Selection and Sequencing of Therapies for Relapsed/Refractory CLL

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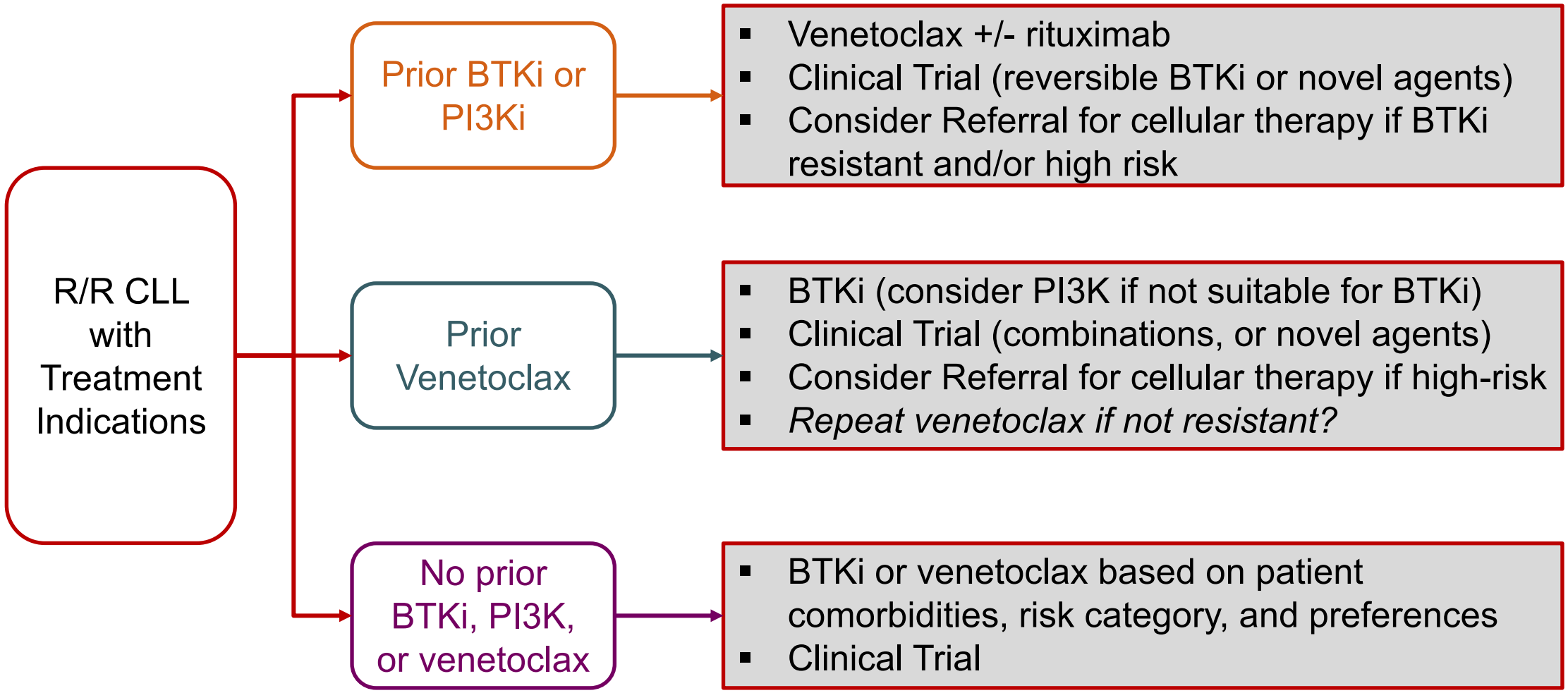
Treatment Selection in R/R CLL

- Targeted agents now preferred over chemoimmunotherapy
- Several classes of approved agents
  - BCL2 inhibitors: venetoclax +/- rituximab
  - BTK inhibitors: ibrutinib, acalabrutinib
  - PI3K inhibitors: idelalisib + rituximab, duvelisib
- Major questions
  - Which is most effective?
  - What side effect profile might be best for my patient?
  - Does the order these drugs are given in matter?

Courtesy of Kerry Rogers, MD

Decision Scheme in R/R CLL in 2020



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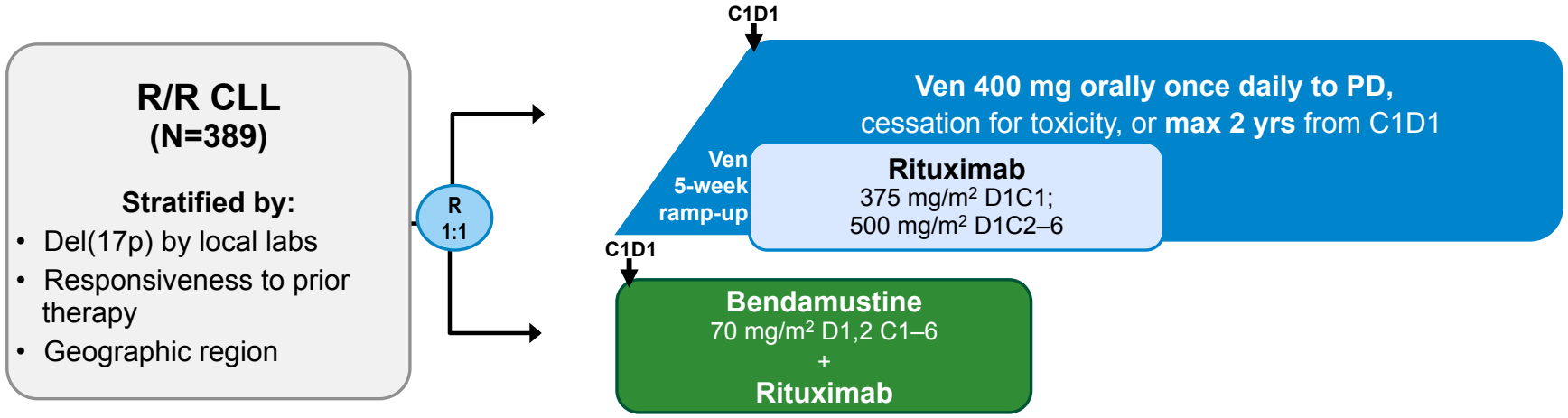
The MURANO Study (venetoclax + rituximab)

- Phase 3 study comparing venetoclax + rituximab (VenR) to BR
- High fraction with del17p (40.4% in VenR, 44.1% BR)
  - Prior chemotherapy >90% both arms
  - Prior BCRi exposure low (1.5% VenR, 2.6% BR)



- Primary endpoint: investigator-assessed PFS; secondary endpoints include rate of undetectable MRD (uMRD)

Seymour JF et al. ASH 2018. Abstract 184. Seymour JF, et al. *New Eng J Med.* 2018;378:1107-20.

