Memorial Sloan Kettering Cancer Center

Idelalisib: First in class PI3Kδ inhibitor, where does it fit?

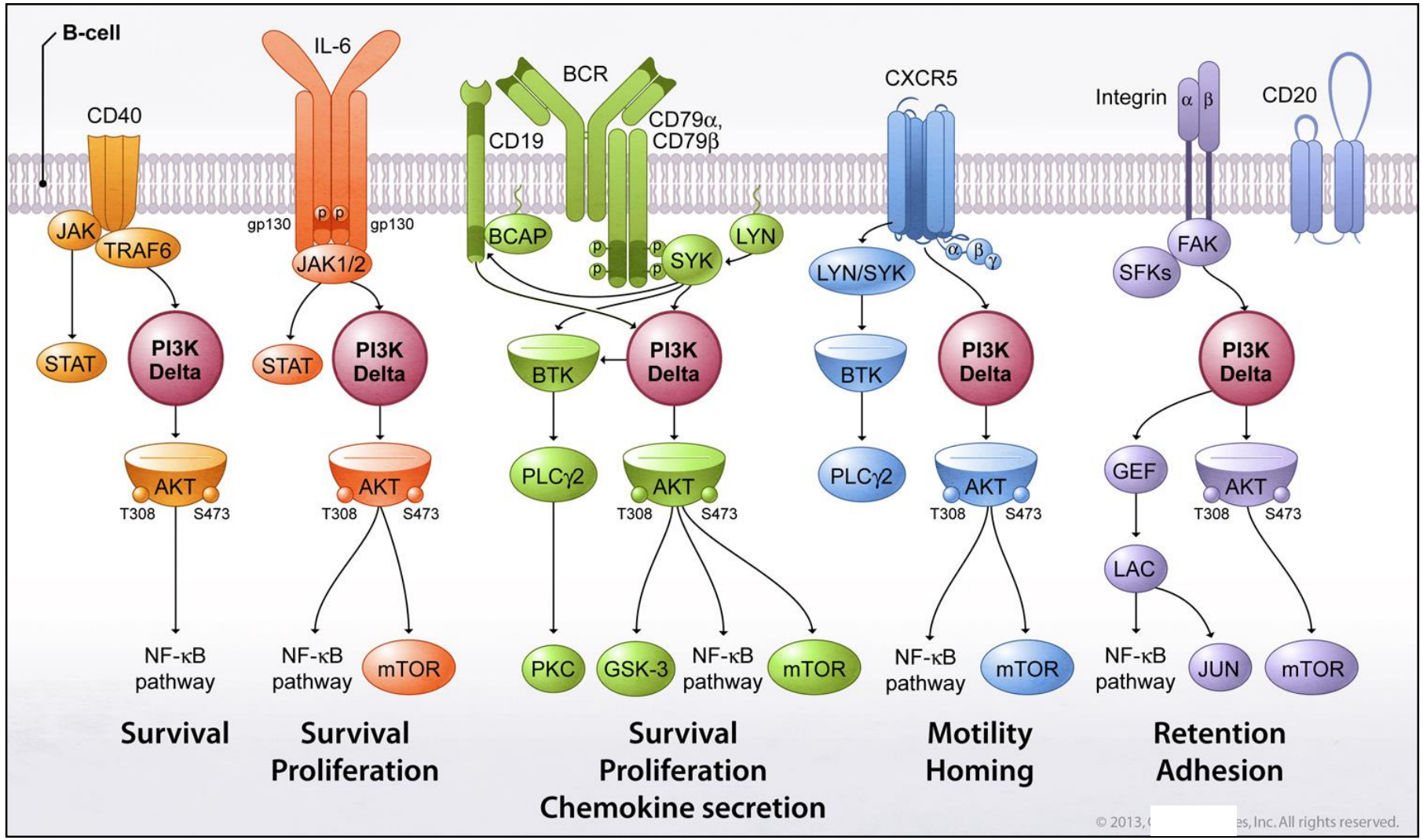
Andrew D. Zelenetz, M.D., Ph.D.
Medical Director, Quality Informatics
Attending Physician, Lymphoma Service
Professor of Medicine, Weill-Cornell Medical College
Chair, NCCN B-Cell Lymphoma Guideline Panel

Disclosures for Andrew D. Zelenetz, MD, PhD

Research Support/P.I.	Genentech/Roche, Gilead, MEI, BeiGene
Employee	None
Consultant	Celegene; Genentech/Roche; Gilead; BeiGene; Amgen; Novartis; Astra-Zeneca; Verastem
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)

