Chronic Lymphocytic Leukemia Targets And Treatments

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Disclosures

Sponsored clinical and/or laboratory research and/or advisory boards

- Pharmacyclics
- Abbvie
- Genentech/Roche
- Celgene
- TG Therapeutics
- Gilead
- Oncternal
- Juno
- Leukemia and Lymphoma Society
- California Institute for Regenerative Medicine
- National Cancer Institute / NIH
- Blood Cancer Research Fund of the San Diego Foundation
- Breast Cancer Research Foundation

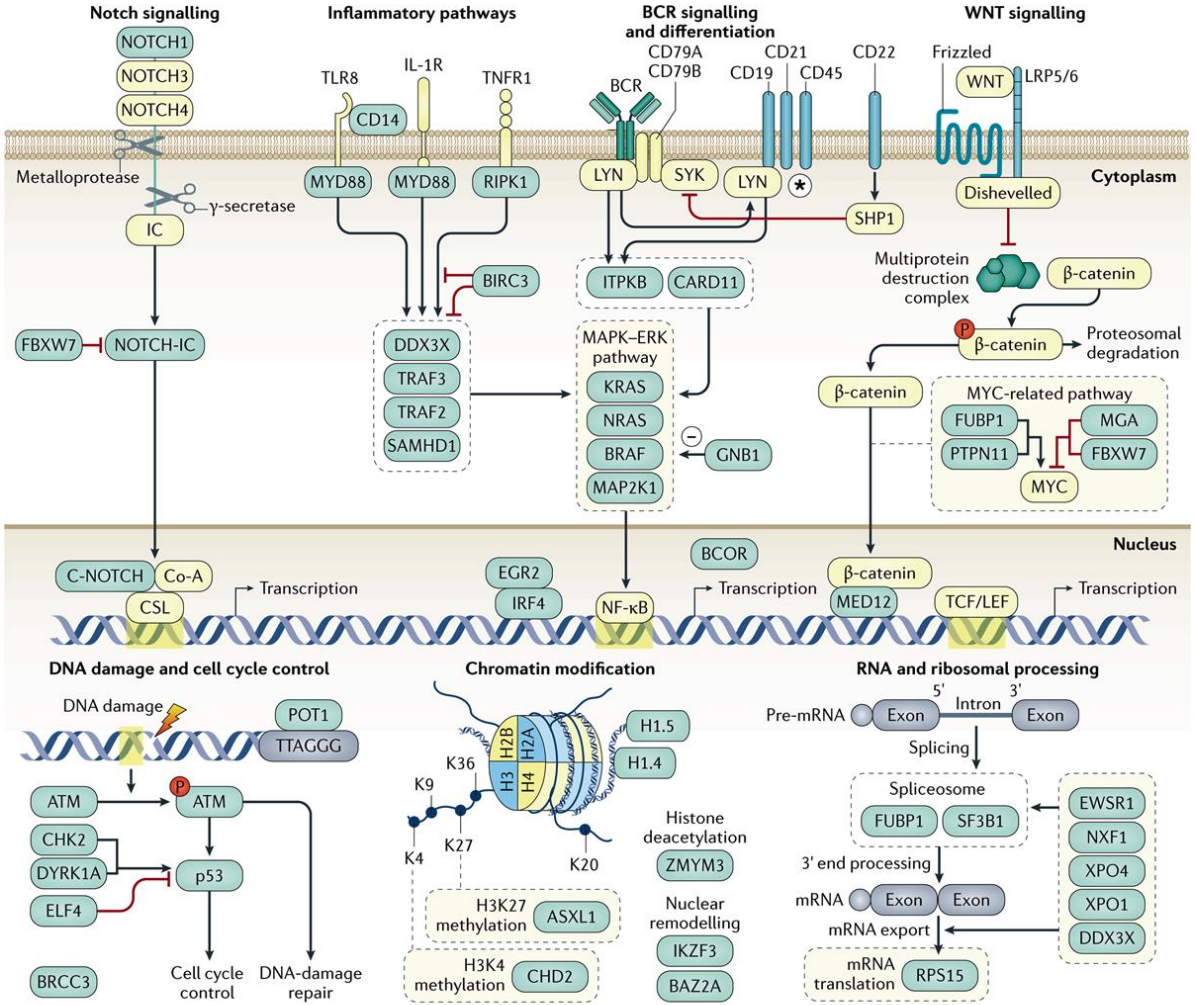
Chronic Lymphocytic Leukemia (CLL)

- Most common adult leukemia in the US/Europe
- Rare in persons of Japanese ancestry
- Familial cases common
  - 8% of over 7,000 cases in the CLL Research Consortium have familial CLL
- >3% of Europeans over age 40 have pre-CLL, or monoclonal B cell lymphocytosis (MBL)
  - Genetic factors influence the level of CD5 B cells (*JI* 139:1060-4, 1987)
  - Monoclonal B-cell Lymphocytosis (MBL) (*Br J Haematol* 130:325, 2005)
- >11% of family members of CLL pts have MBL

TJ *et al, Nature Rev. Disease Primer* 3:16096, 2017

Genetic Lesions In CLL

- ≈80% of cases have at least 1 of 4 common chromosomal alterations detectable by FISH
  - del(13q), del(11q), del(17p), trisomy 12
- Most common genetic lesion is deletion of microRNAs miR-15a/16-1 at 13q14.3
  - miR-15/16 target *BCL2*, *MCL1, ROR1*
- Recurrent mutations in genes that have a role in
  - *Notch signaling*
  - *Inflammation*
  - *B cell receptor (BCR) signaling*
  - *Wnt signaling*
  - *DNA damage repair*
  - *Cell cycle control*
  - *Chromatin modification*
  - *RNA and ribosomal processing*



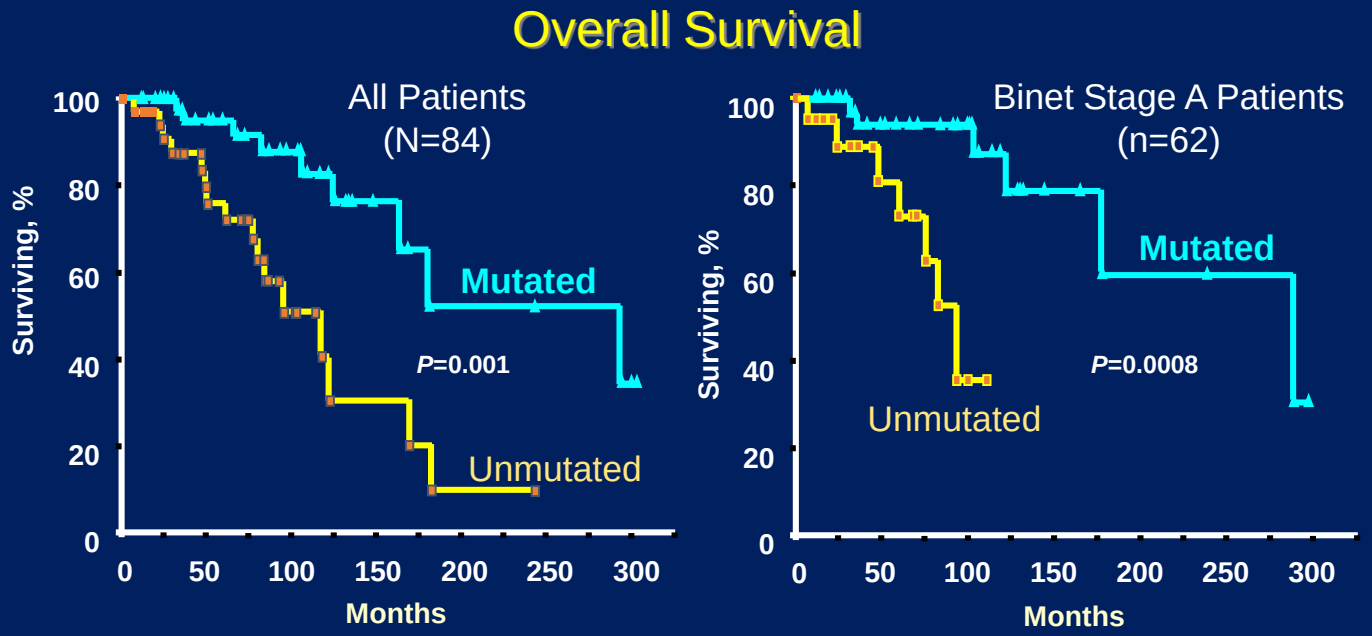
TJ *et al, Nature Rev. Disease Primer* 3:16096, 2017

Chronic Lymphocytic Leukemia (CLL)

- Malignancy of Memory-type CD5 B cells driven by B cell receptor (BCR) signaling
- The expression of immunoglobulin (Ig) by each case is clonal
- ≈ ½ of all cases express Ig with variable region genes (e.g. *IGHV* genes) that have somatic mutations
  - (*Blood* **94**:1848, 1999 & *Blood* **99**:1840, 1999)
- The Ig repertoire of all cases of CLL is highly restricted compared to that of the B cells from any one healthy adult
  - Nearly 1 in 5 cases use the same *IGHV (1-69) (PNAS **86**:5913, 1989)*
  - ≈ 1 in 75 cases use virtually the same Ig (*Blood* **104**:2499, 2004)

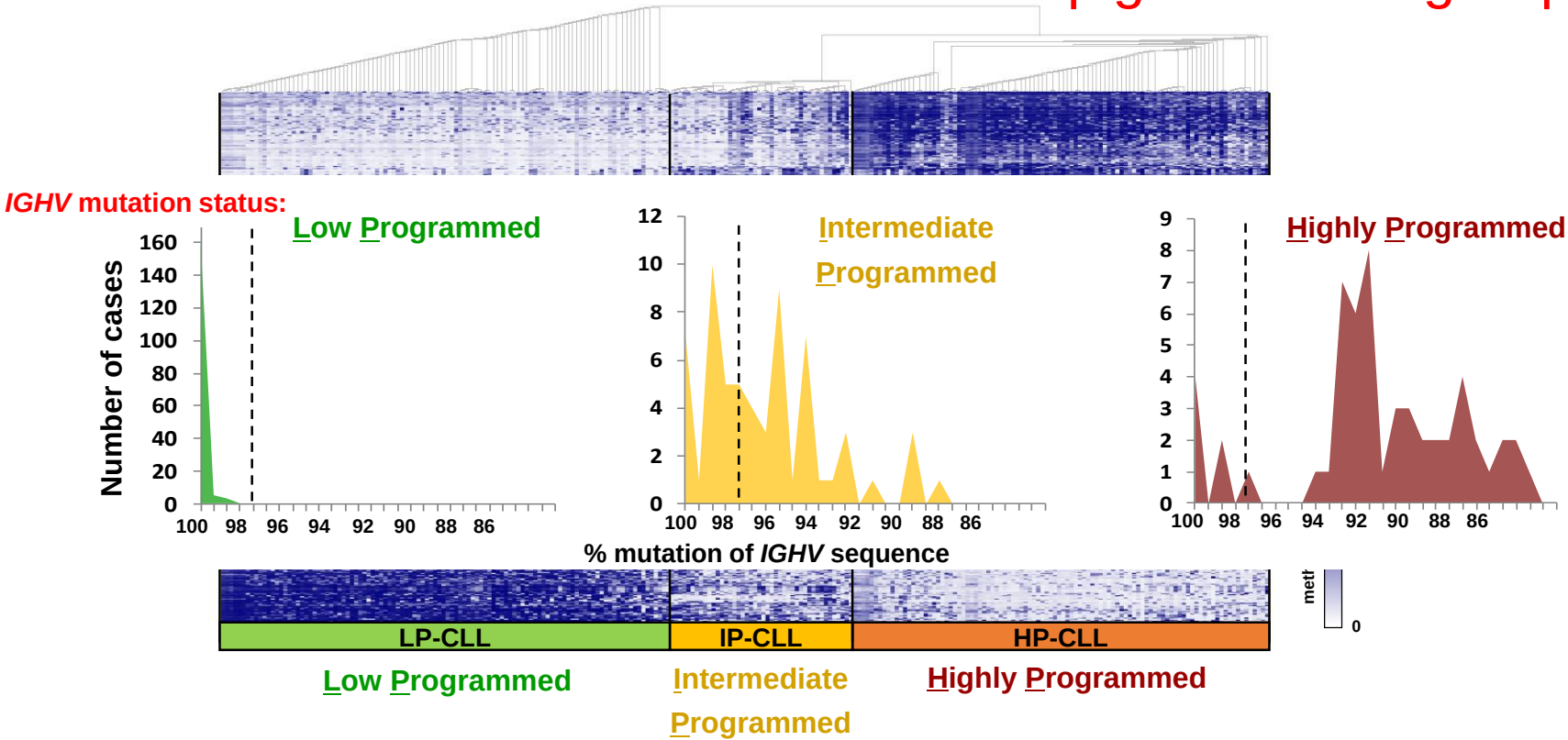
Kipps, TJ *et al, Nature Rev. Disease Primer* 3:16096, 2017

CLL Prognostic Markers
Mutated vs Unmutated IGHV Genes



CLL, chronic lymphocytic leukemia.
Hamblin TJ, et al. *Blood.* 94:1848-1854, 1999

CLL Patients Cluster Into Three Distinct Epigenetic Subgroups



- 450k array (Illumina) analysis of CLL Cells of 249 Patients
- Unsupervised analysis displaying the 500 most discriminating CpGs

Oakes CC, et al. *Nat Genet 48:253-64, 2016*

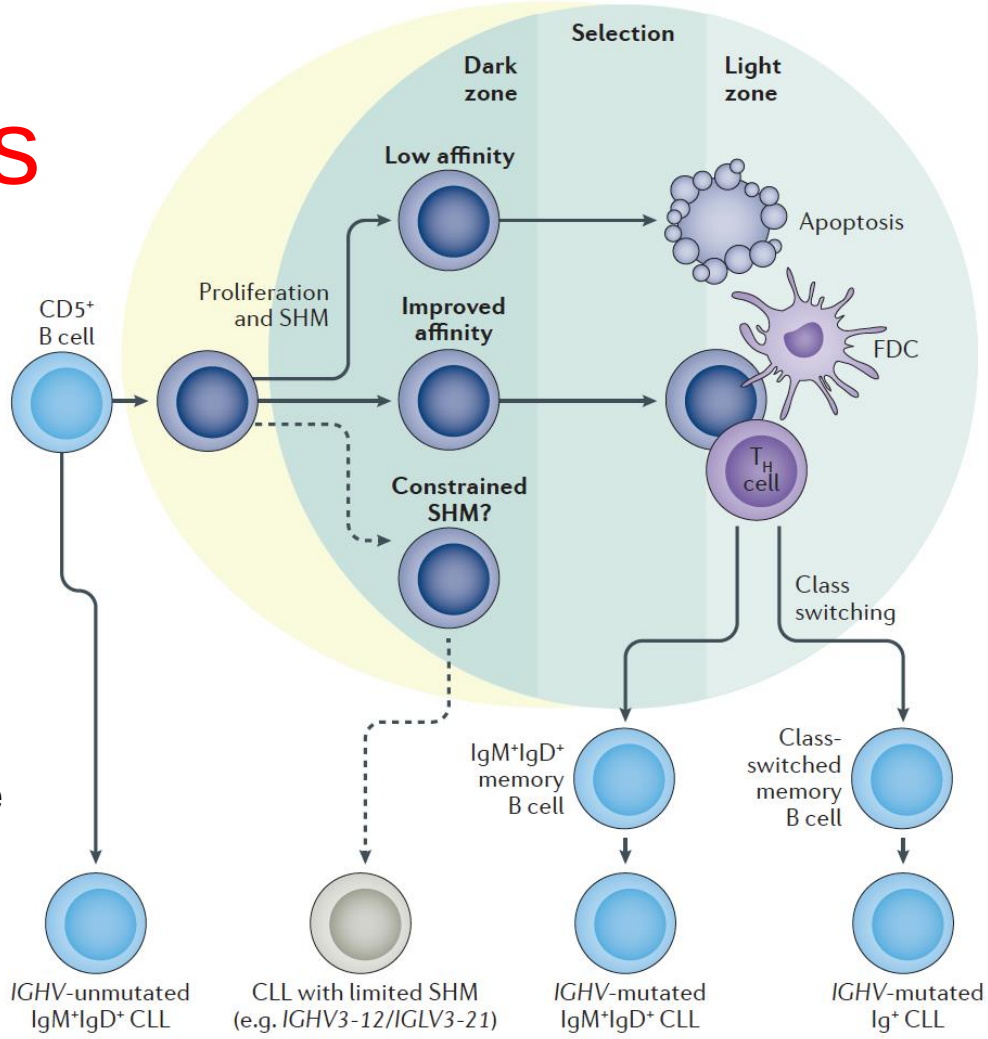
139 CLL profiles downloaded from the ICGC Data Portal (http://dcc.icgc.org/web)

CLL Cytogenesis

- CLL can be divided into two main subsets
  - Pre-germinal center (Pre-GC)
  - Post-germinal center (Post-GC)

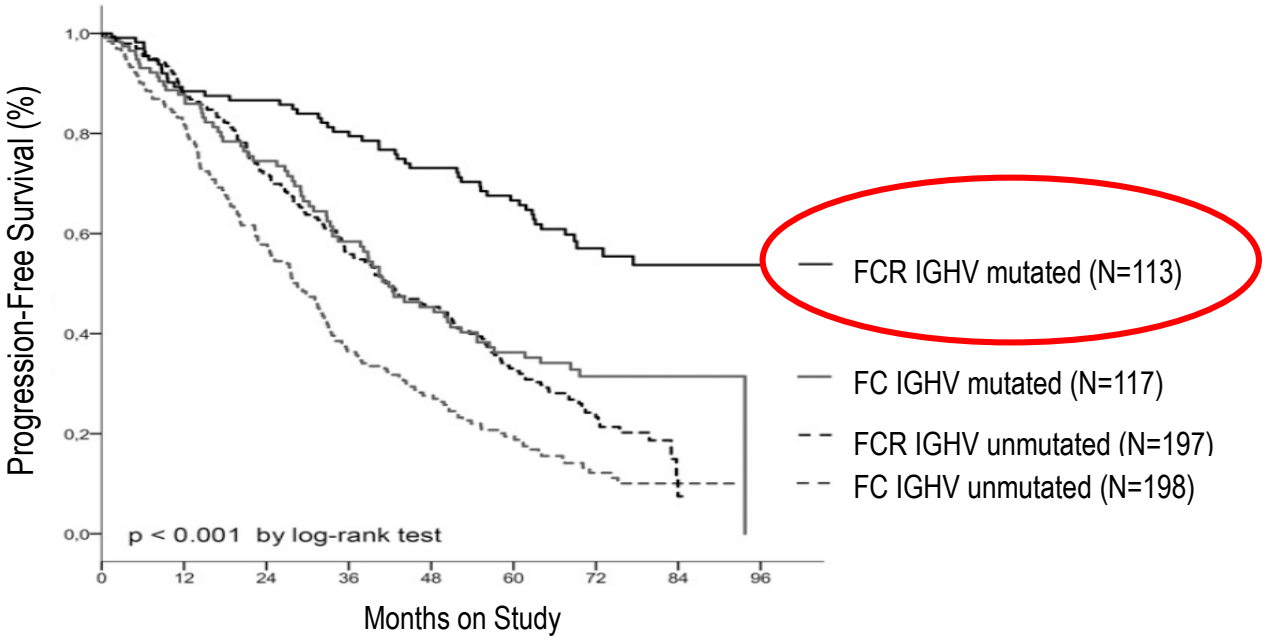
- IgH variable gene (IGHV) mutation status serves as a surrogate marker for cytogenetic origin
  - Pre-GC- unmutated
  - Post-GC – mutated

- The Ig's expressed by CLL B cells are highly restricted, indicating selection for B-cells with the right type of Ig-receptor signaling
  - Stereotypic Ig
  - IGHV1-69 most frequently used



