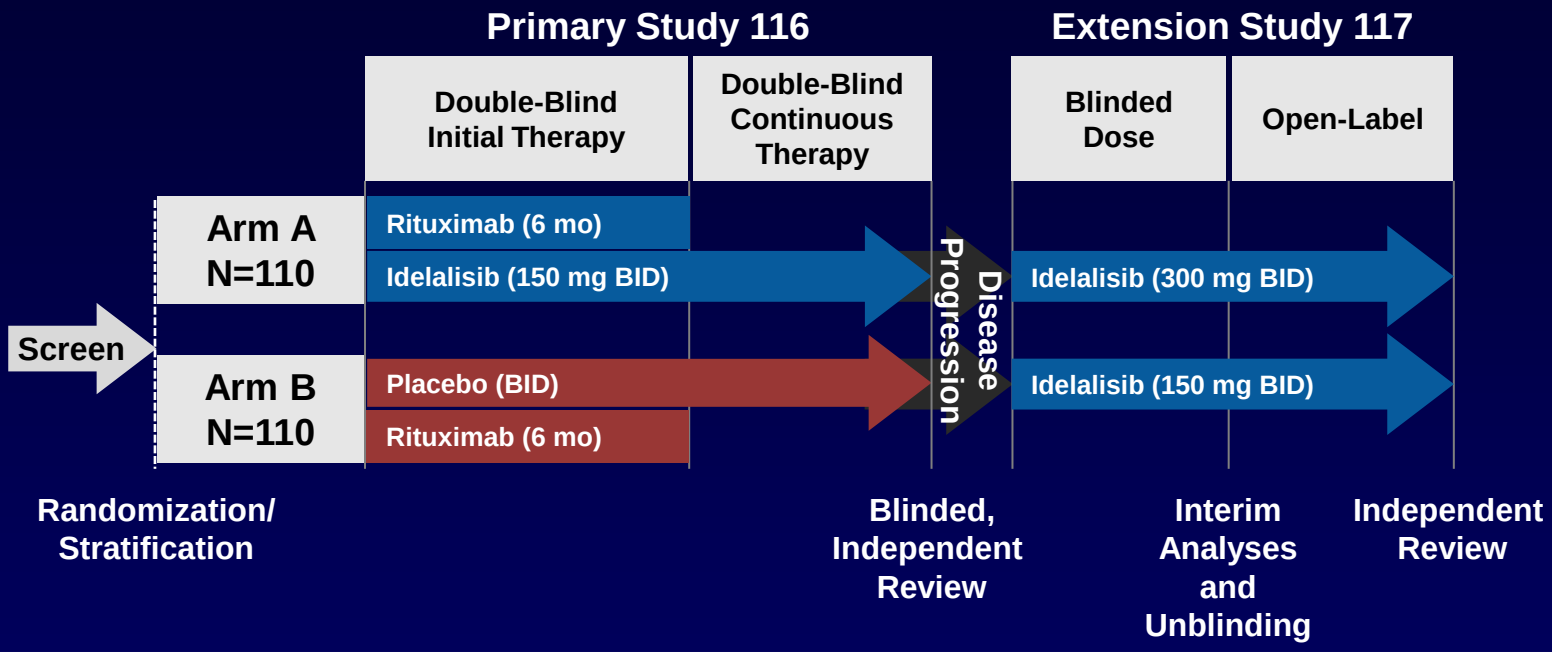
Second Interim Analysis of a Phase 3 Study of Idelalisib (ZYDELIG®) Plus Rituximab for Relapsed Chronic Lymphocytic Leukemia: Efficacy Analysis in Patient Subpopulations With Del(17p) and Other Adverse Prognostic Factors

Abstract 330

Sharman JP, Coutre SE, Furman RR, Cheson BD, Pagel JM, Hillmen P, Barrientos JC, Zelenetz AD, Kipps TJ, Flinn IW, Ghia P, Hallek M, Coiffier B, O'Brien S, Tausch E, Kreuzer K-A, Jiang W, Lazarov M, Li D, Jahn TM, Stilgenbauer S

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

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Key Eligibility Criteria

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 noncytotoxic 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

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Baseline Patient Characteristics