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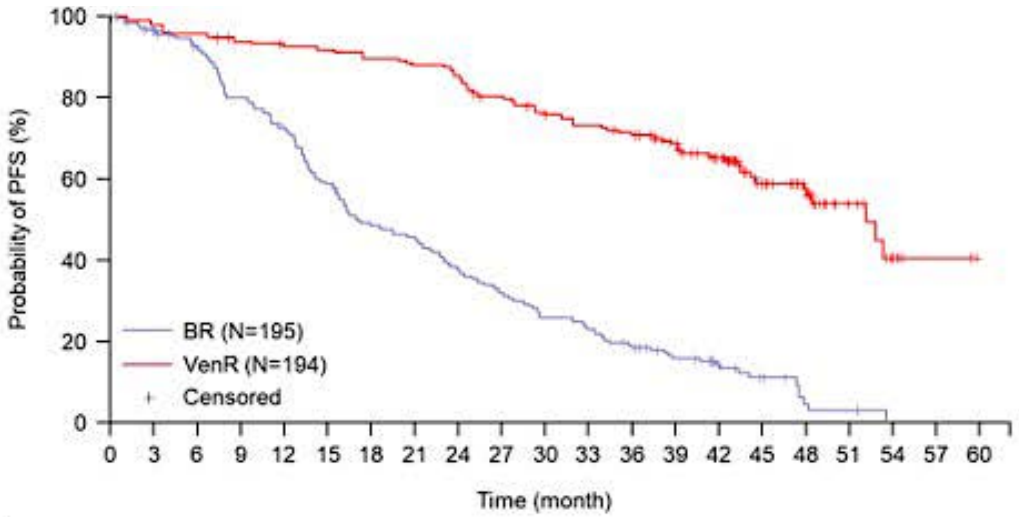
MURANO Study 4-year follow-up

Progression-Free Survival

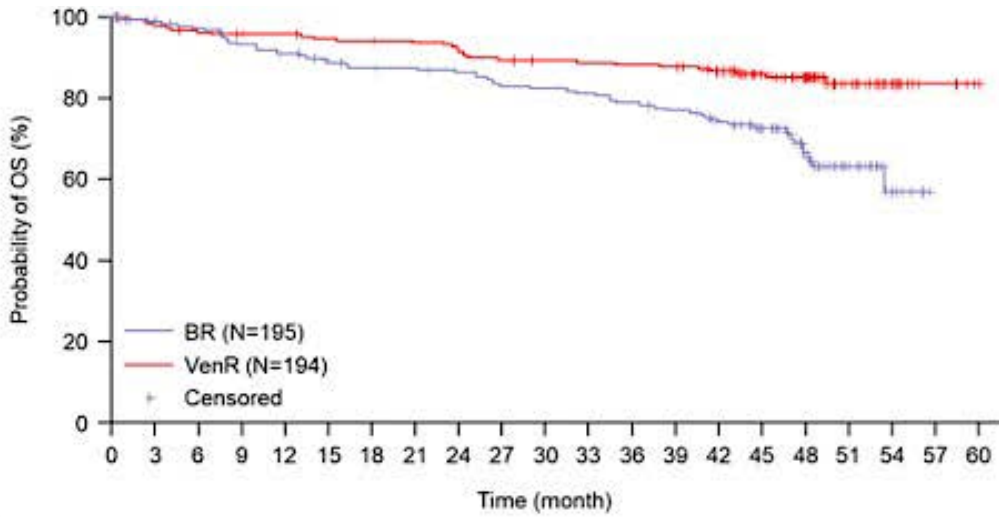


No. of patients at risk:

BR	195	178	165	143	129	104	85	80	66	56	45	40	32	23	14	9	3	2	
VenR	194	190	185	179	176	174	170	167	161	150	141	134	130	118	101	55	40	14	7	2

BR, bendamustine plus rituximab; ITT, intention to treat; PFS, progression-free survival; VenR, venetoclax plus rituximab

Overall Survival



No. of patients at risk:

BR	195	181	175	167	162	155	152	150	147	141	140	138	134	130	116	94	58	29	7					
VenR	194	190	185	183	182	179	178	176	173	168	166	165	164	163	154	110	84	34	15	6	1

BR, bendamustine plus rituximab; ITT, intention to treat; OS, overall survival; VenR, venetoclax plus rituximab

	VenR (n = 194)	BR (n = 195)	HR (95% CI)	P Value
4-yr PFS, %	57.3	4.6	0.19 (0.14-0.25)	< .0001
4-yr OS, %	85.3	66.8	0.41 (0.26-0.65)	< .0001