Kipps, TJ *et al, Nature Rev. Disease Primer* 3:16096, 2017

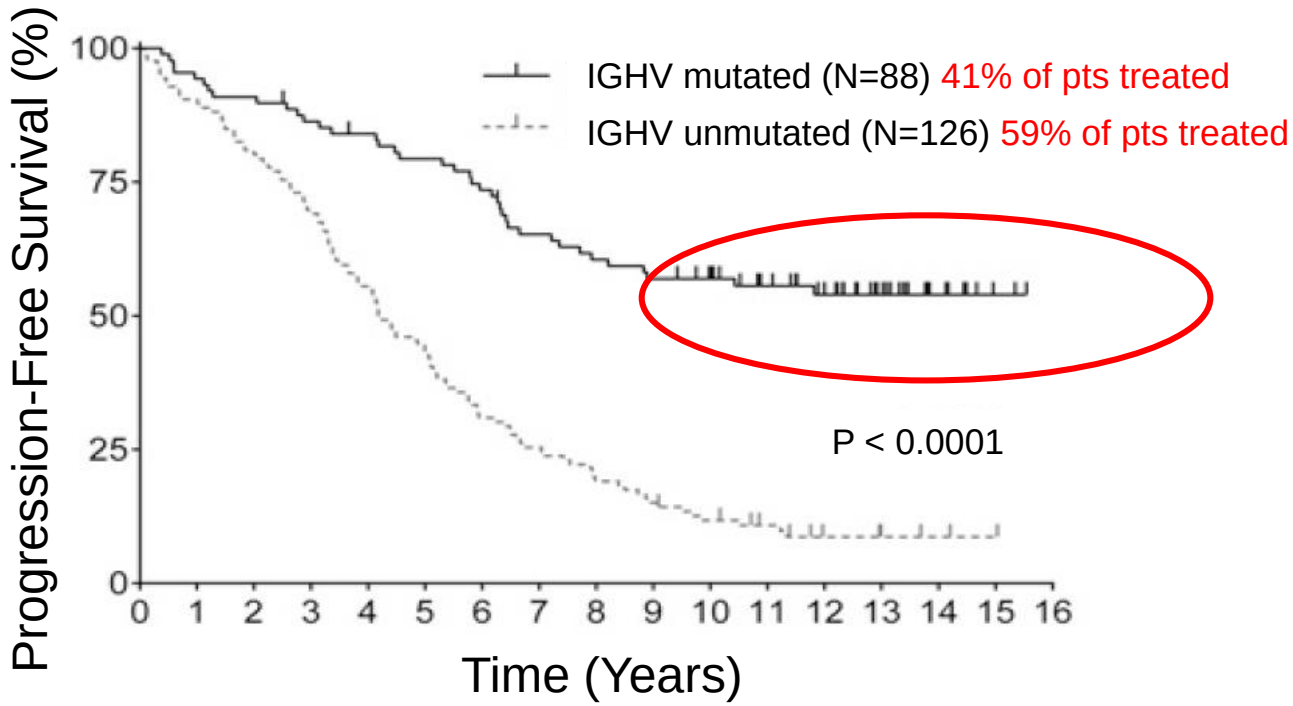
FC vs. FCR In Treatment Naïve Patients Long-term F/U Of CLL8 of GCLLSG



3 Separate Studies Show 50-60% PFS S/P FCR For CLL Pts. With Mutated IGHV Provided They Lack del(17p)

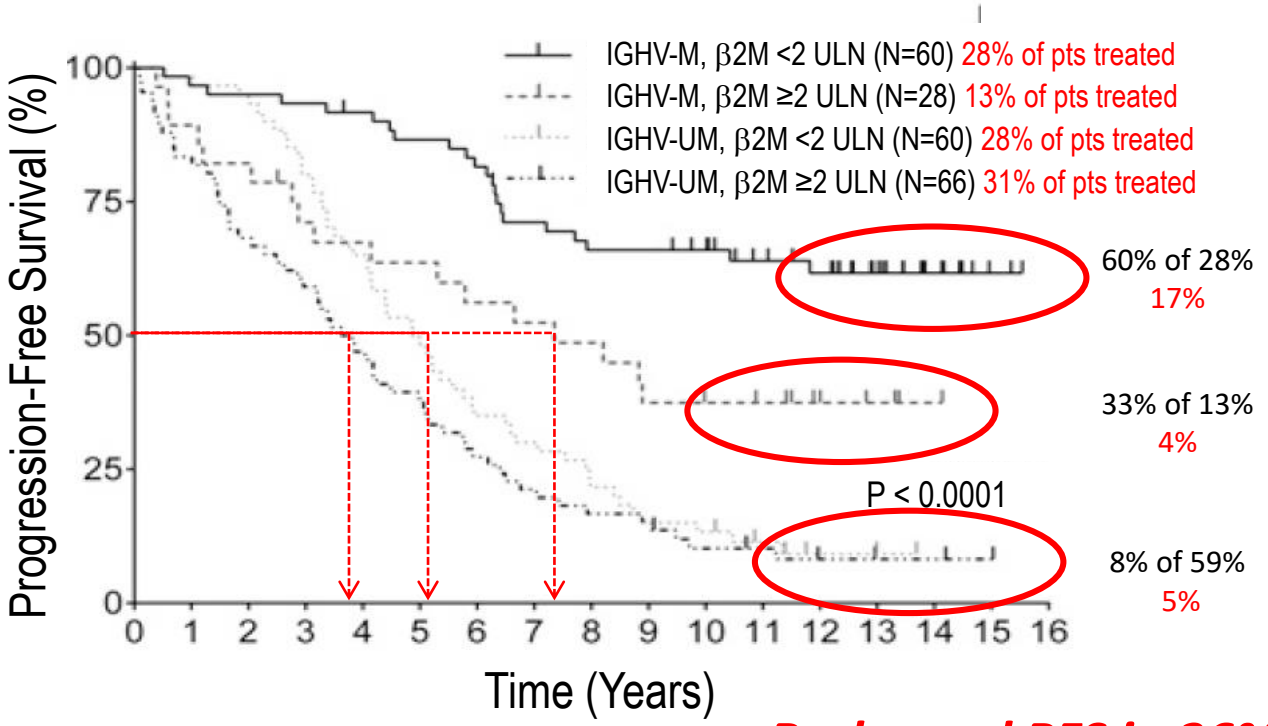
* Thompson, P.A., *et al. Blood* **127**, 303-309 (2016)
* Fischer, K., *et al. Blood* **127**, 208-215 (2016)
* Rossi, D., *et al. Blood* **126**, 1921-1924 (2015)

Seminal Study Of FCR In Treatment Naïve Patients



Thompson, P.A. et al Blood 127:303, 2016

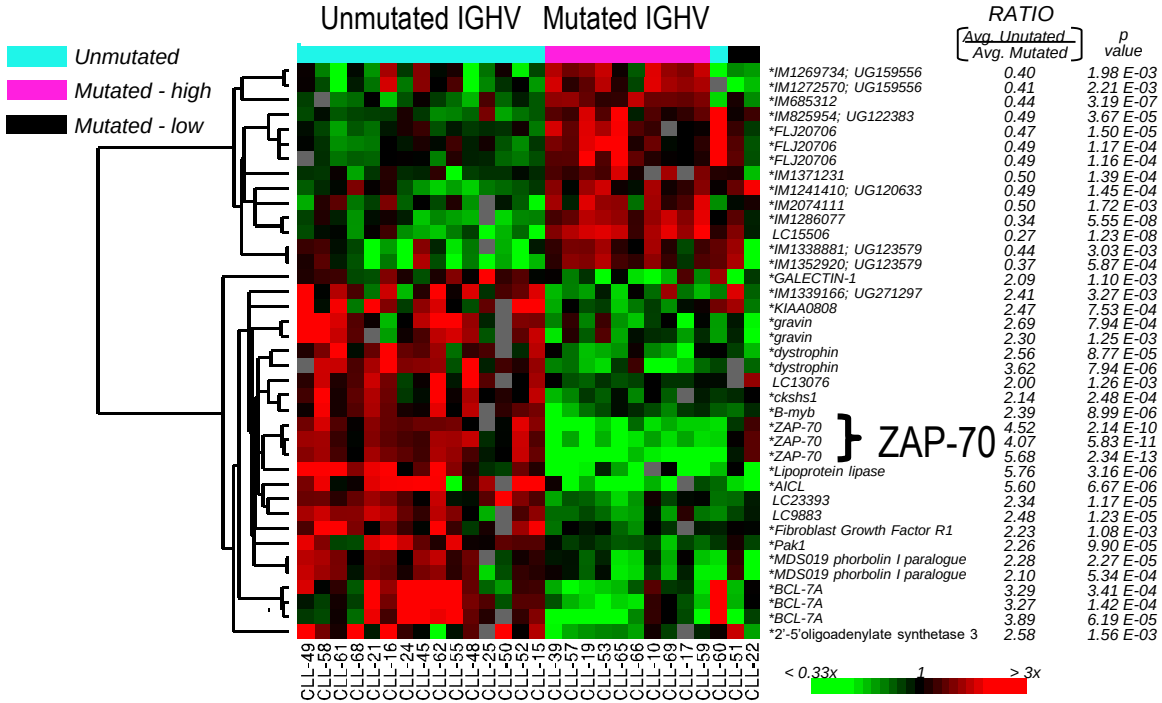
Seminal Study Of FCR In Treatment Naïve Patients



Prolonged PFS in 26%

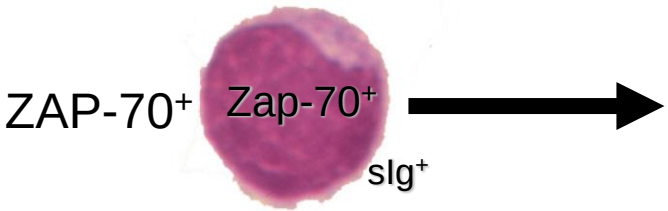
Thompson, P.A. et al Blood 127:303, 2016

Differential Gene Expression in CLL With or Without V_H Gene Somatic Mutations



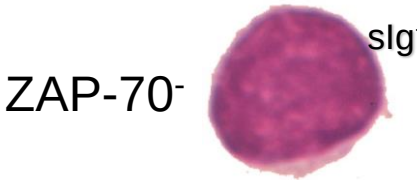
Rosenwald A., et al. *J. Exp. Med*. 194:1639-47, 2001

Surface Immunoglobulin Stimulation in ZAP-70^{+} versus ZAP-70^{-} CLL



- P-Y Syk, BLNK, PLC-γ, AKT, ERK
- Calcium Flux
- Activation of NF-κB
- Enhanced Response to Survival Signals
- Growth and/or Resistance to Apoptosis

Unknown Self- or Environmental- Antigen

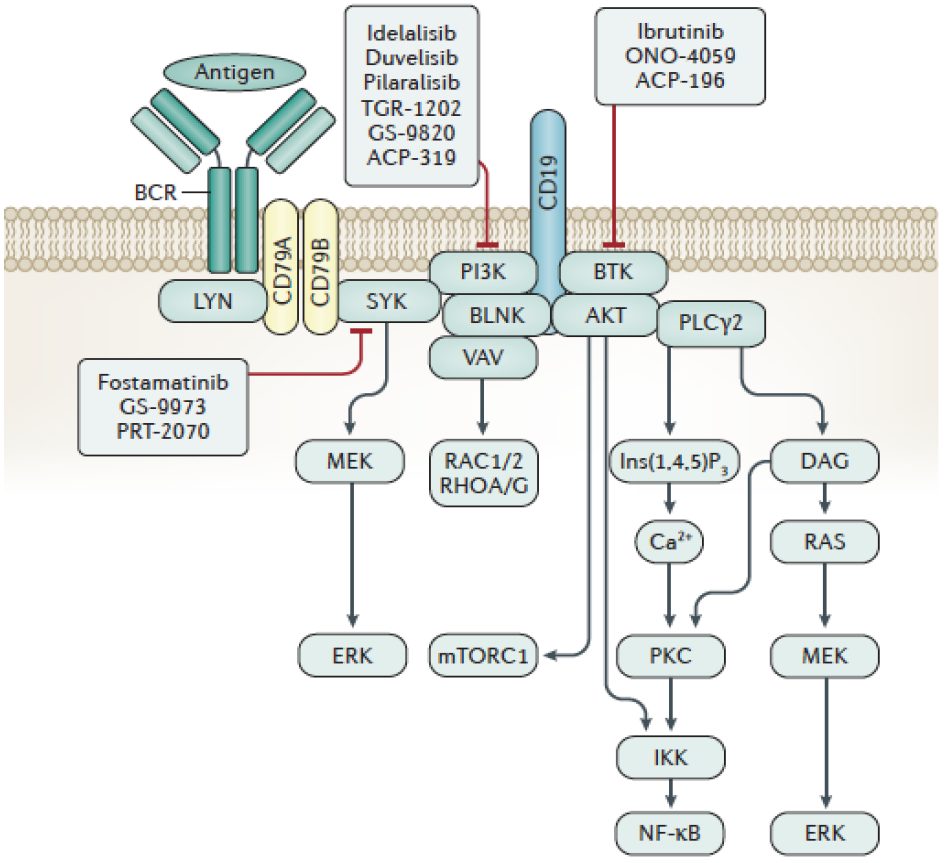


- Weak Receptor Signaling
- Receptor Anergy

Kipps, T.J. Best Pract Res Clin Haematol. 2007 Sep;20(3):415-24

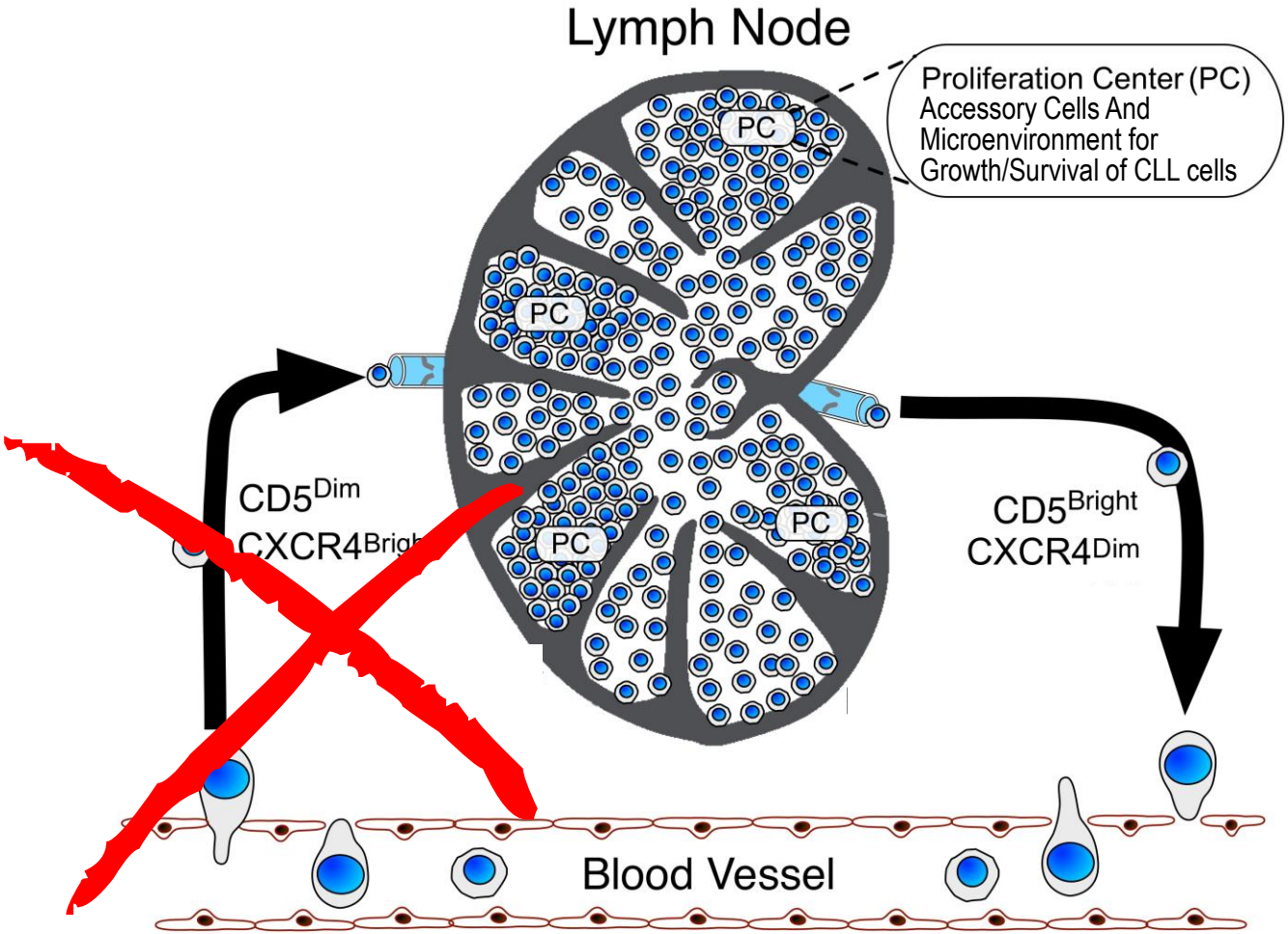
B-cell Receptor (BCR) Signaling In CLL

- BCR signaling stimulates pathways leading to enhanced cell survival and proliferation
- Outcome of BCR signaling ranges from enhanced B-cell activation to B-cell anergy
- Enhanced B-cell activation is more common in CLL with unmutated *IGHV*, whereas anergy predominates in most cases with mutated *IGHV*
- BCR also coordinates the activity of other cell surface receptors, including integrins, such as α4β1 integrin
- Small molecule inhibitors of enzymes required for BCR signaling have clinical activity
  - *Ibrutinib – inhibits BTK*
  - *Idelalisib - inhibits PI3Kδ*

