Management of CLL in the Targeted Therapy Era

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Objectives

- To discuss the diagnosis and risk stratification of CLL
- To discuss novel therapies in the treatment of CLL with a focus on adverse events

Chronic Lymphocytic Leukemia

- The most prevalent type of adult leukemia
- Defined by CD5, CD19, CD20, CD23, sIg (dim)+ cells in blood; < 5 x 10^9/L cells is monoclonal B-cell lymphocytosis (MBL) which still has many CLL-type complications
- Median age of diagnosis of CLL is approximately 72, with only 10% of patients under age 50.
- More common in men than women (2:1 ratio)
- Environmental predisposition uncertain, although Vietnam Veterans with Agent Orange exposure warrant "service-connected status"
- Genetic predisposition present, with approximately 10% of patients having a first-generation relative with CLL

Treatment Indications

- Marrow failure (progressive, hgb <10, plt <100k)
- Massive (≥6 cm below costal margin), symptomatic, or progressive splenomegaly
- Massive (≥10 cm), symptomatic, or progressive lymphadenopathy
- Progressive lymphocytosis (doubling time <6 months)
- Autoimmune cytopenias NOT responding to other treatment
- Organ threatening disease
- Constitutional Symptoms

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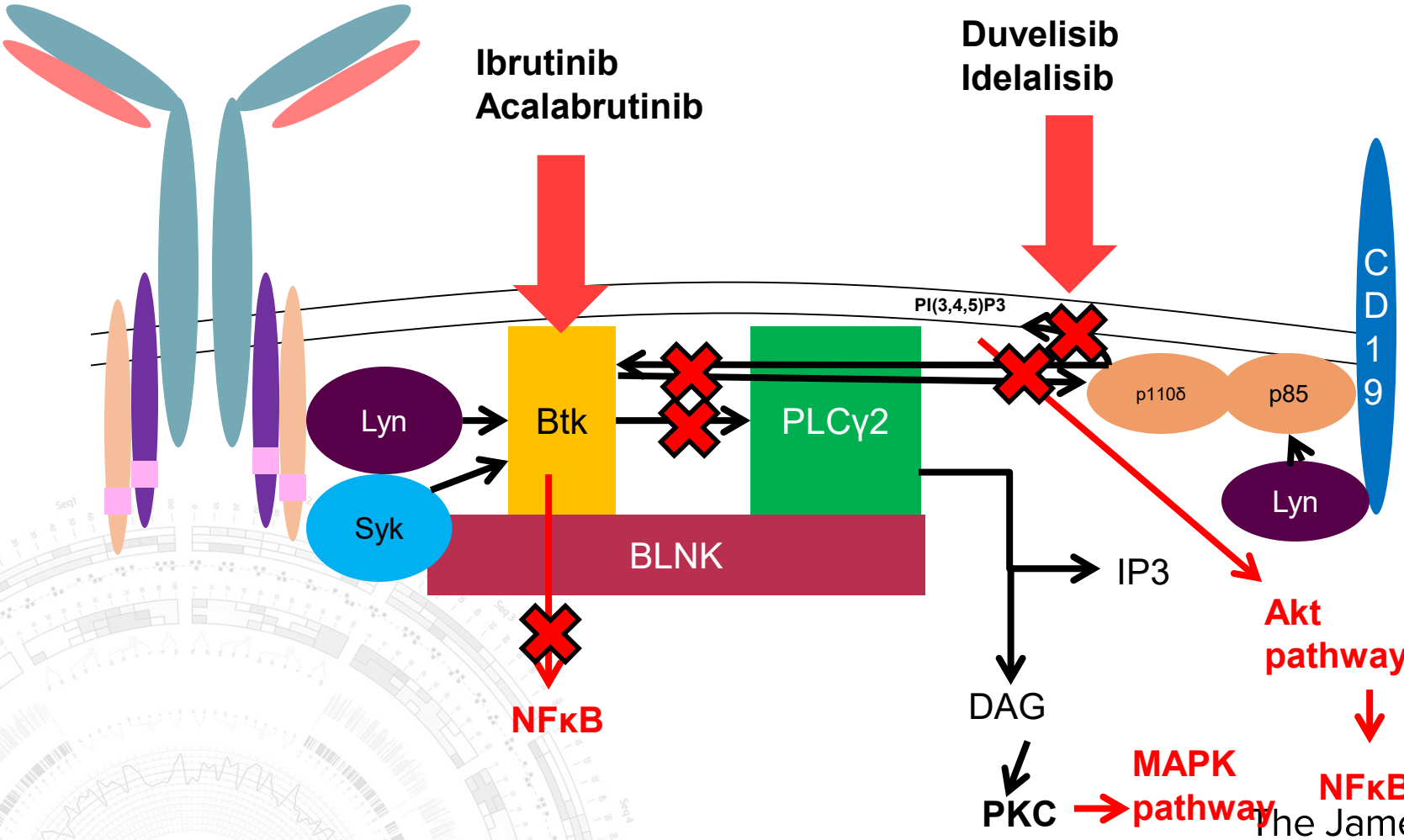
Hallek at al, Blood 2018