Memorial Sloan Kettering Cancer Center

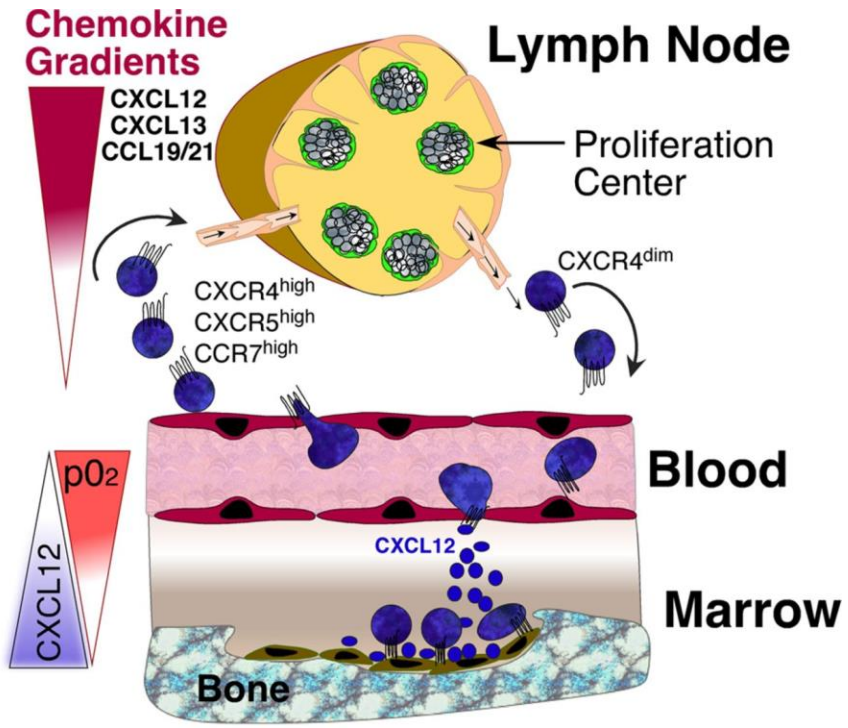
PI3K is Involved in Multiple Critical Signaling Pathways



O'Brien et al. ASCO 2013, EHA 2012

Memorial Sloan Kettering Cancer Center

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

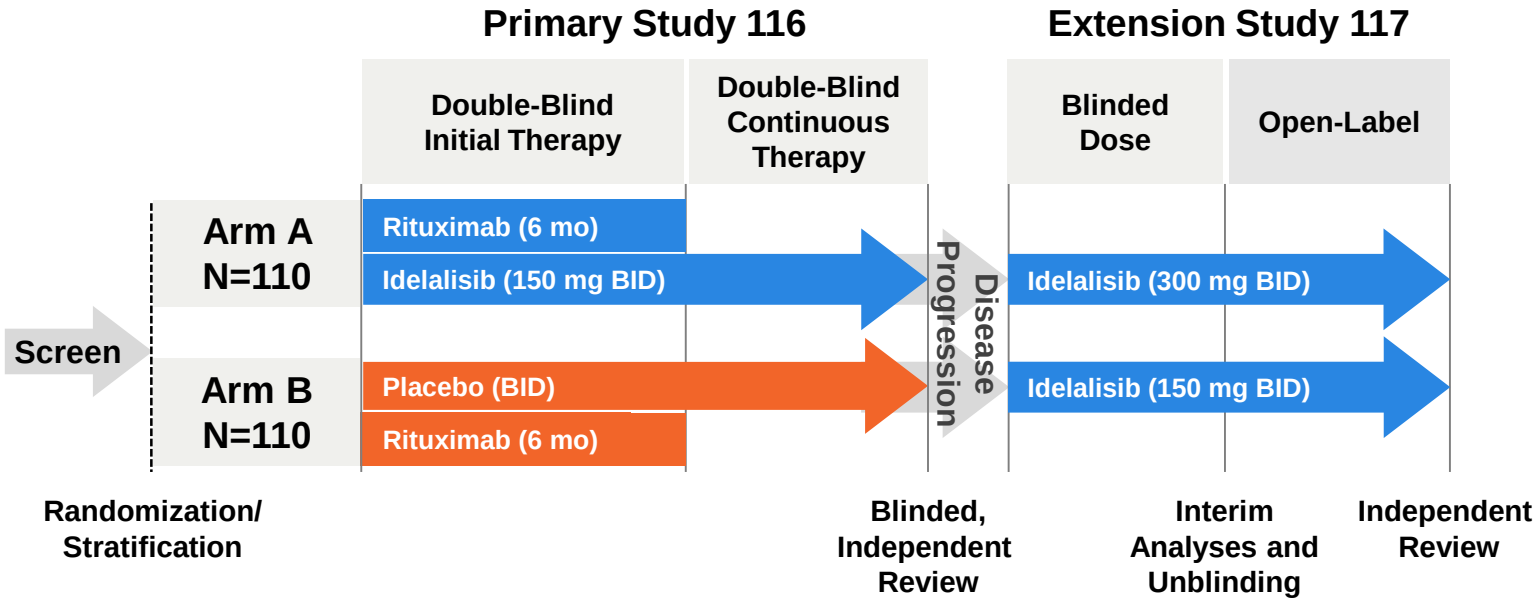
Davids and Burger, Open Journal of Hematology, 2012, 3(S1)-3, Jan A. Burger, and Emili Montserrat Blood 2013;121:1501-1509

Memorial Sloan Kettering Cancer Center

Idelalisib + R v Placebo + R: Second Interim Analysis with Crossover

Population:

Relapsed CLL warranting treatment (iwCLL); progression < 24 mo since last treatment



	Median Follow-up, months		
	Idelalisib + R	PBO + R	
1st Interim Analysis	4	4	DMC halted trial (Furman NEJM 2014) 50% events
2nd Interim Analysis	6	5	Blind ended (Coutre ASCO 2014) 63% events • Arm A continues (amendment to be all 150mg) • Arm B crosses over
Update	13	11	PFS, OS by subgroup analysis

