Sequencing of Targeted Therapies

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Outcomes of CLL Patients Treated With Sequential Kinase Inhibitor Therapy: A Real World Experience

Mato AR, Nabhan C, Barr PM, Ujjani CS, Hill BT, Lamanna N, Skarbnik AP, Howlett C, Pu JJ, Sehgal AR, Strelec LE, Vandegrift A, Fitzpatrick DM, Zent CS, Feldman T, Goy A, Claxton DF, Bachow SH, Kaur G, Svoboda J, Nasta SD, Porter D, Landsburg DJ, Schuster SJ1, Cheson BD, Kiselev P, Evens AM

Mato et al. Blood. 2016 Nov 3;128(18):2199-2205. Epub 2016 Sep 6;

Baseline Characteristics

***178** patients who discontinued KI therapy were identified*
(143 Ibrutinib-based + 35 Idelalisib-based therapy)

Characteristic	Result (range)	Total (N)
Median age at diagnosis	60 years (33-89)	178
Median # prior therapies	3.0 therapies (0-11) 8% untreated (n=14)	178
Del 17p present (FISH)	34%	155
Del 11q present (FISH)	33%	152
p53 mutation present	27%	95
Complex karyotype (≥ 3)	29%	128
Zap 70 positive CLL	67%	60
IGHV unmutated	69%	49

Ibrutinib / Idelalisib Dosing

	Ibrutinib	Idelalisib
Median time from CLL dx → KI start	84 months	81 months
Median time on KI	5 months (.25-41 months)	5.5 months (.5 – 38 months)
Median starting dose	420 mg daily (140-560 mg) 86% FDA approved dose	150 mg BID (100-150 mg) 69% FDA approved dose
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% (mostly paired with anti-CD20)

Best Reported Response to First KI*

Per Investigator	Ibrutinib-based	Idelalisib-based (mostly paired with anti-CD20)
Number with reported response assessment	124/143	34/35
ORR (CR + PR / PR-L)	58%	76%
SD	22%	12%
PD	20%	12%

*Reported responses lower than those reported in clinical trials likely reflects subgroup selected for KI failure

Reasons for Discontinuation

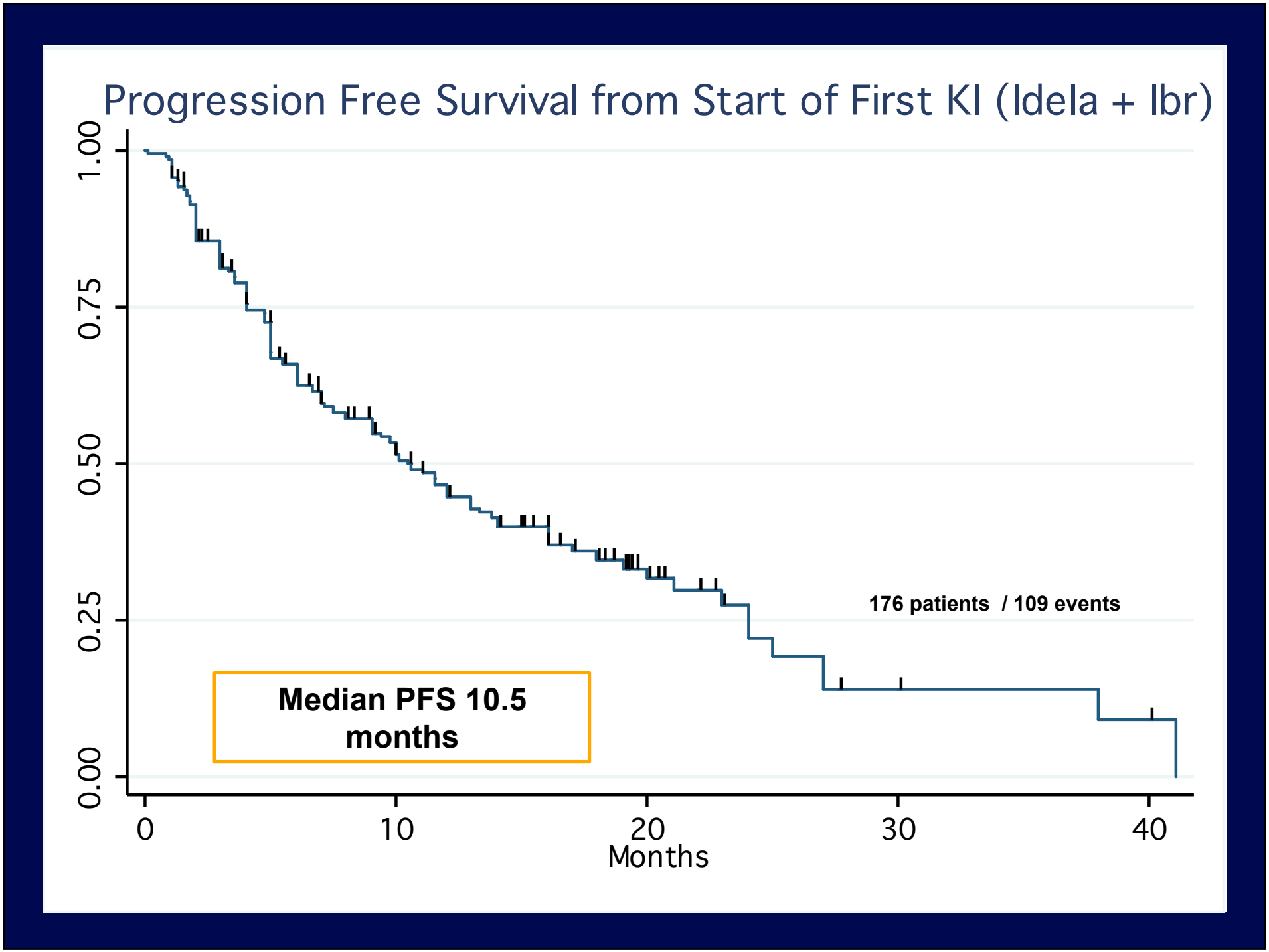
Most Common Reasons for KI Discontinuation		
	Ibrutinib	**Idelalisib**
Toxicity	51%	52%
CLL progression	28%	31%
Richter's transformation	8%	6%
SCT / CAR-T	2%	0%
Unrelated death or other	11%	11%