	Idelalisib + R N = 110	Placebo + R N = 110
Male, %	69	62
Median age, y (range)	71 (48-90)	71 (47-92)
Rai stage 0 / I-II / III-IV, %	0 / 31 / 64	1 / 26 / 66
Median years since diagnosis	7.9	8.6
Prior therapies, median (range)	3 (1-12)	3 (1-10)
Cytopenia*, any Grade, Grade 3/4, %	85, 32	88, 39
Total CIRS score >6, %	88	82
Estimated CrCl <60 mL/min, %	44	36
High-risk parameter, %		
Del(17p) and/or *TP53* mutation	42	45
Del(11q)	34	30
Unmutated *IGHV*	83	85
ZAP70+	92	85
CD38+	57	46
ß2-microglobulin >4 mg/L	85	78

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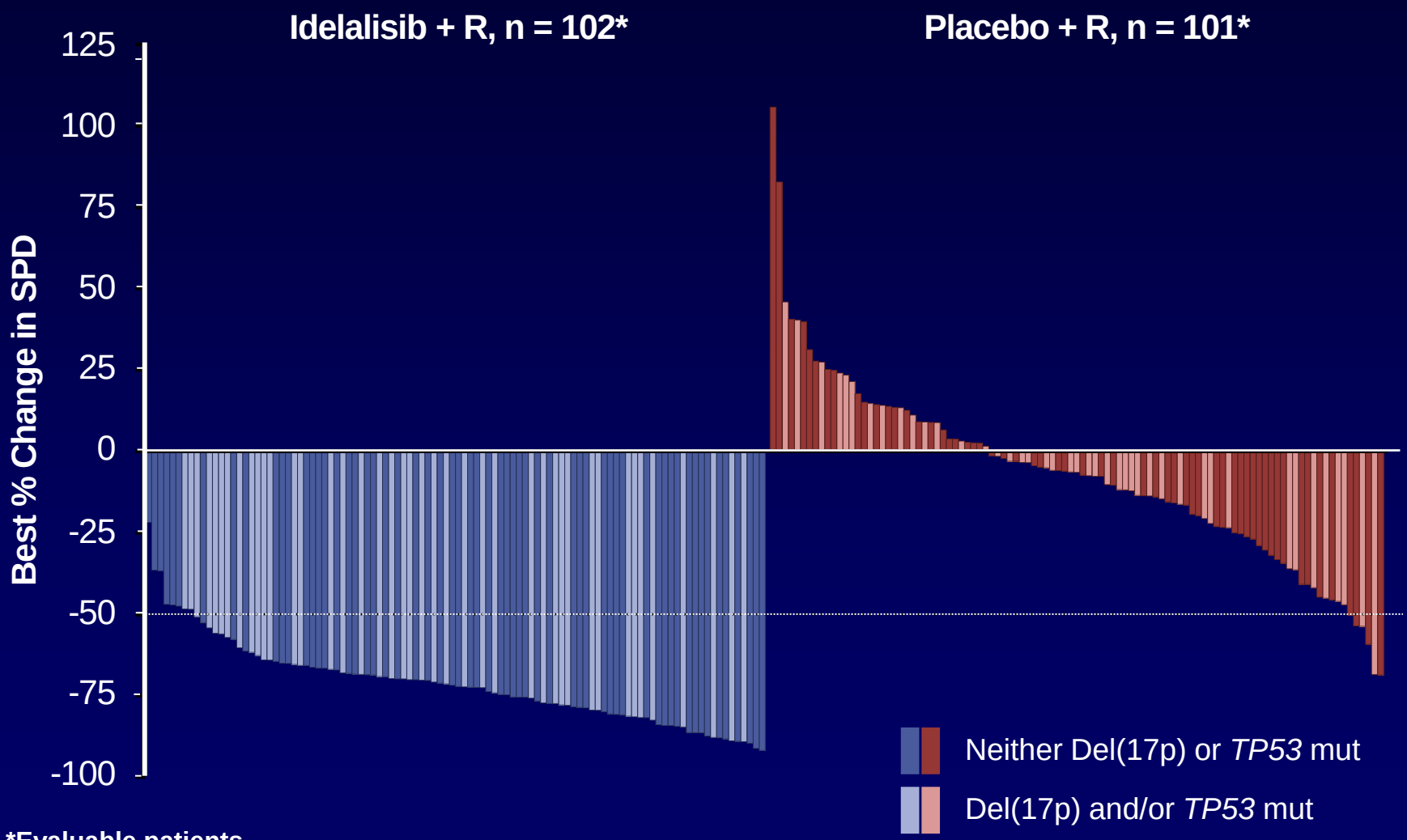
*Anemia and/or thrombocytopenia and/or neutropenia.