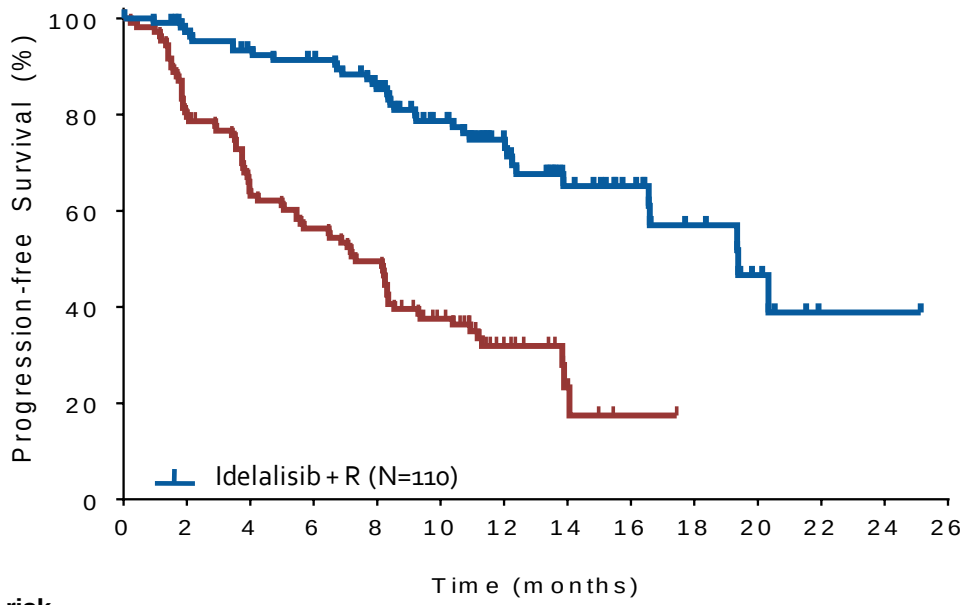
Sharman, ASH, 2014, Abstract 330

Memorial Sloan Kettering Cancer Center

Idelalisib + R v Placebo + R: PFS and OS including crossover

PFS

All Patients



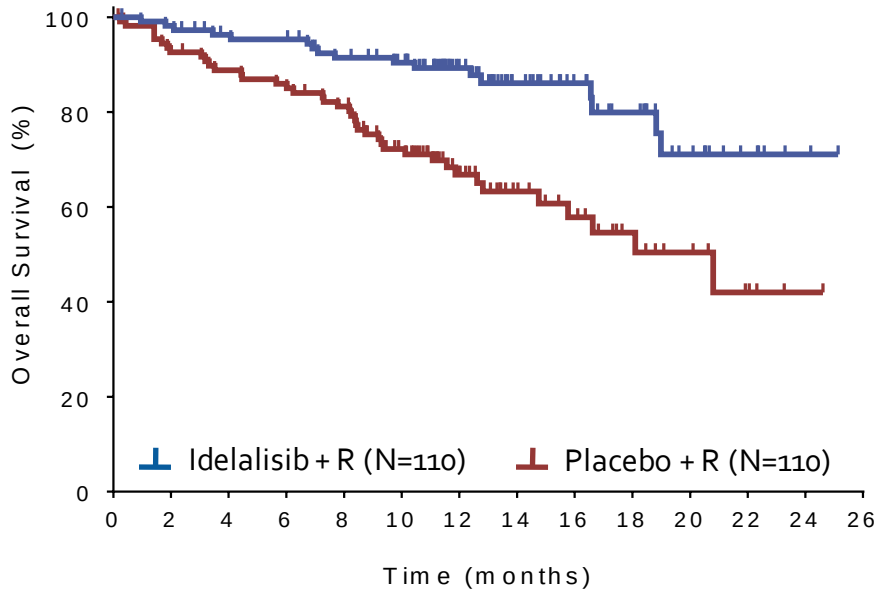
N at risk

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)		

OS

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

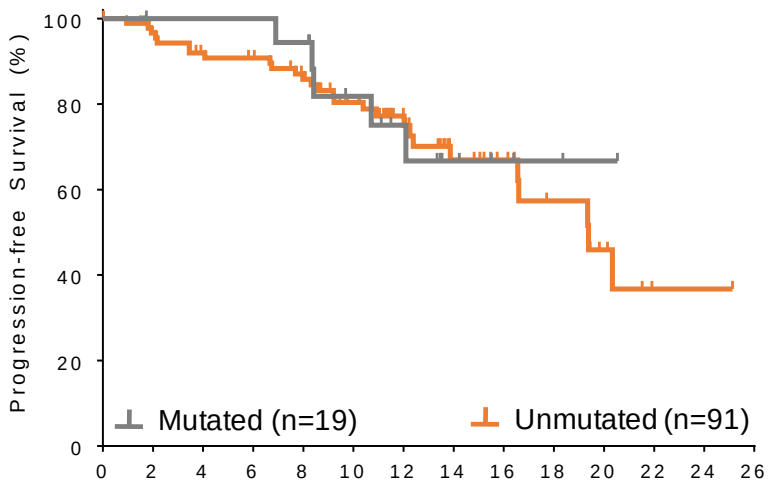
	Median OS (95% CI)	HR (95% CI)	p-value
IDELA + R	NR (–, –)	0.34 (0.19, 0.6)	0.0001
PBO + R	20.8 mo (14.8, –)		