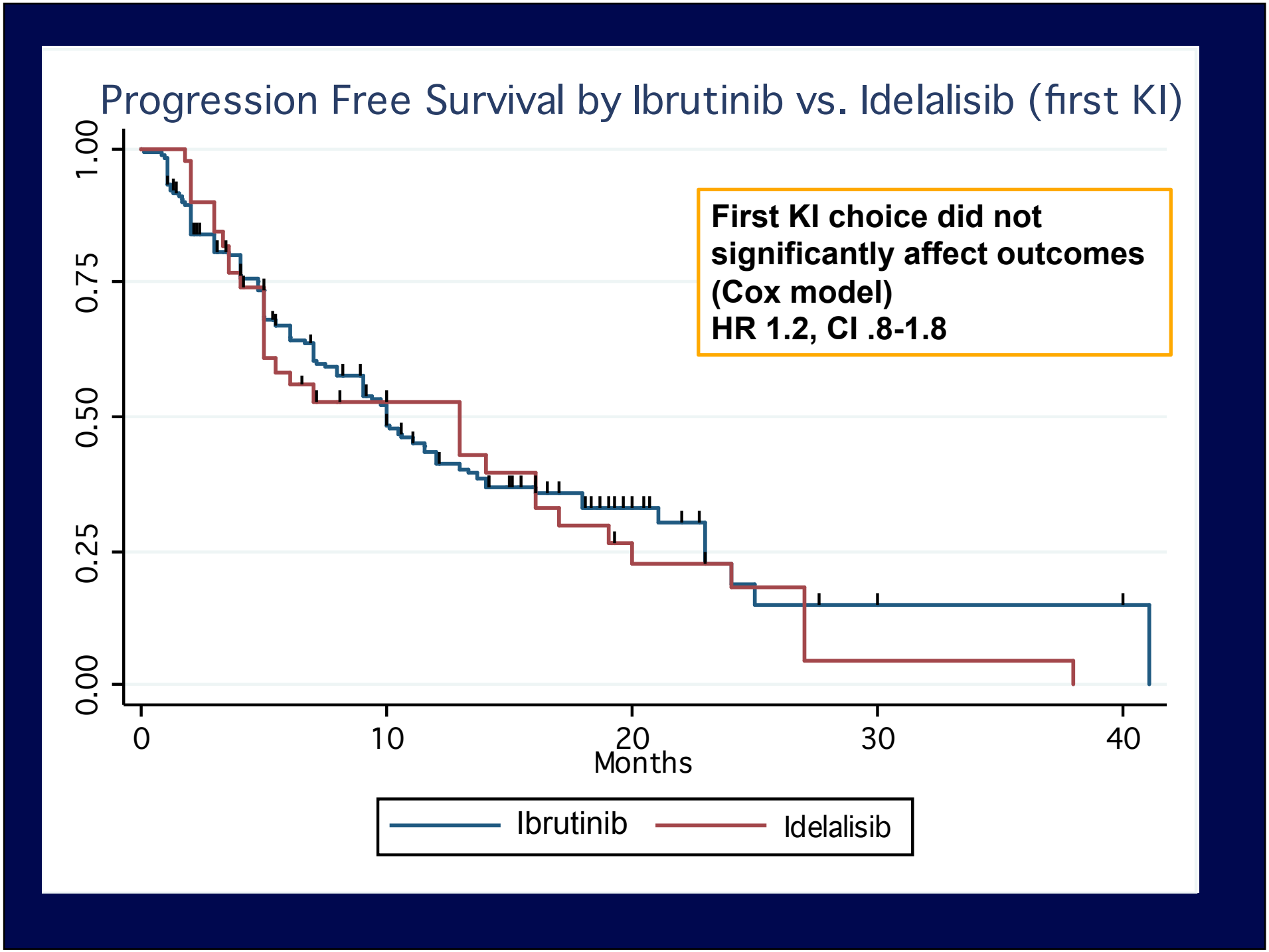
Toxicity as Reason for Discontinuation

"Kinase Inhibitor Intolerant" Patients

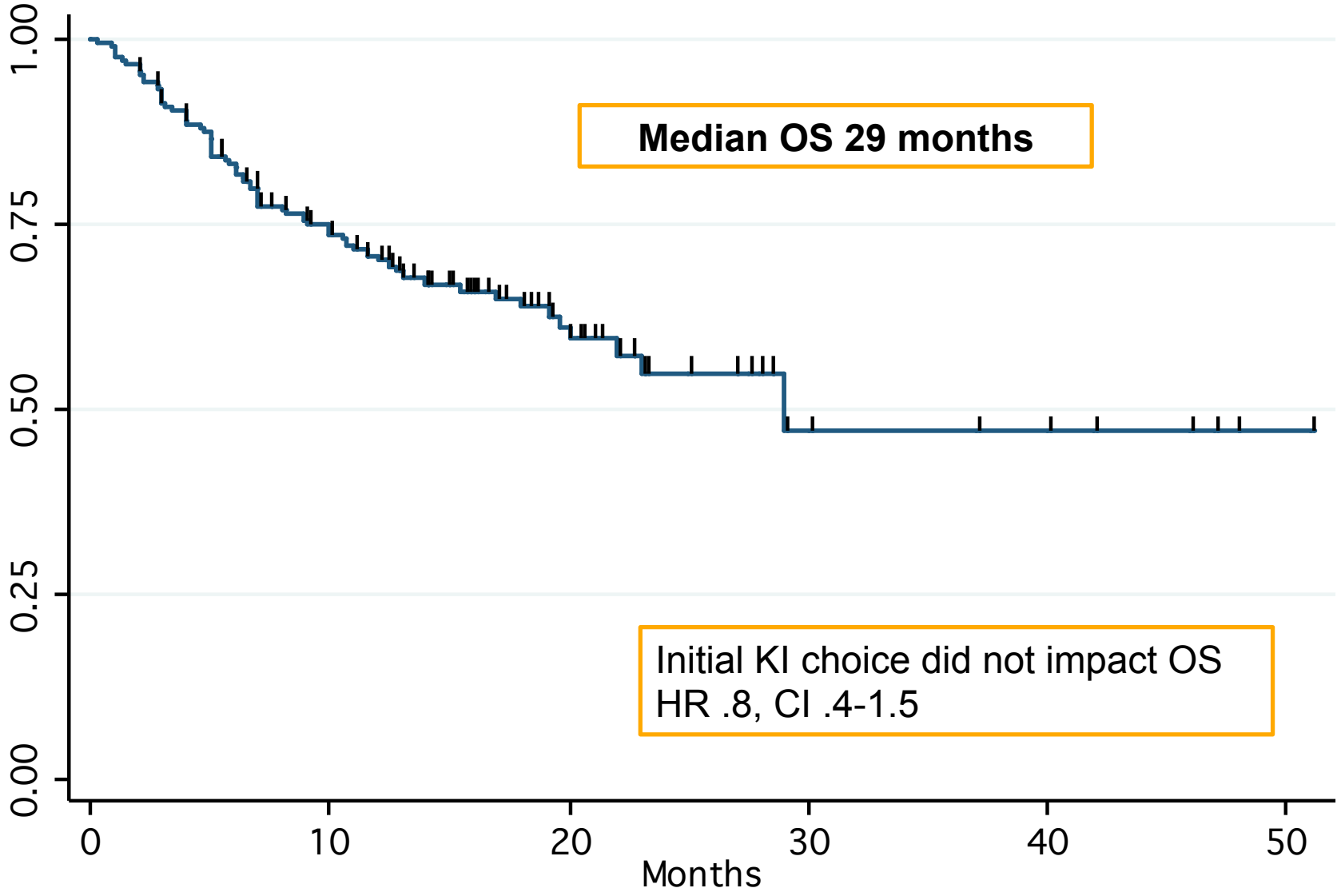
5 Most Common Toxicities as a Reason for Discontinuation