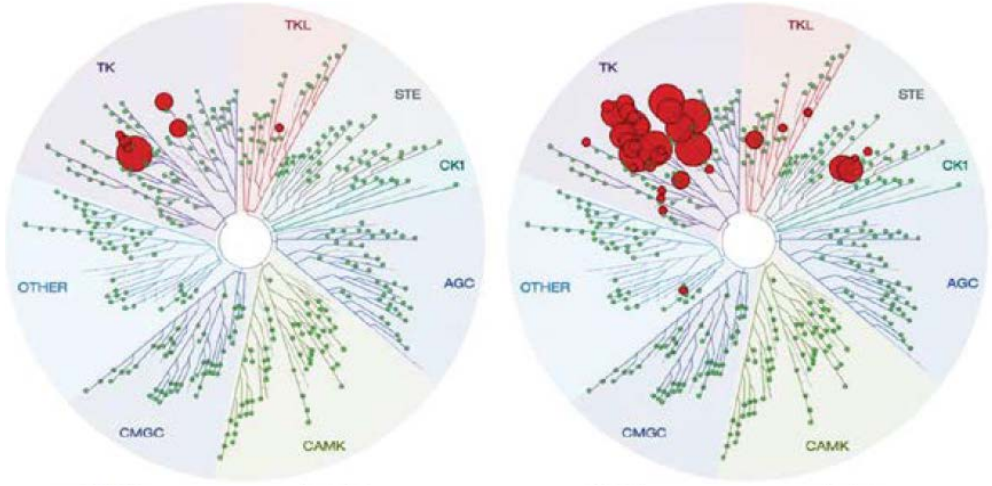
Seymour JF et al. ASH 2019. Abstract 134.

Courtesy of Kerry Rogers, MD

Approved BTKi: Ibrutinib & Acalabrutinib

- Both inhibit BTK by covalently binding to the C481 residue of BTK
- Mechanisms of resistance are the same (BTK and PLCg2 mutations)
- Acalabrutinib is more selective

Acalabrutinib **Ibrutinib**



Larger red circles represent stronger inhibition
(Kinase Selectivity Profiling at 1 μM)

Kinase Inhibition
Average IC_{50} (nM)

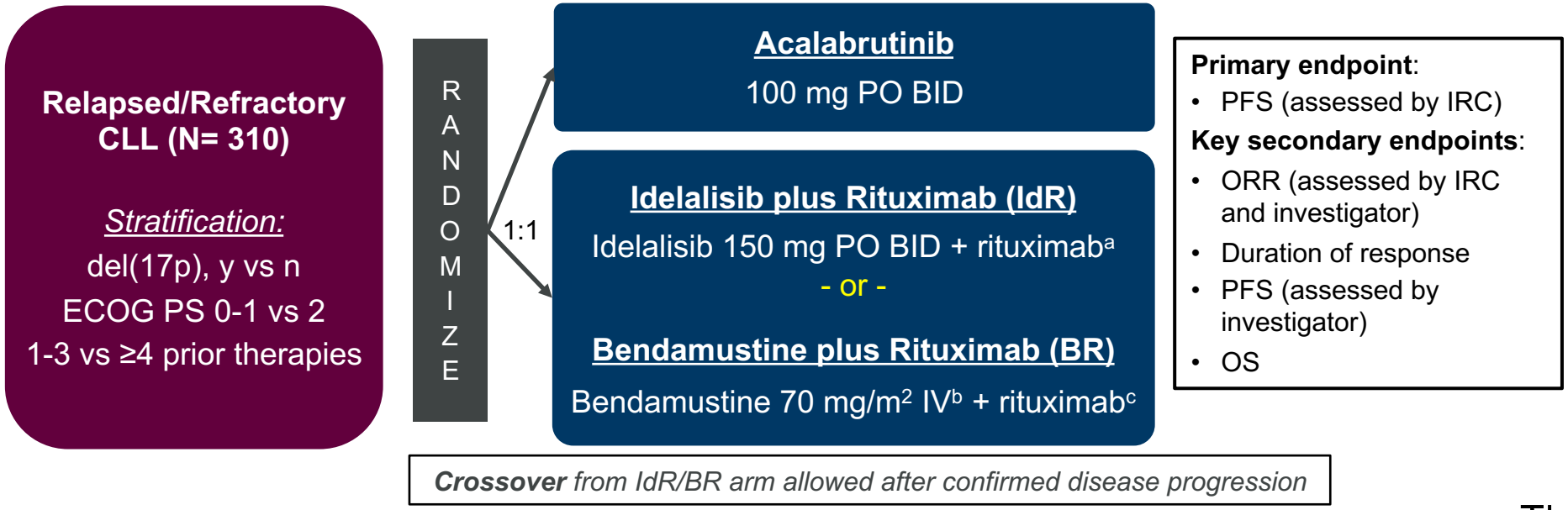
Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	126.0	10.0
ITK	>1000	4.9
BMX	46.0	0.8
TXK	368.0	2.0
EGFR	>1000	5.3
ERBB2	~1000	6.4
ERBB4	16	3.4
BLK	>1000	0.1
JAK3	>1000	32

Woyach et al., ASH 2017; Woyach et al., ASH 2019

Courtesy of Kerry Rogers, MD

Phase 3 Study of Acalabrutinib in R/R CLL (ASCEND)

