Are there advances with combinations of therapies, using targeted agents?

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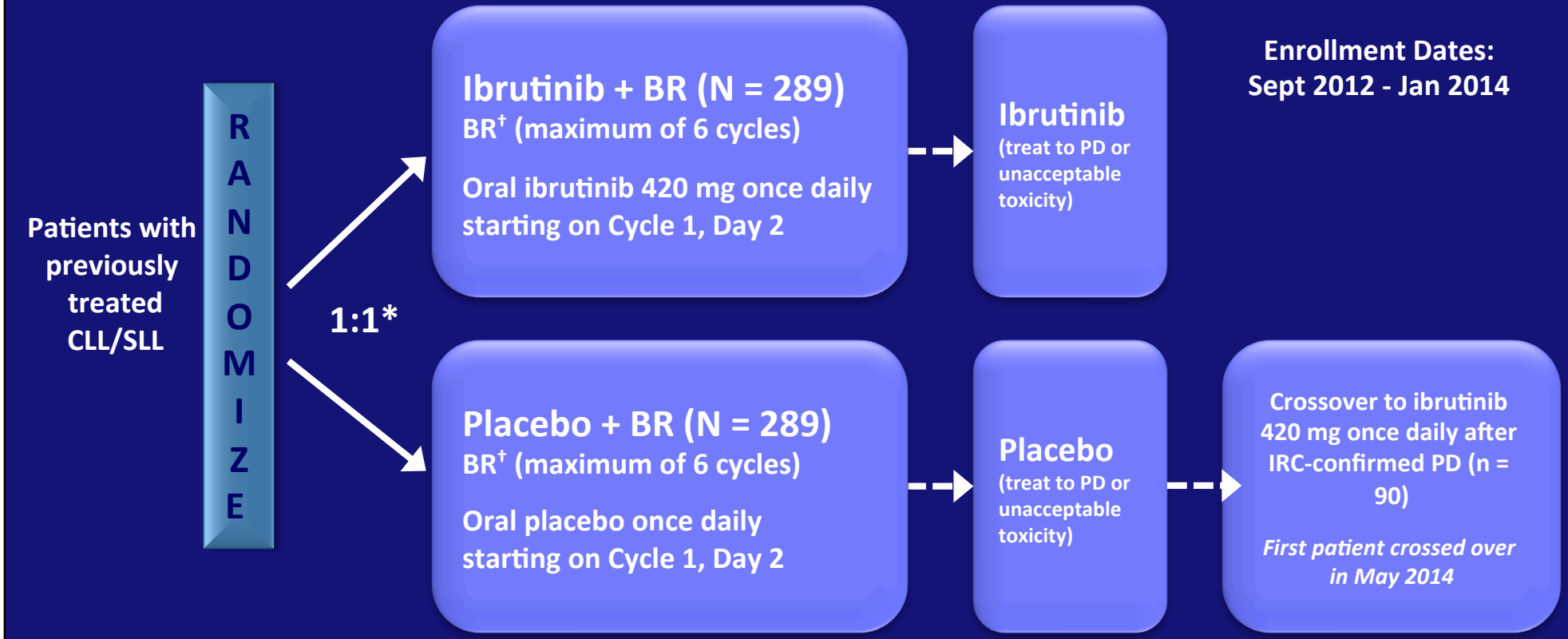
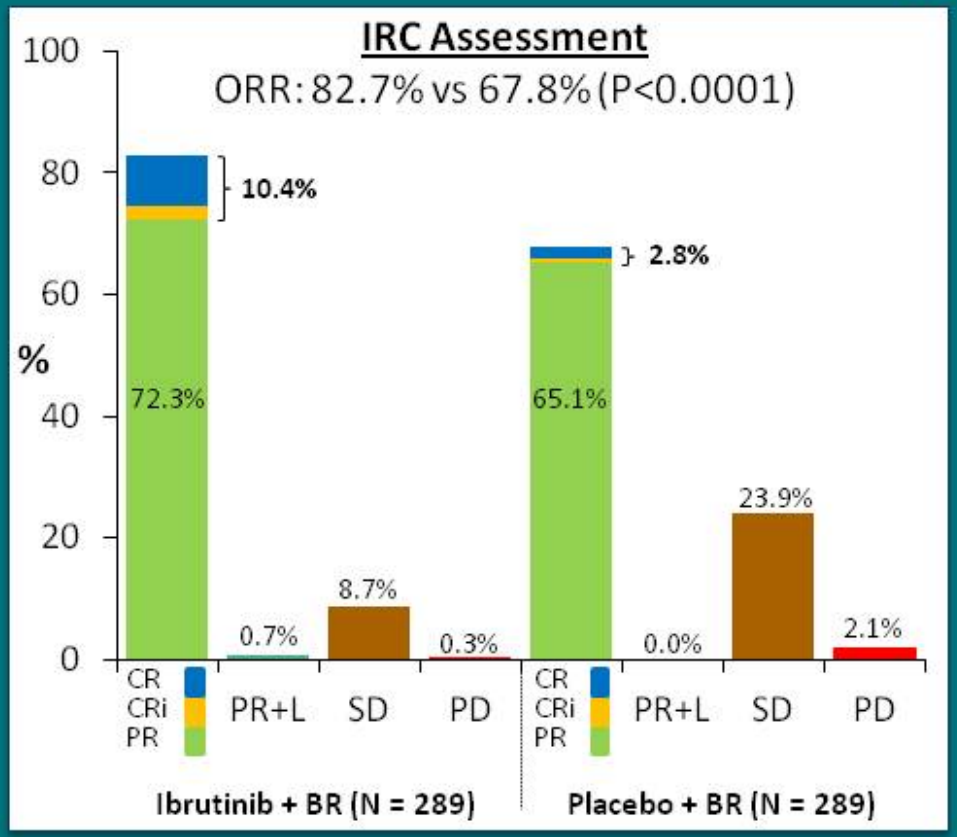
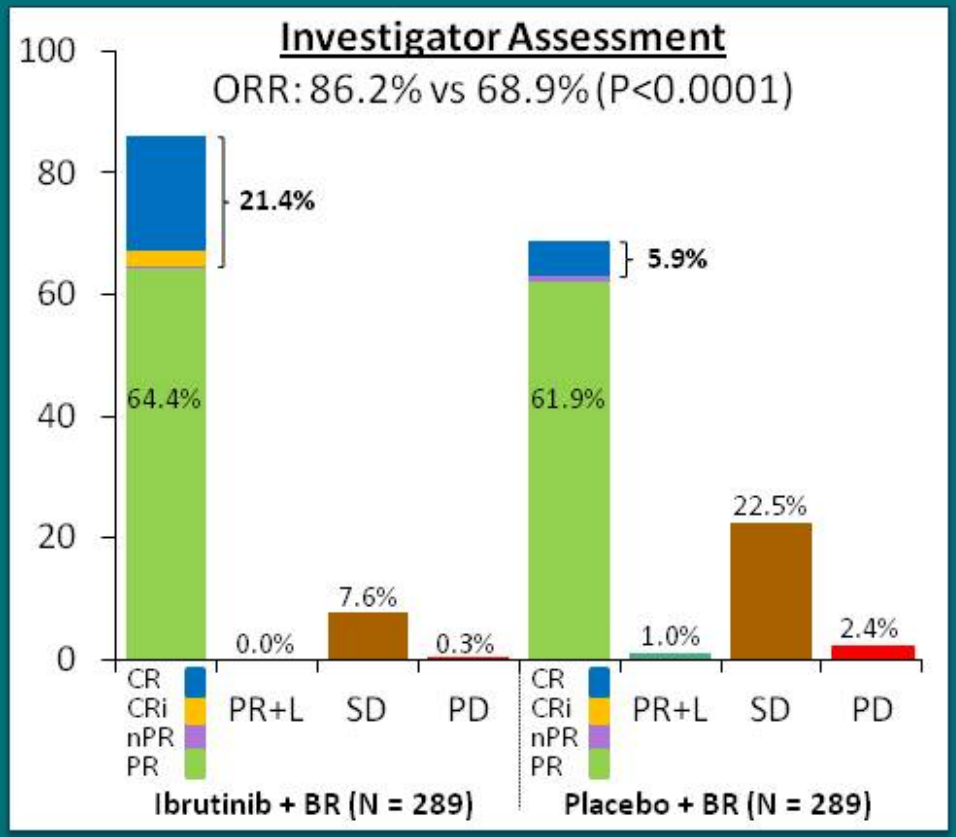
HELIOS: Phase 3 Study Design