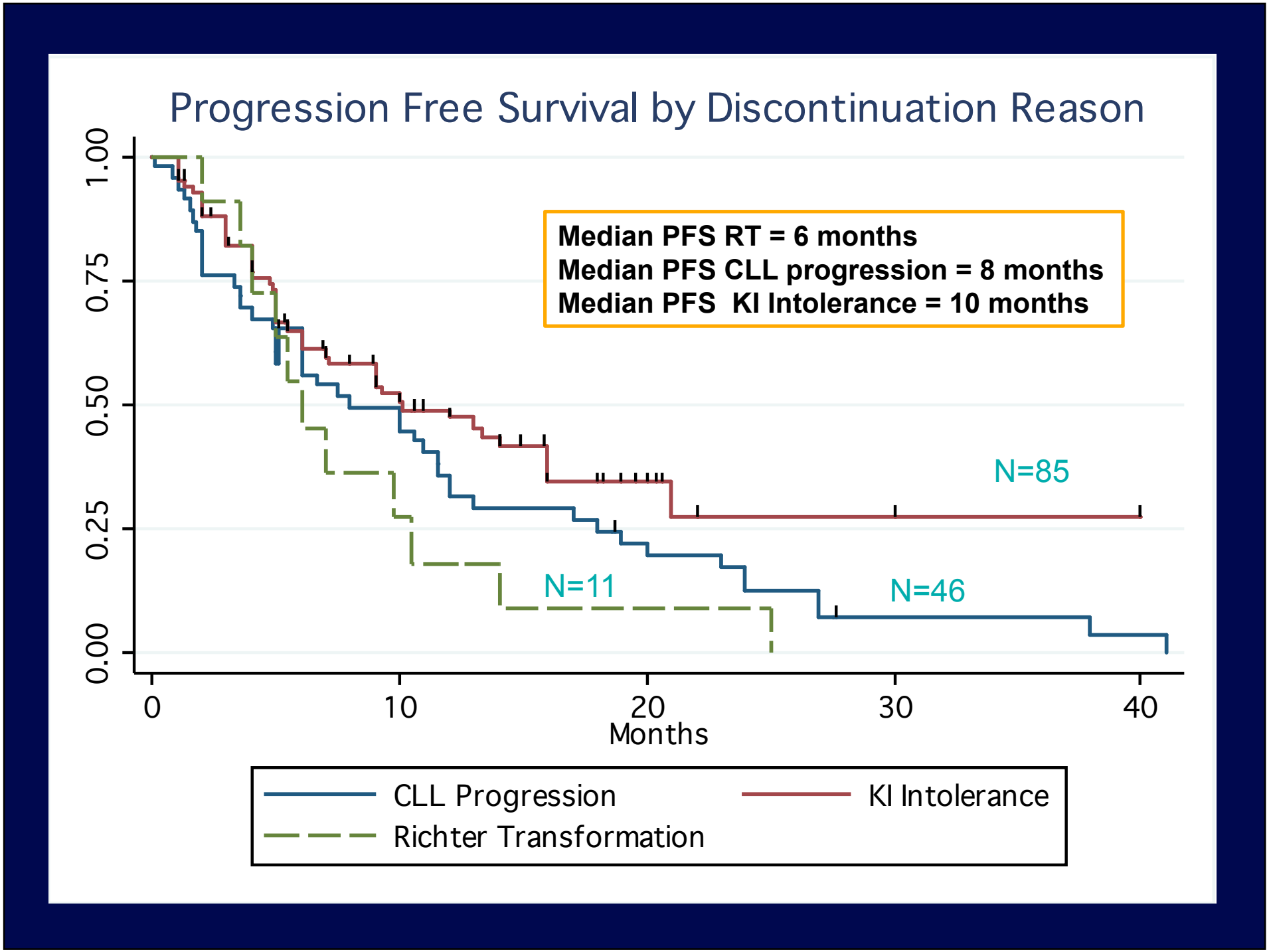
Ibrutinib (N=66)	Idelalisib (N=18)
Atrial fibrillation 20%	Pneumonitis 33%
Infection 12%	Colitis 28%
Hematologic 9%	Rash 17%
Bleeding 9%	Transaminitis 11%
Pneumonitis 8%	Infection 6%