Sharman, ASH, 2014, Abstract 330

Memorial Sloan Kettering Cancer Center

PFS Subgroup Analysis: Idelalisib + R (N=110)

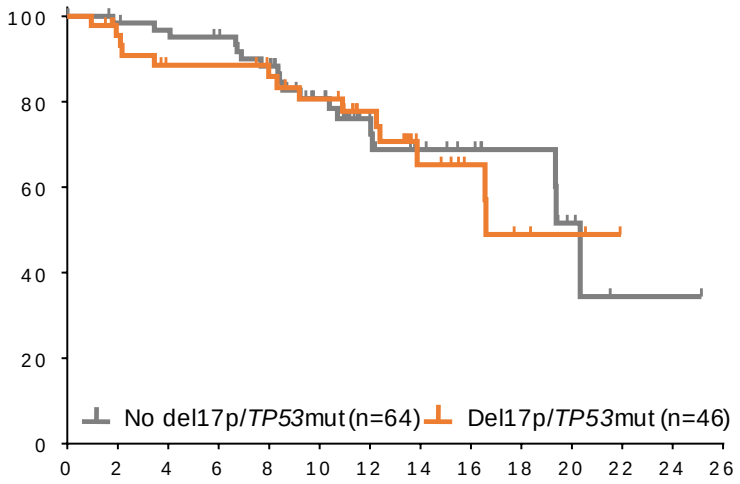
IGHV: Unmutated vs Mutated



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, –)	

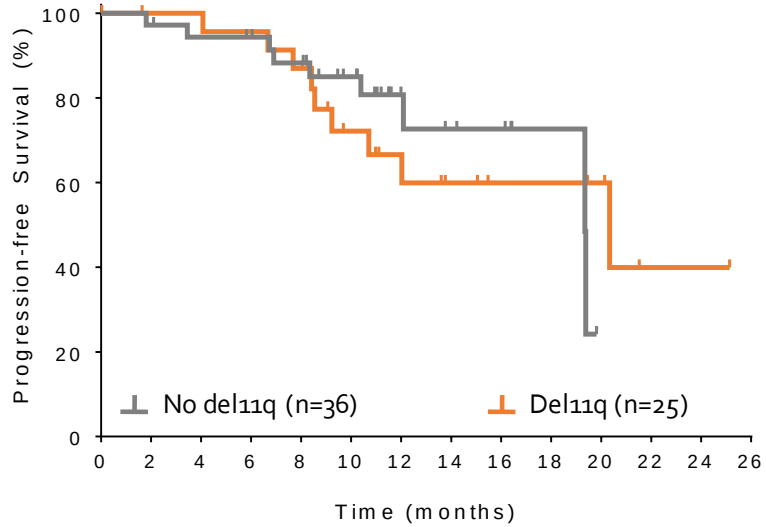
Del17p/TP53mut: Present vs Not Present



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, –)	

Del11q: Present vs Not Present



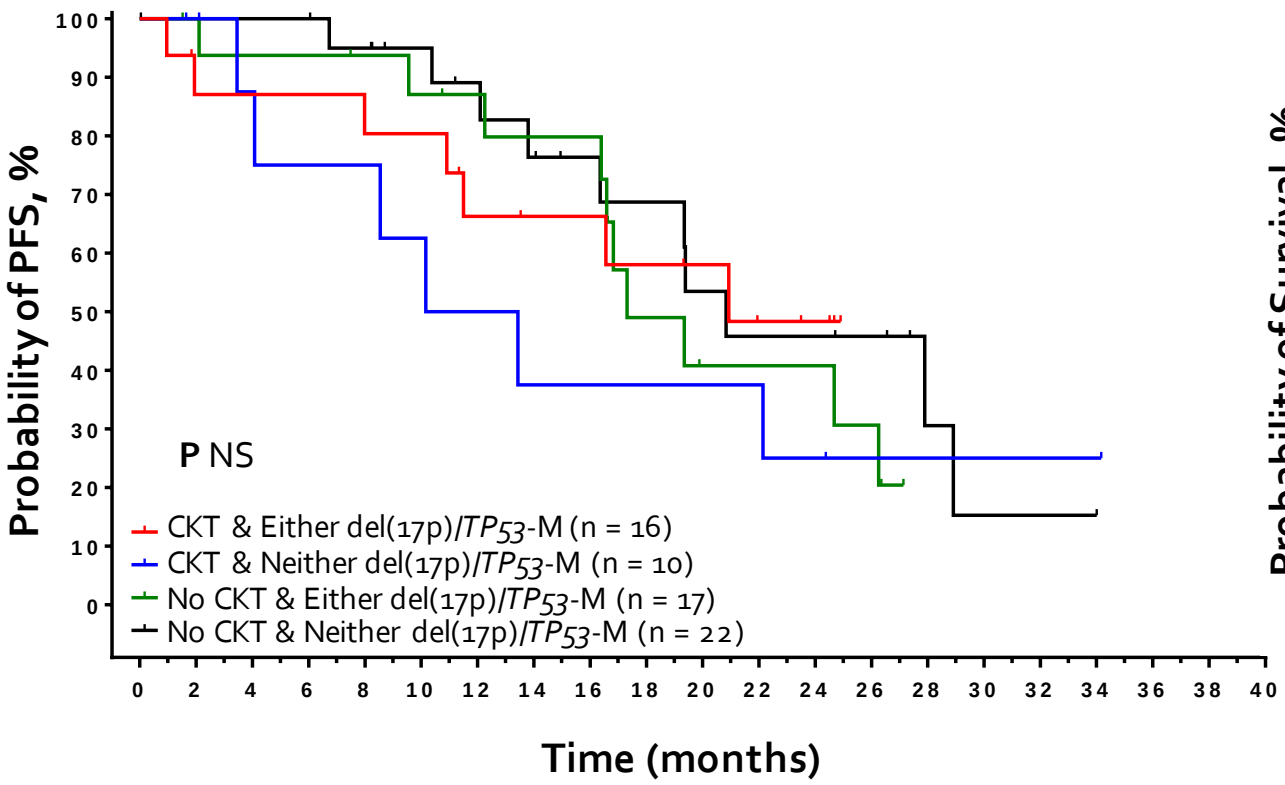
N at risk														
No del	36	35	33	32	29	22	10	7	6	3	0	0	0	0
Del	25	23	23	22	20	13	10	7	5	5	4	1	1	0