Pre-Therapy Testing

- Disease evaluation
  - CT scans can be considered
  - Bone marrow biopsy-especially if cytopenias present

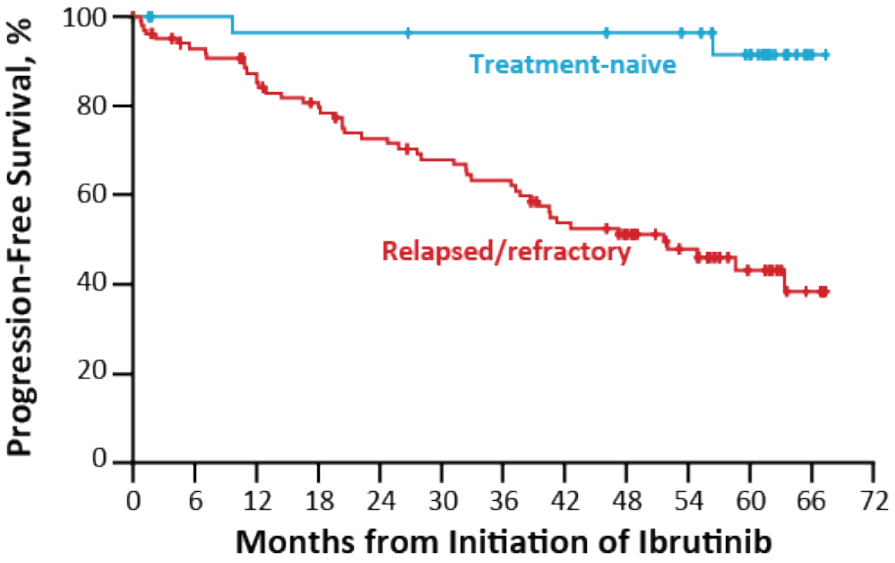
- Molecular/genomic testing
  - IGVH mutational status
  - FISH-del13q, del17p, del11q, trisomy 12
    - Stimulated karyotype can be considered
  - TP53 mutation

Kinase Inhibitors in CLL

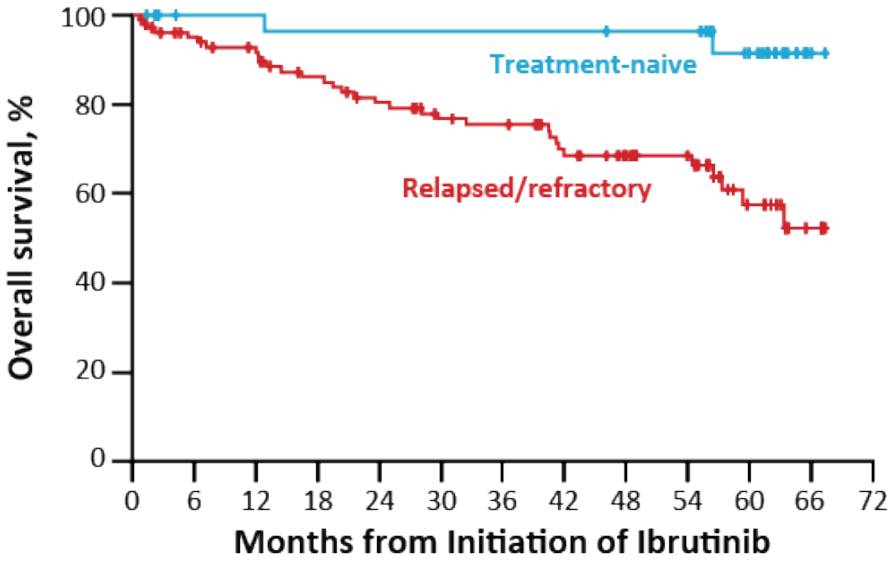


PCYC 1102 5 Year Follow-up

Progression-Free Survival



Overall Survival



	Median PFS	5-year PFS
TN (n=31)	NR	92%
R/R (n=101)	52 mo	43%

	Median OS	5-year OS
TN (n=31)	NR	92%
R/R (n=101)	NR	57%

NR, not reached.

