CRi and 22 patients with a PR using local institutional methods and sensitivity $\leq 10^{-4}$

Response Classification	Evaluated Patients	MRD Negative	MRD Positive	Comments
CR	15	9	6 (range: *0.003%* – 2.3%)	• 1/6 became MRD-negative at 14 months
PR	22	8[a]	14 (range: 0.05 – 0.44%)	• 4/8 with MRD-negative disease have one remaining lymph node >1.5 cm as the only remaining evidence of disease

[a] Remaining lymph node sizes for the 8 patients with MRD negative PR:
4 patients with a single lymph node (1.7, 2.2, 2.3 and 2.7 cm)
4 patients with multiple (2-4) lymph nodes (largest of which is 2.2, 2.3, 2.3, and 2.4 cm)
the last patient also has splenic involvement

Roberts et al., ASH 2014, Abstract 325

Venetoclax (ABT-199)

- Oral Bcl-2 inhibitor with potent monotherapy activity
- Complete remissions in rel/ref CLL
  - MRD-negative CRs
- Active in high-risk CLL: rel/ref CLL with del(17p) & fludarabine-refractory CLL
- TLS and neutropenia AE's to monitor
- Safely combined with rituximab
- Registration trial(s) initiated

Ongoing Studies with BCL-2-inhibitor in CLL

Agent	Combination or Comparator	Phase – Trial #
Venetoclax (ABT-199)	+ BR	I – NCT01671904
	+ Obinutuzumab + Ibrutinib	I/II – NCT02427451
	Monotherapy for BTK-I/PI3K-I Refractory	II – NCT02141282
	Benda ➤ Venetoclax + Obinutuzumab (CLL2-BAG)	II – NCT02401503
	+ Rituximab *vs.* BR	III – NCT02005471
	+ Obinutuzumab *vs.* Chlor + Obinutuzumab	III – NCT02242942

CLL Treatment Directions

- Untreated, high-risk – early intervention
- First-line therapy
  - Fit CIT-eligible – *IGHV*-Mutated
    - FCR with maintenance or Tx for MRD
  - Fit-*IGHV*-Unmutated & Elderly
    - BCR- / Bcl-2-inhibitor
- Second-line Therapy for active disease
- Treatment (consolidation) for persistent disease on BTK-inhibitor (1st and later)
- Richter's transformation work-up and "novel treatments" program

Promising New Non-Chemotherapy Agents for CLL

- BCR small molecule inhibitor combinations
- Bcl-2 small molecule inhibitor – Venetoclax
- Immune modulating mAbs
  - Checkpoint inhibitors - PD-1, PDL-1, CTLA-4
  - CD137
  - KIR
- CAR-T cells
  - CD19
  - ROR1
- Cellular therapies – NK
- Immune modulating agent(s) – CC-122

THANK YOU!

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