IRC, independent review committee; PD, progression of disease.
*Stratified by disease refractory to purine analog chemoimmunotherapy (failure to respond or relapse within 12 months) and the number of prior lines of therapy (1 line vs > 1 line).
†BR (similar to Fischer K, et al. *J Clin Oncol.* 2011;29:3559-3566): bendamustine: 70 mg/m^2 IV on Cycle 1, Days 2-3 and Cycles 2-6, Days 1-2; rituximab: 375 mg/m^2 on Cycle 1, Day 1, and 500 mg/m^2 on Cycles 2-6, Day 1.

ORR*: IRC and Investigator Assessment

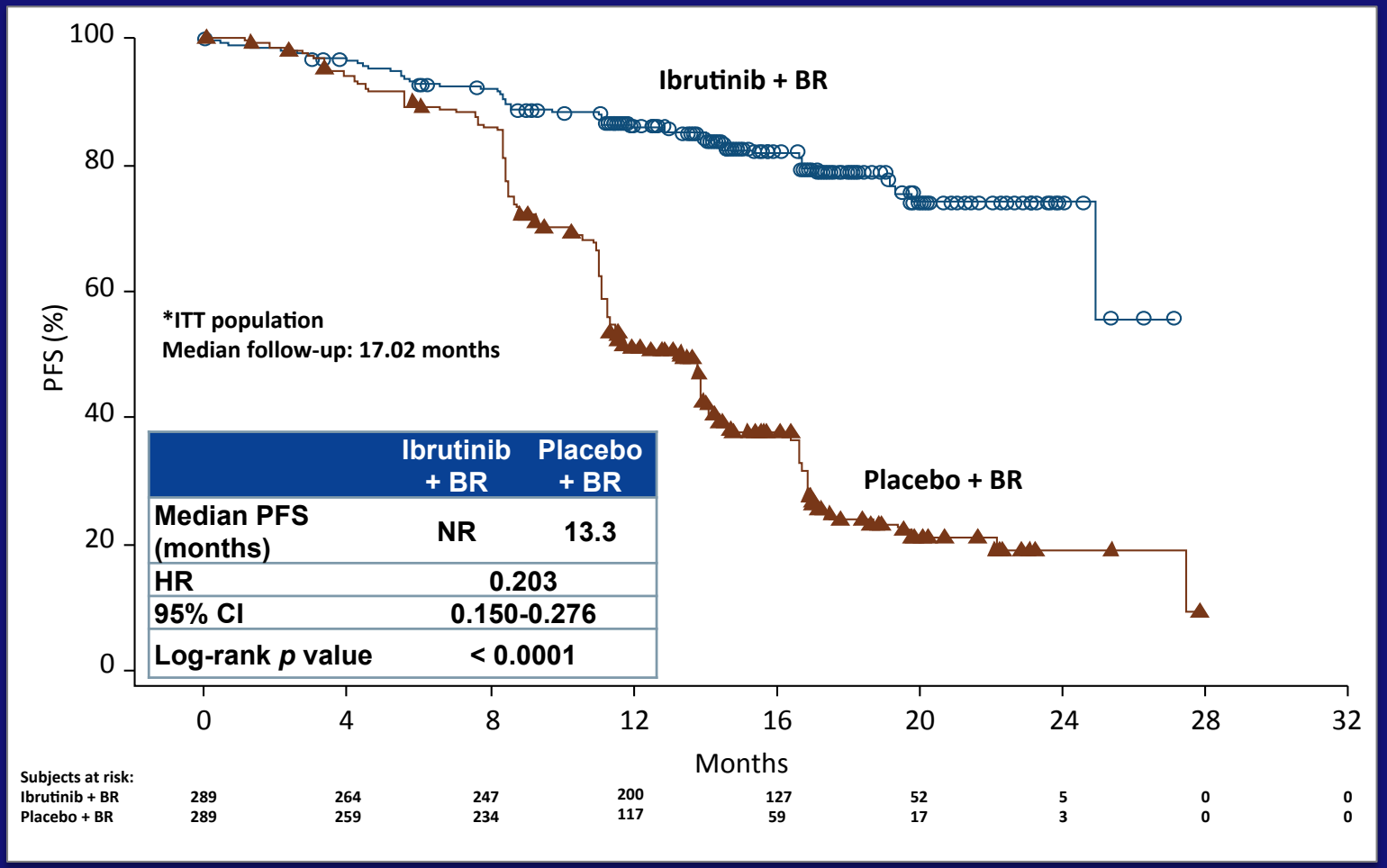




*ORR = CR + CRi + nPR + PR.