Lymph Node Response, 2nd Interim Analysis



*Evaluable patients.

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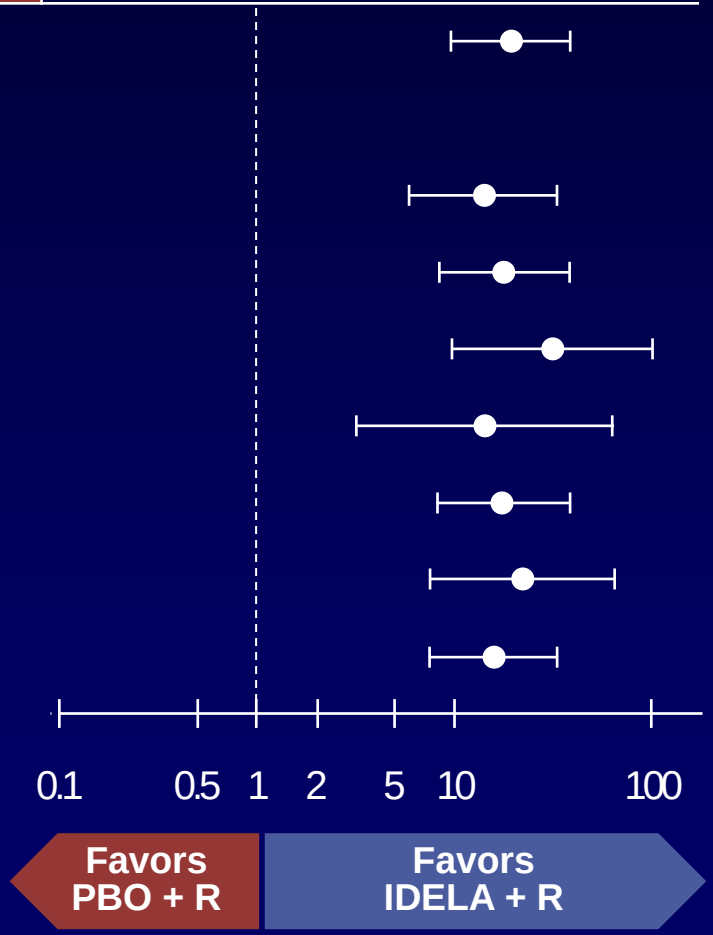
Overall Response Rates, 2nd Interim Analysis

	IDELA + R % (n)*	Placebo + R % (n)*
All patients	77 (106)	15 (107)
Subgroup		
Rai Stage III/IV	70 (67)	13 (70)
Unmutated *IGHV*	77 (87)	16 (90)
Del(17p)/*TP53* mutation	82 (44)	13 (47)
Del(11q)	68 (25)	17 (23)
ZAP70+	76 (94)	17 (91)
CD38+	78 (59)	16 (49)
ß2-microglobulin: >4 mg/L	77 (90)	16 (80)