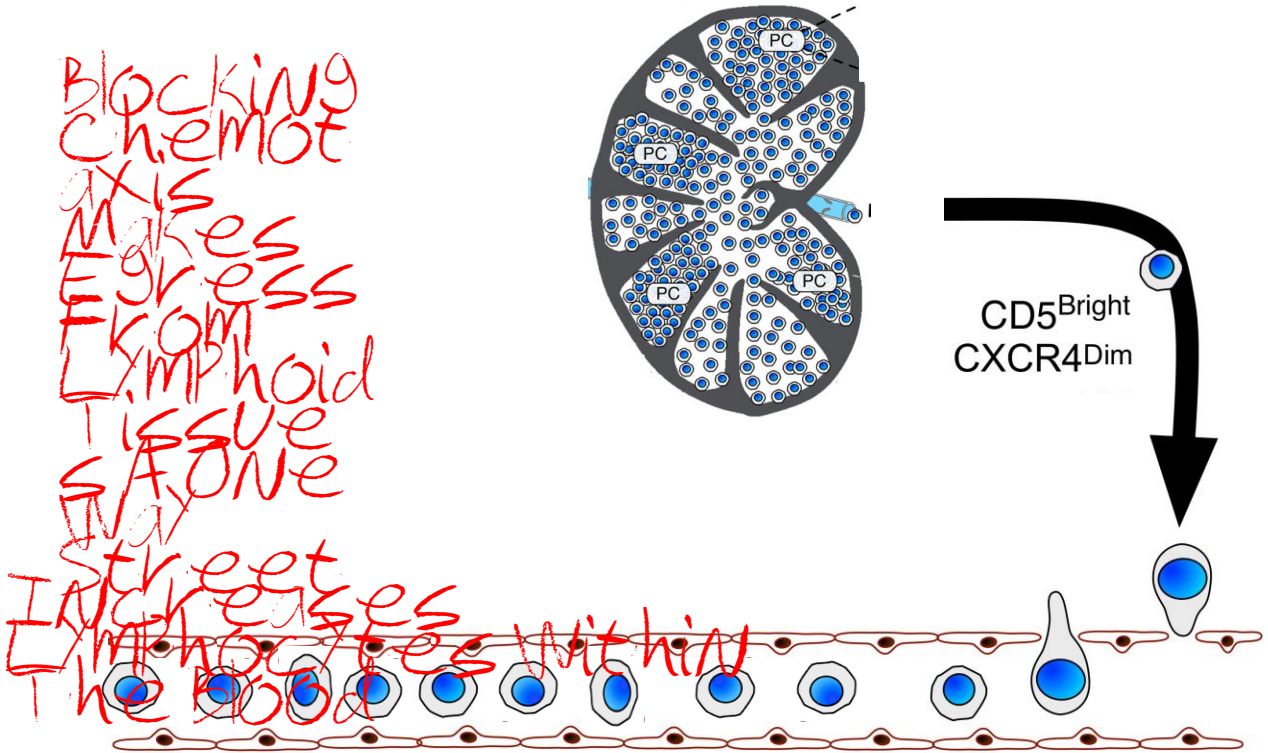


Kipps, TJ *et al, Nature Rev. Disease Primer* 3:16096, 2017; doi;10/nrdp.2016.96

Inhibition Of BTK Or PI3K Also Inhibits CLL Chemotaxis

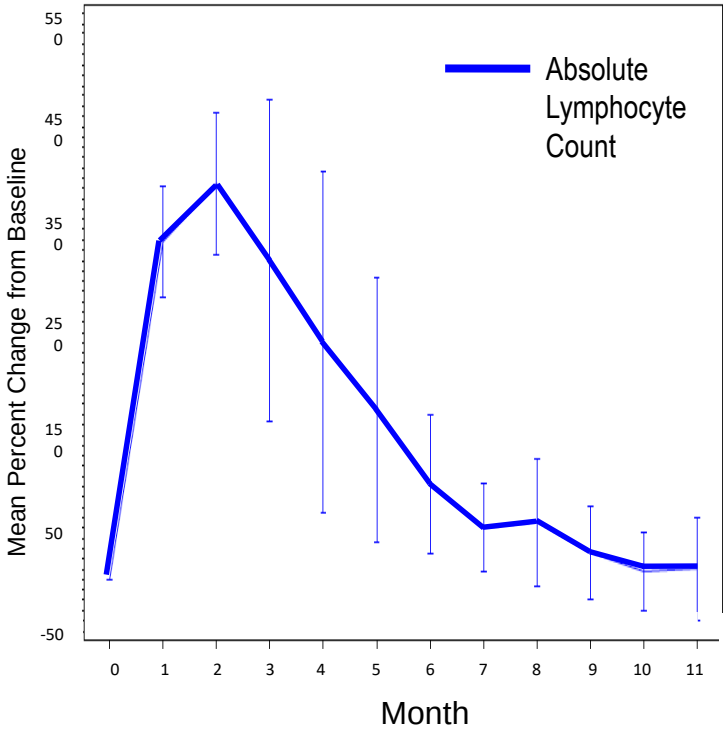


Blocking Chemotaxis Empties Lymphoid Tissues Of CLL Cells

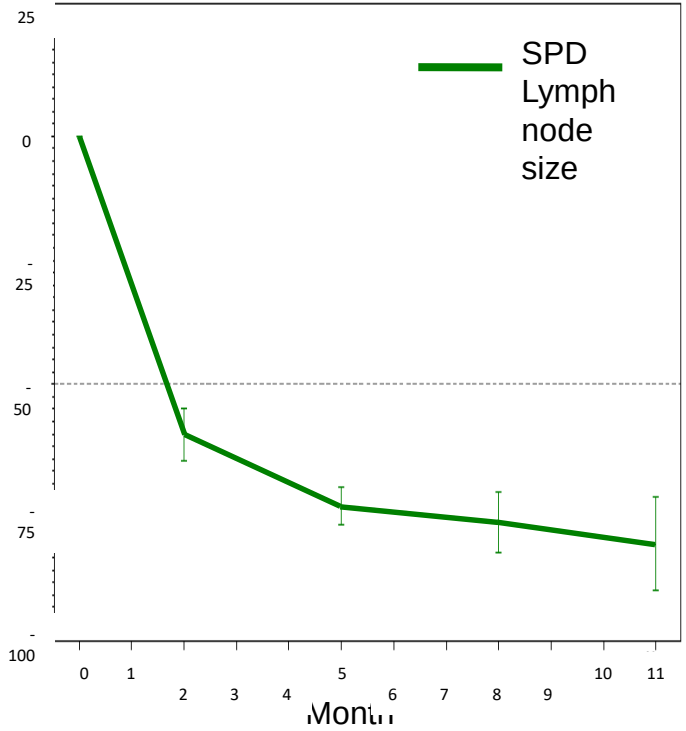


Pattern of Response to Ibrutinib

Blood Lymphocytes



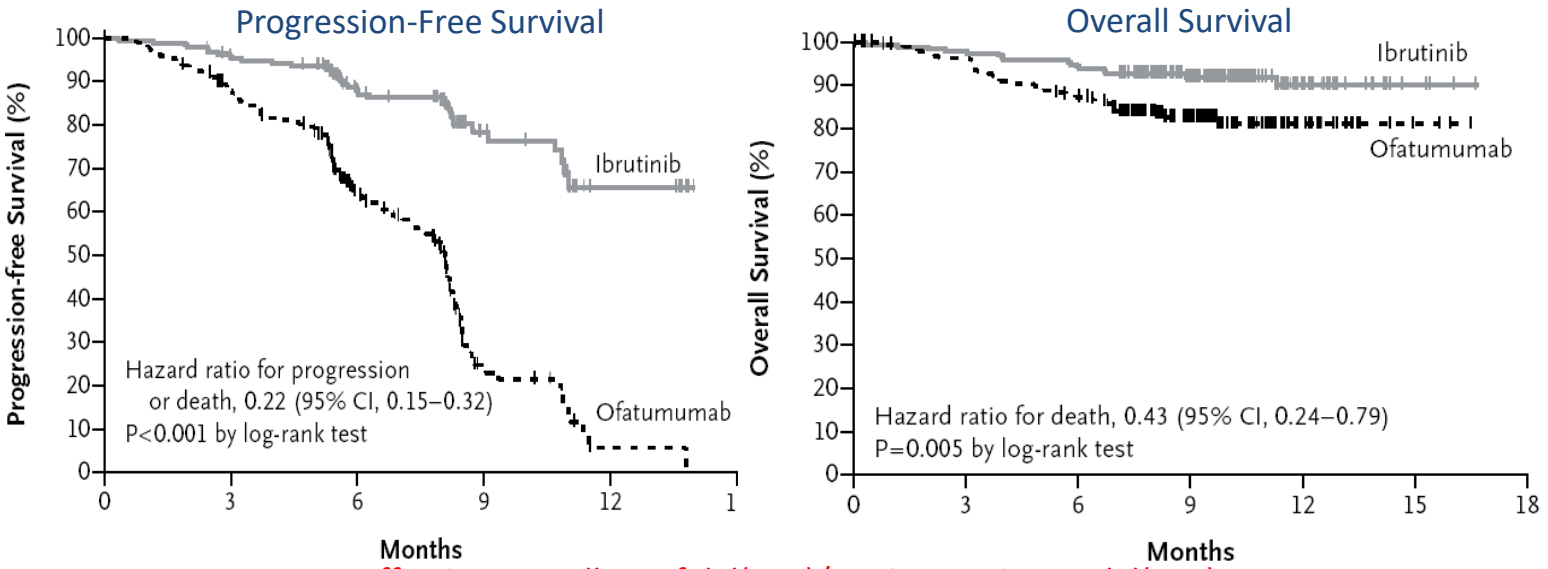
Lymph Nodes



SPD = sum of products of lymph node dimension

Byrd, JC et al, NEJM 369:32-42, 2013

Ibrutinib Versus Ofatumumab in Relapased/Refractory CLL



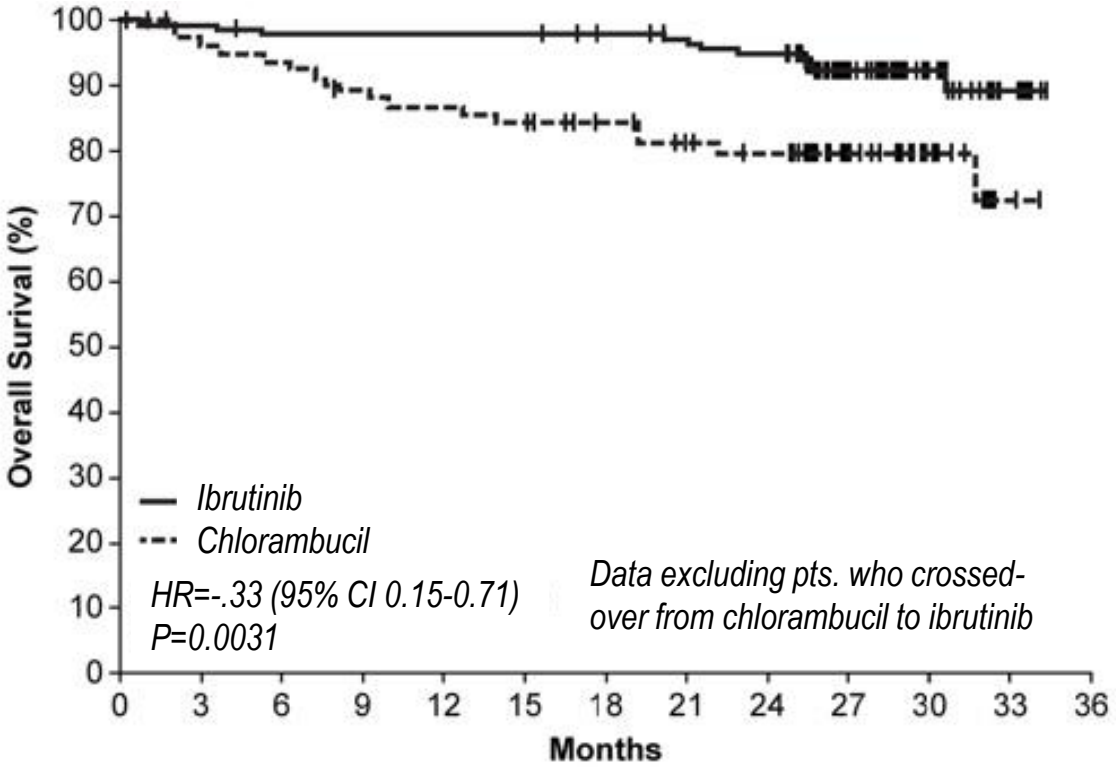
Effective regardless of del(17p)/TP53 mutation or del(11q)

Grade ≥ 3 AEs

- **57% of patients receiving ibrutinib (diarrhea, atrial fibrillation, and bleeding)**
- **47% of patients receiving ofatumumab**

Byrd JC, et al. *N Engl J Med*. 2014;371(3):213-223.

Ibrutinib Versus Chlorambucil As Initial Therapy (RESONATE-2 Trial)

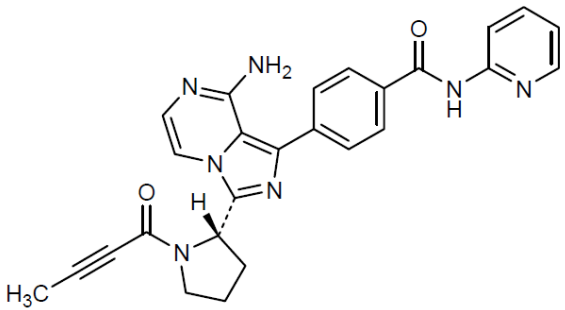


Ibrutinib vs Chlorambucil

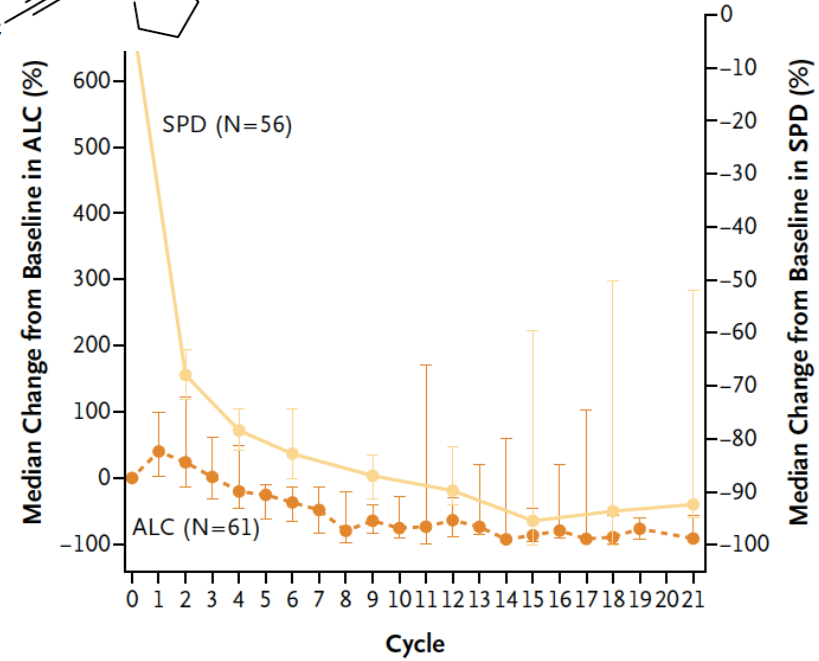
- 269 treatment-naïve patients ≥65 yrs of age
- Significantly longer progression-free survival
- 84% lower risk of progression or death
- Significantly prolonged overall survival (98% vs 85%)
- Significantly higher overall response rate (86% vs 35%)
- Trial used in FDA approval of ibrutinib as initial therapy
- Ibrutinib with higher rate of atrial fibrillation

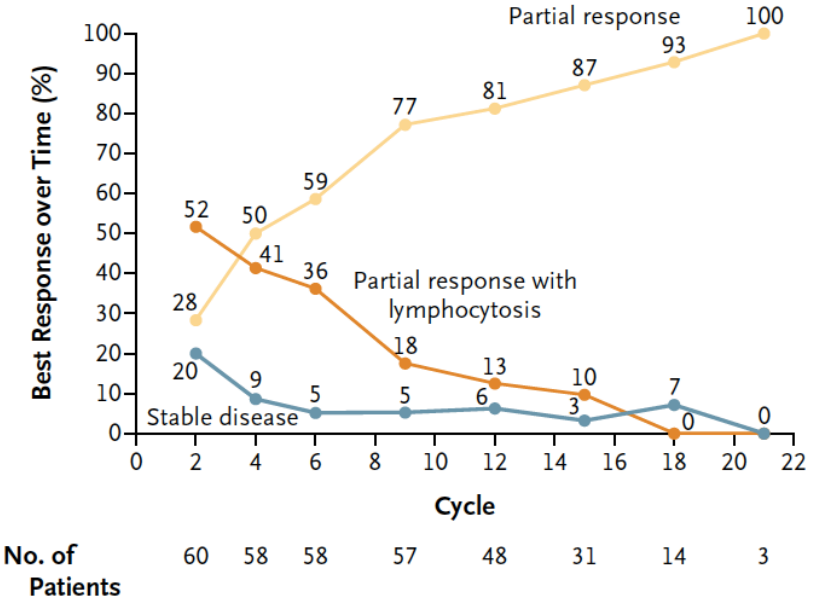
Burger JA, et al. *N Engl J Med*. **373**:2425, 2015; Melo A, et al. *Hematologica* 2017 pii: haematol.2017.175380. doi: 10.3324/haematol.2017.175380.

Acalabrutinib



- Orally active drug that can inhibit BTK
- Twice daily dosing
- Can provide for 100% BTK-occupancy
- Active in patients with CLL

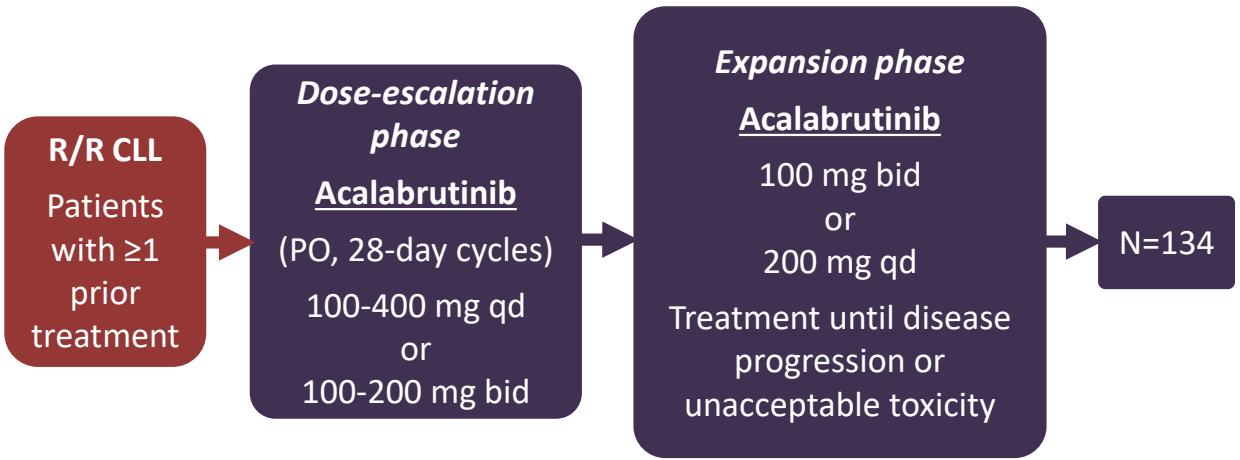




Byrd, JC et al N Engl J Med 374: 323-32, 2016

ACE-CL-001: Acalabrutinib Monotherapy in R/R CLL

Enrollment: 3 February 2014 to 26 November 2015



Primary endpoints:
- Safety

Secondary endpoints:
- ORR (iwCLL 2008 criteria with modification for lymphocytosis)[1,2]
- DOR
- PFS

Ad hoc endpoint:
- Time to response

All patients were switched to 100 mg BID

Data cutoff: 3 April 2017

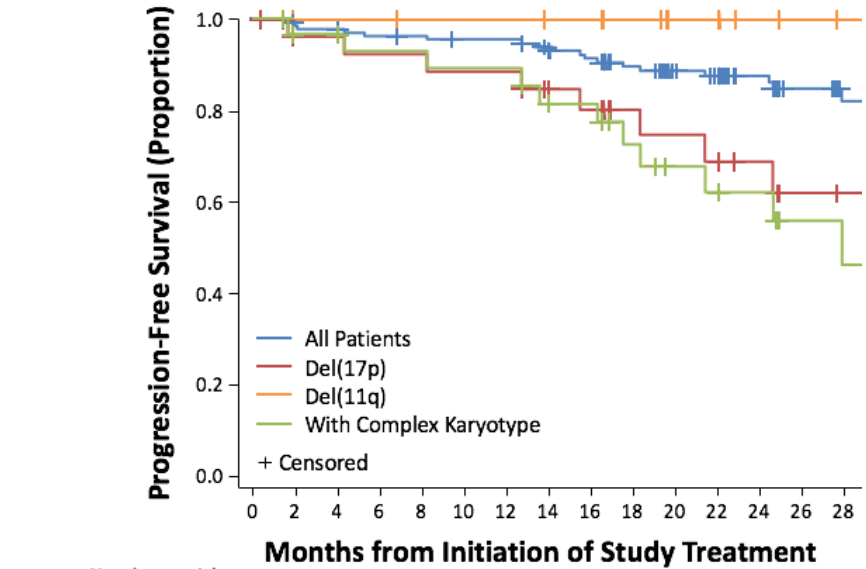
– bid = twice daily; CLL = chronic lymphocytic leukemia; bid = twice daily; DOR = duration of response; IWCLL = International Workshop on Chronic Lymphocytic Leukemia; ORR = overall response rate; PFS = progression-free survival; po = orally; qd = once daily; R/R = relapsed/refractory.

– 1. Hallek M, et al. *Blood*. 2008;111(12):5446-5456. 2. Cheson BD, et al. *J Clin Oncol*. 2012;30:2820-2822.

Time-to-Event Outcomes Acalabrutinib in R/R CLL

- Median PFS in the overall population was not reached
- Median TTR (≥ PR) was 5.3 months (95% CI: 1.7, 22.4), and median DOR was not reached

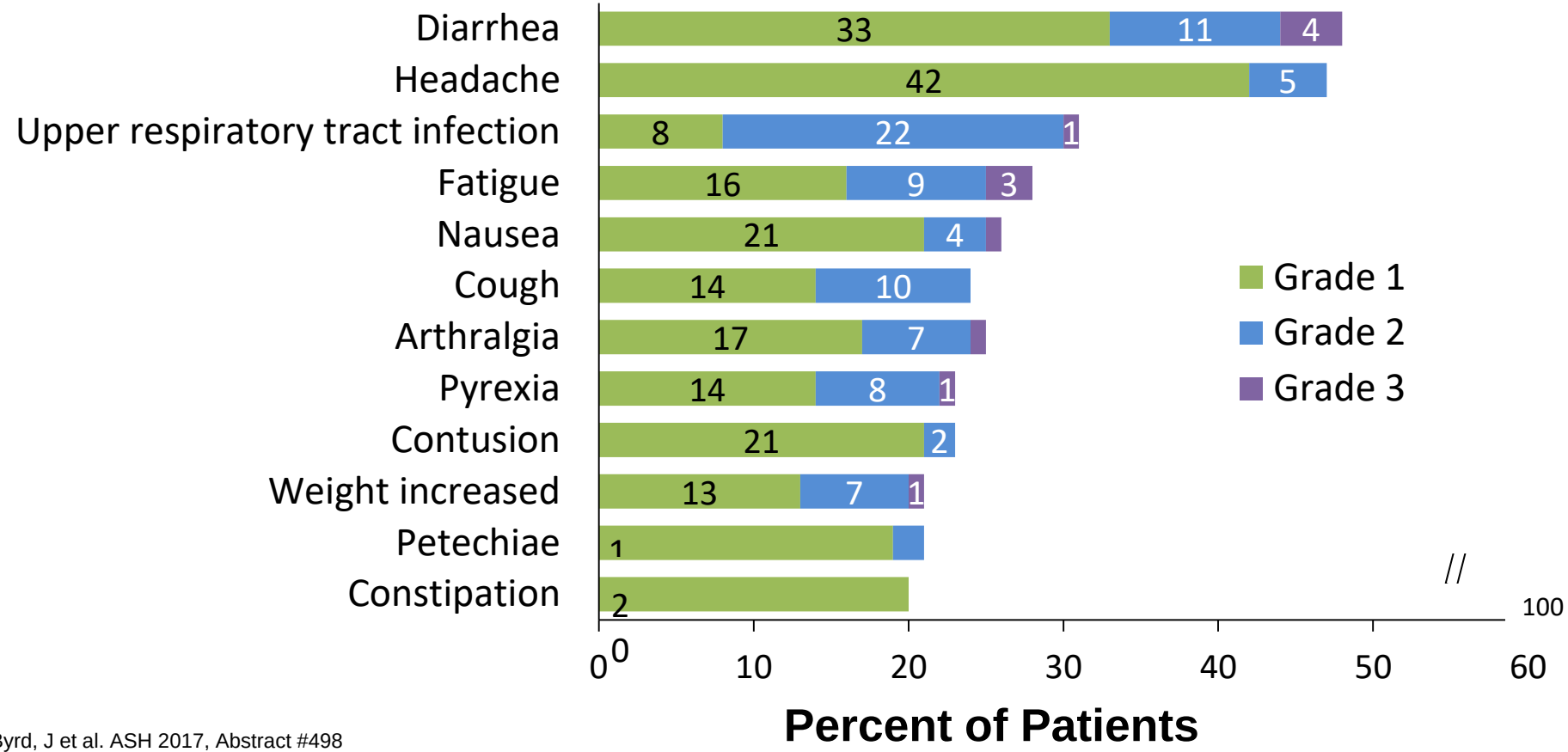
	N=134
Median PFS, mos (95% CI)[b]	NR (35.7, NR)
del(17p)	NR (21.4, NR)
del(11q)	NR (NR, NR)
Complex karyotype	27.9 (18.4, NR)
No complex karyotype	NR (35.7, NR)
18-month PFS, % (95% CI)[b]	90 (83, 94)
del(17p)	80 (59, 91)
del(11q)	100 (100, 100)
No complex karyotype	95 (81, 99)



– DOR = duration of response; NR = not reached; PFS = progression-free survival; PR = partial response; TTR = time to response.

