Memorial Sloan Kettering Cancer Center

Drivers of treatment patterns in patients stopping Ibrutinib, idelalisib or venetoclax

ANTHONY MATO, MD MSCE

MEMORIAL SLOAN KETTERING CANCER CENTER

Anthony Mato - Disclosures

- Research
  - TG Therapeutics
  - Pharmacyclics
  - Abbvie
  - Johnson and Johnson
  - Acerta / AZ
  - Regeneron
  - DTRM BioPharma
  - Sunesis
  - Loxo
- Advisory / Consultancy
  - TG Therapeutics
  - Pharmacyclics
  - Abbvie
  - Johnson and Johnson
  - Acerta / AZ
  - DTRM BioPharma
  - Sunesis
  - Celgene
  - Verastem

2013-2019: a period of exciting transformation

- Several novel agents have been approved since 2013.
- **Ibrutinib +/- Obin** approved for all settings (relapsed, refractory, front-line).
- **Idelalisib + rituximab** approved for relapsed disease.
- **Duvelisib** approved in r/r setting (2 prior therapies)
- **Venetoclax** +/- CD20 approved in the front line and r/r settings.

New challenges have emerged as (1) none of these strategies are curative (2) AEs are significant drivers of discontinuation (3) limited understanding of molecular (BTK / BCL2) resistance (4) what factors to consider in selecting therapies in previously exposed to novel agents

Understanding treatment patterns following first novel agents has not been well-studied

- **Few prospective studies** comparing novel agents to clinically relevant controls and to one another
- **Follow-up** once subjects are censored is lacking.
- Data on sequencing novel agents / chemotherapy have been extrapolated from **retrospective cohort studies** and observational registries conducted in the real world setting with **noted limitations**.
- Outcomes rarely stratified by **reason for discontinuation** of prior novel agent – but this matters!

Goal: *To discuss "drivers" of treatment patterns in patients who discontinue ibrutinib, idelalisib and venetoclax stratified by line of therapy and reason for discontinuation.*

Outline

- Discuss discontinuation **rates** of novel agents in front line and relapse
- Discuss discontinuation **patterns** of novel agents including ibrutinib, idelalisib and venetoclax
- Discuss why **reason for discontinuation** is an important driver of treatment patterns following ibrutinib, idelalisib and venetoclax
- Propose a **sequencing algorithm** that takes into account **novel agent history** and **reason for discontinuation**

What is driving the discontinuation of current novel agents?

Ibrutinib, Idelalisib, Venetoclax

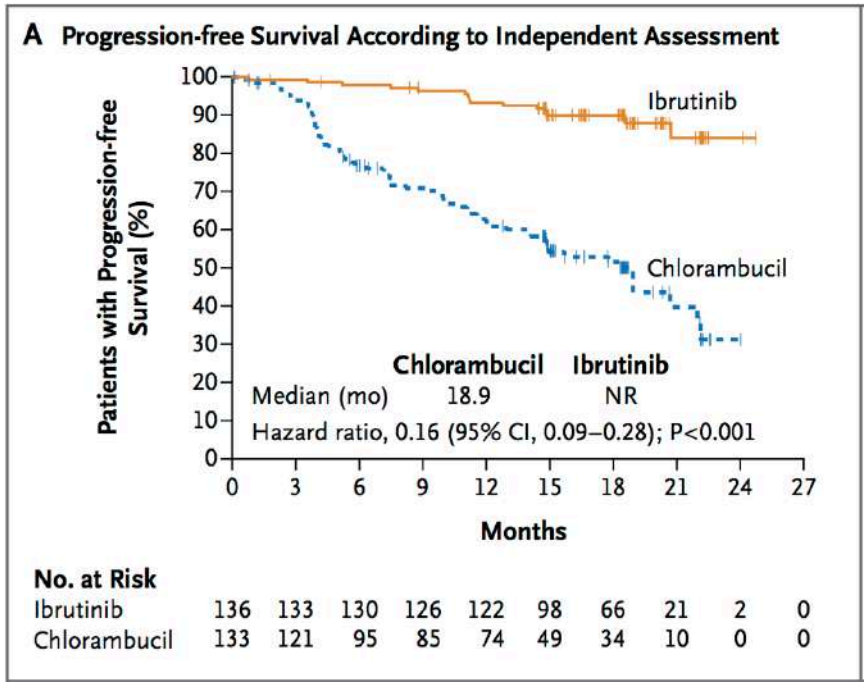
4 major reasons…AE, CLL progression, RT, completion of planned therapy (in the case of Ven)

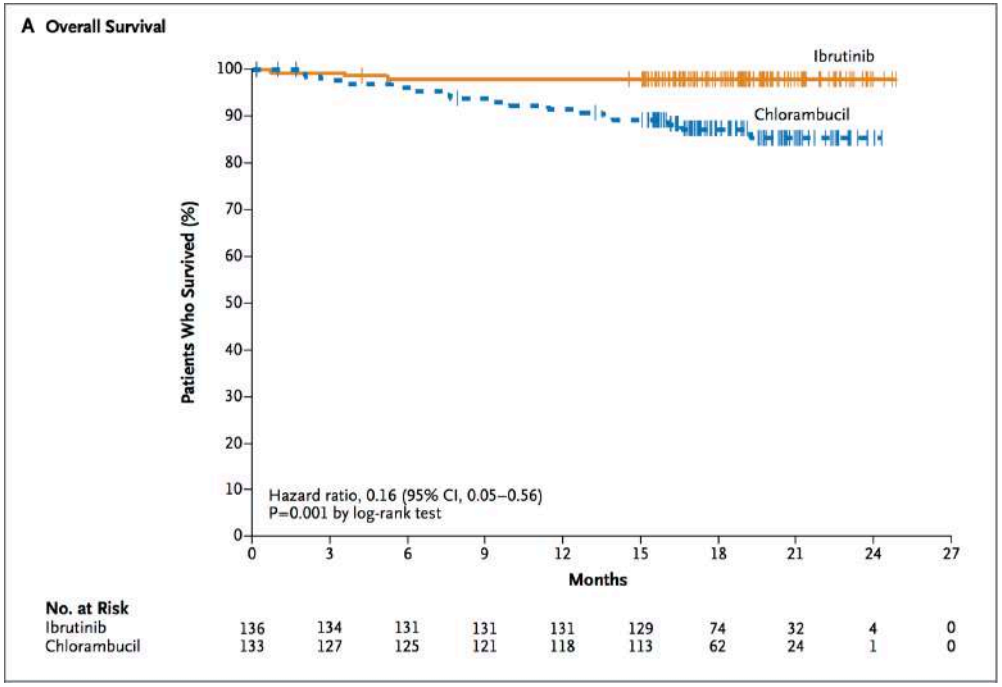
Ibrutinib and Idelalisib

ORIGINAL ARTICLE

Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia

J.A. Burger, A. Tedeschi, P.M. Barr, T. Robak, C. Owen, P. Ghia, O. Bairey, P. Hillmen, N.L. Bartlett, J. Li, D. Simpson, S. Grosicki, S. Devereux, H. McCarthy, S. Coutre, H. Quach, G. Gaidano, Z. Maslyak, D.A. Stevens, A. Janssens, F. Offner, J. Mayer, M. O'Dwyer, A. Hellmann, A. Schuh, T. Siddiqi, A. Polliack, C.S. Tam, D. Suri, M. Cheng, F. Clow, L. Styles, D.F. James, and T.J. Kipps, for the RESONATE-2 Investigators*





Discontinuation rate = 12.5%, most common reason AEs

Chronic lymphocytic leukemia

Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study

Jan A. Burger[1] · Paul M. Barr[2] · Tadeusz Robak[3] · Carolyn Owen[4] · Paolo Ghia[5] · Alessandra Tedeschi[6] · Osnat Bairey[7] · Peter Hillmen[8] · Steven E. Coutre[9] · Stephen Devereux[10] · Sebastian Grosicki[11] · Helen McCarthy[12] · David Simpson[13] · Fritz Offner[14] · Carol Moreno[15] · Sandra Dai[16] · Indu Lal[16] · James P. Dean[16] · Thomas J. Kipps[17]

Table 2 Duration of treatment with first-line ibrutinib

	Ibrutinib $n = 136$
Median (range) duration of ibrutinib treatment, months[a]	57.1 (0.7–66.0)
Treatment duration, *n* (%)	
>3 years	99 (73)
>4 years	88 (65)
>5 years	37 (27)
Continuing ibrutinib on study, *n* (%)	79 (58)
Continuing on commercial ibrutinib, *n* (%)	0 (0)
Discontinued ibrutinib, *n* (%)	56 (41)
Adverse event	29 (21)
Progressive disease	8 (6)
Death	8 (6)
Withdrawal by patient	7 (5)
Investigator decision	4 (3)

52%

Outcomes following ibrutinib discontinuation

Outcomes following discontinuation of first-line ibrutinib treatment are shown in Supplementary Table 2. Median OS following discontinuation was not reached (range, 0–64+ months) in patients who discontinued ibrutinib because of AEs ($n = 29$). Only eight patients discontinued ibrutinib because of PD (including two patients due to Richter's transformation); of these patients, 50% are still alive or had exited study with no known death at the data cut. The median OS following ibrutinib discontinuation due to PD was 20 months (range, 1+ to 28 months). Median PFS for patients who were in CR/CRi at ibrutinib discontinuation was 56 months (95% CI: 44, NE) compared with 33 months (95% CI: 26, 46) for patients who were not CR/CRi at ibrutinib discontinuation (HR [95% CI]: 0.390 [0.118, 1.285]).

Of patients with available follow-up data after ibrutinib discontinuation, 14 patients received subsequent therapy for CLL, including standard chemoimmunotherapy (FCR, BR, or GC) ($n = 8$), chemotherapy ($n = 3$), and novel agents ($n = 3$). Of nine patients with best overall response to subsequent therapy reported, seven responded, one had stable disease, and one had PD. Eleven of the 14 patients remained alive at last follow-up, two patients withdrew consent, and one patient died.