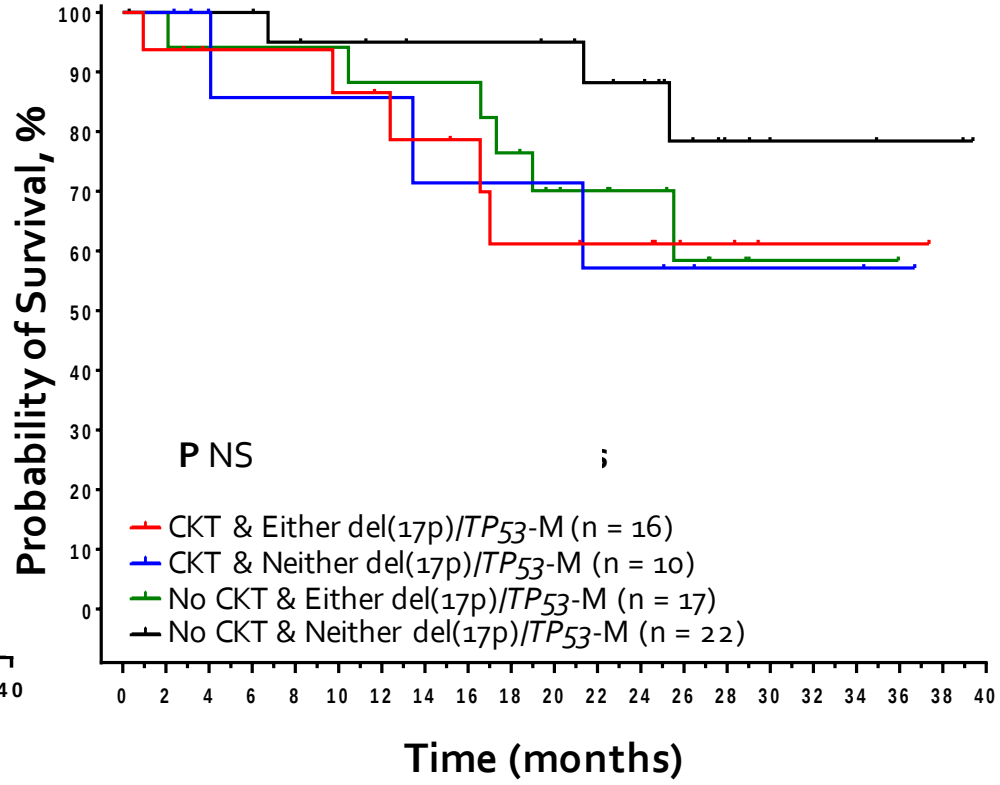
	Median PFS (95% CI)	p-value
No del	19.4 mo (12.1, –)	0.84
Del	20.3 mo (9.2, –)	

