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Does idelalisib still have a role in CLL?

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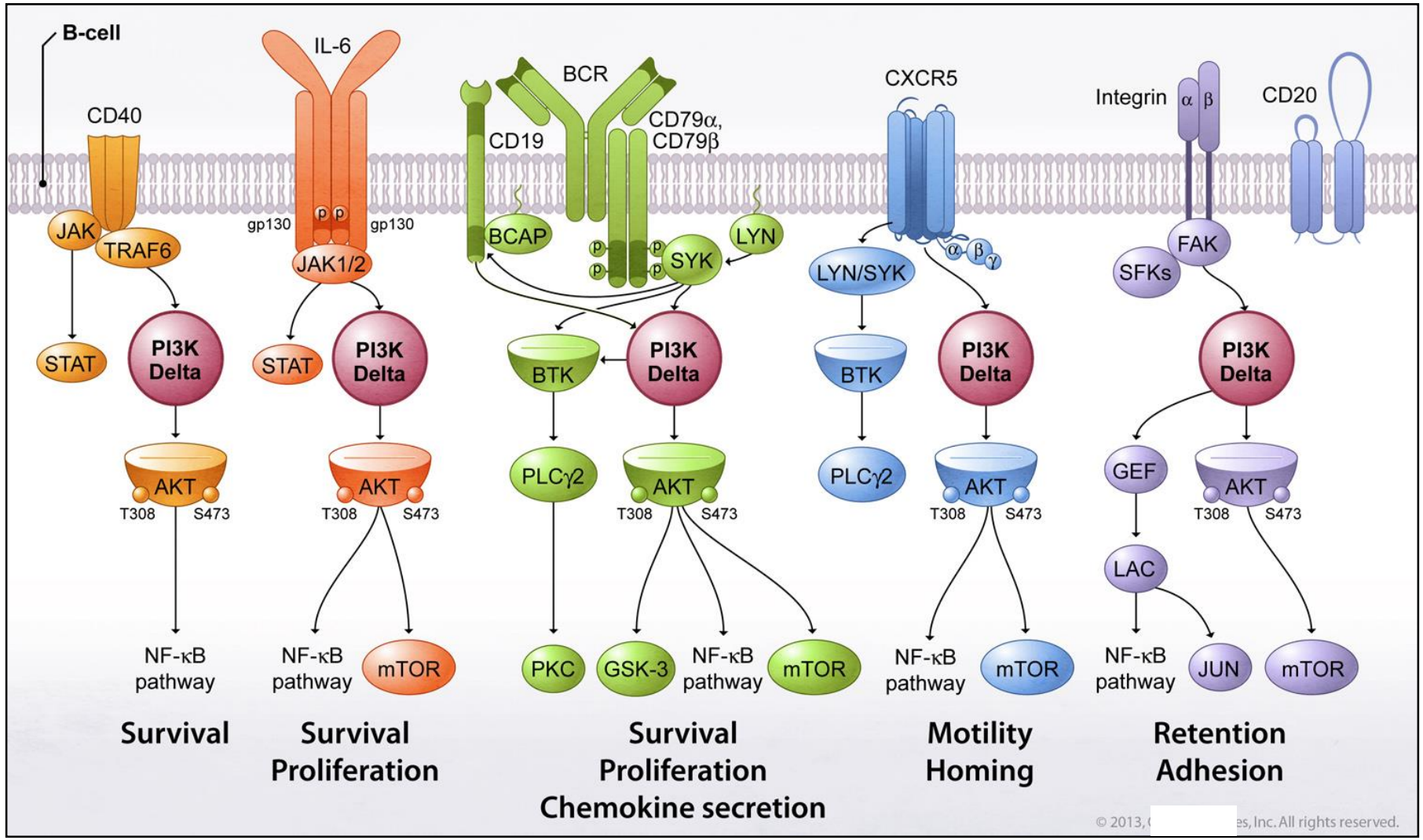
Disclosures for Andrew D. Zelenetz, MD, PhD

Research Support/P.I.	Genentech/Roche, Gilead, MEI, BeiGene
Employee	None
Consultant	BMS/Celgene/JUNO, Genentech/Roche, Gilead; BeiGene; Pharmacyclics, Jansen, Amgen, Astra-Zeneca, Novartis, MEI Pharma
Major Stockholder	None
Speakers Bureau	None
Scientific Advisory Board	Lymphoma Research Foundation, Adaptive Biotechnologies
Stockholder	None (not including potential holding of a 401K mutual fund)

PI3K is Involved in Multiple Critical Signaling Pathways



O'Brien et al. ASCO 2013, EHA 2012

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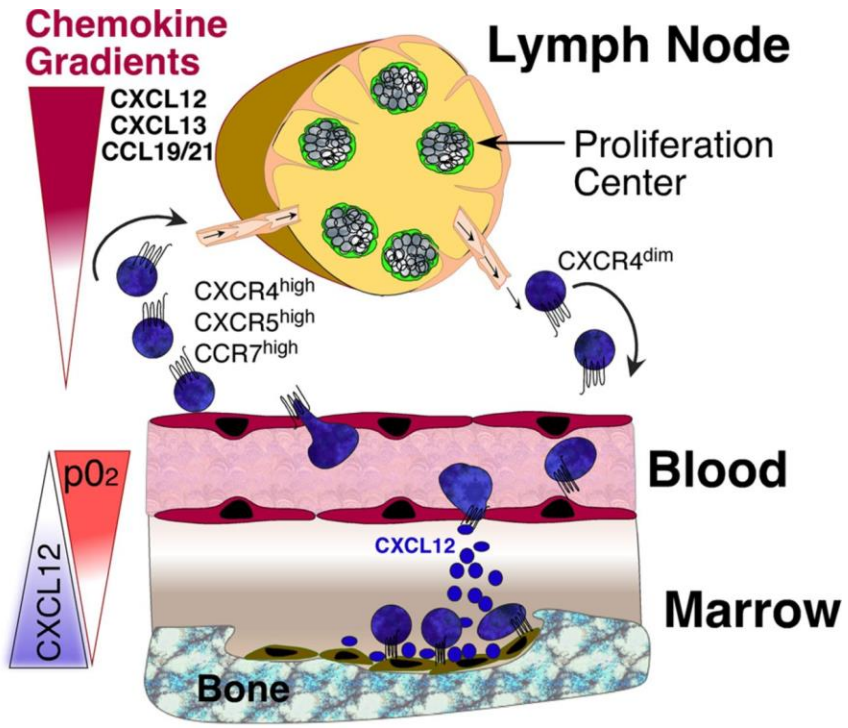
CLL Trafficking to the Microenvironment is Essential for Cell Survival



- CLL cell migrate to the microenvironment via chemokine gradients including CXCL12 binding to CXCR4 on the CLL cells
- CXCR4 signaling in CLL cells is dependent on SYK, BTK and PI3Kδ
- This signal can be disrupted pharmacologically