Presented By Asher Alban Chanan-Khan at 2015 ASCO Annual Meeting

Primary Endpoint: IRC-Assessed PFS*



	Ibrutinib + BR	Placebo + BR
Median PFS (months)	NR	13.3
HR	0.203	
95% CI	0.150-0.276	
Log-rank *p* value	< 0.0001	

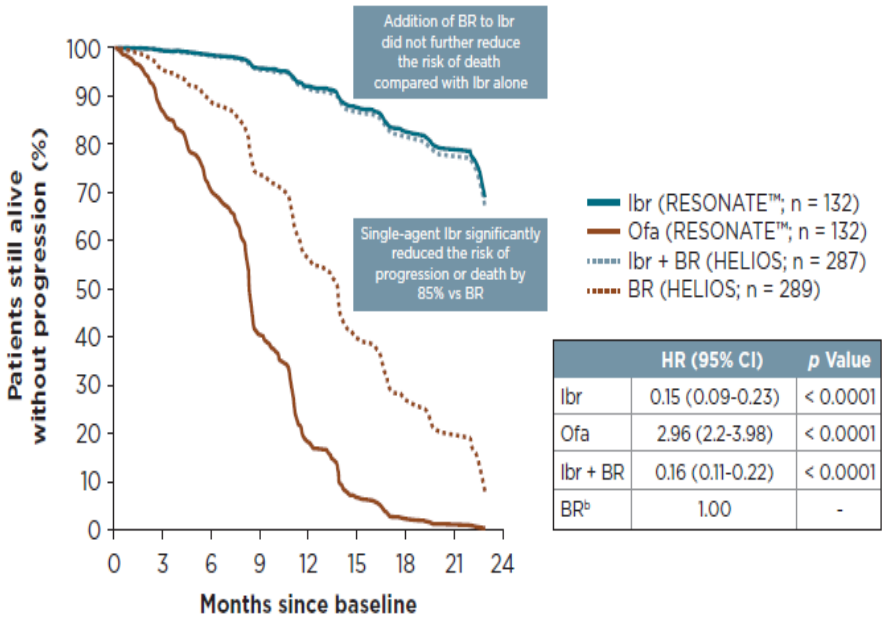
- Investigator-assessed HR for ibrutinib + BR vs placebo + BR was 0.201 (95% CI: 0.145-0.278)
- No Richter's transformations were observed on the ibrutinib arm and 3 on the placebo arm

	Ibrutinib + BR (prior)[1]	*Ibrutinib + BR (current)*	*Ibrutinib alone*[2]
Number	30	289	101
Age	62	64	64
17p permitted?	yes	no	yes
# prior regimens	1-3 (2)	1-? (2)	1-12 (4)
ORR	93%	83%	90%
CR	17%	10%	7%
Median follow-up	16 mo	17 mo	36 mo
PFS	70% @ 36 mo	~72% @ 24 mo	69% @ 30 mo
OS	NS	~88% @ 24 mo	79% @ 30 mo

[1]**Blood 2015;125:2915** [2]**Blood 2015;125:2497**

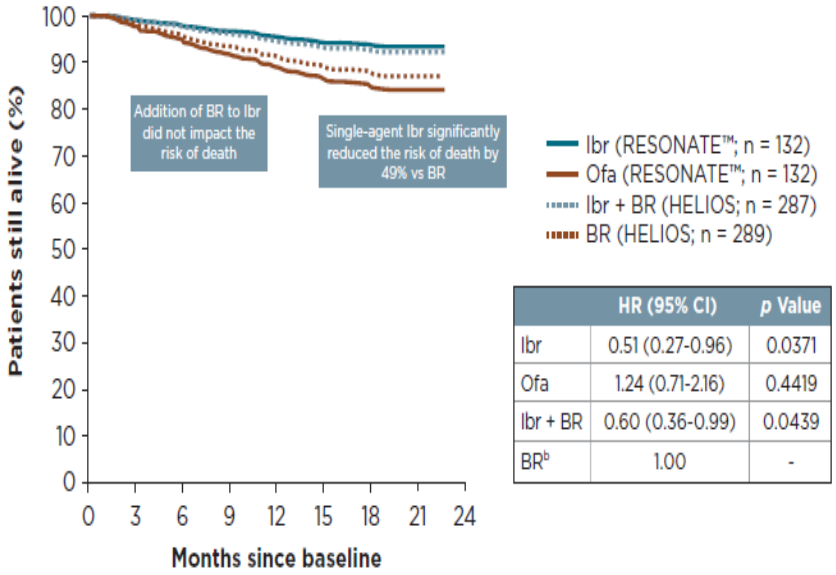
Indirect Comparison of Resonate and Helios Studies

PFS



	HR (95% CI)	*p* Value
Ibr	0.15 (0.09-0.23)	< 0.0001
Ofa	2.96 (2.2-3.98)	< 0.0001
Ibr + BR	0.16 (0.11-0.22)	< 0.0001
BR[b]	1.00	-

OS



	HR (95% CI)	*p* Value
Ibr	0.51 (0.27-0.96)	0.0371
Ofa	1.24 (0.71-2.16)	0.4419
Ibr + BR	0.60 (0.36-0.99)	0.0439
BR[b]	1.00	-

