NAKHLE S. SABA, MD

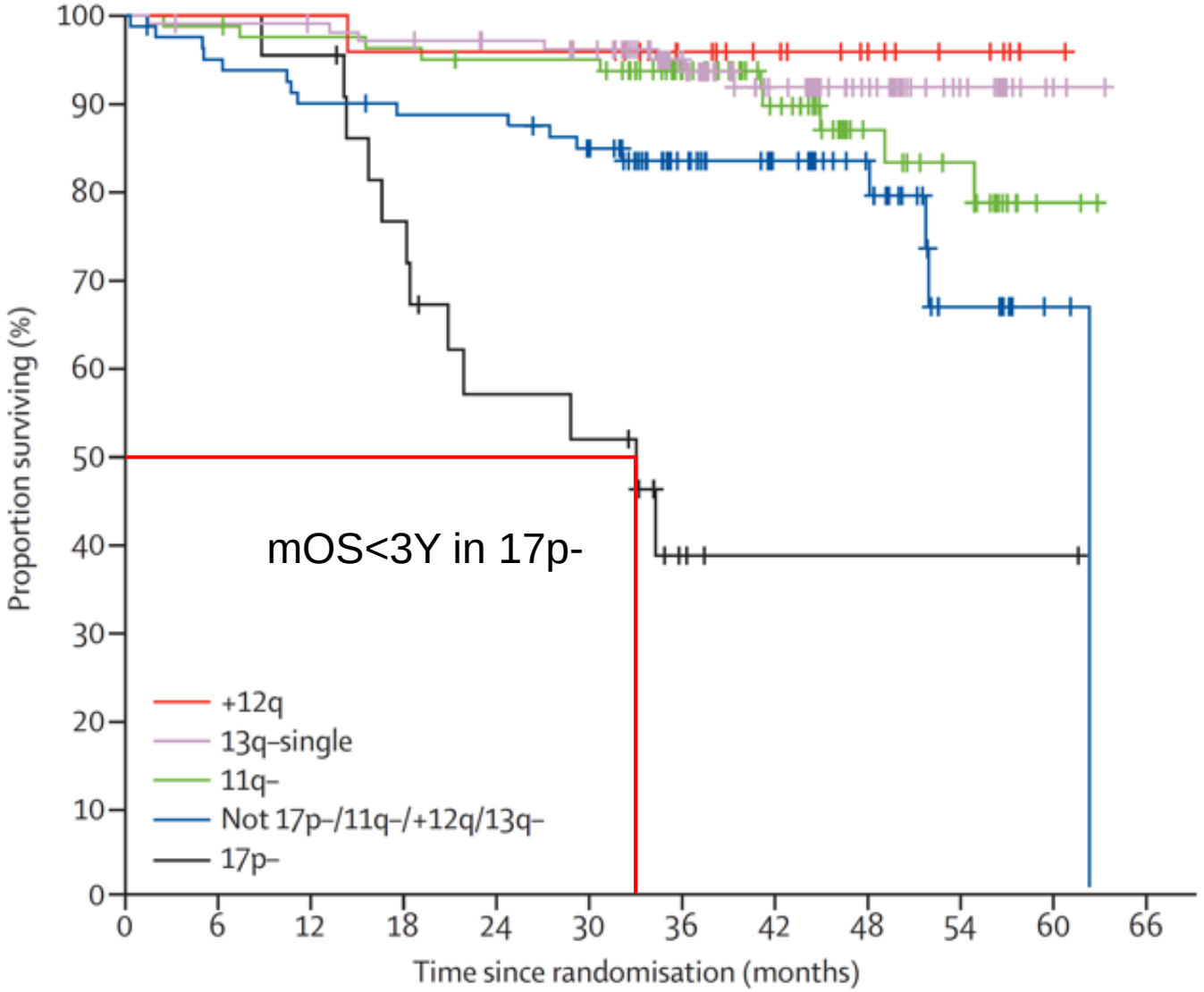
CLL: AT RECURRENCE, WHAT IS THE BEST THERAPY AND WHAT IS COMING FROM THE BENCH LAB?

RELEVANT FINANCIAL RELATIONSHIPS IN THE PAST TWELVE MONTHS BY PRESENTER OR SPOUSE/PARTNER.

CONSULTANT: PHARMACYCLICS, JANSSEN, KYOWA KIRIN, ABBVIE
SPEAKERS BUREAU: PHARMACYCLICS, JANSSEN
GRANT/RESEARCH SUPPORT (SPOUSE): CELGENE

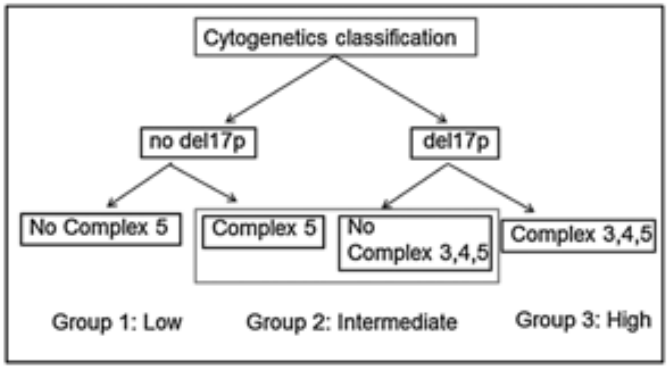
THE SPEAKER WILL DIRECTLY DISCLOSURE THE USE OF PRODUCTS FOR WHICH ARE NOT LABELED (E.G., OFF LABEL USE) OR IF THE PRODUCT IS STILL INVESTIGATIONAL.

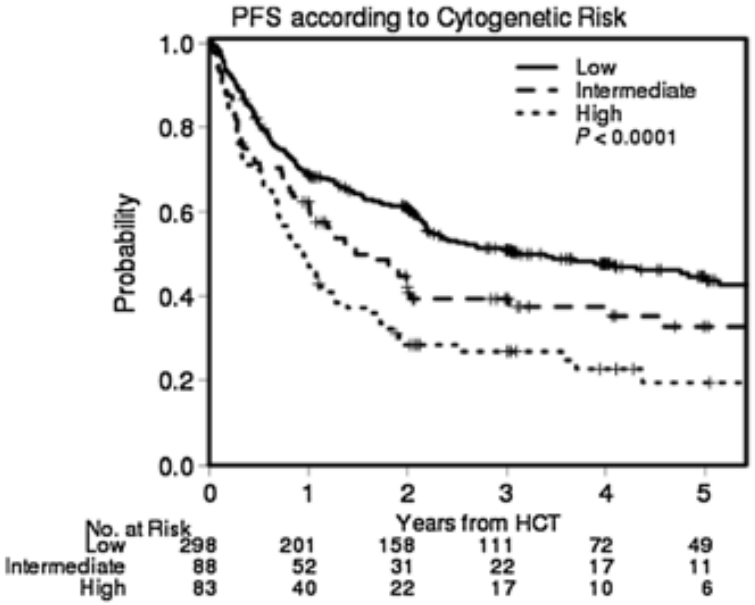
Probability Of OS From The Date Of Diagnosis Among The Patients In The 5 Genetic Categories Following FCR

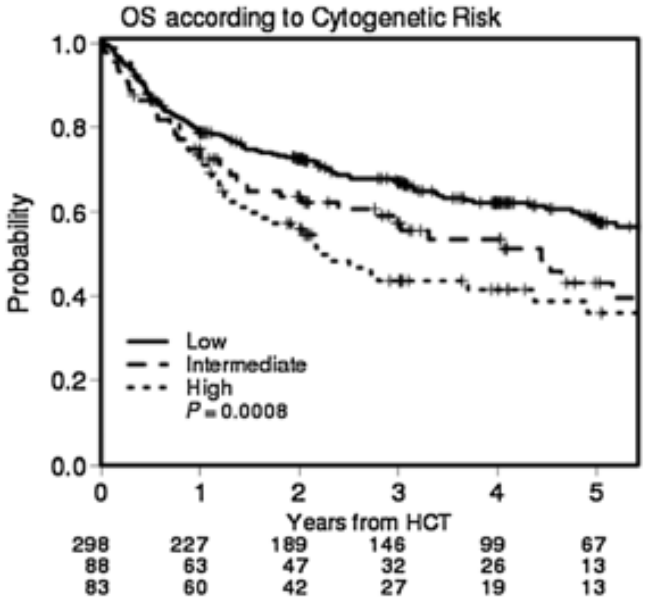


Dohner *et al*. N Engl J Med 2000; 343:1910-6
Kay *et al*. ASH-SAP 2010;2010:555-580

17p Deletion And Complex Karyotype Predict For Inferior Outcomes Post Allogeneic SCT





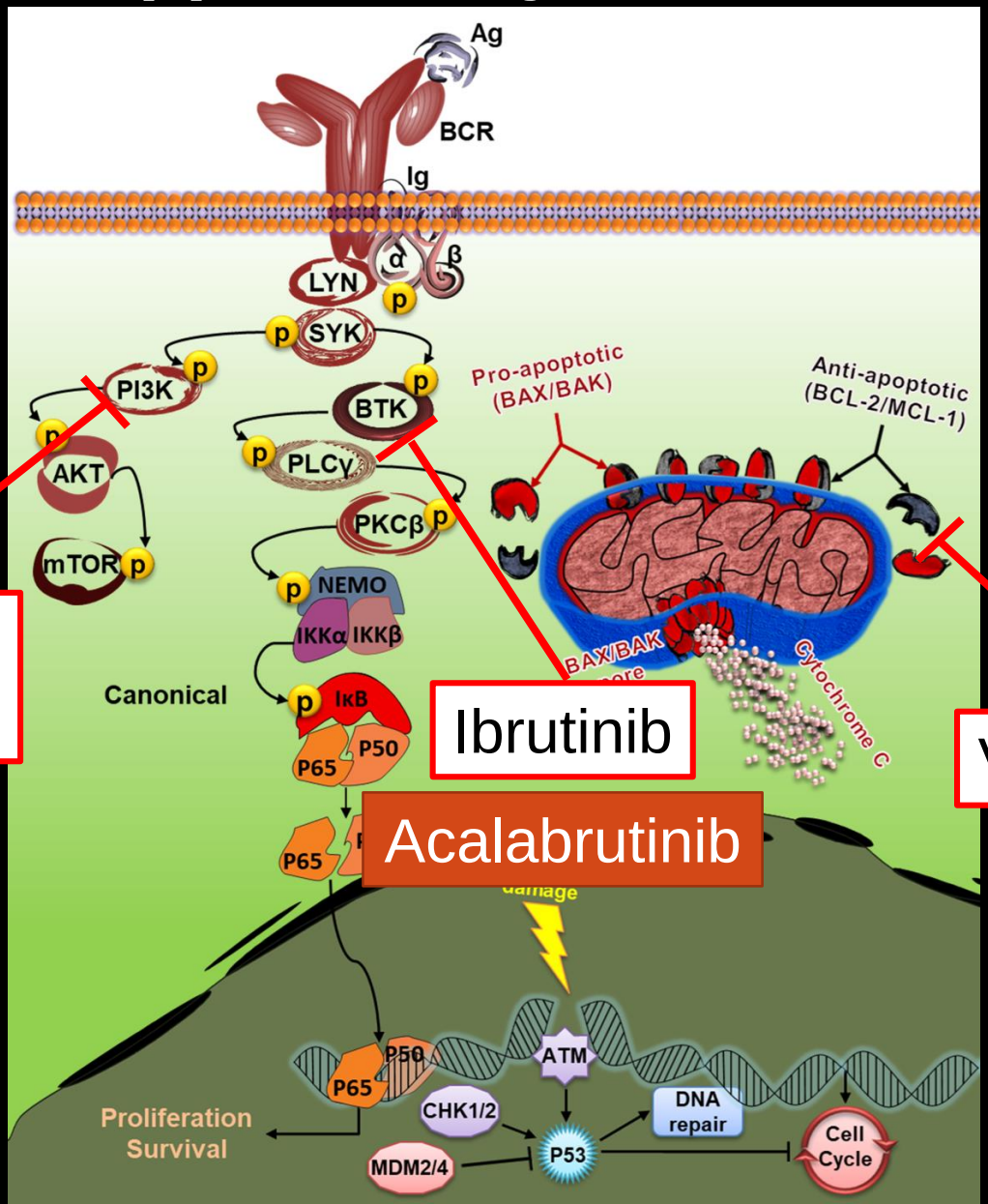


Kim H… Saba N … Brown J, Clin Cancer Res. 2019

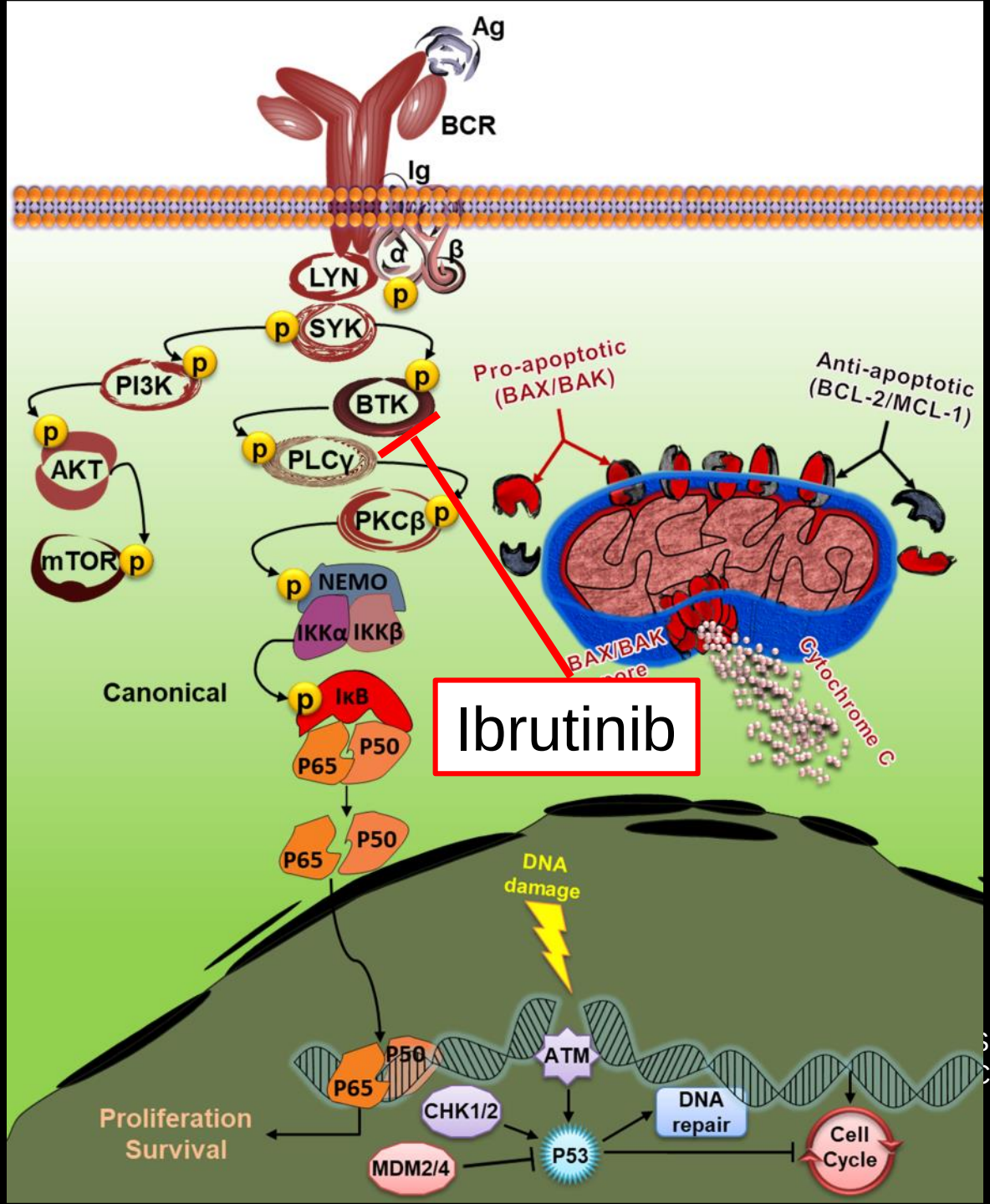
Agenda

- RESONATE: Ibrutinib
- IDEL-R
- DUO: Duvelisib
- MURANO: Venetoclax + R
- ASCEND: Acalabrutinib
- Sequencing Novel Agents
- Agents in the pipeline
- Treatment algorithms

Targeted Therapy In CLL Approved By The FDA

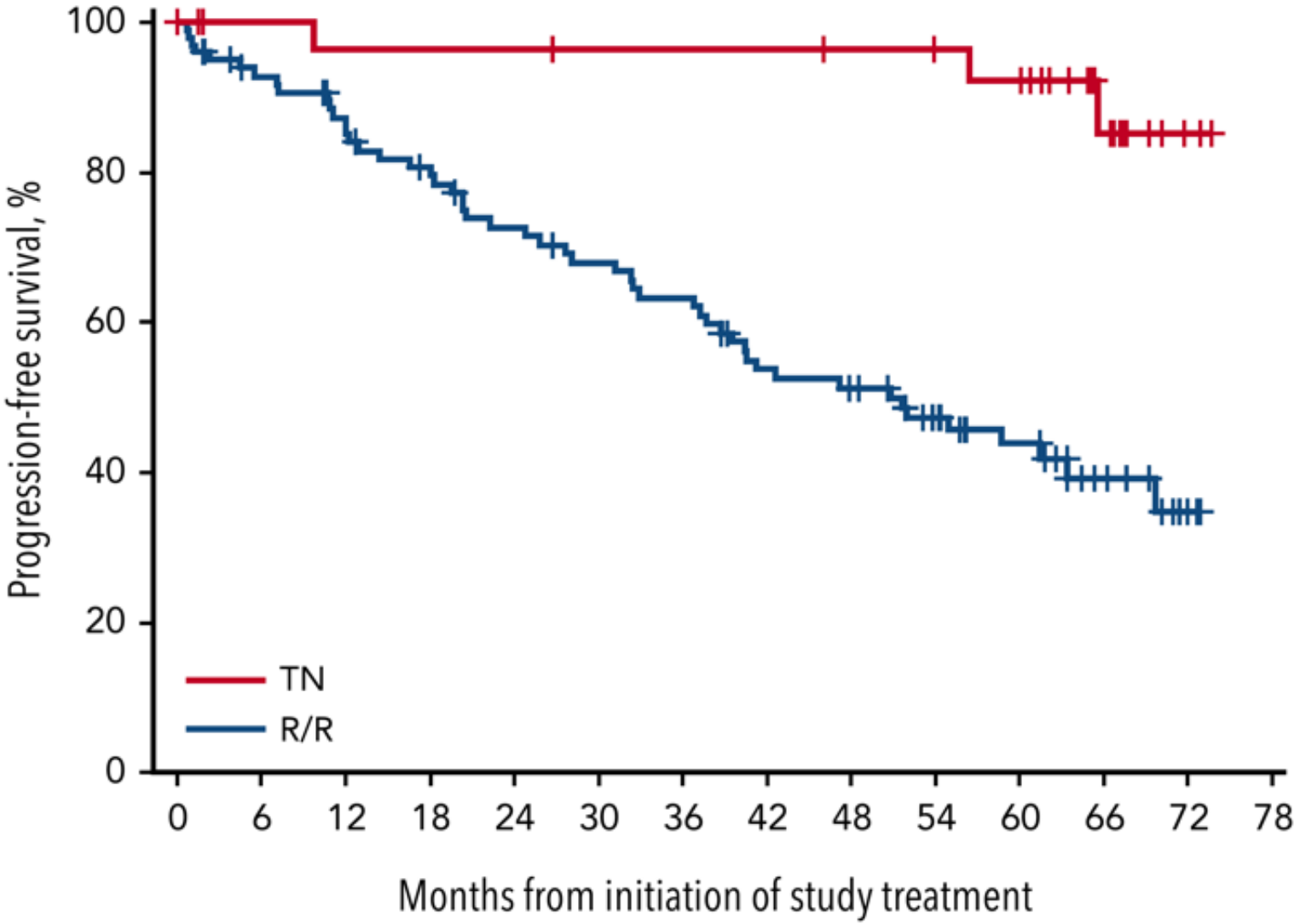


Saba & Wiestner.
Curr Opin Hematol. 2014



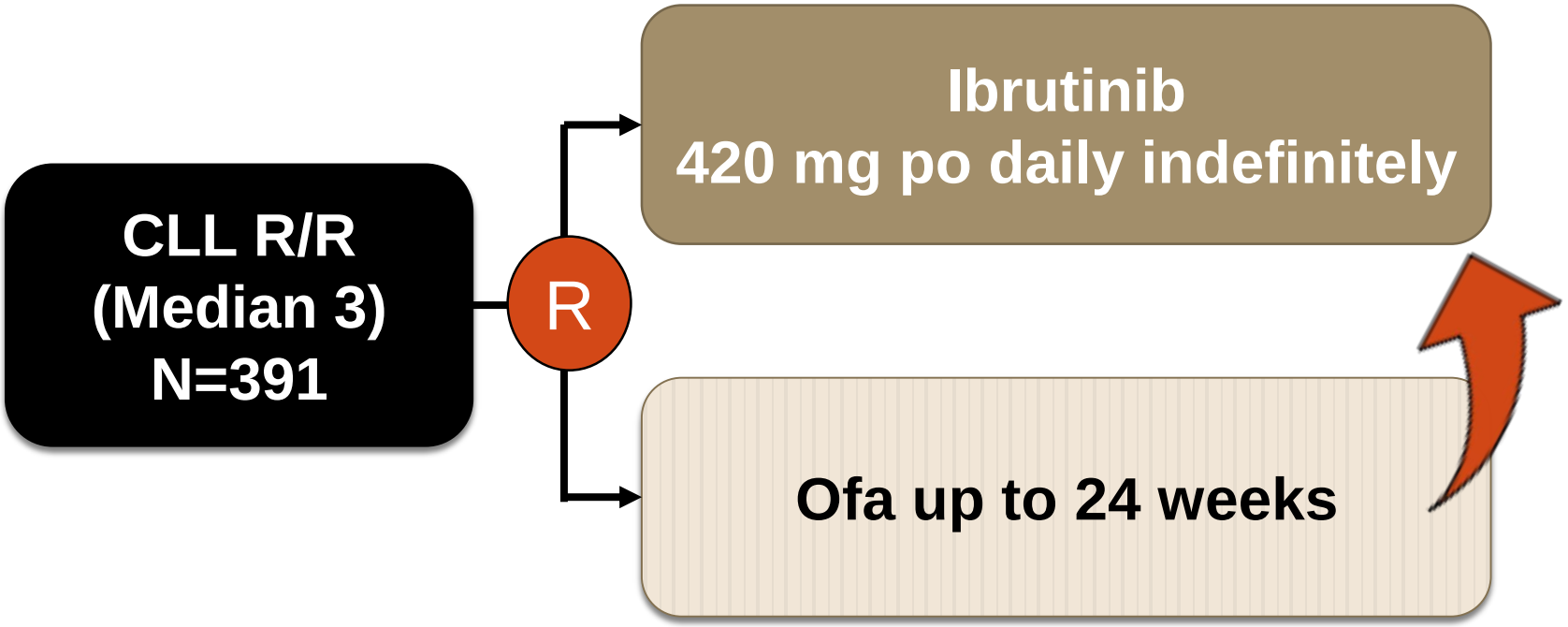
Saba & Wiestner.
Curr Opin Hematol. 2014