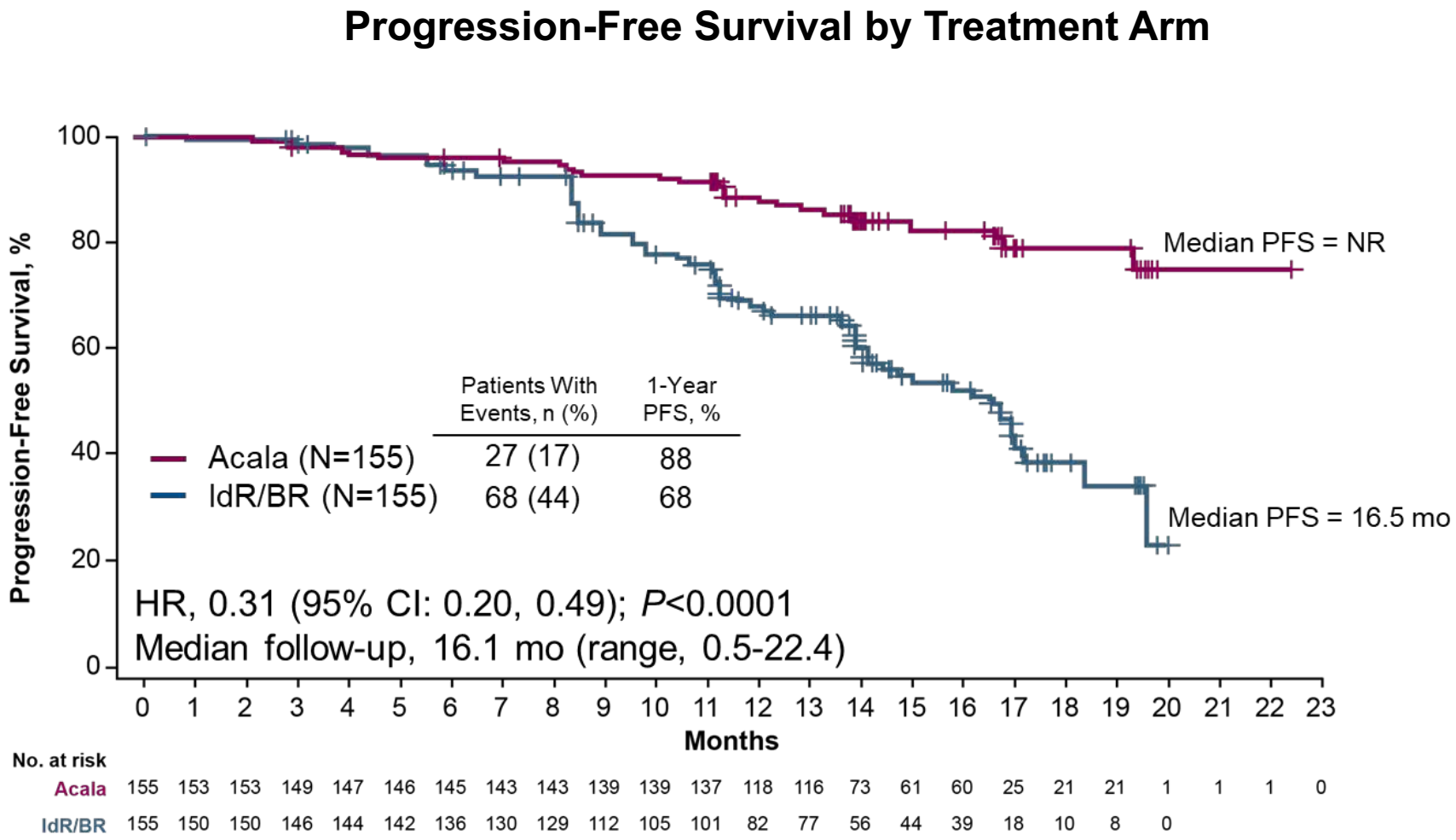
- Phase 3 study comparing acalabrutinib to investigator's choice of BR or IdR
- Comparator arm treatment
  - 36 (23%) BR
  - 118 (77%) Idelalisib + rituximab (IdR)