*Evaluable patients (with at least one follow-up assessment) at time of analysis

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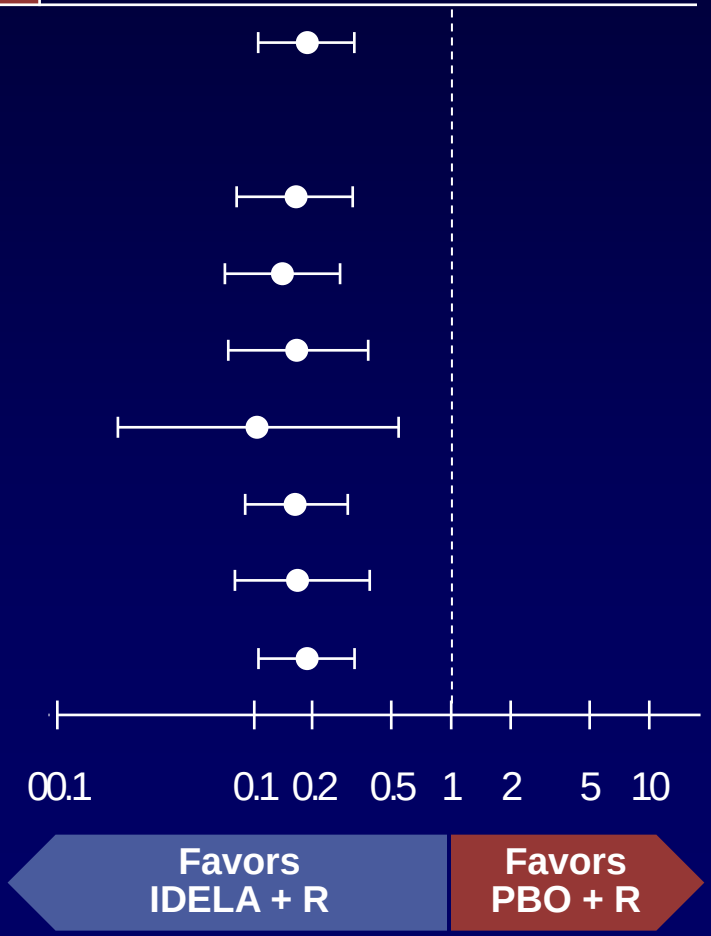
Progression-Free Survival, 2nd Interim Analysis

	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)



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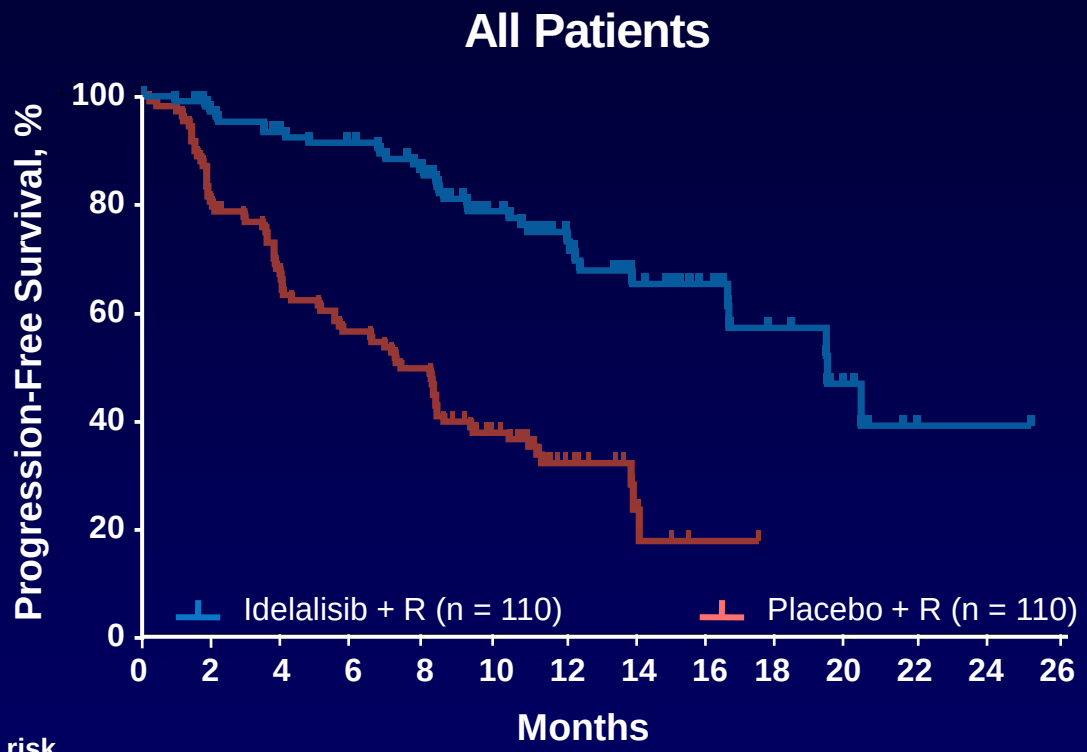
PFS, Including Extension Study*
Idelalisib + R vs Placebo + R



	Median PFS (95% CI)	HR (95% CI)	*P* value
IDELA + R	19.4 mo (16.6, –)	0.25 (0.16, 0.39)	<.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).