Ibrutinib: 5-year experience



O'Brien et al, *Blood* 2018

RESONATE
Ibrutinib vs. Ofa



Primary endpoints: PFS
Secondary endpoints include: OS, ORR

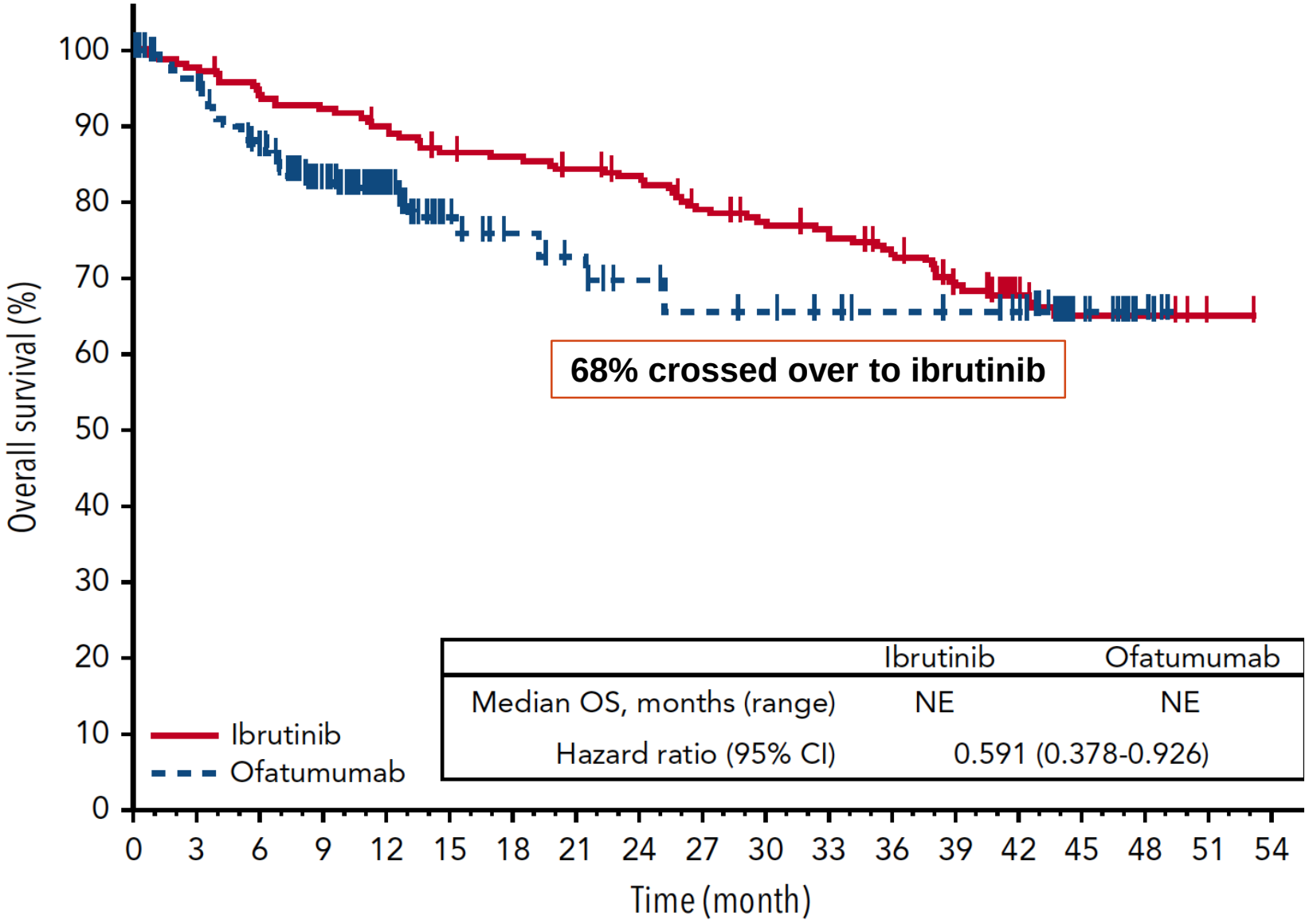
Byrd et al. Blood 2019

RESONATE
Ibrutinib vs. Ofa

Characteristic	Ibrutinib (n = 195)	Ofatumumab (n = 196)
Number of prior therapies		
Median (range)	3 (1-12)	2 (1-13)
1	35 (18)	53 (27)
2	57 (29)	53 (27)
≥3	103 (53)	90 (46)
Genomic abnormalities		
del(17p)(13.1)	63/195 (32)	64/196 (33)
del(11q)(22.3)	63/190 (33)	59/191 (31)
Complex karyotype*	39/153 (25)	33/147 (22)
IGHV unmutated†	98/134 (73)	84/133 (63)
NOTCH1 mutation‡	43/154 (28)	45/149 (30)
TP53 mutation‡	79/154 (51)	68/149 (46)
SF3B1 mutation‡	47/154 (31)	44/149 (30)
BIRC3 mutation‡	21/154 (14)	15/149 (10)
XPO1 mutation‡	26/154 (17)	12/149 (8)

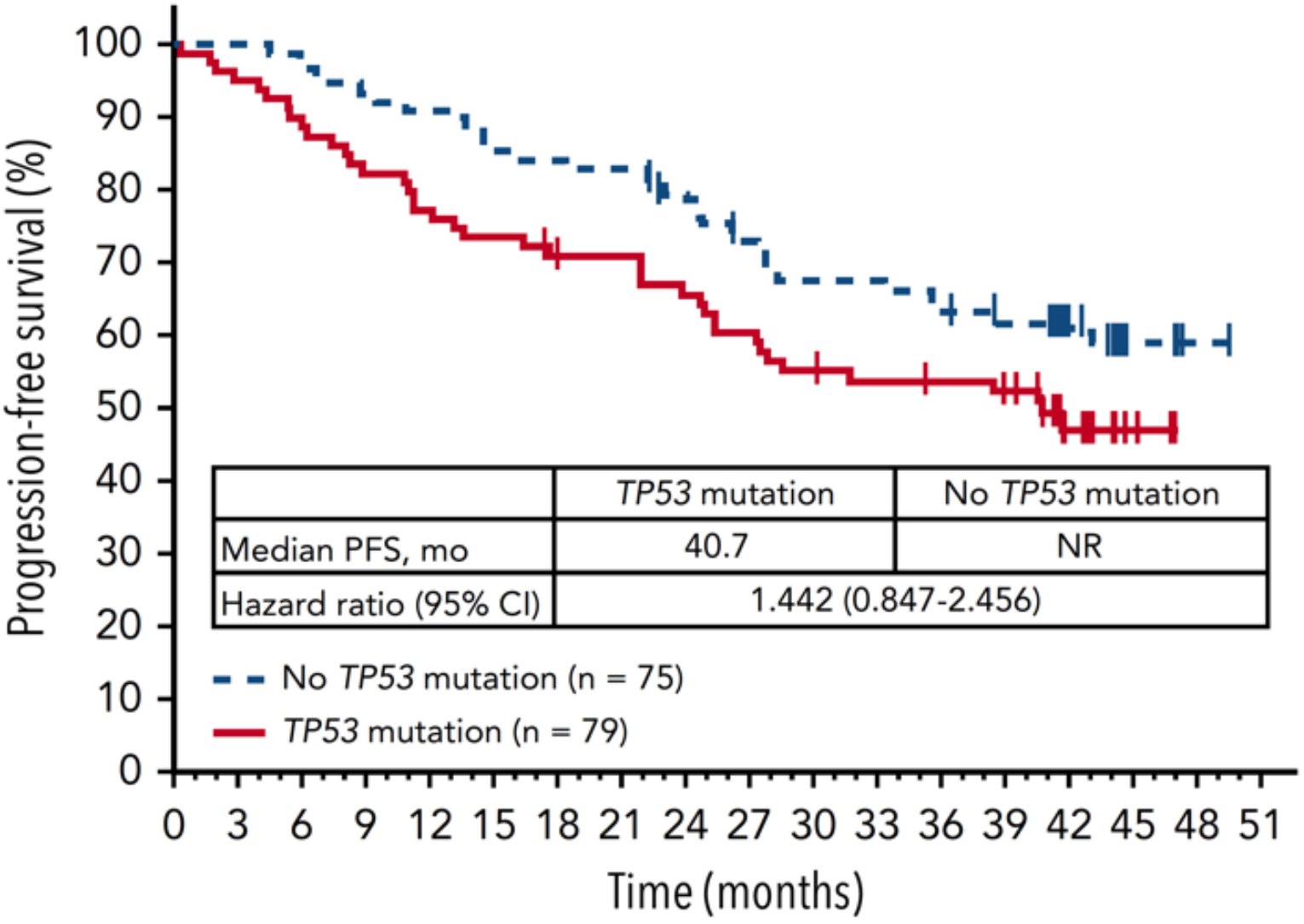
Byrd et al. Blood 2019

Ibrutinib Is Superior To Ofa, And Results In Long Term Disease Control



Byrd et al. Blood 2019

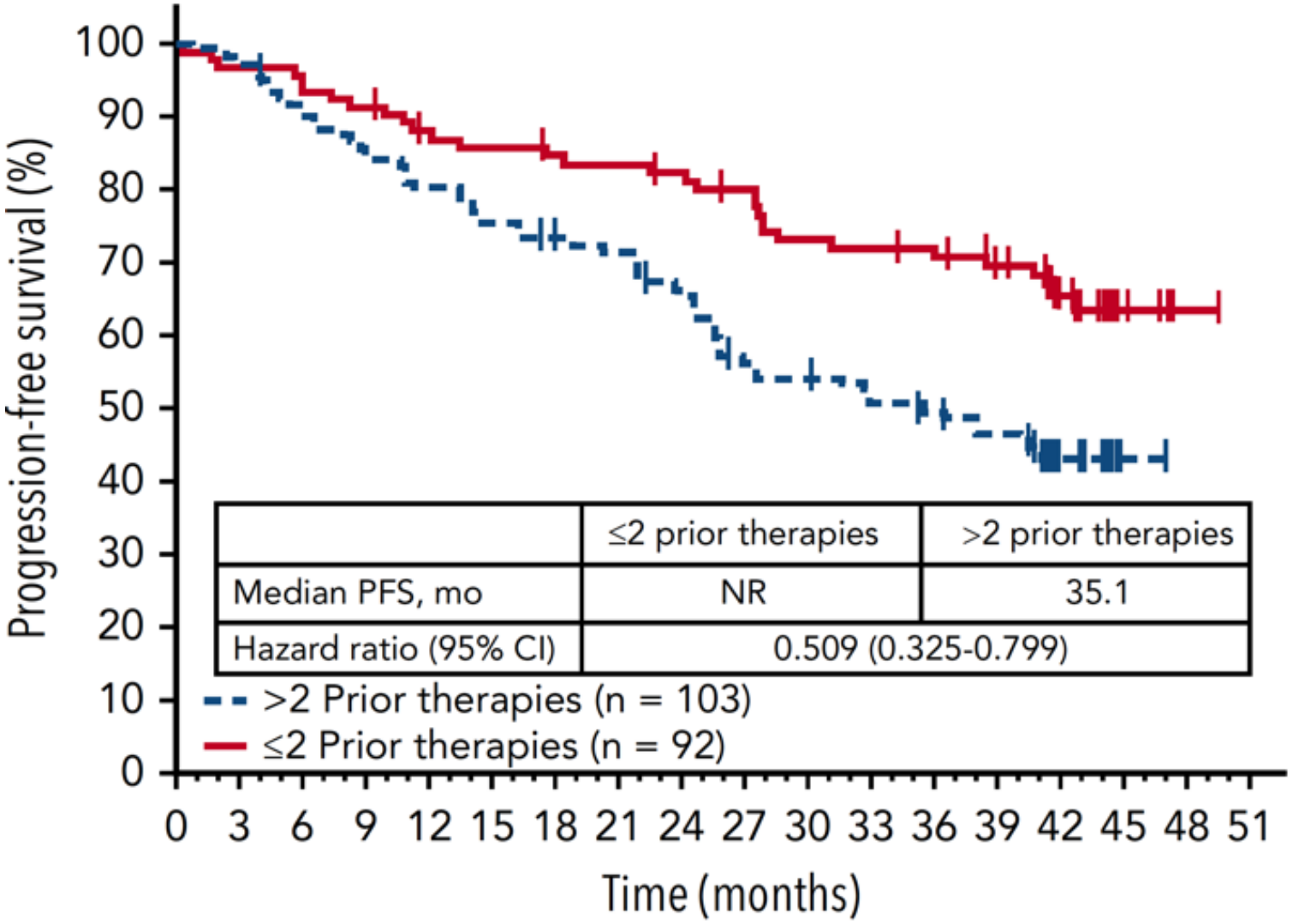
TP53 Alterations Negatively Impacts Survival On Ibrutinib



	TP53 mutation	No *TP53* mutation
Median PFS, mo	40.7	NR
Hazard ratio (95% CI)	1.442 (0.847-2.456)	

Byrd et al. Blood 2019

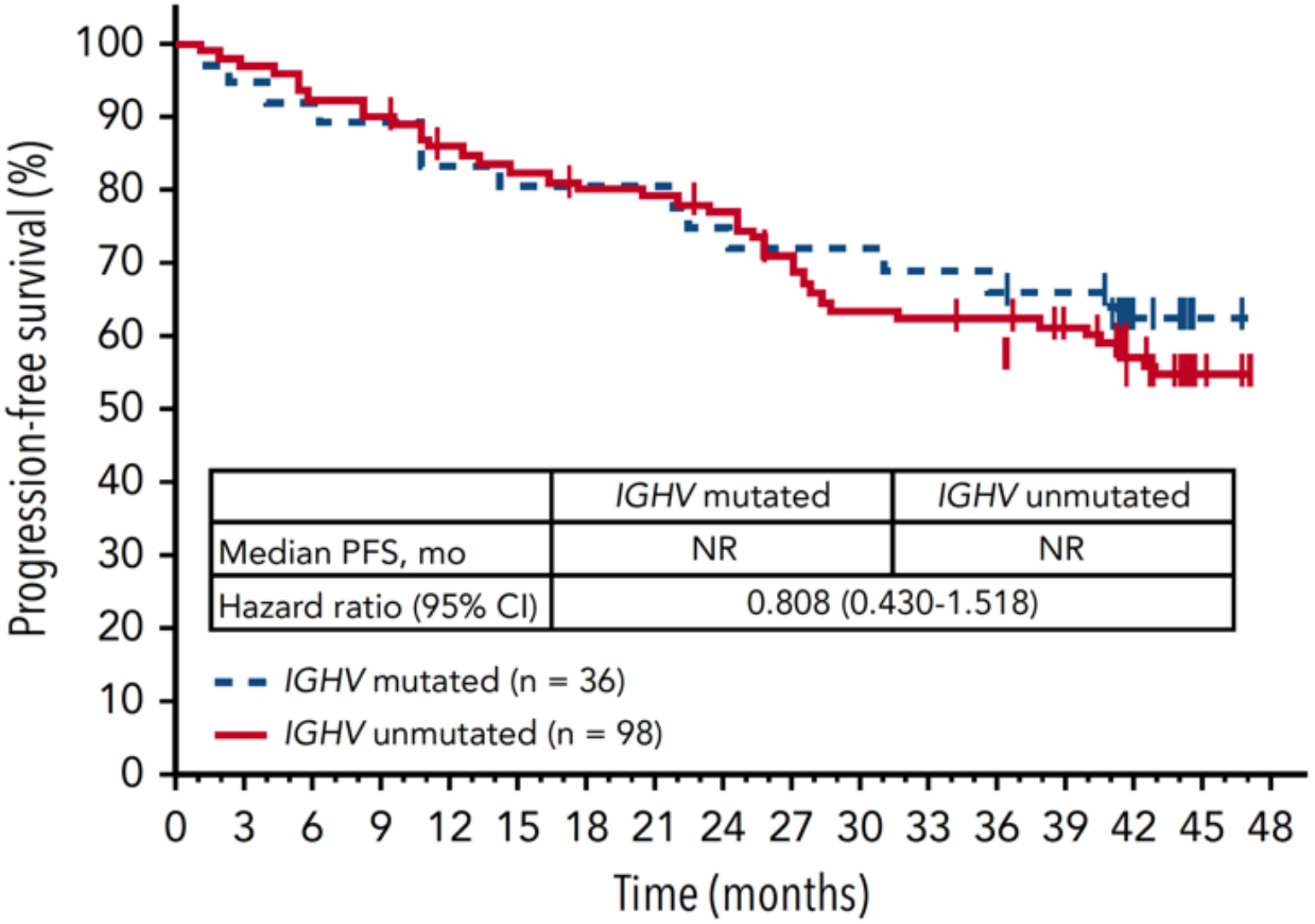
Number Of Prior Therapies Impacts Survival On Ibrutinib



	≤2 prior therapies	>2 prior therapies
Median PFS, mo	NR	35.1
Hazard ratio (95% CI)	0.509 (0.325-0.799)	

Byrd et al. Blood 2019

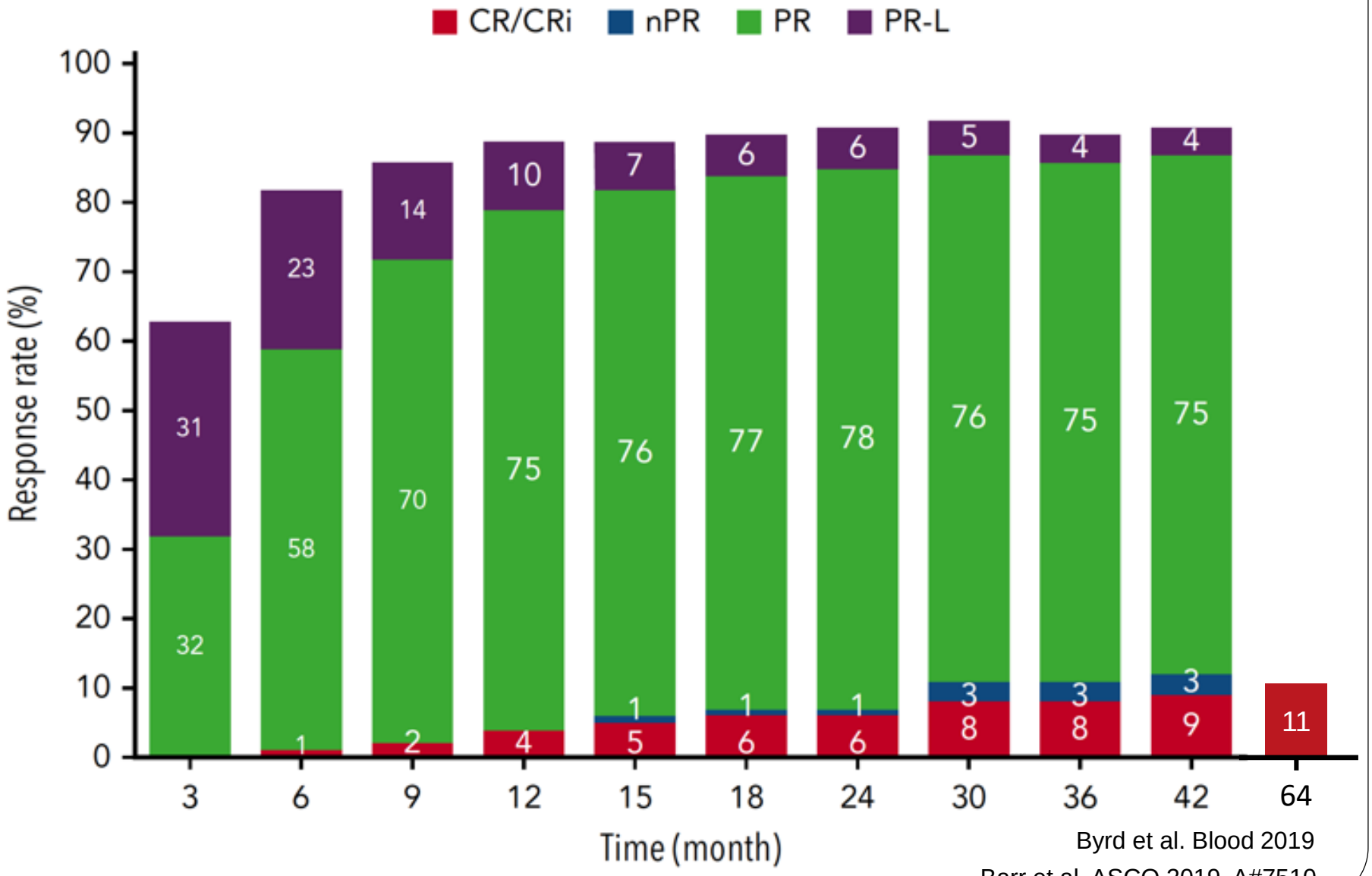
Ibrutinib Overcomes Adverse Prognostic Markers Such As IGHV-U, NOTCH-M, And Complex Karyotype



	IGHV mutated	*IGHV* unmutated
Median PFS, mo	NR	NR
Hazard ratio (95% CI)	0.808 (0.430-1.518)	

Byrd et al. Blood 2019

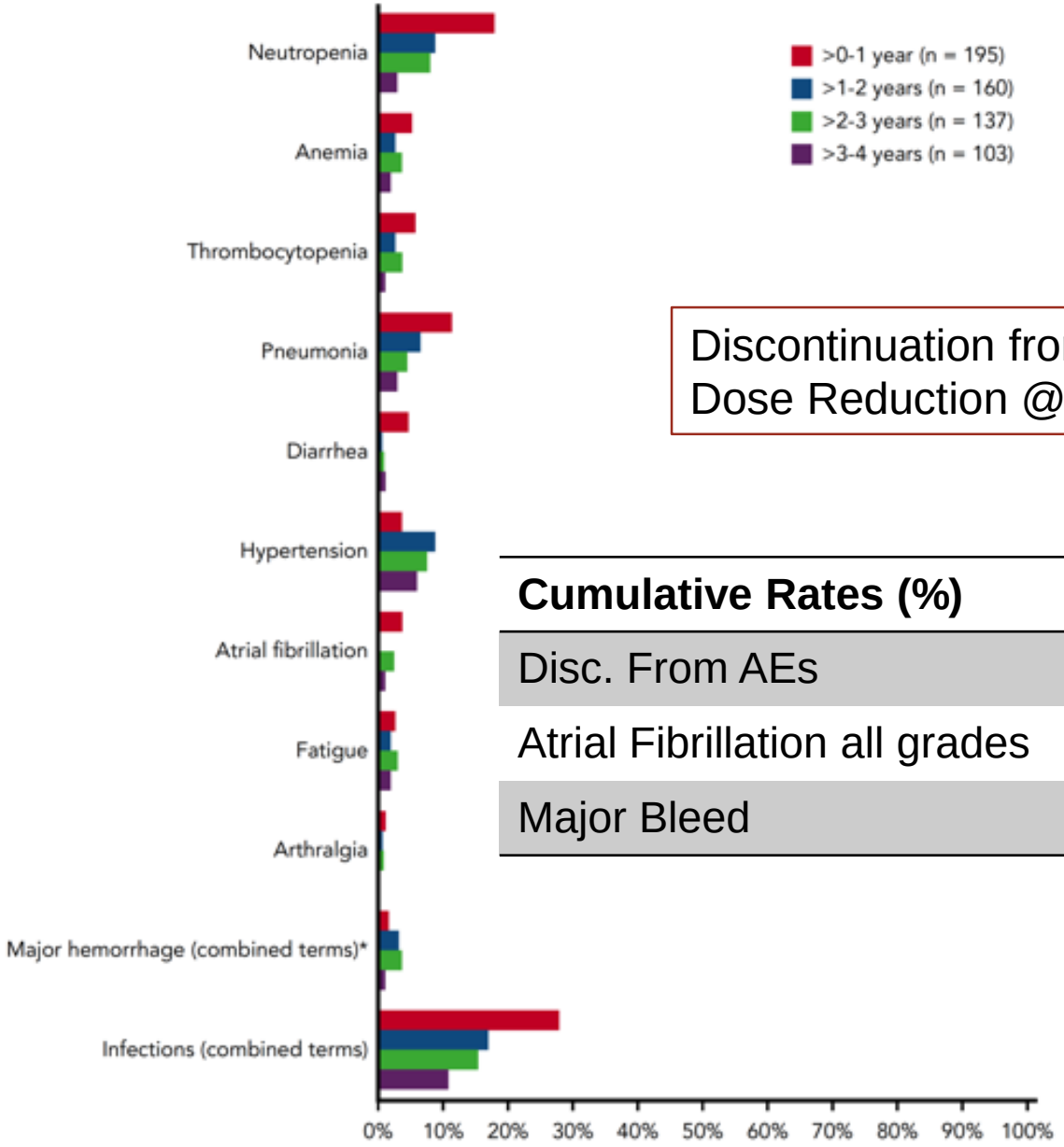
Deeper Responses Are Seen With Continuous BTK Inhibition