Progression Free Survival from Start of First KI (Idela + Ibr)
1.00
0.75
0.50
0.25
0.00
176 patients / 109 events
Median PFS 10.5 months
0
10
20
30
40
Months


Progression Free Survival by Ibrutinib vs. Idelalisib (first KI)
First KI choice did not significantly affect outcomes (Cox model)
HR 1.2, CI .8-1.8
1.00
0.75
0.50
0.25
0.00
0
10
20
30
40
Months
Ibrutinib
Idelalisib

Overall Survival fom Start of Ibrutinib / Idelalisib




Progression Free Survival by Discontinuation Reason
Median PFS RT = 6 months
Median PFS CLL progression = 8 months
Median PFS KI Intolerance = 10 months
N=85
N=11
N=46
1.00
0.75
0.50
0.25
0.00
0
10
20
30
40
Months
CLL Progression
KI Intolerance
Richter Transformation

Treatment Patterns following Ibrutinib or Idelalisib Discontinuation

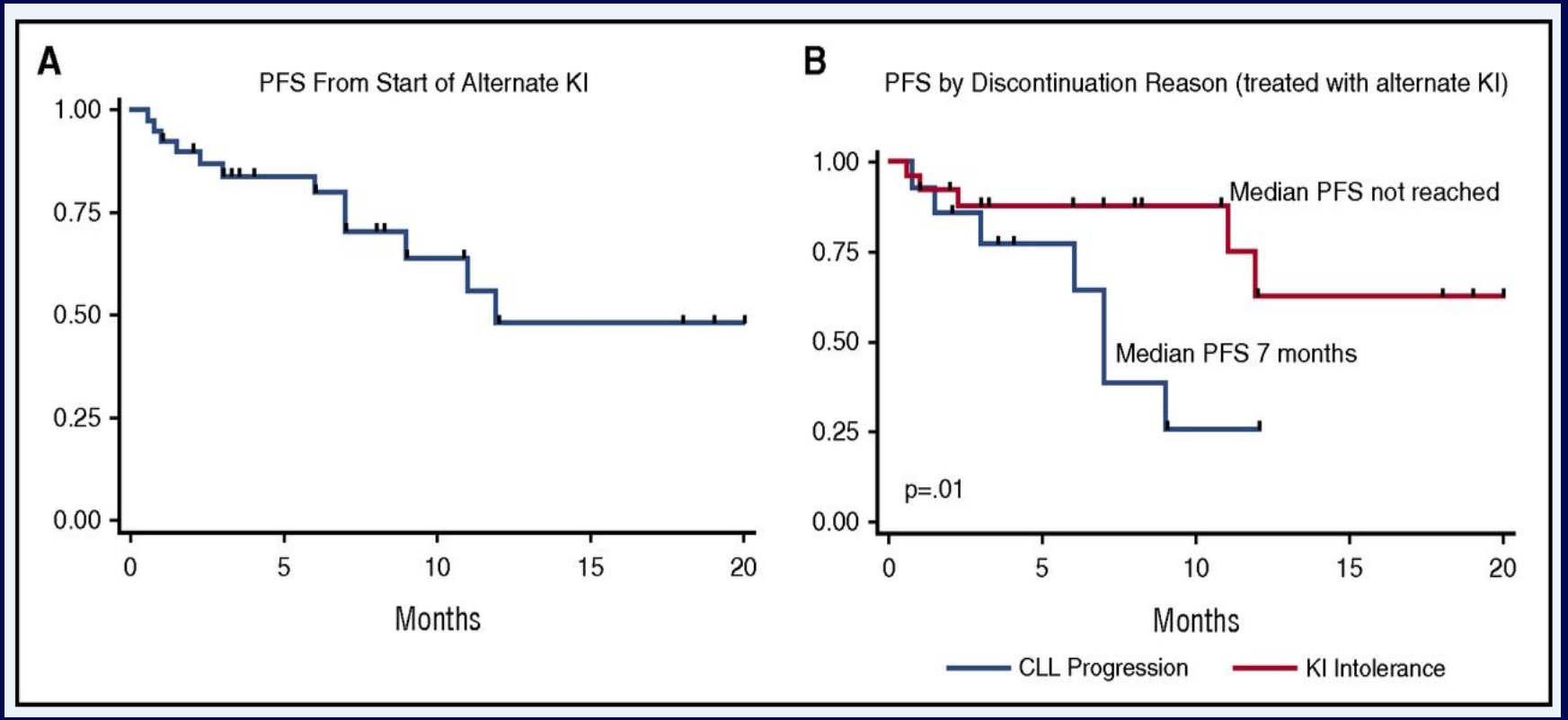
N=114	N	Percentage
Idelalisib-based	25	21.9%
Ibrutinib-based	19	16.7%
BCL2-i (CT)	16	14.0%
Other	10	8.7%
Fludarabine / Bendamustine CIT	9	7.9%
Anthracycline-based	9	7.9%
Cellular-based	8	7.0%
Rituximab	7	6.1%
Obinutuzumab	5	4.4%
Syk-i (CT)	2	1.8%
Ofatumumab	2	1.8%
IMID-based	2	1.8%

Responses following KI Discontinuation

	Alternate KI	BCL2-i (CT)	CITs	CD20 Tx
Number	38	13	12	11
ORR	50%	76%	25%	36%
CR	0%	7%	17%	9%
PR	50%	69%	8%	27%
SD	30%	16%	33%	45%
PD	20%	8%	42%	19%

No direct comparisons performed

Outcomes with Second Kinase Inhibitor Therapy in CLL



PFS for alternate KI. (A) PFS from start of alternate KI (ibrutinib → idelalisib, idelalisib→ ibrutinib). (B) PFS from start of alternate KI stratified by reason for discontinuation (CLL progression vs KI intolerance).