42% discontinuation rate at 5 years, most common reason AE, limited data on next therapies

American Journal of Hematology AJH

RESEARCH ARTICLE | Full Access

Outcomes of front-line ibrutinib treated CLL patients excluded from landmark clinical trial

Anthony R. Mato, Lindsey E. Roeker, John N. Allan, John M. Pagel ... See all authors

RWE: Discontinuation rate and reasons for discontinuation in the front line setting

TABLE 2 Ibrutinib dosing and dose adjustments

	All patients	Age <65 years	del(17p13) present	RESONATE-2 published data
Initial dose <420 mg	7.6%	2.5%	7.2%	0%
Requiring dose reduction to achieve stable dose without further adjustment	17.4%	13.1%	16.3%	Not reported
Requiring temporary dose interruption while on therapy	42%	35.9%	41.9%	Not reported
Median time of dose interruption	12 days	10 days	12 days	Not reported

TABLE 4 Reasons for discontinuation (% patients who discontinued)

	All patients	Age < 65 years	del(17p13) present	RESONATE-2 published data
Discontinuation rate	24% (94 events/391 total)	23% (36 events/159 total)	33% (35 events/110 total)	12.5% (17 events/135 total)
Median time to discontinuation	6.5 months	11.5 months	6.25 months	Not reported
Reasons for discontinuation As (%) of all discontinuation events				
Toxicity / AEs	59.5%	55.5%	40%	64.7% (11/17)
CLL progression	12.8%	16.6%	14.2%	11.8% (2/17)
Transformation	9.6%	11.1%	25.7%	0%
Patient preference	7.4%	2.8%	2.9%	5.9% (1/17)
Death not secondary to CLL or AE	3.2%	2.8%	0%	17.6% (3/17)
Other	3.2%	2.8%	5.7%	0%
Allo-SCT	2.1%	5.6%	5.7%	0%
CAR-T	1.1%	2.8%	2.9%	0%
Cost	1.1%	0%	2.9%	0%
Second malignancy	0%	0%	0%	0%

Long-term safety of single-agent ibrutinib in patients with chronic lymphocytic leukemia in 3 pivotal studies

Steven E. Coutre,[1] John C. Byrd,[2] Peter Hillmen,[3] Jacqueline C. Barrientos,[4] Paul M. Barr,[5] Stephen Devereux,[6] Tadeusz Robak,[7] Thomas J. Kipps,[8] Anna Schuh,[9] Carol Moreno,[10] Richard R. Furman,[11] Jan A. Burger,[12] Michael O'Dwyer,[13] Paolo Ghia,[14] Rudolph Valentino,[15] Stephen Chang,[15] James P. Dean,[15] Danelle F. James,[15] and Susan M. O'Brien[16]

Table 2. Treatment exposure and reasons for discontinuation in integrated safety analysis

	Ibrutinib (N = 330)
Treatment exposure	
Exposure, median (range), mo	29.0 (0.2-42.9)
Duration of treatment, mo	
≤6	32 (10)
>6 to 12	18 (5)
>12 to 24	34 (10)
>24 to 36	193 (58)
>36	53 (16)
Treatment discontinuation	124 (38)
PD	52 (16)
AE	37 (11)
Death	18 (5)
Physician decision	9 (3)
Withdrawal by patient	8 (2)

Unless otherwise noted, all data are n (%).

CLINICAL TRIALS AND OBSERVATIONS

Outcomes of CLL patients treated with sequential kinase inhibitor therapy: a real world experience

Anthony R. Mato,[1,*] Chadi Nabhan,[2,*] Paul M. Barr,[3] Chaitra S. Ujjani,[4] Brian T. Hill,[5] Nicole Lamanna,[6] Alan P. Skarbnik,[7] Christina Howlett,[7] Jeffrey J. Pu,[8] Alison R. Sehgal,[9] Lauren E. Strelec,[1] Alexandra Vandegrift,[1] Danielle M. Fitzpatrick,[1] Clive S. Zent,[3] Tatyana Feldman,[7] Andre Goy,[7] David F. Claxton,[8] Spencer Henick Bachow,[6] Gurbakhash Kaur,[10] Jakub Svoboda,[1] Sunita Dwivedy Nasta,[1] David Porter,[1] Daniel J. Landsburg,[1] Stephen J. Schuster,[1] Bruce D. Cheson,[4] Pavel Kiselev,[11] and Andrew M. Evens[10]

Ibrutinib/idelalisib dosing information		
Number (patients)	143	35
Median time from CLL diagnosis to KI start	84 mo	81 mo
Median time on KI	5 mo (0.25-41)	5.5 mo (0.5-38)
Median starting dose	420 mg daily	150 mg bid
Proportion requiring dose modification	18% (n = 141)	35% (n = 34)
Proportion requiring dose interruption	43% (n = 96)	64% (n = 33)
KI administered as monotherapy	85%	20%

Table 3. Most common reasons for KI discontinuation in patients who have discontinued ibrutinib or idelalisib

	Ibrutinib % (n)	Idelalisib % (n)
Toxicity	51 (73)	52 (18)
CLL progression	28 (40)	31 (11)
RT	8 (11)	6 (2)
Cellular therapies (chimeric antigen receptor T cells or allogeneic stem cell transplantation)	2 (3)	0 (0)
Unrelated death/Other	11 (16)	11 (4)

95% discontinuation rate = idelalisib

Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis

Anthony R. Mato,[1] Chadhi Nabhan,[2] Meghan C. Thompson,[1] Nicole Lamanna,[3] Danielle M. Brander,[4] Brian Hill,[5] Christina Howlett,[6,7] Alan Skarbnik,[7] Bruce D. Cheson,[8] Clive Zent,[9] Jeffrey Pu,[10] Pavel Kiselev,[11] Andre Goy,[7] David Claxton,[10] Krista Isaac,[12] Kaitlin H. Kennard,[1] Colleen Timlin,[1] Daniel Landsburg,[1] Allison Winter,[5] Sunita D. Nasta,[1] Spencer H. Bachow,[3] Stephen J. Schuster,[1] Colleen Dorsey,[1] Jakub Svoboda,[1] Paul Barr[13]* and Chaitra S. Ujjani[8]*

EHA EUROPEAN HEMATOLOGY ASSOCIATION

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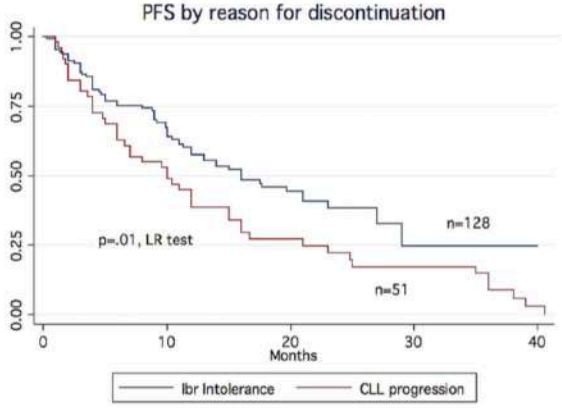

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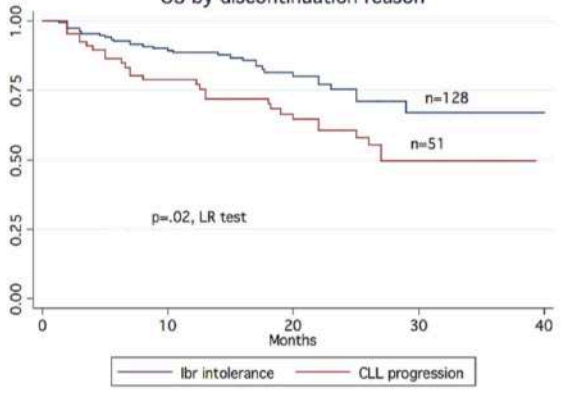


Table 2. Reasons for Ibrutinib discontinuation.

Reason for Ibrutinib discontinuation	Ibrutinib in front-line (n=19)	Ibrutinib in relapse (n=231)
Toxicity	63.1% (n=12)	50.2% (n=116)
CLL progression	15.8% (n=3)	20.9% (n=49)
Other/unrelated death	5.3% (n=1)	12.1% (n=28)
Physician's or patient's preference	10.5% (n=2)	6.7% (n=15)
RT DLBCL	5.3% (n=1)	4.6% (n=10)
Stem cell transplantation/CAR T-cell	0	3.3% (n=8)
Financial concerns	0	0.8% (n=2)
Secondary malignancy	0	0.8% (n=2)
RT Hodgkin lymphoma	0	0.4% (n=1)

CLL: chronic lymphocytic leukemia; RT DLBCL: Richter transformation to diffuse large B-cell lymphoma; CAR T-cell: chimeric antigen receptor T-cell); RT: Richter transformation.

Median times to ibrutinib discontinuation stratified by toxicity	
Bleeding	8 months
Diarrhea	7.5 months
Atrial fibrillation	7 months
Infection	6 months
Arthralgia	5 months
Pneumonitis	4.5 months
Rash	3.5 months

Across clinical trials and in clinical practice **intolerance** is most common reason for discontinuation of a KI followed by CLL progression and transformation (del17p)

Hypothesis: (1) reason for discontinuation and (1) prior exposures should drive clinical decisions in terms of next therapy

Venetoclax

Comprehensive Safety Analysis of Venetoclax Monotherapy for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia

Matthew S. Davids[1], Michael Hallek[2], William Wierda[3], Andrew W. Roberts[4], Stephan Stilgenbauer[5], Jeffrey A. Jones[6], John F. Gerecitano[7], Su Young Kim[8], Jalaja Potluri[8], Todd Busman[8], Andrea Best[8], Maria E. Verdugo[8], Elisa Cerri[8], Monali Desai[8], Peter Hillmen[9], and John F. Seymour[10]

Clinical Cancer Research

Thirty-five (10%) patients discontinued venetoclax due to AEs (Supplementary Table S5). Twenty-nine patients died while on

Table 3. Cytopenias reported during venetoclax monotherapy or up to 30 days posttreatment

		Subgroups of interest	
Event, *n* (%)	**All patients *N* = 350**	**del(17p) CLL *n* = 211[a]**	**Prior BCRi *n* = 148[a]**
Neutropenia	141 (40)	83 (39)	54 (37)
Grade 3/4	128 (37)	76 (36)	47 (32)
SAE	6 (1.7)	5 (2)	2 (1.4)
Leading to dose reduction	17 (5)	13 (6)	4 (3)
Leading to dose interruption	14 (4)	10 (5)	4 (3)
Leading to discontinuation	1 (0.3)	0	0
Anemia[b]	109 (31)	62 (29)	57 (39)
Grade 3/4	60 (17)	33 (16)	33 (22)
SAE	5 (1.4)	3 (1)	1 (0.7)
Leading to dose reduction	1 (0.3)	0	1 (0.7)
Leading to dose interruption	1 (0.3)	0	0
Leading to discontinuation	0	0	0
Thrombocytopenia	74 (21)	46 (22)	34 (23)
Grade 3/4	49 (14)	30 (14)	23 (16)
SAE	6 (1.7)	5 (2)	2 (1.4)
Leading to dose reduction	3 (0.9)	2 (0.9)	0
Leading to dose interruption	8 (2)	5 (2)	3 (2)
Leading to discontinuation	2 (0.6)	2 (0.9)	0

Summary of clinical studies: Outside completion of planned therapy (Murano, CLL14), progression of disease (#1) followed by adverse event (mainly hematologic, ~ 10% of pts) are the main reasons for venetoclax discontinuation

Real-world outcomes and management strategies for venetoclax-treated chronic lymphocytic leukemia patients in the United States

Anthony R. Mato,[1] Meghan Thompson,[2] John N. Allan,[3] Danielle M. Brander,[4] John M. Pagel,[5] Chaitra S. Ujjani,[6] Brian T. Hill,[7] Nicole Lamanna,[8] Frederick Lansigan,[9] Ryan Jacobs,[10] Mazyar Shadman,[11] Alan P. Skarbnik,[12] Jeffrey J. Pu,[13] Paul M. Barr,[14] Alison R. Sehgal,[15] Bruce D. Cheson,[6] Clive S. Zent,[14] Hande H. Tuncer,[16] Stephen J. Schuster,[2] Peter V. Pickens,[17] Nirav N. Shah,[18] Andre Goy,[12] Allison M. Winter,[7] Christine Garcia,[15] Kaitlin Kennard,[2] Krista Isaac,[19] Colleen Dorsey,[2] Lisa M. Gashonia,[2] Arun K. Singavi,[18] Lindsey E. Roeker,[1] Andrew Zelenetz,[1] Annalynn Williams,[14] Christina Howlett,[12] Hanna Weissbrot,[8] Naveed Ali,[17] Sirin Khajavian,[11] Andrea Sitlinger,[4] Eve Tranchito,[7] Joanna Rhodes,[2] Joshua Felsenfeld,[3] Neil Bailey,[5] Bhavisha Patel,[20] Timothy F. Burns,[9] Melissa Yacur,[13] Mansi Malhotra,[16] Jakub Svoboda,[2] Richard R. Furman[3] and Chadi Nabhan[21]

Venetoclax discontinuations and treatment selection following venetoclax

Venetoclax was discontinued in 41 patients (29%). Progression of disease was the most common reason for discontinuation (53.8%, n=21) followed by toxicity (20.5%, n=9), two-thirds of which were hematologic. Other reasons for discontinuation included death not related to progressive disease (10.25%, n=4), second cancer (5.1%, n=2), physician/patient preference (2.5%, n=1), Richter's transformation (2.5%, n=1), and planned alternate therapy including CD19 directed chimeric antigen receptor T cells (CAR-T, 2.5%, n=1) and transplantation (2.5%, n=1).