Byrd et al. Blood 2019

Barr et al. ASCO 2019, A#7510

AEs Are Most Frequent In The First Year On Ibrutinib



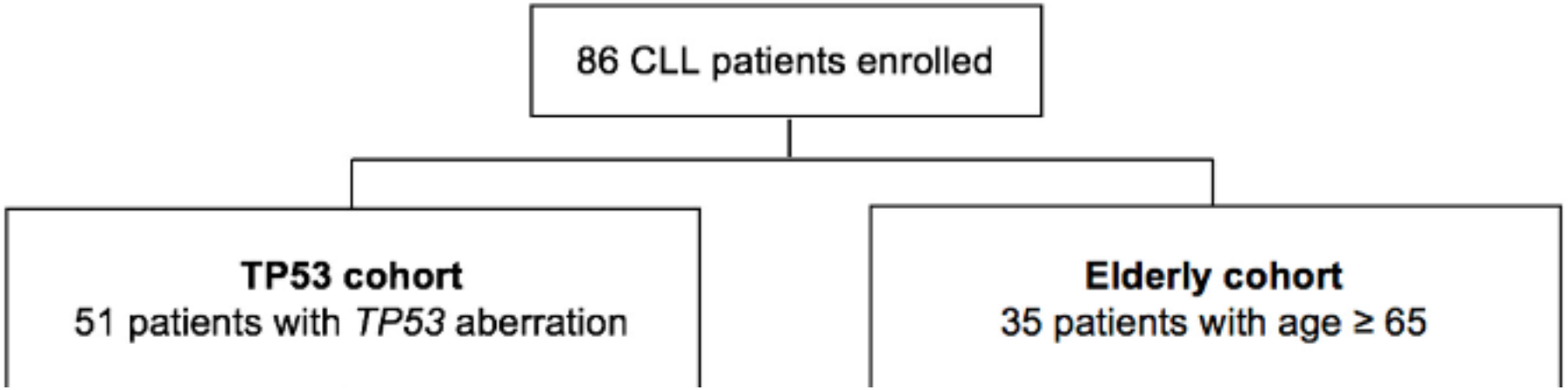
Discontinuation from AEs @ 3.5 years: 12%
Dose Reduction @ 3.5 years: 13%

Cumulative Rates (%)	9 mo	3.5Y	6Y
Disc. From AEs	4	12	16
Atrial Fibrillation all grades	5	11	12
Major Bleed	1	6	10

Byrd et al. Blood 2019

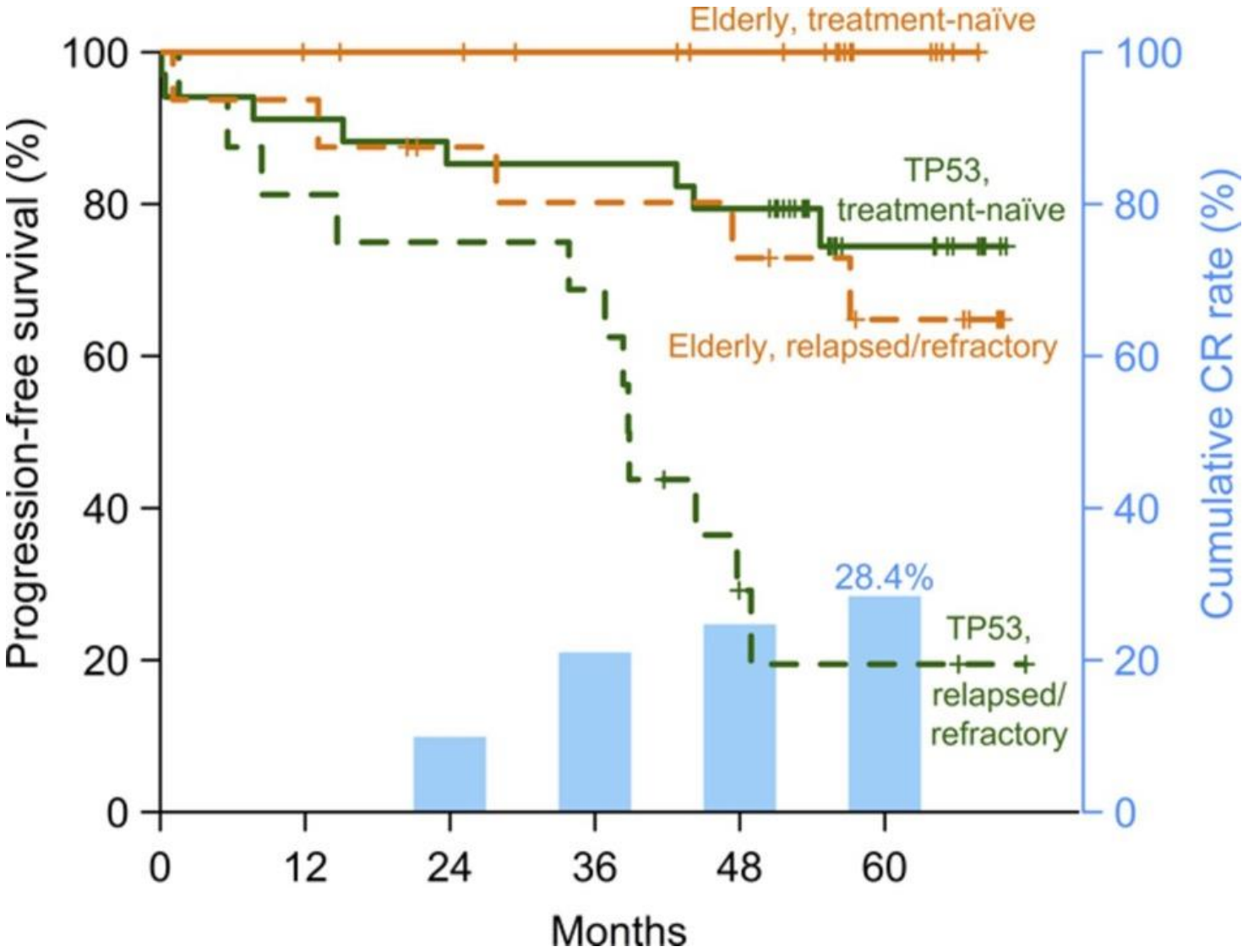
Barr et al. ASCO 2019, A#7510

NIH Experience
Investigator Initiated Open Label Single Arm Phase II

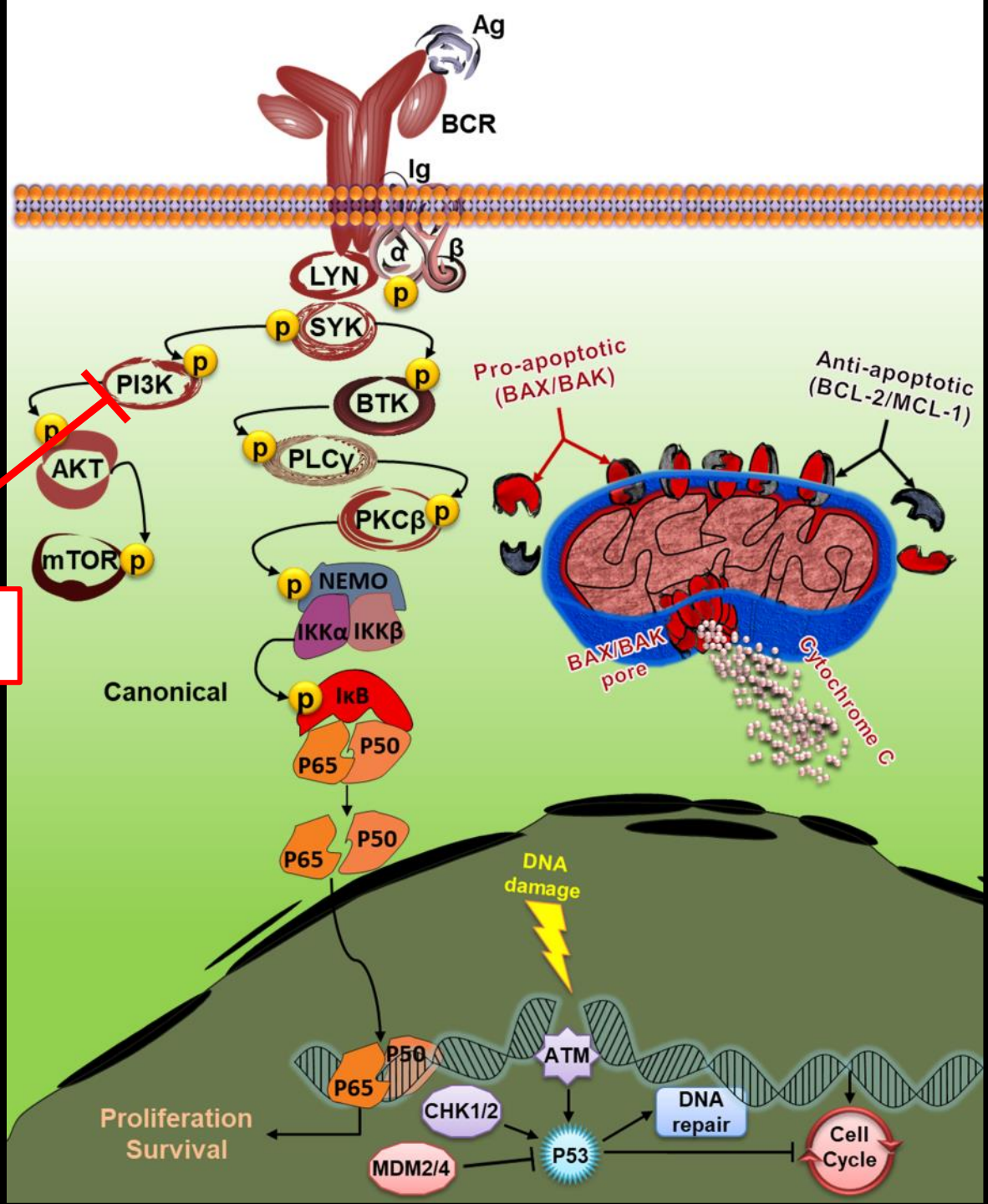


Farouqui… Saba… Wiestner. *Lancet Oncol* 2015
Ahn… Saba… Wiestner, *Blood* 2018

NIH Experience



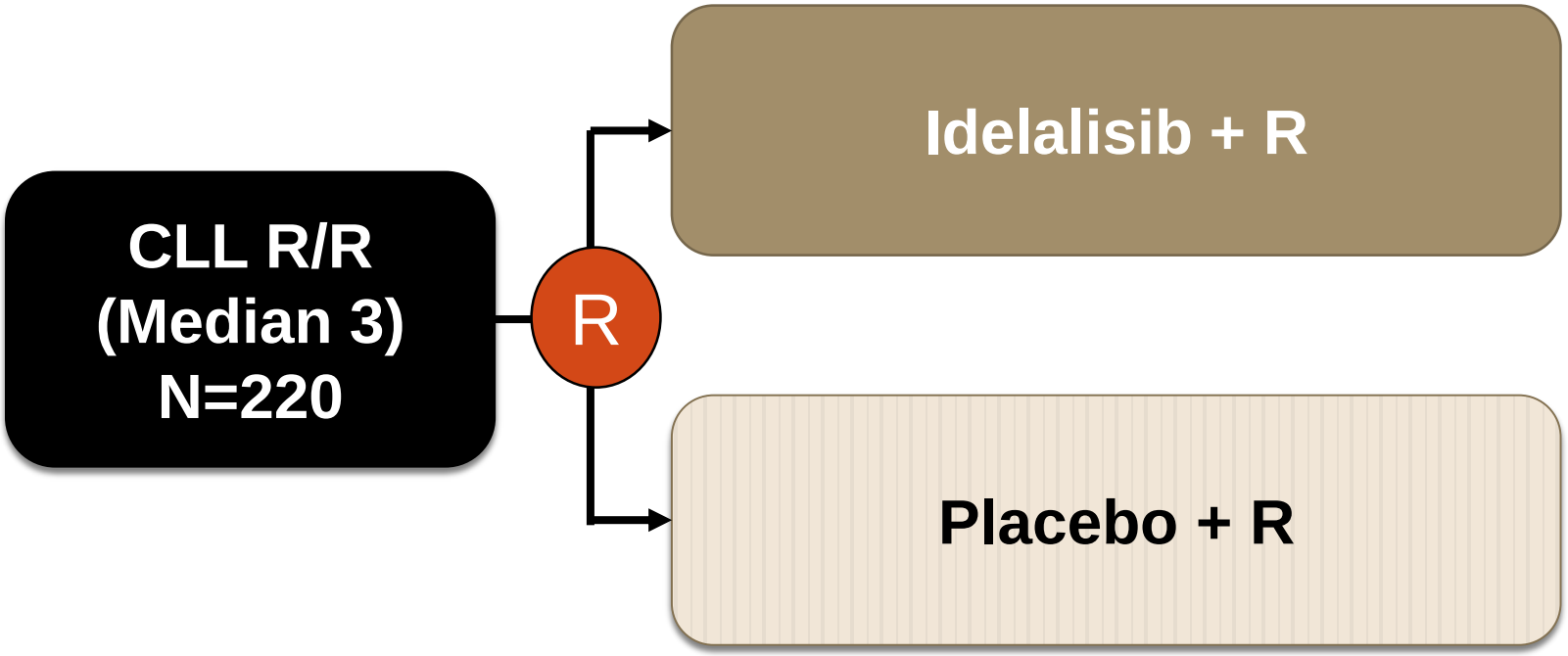
Farouqui… Saba… Wiestner. *Lancet Oncol* 2015
Ahn… Saba… Wiestner, *Blood* 2018



Idelalisib

Saba & Wiestner.
Curr Opin Hematol. 2014

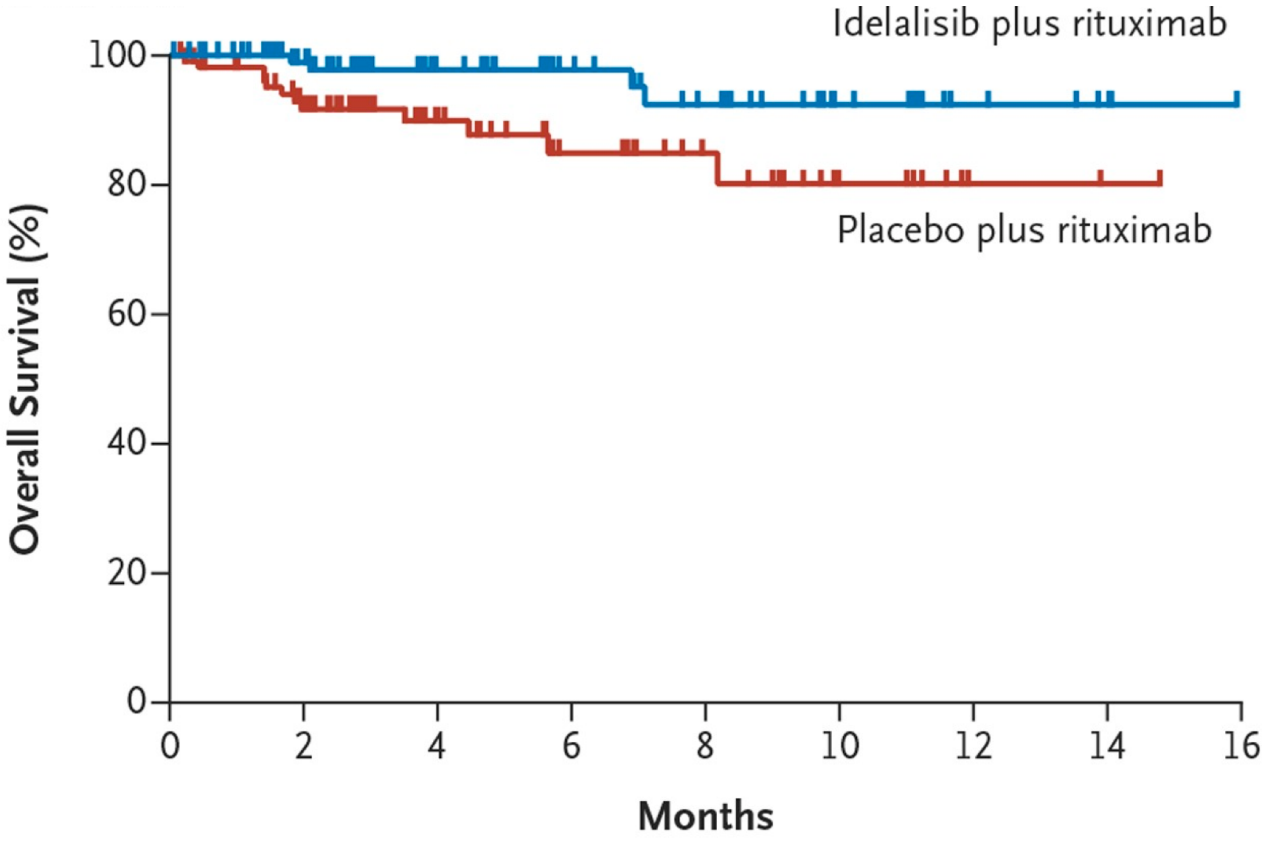
R+Idel vs. R+Plaebo



Primary endpoints: PFS
Secondary endpoints include: OS, ORR

Furman et al. *NEJM* 2014

R+Idel vs. R+Placebo In R/R CLL Phase 3, N=220, 40% 17p-



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. *NEJM* 2014

Grade 3-4 Idelalisib AEs

	Notable Grade 3 or higher
Phase 1	Pneumonitis (20%) Diarrhea (6%) Transaminitis (2%)
Phase 3 + Ofa	Pneumonitis (8%) Colitis (17%) Transaminitis (54%)

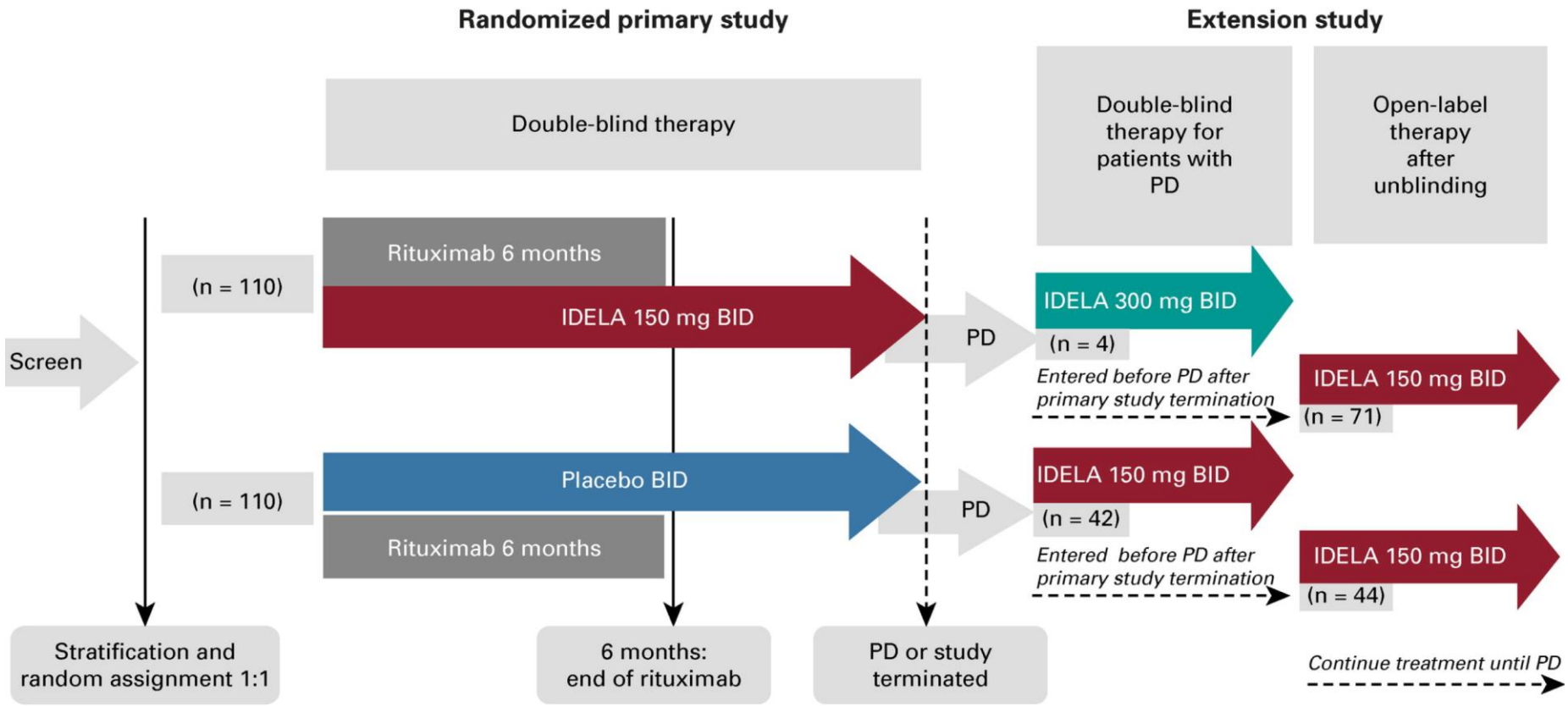
Six trials were stopped in 2016 due to increased mortality, mostly due to infectious complications.