Ghia et al., EHA 2019

Courtesy of Kerry Rogers, MD

ASCEND Primary Endpoint



Ghia et al., EHA 2019

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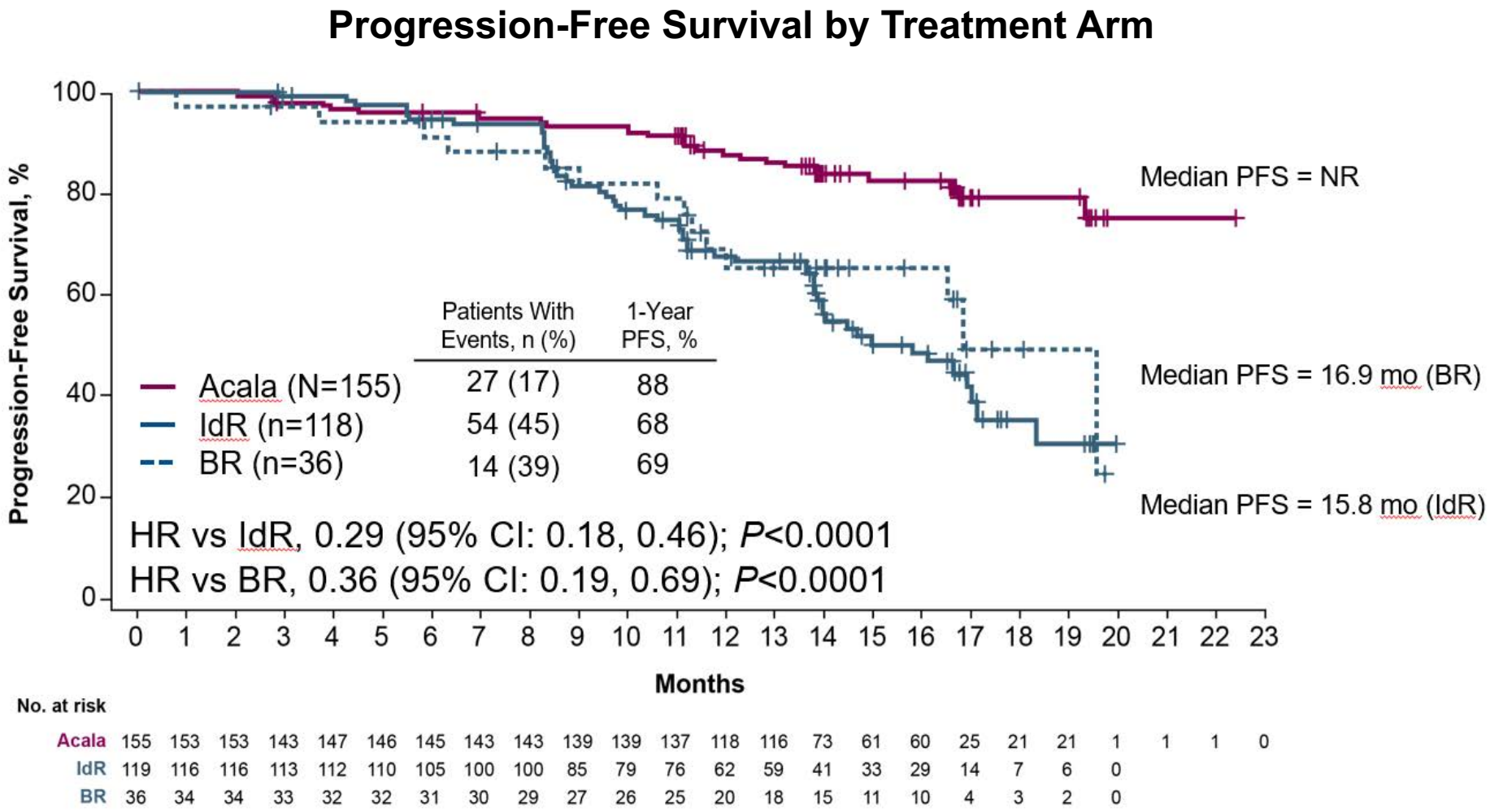
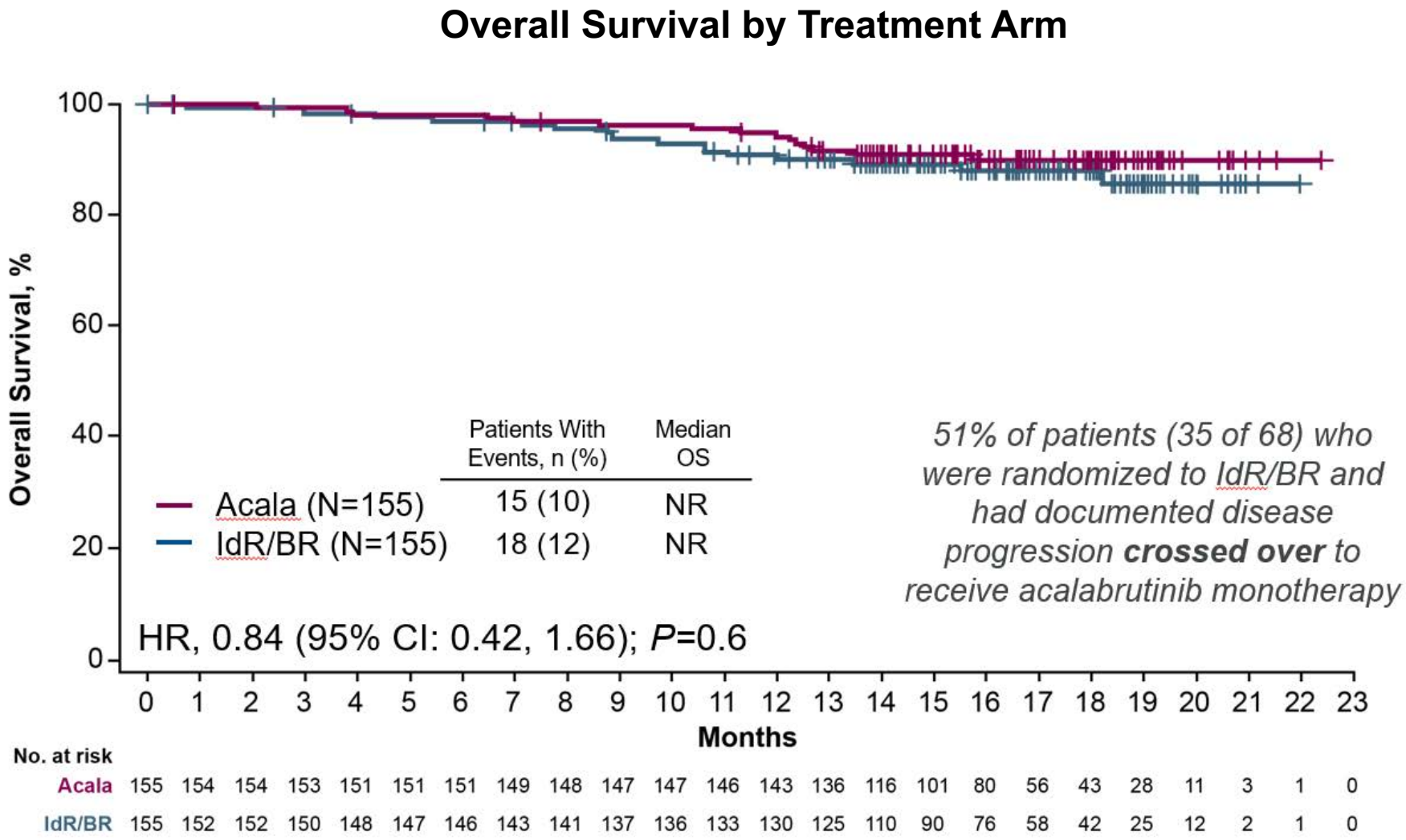
ASCEND PFS w/ Breakdown by Standard Treatment



Ghia et al., EHA 2019

Courtesy of Kerry Rogers, MD

ASCEND Overall Survival



Ghia et al., EHA 2019

Courtesy of Kerry Rogers, MD

ASCEND Most Frequent AEs (≥15%)

	Acalabrutinib n=154		IdR n=118		BR n=35	
AEs, n (%)	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Headache	34 (22)	1 (1)	7 (6)	0	0	0
Neutropenia	30 (19)	24 (16)	53 (45)	47 (40)	12 (34)	11 (31)
Diarrhea	28 (18)	2 (1)	55 (47)	28 (24)	5 (14)	0
Anemia	23 (15)	18 (12)	10 (8)	8 (7)	4 (11)	3 (9)
Cough	23 (15)	0	18 (15)	1 (1)	2 (6)	0
Pyrexia	19 (12)	1 (1)	21 (18)	8 (7)	6 (17)	1 (3)
Fatigue	15 (10)	2 (1)	10 (8)	0	8 (23)	1 (3)
Nausea	11 (7)	0	15 (13)	1 (1)	7 (20)	0
IRR	NA	NA	9 (8)	2 (2)	8 (23)	1 (3)