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ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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ORIGINAL ARTICLE

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]

Mato *et al*, Annals Oncology 2017

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Study Methods

- Multicenter, retrospective cohort study
- 9 US based academic centers
- Celgene Connect Registry (199 centers, 80% community)
- 683 CLL patients treated with KI in front line and relapse-refractory settings

- Baseline demographics
- KI dosing information
- First KI outcomes (stratified by KI / LOT / site / clinical trials)
- Capture reasons for discontinuation
- Toxicity profile first KI
- Subsequent therapies and outcomes to develop treatment sequence

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Baseline characteristics

Table 1. Baseline characteristics at start of first KI and dose modifications

Characteristic	Ibrutinib as first KI	Idelalisib as first KI
Median age at diagnosis	61 (22–95)	61.5 (35–80)
	$n = 611$ (n=subjects with available data)	$n = 62$
Median number of prior therapies	2 (0–10)	2 (0–7)
	$n = 616$	$n = 62$
	n=80, first line	n=14, first line
Elevated LDH	60%	56%
	$n = 322$	$n = 48$
B symptoms present	33%	29%
	$n = 476$	$n = 56$
Median WBC	28.7 (0.5–562.6)	25.5 (2.4–549.9)
	$n = 587$	$n = 57$
Del 17p present (FISH)	28%	31%
	$n = 440$	$n = 54$
p53 mutation present (NGS)	12%	15%
	$n = 185$	$n = 41$
Del 11q present (FISH)	32%	25%
	$n = 443$	$n = 53$
Complex karyotype present (≥3 abnormalities)	35%	25%
	$n = 275$	$n = 49$
IGHV unmutated	59%	63%
	$n = 168$	$n = 27$
Median time to treatment initiation	73 months	78 months
Median starting dose	420 mg daily (9% started at < 420 mg daily, $n = 52$)	150 mg BID (24% started at < 150mg BID, $n = 15$)
Administered as monotherapy	87%	16%
Required dose modification during therapy	19%	24%
Required dose interruption during therapy	35%	51%
Median time to discontinuation	7 months (0.1–41)	6 months (0.5–42)

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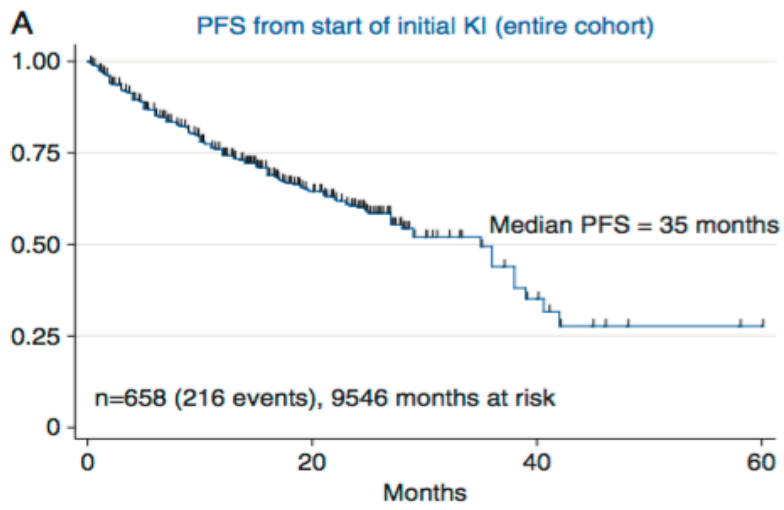
Outcomes from start of first KI and reasons for discontinuation