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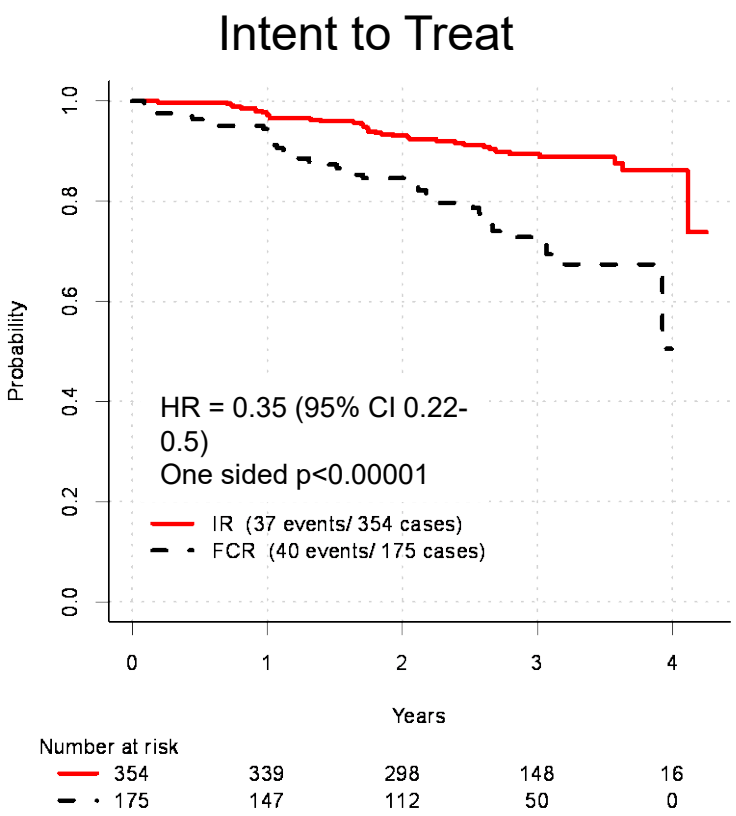
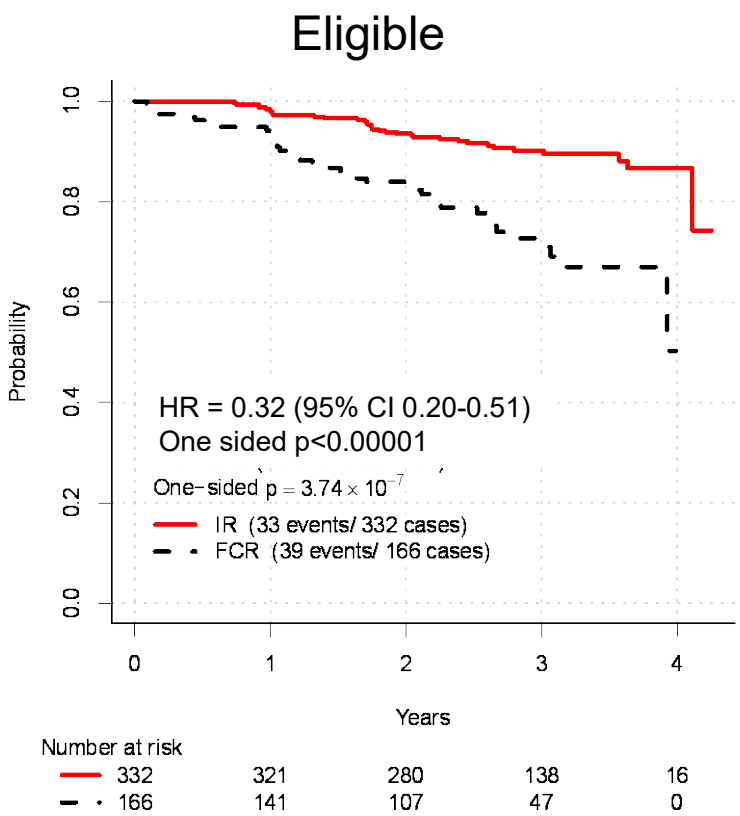
O'Brien ASH 2016