Davids and Burger, Open Journal of Hematology, 2012, 3(S1)-3, Jan A. Burger, and Emili Montserrat Blood 2013;121:1501-1509

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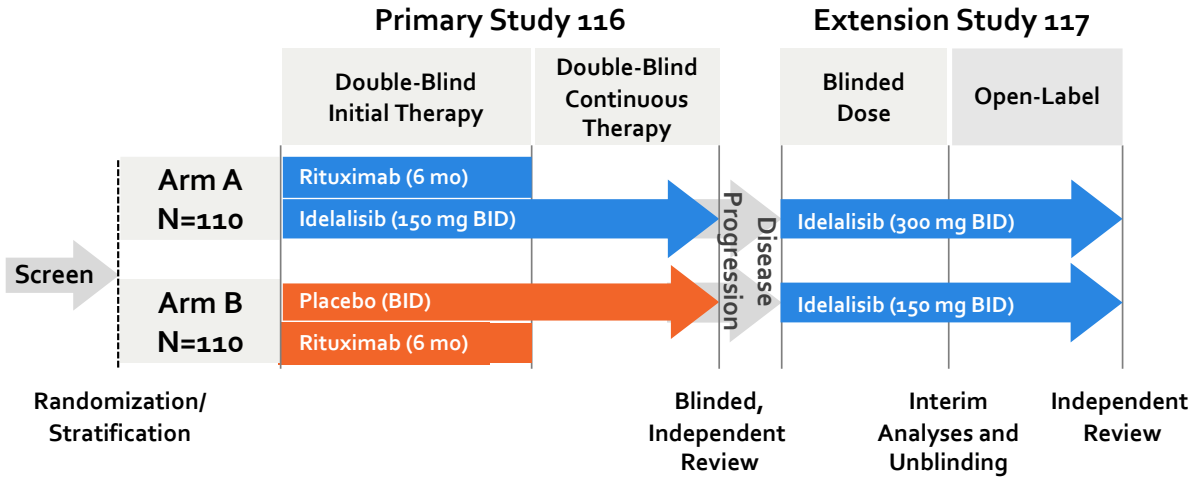
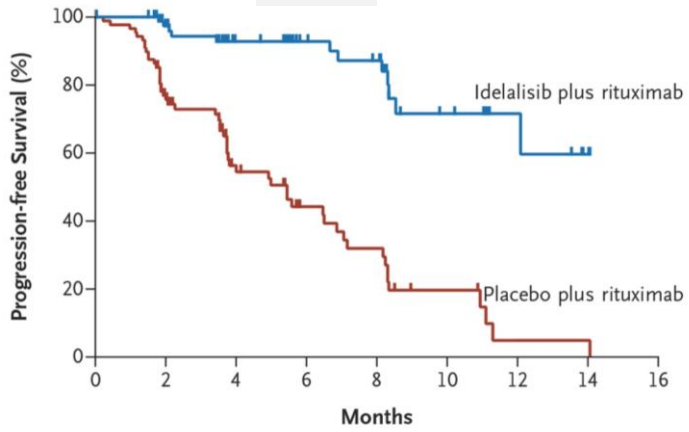
Idelalisib + R v Placebo + R (GS-US-312-116/117) for R/R CLL progressing within 24 months of last therapy: Final Analysis

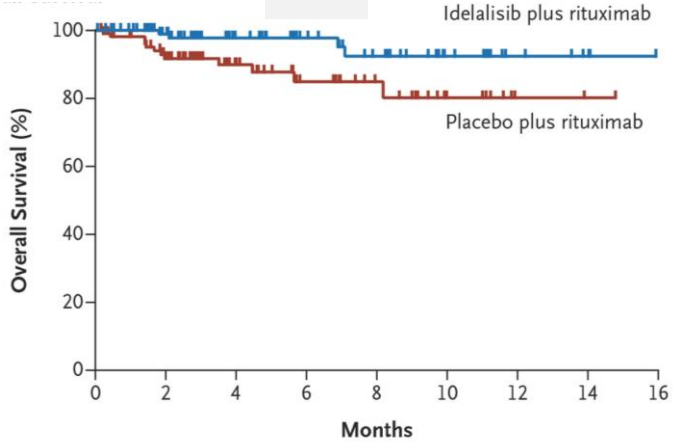


PFS



No. at Risk (events)									
Idelalisib	110 (0)	69 (2)	44 (5)	34 (5)	30 (7)	14 (11)	6 (11)	2 (12)	0 (12)
Placebo	110 (0)	62 (20)	30 (33)	18 (39)	13 (44)	6 (49)	1 (52)	1 (52)	0 (53)

OS



No. at Risk (events)									
Idelalisib	110 (0)	88 (1)	55 (2)	40 (2)	31 (4)	16 (4)	7 (4)	4 (4)	0 (4)
Placebo	110 (0)	76 (8)	43 (9)	25 (11)	18 (11)	8 (12)	2 (12)	1 (12)	0 (12)

Furman et al. N Eng J Med (2014) 370(11):997-1007Sharman et al. J Clin Oncol (2021) 37(16):1391-1402

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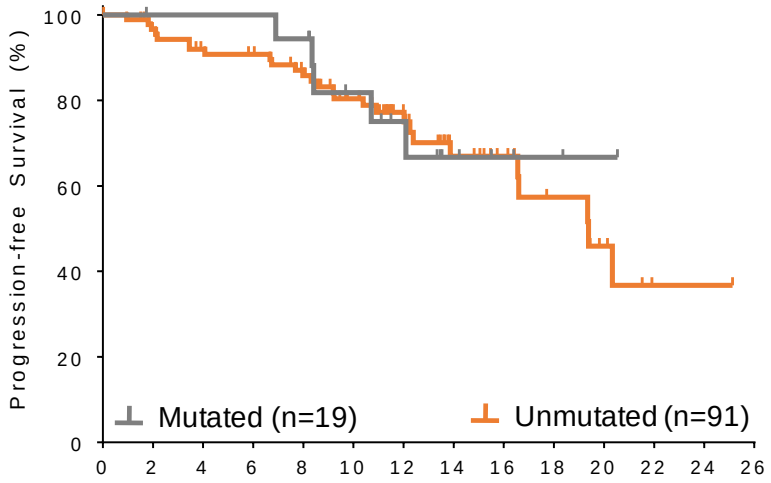
GS-US-312-116/117: PFS subgroup analysis of the idelalisib + R arm