Table 4. First treatment following venetoclax discontinuation and treatment outcomes.

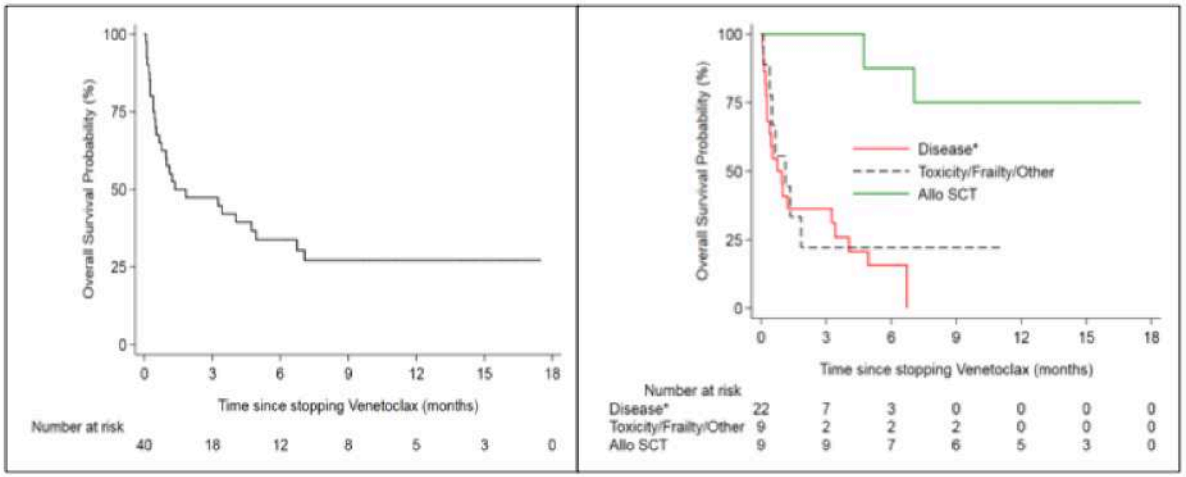
Treatment	Number treated with agent (Percentage of 24 patients who received subsequent line of therapy)	Patient level responses (n)
Ibrutinib-based	5 (20.8%)	PR (1), SD (2), PD (2)
Idelalisib-based	2 (8.3%)	CR (1), No response assessment (1)
Rituximab monotherapy	3 (12.5%)	PR (2), PD (1)
CAR-T	2 (8.3%)	No response assessment (2)
Anthracycline-based (R-CHOP/R-EPOCH)	3 (12.5%)	PD (2), no response assessment (1)
Allogeneic SCT	3 (12.5%)	CR (2), no response assessment (1)
Other	6 (25%)	PR (1), SD (1), PD (2), no response assessment (2)

29% discontinuation rate, POD #1 (21/41), AE #2 (9/41, mostly heme)

UK CLL Forum venetoclax data: OS post stopping VEN[1]

40 patients have stopped Venetoclax for reasons other than death, of these, twenty-eight have since died.

Median survival time after stopping is 1.3 months.



Reason for stopping	Alive	Dead
PD	3	9
Allo SCT	7	2
Toxicity	2	4
Refractory Disease	0	1
Richter's	0	9
Toxicity then Richter's	0	1
Frailty	0	1
Other	0	1

Eyre, BJH 2019

40/105 have discontinued ven in this series – 38%, most common reason is POD
OS survival outcomes did not differ based on DC reason

Across clinical trials and in clinical practice disease progression is most common reasons for discontinuation of venetoclax followed by intolerance (mostly heme toxicity)

Hypothesis: Prior exposure to a KI and ven discontinuation reasons should drive clinical decisions in terms of next therapy post venetoclax

Kinase inhibitor as first novel agent

Regular Article

blood

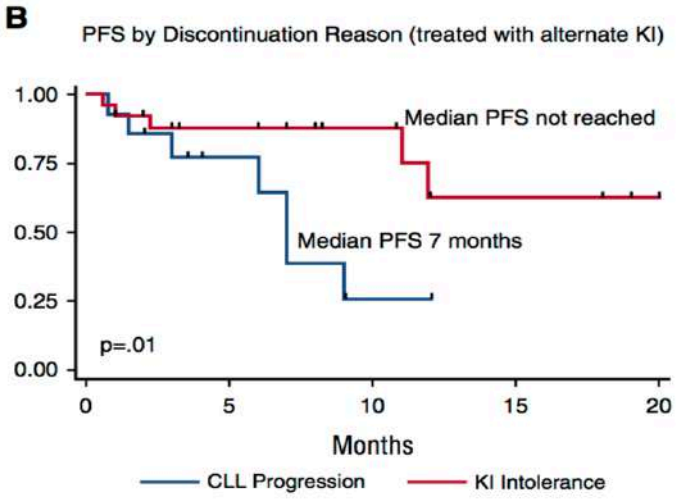
CLINICAL TRIALS AND OBSERVATIONS

Outcomes of CLL patients treated with sequential kinase inhibitor therapy: a real world experience

Anthony R. Mato,[1,*] Chadi Nabhan,[2,*] Paul M. Barr,[3] Chaitra S. Ujjani,[4] Brian T. Hill,[5] Nicole Lamanna,[6] Alan P. Skarbnik,[7] Christina Howlett,[7] Jeffrey J. Pu,[8] Alison R. Sehgal,[9] Lauren E. Strelec,[1] Alexandra Vandegrift,[1] Danielle M. Fitzpatrick,[1] Clive S. Zent,[3] Tatyana Feldman,[7] Andre Goy,[7] David F. Claxton,[8] Spencer Henick Bachow,[6] Gurbakhash Kaur,[10] Jakub Svoboda,[1] Sunita Dwivedy Nasta,[1] David Porter,[1] Daniel J. Landsburg,[1] Stephen J. Schuster,[1] Bruce D. Cheson,[4] Pavel Kiselev,[11] and Andrew M. Evens[10]

Table 2. Responses to subsequent therapy following KI discontinuation

	Alternate KI combined	Ibr → Idela	Idela → Ibr	BCL2-I	CIT	Mo anti-CD20
Number	38	16	22	13	12	11
ORR	50%	28%	64%	76%	25%	36%
CR	0%	0%	0%	7%	17%	9%
PR	50%	28%	64%	69%	8%	27%
SD	30%	45%	23%	16%	33%	45%
PD	20%	27%	13%	8%	42%	19%



- Alternate KI is effective in the setting of intolerance but not effective in the setting of POD / suspected resistance.
- Venetoclax is active in either situation.
- No clear role for CIT and CD20 abs

Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multicenter study of 683 patients

A. R. Mato[1*], B. T. Hill[2], N. Lamanna[3], P. M. Barr[4], C. S. Ujjani[5], D. M. Brander[6], C. Howlett[7,8], A. P. Skarbnik[9], B. D. Cheson[5], C. S. Zent[4], J. J. Pu[10], P. Kiselev[11], K. Foon[11], J. Lenhart[11], S. Henick Bachow[3], A. M. Winter[2], A.-L. Cruz[12], D. F. Claxton[10], A. Goy[9], C. Daniel[1], K. Isaac[1], K. H. Kennard[1], C. Timlin[1], M. Fanning[1], L. Gashonia[1], M. Yacur[10], J. Svoboda[1], S. J. Schuster[1] & C. Nabhan[13]

Table 2. Reasons for discontinuation first KI

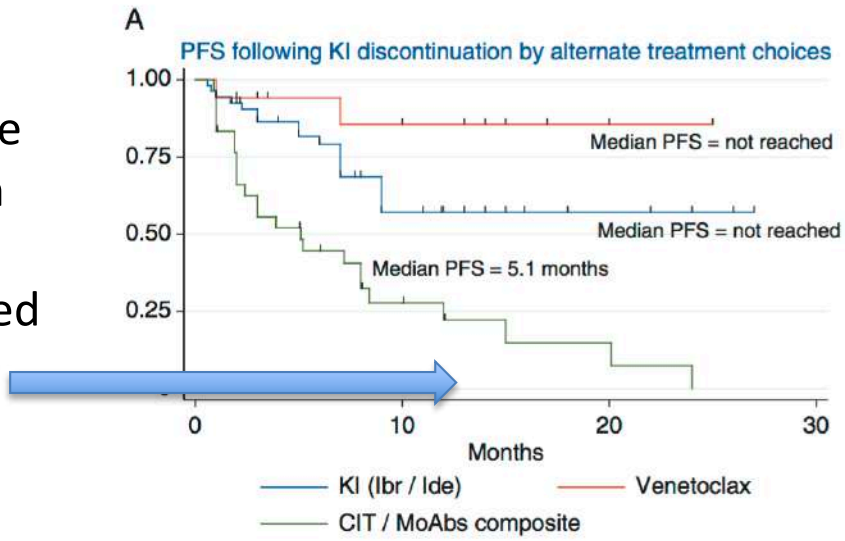
	Ibrutinib (n = 258 discontinuation events)	Idelalisib (n = 58 discontinuation events)
Toxicity	51.2% (n = 132)	44.8% (n = 26)
Progression	20.5% (n = 53)	27.6% (n = 16)
Other/death not secondary to progression	11% (n = 28)	6.9% (n = 4)
MD/patient preference	6.2% (n = 16)	17.2% (n = 10)
Richter's transformation	5.0% (n = 13)	3.5% (n = 2)
Stem cell transplant/CAR T cells	3.9% (n = 10)	0%
Secondary malignancy	1.1% (n = 3)	0%
Cost	1.1% (n = 3)	0%

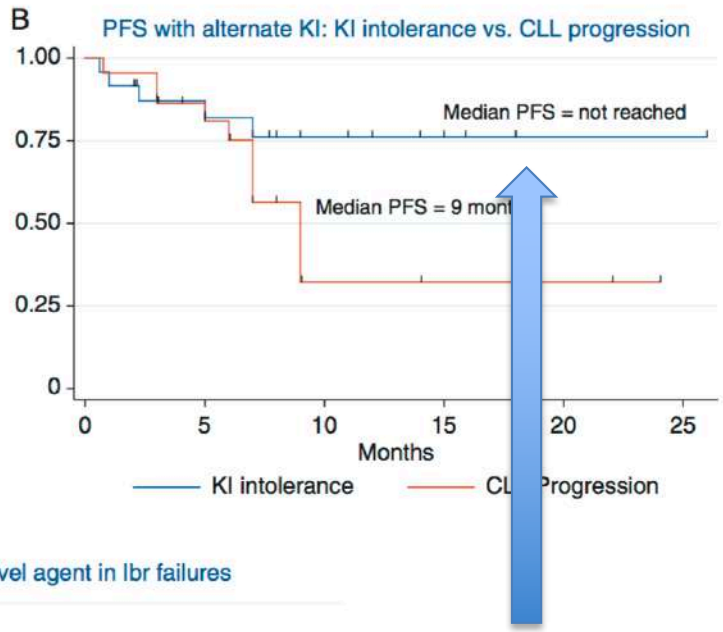
Table 3. Response to subsequent therapy following initial kinase inhibitor therapy