E1912 Progression Free Survival





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Shanafelt, et al. LBA 4 ASH 2018

Primary Endpoint: Progression Free Survival
Eligible Patient Population

% Alive and Progression-Free

Arm	N	24 Month Estimate
BR	176	74% (95% CI: 66-80%)
I	178	87% (95% CI: 81-92%)
IR	170	88% (95% CI: 81-92%)

Pairwise Comparisons

I vs BR:
Hazard Ratio 0.39
95% CI: 0.26-0.58
(1-sided P-value <0.001)

IR vs BR:
Hazard Ratio 0.38
95% CI: 0.25-0.59
(1-sided P-value <0.001)

IR vs I:
Hazard Ratio 1.00
95% CI: 0.62-1.62
(1-sided P-value 0.49)

Patients-at-Risk

176	140	129	122	103	88	57	26	11	0
178	165	154	147	136	120	78	45	22	0
170	159	145	138	132	115	74	40	20	0

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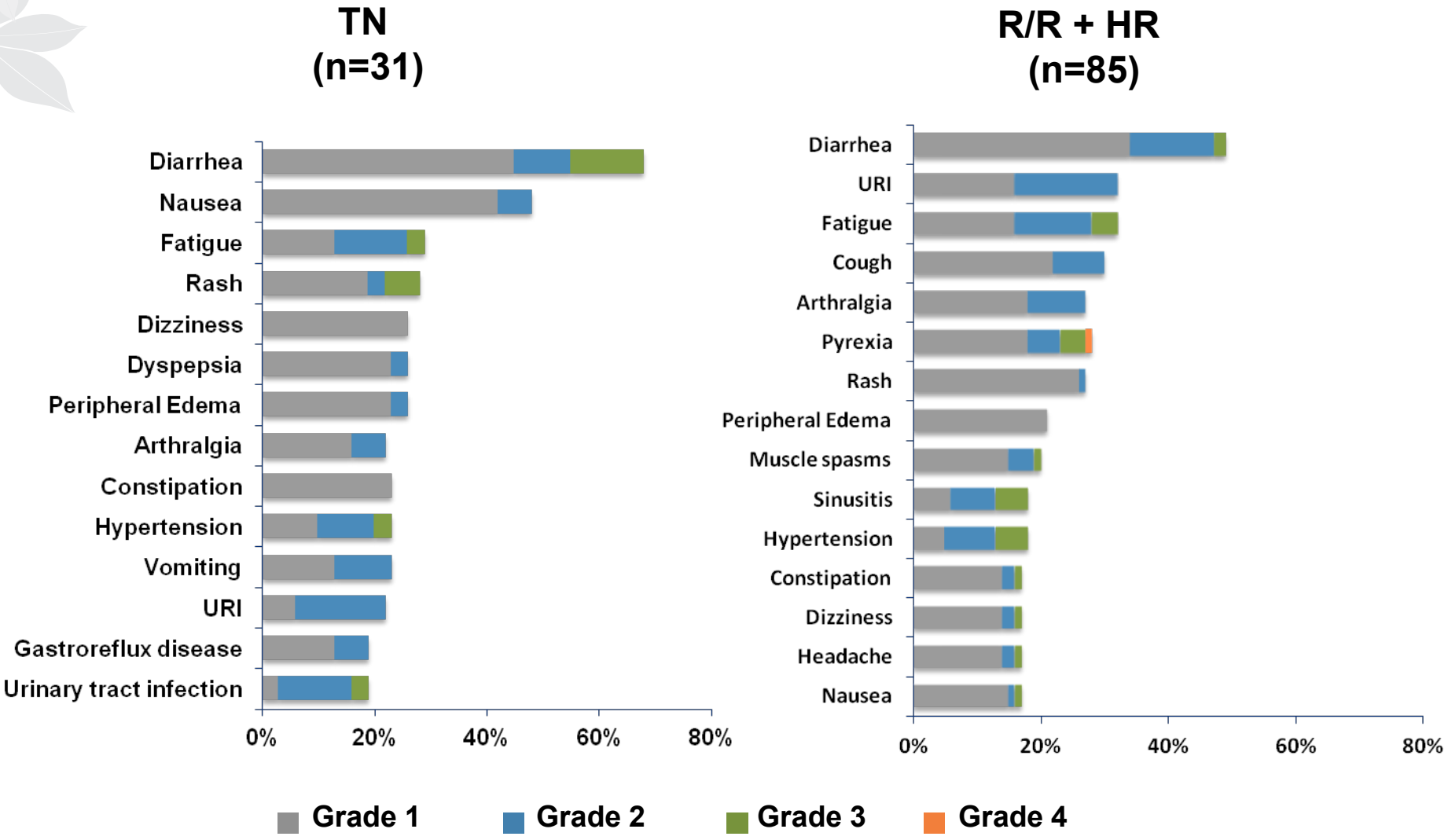
Woyach et al, NEJM 2019