Sharman, ASH, 2014, Abstract 330

Memorial Sloan Kettering Cancer Center

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



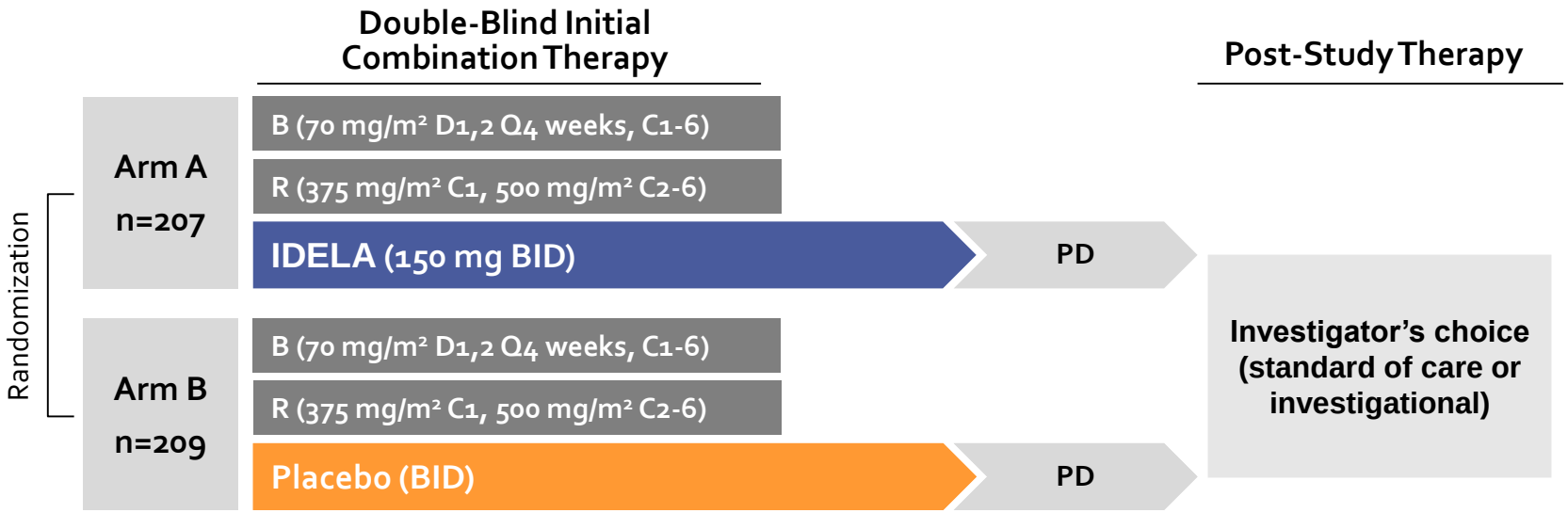


- With a median follow up of 21.4 months, patients treated with idelalisib + R demonstrated similar ORR, PFS, and OS, irrespective of CKT status
  - ORR was 80.8% in CKT vs 89.7% in non-CKT
  - No significant interaction was observed for CKT and other risk factors with respect to PFS and OS

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

Memorial Sloan Kettering Cancer Center

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

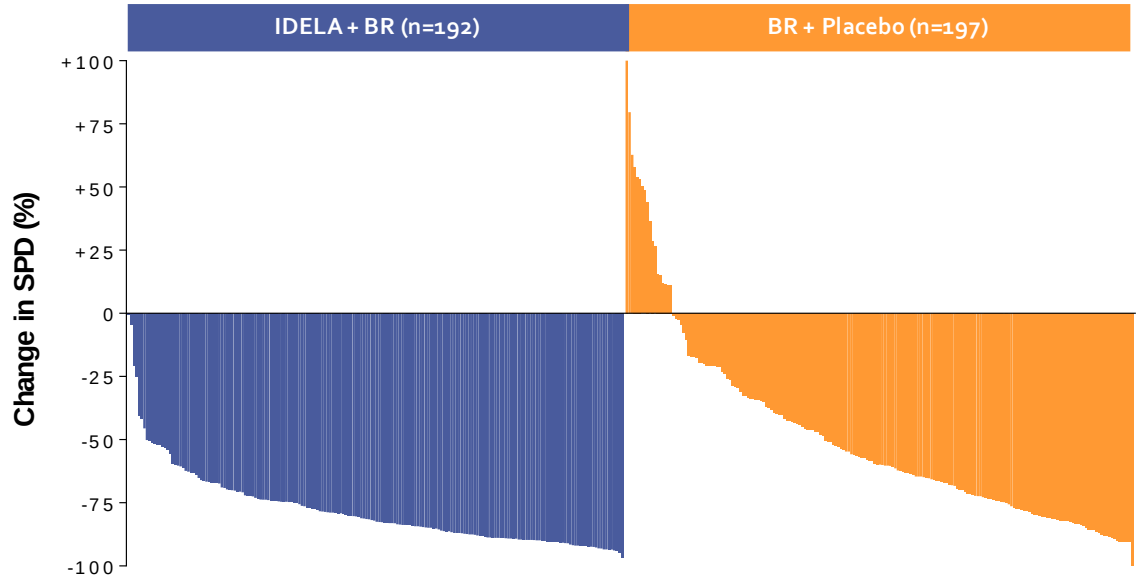
- Primary: PFS
- Secondary: ORR, nodal response, OS, CR

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)



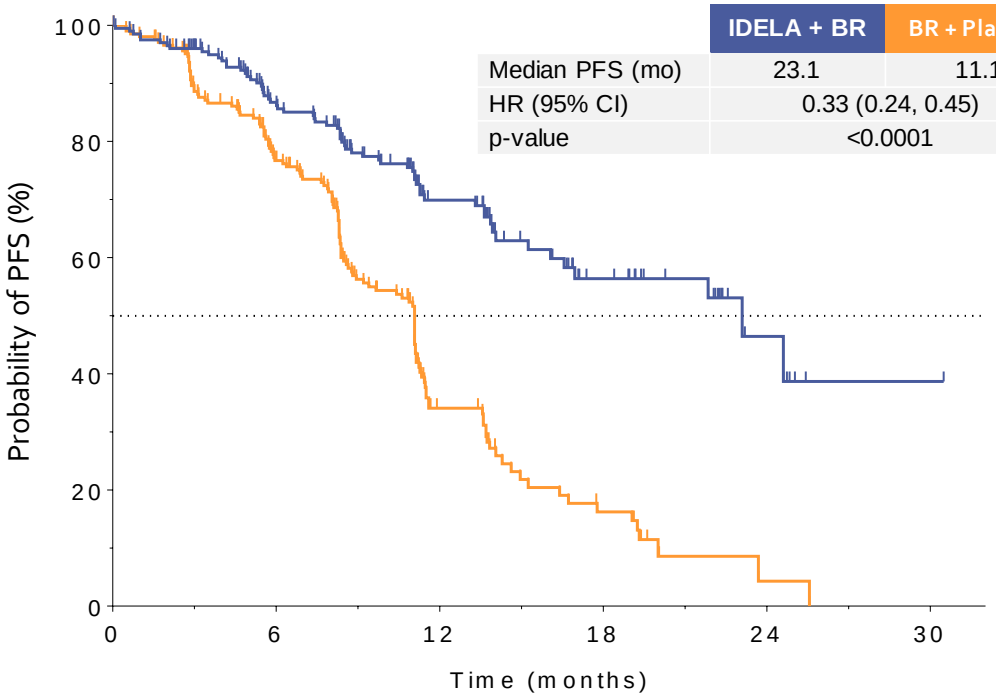
Zelenetz et al., http://dx.doi.org/10.1016/S1470-2045(16)30671-4