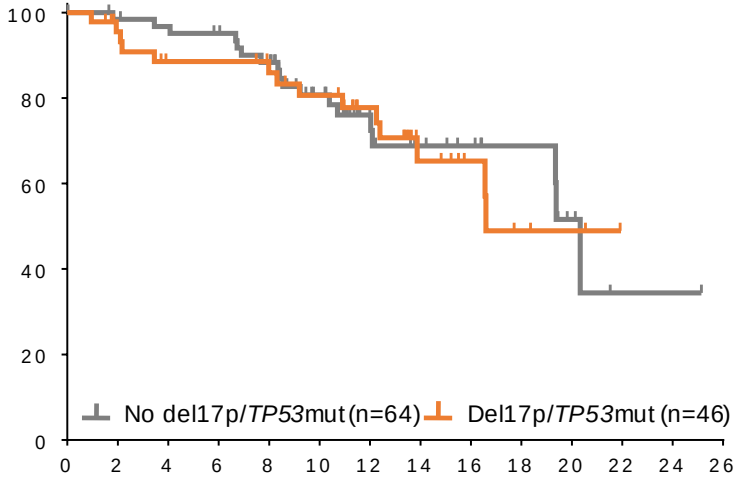
IGHV: Unmutated vs Mutated



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, –)	

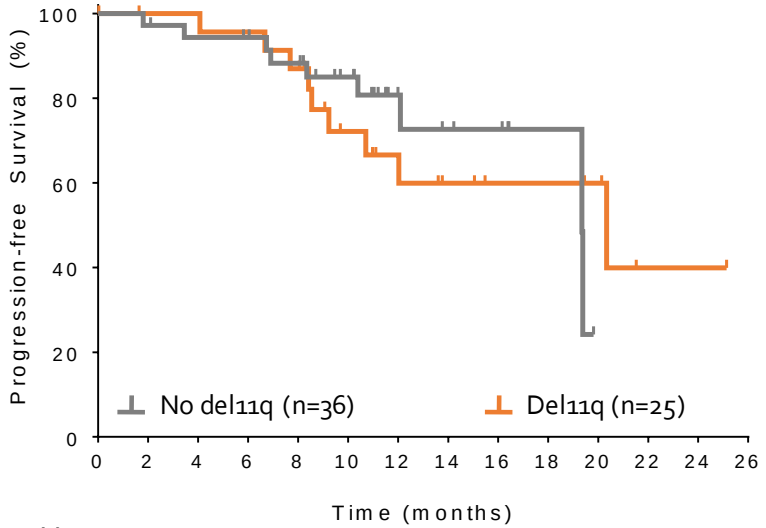
Del17p/TP53mut: Present vs Not Present



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, –)	

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, –)	0.84
Del	20.3 mo (9.2, –)	

Similar results were seen in GS-US-312-119 (Idelalisib + Ofatumumab versus Placebo + Ofatumumab) without an OS benefit (HR 0.75, 0.48-1.18, p=0.27)

Furman et al. N Eng J Med (2014) 370(11):997-1007; Sharman et al. J Clin Oncol (2021) 37(16):1391-1402; Jones et al. Lancet Haematol (2017) 4(3)114-126

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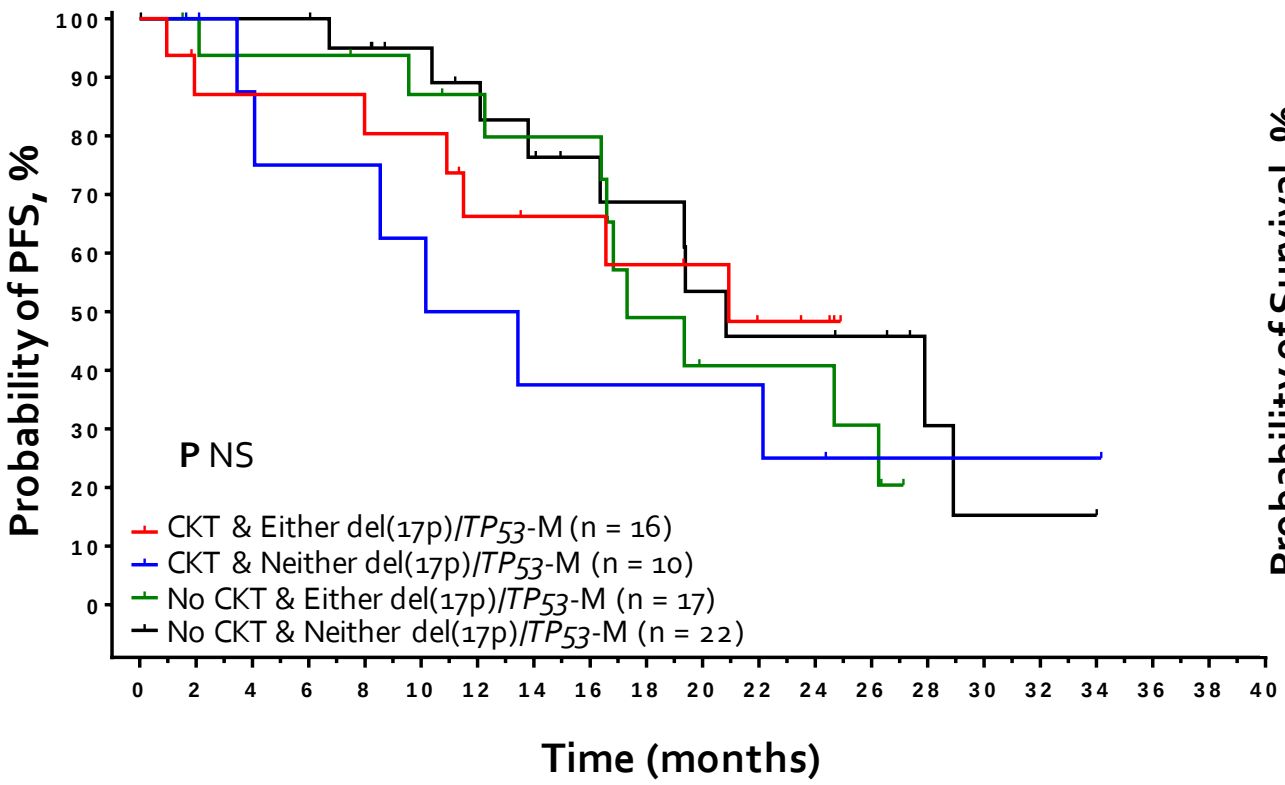
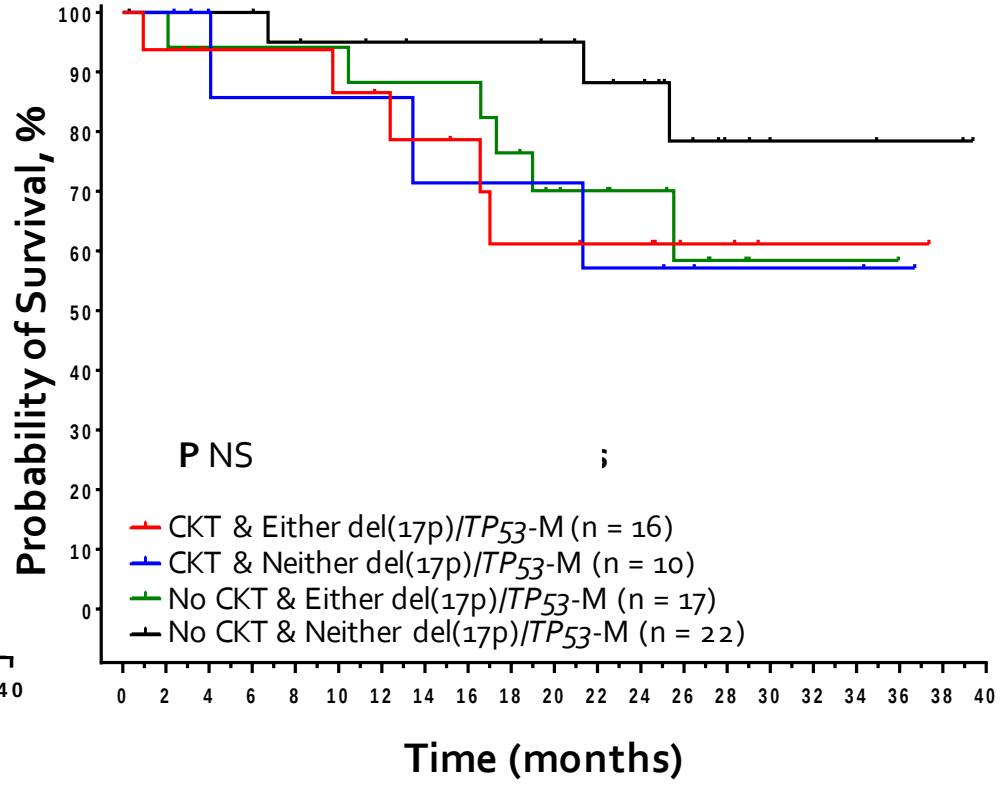
Impact of Complex Karyotype (CKT) on PFS and OS in Idelalisib-Treated Patients