- PFS and OS were comparable for single-agent ibrutinib vs. ibrutinib + BR and were significantly improved for single-agent ibrutinib vs. BR

Hillmen et al. ASH 2015; Abstract 2944 (Poster Presentation)

Study Design

- Relapsed/Refractory CLL (n=179)
- Treatment naïve with high-risk disease features (del17p or TP53 mutated) (n=27)

Total = 206

Arm Ibrutinib (n=102)

Ibrutinib 420 mg PO once daily until disease progression/death/ side effects

Arm Ibrutinib + rituximab (n=104)

Ibrutinib 420 mg PO once daily plus Rituximab (375 mg/m^2 weekly during the first 4 weeks and then monthly for cycles 2-6) then continue on ibrutinib 420 mg

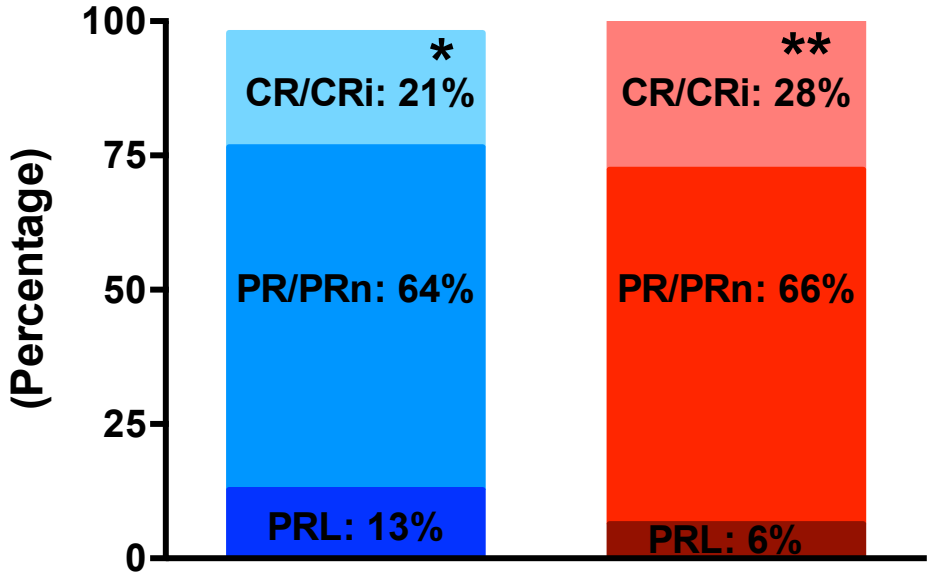
Stratification factors
- ECOG (0-1 vs. 2)
- High-risk cytogenetic abnormalities

Primary end point: PFS

Secondary end points: ORR, safety and tolerability of the treatment

Best Response

Evaluable patients	Ibrutinib (n=94)	Ibrutinib + Rituximab (n=94)
ORR	98%	100%
Median follow-up, months (range)	21 (3 – 35)	19 (2 – 37)