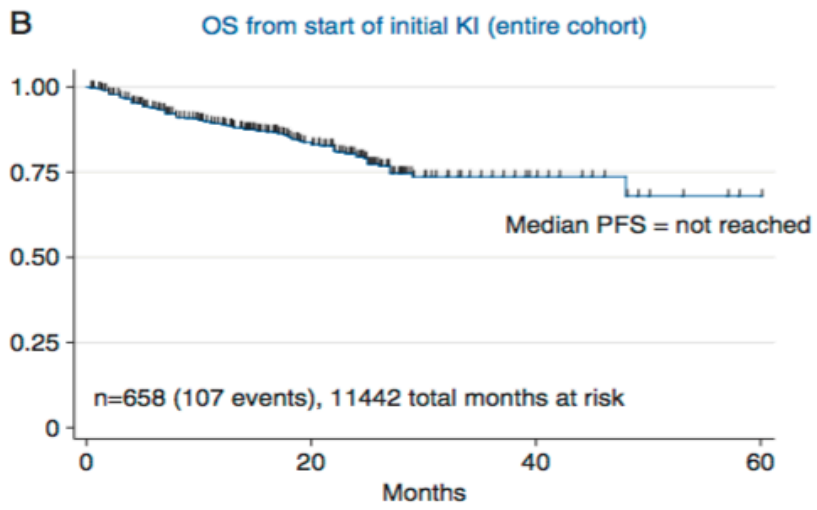


Table 2. Reasons for discontinuation first KI

	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%

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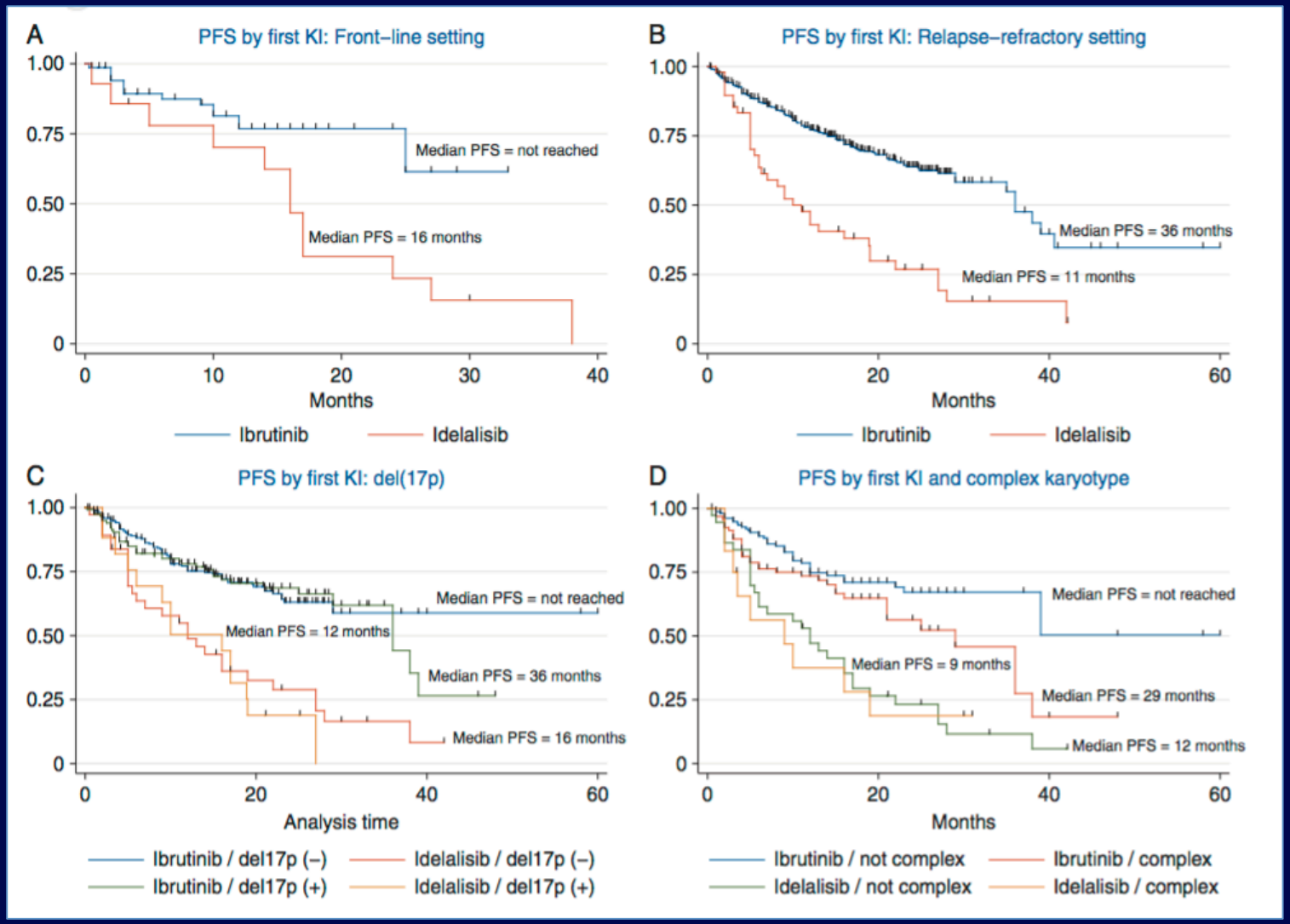
Outcomes stratified by first KI



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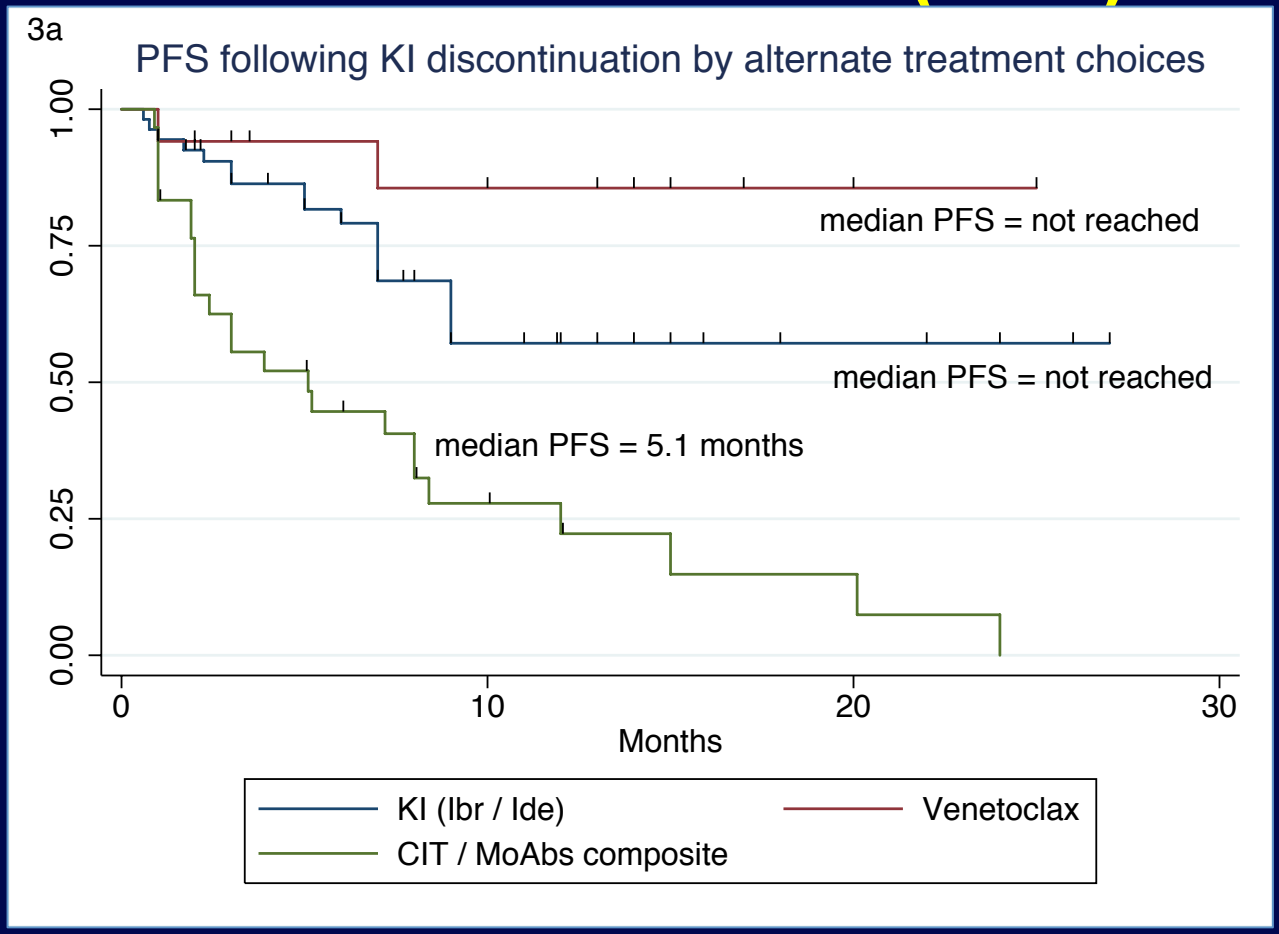
Sequencing after first KI by alternate treatment choices (PFS)