- With a median follow up of 21.4 months, patients treated with idelalisib + R demonstrated similar ORR, PFS, and OS, irrespective of CKT status
  - ORR was 80.8% in CKT vs 89.7% in non-CKT
  - No significant interaction was observed for CKT and other risk factors with respect to PFS and OS

Kreuzer, et al. ASH 2016, Abstract #192, ASH, 2016

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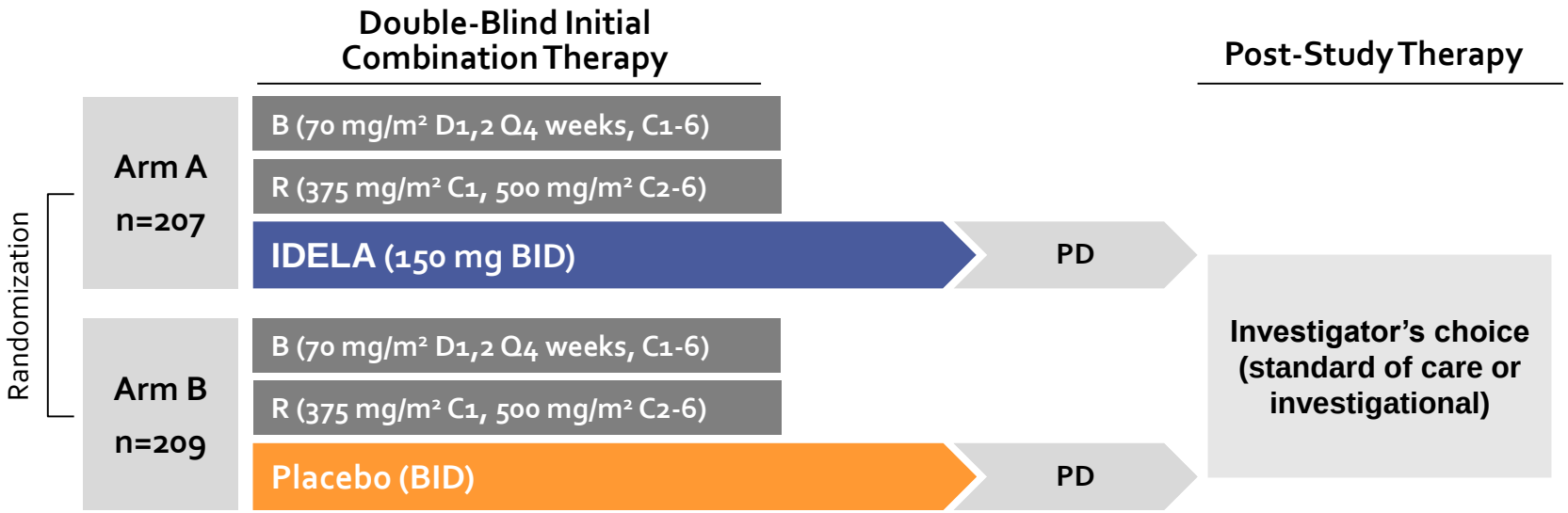
BR ± Idelalisib: Study 115 Design



Enrollment period June 2012 – August 2014

CT/MRI at baseline, then Q12 weeks, or at PD

Pre-specified interim analysis at 67% of events

Stratification

- 17p deletion and/or TP53 mutation
- IGHV mutation status
- Refractory vs relapsed disease

Endpoints

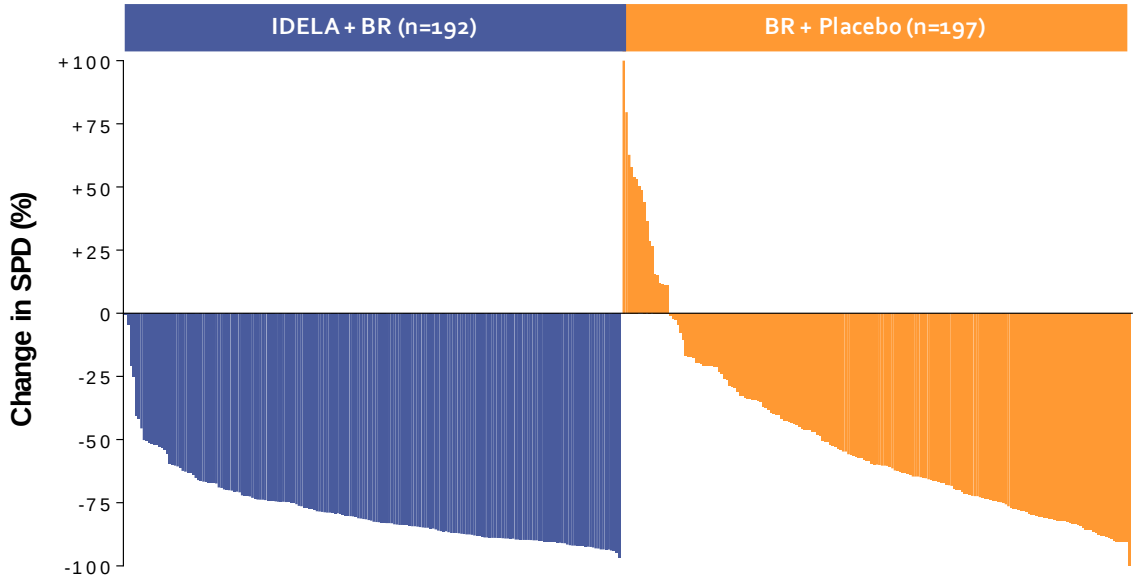
- Primary: PFS
- Secondary: ORR, nodal response, OS, CR