	Ibrutinib → idelalisib	Idelalisib → ibrutinib	Kinase inhibitor → venetoclax
ORR (%)	46	75	74
CR (%)	0	5	32
PR/PR with lymphocytosis (%)	46	70	42
Stable disease (%)	39	15	16
Progressive disease (%)	15	10	10

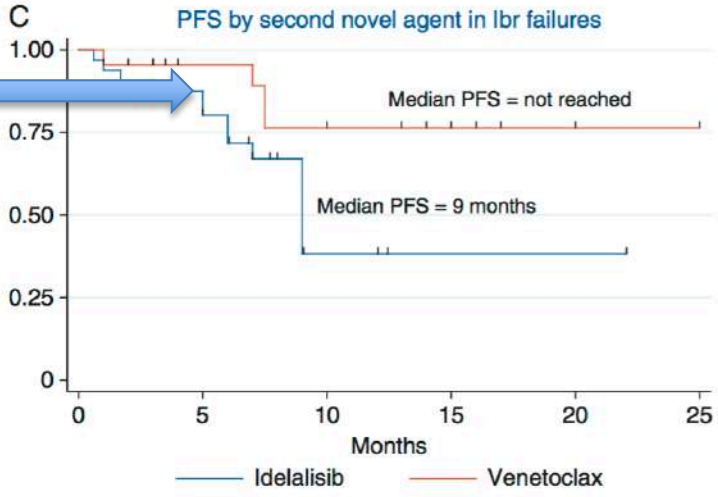
Sequencing following Ibr / Ide discontinuation

1. No role for CIT in heavily pretreated KI pts





2. Ven over alternate KI especially in Ibr resistance



3. KI intolerance: consider alternate KI.

But which one?

Prospective data

Ibr / Ide → Alternate KI

Ibr / Ide → Venetoclax

Hematological ONCOLOGY

SESSION 3 – CLL | Free Access

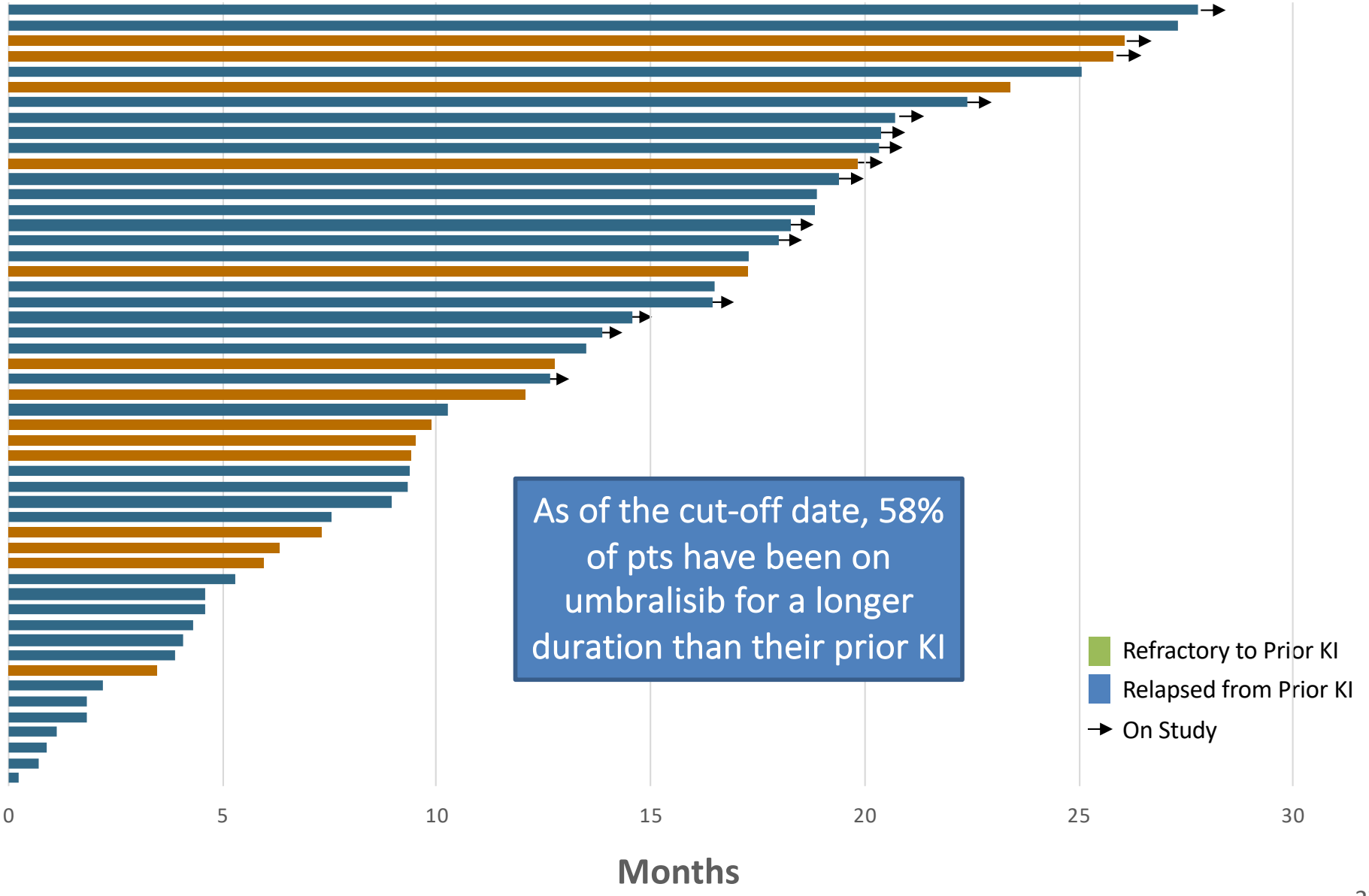
A PHASE 2 STUDY TO ASSESS THE SAFETY AND EFFICACY OF UMBRALISIB IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) WHO ARE INTOLERANT TO PRIOR BTK OR PI3K DELTA INHIBITOR THERAPY

A.R. Mato, S.J. Schuster, N. Lamanna, J.M. Pagel, I.W. Flinn, J. Barrientos, J.A. Reeves, B.D. Cheson, P.M. Barr, S. Kambhampati, F. Lansigan, J.J. Pu, A. Skarbnik, G. Fonseca, C. Dorsey , N.M. LaRatta, H. Weissbrot, J. Svoboda, E.T. Luning Prak, P. Tsao, A. Sitlinger, D. Paskalis, P. Sportelli, H.P. Miskin, M.S. Weiss, D.M. Brander ... See fewer authors

Adverse Events Leading to Prior KI

Intolerant AE on Prior TKI	Grade 2 (n)	Grade 3 (n)	Grade 4 (n)	Total # of events (n)
Rash	6	8		14
Arthralgia	3	5	1	9
Atrial Fibrillation	5	2	1	8
Bleeding	1	3		4
Fatigue	2	2		4
Anorexia/Weight Loss	3			3
Colitis	1	2		3
Congestive Heart Failure	1	1	1	3
Pneumonitis	2	1		3
Thalamic Lesions		1		1
Transaminitis	1			1
TOTAL	39	28	6	73

Efficacy & Tolerability: Duration of Exposure



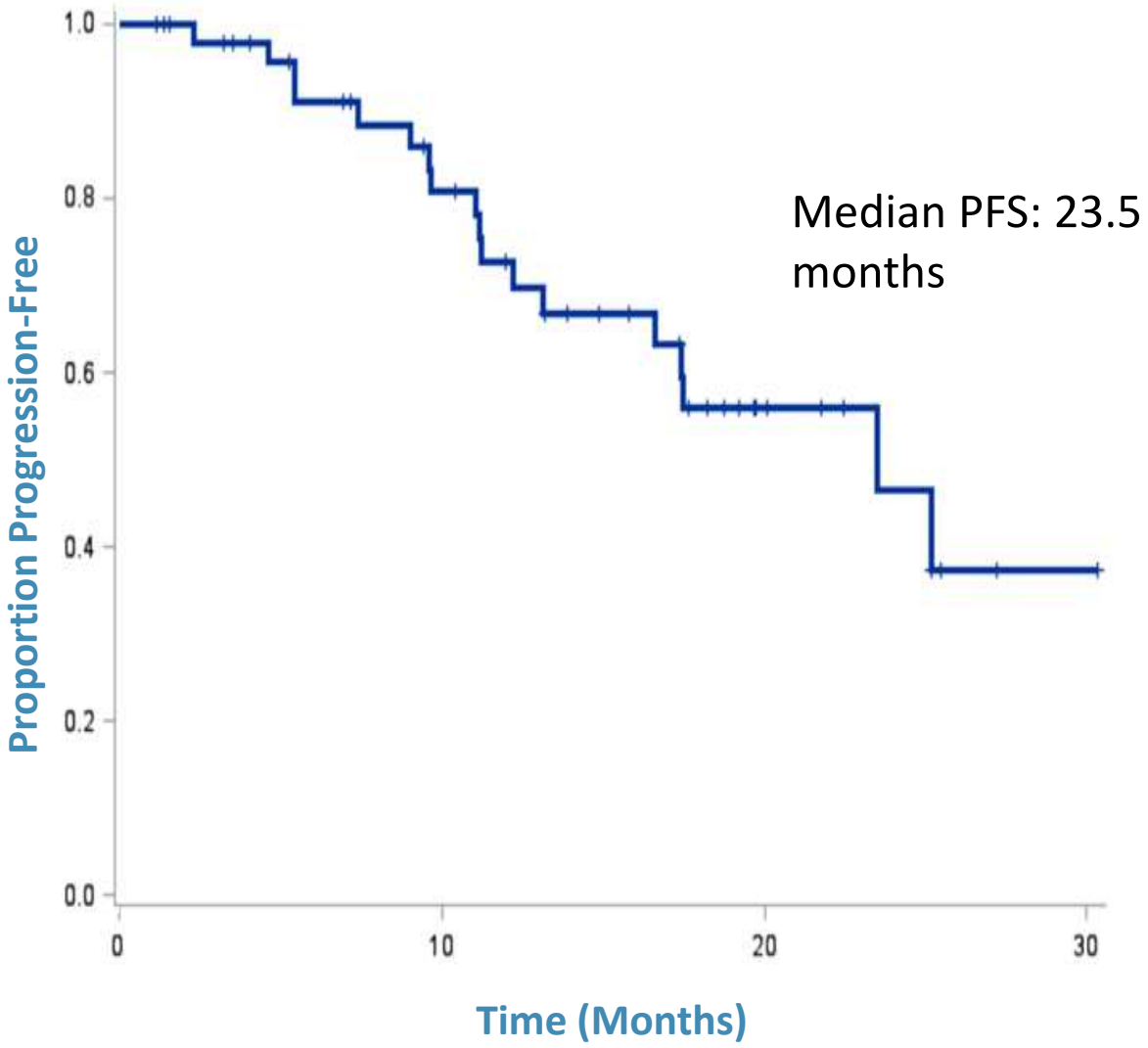
Umbralisib was well tolerated

- **4 patients had recurrence of an AE that led to prior KI intolerance**
  - 3 were of lesser severity and did not lead to dose modification or d/c of umbralisib
  - 1 patient discontinued for recurrent rash (prior ibrutinib)
- **8 pts (16%) had dose reductions** allowing them to continue umbralisib therapy
- **6 pts (12%) discontinued treatment due to an umbralisib AE** (pneumonitis (2), pancreatitis, pneumonia, dermatitis, rash)