- Acyclovir Prophylaxis – VZV
- Bactrim prophylaxis – PJP
- Monitor for CMV reactivation

Lampson et al. *Blood* 2016

Davis. ASH 2017

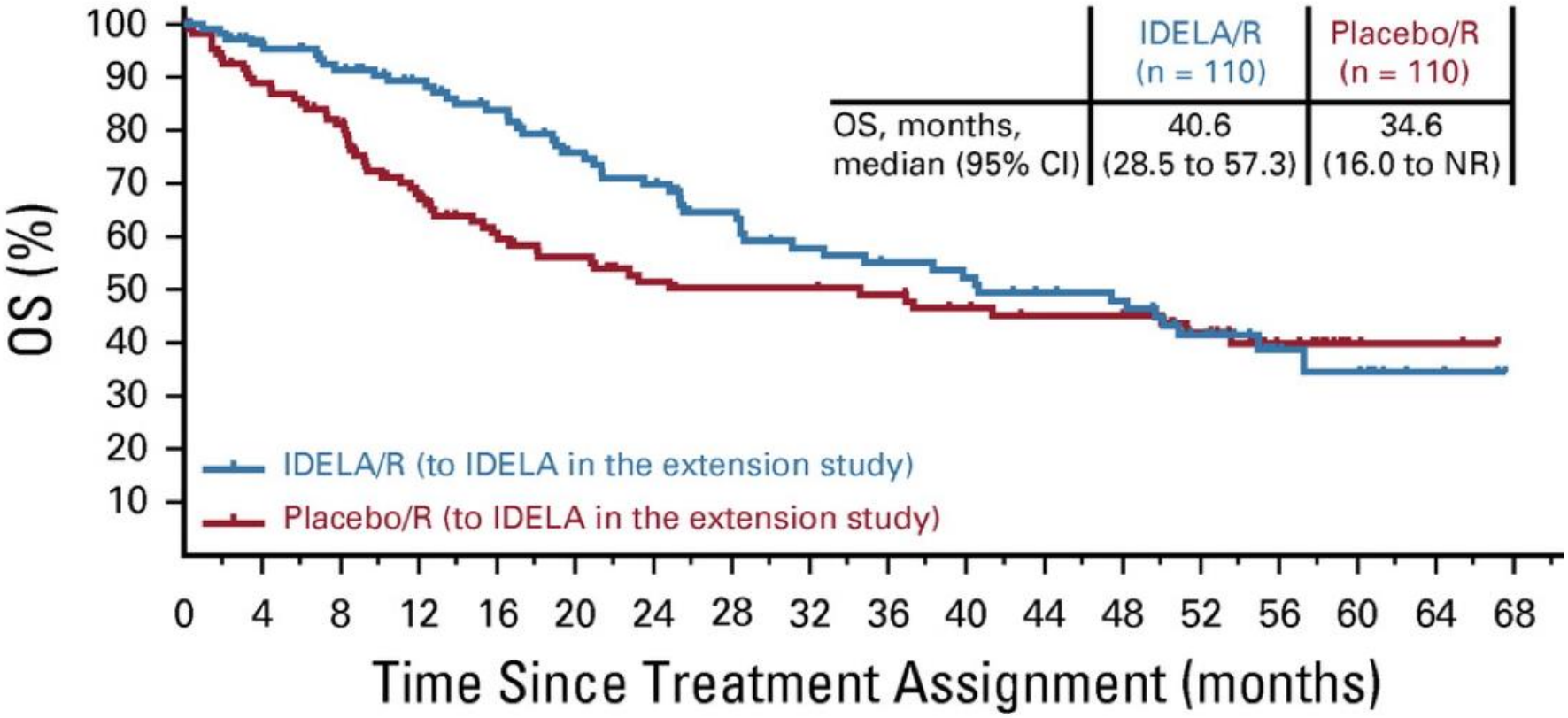
Idel+R vs. Placebo+R, N=220, 43% 17p-



Primary endpoints: PFS
Secondary endpoints include: OS, ORR

Sharman et al. JCO 2019

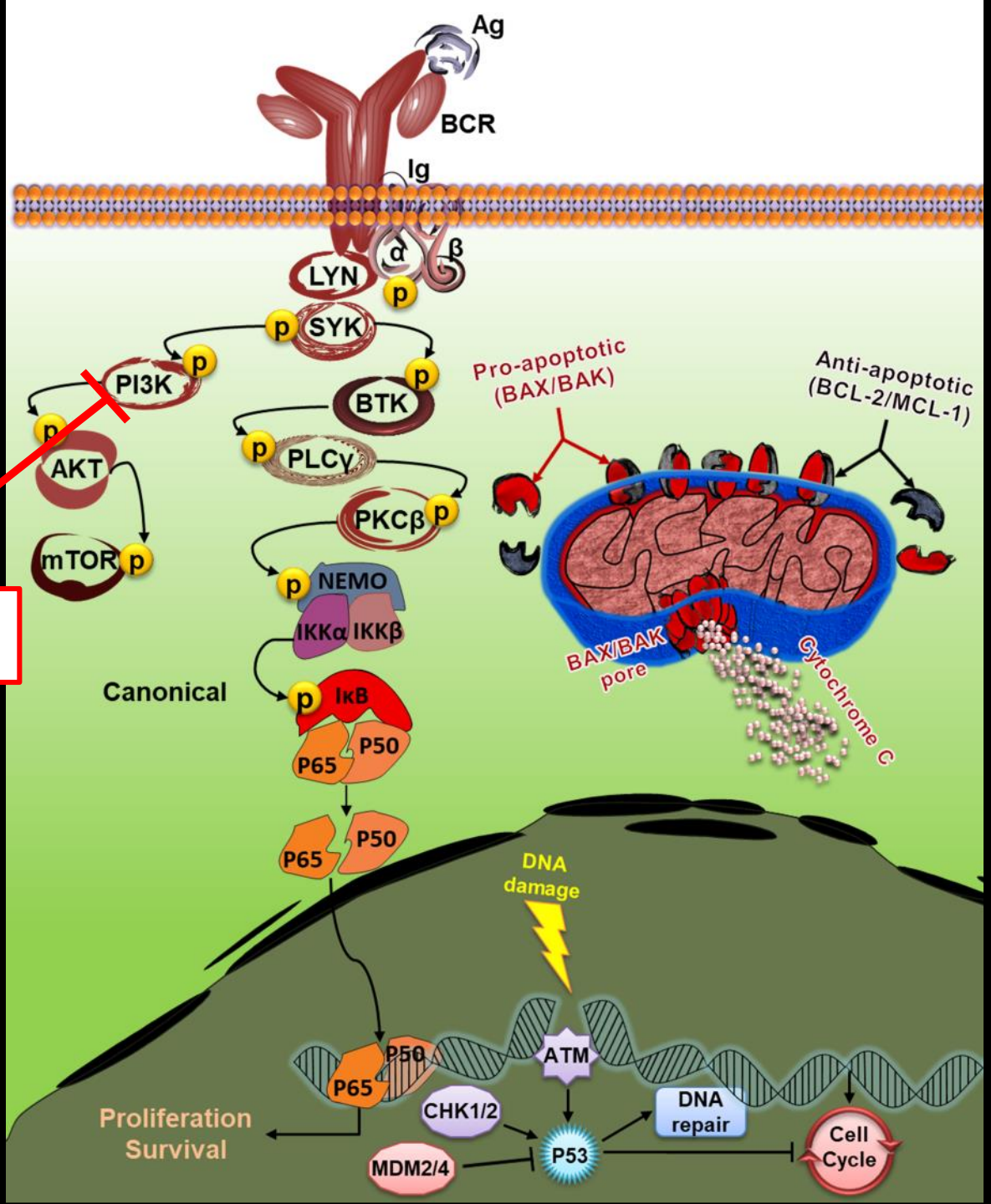
Idelalisib Results In A Superior OS Compared to R



No. at risk (No. of events)

IDELA/R	110 (0)	100 (4)	93 (9)	82 (11)	75 (16)	64 (23)	57 (28)	48 (32)	42 (37)	39 (39)	37 (41)	33 (43)	31 (44)	23 (48)	10 (49)	8 (50)	3 (50)	0 (50)							
Placebo/R	110 (0)	93 (12)	84 (20)	66 (33)	55 (40)	50 (44)	43 (48)	41 (49)	41 (49)	39 (50)	35 (52)	32 (53)	31 (53)	24 (55)	14 (56)	3 (56)	2 (56)	0 (56)							

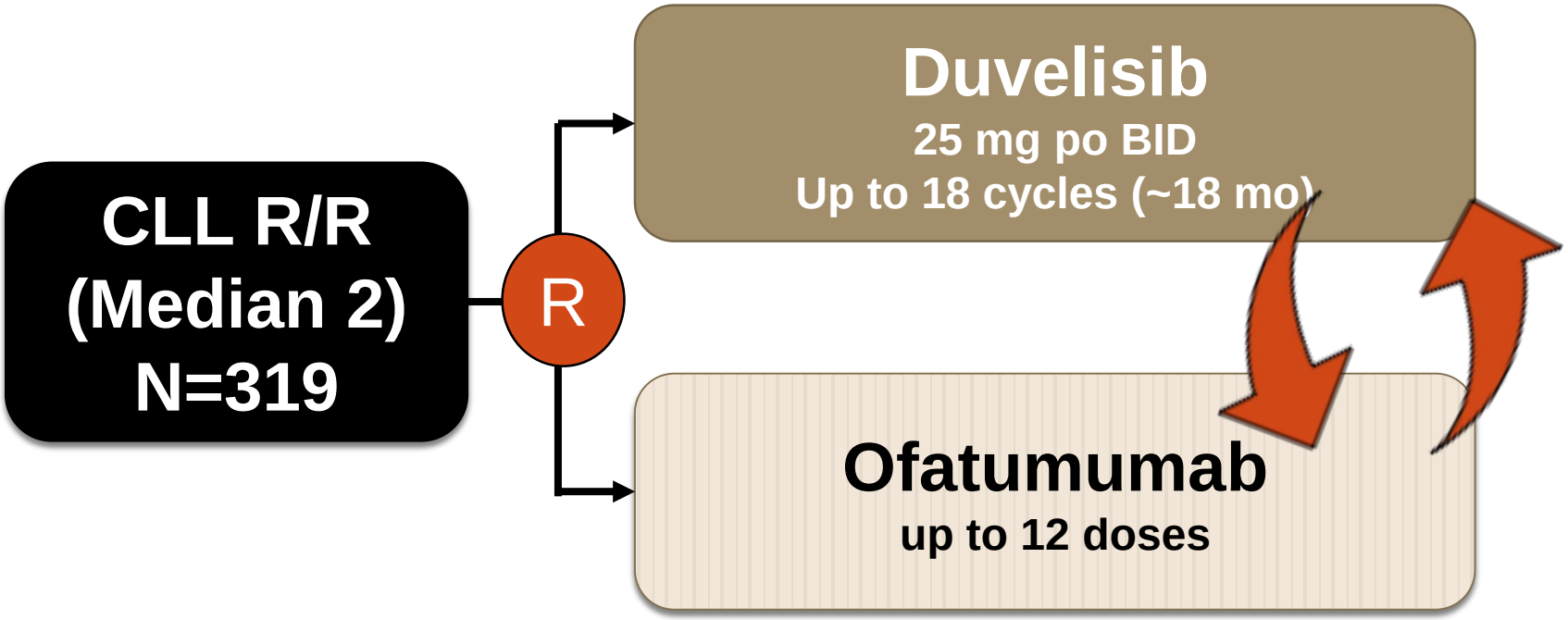
Sharman et al. JCO 2019



Duvelisib

Saba & Wiestner.
Curr Opin Hematol. 2014

DUO
Duvelisib vs. Ofa



Primary endpoints: PFS
Secondary endpoints include: OS, ORR

Byrd et al. Blood 2019

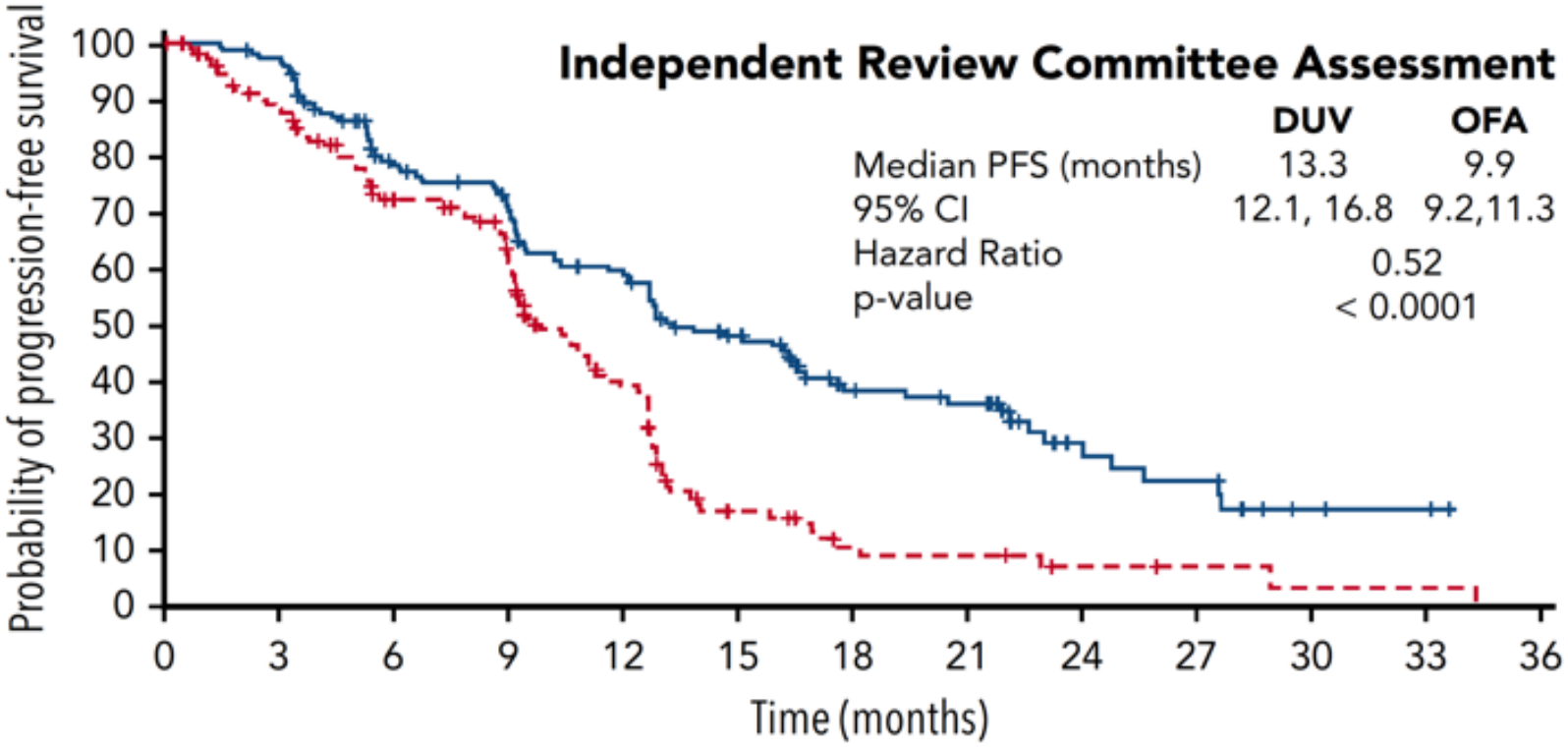
DUO: Duvelisib vs. Ofa

Characteristic	Duvelisib (n = 160)	Ofatumumab (n = 159)
Molecular features (per central laboratory), %		
17p deletion	21	28
TP53 mutation	20	18
17p deletion and/or *TP53* mutation	31	33
Unmutated IGHV	69	73
CD38 positive	43	44
ZAP70 positive (>19%)	54	52

Median # prior therapies: 2 for both arms

Byrd et al. Blood 2019

DUO: Duvelisib Is Superior To Ofa



<u>mOS was similar in both arms:</u>

5% crossed over to Ofa

57% crossed over to Duvelisib

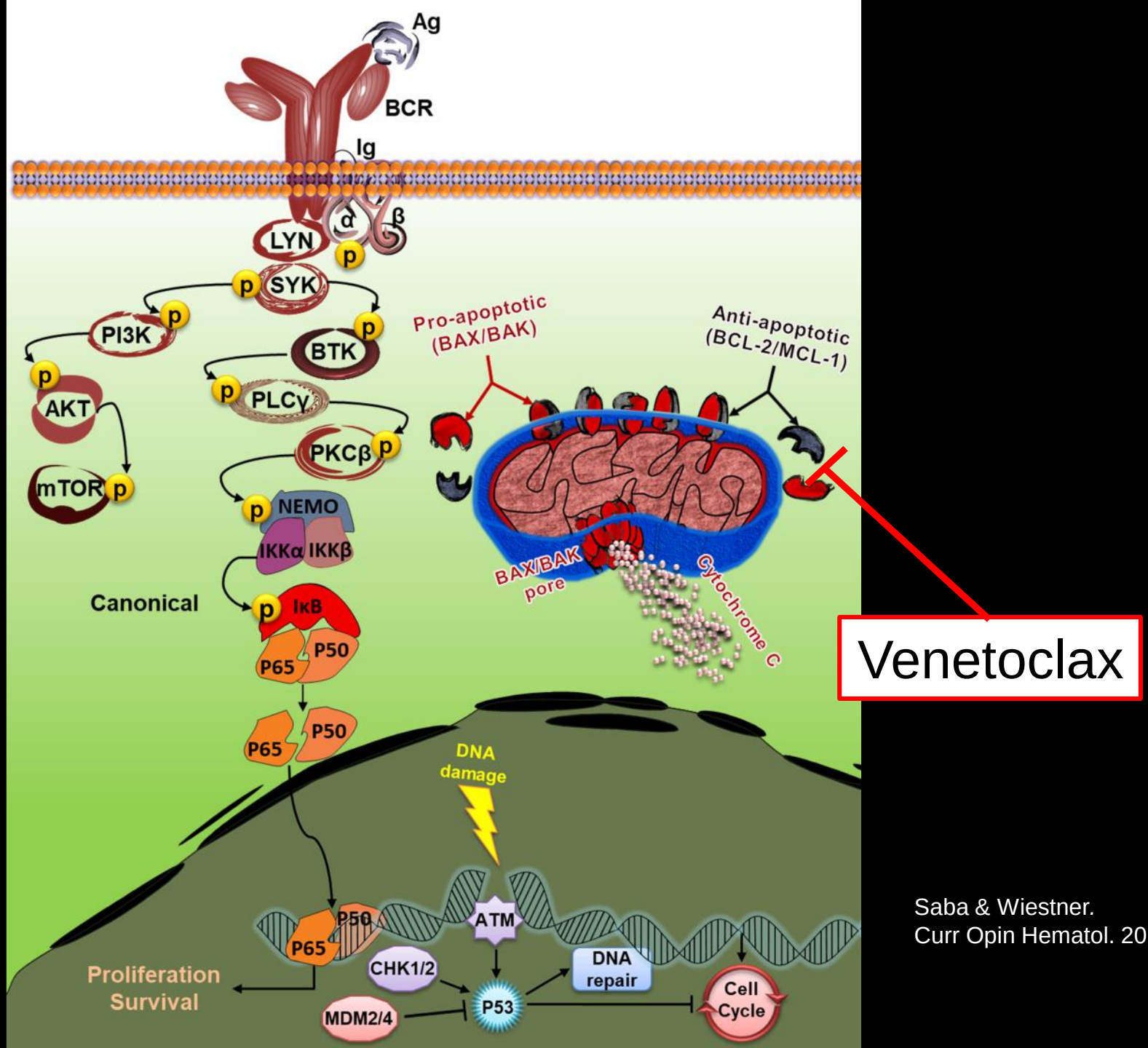
Byrd et al. Blood 2019

DUO: Duvelisib Is Superior To Ofa

Characteristic	Duvelisib	Ofatumumab
Randomized, n	160	159
Treated, n	158	155
Median exposure, wk	50	23
Discontinued treatment, n (%)	124 (79)	155 (100)
AE	55 (35)	6 (4)
Disease progression	35 (22)	31 (20)
Subject withdrawal	13 (8)	7 (5)
Death	12 (8)	3 (2)
Investigator decision	3 (2)	4 (3)
Completed treatment per protocol	1 (1)*	103 (67)*
Other	5 (3)	1 (1)
On treatment, n (%)	34 (22)	0
Crossed over to study IPI-145-12 to receive opposite treatment, n (%)	8 (5)	89 (57)

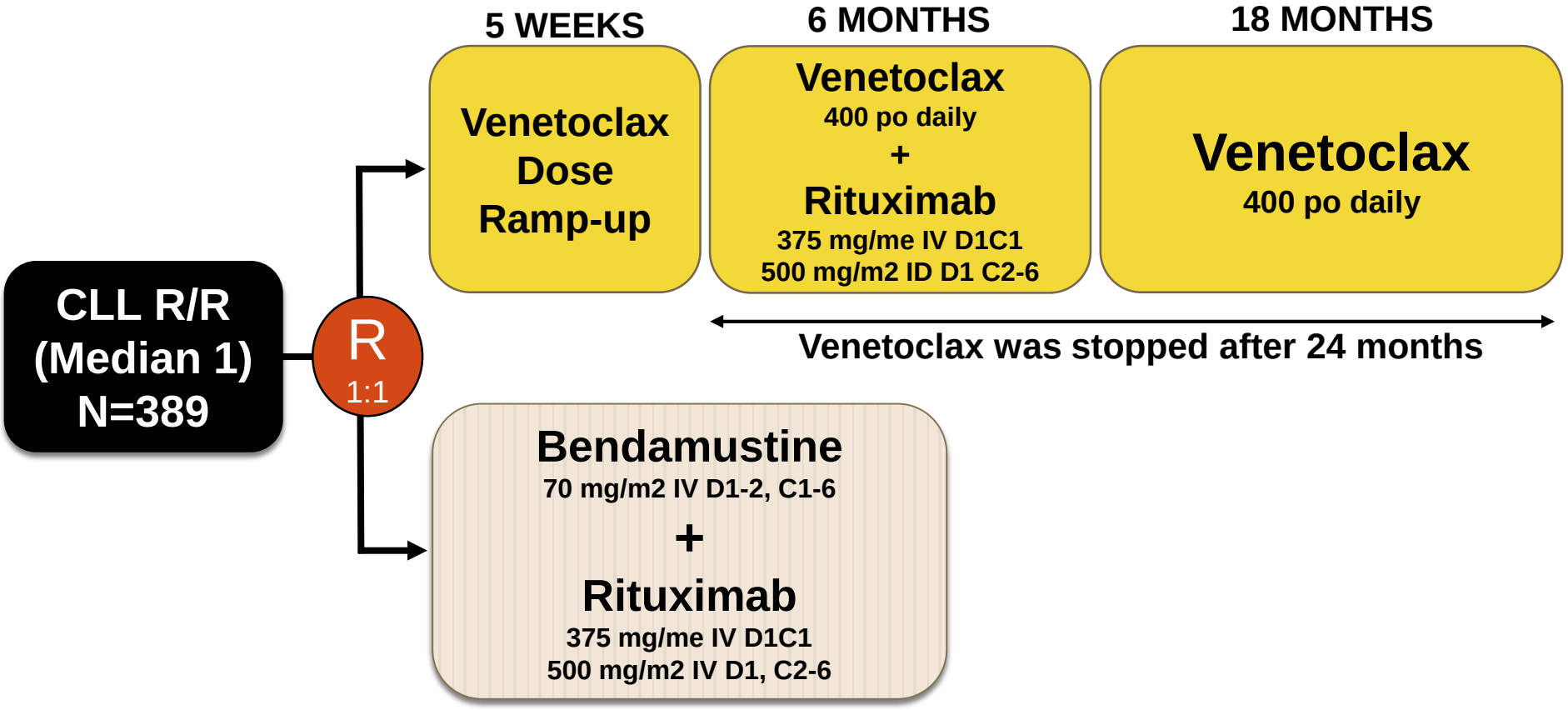
- PJP prophylaxis mandatory
- HSV prophylaxis
- Monitor CMV reactivation