IGHV, immunoglobulin heavy chain variable region; CR, complete response; ORR, overall response rate; OS, overall survival, PD, disease progression; PFS, progression-free survival.

Zelenetz et al., http://dx.doi.org/10.1016/S1470-2045(16)30671-4

Study 115: Response Rates

Response Parameter	IDELA + BR n=207 % (95% CI)	BR + Placebo n=209 % (95% CI)
Overall response	68 (61, 74)	45 (38, 52)
CR	5 (2)	0
≥50% reduction in lymph nodes	96 (93, 99)	61 (54, 68)
Organomegaly response		
Spleen	82 (75, 88)	57 (49, 65)
Liver	56 (46, 66)	40 (31, 50)
Hematologic response		
Hemoglobin	88 (78, 95)	70 (58, 80)
Neutrophils	89 (71, 98)	84 (67, 95)
Platelets	89 (80, 95)	78 (66, 87)



Zelenetz et al., http://dx.doi.org/10.1016/S1470-2045(16)30671-4

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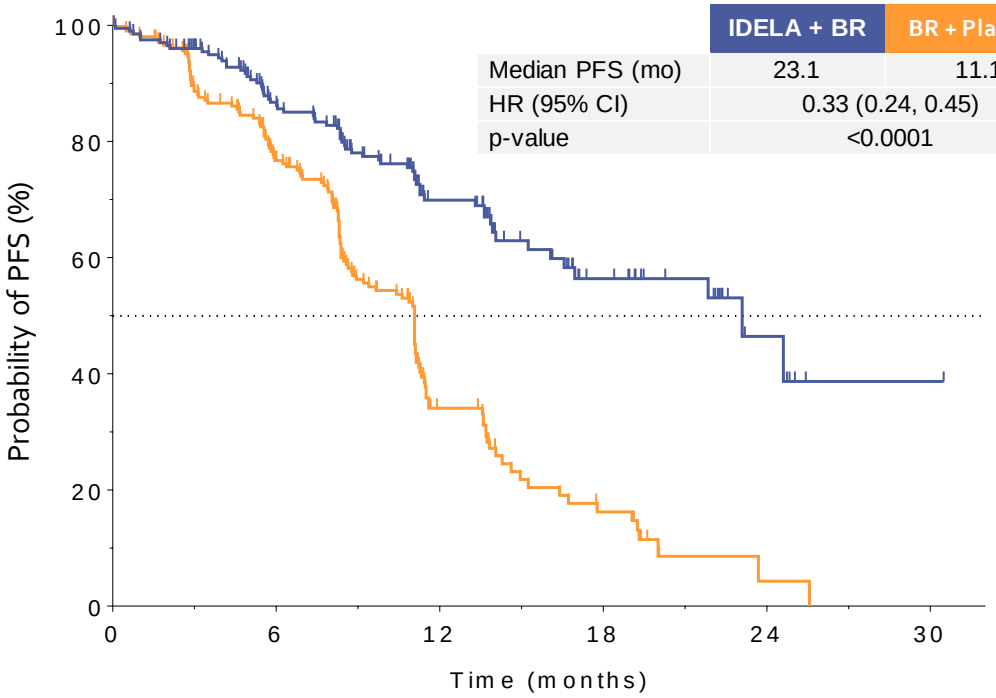
Study 115: Progression-free and overall survival

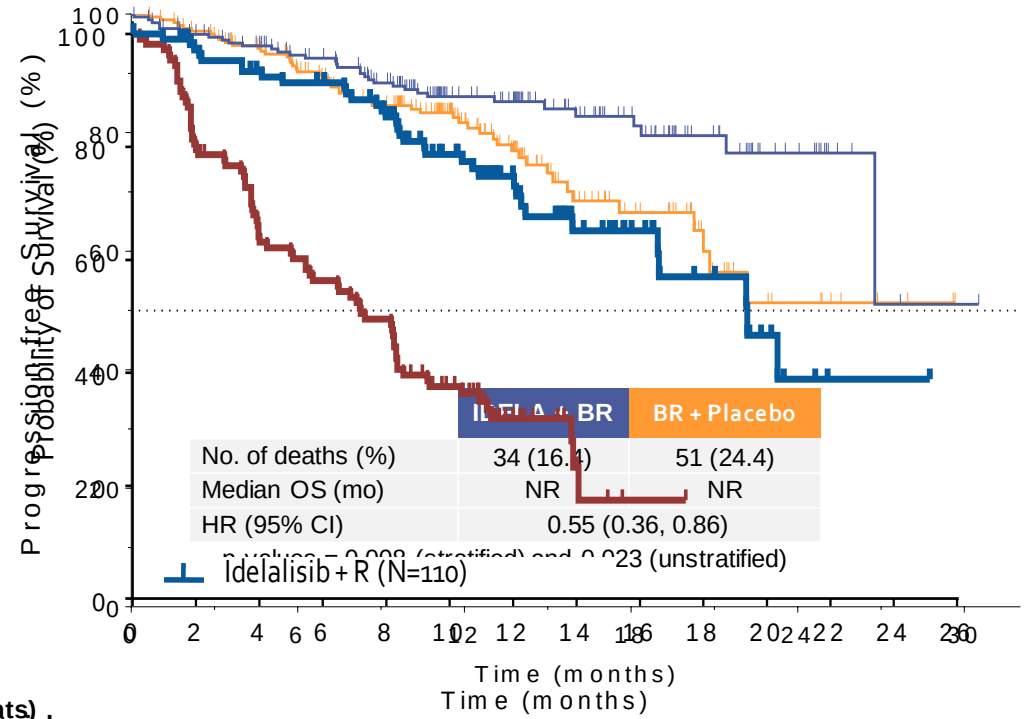
Median follow-up time = 12 months

PFS



No. at risk (events)						
IDELA + BR	207 (0)	154 (25)	74 (51)	27 (61)	6 (63)	1 (64)
BR + Placebo	209 (0)	145 (46)	36 (111)	11 (126)	1 (131)	0 (132)