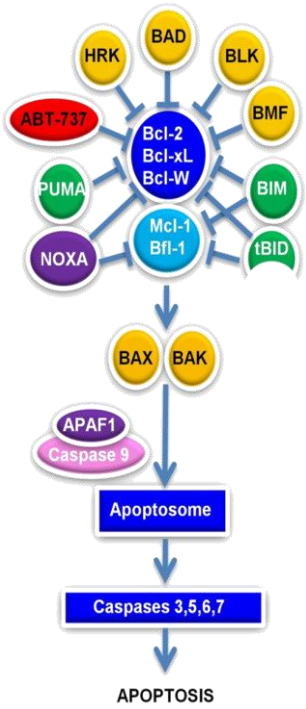
Byrd, J et al. ASH 2017, Abstract #498

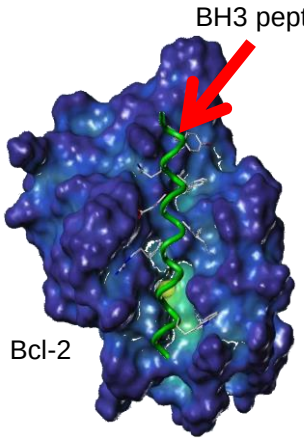
Most Common Adverse Events (≥20% of All Patients) Observed In Patients Treated With Acalabrutinib (N=134)

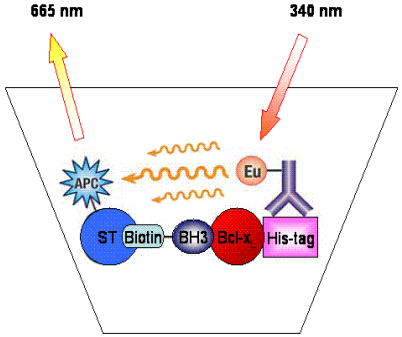


Byrd, J et al. ASH 2017, Abstract #498

Bcl-2 Family Inhibitors







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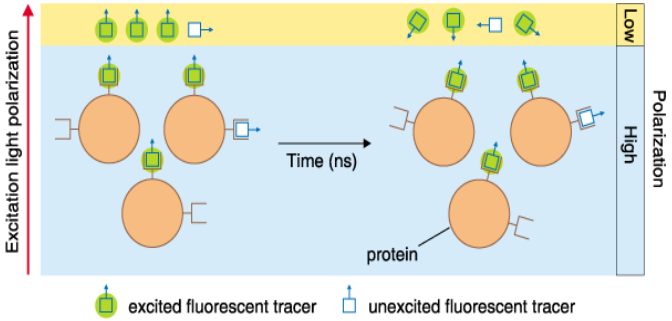


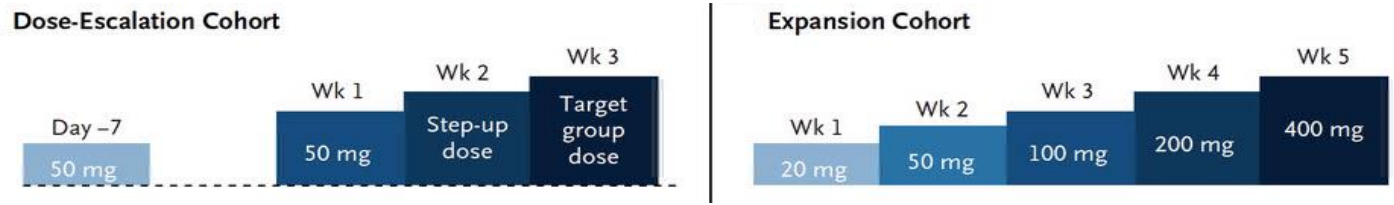
Reference FITC-BH3 Peptide And FPA

Rega et al. Bioorg. Chem. 35:344-353 (2007)

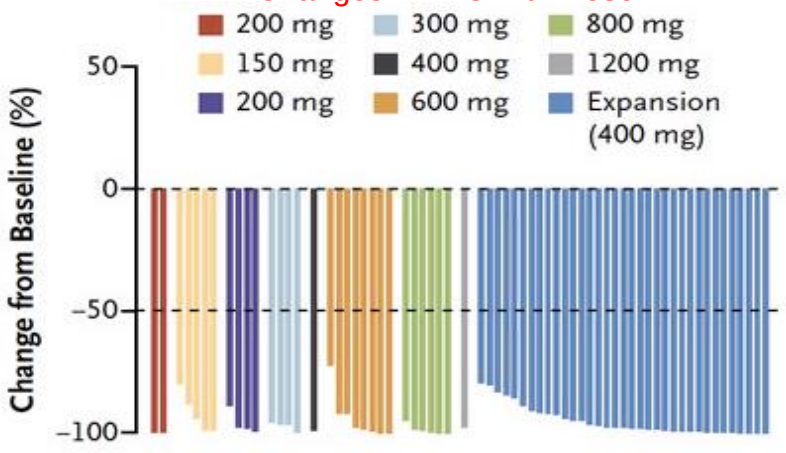
Small Molecule Inhibitors Of Bcl-2 Proteins And IC_{50} Of BID Peptide Displacement

Compound IC_{50} (μM)					
Protein	Gossypol	Apogossypol	Obatoclax	ABT-737	ABT-199
Bcl-xL	3.0	2.8	4.69	0.064	0.048
Bcl-2	0.28	0.64	1.11	0.10	<0.10nM
Bcl-w	1.4	2.1	7.01	0.024	N/A
Bcl-B	0.16	0.37	2.15	>10	N/A
Mcl-1	1.75	3.35	2.90	>20	N/A

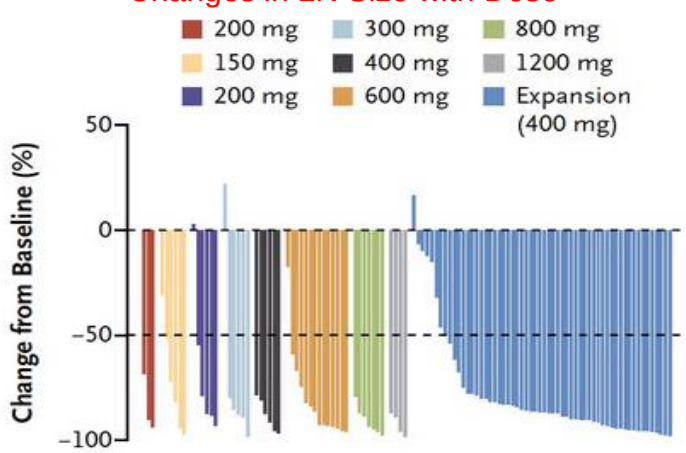
Venetoclax (ABT-199) In R/R CLL



Changes in ALC with Dose



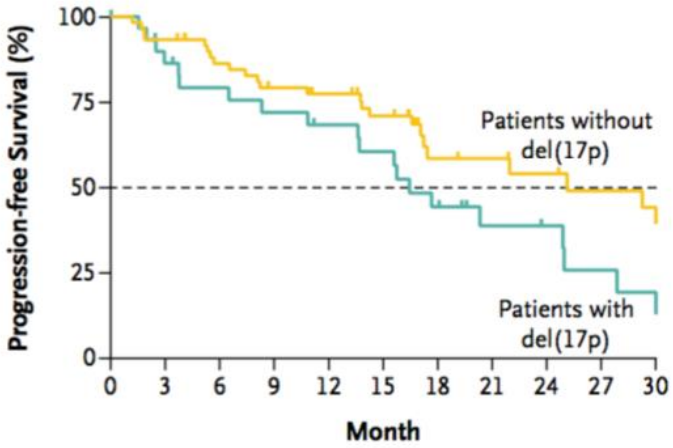
Changes in LN Size with Dose



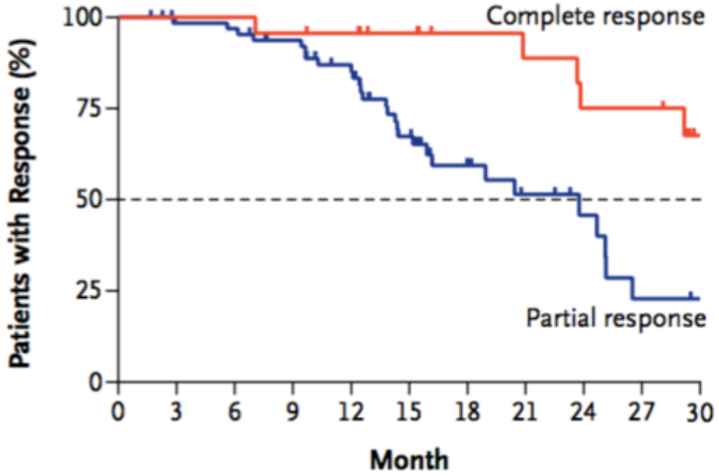
Roberts, A. W. et al. N Engl J Med 374: 311-22, 2016

Venetoclax (ABT-199) In R/R CLL

- 3 of 56 pts in the dose-escalation cohort had tumor lysis syndrome, with one death
- Among 116 pts treated, 92 (79%) had a response
- 20% had complete responses and 5% lacked detectable minimal residual disease (MRD) (<0.01%)
- The 15-month progression-free survival of pts receiving 400 mg QD was 69% (including pts with del(17p)



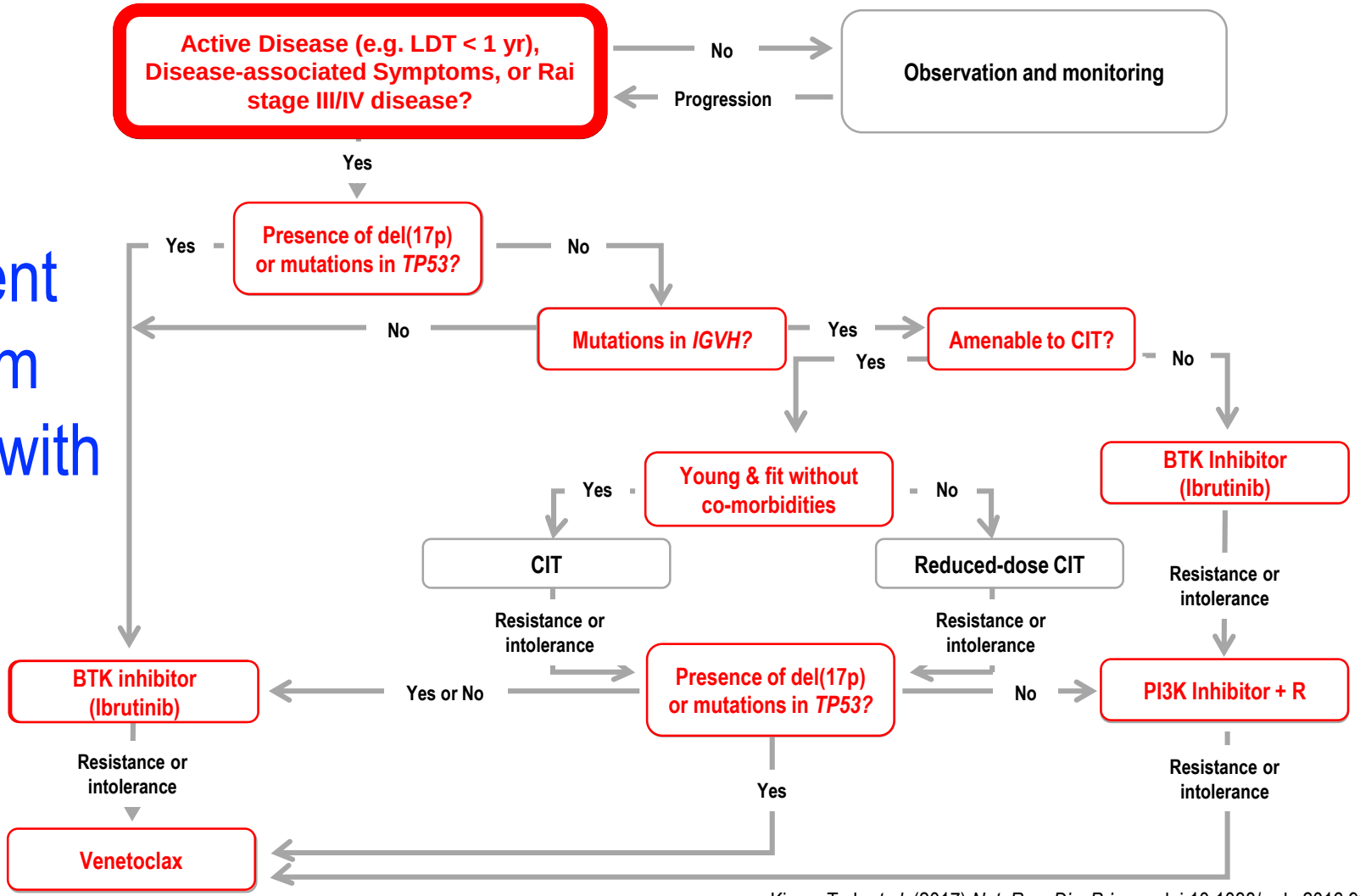
No. at Risk											
Patients without del(17p)	60	56	49	44	39	33	16	14	12	10	9
Patients with del(17p)	31	31	25	22	18	15	11	7	6	4	3



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, A. W., et al. N Engl J Med 374: 311-22, 2016

Current Treatment Algorithm For Pts with CLL



Kipps, T. J. *et al.* (2017) *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2016.96

Combination Therapy

- BTK-inhibitors ± anti-CD20 mAb
- Ibrutinib + anti-ROR1 mAb
- Venetoclax + anti-CD20 mAb
- Combined BTK-inhibitor + Bcl-2 inhibitor ± anti-CD20 mAb
- Combined chemo-immunotherapy and ibrutinib
- PI3K-inhibitor, new, and novel agents

Ibrutinib ± Rituximab: Study Design

- **Relapsed/Refractory** (n=179)
- **Treatment naïve** with 17p del or TP53 mutated (n=27)

Ibrutinib (n=102)

Ibrutinib 420 MG daily until disease progression, death, or unacceptable side effects

Stratification factors

- ECOG PS (0-1 vs. 2)
- High-risk cytogenetic abnormalities (del17p, TP53 mutation, del11q)

Ibrutinib + rituximab (n=104)

Ibrutinib 420 MG daily plus rituximab (375 mg/m^2 weekly x 4, then monthly for cycles 2-6)

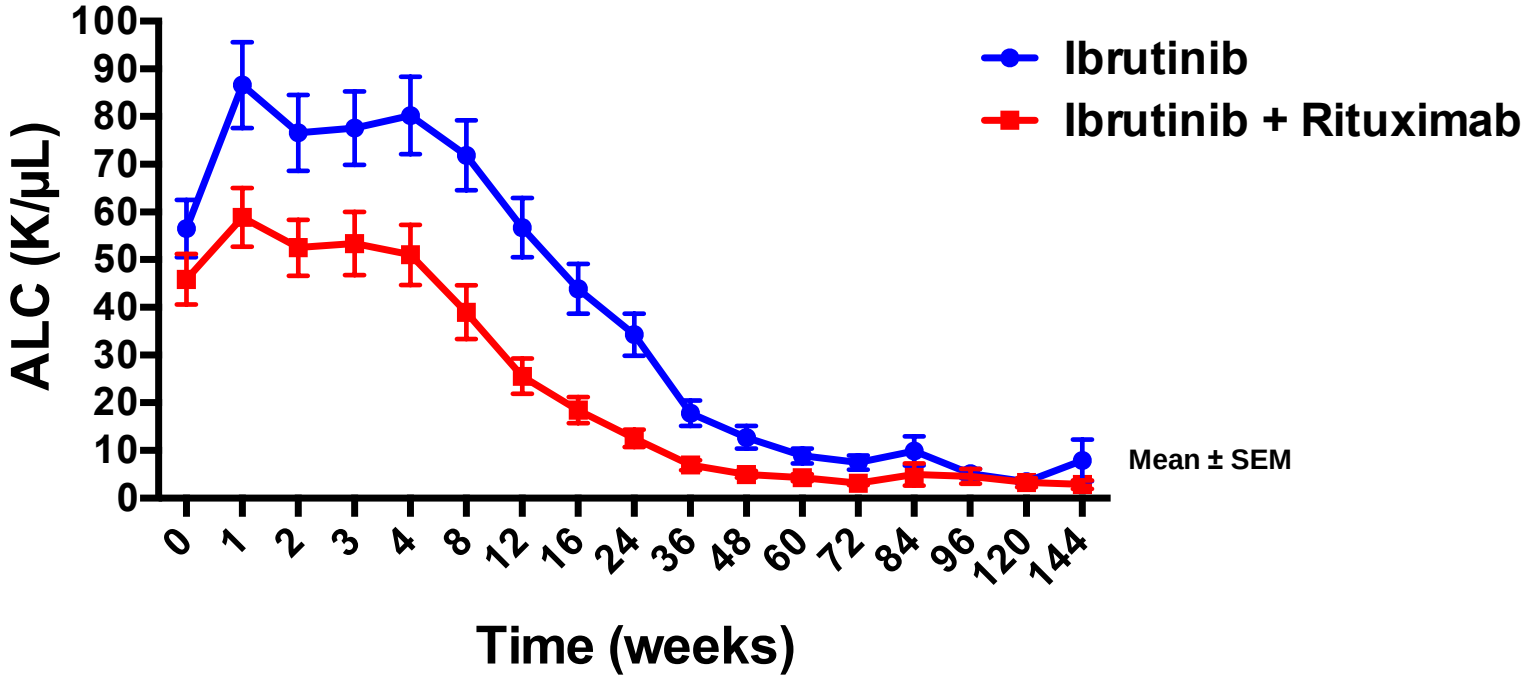
Total = 206

Primary end point: 2-year PFS

Secondary end points: ORR and tolerability

Burger, JA et al. ASH 2017, Abstract #427

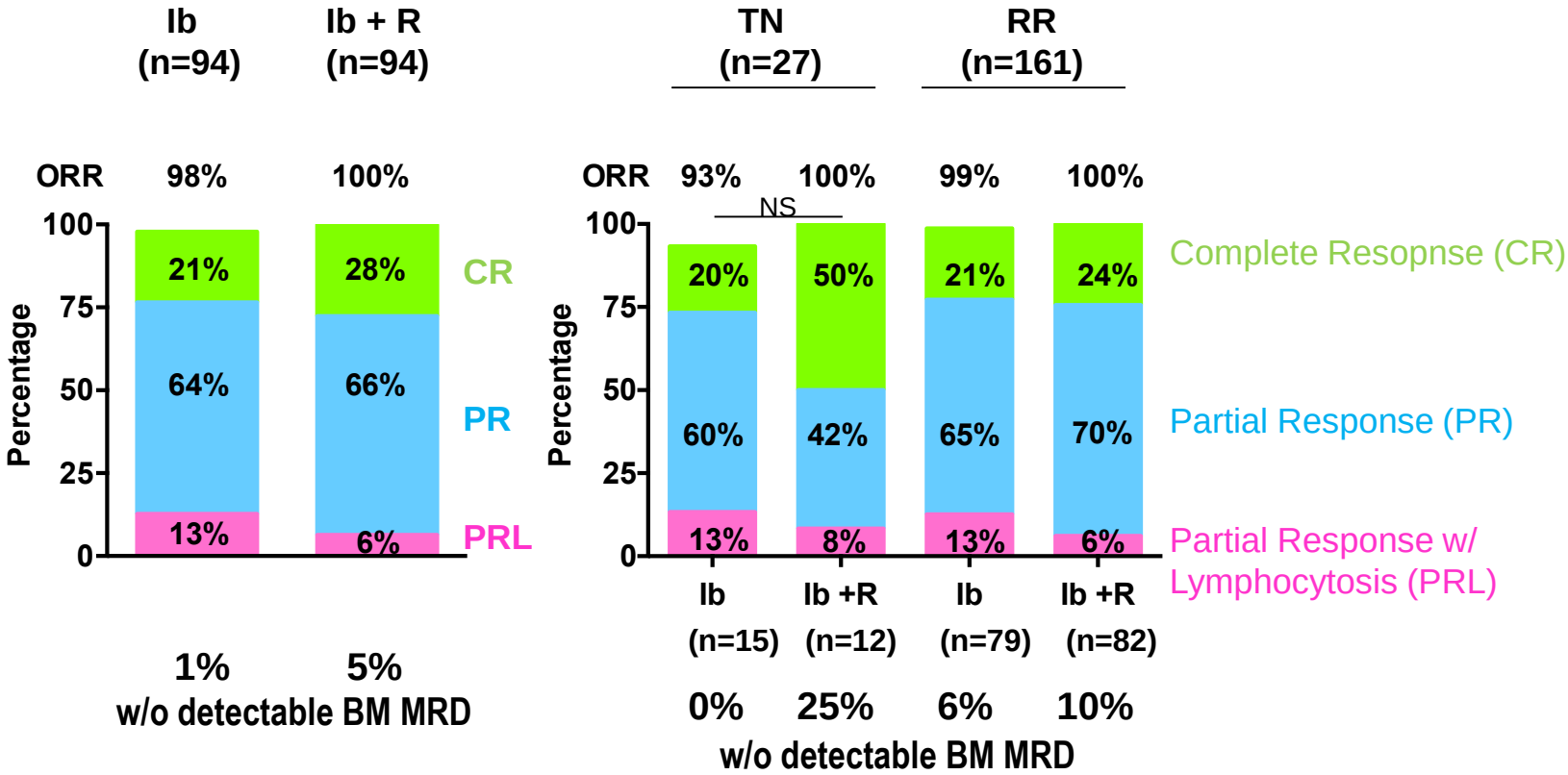
Ibrutinib ± Rituximab: Absolute lymphocyte counts (ALC)



	ibrutinib	ibrutinib + R	p value
Time to normalization of ALC in months (range)	8.9 (0.2 – 29.9)	3.0 (0.2 – 29.9)	<0.001