Ibrutinib in CLL: Toxicity



Byrd et al. NEJM 2013

A041202 Grade 3, 4, or 5 Adverse Events

During treatment or follow-up (excluding crossover)

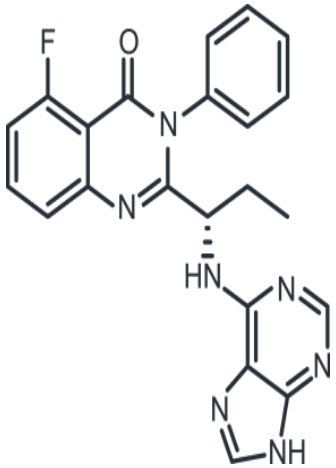
Adverse Event	BR N=176	Ibrutinib N=180	IR N=181	P-value
All Hematologic -- no. (%)	**107 (61)**	**74 (41)**	**70 (38)**	**<0.001**
Anemia	22 (13)	21 (12)	11 (6)	0.09
Neutropenia	71 (40)	27 (15)	39 (22)	<0.001
Thrombocytopenia	26 (15)	12 (7)	9 (5)	0.008
All Non-hematologic -- no. (%)	**111 (63)**	**133 (74)**	**134 (74)**	**0.04**
Bleeding	0 (0)	3 (2)	5 (3)	0.46
Infections	26 (15)	37 (21)	37 (20)	0.62
Febrile neutropenia	13 (7)	3 (2)	1 (1)	<0.001
Atrial fibrillation	5 (3)	17 (9)	10 (6)	0.05
Hypertension	25 (14)	53 (29)	61 (34)	<0.001
Unexplained/unwitnessed death	2 (1)	7 (4)	4 (2)	0.24

- Deaths during active treatment + 30 days: 2 (1%), 13 (7%), 13 (7%)
- Deaths during active treatment + 30 days, up to 6 cycles: 2 (1%), 3 (2%), 6 (3%)

Woyach et al, NEJM 2019

Idelalisib

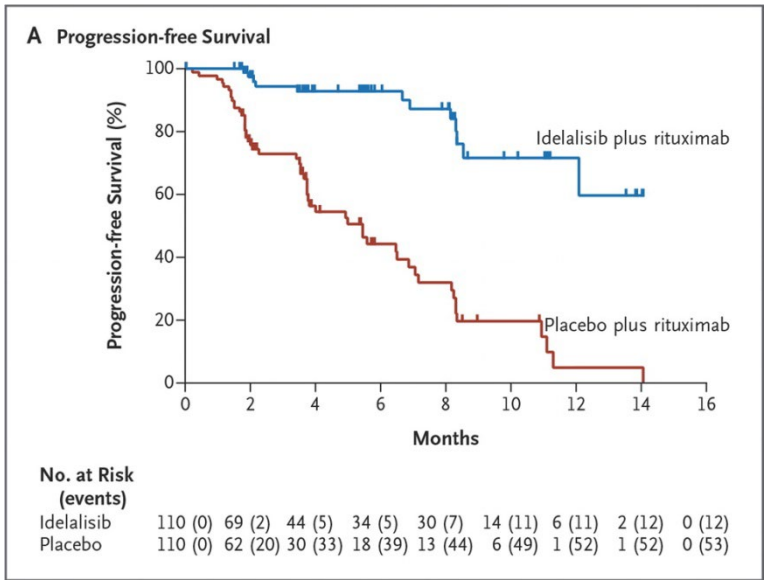
- Selective orally available PI3K-δ inhibitor at doses tested
- Initial phase I dosing done in healthy volunteers with favorable human PK