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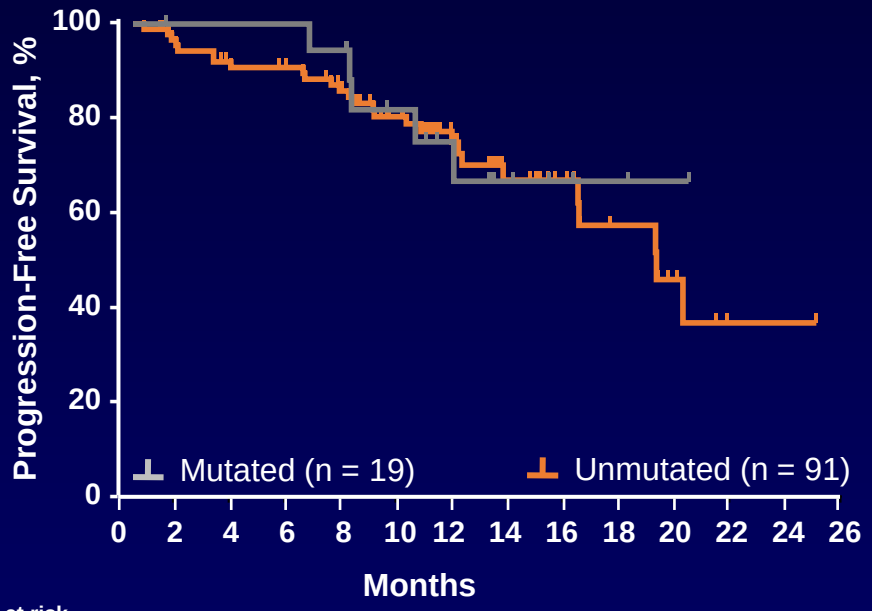
PFS Subgroup Analysis*
Idelalisib + R (n = 110)

IGHV: Unmutated vs Mutated

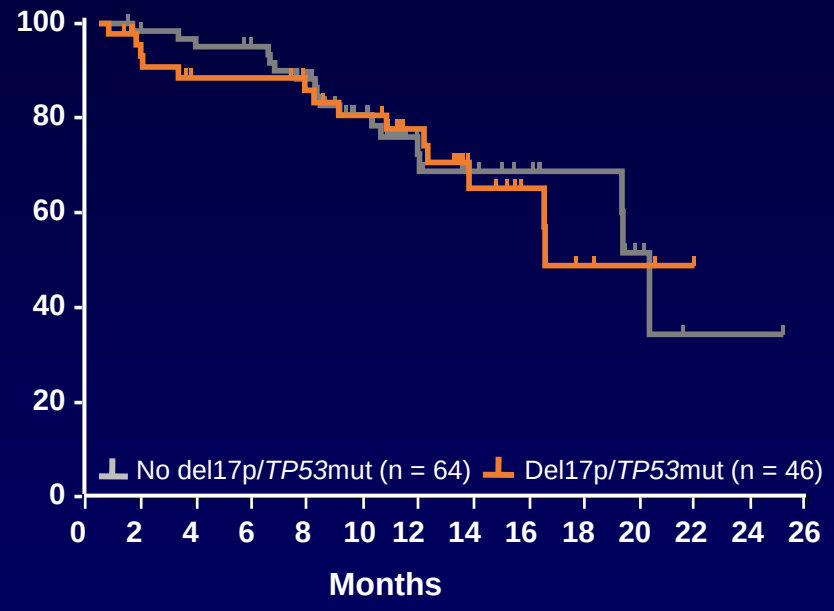


N at risk

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, –)	.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, –)	.94
Del	16.6 mo (13.9, –)	