Flinn et al. Blood 2019



Saba & Wiestner.
Curr Opin Hematol. 2014

MURANO: Venetoclax In R/R CLL
Open-label, Phase 3 Trial

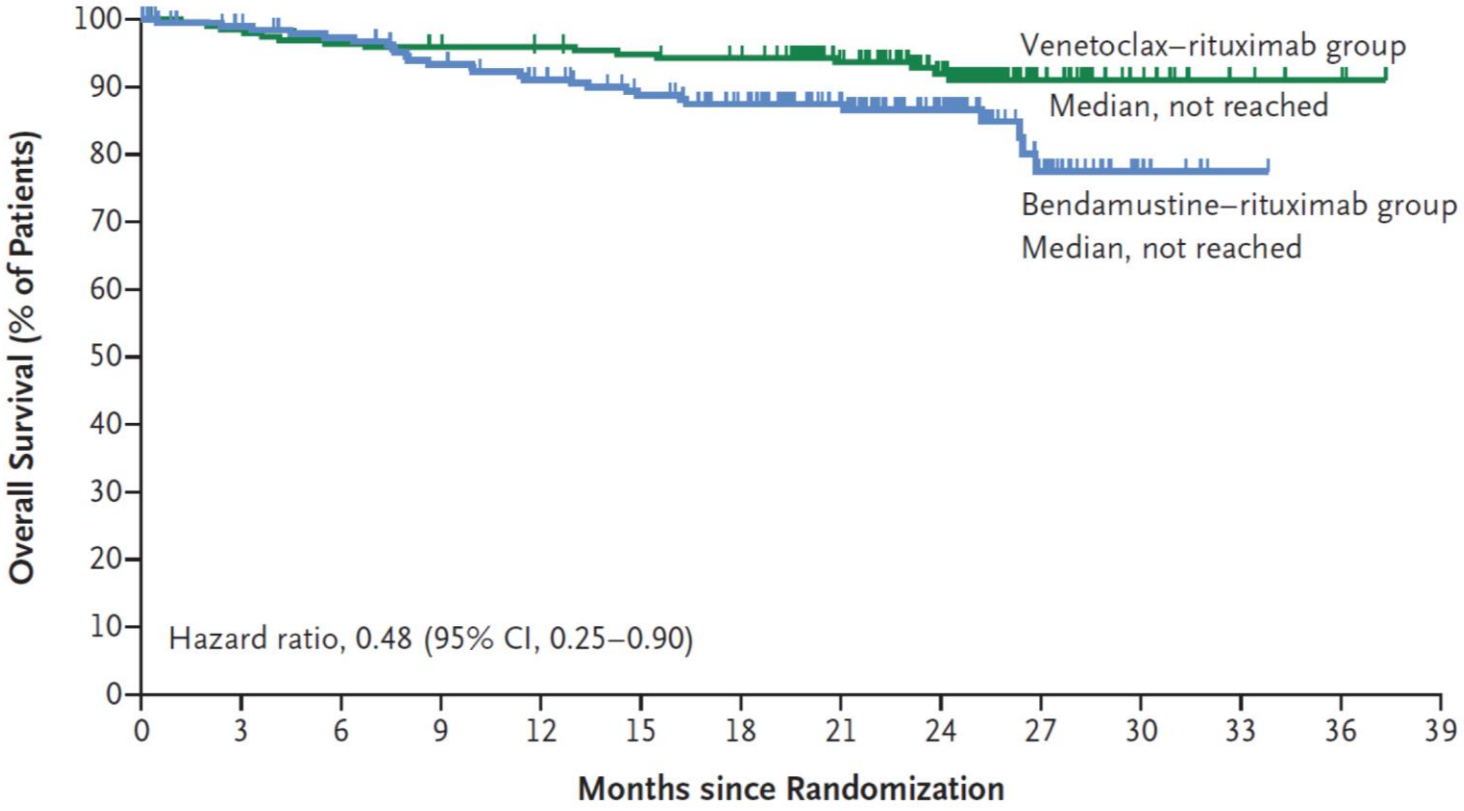


Primary endpoints: PFS

Secondary endpoints include: OS, ORR

Seymour et al. NEJM 2018

MURANO
Open-label, Phase 3 Trial, Randomized, N=389
R/R, 17p/TP53, Ven+R vs. BR

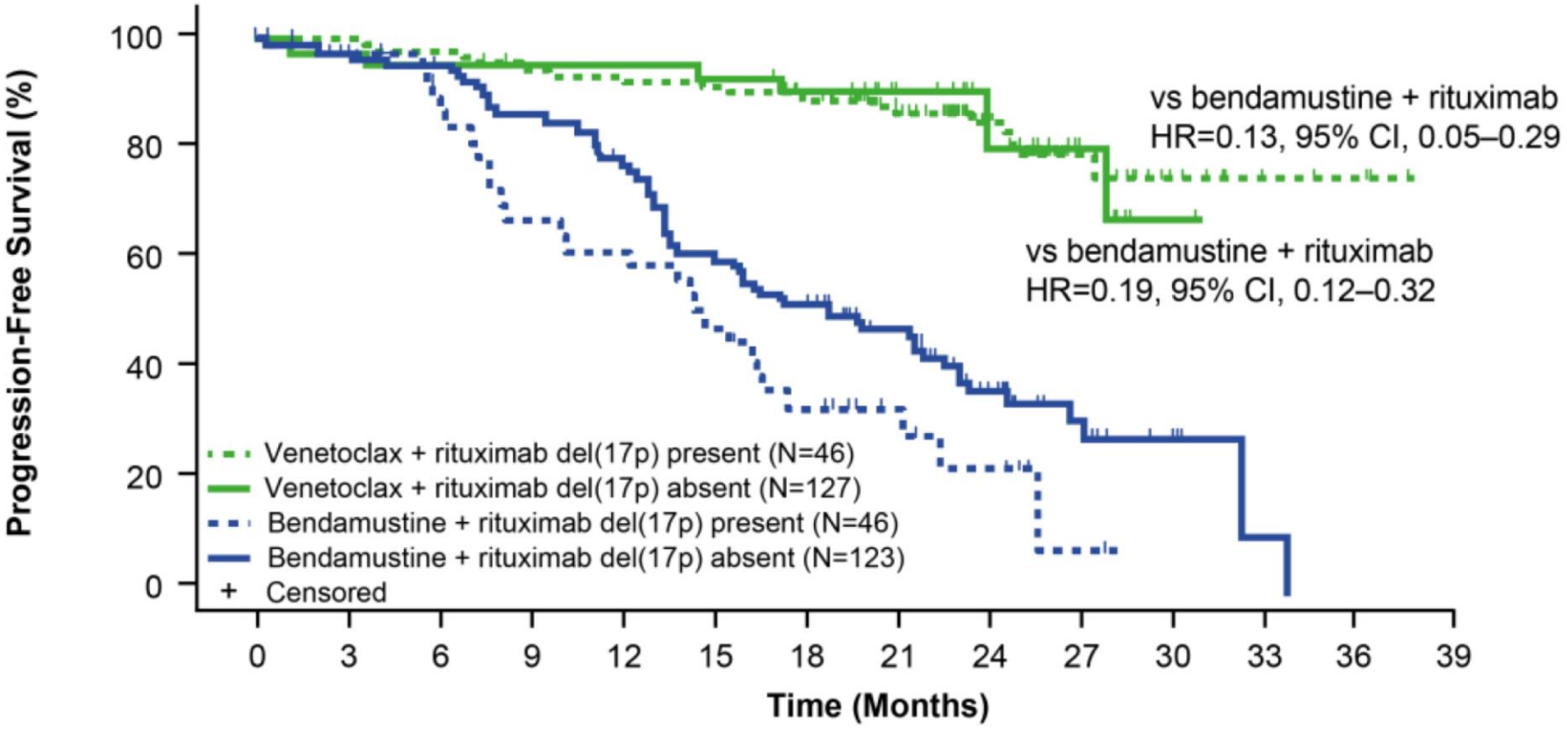


No. at Risk

Venetoclax–rituximab group	194	190	185	183	181	178	175	142	102	36	15	5	3
Bendamustine–rituximab group	195	181	175	166	158	146	134	102	66	29	8	2	

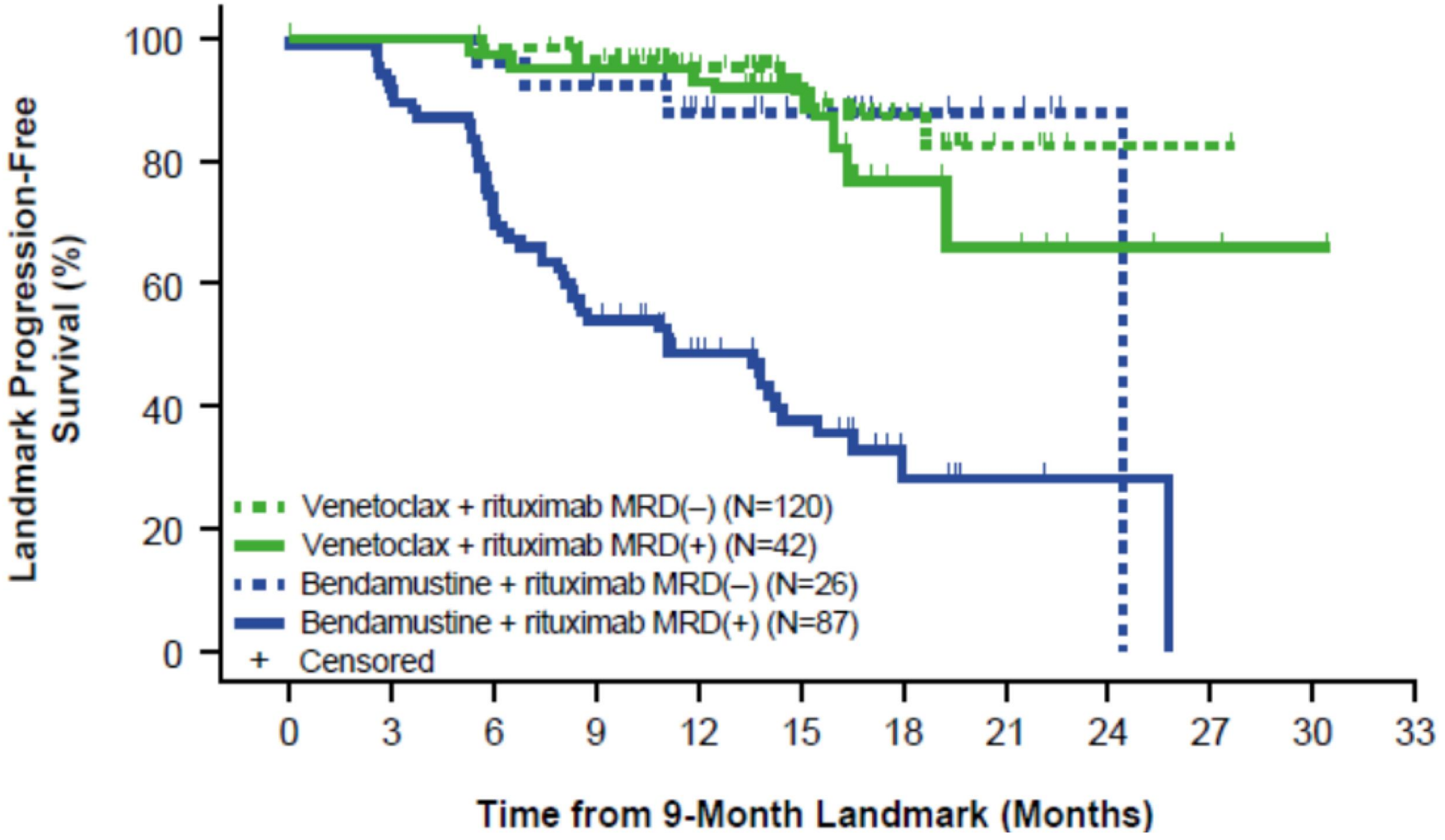
Seymour et al. NEJM 2018

MURANO
17p vs. non-17p



Seymour et al. NEJM 2018

MURANO
MRD- vs. MRD+



Seymour et al. NEJM 2018

Summary Of Key Adverse Events Related To Targeted Agents Studied In CLL

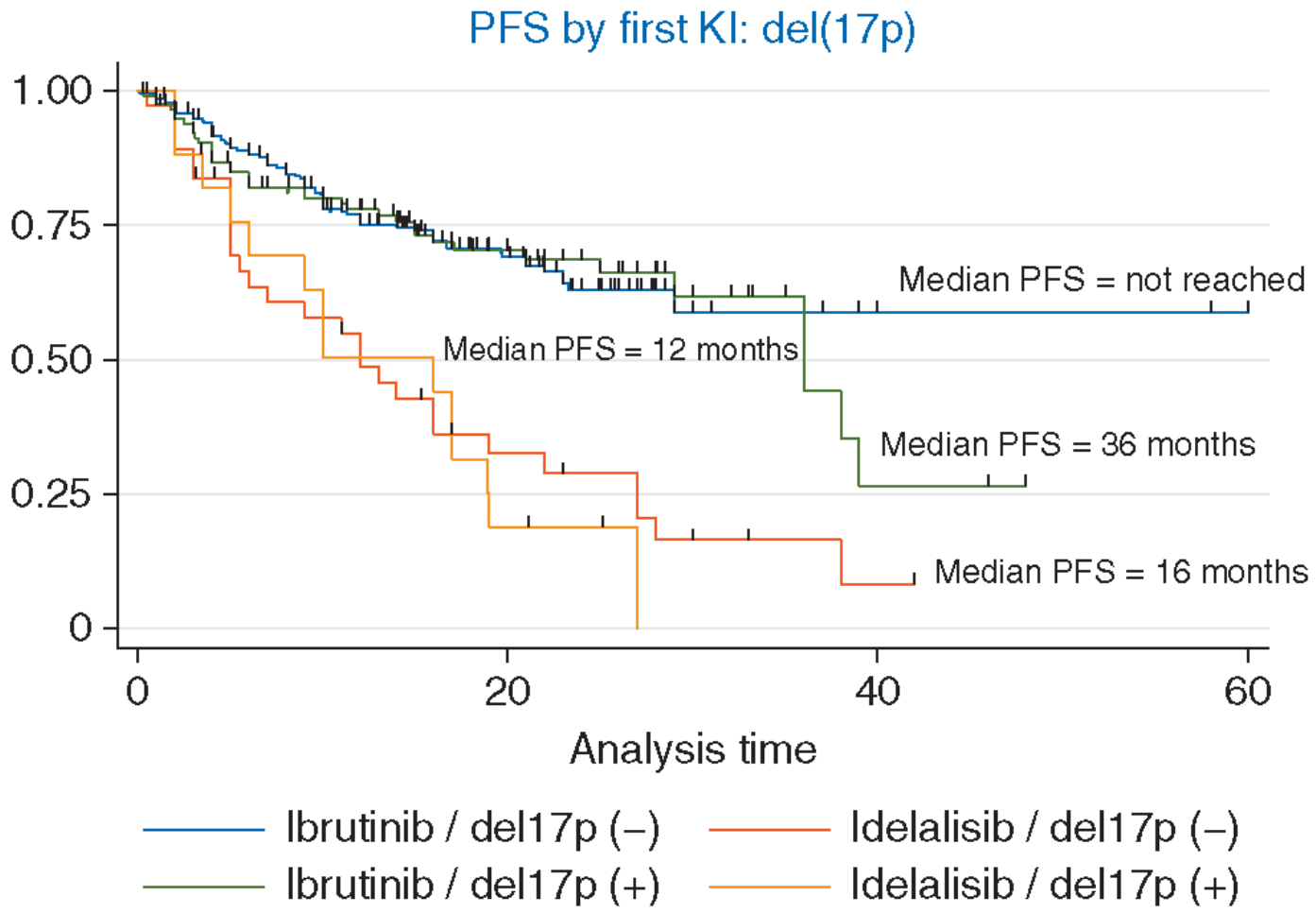
	Ibrutinib			Idelalisib				Venetoclax			Duvelisib
Study	RES	RES17	RES2	Furman	Jones	O'Brien	Lampson	Roberts	Stilgenbauer	Seymour	DUO
N	195	145	135	110	173	64	24	116	107	49	319
Prior treatment	RR	RR	**TN**	RR	RR	**TN**	**TN**	RR	RR	RR	RR
Median age	67	64	73	71	68	71	67	66	67	75	69
Median follow-up (mo)	9	28	18	4*	16	22*	15	21	12	28	22.4
Comments	—	17p	—	+R	+Ofa	+R	+Ofa	—	17p	+R	—
Heme AE (% any grade/% grade 3-4)											
Neutropenia	22 /16	NR/22	16/10	55/34	35/35	53/28	46/29	45/41	43/40	66/53	33/30
Anemia	23/5	26/10	19/6	25/5	23/14	23/3	8/4	25/12	27/18	24/14	23/13
Thrombocytopenia	17/6	NR/11	<15/2	17/10	14/11	14/2	8/0	21/12	19/15	27/17	15/8
Non-heme AE (% any grade/% grade 3-4)											
Hemorrhage	44/1	16/9	15/4	NR	NR/2	NR/3	NR	NR	NR	NR/4	NR
Atrial fibrillation	5/3	NR/7	6/2	7/NR	NR/2	NR	NR	NR	NR/2	6/NR	NR
Hypertension	10/-	27/13	14/4	NR	13/5	NR	8/4	NR	6/4	8/NR	NR
Infections	23/4	14/5	17/4	NR	NR	NR	13/13	48/1	72/19	82/16	69/NR
Pneumonia	10/7	25/13	15/4	6/NR	20/14	28/19	13/13	NR/4	9/5	16/6	18/14
Pneumonitis	NR	NR	NR	NR/0	6/5	19/3	13/8	NR 4	NR	NR	NR/3
Diarrhea or colitis	48/4	41/3	42/4	19/4	54/19	64/42	46/ 21	52/2	29/0	57/2	51/15
Abnormal AST/ALT	NR	NR/<1	NR	35/5	47/ 12	67/23	79/54	NR	1/1	7/3	NR/3
Tumor lysis syndrome	NR	NR/<1	NR	NR	NR/<1	NR	NR	4/3	5/5	10/4	NR

Flinn et al. Blood 2019
Edited from Ahn et al. Hematology ASH Educ Program 2017

	IBRUTINIB	VEN/R	IDELA+R	DUVELISIB
Target	BTK	BCL-2	PI3K-δ	PI3K-δ,γ
Route	Oral	Oral	Oral	Oral
Trial Type	Phase 3	Phase 3	Phase 3	Phase 3
Duration of therapy	Indefinite	2 years	Indefinite	1.5 years
Prophylaxis	None	None	PJP	PJP
Comparator	Ofa	BR	Placebo+R	Ofa
N	391	389	220	319
17p and/or TP53 (%)	51	38	43.2	31
# prior therapies, median	3	1	3	2
Median Follow-up (m)	44	23.8	18	22.4

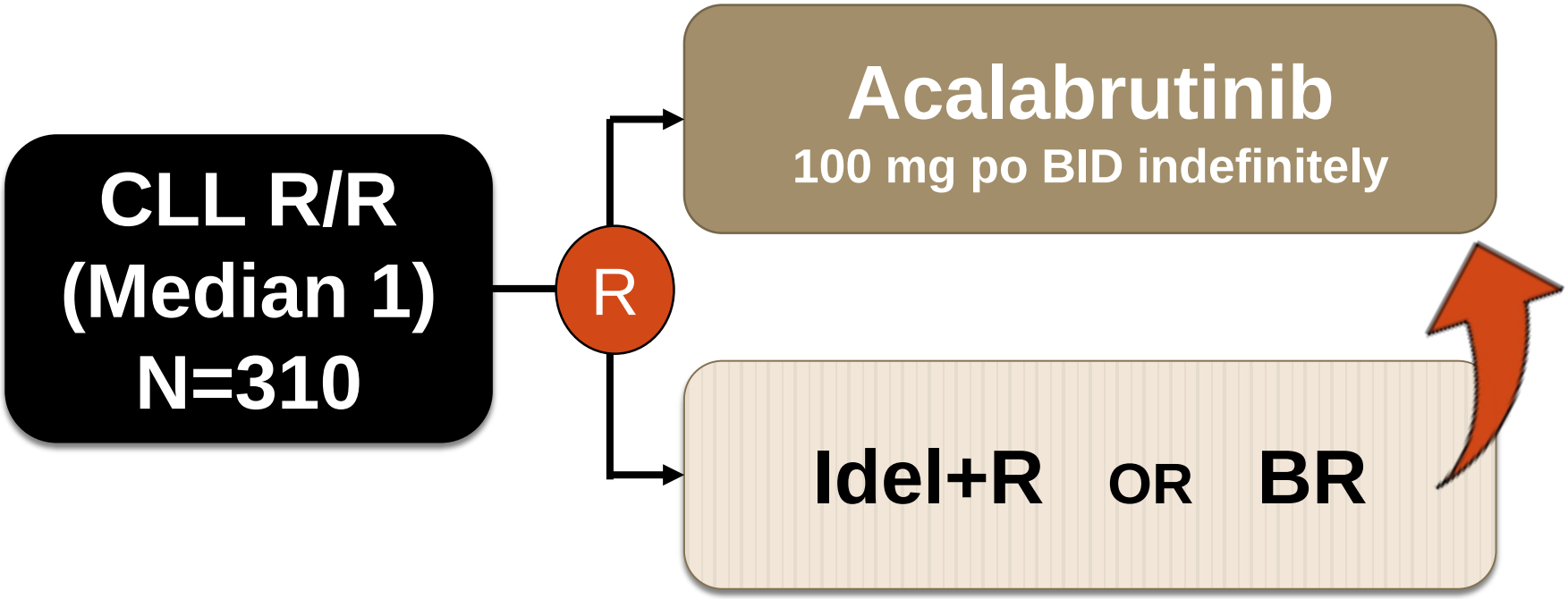
	IBRUTINIB	VEN/R	IDELA+R	DUVELISIB
Target	BTK	BCL-2	PI3K-δ	PI3K-δ,γ
Route	Oral	Oral	Oral	Oral
Trial Type	Phase 3	Phase 3	Phase 3	Phase 3
Duration of therapy	Indefinite	2 years	Indefinite	1.5 years
Prophylaxis	None	None	PJP	PJP
Comparator	Ofa	BR	Placebo+R	Ofa
N	391	389	220	319
17p and/or TP53 (%)	51	38	43.2	31
# prior therapies, median	3	1	3	2
Median Follow-up (m)	44	23.8	18	22.4
ORR (CR)	91 (9)	92.3 (26.8)	85.5 (0.9)	73.8 (0.6)
mPFS	NR	NR	20.3	17.6 (IRC13.3)
mPFS (17p)	40.1	NR	18.7	13.8 (IRC12.7)
1Y OS (%)	90	93.3	89.3	86
mOS	NR	NR	40.6	NR
mOS (17p)	NR	NR	28.5	NR
Disc. From AEs (%)	12	12.9	8.1	35