Burger, JA et al. ASH 2017, Abstract #427

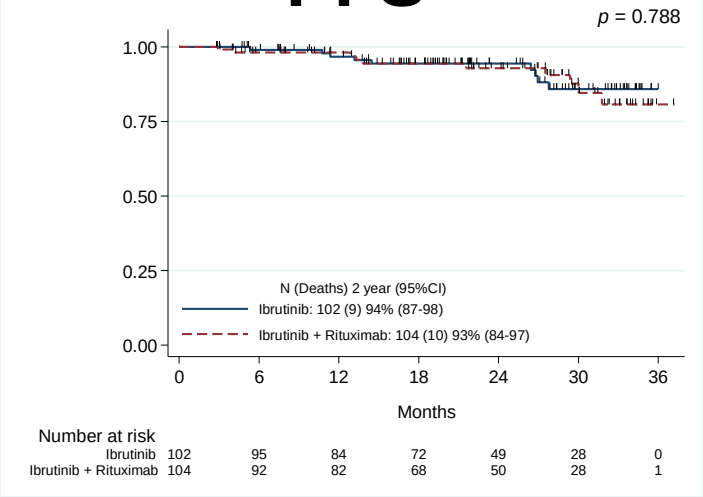
Ibrutinib ± Rituximab: Best Response



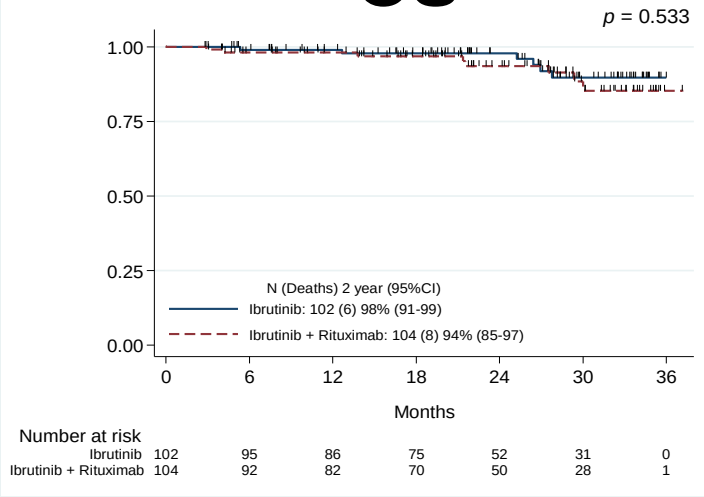
Burger, JA et al. ASH 2017, Abstract #427

Ibrutinib ± Rituximab: Outcomes

PFS



OS



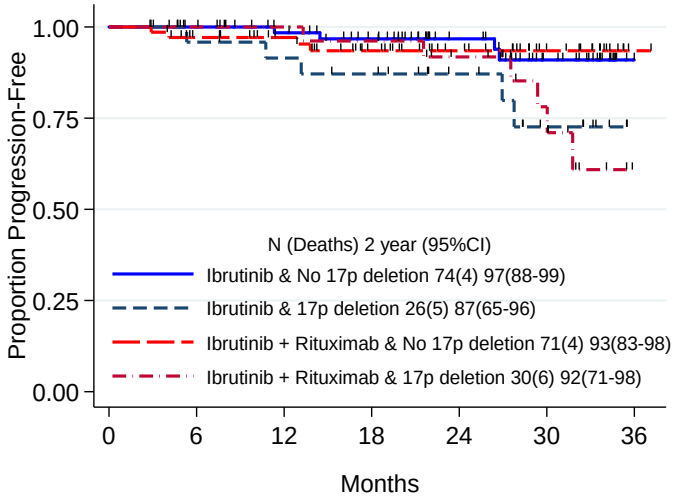
	Ibrutinib (n=102)	Ibrutinib +R (n=104)
F/U in months (range)	**25.2 (2.7 – 35.9)**	**22.7 (2.8 – 37.1)**

No difference in PFS or OS Between Treatment Groups

Burger, JA et al. ASH 2017, Abstract #427

Ibrutinib ± Rituximab: Outcome By 17p Status

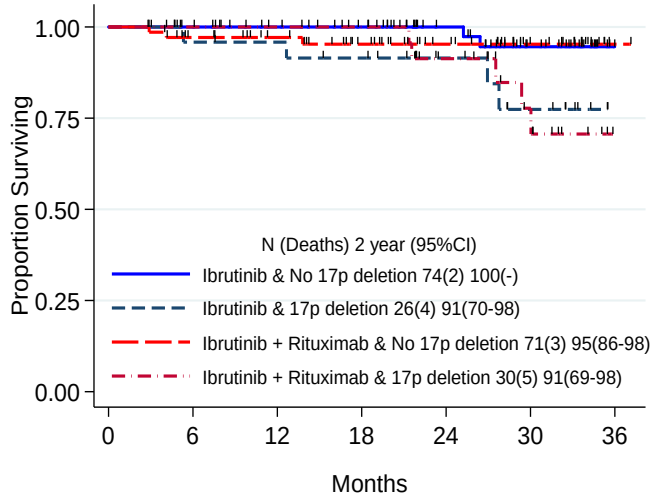
PFS



Number at risk

Ibrutinib & No 17p deletion	74	70	62	53	36	21	0
Ibrutinib & 17p deletion	26	23	21	19	13	7	0
Ibrutinib + Rituximab & No 17p deletion	71	62	54	42	30	16	1
Ibrutinib + Rituximab & 17p deletion	30	28	26	24	18	11	0

OS



Number at risk

Ibrutinib & No 17p deletion	74	70	63	55	38	23	0
Ibrutinib & 17p deletion	26	23	22	20	14	8	0
Ibrutinib + Rituximab & No 17p deletion	71	62	54	43	30	16	1
Ibrutinib + Rituximab & 17p deletion	30	28	26	25	18	11	0

No difference in PFS or OS Between Treatment Groups

Burger, JA et al. ASH 2017, Abstract #427

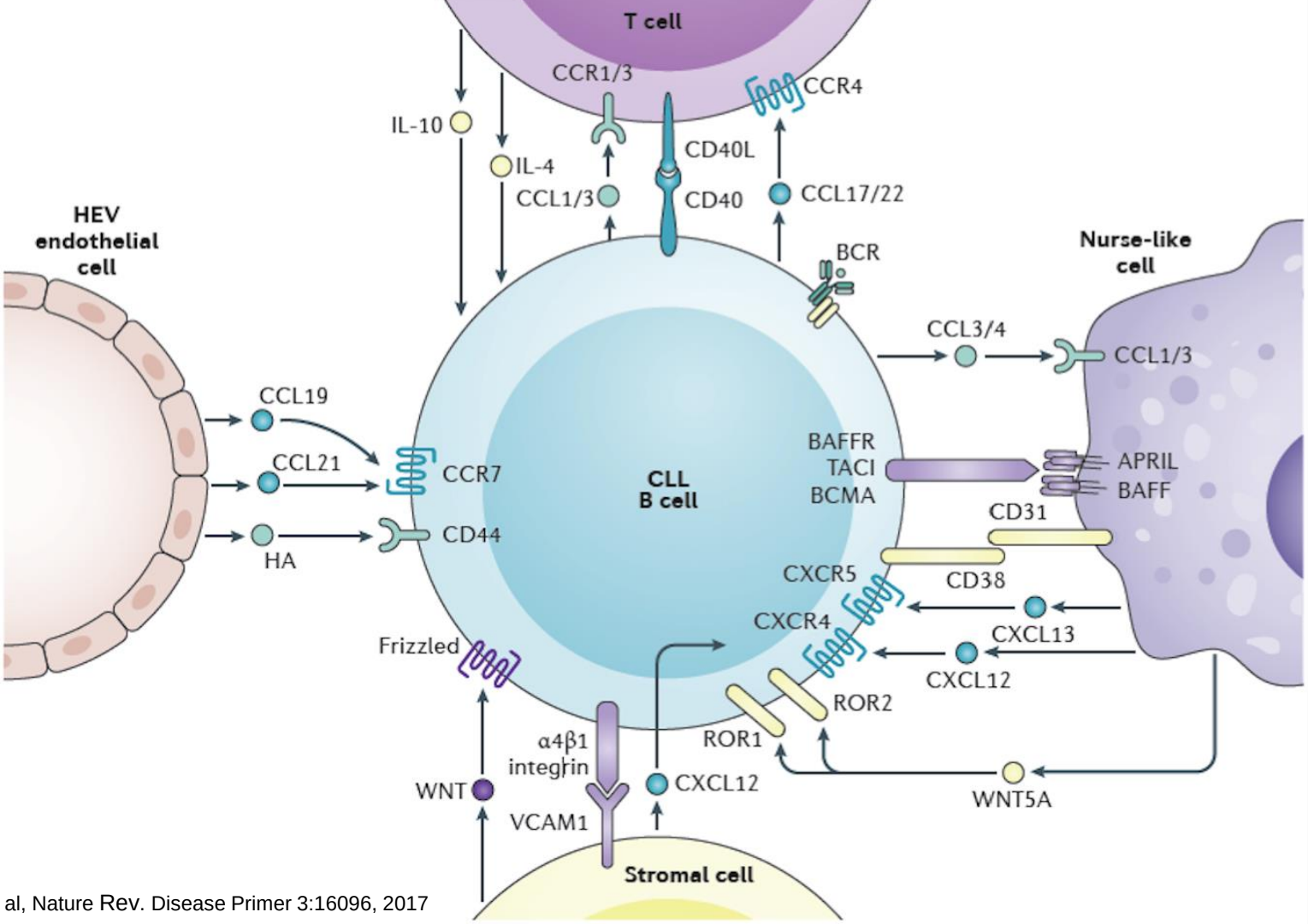
Summary BTK-inhibitors ± Anti-CD20 mAb

- Rituximab combined with ibrutinib attenuates lymphocytosis upon initiation, but doesn't impact on response rate or PFS
- Obinutuzumab combined with ibrutinib has low CR rate and low rate of undetectable MRD in first-line
- It is uncertain whether obinutuzumab improves the outcome of patients treated with acalabrutinib

Burger, JA et al. ASH 2017, Abstract #427
Michallet, A et al. ASH 2017, Abstract #497
Woyach, J et al. ASH 2017, Abstract #432

Combination Therapy

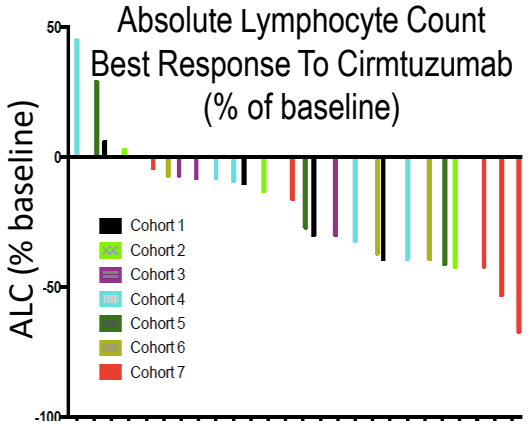
- BTK-inhibitors ± anti-CD20 mAb
- Ibrutinib + anti-ROR1 mAb
- Venetoclax + anti-CD20 mAb
- Combined BTK-inhibitor + Bcl-2 inhibitor ± anti-CD20 mAb
- Combined chemo-immunotherapy and ibrutinib
- PI3K-inhibitor, new, and novel agents

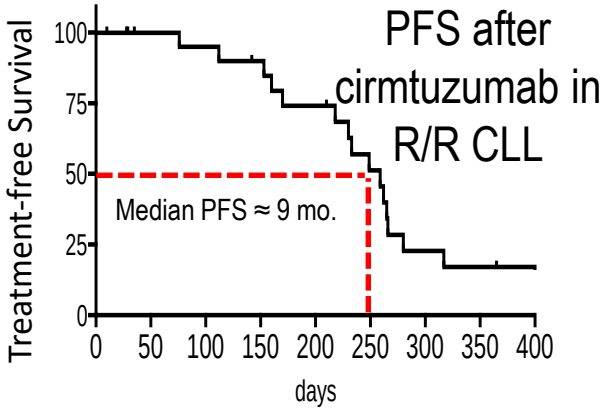


Kipps, TJ et al, Nature Rev. Disease Primer 3:16096, 2017

Receptor Tyrosine Kinase-Like Orphan Receptor 1 (ROR1)

- Expressed during embryogenesis, but not most post-partem tissues
- Expressed CLL, SLL, mantle cell lymphoma (MCL), and most solid tumors
- Receptor for Wnt5a, which is found in plasma of patients with CLL
- ROR1-signaling induces Rho-GTPase activation and promotes leukemia migration, proliferation, and survival
- Anti-ROR1 mAb cirmtuzumab inhibits ROR1-signaling, which is highly active in CLL cells of patients treated with ibrutinib





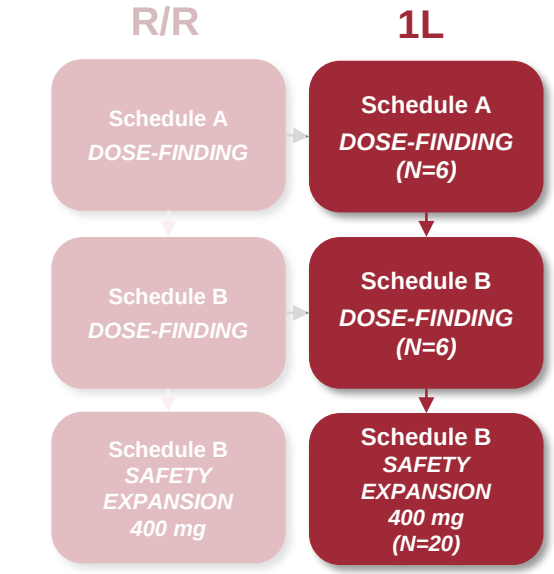
Matsuda T, et al. Mech Dev. 2001; Fukuda, T, et al Blood,104:772, 2004; Fukuda T, et al PNAS USA 105:3047, 2008
Baskar, S. Clin Cancer Res, 2008; Daneshmanesh, A. H., Int J. Cancer, 2008; Broome HE, Leuk Res. 35:1390, 2011;
Zhang S et al, Am J Pathol.181:1903, 2012; Widhopf, G, et al PNAS USA 111:793, 2014; Zhang, S, et al. PNAS USA, 2014
Choi, M.Y. et al, Clin Lymphoma Myeloma Leuk. Suppl:S167-9, 2015; Yu, J. et al J Clin Invest. 126:585, 2016;
Cui, B, Ghia E, et al, Blood 128:2931, 2016; Yu et al, Leukemia 31:2608, 2017; Hasan et al, Leukemia 31: 2615, 2017

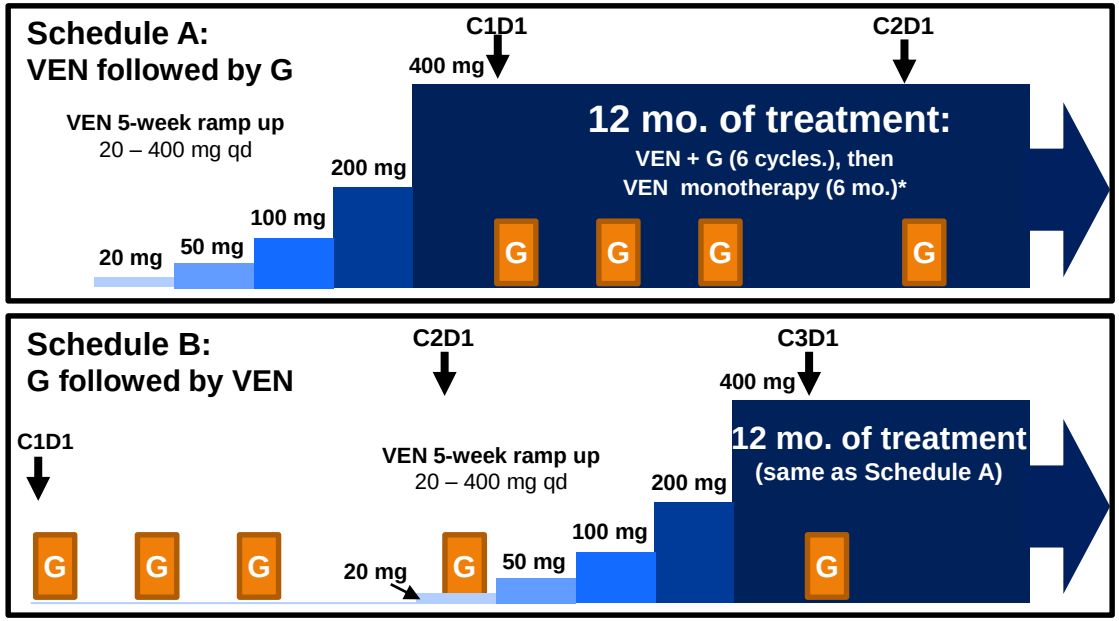
Choi, M et al. ASH 2017, Abstract #829

Combination Therapy

- BTK-inhibitors ± anti-CD20 mAb
- Ibrutinib + anti-ROR1 mAb
- Venetoclax + anti-CD20 mAb
- Combined BTK-inhibitor + Bcl-2 inhibitor ± anti-CD20 mAb
- Combined chemo-immunotherapy and ibrutinib
- PI3K-inhibitor, new, and novel agents

GP28331 Study – Venetoclax (Ven) And Obinutuzumab (G)





***Potential VEN extension if BM MRD+ or PR; G=obinutuzumab; VEN=venetoclax.**

- MTD not reached. Safety monitoring team recommended Schedule B (G followed by VEN) and the 400 mg dose for expansion cohorts after reviewing the study data

G dosing schedule: C1D1: 100 mg, C1D2: 900 mg, C1D8 and 15:1000 mg, C2–6D1: 1000 mg.

Flinn, I et al. ASH 2017, Abstract #430

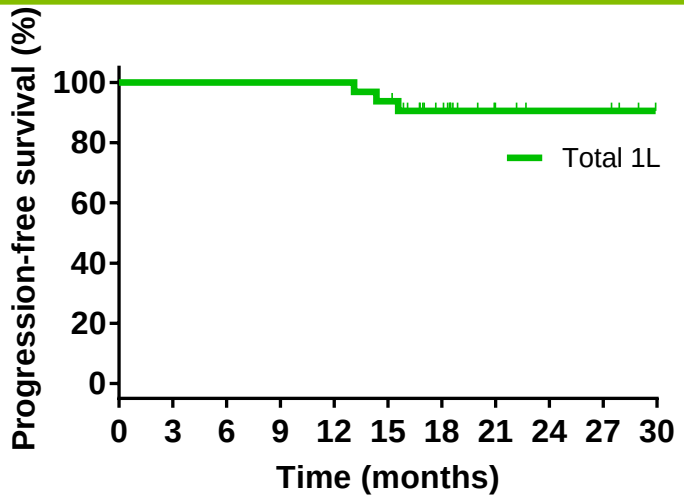
Efficacy of VEN + G: Response in All Patients and High CR Rates in All CLL Subgroups

Response n (%)	All 1L patients (N=32)	By cytogenetic abnormalities[b] (n=29)					By IGHV gene mutational status (n=27)	
		del(17p) n=5	del(11q) n=6	Trisomy 12 n=6	No abnormalities n=1	del(13q) n=11	Mut n=11	Unmut n=16
ORR	32 (100)	5 (100)	6 (100)	6 (100)	1 (100)	11 (100)	11 (100)	16 (100)
CR/CRi	23 (72)	3 (60)	5 (83)	5 (83)	1 (100)	7 (64)	9 (82)	11 (69)
PR	9 (28)[a]	2 (40)	1 (17)	1 (17)	--	4 (36)	2 (18)	5 (31)

[a]One patient downgraded to PR due to a mild splenomegaly 16cm (by imaging) and hypocellular BM (by histology); all other components consistent with CR.
[b]Responses by cytogenetic abnormalities according to the hierarchical model.