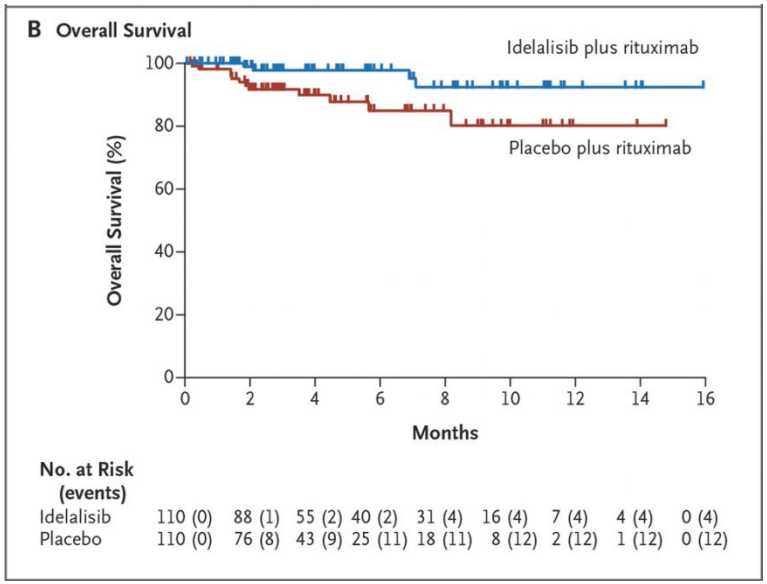
Herman, Blood 2010
Lanutti, Blood 2011

Idelalisib + Rituximab

- 220 total patients
- ORR 81% for Idelalisib arm



5.5 mo vs NR (HR 0.15)



80% at 12mo vs 92% at 12mo (HR 0.28)

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Furman et al. NEJM 2014

Idelalisib + Rituximab: Adverse Events

Adverse Event	Any Grade N (%)	Grade ≥ 3 N (%)
Pyrexia	32 (29)	3 (3)
Fatigue	26 (24)	3 (3)
Chills	24 (22)	2 (2)
Diarrhea	**21 (19)**	**4 (4)**
Dyspnea	12 (11)	2 (2)
Rash	11 (10)	2 (2)
ALT/AST elevation	**38 (35)**	**6 (5)**
Anemia	28 (25)	6 (5)
Neutropenia	60 (55)	37 (34)
Thrombocytopenia	19 (17)	11 (10)

Serious Adverse Event	Any Grade N (%)
Pneumonia	7 (6)
Pyrexia	7 (6)
Febrile Neutropenia	5 (5)
Sepsis	4 (4)
Pneumonitis	**4 (4)**
Diarrhea	**3 (3)**
Neutropenia	3 (3)
***Pneumocystis* Pneumonia**	**3 (3)**
Neutropenic Sepsis	3 (3)
Dyspnea	1 (1)
Cellulitis	1 (1)

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Furman et al. NEJM 2014

Idelalisib: Considerations for Patient Management

Manufacturer Recommended Dose Modifications

Toxicity	Recommended Management		
Pneumonitis **Severe skin rash**	**Any Symptomatic Occurrence**		
	Discontinue idelalsib		
ALT/AST	**>3-5 x ULN**	**5-20 x ULN**	**>20 x ULN**
	-Continue idelalsib -Monitor weekly until ≤1 x ULN	-Hold Idelalisib -Monitor weekly until ≤1 x ULN -Resume at 100 mg bid	Discontinue idelalisib
Bilirubin	**>1.5-3 x ULN**	**>3-10 x ULN**	**>10 x ULN**
	-Continue idelalisib -Monitor weekly until ≤1 x ULN	-Hold idelalisib -Monitor weekly until ≤1 x ULN -Resume at 100 mg bid	Discontinue idelalslib
Diarrhea	**Moderate**	**Severe or Hospitalized**	**Life Threatening**
	-Continue idelalisib -Monitor until resolved	-Hold idelalisib -Monitor weekly until resolved -Resume at 100 mg bid	Discontinue idelalisib

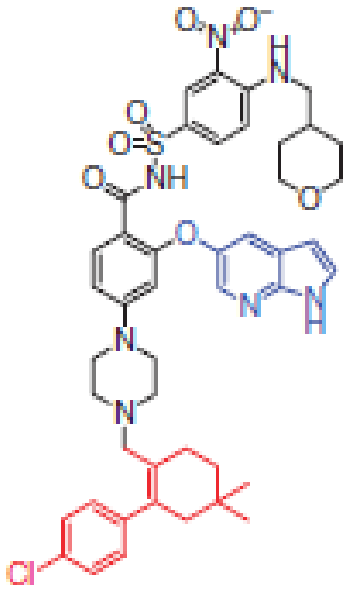
Gilead Sciences, Inc. Idelalisib (Zydelig) Prescribing Information (2014)

Precautions with idelalisib

- Prophylaxis for Pneumocystis pneumonia throughout treatment.
- Monitor patients for cytomegalovirus (CMV) and d/c idelalisib with evidence of infection or viremia.
  - Consider prophylaxis with antivirals.