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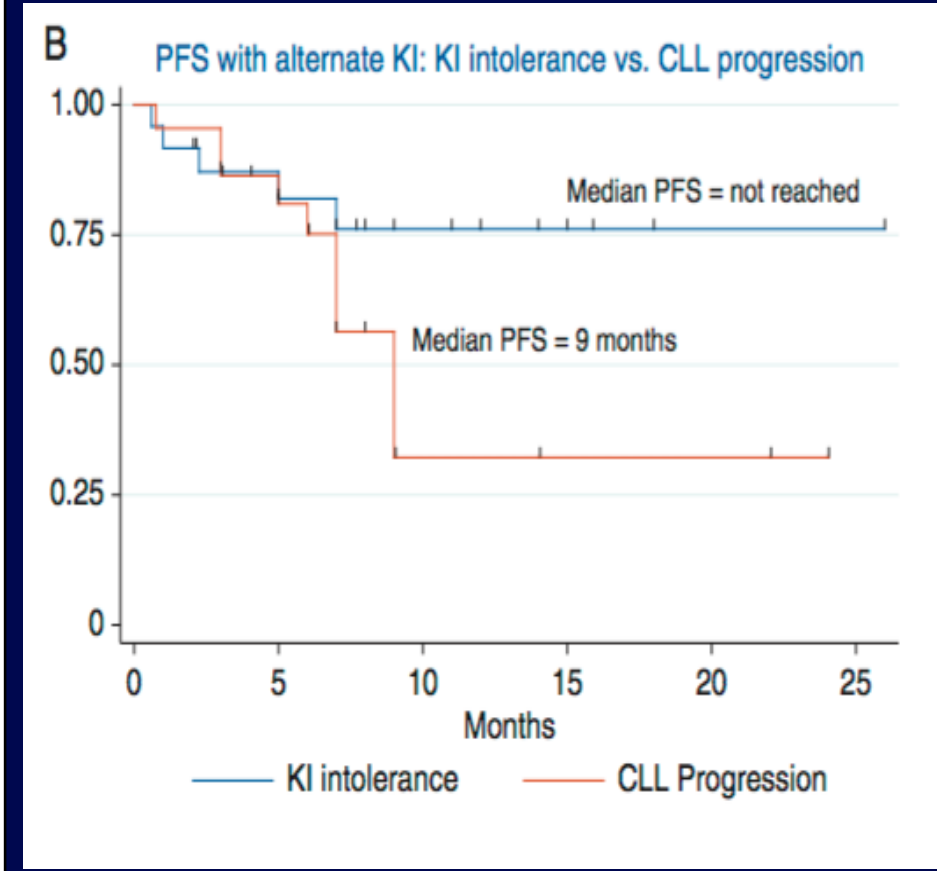
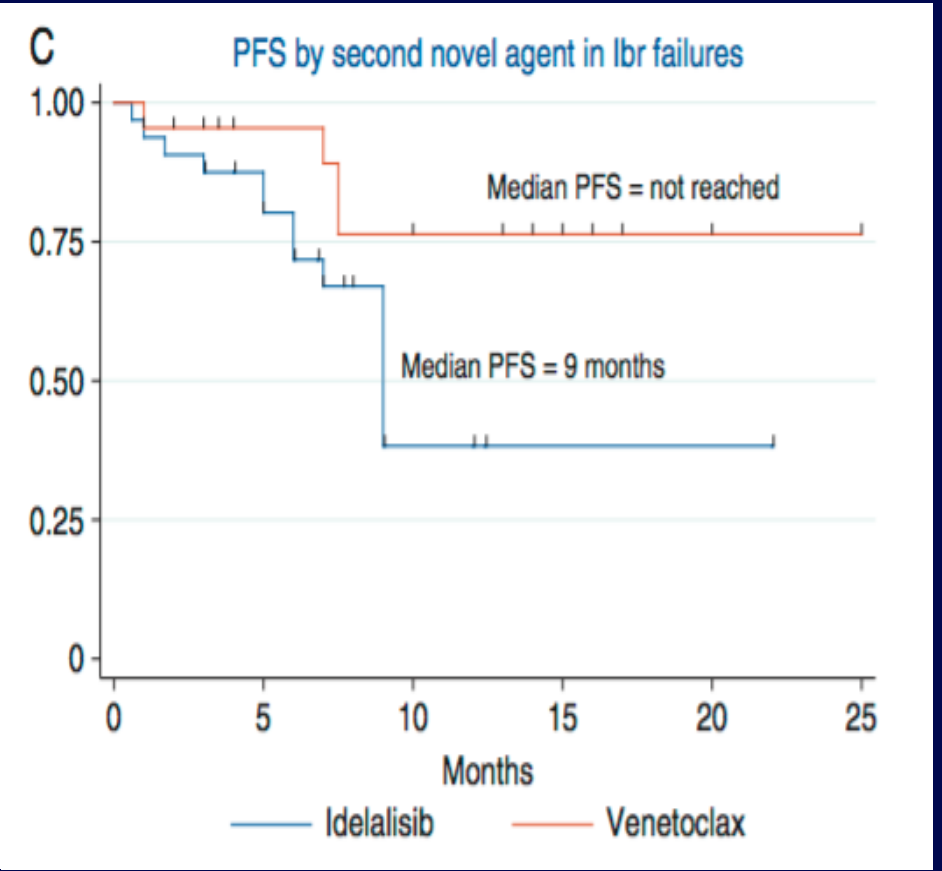
Sequencing in KI / Ibrutinib failures