- 11% discontinued acalabrutinib due to an AE compared to 49% IdR and 17% BR
- Grade 3 or 4 AEs were highest with IdR (86% vs 45% acalabrutinib, 43% BR)
- Grade 5 AEs were similar: 4% acalabrutinib, 5% IdR, and 6% BR

Ghia et al., EHA 2019

Courtesy of Kerry Rogers, MD

ASCEND: Acalabrutinib AEs of Special Interest

	Acalabrutinib n=154		IdR n=118		BR n=35	
AEs, n (%)	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Cardiovascular AEs: Atrial fibrillation	8 (5)	2 (1)	4 (3)	1 (1)	1 (3)	1 (3)
Cardiovascular AEs: Hypertension	5 (3)	3 (2)	5 (4)	1 (1)	0	0
Bleeding	40 (26)	3 (2)[a]	9 (8)	3 (3)[b]	2 (6)	1 (3)[c]
Infections	87 (56.5)	23 (14.9)	77 (65.3)	33 (28.0)	17 (48.6)	4 (11.4)
SPM, excluding NMSC	10 (6)[d]	5 (3)	3 (3)	0	1 (3)	1 (3)

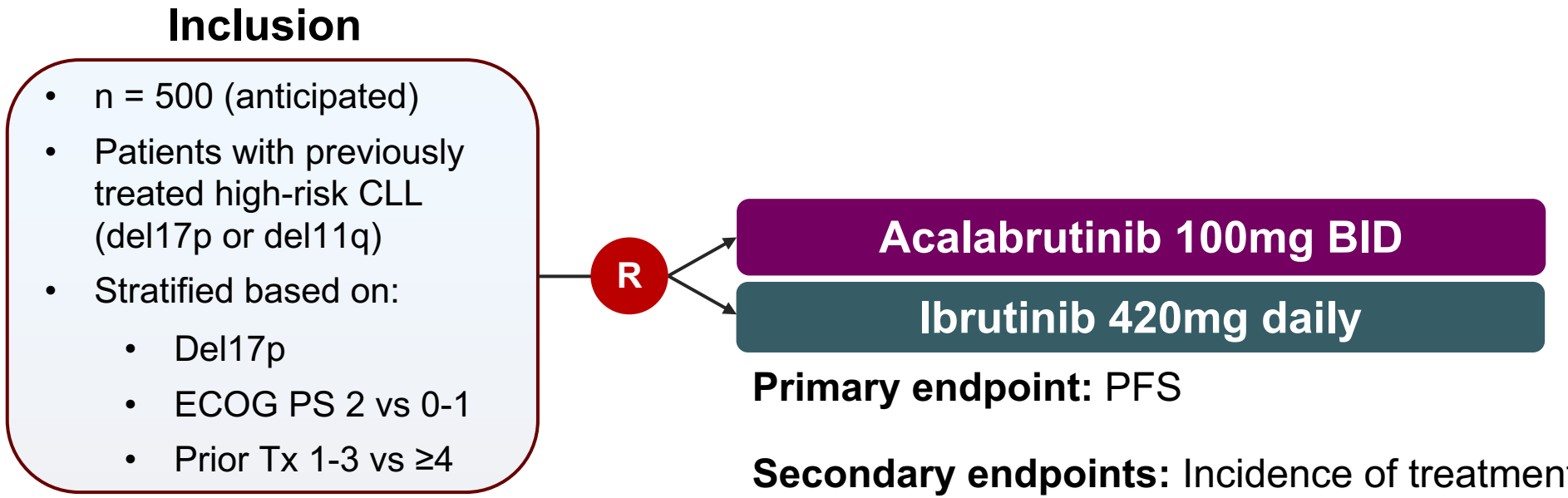
- Atrial fibrillation and hypertension occur at a high frequency with ibrutinib
- Bleeding complications are common with BTKi

Ghia et al., EHA 2019

Courtesy of Kerry Rogers, MD

ELEVATE-RR: Ibrutinib vs Acalabrutinib

- Ongoing randomized phase 3 study in high-risk R/R CLL
- The primary hypothesis is acalabrutinib is non-inferior to ibrutinib for PFS
- Will show differences in AEs between arms



Primary endpoint: PFS

Secondary endpoints: Incidence of treatment-emergent Grade ≥3 infections; incidence of Richter's transformation; incidence of atrial fibrillation; and overall survival

Estimated study completion date: March 2021

Clinicaltrals.gov (NCT02477696)

Courtesy of Kerry Rogers, MD

The PI3K Inhibitors

	Idelalisib	Duvelisib	*Umbralisib*
Isoform Specificity	**δ**	**δ/γ**	**δ**
Approval	▪ R/R CLL in combination with rituximab ▪ R/R SLL CLL after ≥2 prior treatments	▪ R/R CLL after ≥2 prior treatments	*Currently being investigated in combination trials*
Phase 3 Trial	▪ **Median PFS not Reached** ▪ R-Placebo 5.5 mo ▪ HR 0.15, P<0.001	▪ **Median PFS 13.3 months** ▪ Ofatumumab 9.9 mo ▪ HR 5 0.52, P<.0001	
Major Toxicities	▪ Colitis ▪ Pneumonitis ▪ Hepatitis ▪ Infections	▪ Infection ▪ Colitis ▪ Rash ▪ Pneumonitis	

Furman et al., NEJM 2014; Flinn et al., Blood 2018

Courtesy of Kerry Rogers, MD

Venetoclax After BTKi or PI3Ki

- Phase 2 study of continuous venetoclax monotherapy after BCRi
- Reported by most recent prior BCRi
- Ibrutinib Patients (n=91)
  - Median prior Tx = 4
  - 12% prior idelalisib
  - Median PFS = 24.7 months
  - Estimated 12-mo PFS = 75%
- Idelalisib Patients (n=36)
  - Median prior Tx = 3
  - 28% prior ibrutinib
  - Median PFS = NR
  - Estimated 12-month PFS = 79%