Venetoclax

- BH3 mimetic
- Ora
- Sel of BCL-2 that does not target BCL-xL



ABT-199

Souers, et al Nature Medicine 2013

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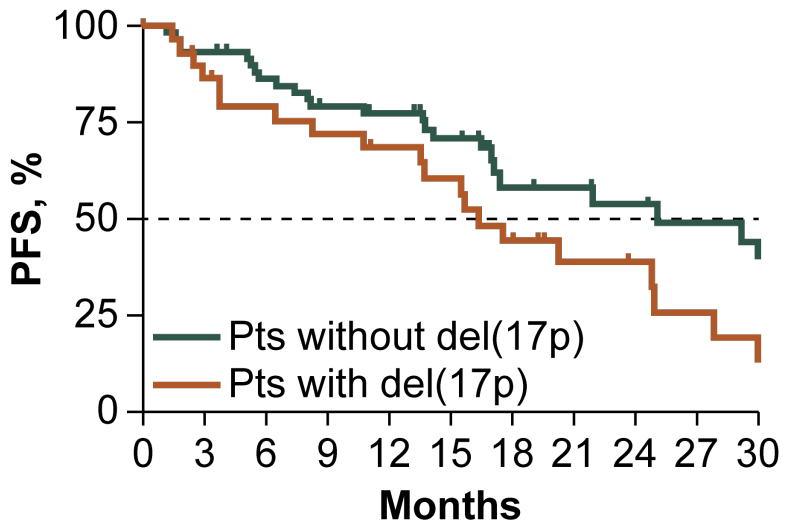
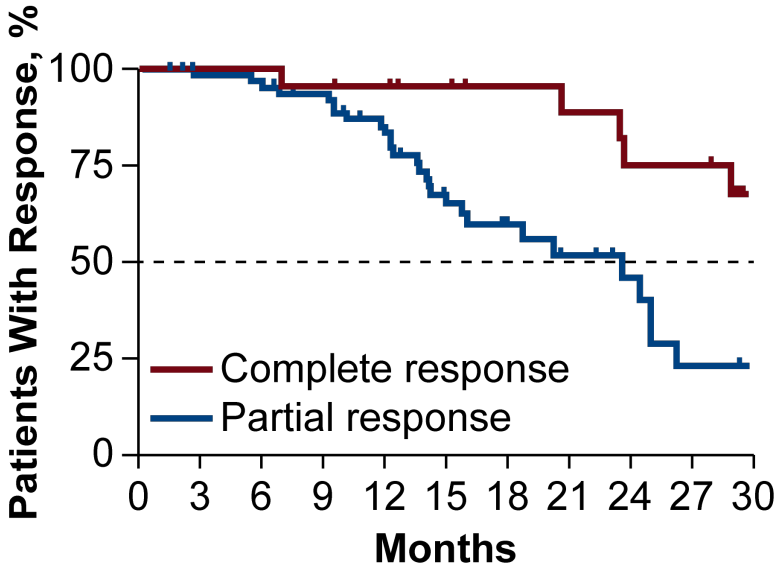
Venetoclax in Relapsed CLL (Phase I)





No. at Risk

Pts without del(17p)	60	56	49	44	39	33	16	14	12	10	9
Pts with del(17p)	31	31	25	22	18	15	11	7	6	4	3