Retrospective Analysis, N = 584 R/R, Ibrutinib vs. Idela



Mato et al. Annals of Oncol 2017

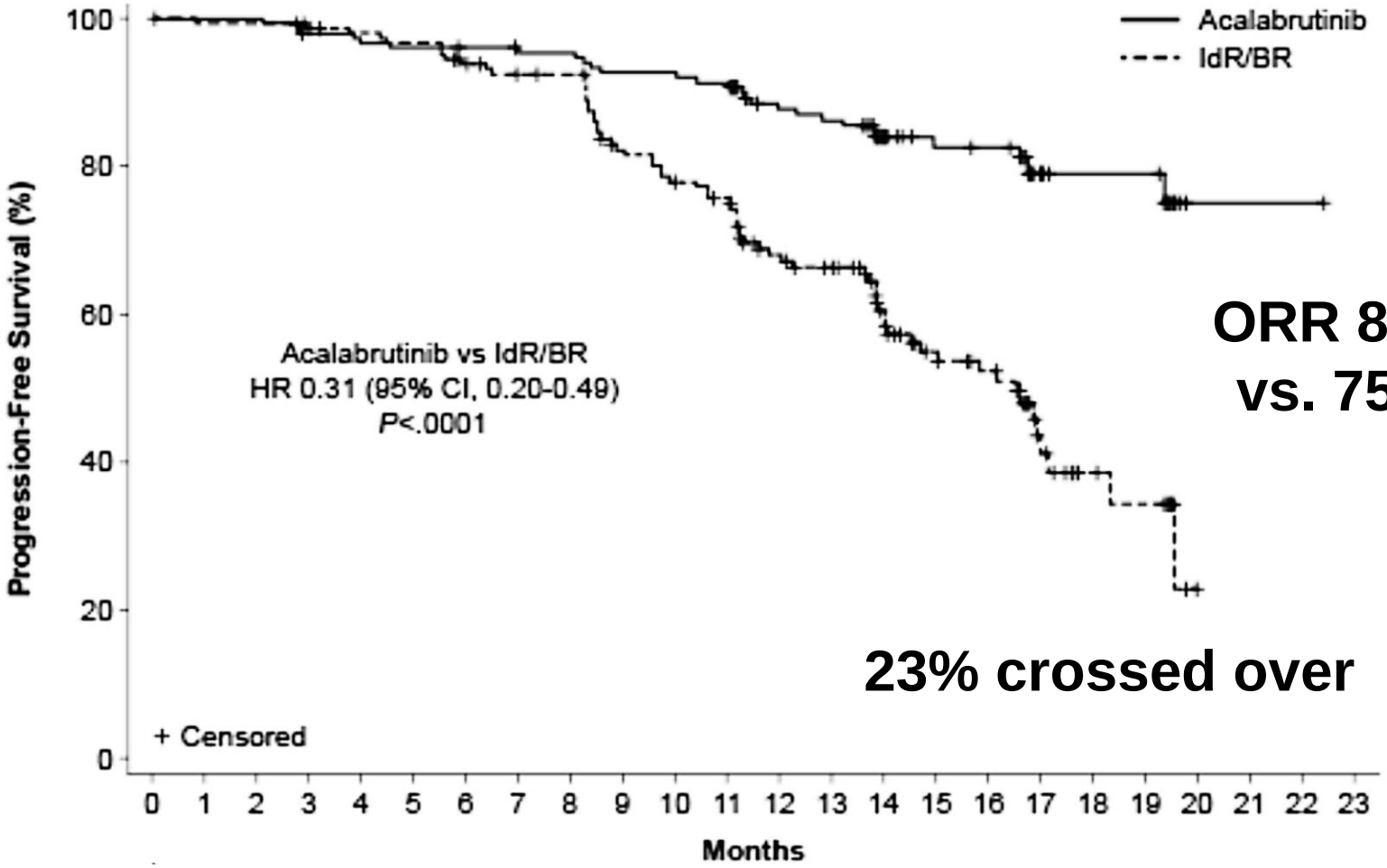
ASCEND Phase III
Acalabrutinib vs. Idel-R or BR



Primary endpoints: PFS
Secondary endpoints include: OS, ORR

Ghia et al. EHA 2019, LB2606

Acalabrutinib Resulted In A Superior PFS At A Median Follow-up Of 16.1 Mo



ORR 81% vs. 75%

23% crossed over

Ghia et al. EHA 2019, LB2606

National Comprehensive Cancer Network®

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL with del(17p)/*TP53* mutation
(alphabetical by category)

RELAPSED/REFRACTORY THERAPY

Preferred regimens

- Ibrutinib[e] (category 1)
- Venetoclax[e,f] + rituximab (category 1)
- Duvelisib[e]
- Idelalisib[e] + rituximab[o]
- Venetoclax[e,f]

Other recommended regimens

- Acalabrutinib[e,p]
- Alemtuzumab[q] ± rituximab
- HDMP + rituximab
- Idelalisib[e]
- Lenalidomide[r] ± rituximab
- Ofatumumab[s]

SUGGESTED TREATMENT REGIMENS[a,b,c,d]
CLL/SLL without del(17p)/*TP53* mutation
(alphabetical by category)

RELAPSED/REFRACTORY THERAPY

	Preferred regimens	Other recommended regimens	
Frail patient with significant comorbidity OR Patients age ≥65 y and younger patients with significant comorbidities	• Ibrutinib[e] (category 1) • Venetoclax[e,f] + rituximab (category 1) • Duvelisib[e] • Idelalisib[e] + rituximab[o]	• Acalabrutinib[e,p] • Alemtuzumab[q] ± rituximab • Chlorambucil + rituximab • Reduced-dose FCR[j,k] • HDMP + rituximab • Idelalisib[e] • Lenalidomide[r] ± rituximab	• Obinutuzumab • Ofatumumab • Reduced-dose PCR • Venetoclax[e,f] • Dose-dense rituximab (category 2B) • Bendamustine, rituximab ± ibrutinib,[e] or idelalisib[e] (category 2B for BR and BR + ibrutinib; category 3 for BR + idelalisib)
Patients age <65 y without significant comorbidities	• Ibrutinib[e] (category 1) • Venetoclax[e,f] + rituximab (category 1) • Duvelisib[e] • Idelalisib[e] + rituximab[o]	• Acalabrutinib[e,p] • Alemtuzumab[q] ± rituximab • Bendamustine + rituximab • FC[j,k] + ofatumumab • FCR[j,k] • HDMP + rituximab • Idelalisib[e] • Lenalidomide[r] ± rituximab	• Obinutuzumab • Ofatumumab • PCR • Venetoclax[e,f] • Bendamustine, rituximab + ibrutinib[e] (category 2B) • Bendamustine, rituximab + idelalisib[e] (category 2B)

	IBRUTINIB	ACALABRUTINIB
Target	BTK	BTK
Route	Oral once daily	Oral BID
Trial Type	Phase 3	Phase 3
Duration of therapy	Indefinite	Indefinite
Prophylaxis	None	None
Comparator	Ofa	BR or Idel+R
N	391	310
# prior therapies, median	3	1
Median Follow-up (m)	44	16.1
1Y OS (%)	90	94
Disc. From AEs (4 @ 9 mo)	12 (16 @ 6Y	11
Atrial Fibrillation (5 @ 9 mo)	11 (12 @ 6Y	5.2
Major Bleed (1 @ 9mo)	6 (10@ 6Y	1.9

Elevate CLL R/R: Study of **Acalabrutinib** (ACP-196) Vs. **Ibrutinib** in Previously Treated Subjects With High Risk Chronic Lymphocytic Leukemia - NCT02477696

Byrd et al. Blood 2019; Barr et al. ASCO 2019, A#7510; Ghia et al. EHA 2019, LB2606

Sequencing Novel Agents

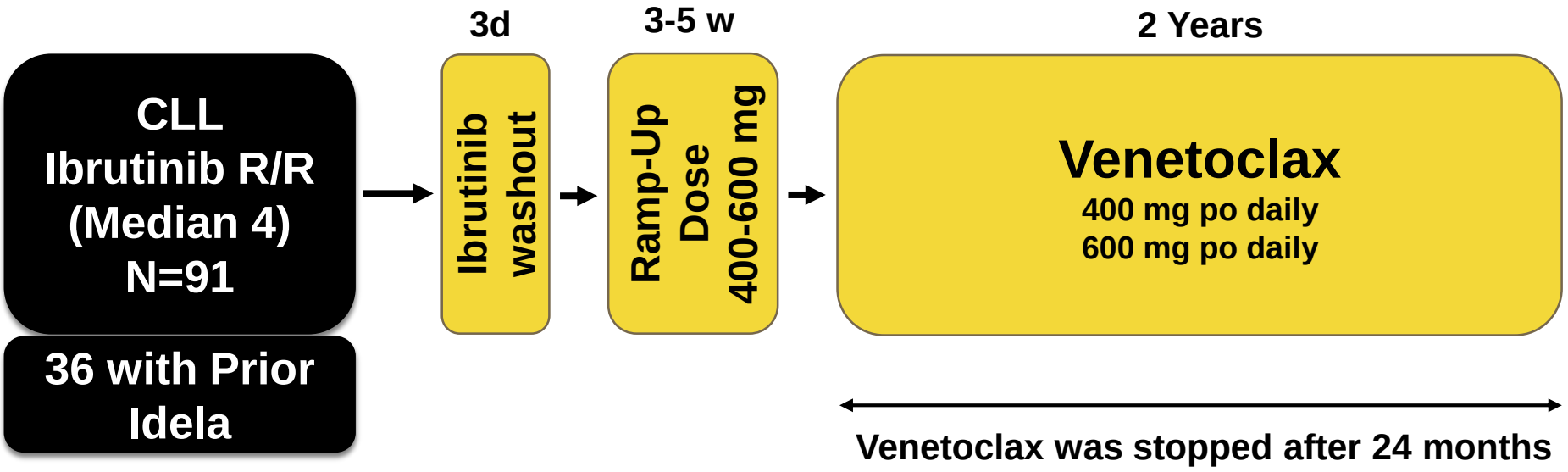
- **Progression:**
  - **Ibrutinib → Venetoclax**
  - **Idelalisib → Venetoclax**
  - **Ibrutinib ⇄ Idelalisib**

- **Intolerance:**
  - **Ibrutinib → Acalabrutinib**
  - **Ibrutinib ⇄ Idelalisib**

Sequencing Novel Agents

- **Progression:**
  - **Ibrutinib → Venetoclax**
  - **Idelalisib → Venetoclax**