Flinn, I et al. ASH 2017, Abstract #430

Progression Free Survival With Frontline Therapy (Ven + G)

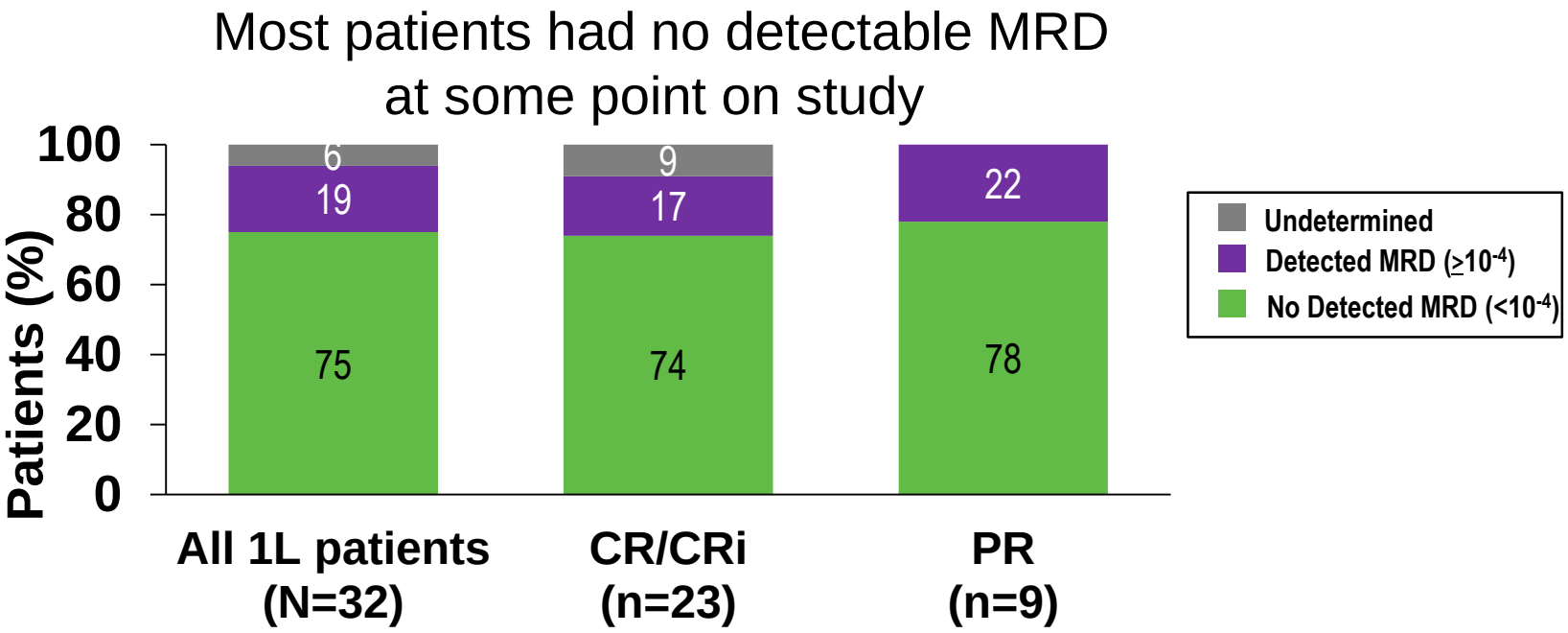


- Median time on study: 18.5 months (range: 15–30)
- Median PFS = not reached
  - 12-month estimate: 100%
  - 15-month estimate: 93.8% (95% CI: 85.4, 100.0)
  - 18-month estimate: 90.5% (95% CI: 80.3, 100.0)

- Disease progression: 3 patients; no deaths
  - 2 patients had Richter transformation
    - Pt 1 (DLBCL): Day 437 (on VEN); del(17p) at baseline; BM MRD+ all assessments
    - Pt 2 (HL): Day 474 (off VEN); trisomy 12, unmutated IGHV at baseline; BM MRD– all assessments (before PD)
  - 1 patient with PD
    - Day 399 (on VEN); del(11q), del(17p), unmutated IGHV at baseline; BM MRD+ all assessments

Flinn, I et al. ASH 2017, Abstract #430

High Rates Of Clearing Detectable MRD In The Marrow With Ven + G



- 4 of 7 PR patients with no detectable MRD in the marrow were classified as PR (2008 iwCLL criteria) due to presence of residual lymphadenopathy (between 16–34 mm)
  - All other parameters were consistent with CR

Flinn, I et al. ASH 2017, Abstract #430

Undetermined Indicates No Detectable MRD, but <200,000 leukocytes analyzed

Summary of Adverse Events In Pts Treated With Ven+G

AEs, n (%)	All grade AEs >25% total pts (N=32)	Grade 3–4 AEs (N=32)
Nausea	22 (69)	--
Infusion-related reaction	21 (66)	--
Neutropenia	21 (66)	17 (53)
Febrile neutropenia	--	4 (13)
Diarrhea	18 (56)	1 (3)[a]
Pyrexia	15 (47)	1 (3)
Fatigue	14 (44)	1 (3)
Thrombocytopenia	13 (41)	5 (16)
Headache	12 (38)	--
Chills	11 (34)	--
Vomiting	11 (34)	--
Cough	10 (31)	--
Flushing	10 (31)	--
Anemia	9 (28)	1 (3)
Dyspnea	9 (28)	--

- No clinical TLS; 1 laboratory TLS – C1D1 with G administration (before any VEN)
- Four events of Grade 3–4 infection: appendicitis, diverticulitis, enterobacter bacteremia, respiratory tract infection

Flinn, I et al. ASH 2017, Abstract #430

[a]Discontinued VEN.

MURANO Study Design

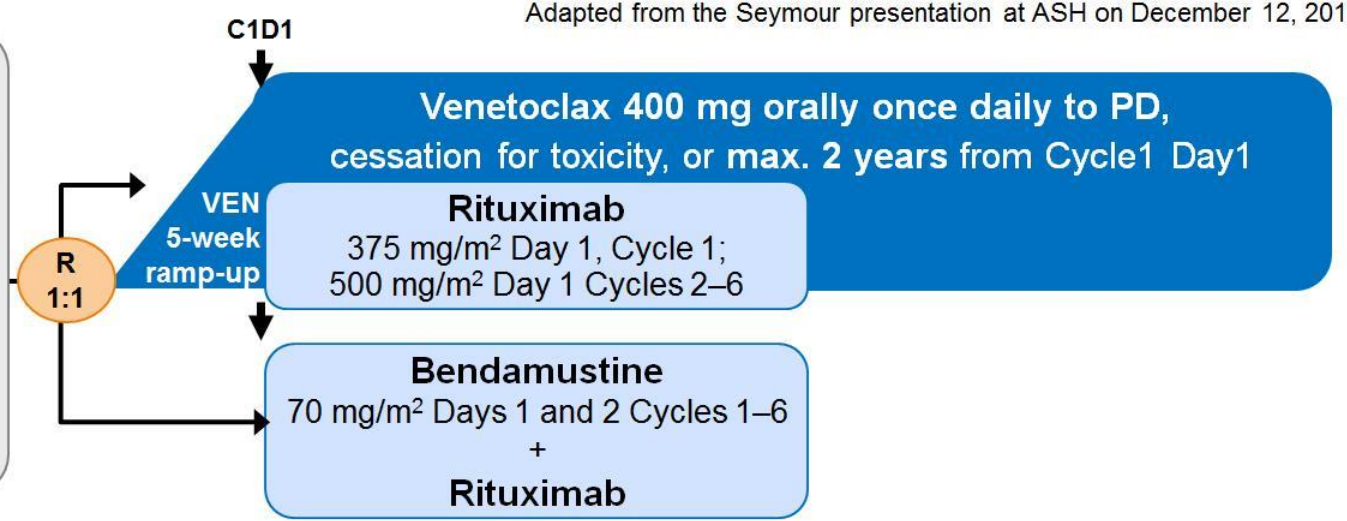
Adapted from the Seymour presentation at ASH on December 12, 2017

Relapsed/refractory CLL (N=389)

- ≥18 years of age
- Prior 1–3 lines of therapy, including ≥1 chemo-containing regimen
- Prior bendamustine only if DoR ≥24 months

Stratified by:

- Del(17p) by local labs
- Responsiveness to prior therapy*
- Geographic region



Primary Endpoint	INV-assessed PFS
Major Secondary Endpoints	• IRC-CR ⇒ IRC-ORR ⇒ OS (hierarchical testing) • IRC-assessed PFS and MRD-negativity
Key Safety Endpoints	Overall safety profile, focusing on serious adverse events and Grade ≥3 adverse events
Interim Analysis	Approximately 140 INV-assessed PFS events (75% of total information)

NCT02005471

*High-risk CLL – any of following features: del(17p) or no response to front-line chemotherapy-containing regimen or relapsed ≤12 months after chemotherapy or within ≤24 months after chemoimmunotherapy.

Grade 3–4 AEs; ≥2% Difference in Incidence Between Arms

Note: *AE Reporting Period Longer with VenR vs. BR*

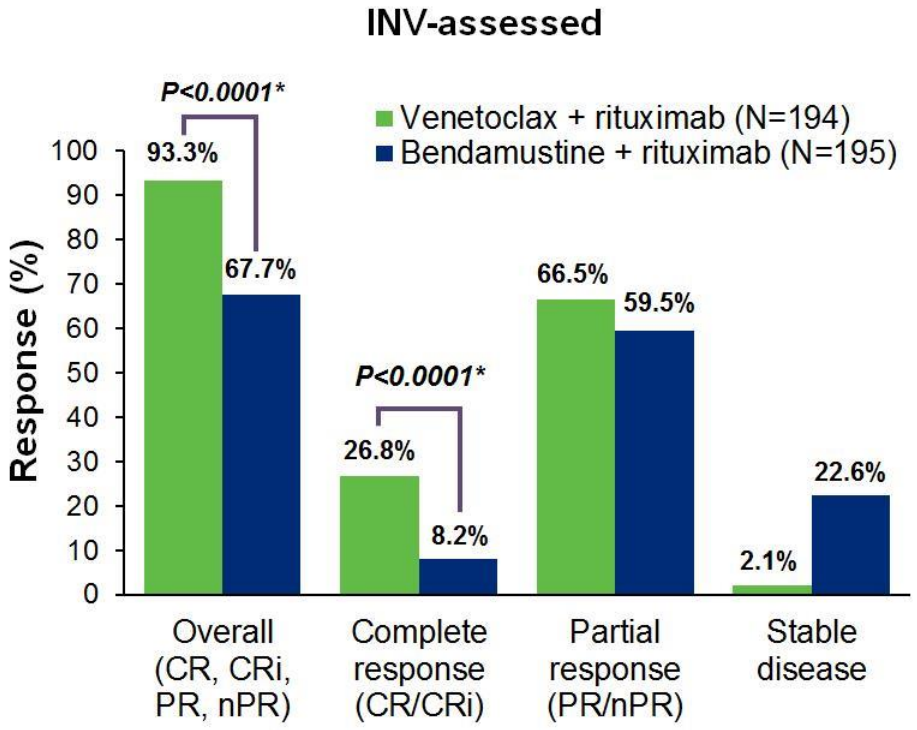
AEs, n (%)	Venetoclax + Rituximab (N=194)	Bendamustine + Rituximab (N=188)
Neutropenia	112 (58)	73 (39)
Anemia	21 (11)	26 (14)
Thrombocytopenia	11 (6)	19 (10)
Febrile Neutropenia	7 (4)	18 (10)
Pneumonia	10 (5)	15 (8)
Infusion-Related Reaction	3 (2)	10 (5)
Tumor Lysis Syndrome	6 (3)	2 (1)
Hypotension	0	5 (3)
Hyperglycemia	4 (2)	0
Hypogammaglobulinemia	4 (2)	0

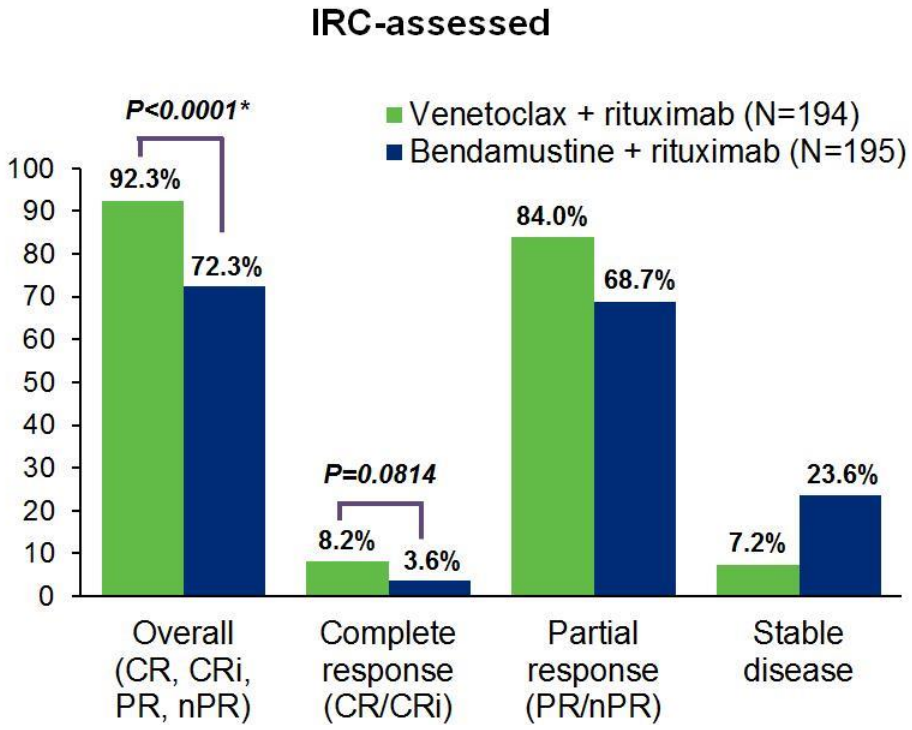
Adapted from the Seymour presentation at ASH on December 12, 2017

Adverse event reporting period: up to 90 days after end of bendamustine treatment (maximum 6 months); up to 28 days after end of venetoclax treatment (maximum 2 years).

As of 8 May 2017

Improved Response Rates for VenR vs. BR



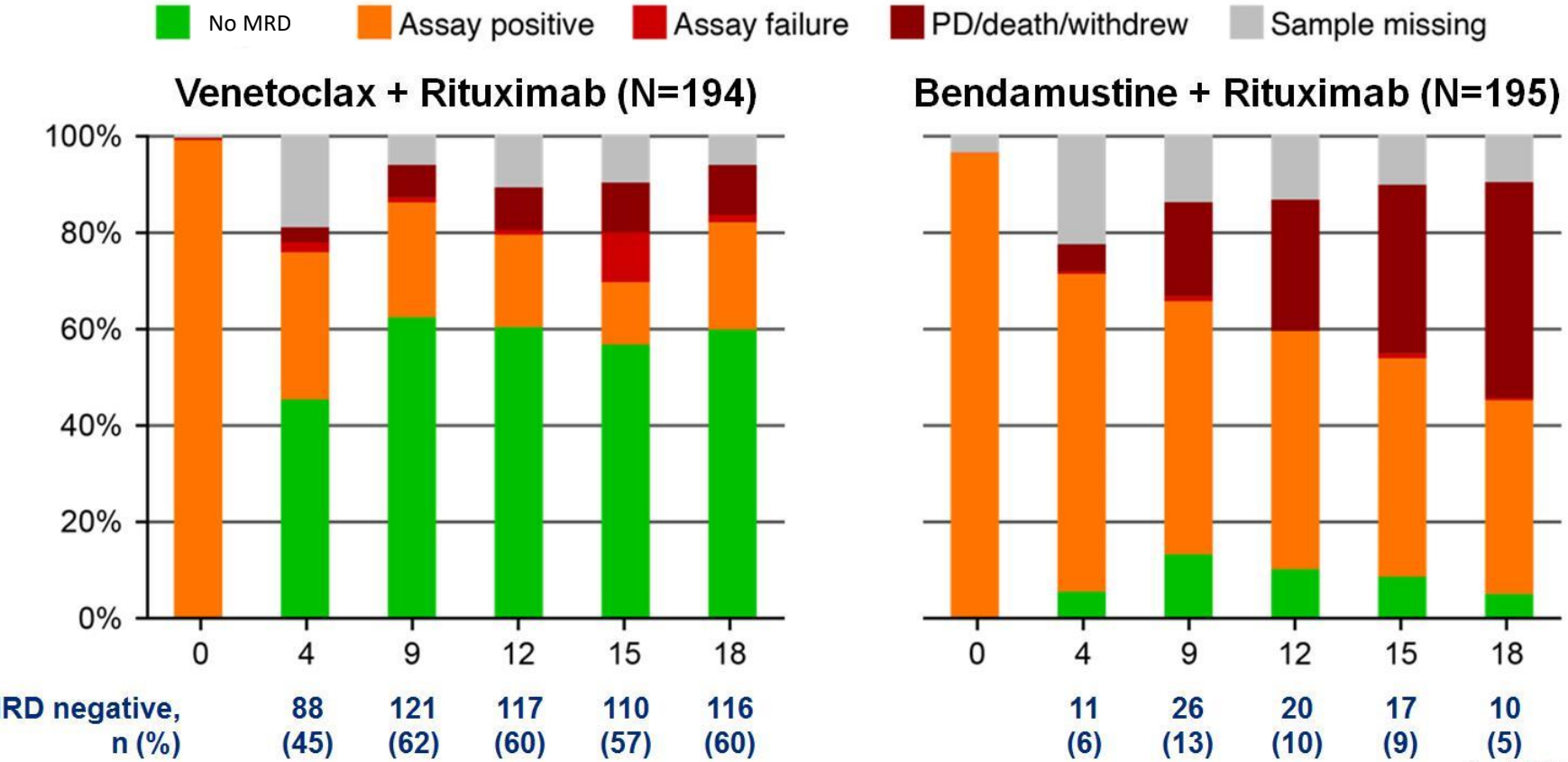


Adapted from the Seymour presentation at ASH on December 12, 2017

* Descriptive P-values.

Of 42 INV-assessed CRs discrepant in VenR arm, 28 were due to residual LN on CT scan of 16-30 mm in diameter; 88% of these pts had no detectable MRD in the blood.

High Rate of Undetectable MRD In the Blood Of Patients Treated With VenR Relative To Those Treated With BR

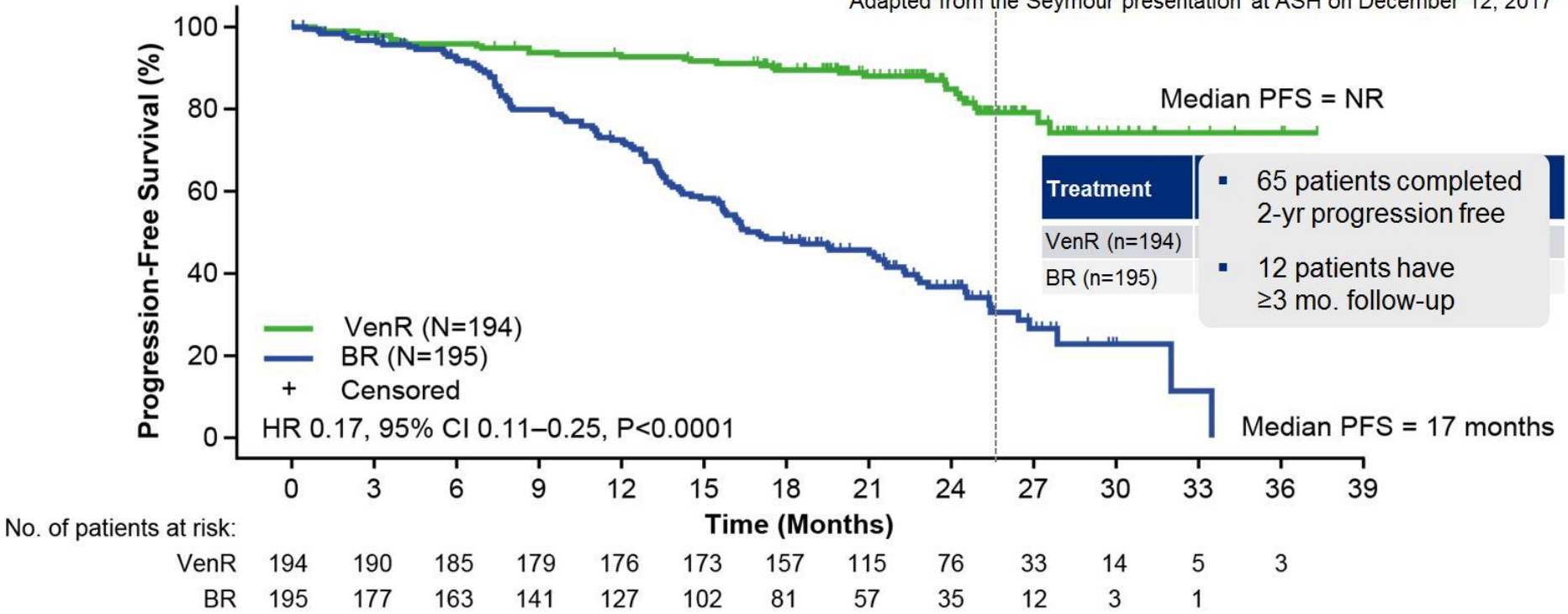


Adapted from the Seymour presentation at ASH on December 12, 2017

As of 8 May 2017

Investigator-Assessed PFS Superior for VenR vs. BR

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



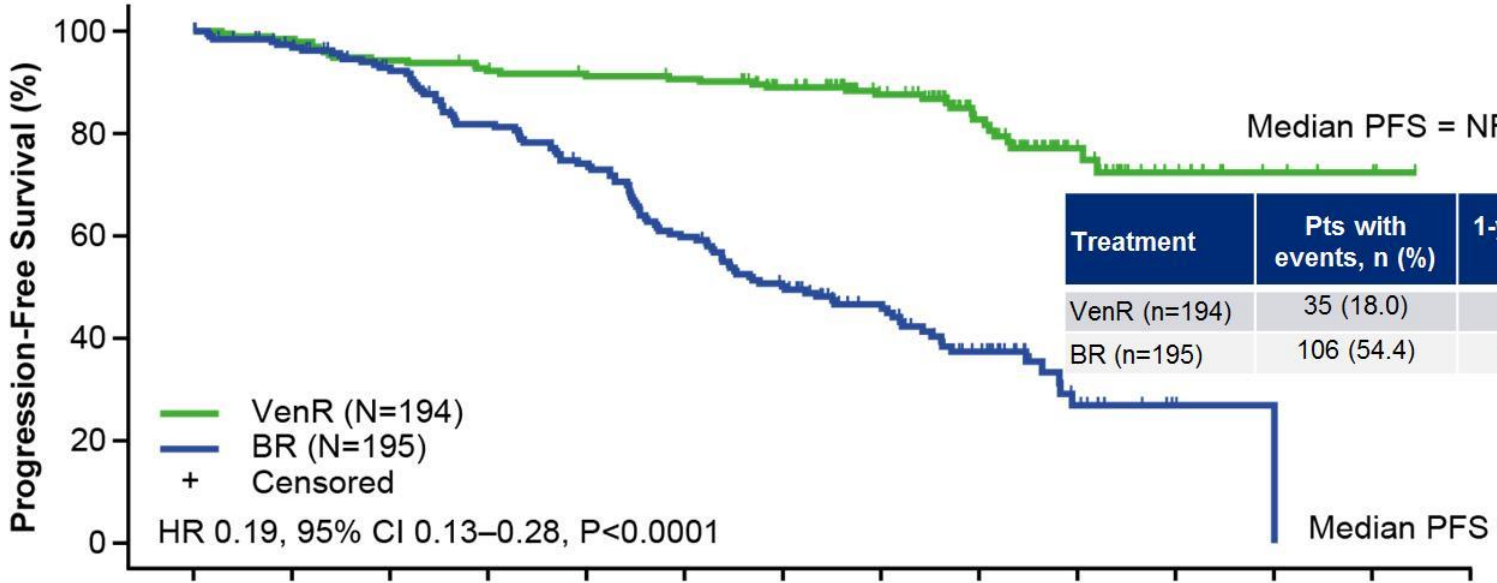
Treatment
VenR (n=194)
BR (n=195)