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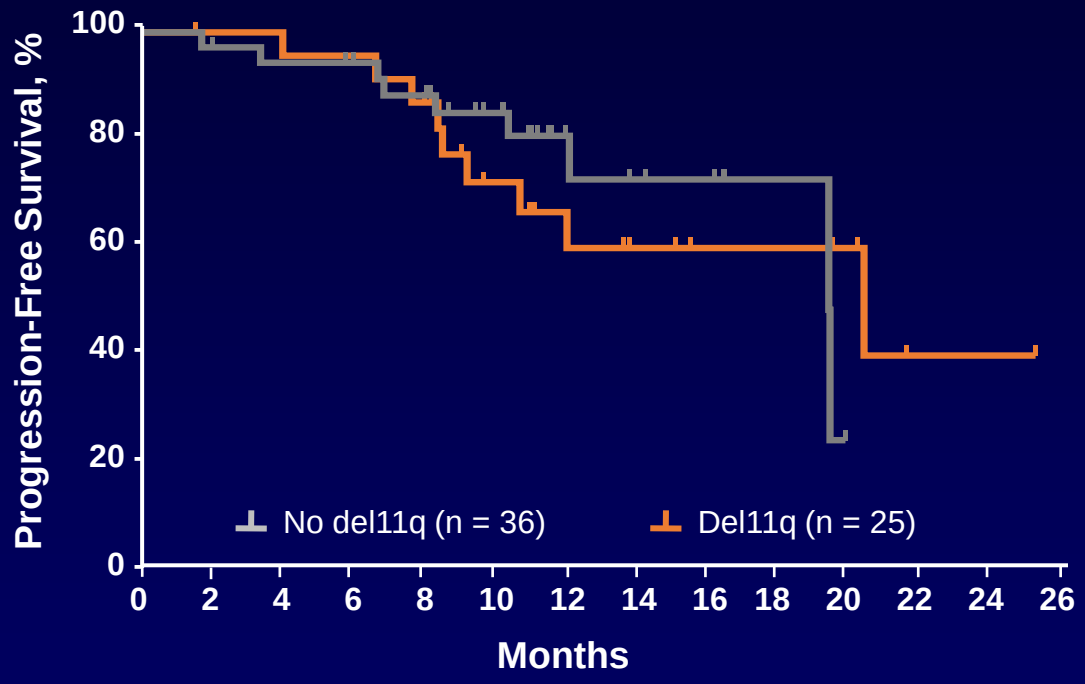
*Including extension study

PFS Subgroup Analysis*
Idelalisib + R (n = 110)

Del11q: Present vs Not Present



N at risk														
No del	36	35	33	32	29	22	10	7	6	3	0	0	0	0
Del	25	23	23	22	20	13	10	7	5	5	4	1	1	0

	Median PFS (95% CI)	*P* value
No del	19.4 mo (12.1, –)	.84
Del	20.3 mo (9.2, –)	

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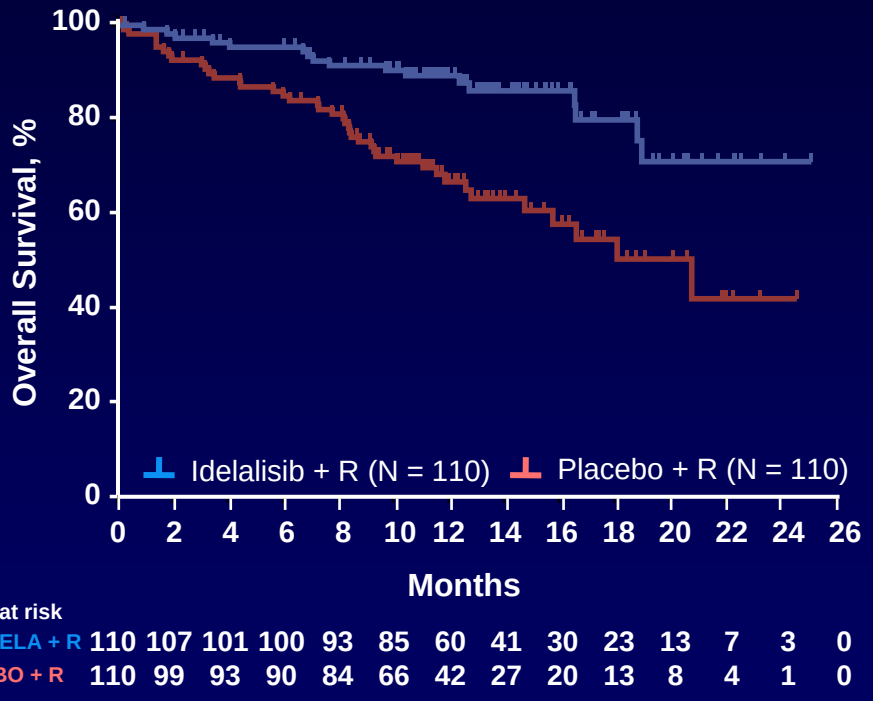
*Including extension study