All Causality AEs in >10% of Patients (N=51)

	All Grades		Grade 3/4	
	N	%	N	%
Diarrhea	32	63%	4	8%
Nausea	27	53%		
Thrombocytopenia	13	25%	6	12%
Fatigue	13	25%		
Insomnia	13	25%		
Neutropenia	12	24%	9	18%
Headache	12	24%		
Dizziness	10	20%		
Peripheral Edema	9	18%		
Cough	8	16%		
Rash	8	16%		
Leukocytosis	7	14%	7	14%
Pneumonia	7	14%	6	12%
Anemia	7	14%	2	4%
Pyrexia	7	14%	1	2%
Arthralgia	7	14%		
Contusion	7	14%		
Decreased appetite	7	14%		
Myalgia	7	14%		
Upper respiratory tract infection	7	14%		
Vomiting	7	14%		
AST/ALT Increase	6	12%	3	6%

Efficacy – Progression-Free Survival

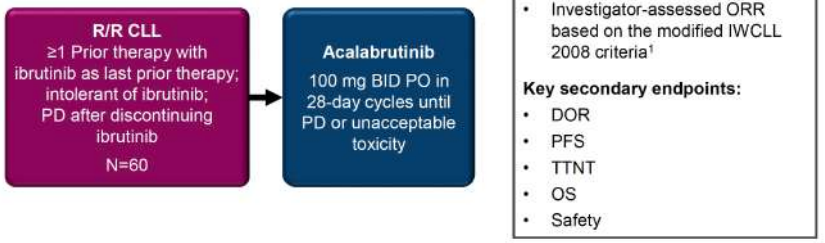


- With a median follow-up of 14 months, Median PFS: 23.5 months (95% CI 13.1 – NE)

Phase 2 Study of Acalabrutinib in Ibrutinib-Intolerant Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia

Kerry A. Rogers,[1] Philip A. Thompson,[2] John N. Allan,[3] Morton Coleman,[3] Jeff P. Sharman,[4] Bruce D. Cheson,[5] Raquel Izumi,[6] Melanie M. Frigault,[6] Cheng Quah,[6] Rakesh K. Raman,[6] Min Hui Wang,[6] and Thomas J. Kipps[7]

[1]The Ohio State University, Columbus, OH, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]Weill Cornell Medicine, New York, NY, USA; [4]Willamette Valley Cancer Institute, Eugene, OR, USA; [5]Georgetown University Hospital, Washington, DC, USA; [6]Acerta Pharma, South San Francisco, CA, USA; and [7]UC San Diego Moores Cancer Center, San Diego, CA, USA

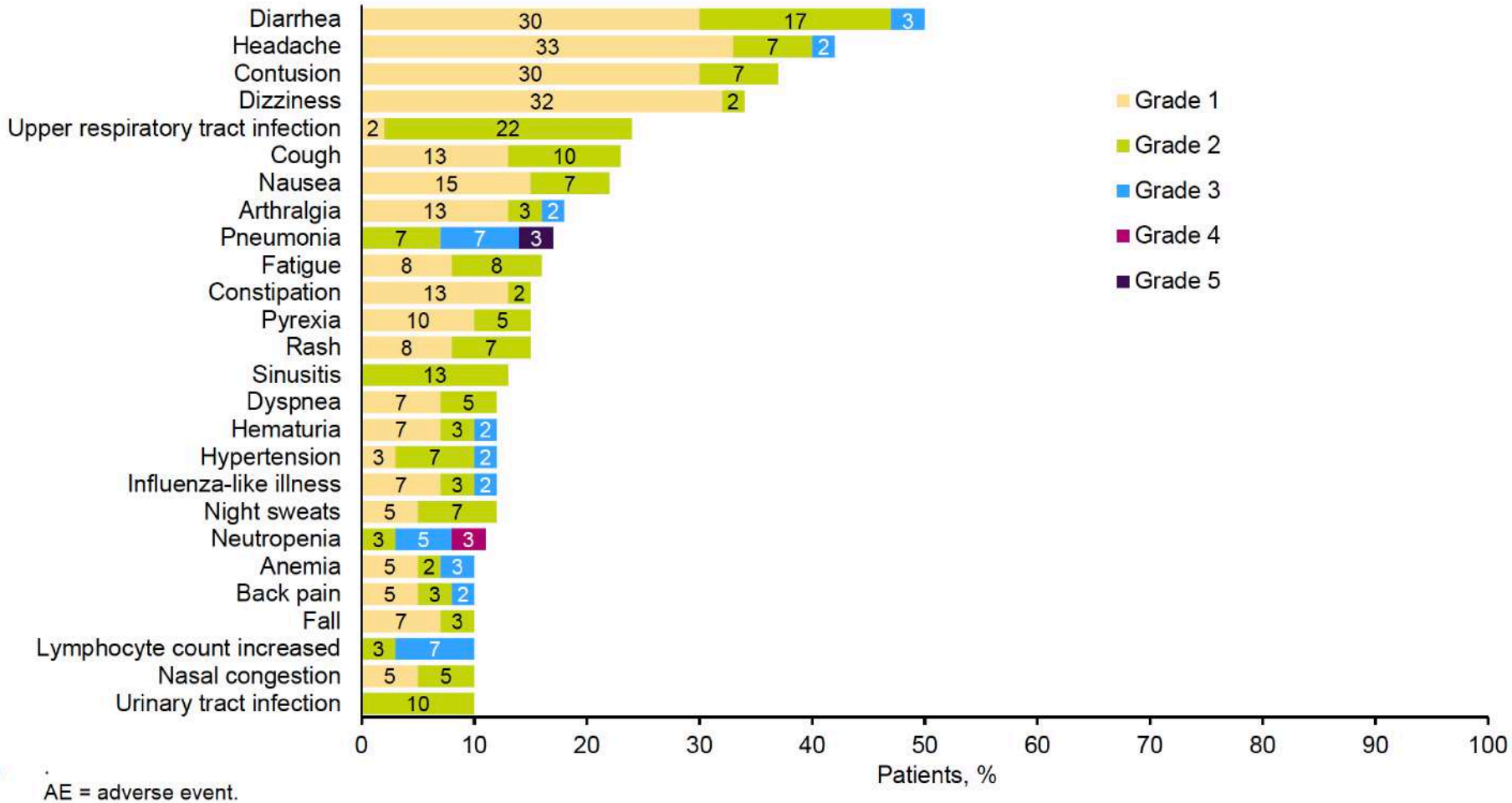


- The median duration of prior ibrutinib therapy was 6 months (range, <1 to 56)
- The median time from last dose of ibrutinib to starting acalabrutinib was 9.2 months (range, 0.8 to 31.1)

At a median follow-up of 23 months, 62% of patients remain on acalabrutinib

	N=60
Follow-up, median (range), mo	23 (<1-35)
On acalabrutinib, n (%)	37 (62)
On study, n (%)	48 (80)
Discontinued acalabrutinib, n (%)	23 (38)
Disease progression	9 (15)
Adverse event[a]	7 (12)
Patient withdrawal	3 (5)
Physician decision	2 (3)
Death[b]	1 (2)
Other[c]	1 (2)
Deaths on study, n (%)[d]	8 (13)

Most Commons AEs in ≥10% of Patients



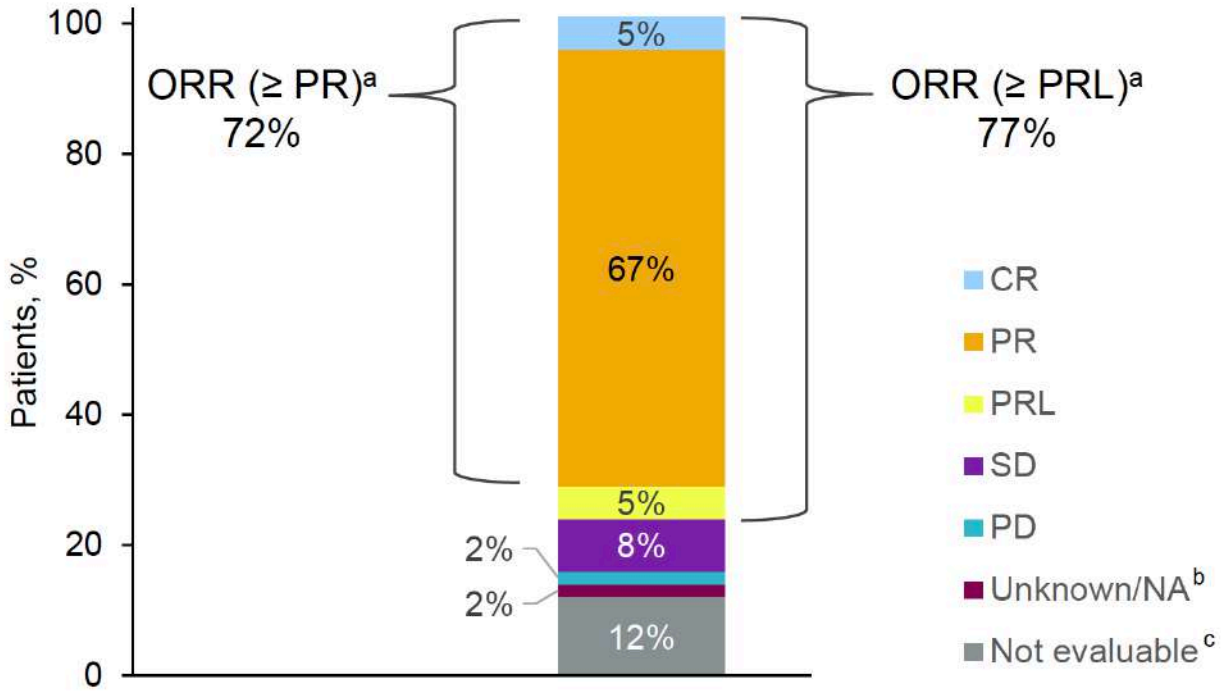
AE = adverse event.