- 65 patients completed 2-yr progression free
- 12 patients have ≥3 mo. follow-up

- Median (range) duration of follow-up, 23.8 (0.0–37.4) months: Venetoclax + rituximab, 24.8 months; bendamustine + rituximab, 22.1 months

As of 8 May 2017

Superiority of VenR vs. BR Confirmed by Independent Review Committee-Assessed PFS



Treatment	Pts with events, n (%)	1-yr PFS %	2-yr PFS %
VenR (n=194)	35 (18.0)	91.2	82.8
BR (n=195)	106 (54.4)	74.1	37.4

No. of patients at risk:

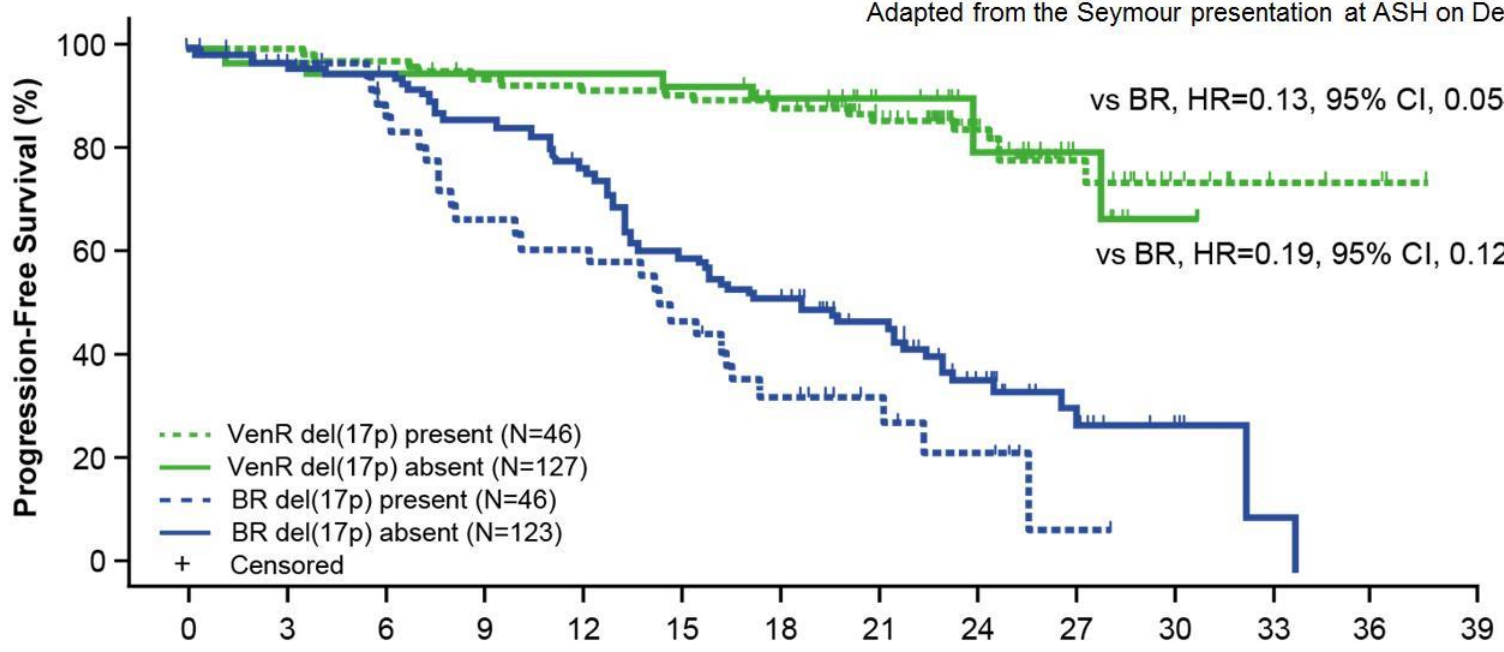
VenR	194	190	182	177	173	171	157	116	75	34	14	5	3
BR	195	178	162	138	124	100	82	56	34	11	2	1	

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

As of 8 May 2017

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

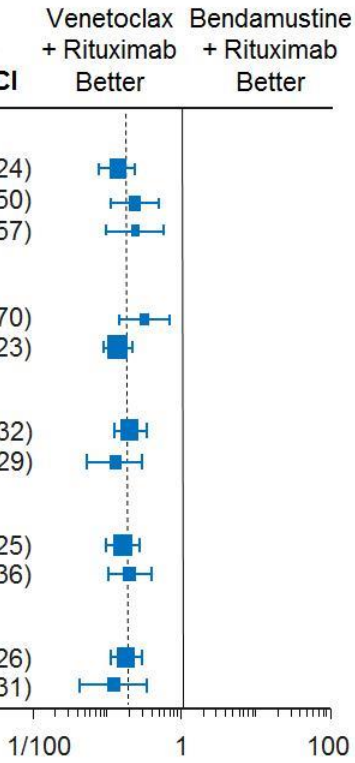


No. of patients at risk:													
VenR del(17p) present	46	44	43	43	43	42	36	25	17	7	2		
VenR del(17p) absent	127	127	124	118	116	114	105	76	48	20	10	4	3
BR del(17p) present	46	40	34	27	25	20	14	8	5	1			
BR del(17p) absent	123	114	108	99	88	70	60	44	26	10	3	1	

As of 8 May 2017

Treatment Effect With VenR Consistent Across Subgroups; Investigator-assessed PFS

Subgroups	Total N	Venetoclax + Rituximab (N=194) n	Venetoclax + Rituximab (N=194) Median (Months)	Bendamustine + Rituximab (N=195) n	Bendamustine + Rituximab (N=195) Median (Months)	Hazard Ratio	95% Wald CI
Number of prior therapies							
1	228	111	NR	117	16.6	0.14	(0.08–0.24)
2	100	57	NR	43	21.2	0.24	(0.11–0.50)
≥3	61	26	NR	35	10.5	0.24	(0.10–0.57)
Refractory vs. relapse to most recent prior therapy							
Refractory	59	30	NR	29	13.6	0.32	(0.15–0.70)
Relapse	330	164	NR	166	18.6	0.14	(0.09–0.23)
del(17p) status*							
Absent	250	127	NR	123	21.4	0.19	(0.12–0.32)
Present	92	46	NR	46	15.4	0.13	(0.05–0.29)
TP53* mutational status							
Unmutated	277	144	NR	133	21.2	0.15	(0.09–0.25)
Mutated	99	48	NR	51	12.9	0.19	(0.10–0.36)
Baseline IGHV mutational status*							
Unmutated	246	123	NR	123	15.7	0.16	(0.10–0.26)
Mutated	104	53	NR	51	22.9	0.11	(0.04–0.31)



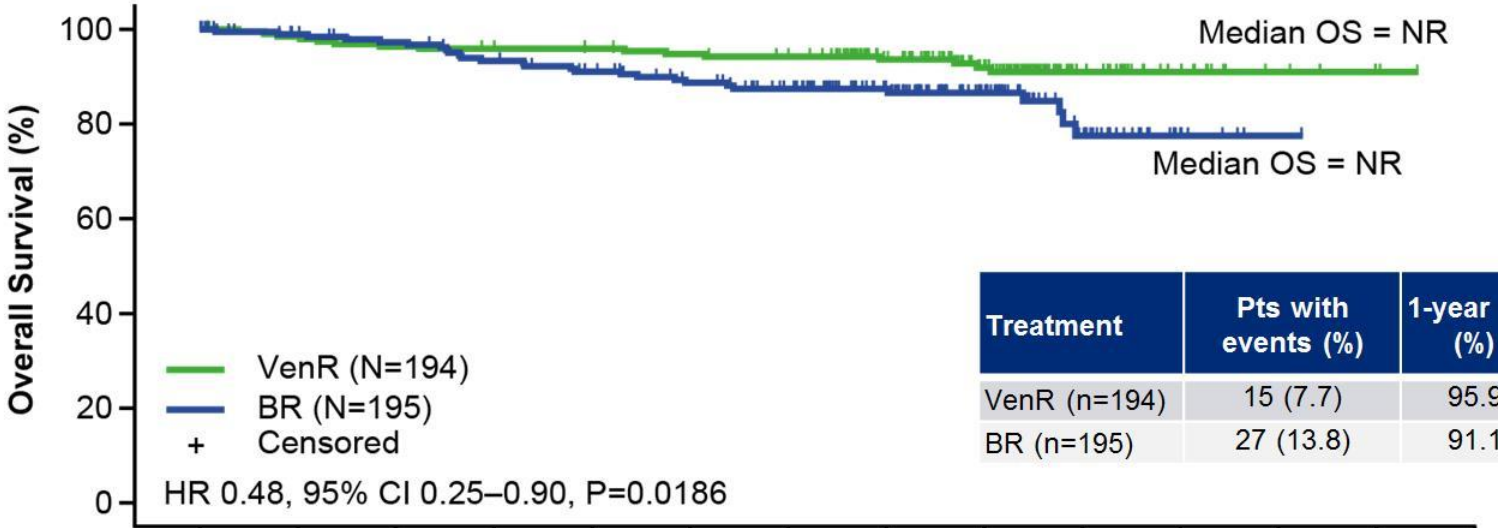
*Central lab

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

Overall HR = 0.17

As of 8 May 2017

Clinically Meaningful Improvement in Overall Survival for VenR vs. BR



Treatment	Pts with events (%)	1-year OS (%)	2-year OS (%)
VenR (n=194)	15 (7.7)	95.9	91.9
BR (n=195)	27 (13.8)	91.1	86.6

No. of patients at risk:

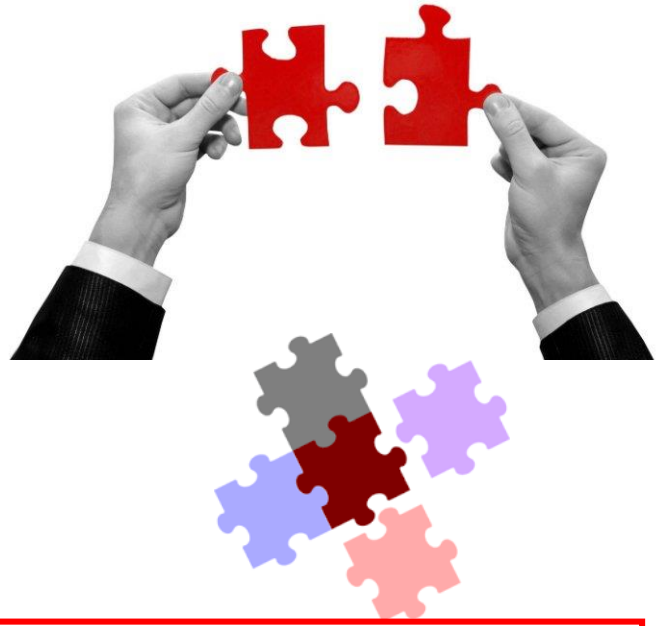
VenR	194	190	185	183	181	178	175	142	102	36	15	5	3
BR	195	181	175	166	158	146	134	102	66	29	8	2	

Descriptive p-values
Pre-specified boundary, P=0.0001.

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

As of 8 May 2017

Combination Therapy



- BTK-inhibitors ± anti-CD20 mAb
- Ibrutinib + anti-ROR1 mAb
- Venetoclax + anti-CD20 mAb
- Combined BTK-inhibitor + Bcl-2 inhibitor ± anti-CD20 mAb
- Combined chemo-immunotherapy and ibrutinib
- PI3K-inhibitor, new, and novel agents

Ibrutininb (IBR) + Venetoclax (VEN) Treatment Schema

	C1	C2	C3	C4 ---> C27
Ibrutinib	420mg daily	420mg daily	420mg daily	420mg daily until progression
Venetoclax	-	-	-	20mg daily x1 wk then; 50mg daily x1 wk then; 100mg daily x1 wk then; 200mg daily x1 wk then; 400mg daily continuous

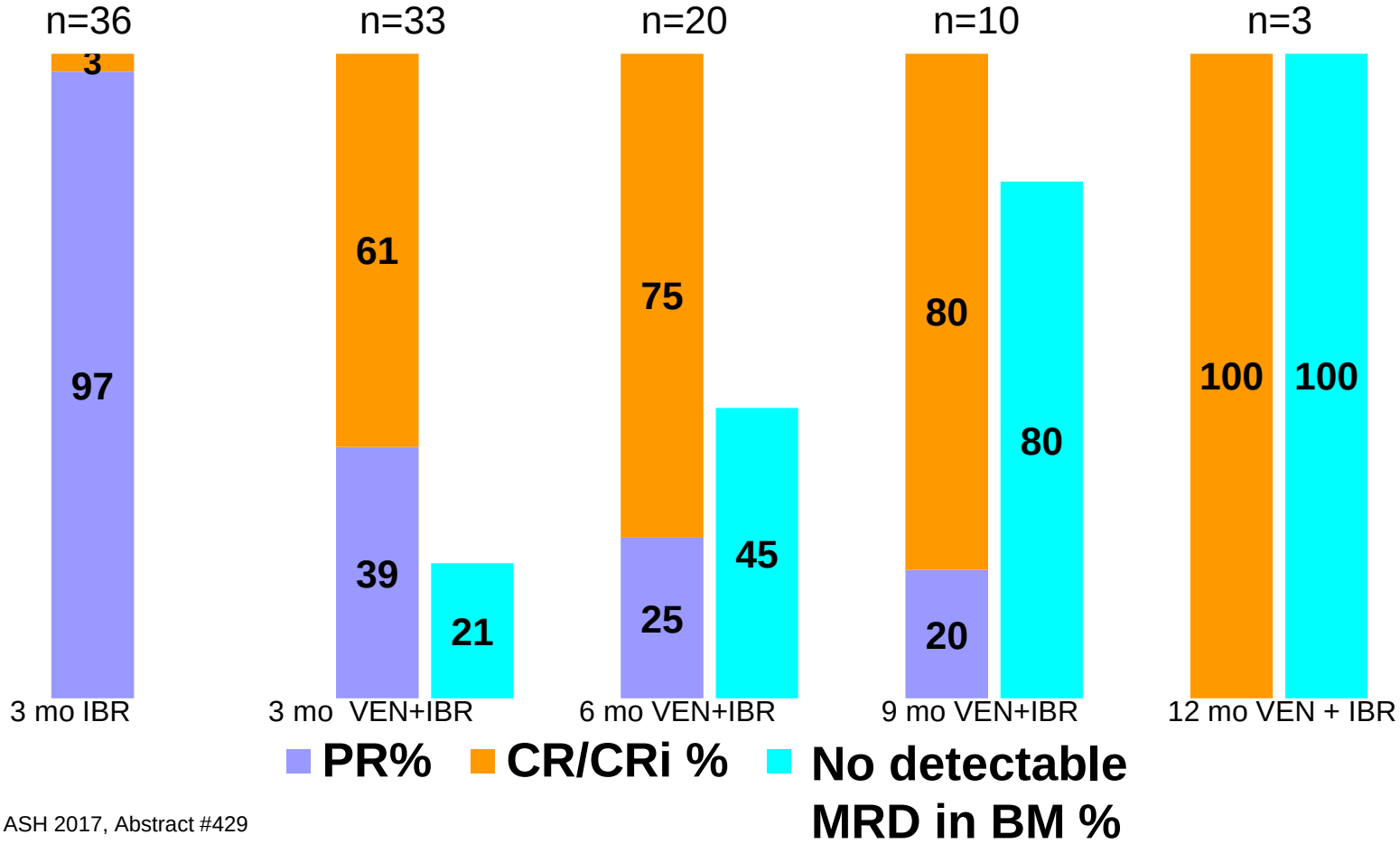
VEN duration 2 years, IBR until progression

Primary endpoint: CR/CRi

- 38 of 70 pts (54%) had down-grading of TLS risk category
- 2 pts had lab TLS. No clinical TLS

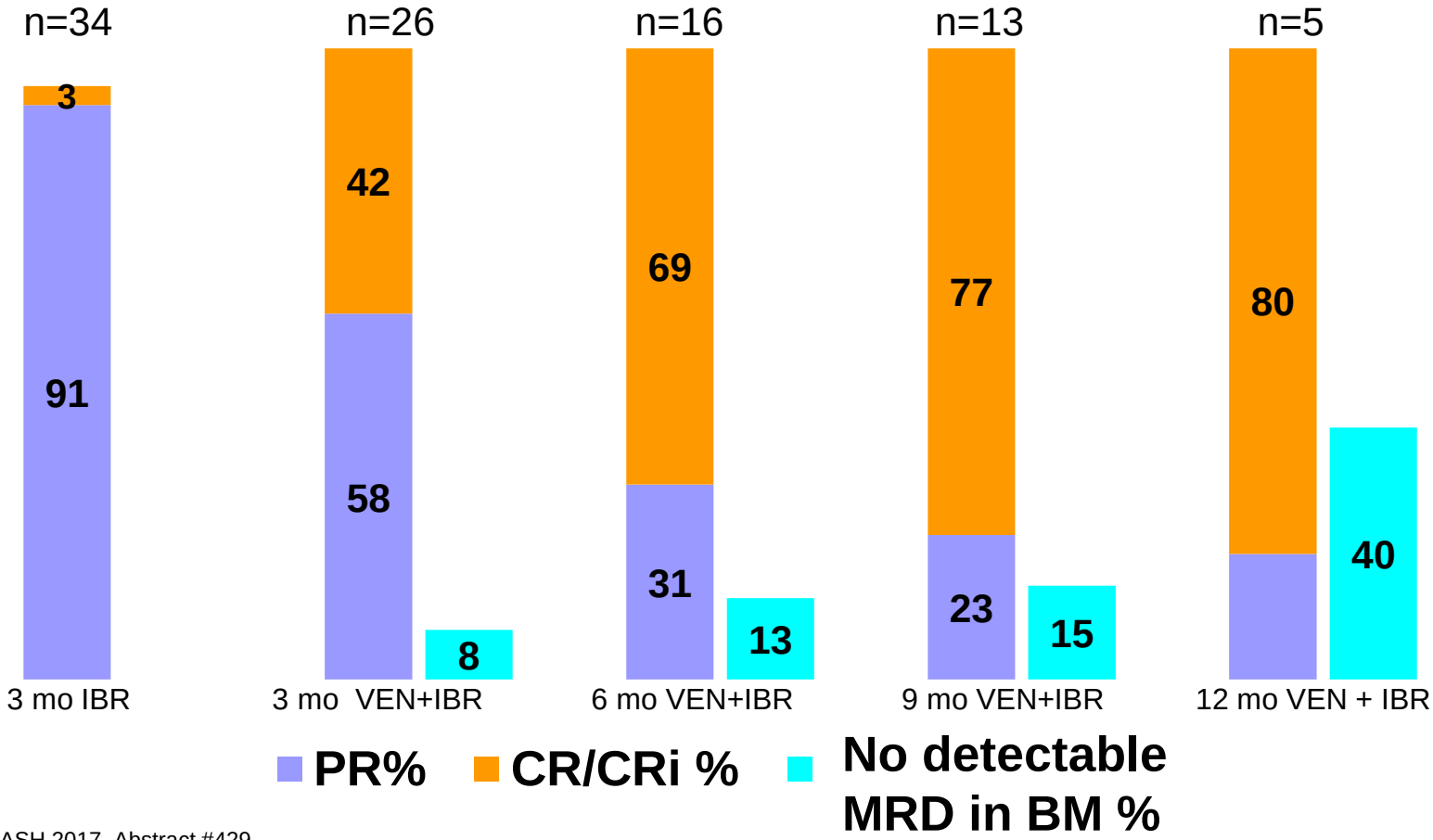
Jain, N et al. ASH 2017, Abstract #429

Ibrutininb (IBR) + Venetoclax (VEN) Response In 1L Therapy



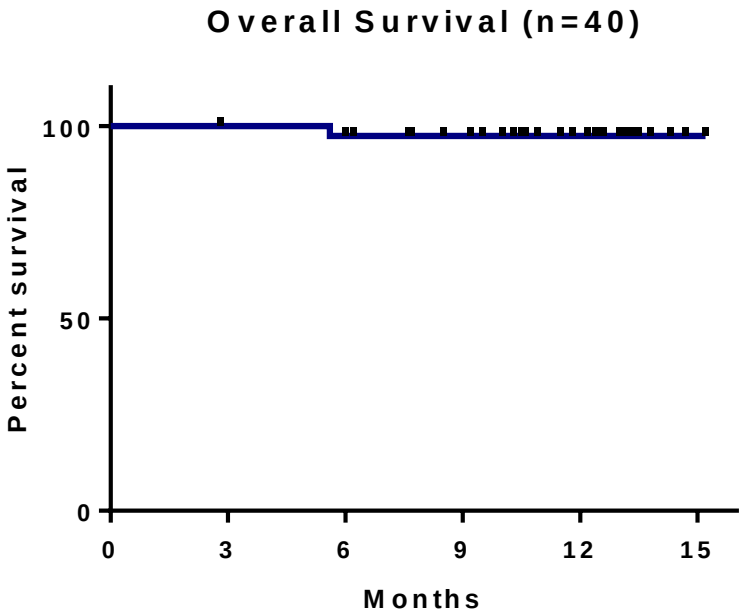
Jain, N et al. ASH 2017, Abstract #429

Ibrutininb (IBR) + Venetoclax (VEN) Response In R/R CLL

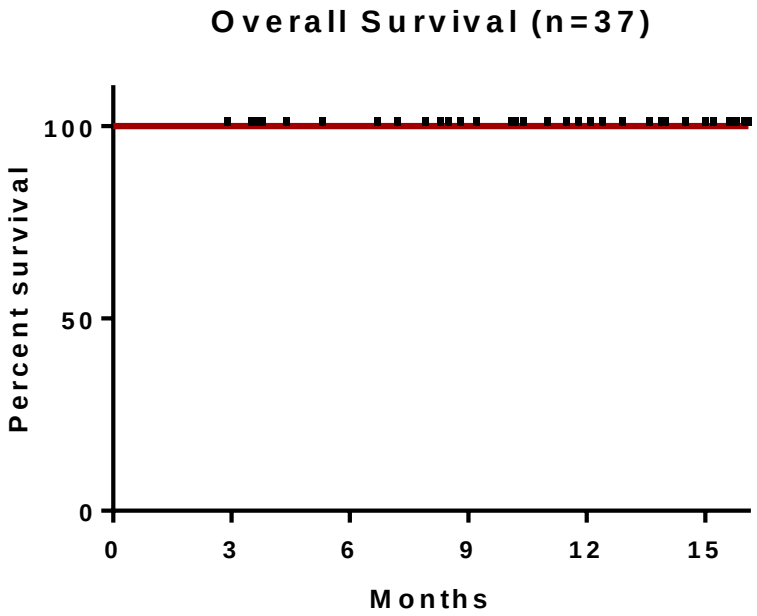


Jain, N et al. ASH 2017, Abstract #429

OS Of Patients Treated With Ibrutinib And Venetoclax



Firstline Cohort



R/R Cohort

1 death in the firstline cohort due to CNS cryptococcus (pt recd only 1 day of ibrutinib)