Memorial Sloan Kettering Cancer Center

Study 115: Progression-free and overall survival

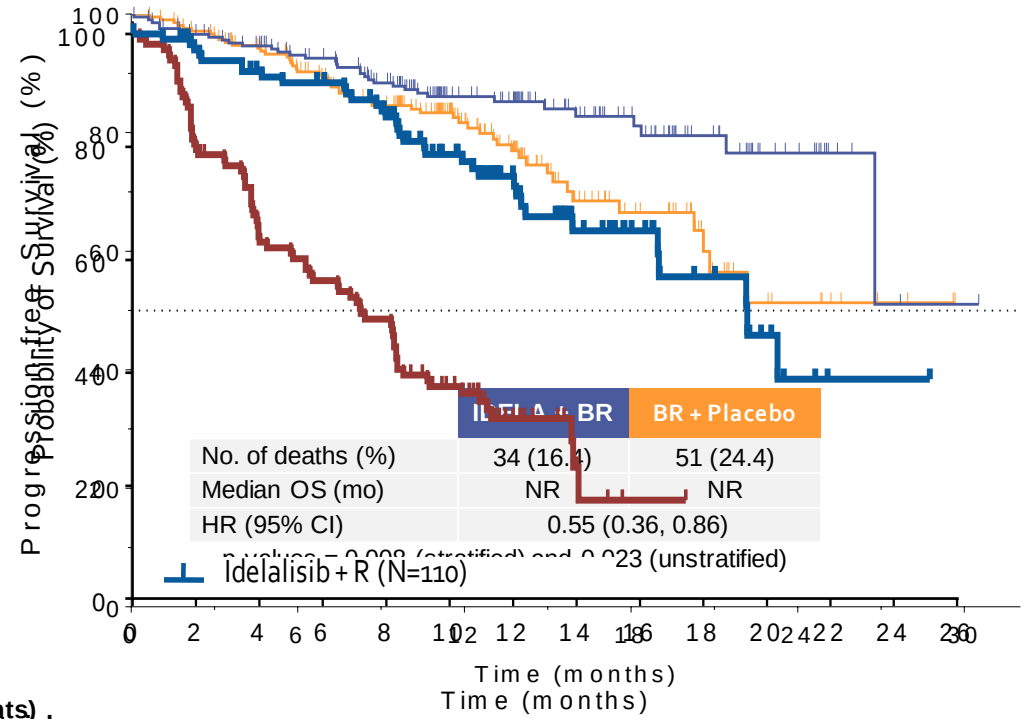
Median follow-up time = 12 months

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

Memorial Sloan Kettering Cancer Center

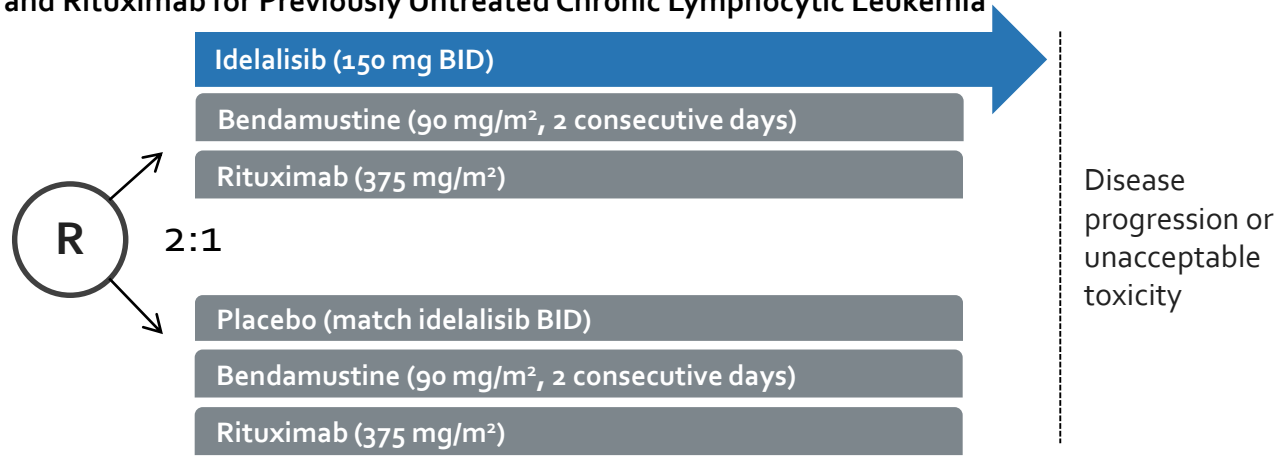
Safety Signal in Phase III

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.