Jones et al., Lancet Oncology 2018; Coutre et al., Blood 2018

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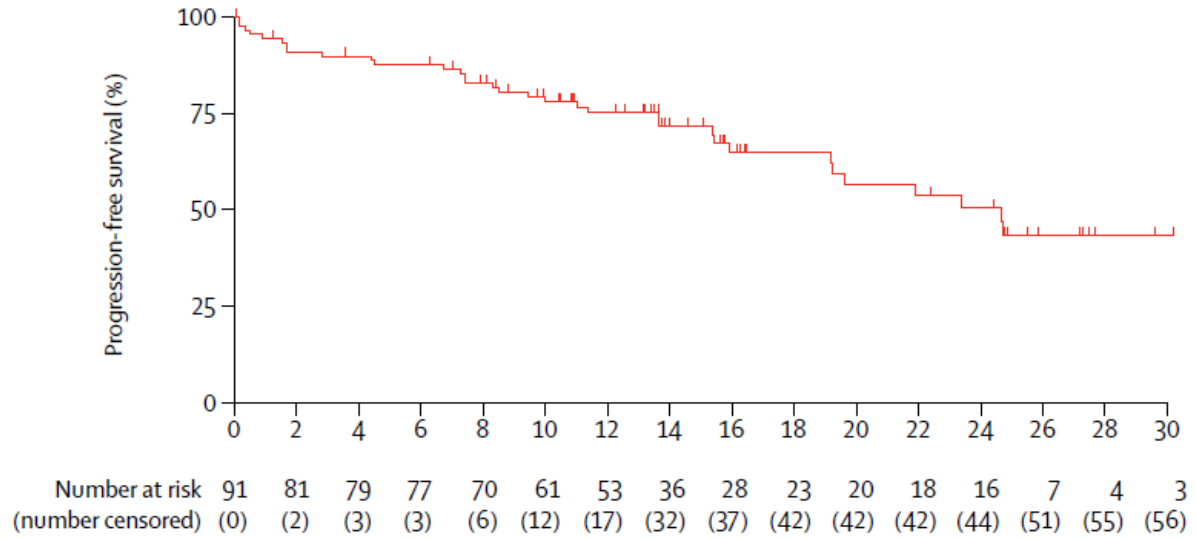
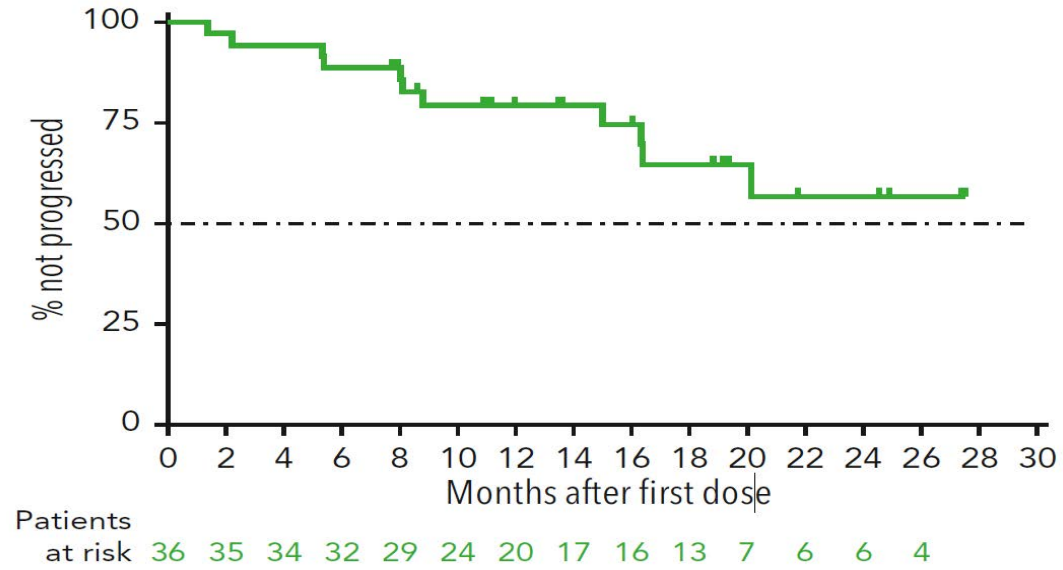
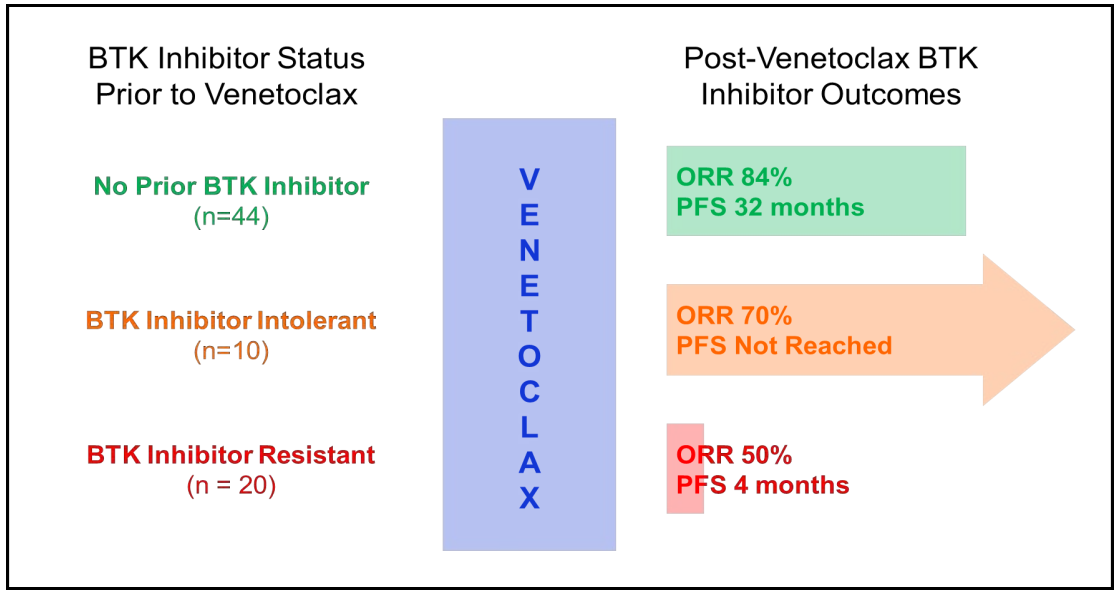
PFS – Ibrutinib Patients



PFS – Idelalisib Patients



Ibrutinib After Venetoclax?