Jain, N et al. ASH 2017, Abstract #429

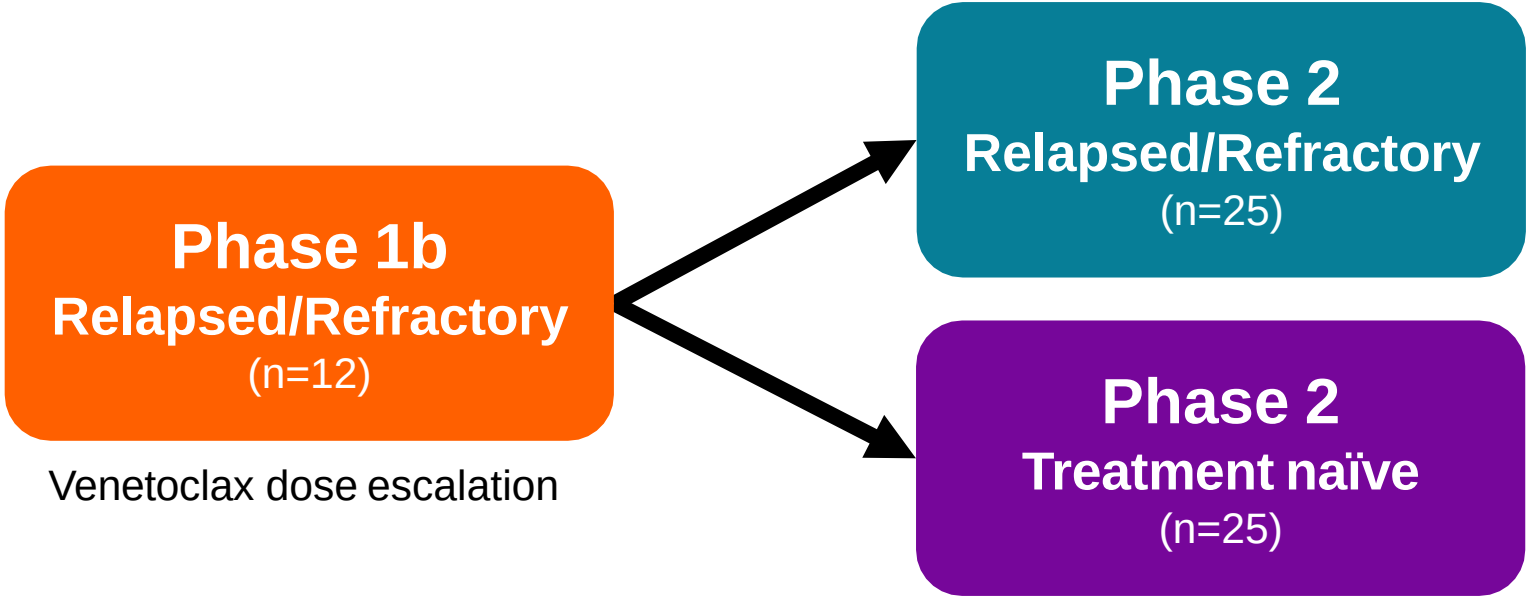
Ibrutininb (IBR) + Venetoclax (VEN) Toxicities (N=77)

- **Infections** **n (%)**
  - **Neutropenic fever*** **6 (8)**
  - **Pneumonia** **1 (2)**
  - **Cellulitis** **1 (2)**
  - **Septic arthritis** **1 (2)**
- **2/3 of infections occurred during ibrutinib monotherapy phase**
- **Atrial fibrillation: 10 (13%)**
- **Dose reduction**
  - **Ibrutinib 36%**
  - **Venetoclax 26%**

* Aspergillosis (n=1), Anaplasmosis (n=1), Vibrio (n=1), culture negative (n=3)

Jain, N et al. ASH 2017, Abstract #429

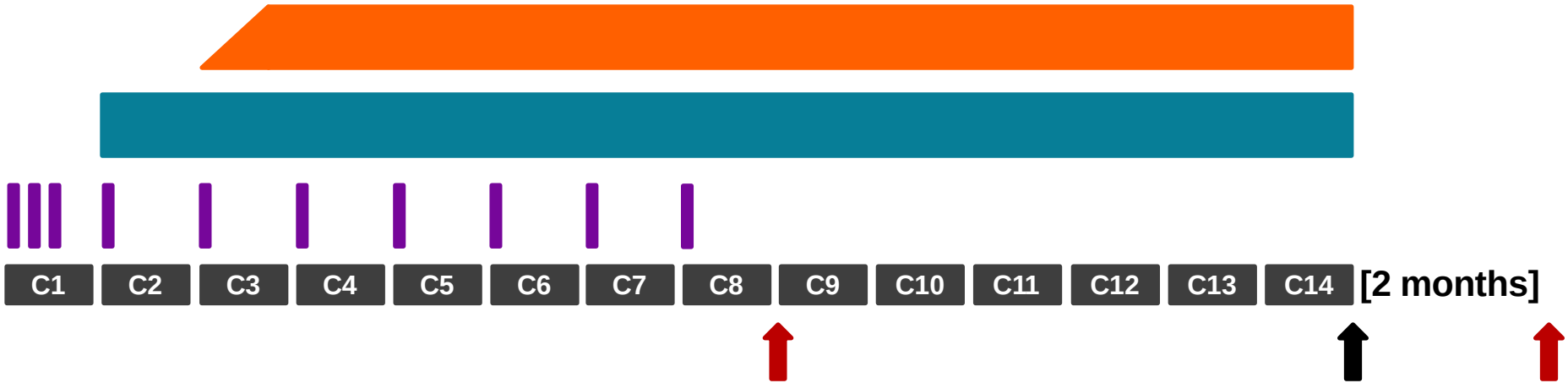
Ibrutinib + Venetoclax + Obinutuzumab: Study Overview



- Primary endpoint in the phase 2 studies is rate of having a CR with no detectable minimal residual disease (MRD)
- These are the initial results of the phase 2 treatment naïve cohort

Rogers, K et al. ASH 2017, Abstract #431

Study Diagram



Obinutuzumab 1000 mg IV

Ibrutinib 420 mg daily PO*

Venetoclax 400 mg daily PO

End of Treatment

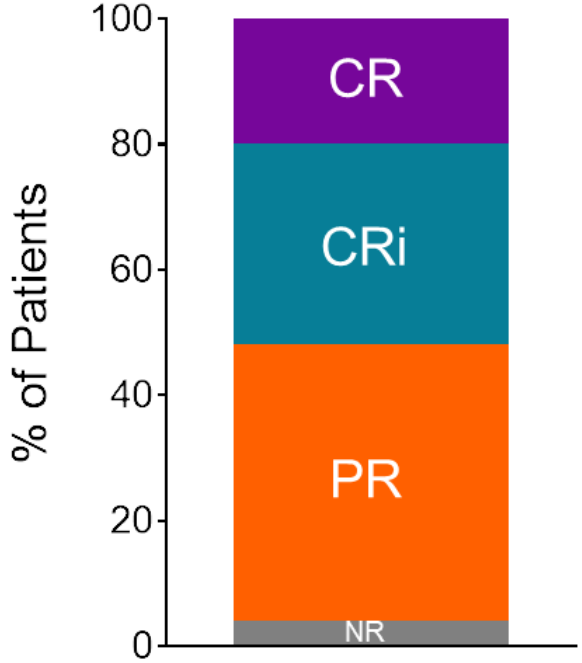
Response assessed
(CT + Bone Marrow Biopsy)

*Patients may continue ibrutinib past C14 at the discretion of the treating investigator

Rogers, K et al. ASH 2017, Abstract #431

Cycle length = 28 days

Mid-point (post-Cycle 8) Responses To G+IBR+VEN



CR = complete remission, CRi = CR with incomplete marrow recovery
PR = partial remission, NR = not reached

- **ORR= 96%** (95% CI: 80-100%)
  - CR 5 (20%)
  - CRi 8 (32%)
  - PR 11 (44%)
  - NR 1 (4%)
- CRi was due to cytopenias (4/8, 50%) or cytopenias and hypocellular marrow (4/8, 50%)
- 6/11 (55%) PR patients met count and marrow requirements for CR but had LN >1.5cm
- All but 1 patient did not have morphologic evidence of CLL in the marrow
- 14/24 (58%) of patients had no detectable MRD (0.01%)
  - 8/13 (46%) CR/Cri
  - 6/11 (55%) PR

Rogers, K et al. ASH 2017, Abstract #431

Non-Hematologic Treatment-Related Adverse Events*

Grade 1/2 Adverse Events	n (%)
Infusion related reaction	19 (76)
Nausea	15 (60)
Bruising	14 (56)
Oral Mucositis	13 (52)
Dyspepsia	12 (48)
Hypertension	11 (44)
Diarrhea	11 (44)
Fatigue	10 (40)
Maculo-papular rash	10 (40)
Myalgia	9 (36)
Arthralgia	8 (32)
Hyperuricemia	8 (32)
Weight gain	8 (32)
Bilirubin increased	7 (28)
Chills	7 (28)
Hypocalcemia	7 (28)

Grade 3/4 Adverse Events	n (%)
Hypertension	9 (36)
Dyspepsia	1 (4)
Arthralgia	1 (4)
Hyperuricemia	1 (4)
Aspartate aminotransferase increased	1 (4)
Alanine aminotransferase increased	1 (4)
Atrial fibrillation	1 (4)
Colitis	1 (4)
Pneumonia	1 (4)
Menorrhagia	1 (4)
Sepsis	1 (4)

There were no cases of clinical or laboratory tumor lysis syndrome of any grade

*Grade 1/2 AEs occurring at >25% and all grade 3/4 As

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Hematologic Treatment-Related Adverse Events*

Adverse Event	Grade 1/2 n (%)	Grade 3/4 n (%)	Any Grade n (%)
Thrombocytopenia	12 (48)	9 (36)	21 (84)
Lymphopenia*	11 (44)	8 (32)	19 (76)
Neutropenia	7 (28)	12 (48)	19 (76)
Leukopenia*	10 (40)	9 (36)	19 (76)
Lymphocytosis*	5 (20)	1 (4)	6 (24)
Anemia	4 (16)	0 (0)	4 (16)

*Anticipated therapeutic drug effect

- Hematologic adverse events were the most frequently reported toxicity
- There were no cases of neutropenic fever

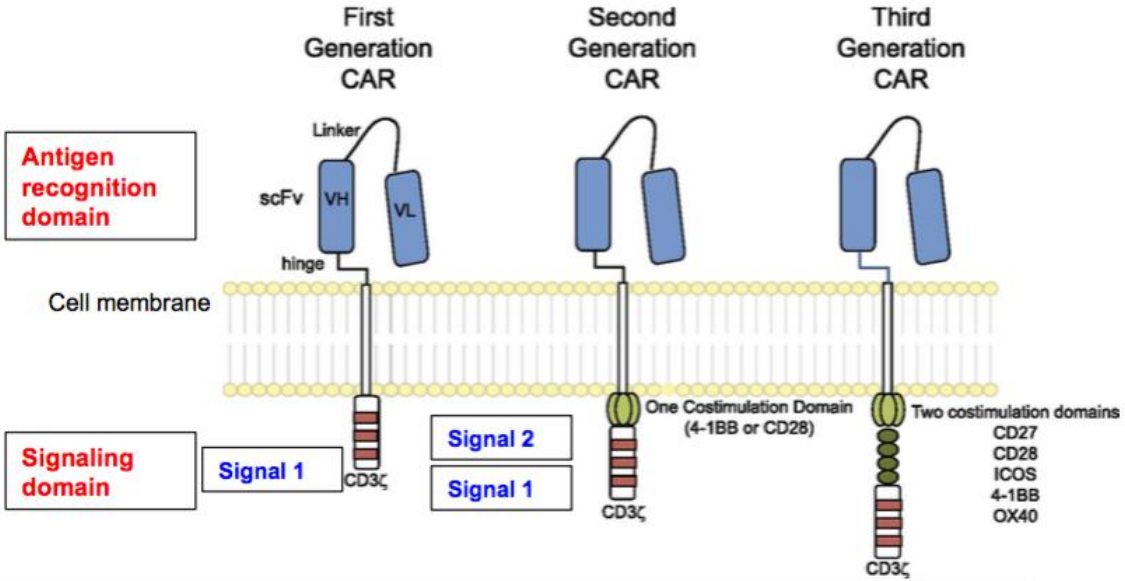
*All hematologic AEs of any grade

Rogers, K et al. ASH 2017, Abstract #431

Combination Therapy

- BTK-inhibitors ± anti-CD20 mAb
- Ibrutinib + anti-ROR1 mAb
- Venetoclax + anti-CD20 mAb
- Combined BTK-inhibitor + Bcl-2 inhibitor ± anti-CD20 mAb
- Combined chemo-immunotherapy and ibrutinib
- PI3K-inhibitor, new, and novel agents

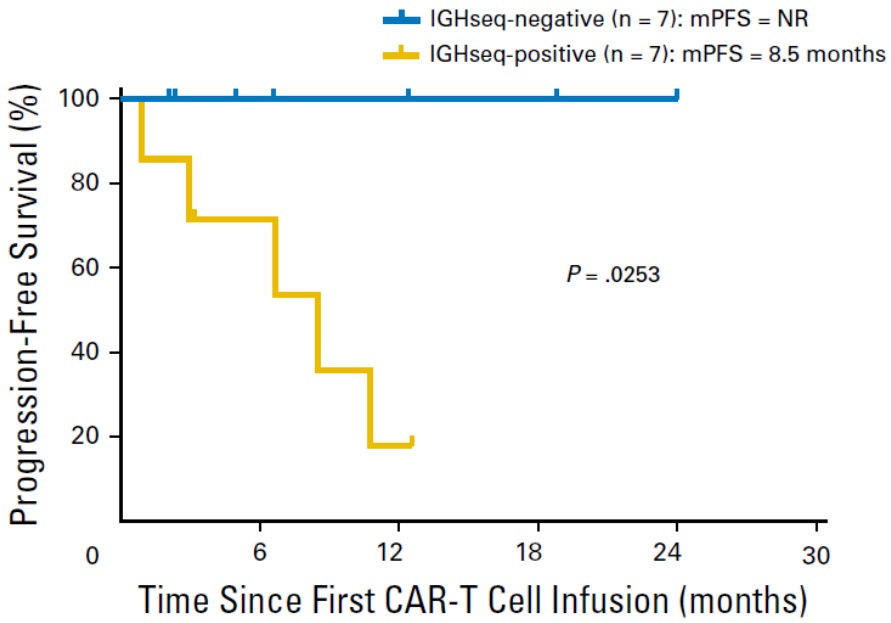
Chimeric Antigen Receptor T Cell Therapy

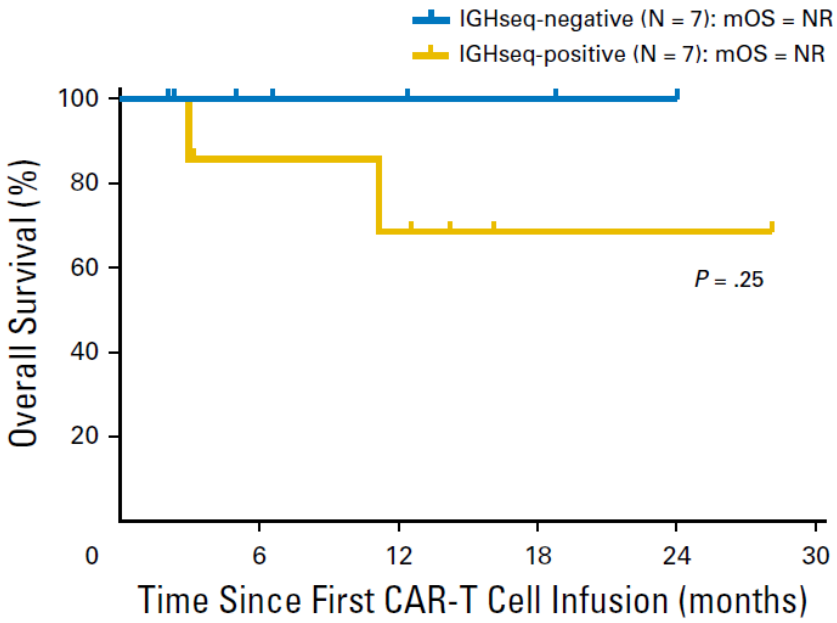


Killing ability	+	+	++
Ability to multiply		+	++
Cytokine secretion		+	++
Persistence		+	++

Adapted from Maus et al. Blood 123:2625, 2014

Durable Molecular Remissions in Refractory Pts CLL With CD19-CAR-T Cells After Failure of Ibrutinib





Turtle, CJ. JCO 2017, 35, 3010-3020

Challenges	Potential Mitigating Strategies
• Poor CAR T Cell Expansion In Vivo	Optimize lympho-depletion prior to CAR T cell infusion. Optimize co-stimulatory domain of the CAR. Modify CAR T cells to express co-stimulatory ligands or cytokines or delete genes involved in T-cell senescence (e.g. TET2)
• Suboptimal CAR-T-Cell Function	Co-administer immune checkpoint inhibitors or ibrutinib. Modify CAR T cells, as outline above.
• Loss Of Target Antigen Expression	Target multiple tumor-associated antigens
• Cytokine Release Syndrome	Develop risk-adapted CAR-T-cell dosing. Improve understanding of pathogenesis to define markers predictive of adverse outcome and/or develop pre-emptive treatment strategies. Incorporate “suicide genes” in CAR-T cells to eliminate them, if necessary.
• Neurologic Toxicity	As above
• B-Cell Aplasia w/CD19-CAR T Cells	Use IVIG for anticipated severe hypogammaglobulinemia. Use CAR T cells that do not target all B cells.

Geyer, MB and Brentjens RJ Cytotherapy 18:1393, 2016; Fraietta, JA et al, ASH 2017, Abstract #1909

Chronic Lymphocytic Leukemia

- *Improved Treatment Outcomes Through*
  - Understanding of CLL Biology
  - Knowledge of Disease Subgroups That Affect Outcome
    - Del(17p)
    - CLL with mutated vs. unmutated *IGHV*
  - Targeted Therapies

- *Future Challenges*
  - Development Of Finite Treatment Strategies
  - Resistance To Targeted Therapies
  - Richter Transformation
  - Costs Of Therapy