Additional Safety Outcomes

- The most common Grade ≥3 AEs (≥5% of patients) were pneumonia (n=6 [10%]), neutropenia (n=5 [8%]), neutrophil count decreased (n=4 [7%]), lymphocyte count decreased (n=4 [7%]), lymphocytosis (n=4 [7%]), platelet count decreased (n=3 [5%]), and anemia (n=2 [3%])
- Bleeding events occurred in 37 patients (62%), 2 (3%) had major hemorrhage
- Hypertension occurred in 7 patients (12%), 1 (2%) grade 3
  - One patient (2%) experienced Grade 3 hypertension
- Grade 3/4 infections occurred in 10 patients (17%)
- Seven patients (12%) discontinued acalabrutinib due to AEs
  - AEs that lead to treatment discontinuation were pneumonia (n=2), diarrhea (n=1), headache (n=1), endometrial cancer (n=1), arthralgia (n=1), and subdural hematoma (each n=1)
- There were 4 Grade 5 AEs, none of which were considered related to treatment:
  - Grade 5 AEs were pneumonia (n=2), bronchopulmonary aspergillosis (n=1), and ventricular fibrillation (n=1)

Response to Acalabrutinib

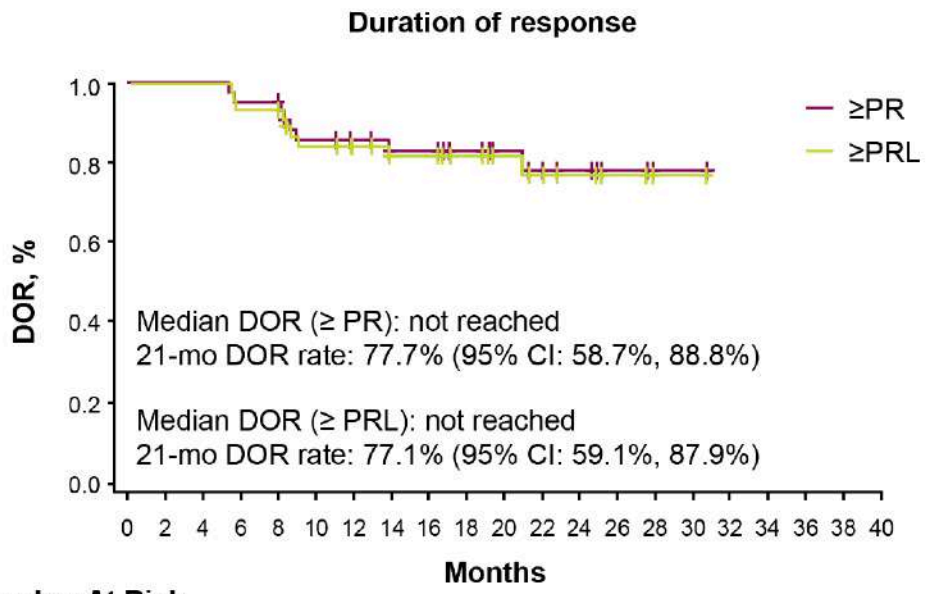
- Investigator-assessed ORR (≥ PR) was 72%, with a 5% complete response rate
  - ORR including PRL was 77%
- In the 17 patients with del(17p), ORR (≥ PR) was 71% (95% CI: 44%, 90%)



[a] Assessed using IWCLL 2008 criteria.[1]
[b] One patient had a disease assessment performed by the investigator who reported the result as unknown/NA.
[c] Seven patients (12%) terminated the study before the first disease assessment on Cycle 3 Day 28.
CR = complete response; IWCLL = International Workshop on Chronic Lymphocytic Leukemia;
NA = not applicable; ORR = overall response rate; PD = progressive disease; PR = partial response; PRL = PR with lymphocytosis; SD = stable disease.

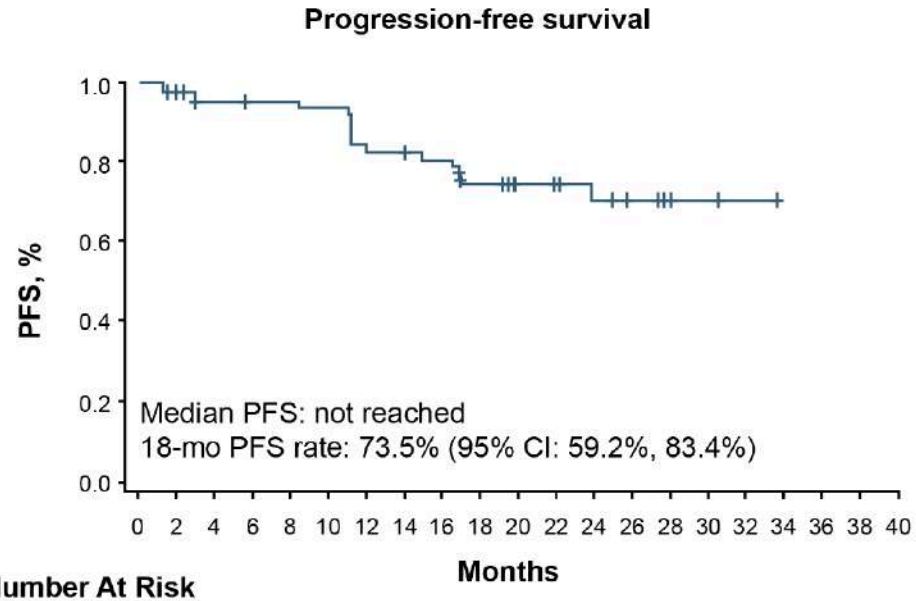
1. Hallek M, et al. *Blood*. 2008;111(12):5446-5456.

Duration of Response and Progression-Free Survival



Number At Risk

≥PR	43	43	43	41	40	35	32	27	27	20	16	14	10	4	1	1
≥PRL	46	46	46	43	42	37	34	29	29	21	17	15	11	4	1	1



Number At Risk

	60	55	51	50	50	49	43	42	41	3	24	23	17	13	7	7	1

13

DOR = duration of response; PR = partial response; PRL = PR with lymphocytosis.

Prospective data

Ibr / Ide → Alternate KI

Ibr / Ide → Venetoclax

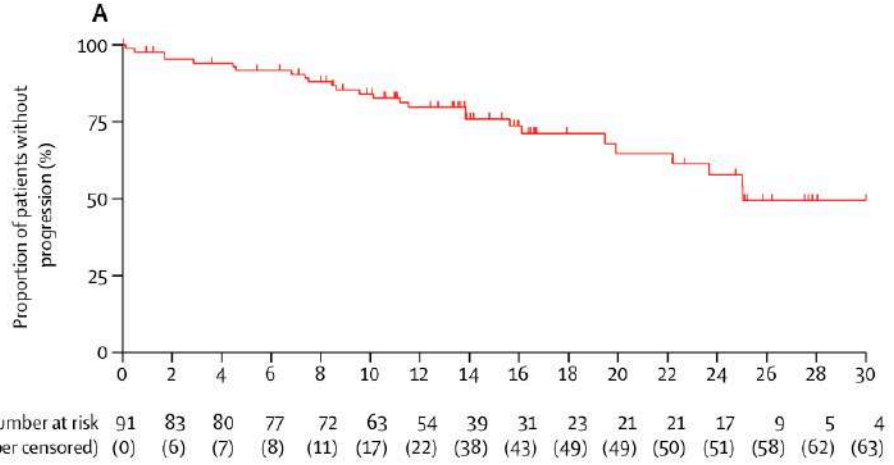
Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial

Jeffrey A Jones, Anthony R Mato, William G Wierda, Matthew S Davids, Michael Choi, Bruce D Cheson, Richard R Furman, Nicole Lamanna, Paul M Barr, Lang Zhou, Brenda Chyla, Ahmed Hamed Salem, Maria Verdugo, Rod A Humerickhouse, Jalaja Potluri, Steven Coutre, Jennifer Woyach, John C Byrd**

	Main cohort (n=43)	Expansion cohort (n=48)	All patients (n=91)
Overall response	30 (70%, 54–83)	29 (60%, 43–72)	59 (65%, 53–74)
Complete response or complete response with incomplete bone marrow recovery	4 (9%)	4 (8%)	8 (9%)
Nodular partial response	2 (5%)	1 (2%)	3 (3%)
Partial response	24 (56%)	24 (48%)	48 (52%)
Stable disease	8 (19%)	14 (29%)	22 (24%)
Disease progression	1* (2%)	4* (8%)	5 (5%)
Discontinued before response assessment	4 (9%)	2 (4%)	6 (7%)

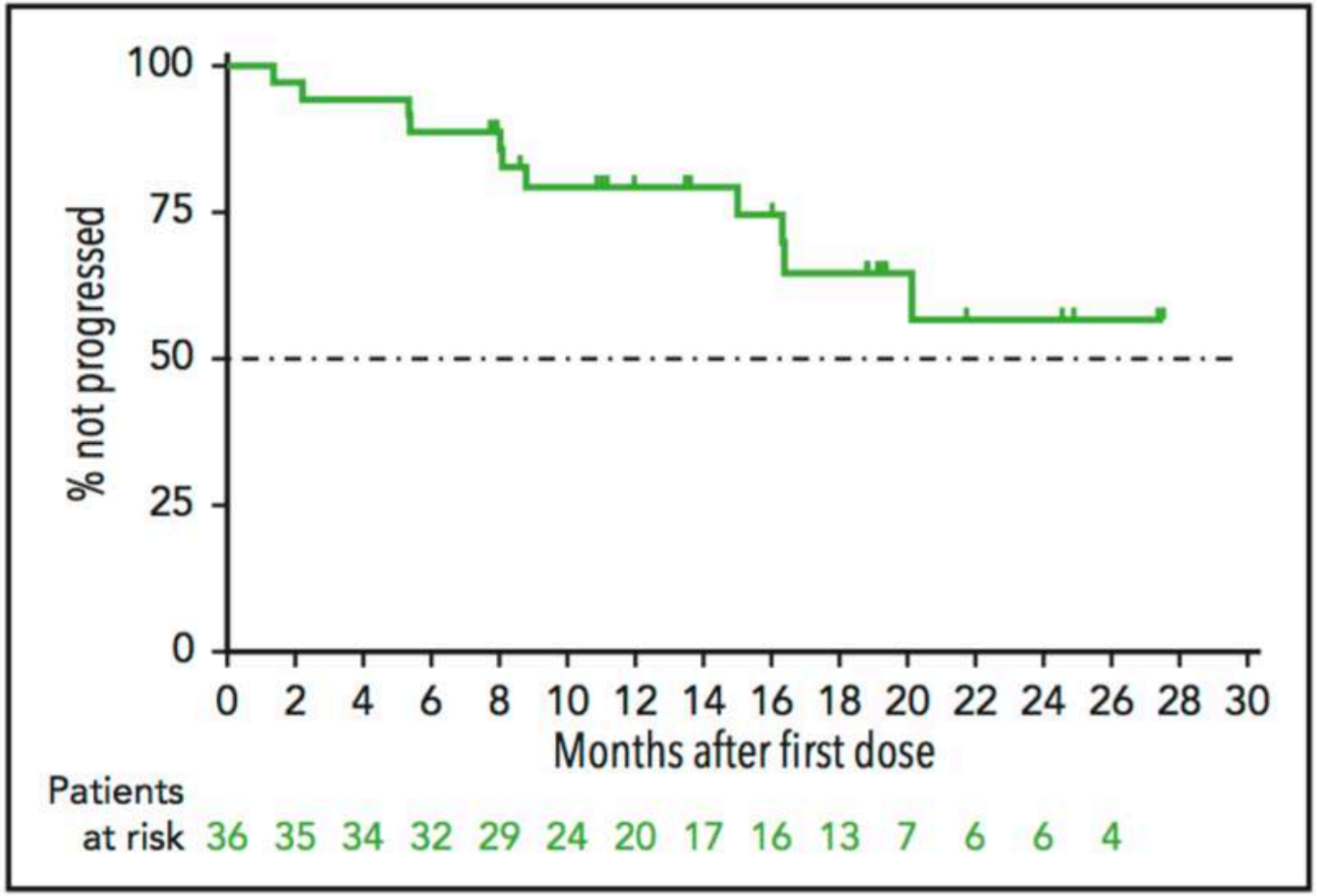
Data are n (%) or n (%, 95% CI). *Patients who discontinued because of progression.