* MRD Neg: 1

** MRD Neg: 5

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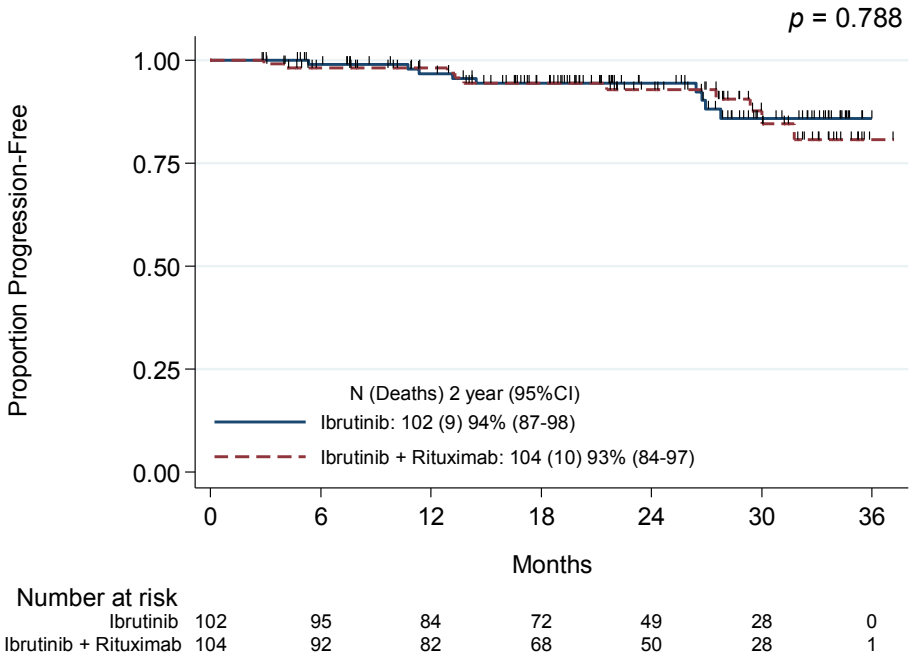
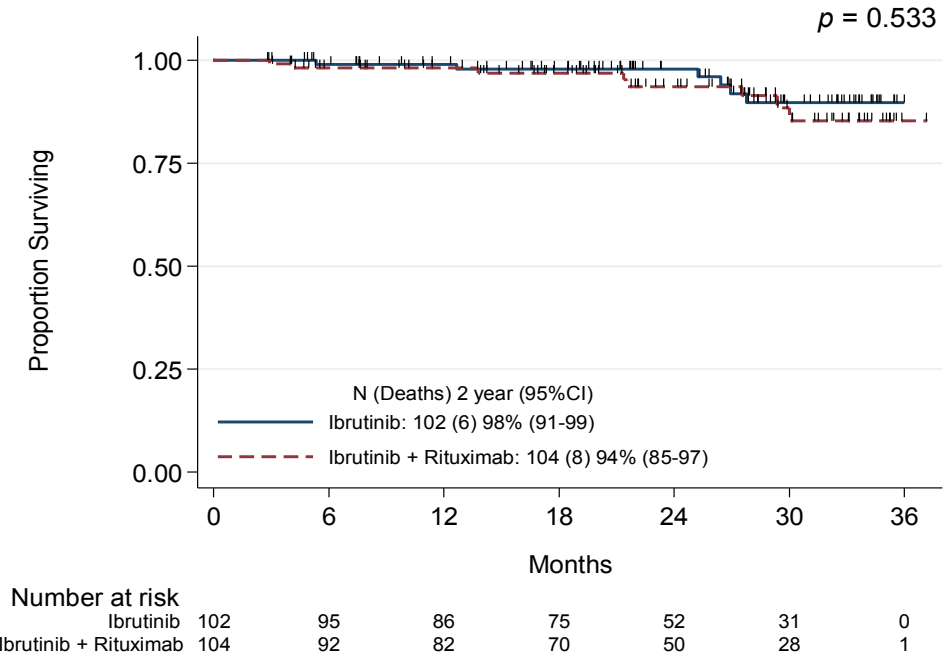
Survival Outcomes: Overall population

Progression- Free Survival



Overall Survival



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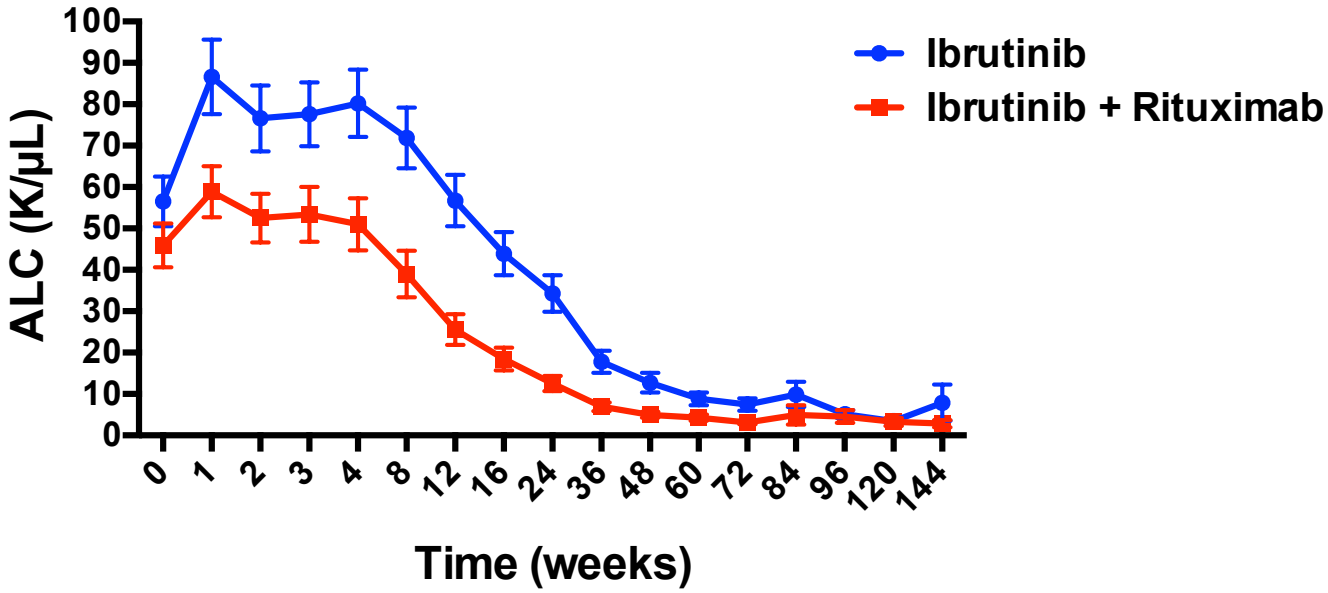
Hematological parameters