116/117 OS-Idela v R



No. at risk (events)														
IDELA + BR	207 (0)	181 (14)	104 (27)	52 (30)	13 (33)	1 (34)								
BR + Placebo	209 (0)	180 (20)	93 (35)	33 (47)	8 (51)	0 (51)								
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	4	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)		

Zelenetz et al. Lancet Oncol. 2017 18(3):297-311; Sharman, ASH, 2014, Abstract 330

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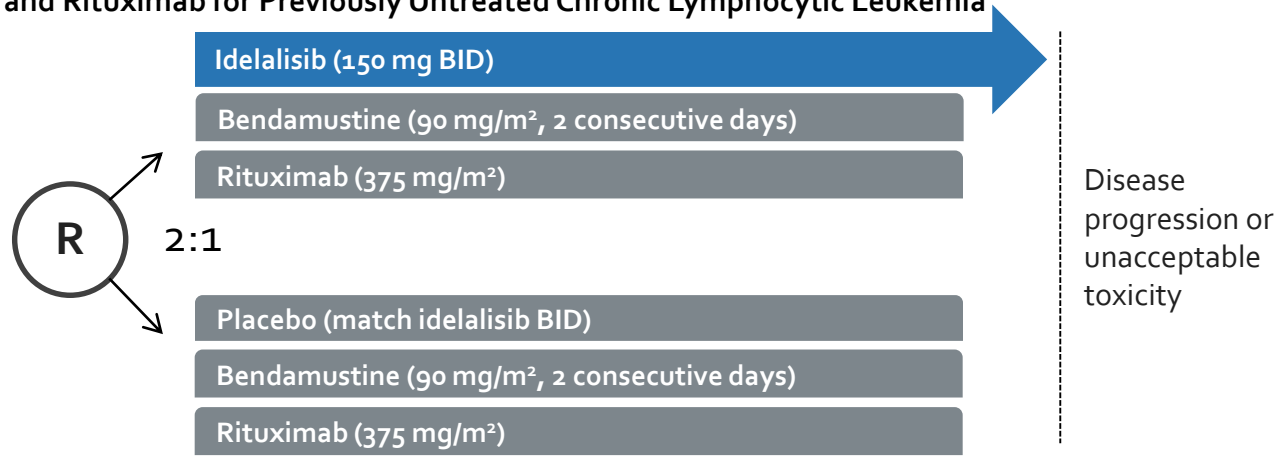
Safety Signal in Phase III

Study 123 Trial (Bridalveil) Schema—Phase 3 in 1L CLL

Key Clinical Trials in NHL

NCT01980888

Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib in Combination With Bendamustine and Rituximab for Previously Untreated Chronic Lymphocytic Leukemia



Patient Population	Endpoints	Timeline
• 311 patients with CLL • Age ≥ 18 years	Primary • PFS Secondary • ORR • Nodal RR • CRR • OS • MRD	Study start • February 2014 Primary completion • May 2016

1. ClinicalTrials.gov. http://www.clinicaltrials.gov/ct2/show/NCT01980888. Accessed 06/21/2016.

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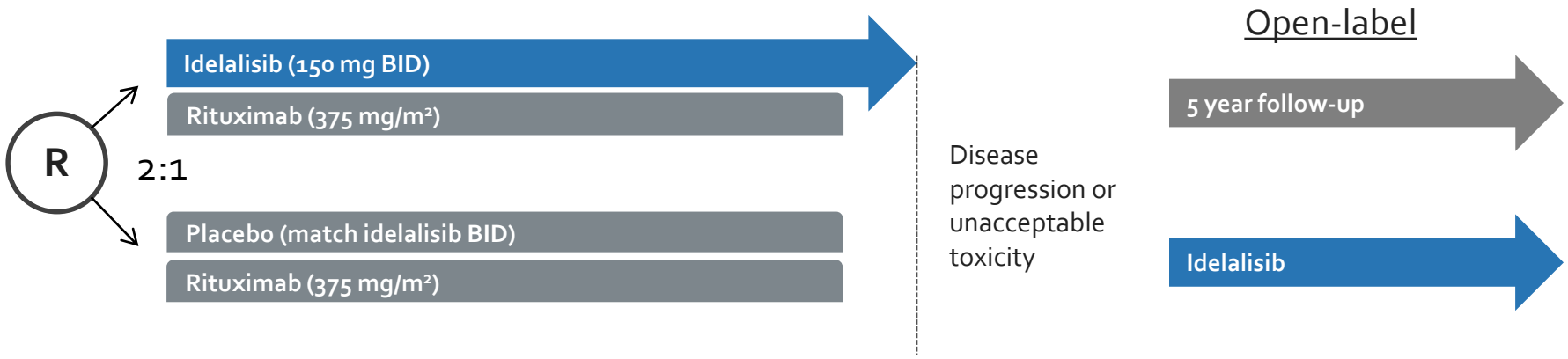
Study 124 Trial (Yosemite) Schema—Phase 3 in Relapsed iNHL

Key Clinical Trials in NHL

NCT01732913

Phase 3, randomized, double-blind study of efficacy and safety of idelalisib + rituximab for previously treated iNHL



Patient Population	Endpoints	Timeline
• 375 patients with follicular lymphoma (grade 1, 2, or 3a), SLL, LPL/WM, or MZL (splenic, nodal, or extranodal) • Age ≥ 18 years • Prior treatment for iNHL comprising: 1 or more regimens containing 2 or more doses of a monoclonal antibody such as rituximab, ofatumumab, or obinutuzumab	Primary • PFS Secondary • ORR • LNR rate • OS • CR rate	Study start • January 2013 Primary completion • June 2019

1. ClinicalTrials.gov. http://www.clinicaltrials.gov/ct2/show/NCT01732913. Accessed 09/08/2015. 2. http://www.waterfallstudies.com/yosemite/ Accessed 02/23/2016.