Table 2: **Response with venetoclax monotherapy as assessed by the investigator**



Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy

Steven Coutre,[1] Michael Choi,[2] Richard R. Furman,[3] Herbert Eradat,[4] Leonard Heffner,[5] Jeffrey A. Jones,[6] Brenda Chyla,[7] Lang Zhou,[7] Suresh Agarwal,[7] Tina Waskiewicz,[7] Maria Verdugo,[7] Rod A. Humerickhouse,[7] Jalaja Potluri,[7] William G. Wierda,[8] and Matthew S. Davids[9]



Ven → Ibr (KI naïve vs. resistant vs. intolerant)

Real-world outcomes and management strategies for venetoclax-treated chronic lymphocytic leukemia patients in the United States

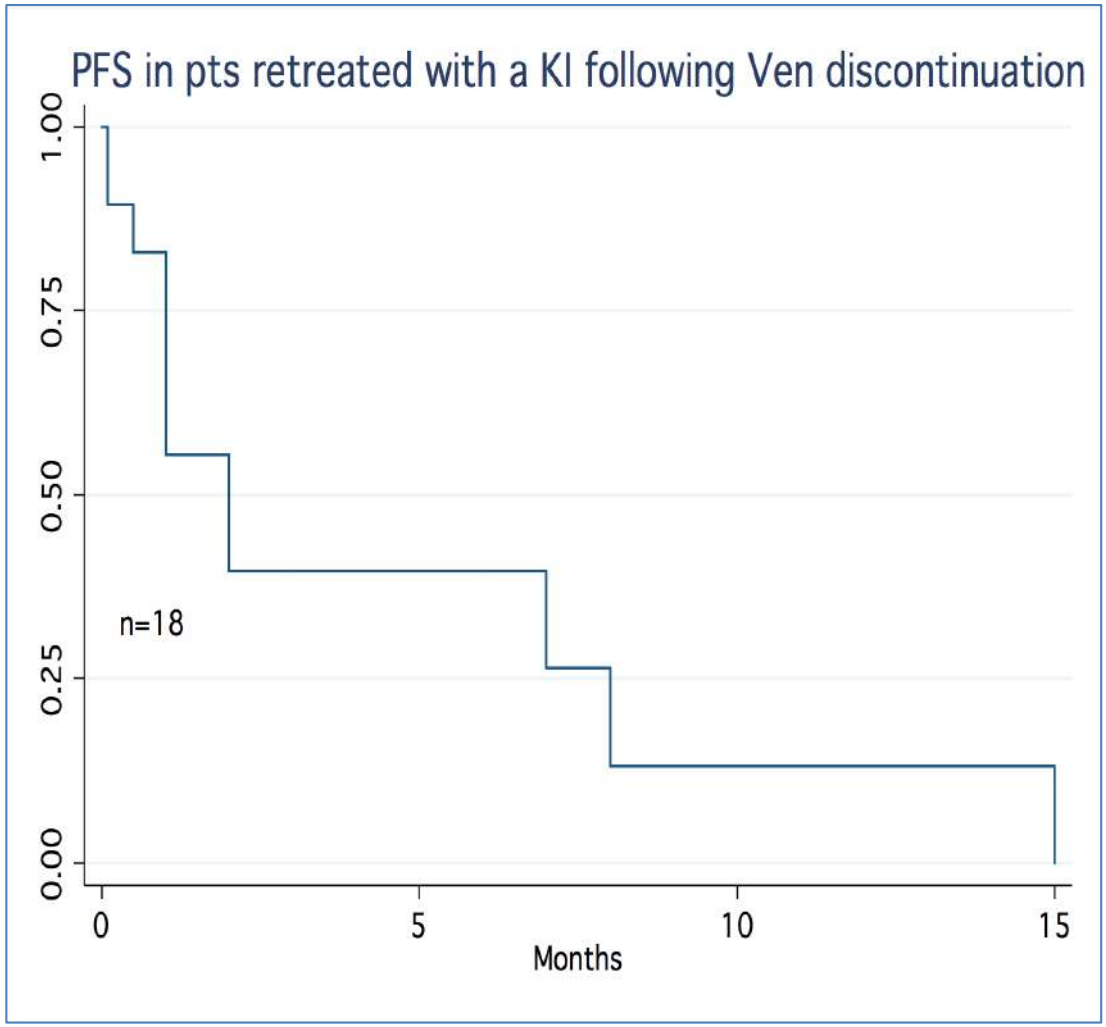
Anthony R. Mato,[1] Meghan Thompson,[2] John N. Allan,[3] Danielle M. Brander,[4] John M. Pagel,[5] Chaitra S. Ujjani,[6] Brian T. Hill,[7] Nicole Lamanna,[8] Frederick Lansigan,[9] Ryan Jacobs,[10] Mazyar Shadman,[11] Alan P. Skarbnik,[12] Jeffrey J. Pu,[13] Paul M. Barr,[14] Alison R. Sehgal,[15] Bruce D. Cheson,[6] Clive S. Zent,[14] Hande H. Tuncer,[16] Stephen J. Schuster,[2] Peter V. Pickens,[17] Nirav N. Shah,[18] Andre Goy,[12] Allison M. Winter,[7] Christine Garcia,[15] Kaitlin Kennard,[2] Krista Isaac,[19] Colleen Dorsey,[2] Lisa M. Gashonia,[2] Arun K. Singavi,[18] Lindsey E. Roeker,[1] Andrew Zelenetz,[1] Annalynn Williams,[14] Christina Howlett,[12] Hanna Weissbrot,[8] Naveed Ali,[17] Sirin Khajavian,[11] Andrea Sitlinger,[4] Eve Tranchito,[7] Joanna Rhodes,[2] Joshua Felsenfeld,[3] Neil Bailey,[5] Bhavisha Patel,[20] Timothy F. Burns,[9] Melissa Yacur,[13] Mansi Malhotra,[16] Jakub Svoboda,[2] Richard R. Furman[3] and Chadi Nabhan[21]

Table 4. First treatment following venetoclax discontinuation and treatment outcomes.

Treatment	Number treated with agent (Percentage of 24 patients who received subsequent line of therapy)	Patient level responses (n)
Ibrutinib-based	5 (20.8%)	PR (1), SD (2), PD (2)
Idelalisib-based	2 (8.3%)	CR (1), No response assessment (1)
Rituximab monotherapy	3 (12.5%)	PR (2), PD (1)
CAR-T	2 (8.3%)	No response assessment (2)
Anthracycline-based (R-CHOP/R-EPOCH)	3 (12.5%)	PD (2), no response assessment (1)
Allogeneic SCT	3 (12.5%)	CR (2), no response assessment (1)
Other	6 (25%)	PR (1), SD (1), PD (2), no response assessment (2)

In BTK exposed patients, no clear effective treatment pattern identified

Venetoclax does not appear to re-sensitize CLL cells to covalent BTKi in previously BTK-exposed CLL pts



Mato et al , ASH 2018

Clinicopathological features and outcomes of progression of CLL on the BCL2 inhibitor venetoclax

Mary Ann Anderson,[1-4,*] Constantine Tam,[3-5,*] Thomas E. Lew,[2,*] Surender Juneja,[1,4] Manu Juneja,[2] David Westerman,[4,5] Meaghan Wall,[3,6,7] Stephen Lade,[4,5] Alexandra Gorelik,[8] David C. S. Huang,[2,3] John F. Seymour,[3-5] and Andrew W. Roberts[1-4]

Table 4. Treatments and outcome for patients with PD

Case no.	Treatment	Response	Later CLL PD (treatment)	Status	PPS (mo)
RT–DLBCL					
1	R-CHOP	PD	—	Dead	2.3
2	No treatment	—	—	Dead	0.9
3	Vin/Gem	PR	—	Alive	32.3
4	R-CHOP	SD	—	Dead	24.6
5	HyperCVAD	PD	—	Dead	14.9
6	R-CHOP	PD	—	Dead	5.6
7	OFAR	PD	—	Dead	10.9
8	CHOP + AlloSCT	PR	—	Dead	13
9	R-ICE + AuSCT	CR	+ (Novel BTKI on trial)	Alive	36.9
10	R-ICE + AuSCT	CR	+ (Ibr)	Alive	45.0
11	XRT + R-MVP	PR	+ (Ibr)	Alive	40.5
12	R-CHOP	SD	—	Dead	9.3
13	R-CHOP	Death	—	Dead	1
14	R-ICE	SD	—	Dead	10.7
RT-HL					
15	ABVD	CR	—	Alive	29.3
16	R-CHOP + AlloSCT	CR	—	Alive	49.9
17	CHEP + XRT	CR	+ (Ibr)	Alive	30.2
CLL progression					
1	No treatment	—	—	Dead	<1.0
2	Ibr	SD	+	Dead	11.4
3	Ibr	PR	—	Alive	6.2
4	FCR	Unk	—	Dead	5.6
5	Ibr	PR	—	Dead (toxicity)	8.6
6	Ibr	PR	—	Alive	15.7
7	Ibr	PR	—	Alive	13.2
8	Ibr	PR	—	Dead (toxicity)	8.3

4/6 pts dead, 2/4 from AEs

EFFICACY AND SAFETY OF IBRUTINIB IN RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS PREVIOUSLY TREATED WITH VENETOCLAX IN THE MURANO STUDY

PS1161

Greil, R.[1]; Fraser, G.[2]; Leber, B.[3]; Marks, R.[4]; Quaresmini, G.[5]; Middeke, Moritz J.[6]; Semenzato, G.[7]; Schary, W.[8]; Boyer, M.[9]; Breuleux, M.[10]; Crompton, N.[9]; Humphrey, K.[9]; Marlton, P.[11]

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Table 1. Pts transitioning to IBR after PD on VenR in MURANO