Absolute lymphocyte counts (ALC)



Median time to normalization of ALC, months (range)	8.9 (0.2 – 29.9)	3.0 (0.2 – 29.9), p<0.001

Are there advances with combinations of therapies, using targeted agents?

NO

?Really?

First-line Therapy

- Current efforts based on recent data
- Individualizing treatment
  - Younger, fit, *IGHV*-M – 20%
    - Ibrutinib + FC + Obinutuzumab (iFCG)
  - *IGHV*-UM, older (>65 yrs) – 75%
    - Ibrutinib + Venetoclax
  - Del(17p) – 5%
    - Ibrutinib + Venetoclax

First-line iFCG protocol

- First-line protocol for CIT-eligible patients with **mutated *IGHV*** and non-del(17p)
- Primary objective MRD NEG after 3 courses

	C1D1	C1D2	C1D3	C1D4	C1D8	C1D15	C2-3 D1	C2-3 D2	C2-3 D3
Obinutuzumab	100mg	900mg	-	-	1000mg	1000mg	1000mg	-	-
Fludarabine	-	25mg	25mg	25mg	-	-	25mg	25mg	25mg
Cyclophosphamide	-	250mg	250mg	250mg	-	-	250mg	250mg	250mg
Ibrutinib	420 mg once daily continuous								

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Making Cancer History®

Responses after 10.9 months follow-up on the iFCG Trial

Table 1

	N (%) or median [range] N=32	
Age, yrs	60 [25-71]	
Gender, M	26 (81)	
FISH	del(13q)	23 (72)
	Trisomy 12	6 (19)
	Negative	3 (9)
WBC, K/μL	58.7 [2.4-224]	
Platelet, K/μL	116 [62-292]	
Hemoglobin, g/dL	12.1 [8.5-15.6]	
B2M, mg/L	2.6 [1.4-8.1]	
Karyotype (n=27)	Diploid	17 (63)
	del(13q)	6 (22)
	Trisomy 12	4 (15)

Table 2

	Response at 3 Months (N=28)		Best Response (N=28)	
		BM MRD		BM MRD
ORR	28 (100)	24/28 (86) neg	28 (100)	All neg
CR/CRi	13 (46)	All neg	22 (78)	All neg
PR	15 (56)	11/15 (73) neg	6 (22)	All neg

Figure 1

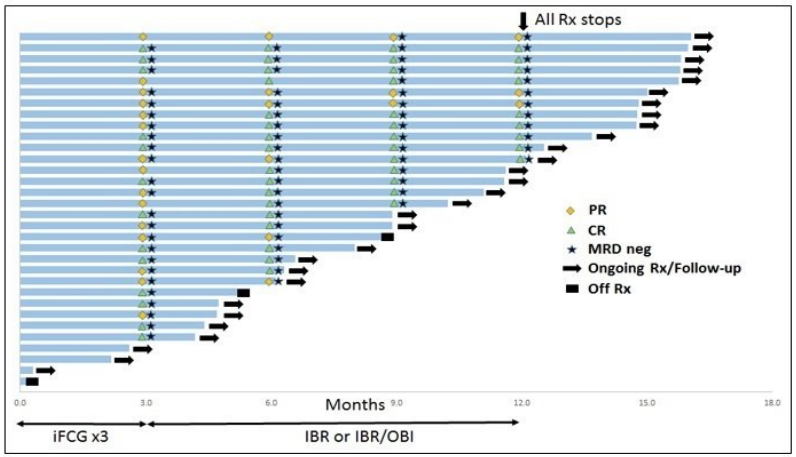
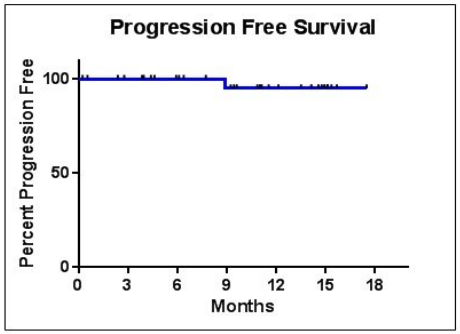