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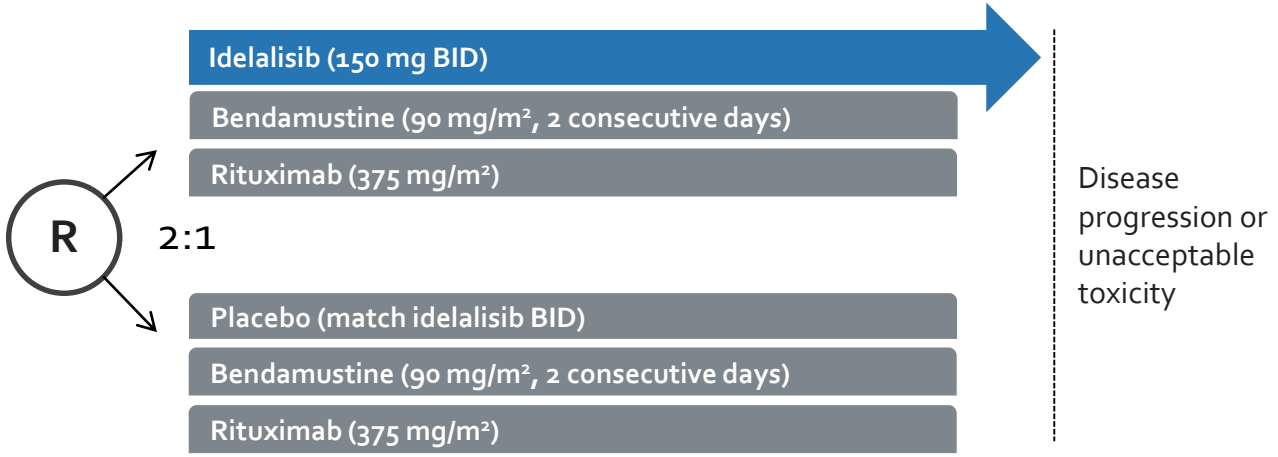
Study 125 Trial (Bridalveil) Schema—Phase 3 in Relapsed iNHL

Key Clinical Trials in NHL

NCT01732926

Phase 3, randomized, double-blind study of the efficacy and safety of idelalisib + bendamustine + rituximab for previously treated iNHL



Patient Population	Endpoints	Timeline
• 475 patients with follicular lymphoma (grade 1, 2, or 3a), SLL, LPL/WM, or MZL (splenic, nodal, or extranodal) • Age ≥ 18 years • Prior treatment for iNHL comprising: 1 or more regimens containing 2 or more cycles of chemotherapy and 2 or more doses of a monoclonal antibody such as rituximab, ofatumumab, or obinutuzumab	Primary • PFS Secondary • CR rate • ORR • LNR rate • OS	Study start • January 2013 Primary completion • September 2017

LPL, lymphoplasmacytic lymphoma.

1. ClinicalTrials.gov. http://www.clinicaltrials.gov/ct2/show/NCT01732926. Accessed 09/08/2015. http://www.waterfallstudies.com/bridalveil/ Accessed 02/13/2016.

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Safety Signals in Phase III Randomized Controlled Trials

123: CLL 1L BR + idelalisib v BR + placebo

124: FL R/R R + idelalisib v R + placebo

not chemotherapy candidates, median prior 1

125: FL R/R BR + idelalisib v BR + placebo

median prior 1

Study 123/124/125	Idelalisib	Placebo
All Deaths	49 (7.4%)	14 (3.5%)

PJP: Any Grade AE

Study	Idelalisib	Placebo
123	1	0
124	1	0
125	9	0
Death	2	0

CMV: Any Grade AE

Study	Idelalisib	Placebo
123	6	0
124	1	0
125	14	0
Death	4	0

Additional information

- Higher rates of
  - Infectious events
  - Febrile neutropenia

- Risk is greatest in first 6 months, then diminishes

- Risk increases with **LESS** prior therapy
  - Hypothesis is that this is T-cell mediated and may be related to PI3K inhibition of T_{REGS}

- Increased risk of death not seen in studies of R/R CLL or double refractory FL

Study 115, 116, 119*	Idelalisib	Placebo
All Deaths	114 (23.2%)	128 (31.5%)

*R/R CLL studies: 115 BR+P v BR+I; 116 R+P v R+I; 119: Ofa+P v Ofa+I

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Where dose idelalisib fit?

ASCEND: Acalabrutinib monotherapy versus investigator choice (BR or Idela-R)

R/R CL (N=310)

Stratified by:
- Del(17p)
- ECOG PS 0-1 vs 2
- 1-3 vs ≥ 4 prior therapies

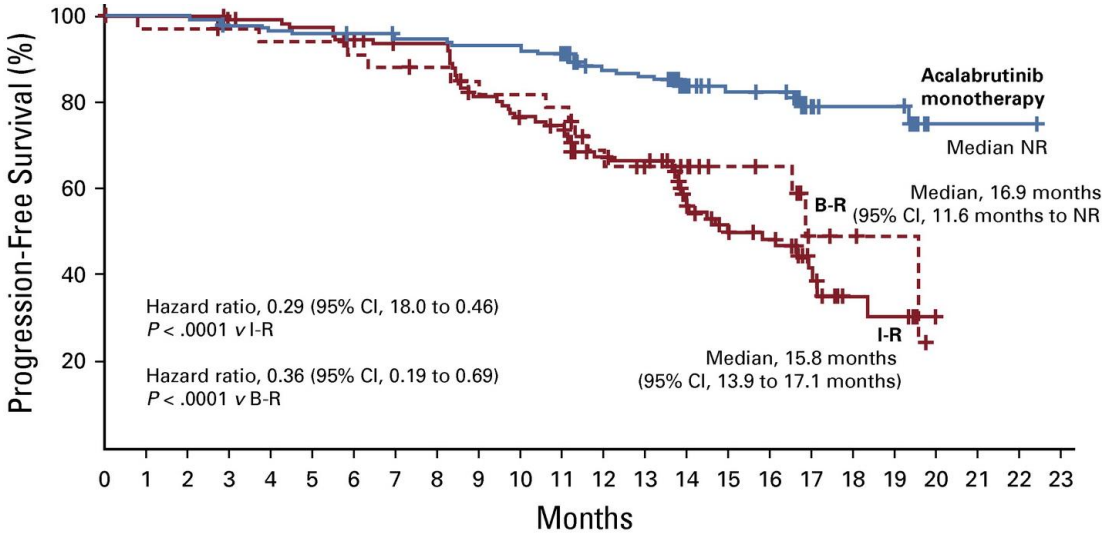
Randomized 1:1

Acalabrutinib

Idelalisib + Rituximab (IdR)
-OR-
Bendamustine + Rituximab (BR)

Primary Endpoint: PFS (IRC)

Crossover from IdR/BR allowed after confirmed PD



No. at risk (censored)

Acalabrutinib monotherapy	155	153	153	149	147	146	145	143	143	139	139	137	118	116	73	61	60	25	21	21	1	1	1	0
	(0)	(2)	(2)	(3)	(3)	(3)	(4)	(5)	(5)	(5)	(5)	(5)	(19)	(19)	(59)	(70)	(71)	(104)	(108)	(108)	(127)	(127)	(127)	(128)
I-R	119	116	116	113	112	110	105	100	100	85	79	76	62	59	41	33	29	14	7	6	0			
	(0)	(3)	(3)	(5)	(6)	(6)	(8)	(12)	(12)	(14)	(15)	(16)	(23)	(25)	(36)	(40)	(42)	(54)	(59)	(59)	(65)			
B-R	36	34	34	33	32	32	31	30	29	27	26	25	20	18	15	11	10	4	3	2	0			
	(0)	(1)	(1)	(2)	(2)	(2)	(2)	(2)	(3)	(4)	(4)	(4)	(6)	(7)	(10)	(14)	(15)	(19)	(20)	(21)	(22)			