Overall Survival, Including Extension Study*

Idelalisib + R vs Placebo + R → Idelalisib

All Patients

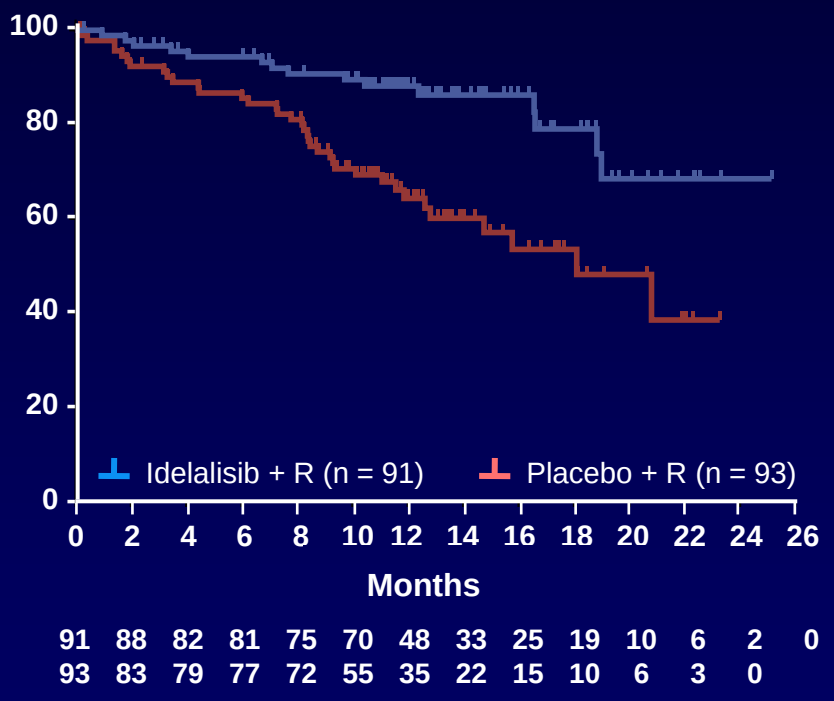


N at risk

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)	.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)	.0003
18.1 mo (14.8, –)		

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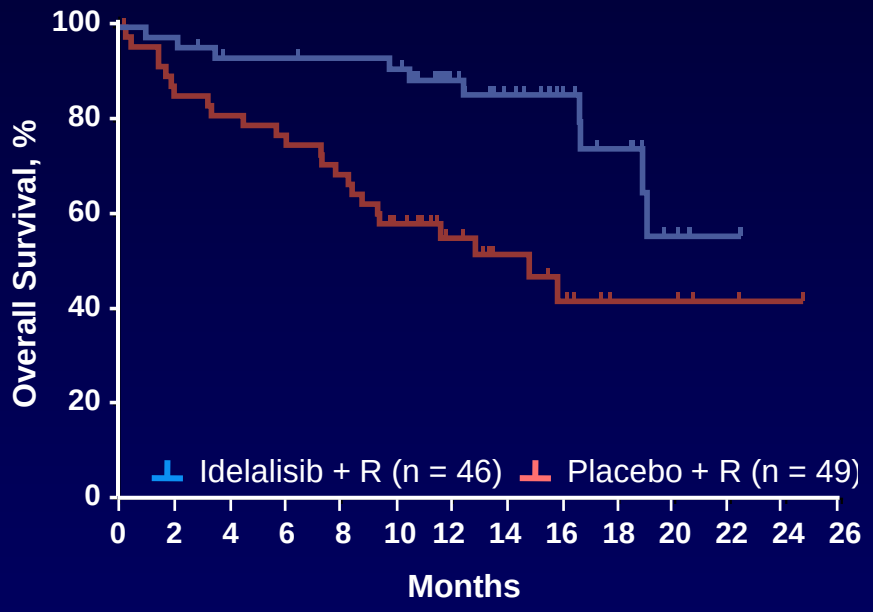
*As randomized, including crossover

Overall Survival, Including Extension Study*

Idelalisib + R vs Placebo + R → Idelalisib

Del17p/TP53 Mutation (Either)