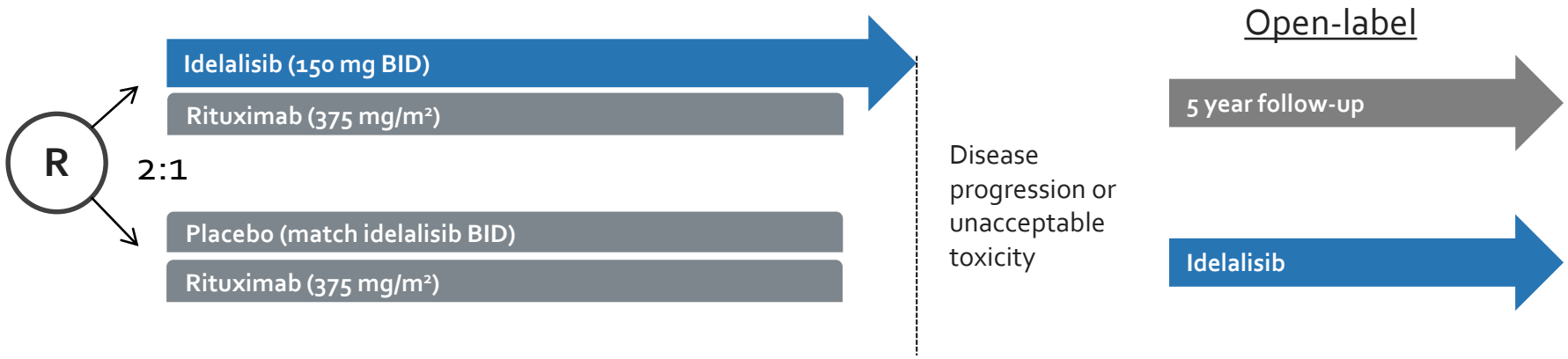
Memorial Sloan Kettering Cancer Center

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.

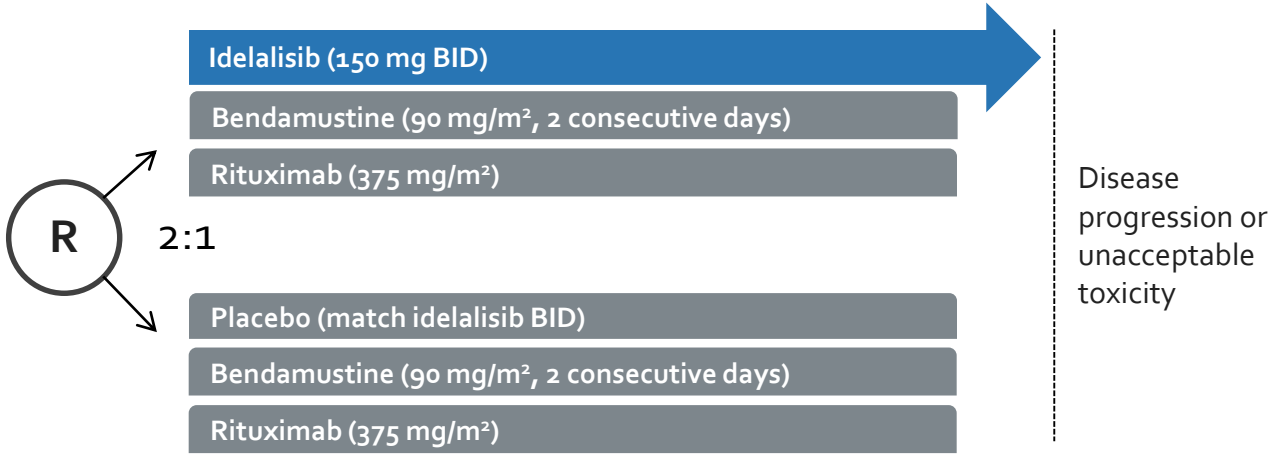
Memorial Sloan Kettering Cancer Center

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.

Memorial Sloan Kettering Cancer Center

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

Actions

- All upfront studies were discontinued including investigator initiated studies
  - This includes 11-108 (MSKCC 10-224) COHORT 2 only (single agent idelalisib), COHORT 1 remains open (rituximab + idelalisib)
    - All patients have been notified and drug stopped
  - FDA suggested that patients taken off study with no toxicity could get commercial drug

- Discontinuation of the current FL trials 124 and 125 (we do not have these open)

Recommendations

- Currently, the CLL and FL indications stand but I recommend:
  - Using only in the study population
    - CLL: R/R and not candidate for chemotherapy
      - Suitable for patients either not optimal for ibrutinib or *intolerant* to ibrutinib
      - Not suitable for patients *progressing* on ibrutinib
      - Unclear if adding bendamustine to R-Idelalisib adds any additional benefit
    - FL: Refractory to both alkylators and rituximab, minimum of 2 prior lines of therapy
      - Suitable as a bridge to alloBMT

- During first 6 months:
  - CMV monitoring monthly
    - If positive, stop drug and treat
  - PJP prophylaxis
    - Dapsone (check G6PD) or atovaquone
    - TMP-sulfamethoxazole can be used but can exacerbate neutropenia
  - CBC every 2 weeks x3 months then monthly x 3
    - Treat with growth factors if neutropenia develops