Ghia et al. J Clin Oncol (2020) 38(25): 2849-2861

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Sequencing: Ibrutinib / Idelalisib Dosing

	Ibrutinib N=143	Idelalisib N=35
Median time from CLL dx → KI start	84 months	81 months
Median time on KI	5 months (0.25–41 months)	5.5 months (0.5–38 months)
Median starting dose	420 mg daily (140–560 mg) 86% FDA approved dose	150 mg BID (100–150 mg) 69% FDA approved dose
Proportion requiring dose modification	18% (n=141)	35% (n=34)
Proportion requiring dose interruption	43% (n=96)	64% (n=33)
KI administered as monotherapy	85%	20% (mostly paired with anti-CD20)*

* Idelalisib is licensed in combination with an anti-CD20 monoclonal antibody (rituximab or ofatumumab) Idelalisib SmPC (Dec 2016; available at www.ema.europa.eu).

Mato et al. Blood 2016 128:2199-2205

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Sequencing: Reasons for KI Discontinuation

	Ibrutinib % (n)	Idelalisib % (n)
Toxicity	51 (73)	52 (18)
CLL progression	28 (40)	31 (11)
RT	8 (11)	6 (2)
Cellular therapies (CAR-T or alloSCT)	2 (3)	0 (0)
Unrelated death/Other	11 (16)	11 (4)

Most Common Toxicities as a Reason for Discontinuation (KI intolerant patients)	
Ibrutinib (n=66) % (n)	**Idelalisib (n=18) % (n)**
Atrial fibrillation 20 (14)	Pneumonitis 33 (6)
Infection 12 (8)	Colitis 28 (5)
Cytopenias 9 (6)	Rash 17 (3)
Bleeding 9 (6)	Transaminitis 11 (2)
Pneumonitis 8 (5)	Infection 6 (1)

Mato et al. Blood 2016 128:2199-2205

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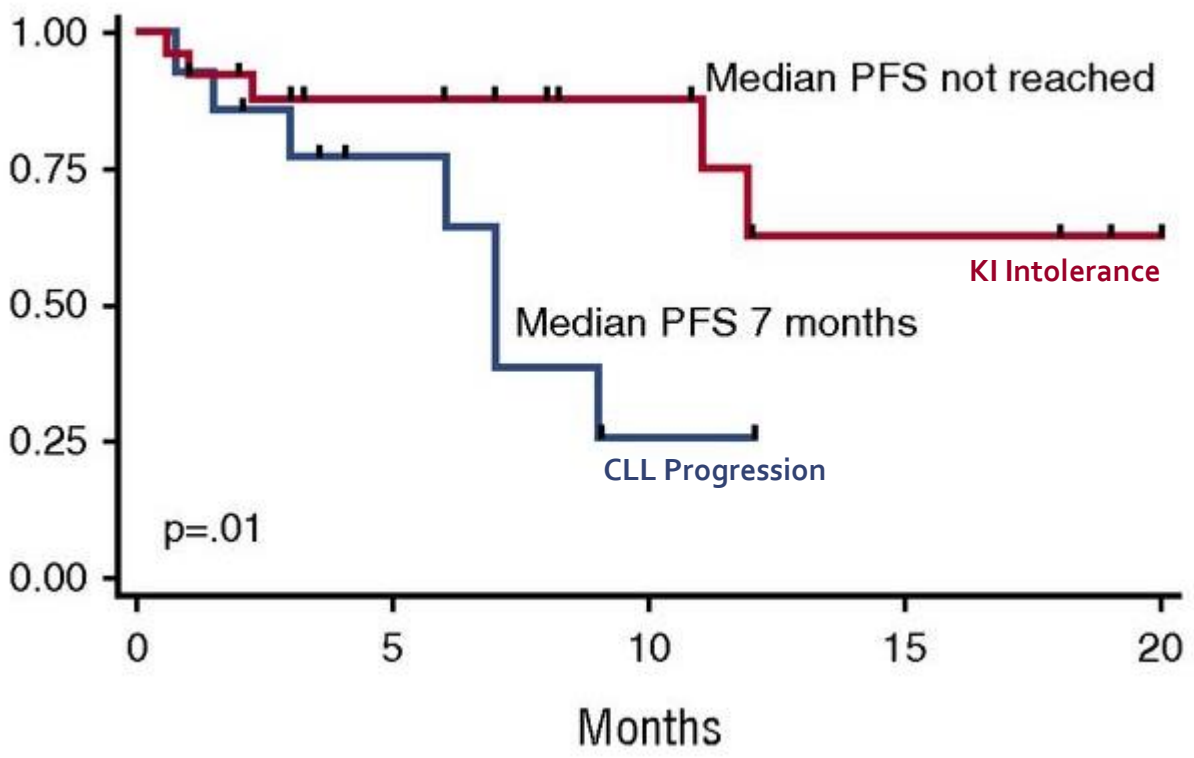
Sequencing: Responses following kinase inhibitor (KI) discontinuation

	Alternate KI	Ibrutinib → Idelalisib	Idelalisib → Ibrutinib	KI→BH3 mimetic
Number	38	16	22	13
ORR	50%	28%	64%	76%
CR	0%	0%	0%	7%
PR	50%	28%	64%	69%
SD	30%	45%	23%	16%
PD	20%	27%	13%	8%

PFS of Alternative KI

Following Discontinuation for CLL Progression vs Intolerance



Sequencing an alternative kinase inhibitor after POD has limited benefit and idelalisib after ibrutinib has a low response rate

Mato et al. Blood 2016 128:2199-2205

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Positioning of Idelalisib

- **PI3Kδ is a validated target in relapsed/refractory CLL**
  - Idelalisib improves PFS (versus rituximab, ofatumumab, BR) as well as OS (versus rituximab and BR)
  - Exposure to idelalisib is limited by treatment emergent adverse events particular diarrhea/colitis and less commonly pneumonitis and infection

- **Toxicity limits utility of the drug**
  - Use of idelalisib in 1L CLL is limited by toxicity with excess deaths in idelalisib containing arm in a phase 3 trial (BR v BR-Idelalisib)

- **BTKi is superior to PI3Kδi in R/R CLL**
  - Acalabrutinb versus idelalisib or BR demonstrated superiority of BTKi over PI3Kδi
  - Idelalisib has limited activity in patients progressing on BTKi
  - Idelalisib potentially has a role in patients who are intolerant of BTKi
    - Activity of idelalisib following BTKi and BH_3 mimetic has not been studied

- **Alternative doses and schedules need further exploration to decrease toxicity while maintaining efficacy**