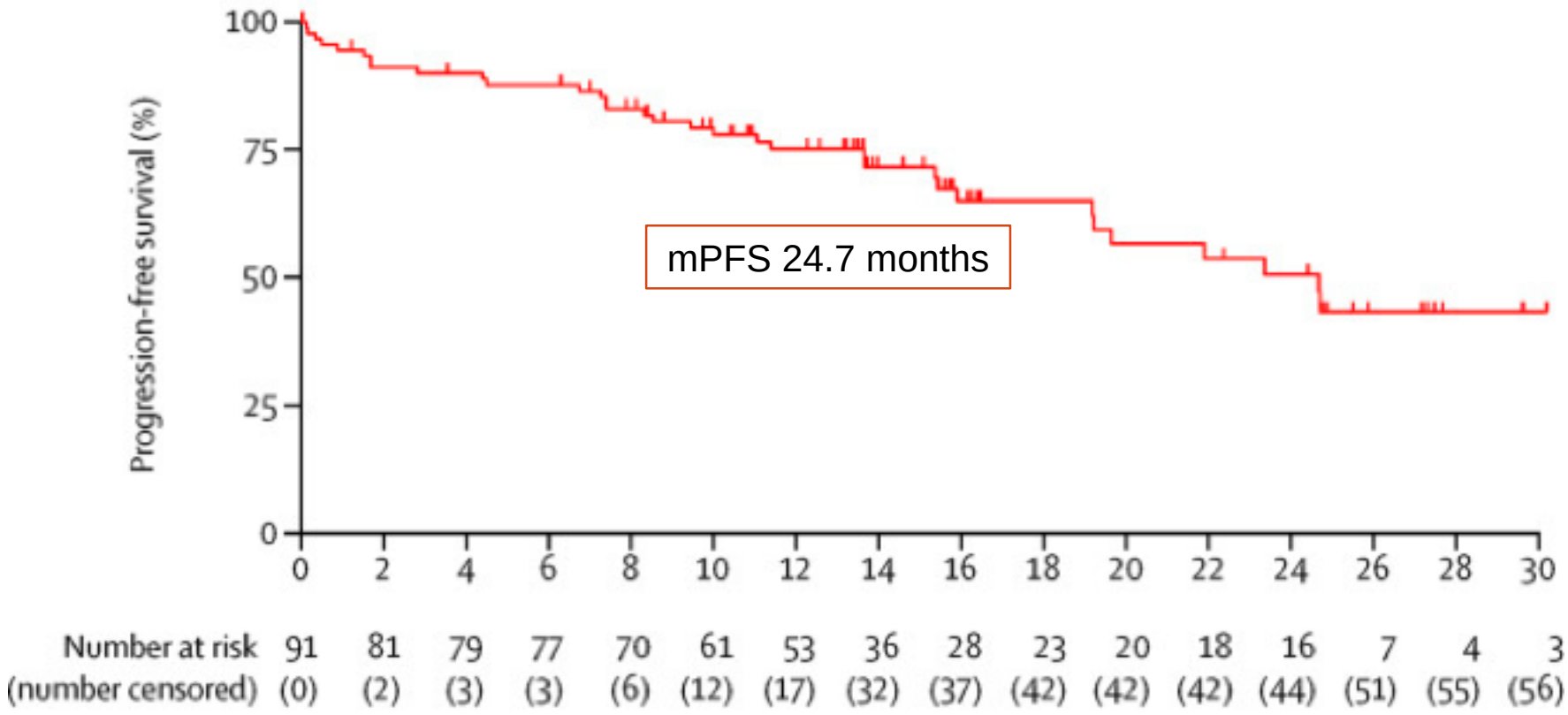
Open-label, Non-Randomized Phase 2



Primary endpoints: ORR
Secondary endpoints include: DOR, PFS

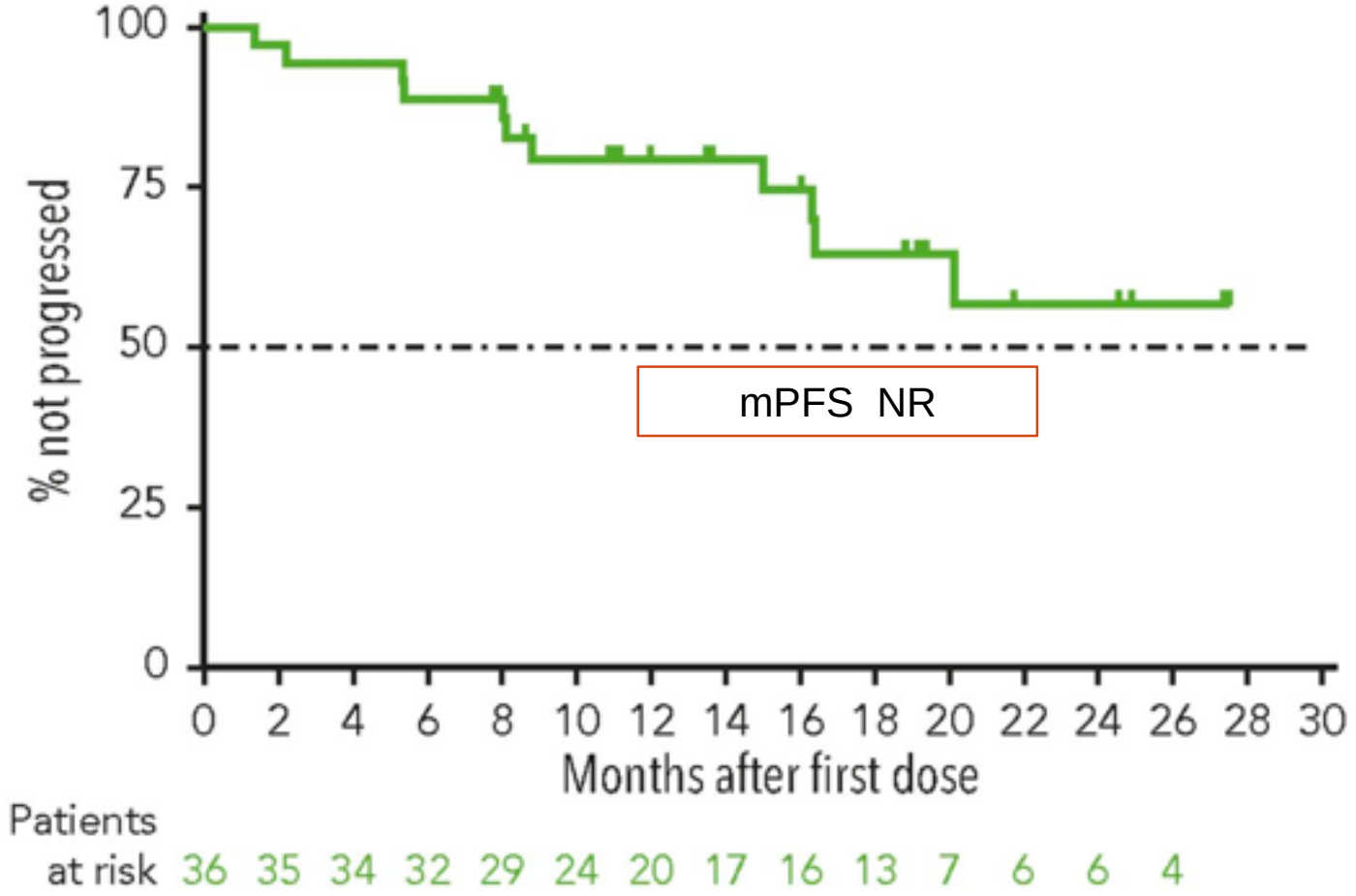
Jones et al. Lancet Oncol 2018

Following Progression On Ibrutinib, ORR Is 65% With CR Of 9% To Venetoclax



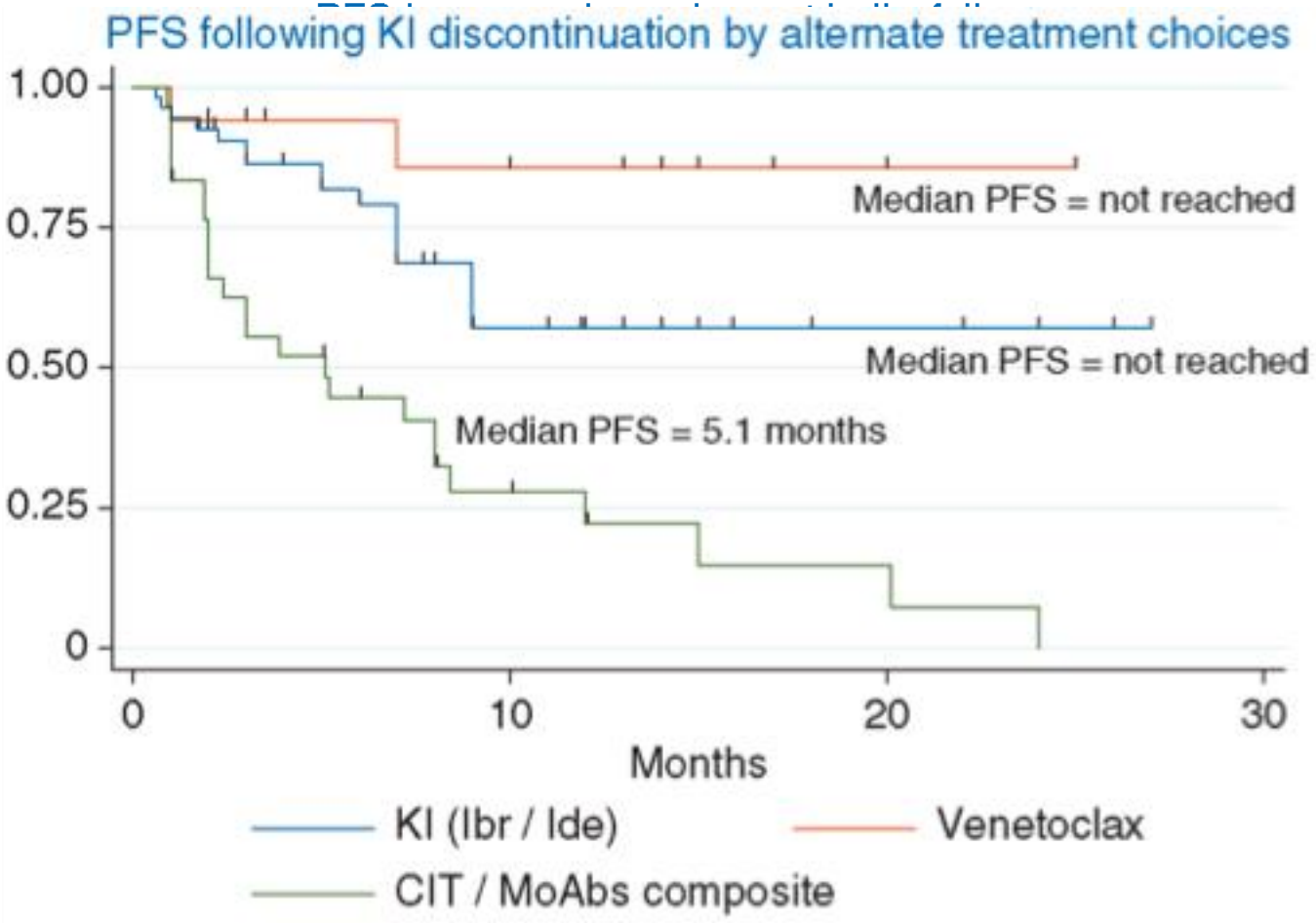
Jones et al. Lancet Oncol 2018

Following Progression On Idelalisib, ORR Is 67% With CR Of 8% To Venetoclax



Courte et al. Blood 2018

Retrospective Analysis Following Ibrutinib Resistance

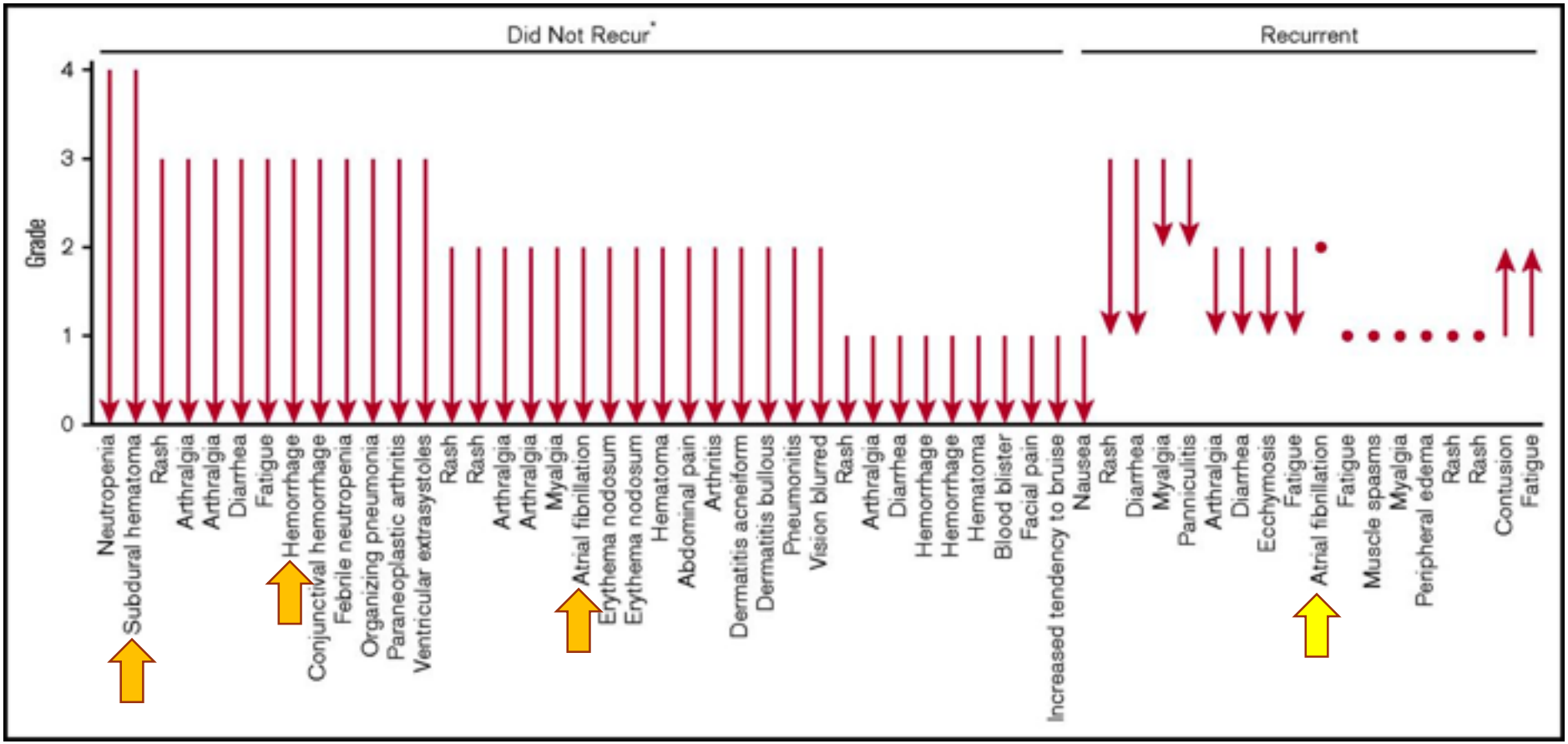


Mato et al. Annals of Oncol 2017

Sequencing Novel Agents

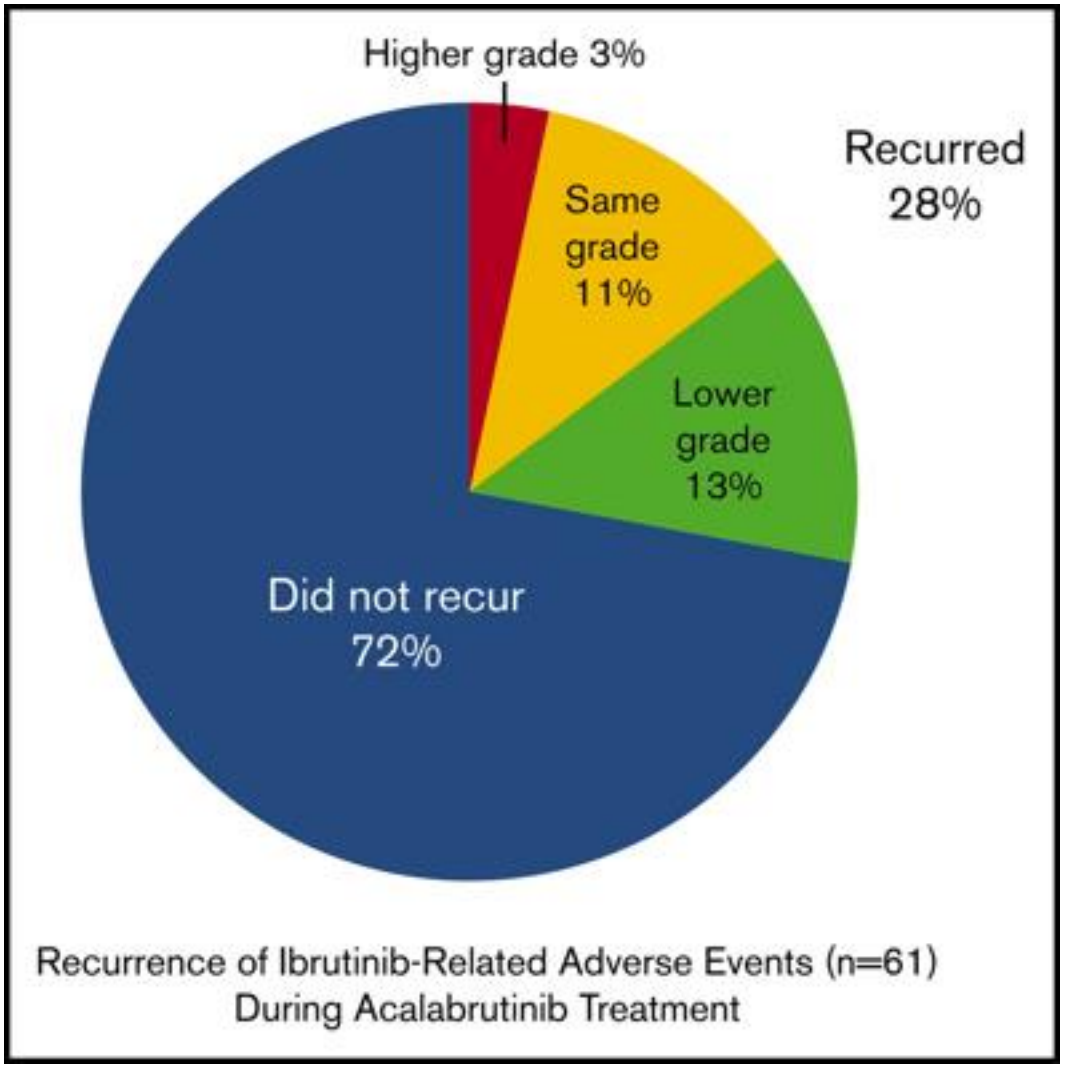
- **Intolerance:**
  - **Ibrutinib → Acalabrutinib**

Acalabrutinib Monotherapy In 33 CLL Patients Intolerant To Ibrutinib



Awan et al. Blood Advances 2019

Acalabrutinib Monotherapy In 33 CLL Patients Intolerant To Ibrutinib

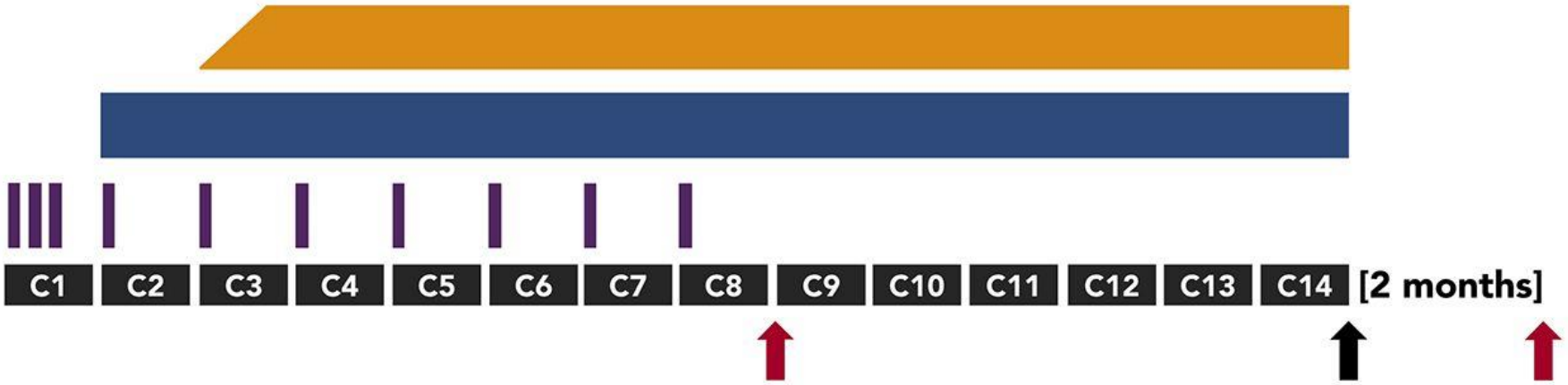


Awan et al. Blood Advances 2019

Novel Agents in Combination

- Monoclonal antibody
- Novel agent
- Chemo-Immunotherapy
  - More efficacious than single agents?
  - Can we stop therapy at some point?

Novel Agents In Combination



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

†Venetoclax dosed based on dose level.

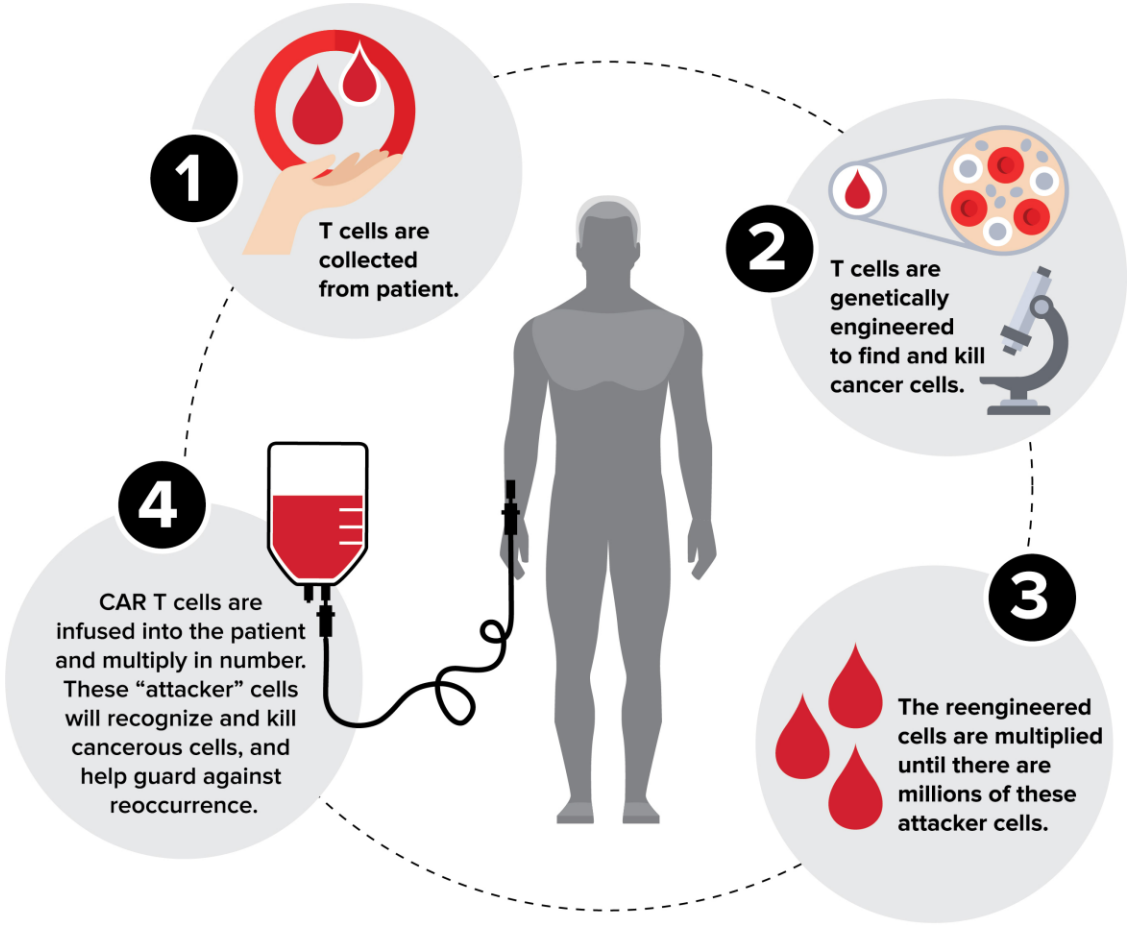
Cycle length = 28 days

Investigational Agents

Agents	MOA
Ublituximab	Anti-CD20
Acalabrutinib	Second Generation inhibitor of BTK
Zanubrutinib	Next Generation inhibitor of BTK
TGR-1202-Umbralisib	inhibitor of PI3Kδ
Copanlisib	Dual inhibitor of PI3Kδ and PI3Kα
CAR-T	chimeric antigen receptor (CAR) T-cell targeting CD19

CAR-T in CLL

The process to generate CAR-modified T cells



The Leukemia & Lymphoma Society (LLS)

Selected Trials Of Cd19-targeted CAR T Cells In CLL

Source	Institution	Number of patients with CLL	Costimulatory domain	Lymphodepletion regimen	Dose (cells/kg)	ORR (%, by iwCLL criteria)	CR (%, by iwCLL criteria)
Autologous							
Kalos et al. (2011)	Penn	3	4-1BB	Bendamustine (n = 1) Bendamustine/rituximab (n = 1) Pentostatin/Cyclophosphamide (n = 1)	1.46×10^5 to 1.6×10^7	3/3 (100%)	2/3 (67%)
Brentjens et al. (2011)	MSKCC	8	CD28	No conditioning (n = 3) Cyclophosphamide (n = 4)	0.4×10^7 to 1.0×10^7	1/8 (12%)	0/8 (0%)
Kochenderfer et al. (2012) and Kochenderfer et al. (2015)	NCI	8	CD28	Fludarabine/cyclophosphamide (n = 8)	1.0×10^6 to 5.5×10^7	7/8 (87%)	4/8 (50%)
Porter et al. (2014)	Penn	14	4-1BB	Fludarabine/cyclophosphamide (n = 3) Pentostatin/Cyclophosphamide (n = 5) Bendamustine (n = 6)	0.14×10^8 to 11×10^8	8/14 (58%)	4/14) (29%)
Porter et al. (2016)	Penn	13	4-1BB	Fludarabine/cyclophosphamide (n = 13)	5.0×10^7	4/13 (31%)	1/13 (8%)
		17		Fludarabine/cyclophosphamide (n = 17)	5.0×10^8	9/17 (53%)	6/17 (35%)
Turtle et al., (2016) and Turtle et al. (2017)	FHCRC	24	4-1BB	Fludarabine (n = 2) Cyclophosphamide (n = 1) Fludarabine/cyclophosphamide (n = 21)	2.0×10^5 to 2.0×10^7	14/19 (74%)	4/19 (21%)
Siddiqi et al. (2018)[a]	Multicenter	16	4-1BB	Fludarabine/cyclophosphamide (n = 10)	5.0×10^7 to 1.0×10^8	13/15 (87%)	7/15(47%)
Gill et al. (2018)[b]	Penn	14	4-1BB	Fludarabine/cyclophosphamide (n = 14)	1.0×10^8 to 5.0×10^8	10/14 (71%)	6/14 (43%)
Gauthier et al. (2018)[b]	FHCRC	17	4-1BB	Fludarabine/cyclophosphamide (n = 17)	2.0×10^6	14/16 (88%)	NR
Allogeneic							
Brudno et al. (2015) and Brudno et al. (2016)	NCI	5	CD28	None	0.4×10^6 to 8.2×10^6	8/20 (40%)	4/20 (20%)

Abbreviations: CR, complete response; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; NR, not reported; ORR, overall response rate.
[a]CAR T cell product designed to contain 1:1 ratio of CD8+ and CD4+ cells.
[b]Indicates combined treatment with ibrutinib.

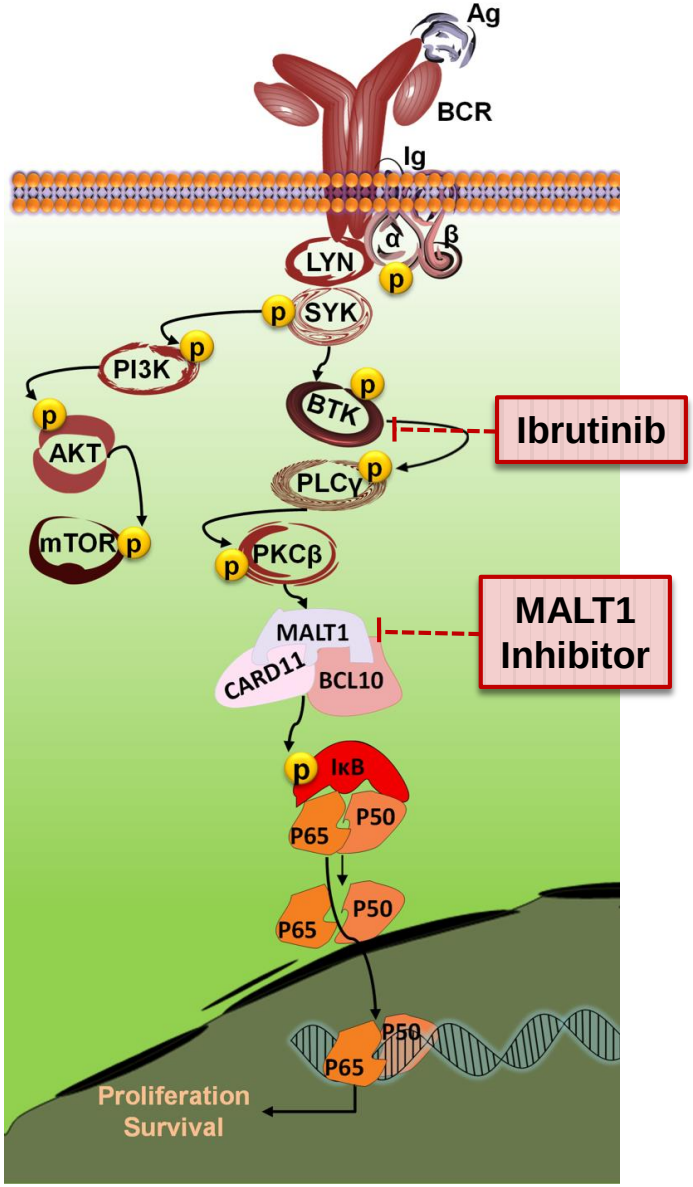
Modified from Bair & Potter, AJH 2019

Selected Trials Of Cd19-targeted CAR T Cells In CLL

Modified from Bair & Potter, AJH 2019

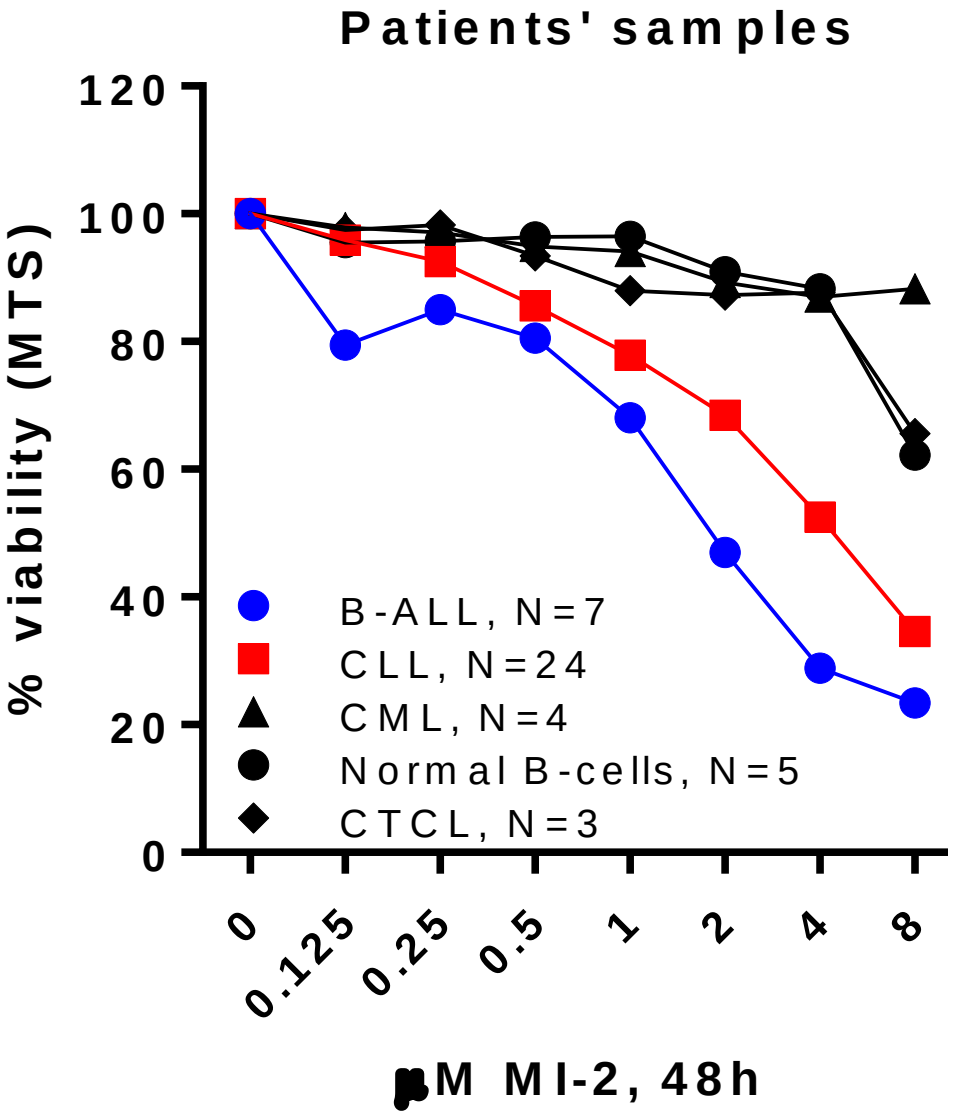
ORR (%, by iwCLL criteria)	CR (%, by iwCLL criteria)
3/3 (100%)	2/3 (67%)
1/8 (12%)	0/8 (0%)
7/8 (87%)	4/8 (50%)
8/14 (58%)	4/14) (29%)
4/13 (31%)	1/13 (8%)
9/17 (53%)	6/17 (35%)
14/19 (74%)	4/19 (21%)
13/15 (87%)	7/15(47%)
10/14 (71%)	6/14 (43%)
14/16 (88%)	NR
8/20 (40%)	4/20 (20%)

Mutations In *BTK* (C481S) And *PLCG2* (R665W, L845F) Induce Resistance To Ibrutinib