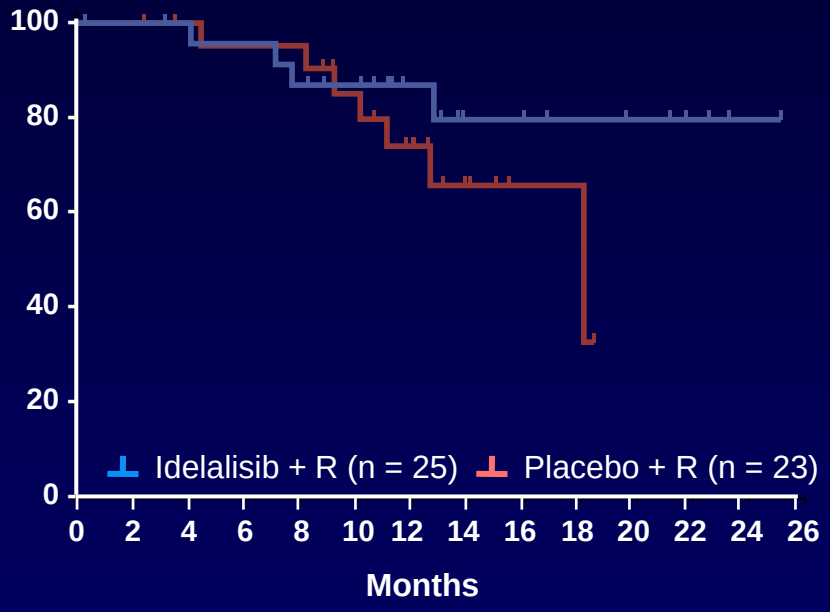


N at risk

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

	Median OS (95% CI)	HR (95% CI)	*P* value
IDELA + R	NR (18.8, –)	0.31 (0.15, 0.65)	.001
PBO + R	14.8 mo (8.4, –)		

Del11q Positive



N at risk

	25	24	23	22	20	17	12	8	7	6	5	3	1	0
	23	23	21	20	20	16	11	5	2	2	0			

Median OS (95% CI)	HR (95% CI)	*P* value
NR (–, –)	NA	.21
18.1 (11.1, –)		

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*As randomized, including crossover

Adverse Events in ≥15% of Patients

Idelalisib + R vs Placebo + R → Idelalisib

	IDELA + R (N = 110)				PBO + R → IDELA (N = 108)			
	Any Grade, %		Grade ≥3, %		Any Grade, %		Grade ≥3, %	
AE by Preferred Term	2nd IA	Update	2nd IA	Update	2nd IA	Update	2nd IA	Update
Any AE	96	98	64	80	98	100	52	78
Pyrexia	35	44	3	6	17	32	1	3
Diarrhea/Colitis	21	42	6	16	16	44	–	13
Fatigue	26	36	5	5	28	43	3	5
Cough	17	34	1	2	28	44	2	2
Nausea	26	31	–	2	21	36	–	1
Chills	21	26	2	2	16	22	–	–
Infusion reaction	19	20	–	–	30	32	4	4
Constipation	13	19	–	–	11	21	–	1
Decreased appetite	12	19	–	2	10	17	2	3
Pneumonia	10	18	8	13	13	31	9	20
Dyspnea	13	17	3	6	19	25	3	5
Rash	10	17	1	3	5	12	–	1
Vomiting	13	17	–	–	8	21	–	1
Upper respiratory infection	7	15	2	1	11	24	2	2
Edema, peripheral	10	15	–	–	9	19	2	3
Night sweats	11	14	–	2	10	20	–	–
Asthenia	7	12	1	–	9	19	4	6
Abdominal pain	7	10	1	2	9	19	1	2

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Select Lab Abnormalities

Idelalisib + R vs Placebo + R → Idelalisib

	Idelalisib + R (N = 110)				Placebo + R→ Idelalisib (N = 108)			
	Any Grade, %		Grade ≥3, %		Any Grade, %		Grade ≥3, %	
	2nd IA	Update	2nd IA	Update	2nd IA	Update	2nd IA	Update
ALT/AST elevation	40	49	9	6	20	53	1	6
Neutropenia	60	66	37	41	60	68	27	43
Anemia	29	33	7	8	32	50	17	24
Thrombocytopenia	19	29	11	14	32	40	18	20

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Summary and Conclusions

- **Phase III subgroup analysis demonstrates comparable efficacy of idelalisib + rituximab in the presence or absence of high-risk genomic alterations like unmutated *IGHV*, del17p/*TP53* mutation, and del11q**
- **Overall survival is significantly better for patients on idelalisib + rituximab despite crossover in extension design**
- **Idelalisib + rituximab has a manageable safety profile in patients with relapsed/refractory CLL**

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