Figure 2



Jain N, ASH 2017
Abstract 495

- 24/28 (86%) achieved MRD-negative BM remission at 3 month Comparison: FCR 3 cycles, 26% marrow MRD neg
- Overall, 13/28 (46%) achieved CR/CRi with undetectable MRD at 3 months.
- All PR pt had bulky adenopathy, residual lymphadenopathy (1.6 to 3.5 cm) after 3 courses of iFCG
- All 12 pts who reached 1 year are MRD-negative and stopped all therapy including ibrutinib

Ibrutinib-Venetoclax Treatment Plan

	C1=3 D1-28	C4D1 ---> C27D28
Ibrutinib	420mg once daily	420mg once daily until progression
Venetoclax	-	- - 20mg daily x1 week then; 50mg daily x1 week then; 100mg daily x1 week then; 200mg daily x1 week then; 400mg daily continuous

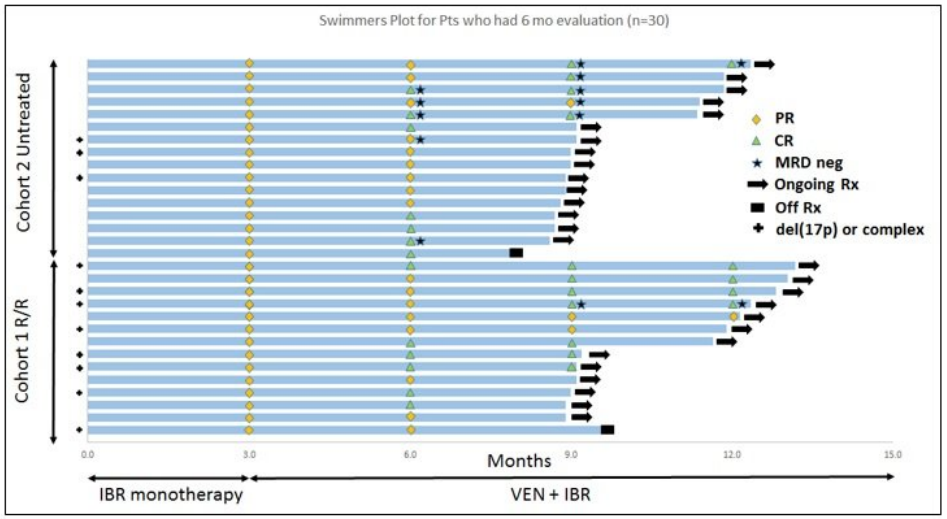
Abstract 429 Combined Venetoclax and Ibrutinib for Patients with Previously Untreated High-Risk CLL, and Relapsed/Refractory CLL: A Phase II Trial

Table

		N (%) or median [range]	
		Cohort 1 (N=33) R/R CLL	Cohort 2 (N=39) TN CLL
Age, yrs		59 [32-76]	65 [35-82]
Gender, M		27 (82)	29 (74)
Prior Therapies		1 [1-4]	-
FISH	del(17q)	9 (27)	7 (18)
	del(11q)	13 (39)	10 (26)
	Trisomy 12	5 (15)	5 (13)
	Negative	2 (6)	4(10)
	del(13q)	4(12)	13 (33)
IGHV mutation	Unmutated	23/27 (85)	27/34 (79)
	Mutated	4/27 (15)	7/34 (21)
Karyotype	Diploid	9/26 (35)	16/38 (42)
	Complex	5/26 (19)	6/38 (16)
	Others	12/26 (46)	16/38 (42)

TN: Treatment naïve

Figure



In Cohort 1, all 14 pts who completed at least 3 months of combination therapy had a response (9 CR/CRi, 5 PR). There was a significant decrease in bone marrow infiltrate with the addition of VEN (Figure), including MRD-negativity or MRD <0.1% in several pts with high-risk cytogenetics.

In Cohort 2, all 16 pts who completed at least 3 months of the combination therapy had a response (9 CR/CRi, 7 PR). Several of these pts achieved undetectable bone marrow MRD status with addition of VEN (Figure).

Conclusions

- Novel agent combination therapy now successful in achieving MRD-negative remissions
- **High-risk CLL:** ibrutinib + venetoclax
- **Low-risk** (mutated *IGHV*): iFCG
- Treatment discontinuation now possible
- Advantages of treatment discontinuation: reduced risk of resistance development, reduced risk of long-term toxicities