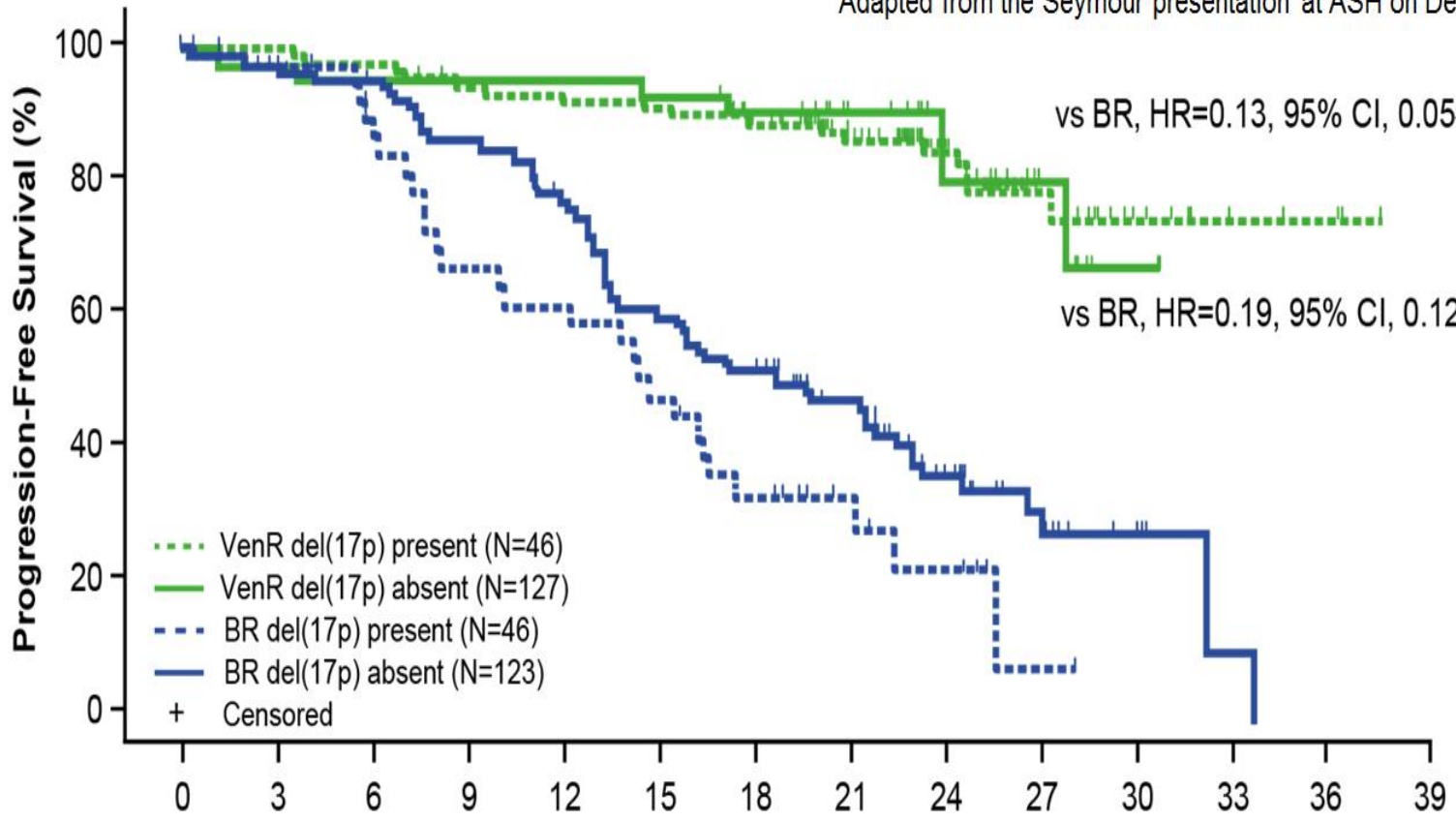
No. at Risk

Complete response	23	23	23	22	21	18	14	13	11	11	6
Partial response	69	63	62	56	48	32	18	12	8	4	3

Roberts AW et al. NEJM 2016

Investigator-assessed PFS Superior for VenR vs. BR Among Patients With and Without del(17p)

Adapted from the Seymour presentation at ASH on December 12, 2017



No. of patients at risk:													
VenR del(17p) present	46	44	43	43	43	42	36	25	17	7	2		
VenR del(17p) absent	127	127	124	118	116	114	105	76	48	20	10	4	3
BR del(17p) present	46	40	34	27	25	20	14	8	5	1			
BR del(17p) absent	123	114	108	99	88	70	60	44	26	10	3	1	

As of 8 May 2017

Venetoclax Toxicities

- Most common toxicities: neutropenia, diarrhea, nausea, anemia, upper respiratory tract infection, thrombocytopenia, and fatigue
- Tumor lysis syndrome
- Neutropenia
  - May require G-CSF in some cases

Conclusions

- CLL therapy has advanced significantly with the introduction of kinase inhibitors and venetoclax
- Side effect profiles of these agents are different from chemotherapy, and sometimes are unexpected
- With the rapid approval of new agents in CLL with new toxicities and the potential for life-long therapy, a collaborative approach is necessary to manage these increasingly complex patients