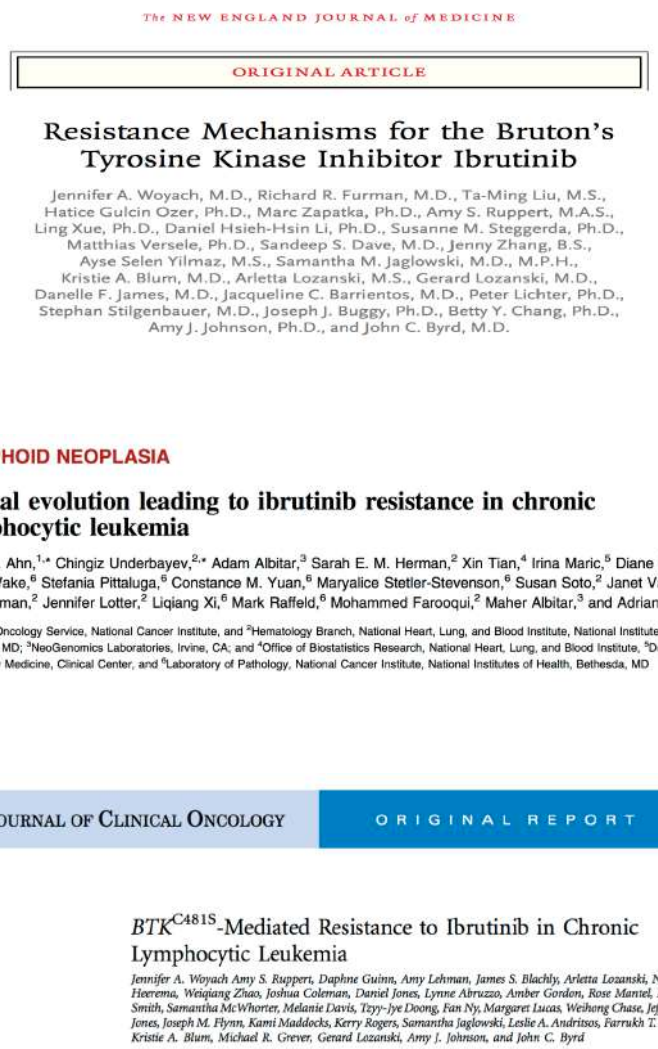
Patient	Number of treatments prior to Ven	Prior treatment (best response)	Baseline 17p status (pre-Ven)	VenR treatment duration (months)	VenR best response	Time after starting VenR to PD (months)	IBR best response	Time on IBR (months)
1	1	FCR (PR)	Not deleted	11	PR	9	PR	42[††] (ongoing)
2	1	FCR (PR)	Deleted	25*	PR	27	PR	19[†] (ongoing)
3	1	FCR (CR)	Not deleted	28*	nPR	36	PR	14[†] (ongoing)
4	1	FCR (CR)	Deleted	26*	CR	24	PR (nodal CR)	13[†] (ongoing)
5	1	FCR (PR)	Not deleted	26*	PR	32	PR	10[†] (ongoing)
6	4	CLB+P (PR) CLB (UE) CLB+R (PR) CLB (SD)	Not deleted	25*	CR	28	PR	15[†] (ongoing)
7	1	FCR (SD)	Deleted	19	PR	19	VGPR	3[‡‡]
8	1	FCR (CR)	Not deleted	25*	CR	25	PR	7[‡]
Median (range)	1 (1–4)			25 (11–28)		26 (9–36)		13.5 (3–42)

CLB, chlorambucil; CR, complete response; FCR, fludarabine, cyclophosphamide, and rituximab; IBR, ibrutinib; nPR, nodular partial response P, prednisone PD, progressive disease; PR, partial response; R, rituximab; SD, stable disease; UE, unevaluable; Ven, venetoclax; VGPR, very good partial response; *Time on treatment was 2 years; durations shown include time when Ven dose was ramped up. †Censored at time of data analysis. ††Patient had PD 40 months after starting IBR; still on IBR at time of last follow-up but due to be discontinued. ‡IBR discontinued due to PD; ‡‡Following allogeneic stem cell transplantation, pt restarted on IBR.

HEMASPHERE

8/8 pts responed to BTKi post ven which appear durable

Ibrutinib Resistance



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Resistance Mechanisms for the Bruton's Tyrosine Kinase Inhibitor Ibrutinib

Jennifer A. Woyach, M.D., Richard R. Furman, M.D., Ta-Ming Liu, M.S., Hatice Gulcin Ozer, Ph.D., Marc Zapatka, Ph.D., Amy S. Ruppert, M.A.S., Ling Xue, Ph.D., Daniel Hsieh-Hsin Li, Ph.D., Susanne M. Steggerda, Ph.D., Matthias Versele, Ph.D., Sandeep S. Dave, M.D., Jenny Zhang, B.S., Ayse Selen Yilmaz, M.S., Samantha M. Jaglowski, M.D., M.P.H., Kristie A. Blum, M.D., Arletta Lozanski, M.S., Gerard Lozanski, M.D., Danelle F. James, M.D., Jacqueline C. Barrientos, M.D., Peter Lichter, Ph.D., Stephan Stilgenbauer, M.D., Joseph J. Buggy, Ph.D., Betty Y. Chang, Ph.D., Amy J. Johnson, Ph.D., and John C. Byrd, M.D.

LYMPHOID NEOPLASIA

Clonal evolution leading to ibrutinib resistance in chronic lymphocytic leukemia

Inhye E. Ahn,[1,*] Chingiz Underbayev,[2,*] Adam Albitar,[3] Sarah E. M. Herman,[2] Xin Tian,[4] Irina Maric,[5] Diane C. Arthur,[6] Laura Wake,[6] Stefania Pittaluga,[6] Constance M. Yuan,[6] Maryalice Stetler-Stevenson,[6] Susan Soto,[2] Janet Valdez,[2] Pia Nierman,[2] Jennifer Lotter,[2] Liqiang Xi,[6] Mark Raffeld,[6] Mohammed Farooqui,[2] Maher Albitar,[3] and Adrian Wiestner[2]

[1]Medical Oncology Service, National Cancer Institute, and [2]Hematology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD; [3]NeoGenomics Laboratories, Irvine, CA; and [4]Office of Biostatistics Research, National Heart, Lung, and Blood Institute, [5]Department of Laboratory Medicine, Clinical Center, and [6]Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

BTK^{C481S}-Mediated Resistance to Ibrutinib in Chronic Lymphocytic Leukemia

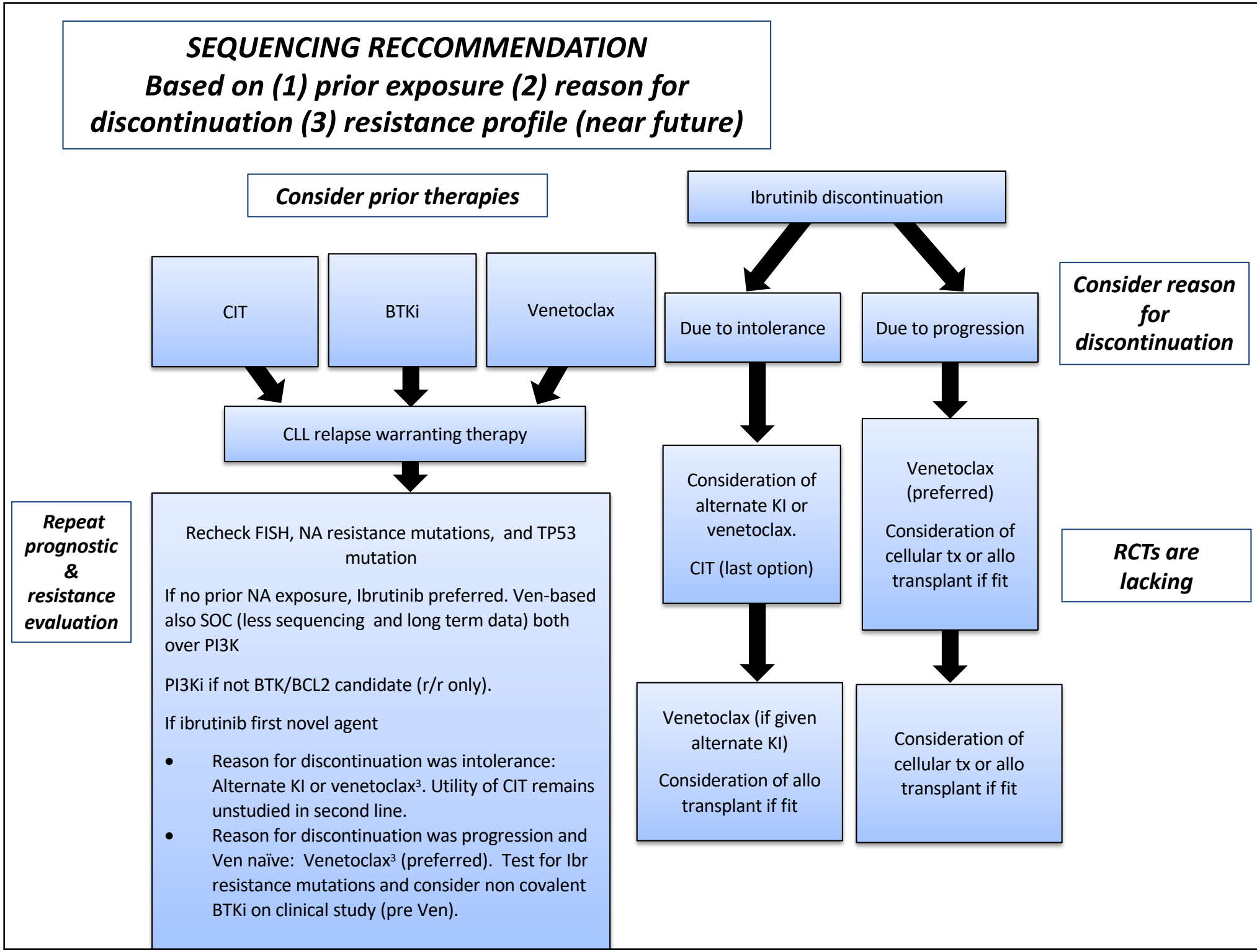
Jennifer A. Woyach Amy S. Ruppert, Daphne Guinn, Amy Lehman, James S. Blachly, Arletta Lozanski, Nyla A. Heerema, Weiqiang Zhao, Joshua Coleman, Daniel Jones, Lynne Abruzzo, Amber Gordon, Rose Maniel, Lisa L. Smith, Samantha McWhorter, Melanie Davis, Tzyy-Jye Doong, Fan Ny, Margaret Lucas, Weihong Chase, Jeffrey A. Jones, Joseph M. Flynn, Kami Maddocks, Kerry Rogers, Samantha Jaglowski, Leslie A. Andritsos, Farrukh T. Awan, Kristie A. Blum, Michael R. Grever, Gerard Lozanski, Amy J. Johnson, and John C. Byrd

In development

Non covalently binding BTK inhibitors to address BTK Cys481 mutant CLL:

- Vecabrutinib (SNS-062)
- LOXO 305
- ARC 531

If effective, this class of agents may affect how we consider treatment in the setting of discontinuation due to BTK resistant disease


SEQUENCING RECCOMMENDATION
Based on (1) prior exposure (2) reason for discontinuation (3) resistance profile (near future)
Consider prior therapies
CIT
BTKi
Venetoclax
CLL relapse warranting therapy
Repeat prognostic & resistance evaluation
Recheck FISH, NA resistance mutations, and TP53 mutation
If no prior NA exposure, Ibrutinib preferred. Ven-based also SOC (less sequencing and long term data) both over PI3K
PI3Ki if not BTK/BCL2 candidate (r/r only).
If ibrutinib first novel agent
Reason for discontinuation was intolerance: Alternate KI or venetoclax[3]. Utility of CIT remains unstudied in second line.
Reason for discontinuation was progression and Ven naïve: Venetoclax[3] (preferred). Test for Ibr resistance mutations and consider non covalent BTKi on clinical study (pre Ven).
Ibrutinib discontinuation
Due to intolerance
Due to progression
Consider reason for discontinuation
Consideration of alternate KI or venetoclax.
CIT (last option)
Venetoclax (preferred)
Consideration of cellular tx or allo transplant if fit
RCTs are lacking
Venetoclax (if given alternate KI)
Consideration of allo transplant if fit
Consideration of cellular tx or allo transplant if fit

SEQUENCING RECCOMMENDATION
Based on (1) prior exposure (2) reason for discontinuation (3) resistance profile