- Multi-institution cohort study of venetoclax discontinuation (n=326; BTKi n=74)
  - BTKi were effective if not previously resistant
- (MURANO Study Subsequent BTKi Treatment (n=12)
  - BTKi 10/10 (100%) evaluable responded
  - Venetoclax re-treatment 6/11 (55%) evaluable

Mato et al., Clinical Cancer Research 2020; Seymour JF et al. ASH 2019. Abstract 134.

Courtesy of Kerry Rogers, MD

Case 1: 78 y/o man with R/R CLL

- 2006 – Presented with fatigue
  - Diagnosed with CLL by peripheral blood flow
  - FISH +del11q, normal karyotype
- April 2007 – FCR x6
  - Required treatment due to enlarged lymph nodes
  - Tolerated well with no hospitalizations
  - Platelets remained around 100k after treatment
  - Followed on observation

PHM/PSH:
Osteoarthritis
Type 2 DM
Prostate Cancer
s/p prostatectomy
s/p BCC removal
Meds:
Metformin
Tamsulosin
Allergies:
Sitagliptin
Social:
Never smoker
No alcohol use
Widowed and with a new partner
Family:
CLL

Courtesy of Kerry Rogers, MD

Case 1: 78 y/o man with R/R CLL

- December 2013 – BR x6
  - Again developed enlarged lymph nodes
  - Tolerated treatment well
  - Observed after treatments
- January-October 2017
  - WBC increased from 17.7 k/uL to 93.7 k/uL
  - Repeat FISH: +del17p
  - Discussed treatment options

PHM/PSH:
Osteoarthritis
Type 2 DM
Prostate Cancer
s/p prostatectomy
s/p BCC removal
Meds:
Metformin
Tamsulosin
Allergies:
Sitagliptin
Social:
Never smoker
No alcohol use
Widowed and with a new partner
Family:
CLL

Courtesy of Kerry Rogers, MD

Case 1: 78 y/o man with R/R CLL

- October 2017
  - Screened for a clinical trial but was found to have a new lung nodule concerning for stage 1 lung cancer
  - Lung cancer successfully resected
- December 2017
  - Started ibrutinib
- October 2020
  - Doing well in clinical remission
  - Mild joint pain and nail changes from ibrutinib

PHM/PSH:
Osteoarthritis
Type 2 DM
Prostate Cancer
Lung Cancer
s/p RUL lobectomy
s/p prostatectomy
s/p BCC removal

Meds:
Metformin
Tamsulosin

Allergies:
Sitagliptin

Social:
Never smoker
No alcohol use
Widowed and with a new partner

Family:
CLL

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Case 2: 53 y/o woman with R/R CLL

- 2007 – Lymphocytosis noted on routine CBC
  - Diagnosed by peripheral blood flow
  - Observed
- June 2011 – FCR x5
  - Treatment started due to LAD
  - IGHV indeterminate, FISH panel negative
  - Stopped after 5 cycles due to prolonged neutropenia
  - Observed after treatment
- January 2015
  - Again noted enlarging lymph nodes
  - Repeat FISH panel +del17p
  - Discussed treatment options

PHM/PSH:
Depression
Hypertension
Insomnia
Endometriosis
s/p tubal ligation
s/p cholecystectomy
s/pORIF R ankle

Meds:
Lisinopril
Sertraline
Valacyclovir

Allergies:
Trimethoprim-sulfamethoxazole

Social:
Never smoker
No alcohol use
Married
Social worker

Family:
Hypertension

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Case 2: 53 y/o woman with R/R CLL

- March 2015 – Started ibrutinib 420mg
  - Lymph nodes improved
  - Some diarrhea and arthritis
- May 2015 – Developed painful skin nodules
  - Biopsy proven panniculitis
  - Recurred after several courses of prednisone 20mg
  - Did not improve with dose reduction to 280mg
  - Ibrutinib discontinued
- December 2015
  - Developed debilitating fatigue, night sweats, and enlarging lymph nodes
  - Testing for BTK mutations showed BTK C481S mutation
  - Discussed treatment options

PHM/PSH:
Depression
Hypertension
Insomnia
Endometriosis
s/p tubal ligation
s/p cholecystectomy
s/pORIF R ankle

Meds:
Lisinopril
Sertraline
Valacyclovir

Allergies:
Trimethoprim-sulfamethoxazole

Social:
Never smoker
No alcohol use
Married
Social worker

Family:
Hypertension

Courtesy of Kerry Rogers, MD

Case 2: 53 y/o woman with R/R CLL

- January 2016 – Started acalabrutinib
  - All symptoms improved
  - Developed a few non-painful skin nodules
  - Good disease response
- October 2018 – Progressive disease
  - Developed enlarged lymph nodes and night sweats
  - ALC increased
  - Discussed treatment options
- October 2018 – Started venetoclax
  - Good response of the CLL
  - Chronic diarrhea impairing her lifestyle
- October 2020 – Progressive disease

PHM/PSH:
Depression
Hypertension
Insomnia
Endometriosis
s/p tubal ligation
s/p cholecystectomy
s/pORIF R ankle

Meds:
Lisinopril
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Allergies:
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Family:
Hypertension

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