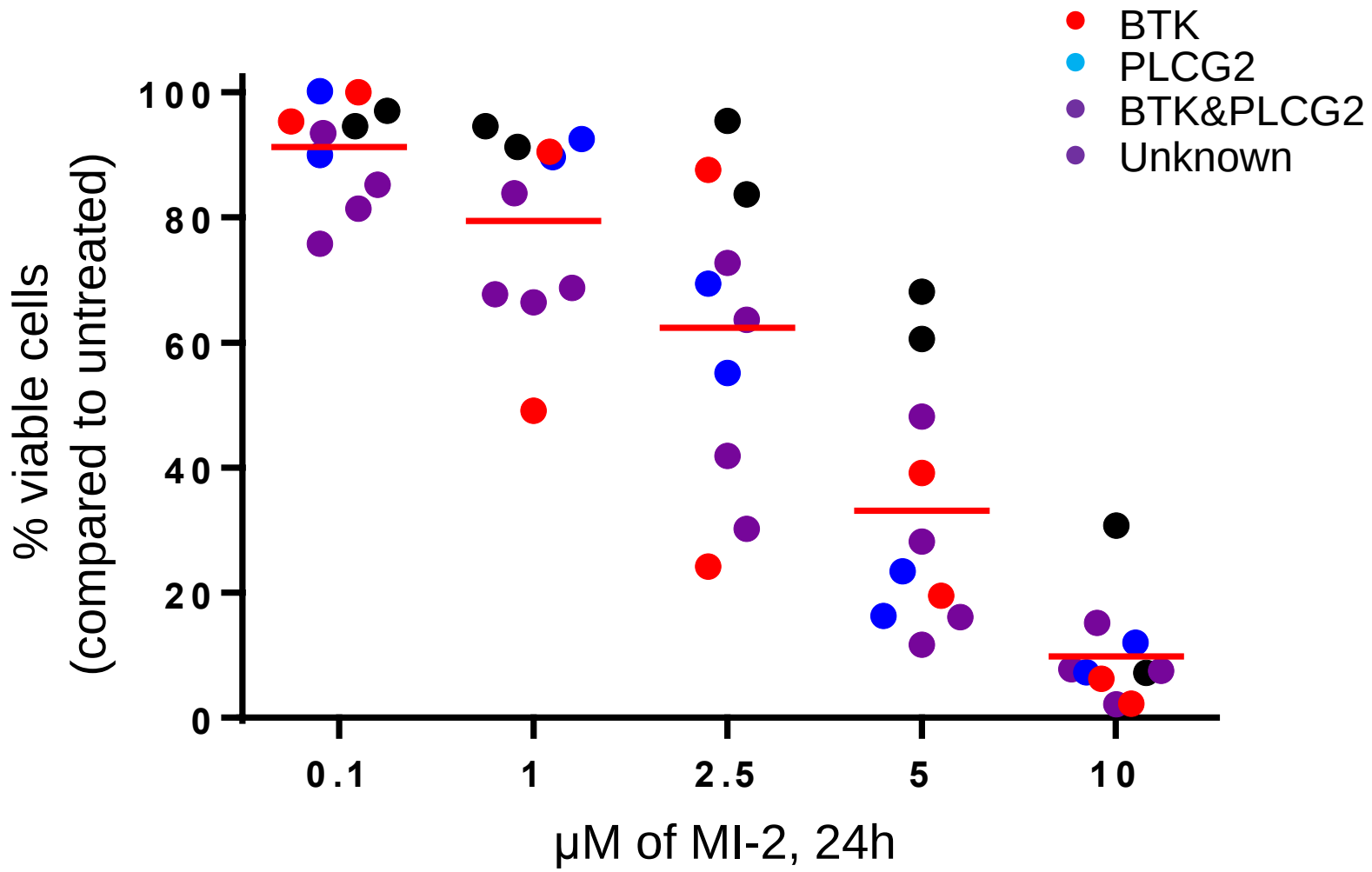


Modified from Saba & Wiestner. Curr Opin Hematol. 2014

CLL Patients' Samples Depend On MALT1 For Survival

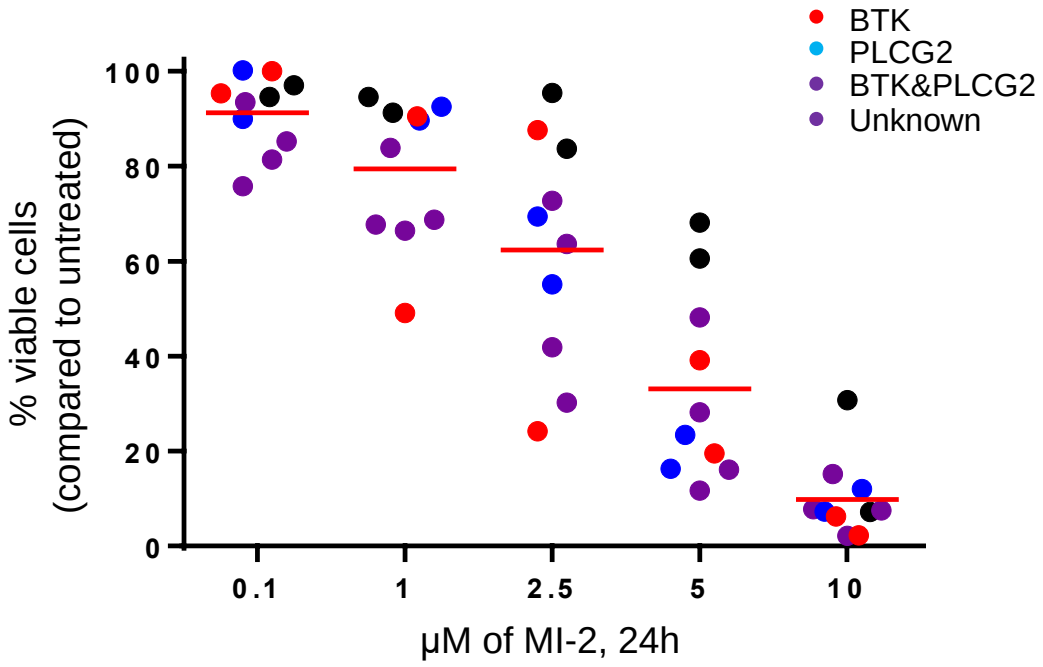


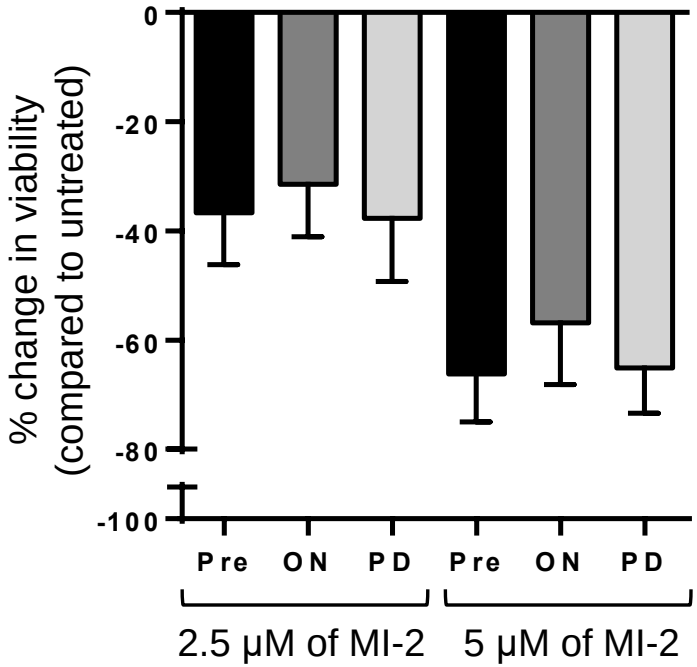
MALT1 Inhibition Overcomes Ibrutinib's Resistance



Saba et al. Cancer Research 2017

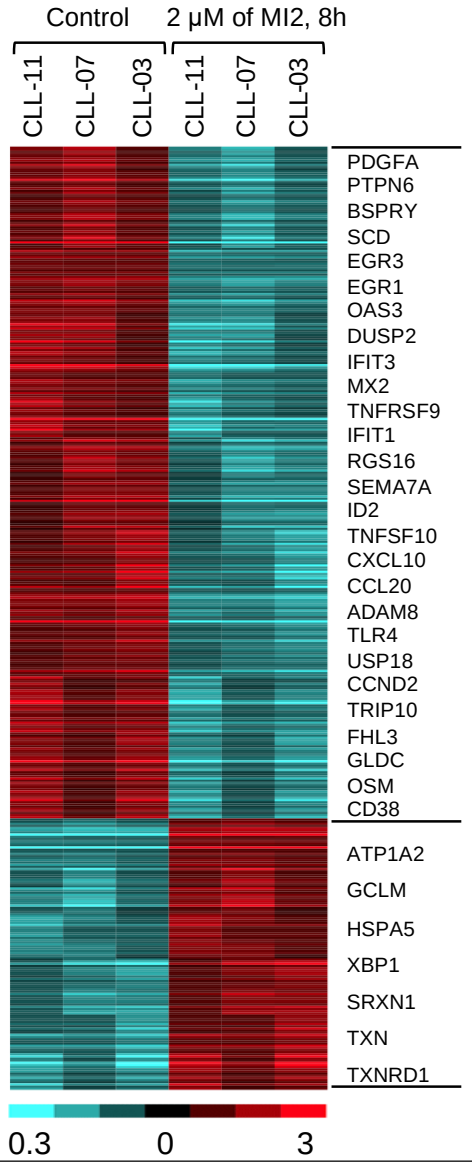
MALT1 Inhibition Overcomes Ibrutinib's Resistance





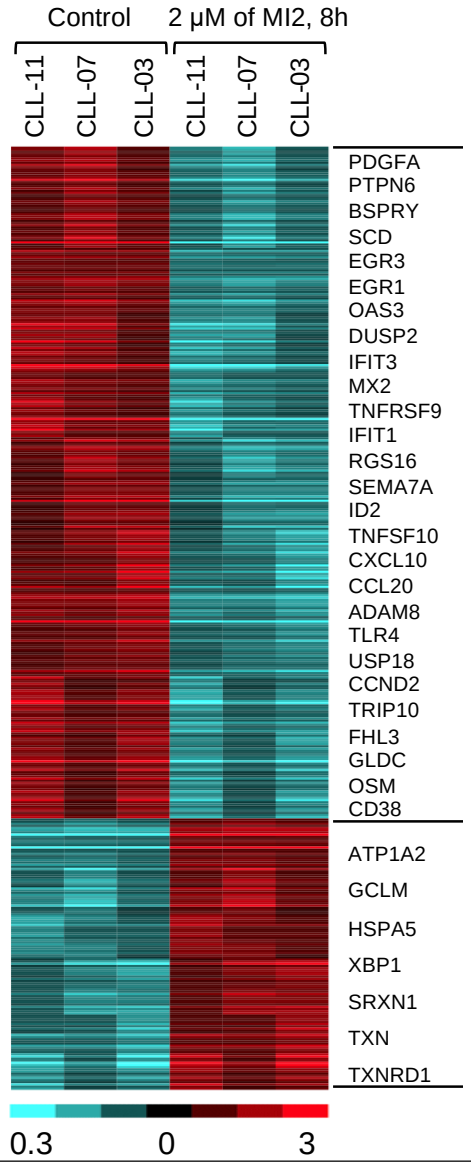
Saba et al. Cancer Research 2017

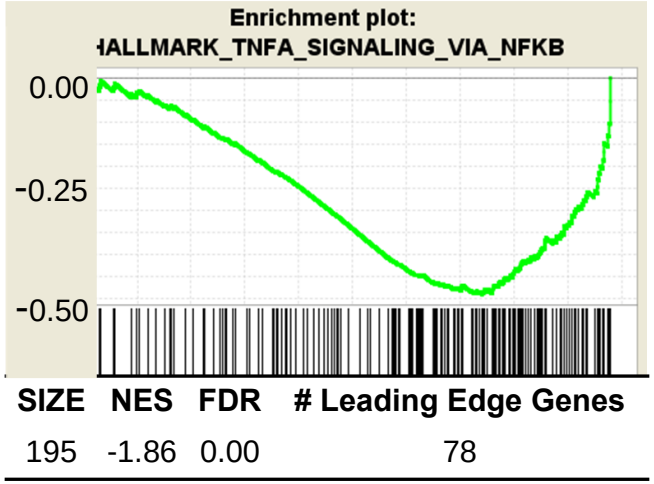
MALT1 Inhibition Disrupts NF-κB Signaling And Multiple Biologic Networks In CLL

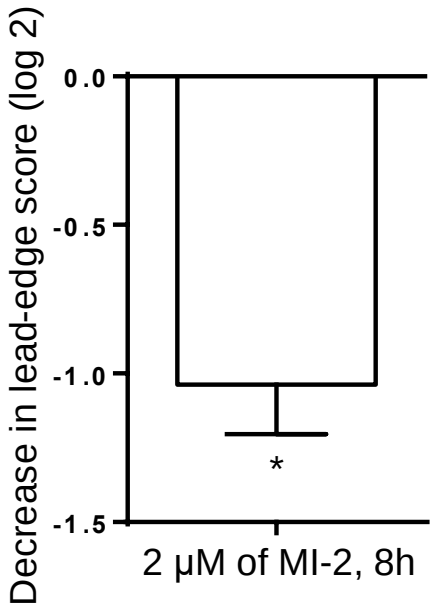


Saba et al. Cancer Research 2017

MALT1 Inhibition Disrupts NF-κB Signaling And Multiple Biologic Networks In CLL

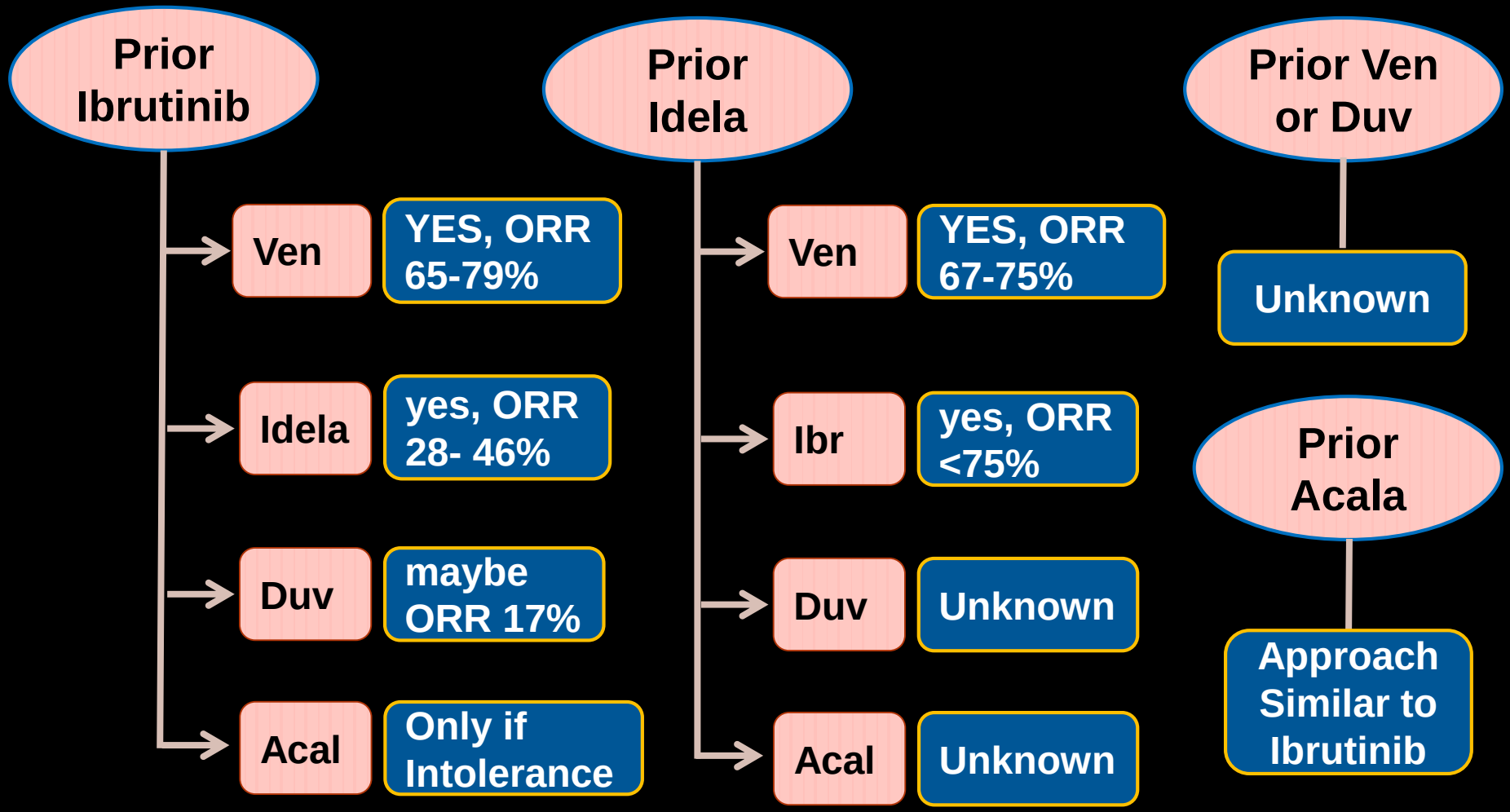




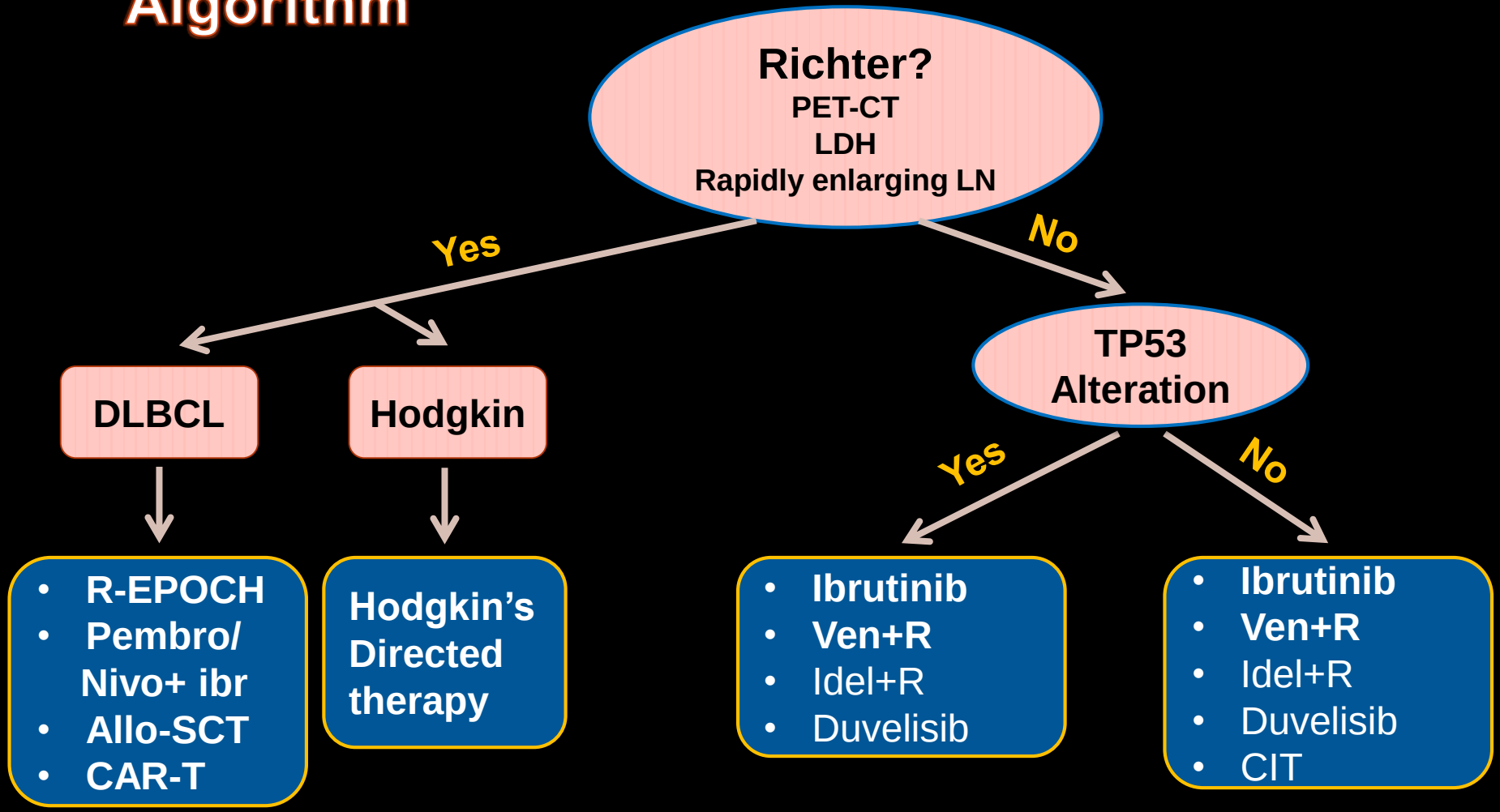


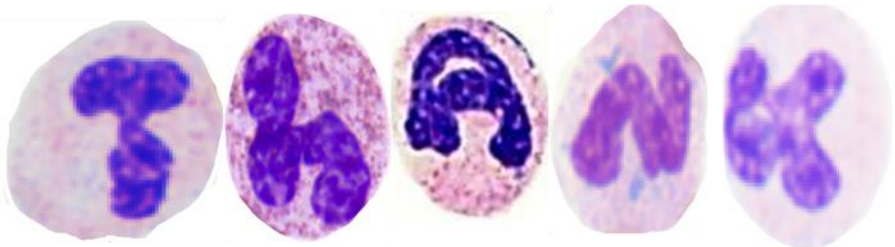
Saba et al. Cancer Research 2017

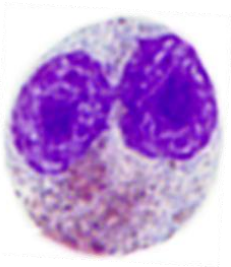
Sequencing Novel Agents At Progression



R/R CLL Treatment Algorithm







nsaba@tulane.edu
Clinic: 504-988-6460
Cell: 423-946-1366

	IBRUTINIB	VEN/R	IDELA+R	DUVELISIB
Target	BTK	BCL-2	PI3K-δ	PI3K-δ,γ
Route	Oral	Oral	Oral	Oral
Trial Type	Phase 3	Phase 3	Phase 3	Phase 3
Duration of therapy	Indefinite	2 years	Indefinite	1.5 years
Prophylaxis	None	None	PJP	PJP
Comparator	Ofa	BR	Placebo+R	Ofa
N	391	389	220	319
17p and/or TP53 (%)	51	38	43.2	31
# prior therapies, median	3	1	3	2
Median Follow-up (m)	44	23.8	18	22.4
ORR (CR)	91 (9)	92.3 (26.8)	85.5 (0.9)	73.8 (0.6)
mPFS	NR	NR	20.3	17.6 (IRC13.3)
mPFS (17p)	40.1	NR	18.7	13.8 (IRC12.7)
1Y OS (%)	90	93.3	89.3	86
2Y OS(%)	82	91.9	69.8	N/A
mOS	NR	NR	40.6	NR
mOS (17p)	NR	NR	28.5	NR
Disc. From AEs (%)	12	12.9	8.1	35

Summary of key adverse events related to targeted agents studied in CLL

Ibrutinib			Idelalisib				Venetoclax			Duvelisib
RES	RES17	RES2	Furman	Jones	O'Brien	Lampson	Roberts	Stilgenbauer	Seymour	DUO
195	145	135	110	173	64	24	116	107	49	319
RR	RR	**TN**	RR	RR	**TN**	**TN**	RR	RR	RR	RR
67	64	73	71	68	71	67	66	67	75	69
9	28	18	4*	16	22*	15	21	12	28	22.4
—	17p	—	+R	+Ofa	+R	+Ofa	—	17p	+R	—
ade 3-4)										
22 /16	NR/22	16/10	55/34	35/35	53/28	46/29	45/41	43/40	66/53	33/30
23/5	26/10	19/6	25/5	23/14	23/3	8/4	25/12	27/18	24/14	23/13
17/6	NR/11	<15/2	17/10	14/11	14/2	8/0	21/12	19/15	27/17	15/8
% grade 3-4)										
44/1	16/9	15/4	NR	NR/2	NR/3	NR	NR	NR	NR/4	NR
5/3	NR/7	6/2	7/NR	NR/2	NR	NR	NR	NR/2	6/NR	NR
10/-	27/13	14/4	NR	13/5	NR	8/4	NR	6/4	8/NR	NR
23/4	14/5	17/4	NR	NR	NR	13/13	48/1	72/19	82/16	69/NR
10/7	25/13	15/4	6/NR	20/14	28/19	13/13	NR/4	9/5	16/6	18/14
NR	NR	NR	NR/0	6/5	19/3	13/8	NR 4	NR	NR	NR/3
48/4	41/3	42/4	19/4	54/19	64/42	46/ 21	52/2	29/0	57/2	51/15
NR	NR/<1	NR	35/5	47/ 12	67/23	79/54	NR	1/1	7/3	NR/3
NR	NR/<1	NR	NR	NR/<1	NR	NR	4/3	5/5	10/4	NR

Ahn et al. Hematology ASH Educ Program 2017