Alternate KI validated in larger data set for KI intolerant patients

Venetoclax may be better choice in Ibr failures – particularly CLL progression

Mato *et al*, Annals Oncology 2017

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Venetoclax Monotherapy for Patients with Chronic Lymphocytic Leukemia (CLL) who Relapsed After or Were Refractory to Ibrutinib or Idelalisib

Jeffrey Jones,[1] Michael Y. Choi,[2] Anthony R. Mato,[3] Richard R. Furman,[4] Matthew S. Davids,[5] Leonard Heffner,[6] Bruce D. Cheson,[7] Nicole Lamanna,[8] Paul M. Barr,[9] Herbert Eradat,[10] Ahmad Halwani,[11] Brenda Chyla,[12] Maria Verdugo,[12] Rod A. Humerickhouse,[12] Jalaja Potluri,[12] William G. Wierda,[13] Steven Coutre[14]

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American Society of Hematology • San Diego, California • 5 December 2016

M14-032 Study Overview

- Phase 2, open-label study evaluating venetoclax for patients with CLL who relapsed after or are refractory to ibrutinib (Arm A) or idelalisib (Arm B)
- Primary study objectives: ORR and safety
- Secondary and exploratory objectives: DoR, PFS, OS, MRD

Inclusion criteria:

- Indication for treatment by iwCLL criteria[1]
- ECOG 0, 1, or 2
- Adequate bone marrow function
  - ANC ≥1000/μL
  - Hg ≥8 g/dL
  - Platelets ≥30,000/mm^3
- CrCl ≥50 mL/min

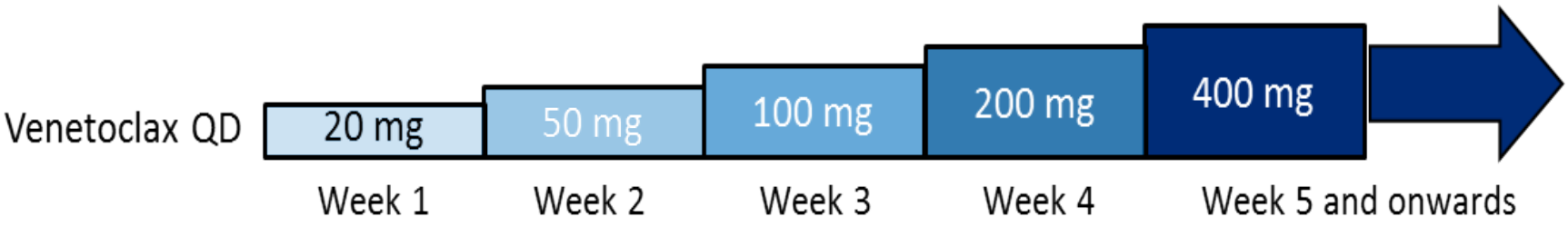
Exclusion criteria:

- Richter's transformation confirmed by PET scan and biopsy
- Active and uncontrolled autoimmune cytopenias
- Allogeneic stem cell transplant within 1 year of study entry

ORR, objective response rate; DoR, duration of response; PFS, progression-free survival; OS, overall survival; MRD, minimal residual disease.

1. Hallek et al, Blood 2008.

Venetoclax Dosing Schedule and TLS Mitigation



- To mitigate TLS risk, patients received prophylaxis with uric acid lowering agents and hydration starting at least 72 hours before first venetoclax dose
- Patients with high tumor burden were hospitalized for first dose at 20 and 50 mg and received IV hydration and rasburicase
- Laboratory values were monitored at first dose and each subsequent dose increase

High tumor burden: any lymph node ≥10 cm; or both lymph node ≥5 cm and ALC ≥25x10^9/L

Patient Characteristics

	Arm A n=43	Arm B n=21
Age, median (range), years	66 (48 – 80)	68 (56 – 85)
Unmutated *IGVH*,* n/N (%)	25/29 (86)	11/13 (85)
del(17)(p13.1),* n/N (%)	21/43 (49)	2/21 (10)
Baseline laboratory values, median (range)		
CrCl, mL/min	83 (54 – 119)	75 (44 – 140)
Hemoglobin, g/dL	11.2 (5.8 – 14.6)	12.2 (7.1 – 14.4)
Platelet count, $x10^9$/L	117 (20 – 446)	115 (30 – 439)
Neutrophil count, $x10^9$/L	3.5 (0 – 24)	2.4 (0 – 49)
Lymphocyte count, $x10^9$/L	19 (.2 – 263)	14 (.3 – 407)
Bulky nodal disease, n (%)		
≥5 cm	15 (35)	11 (52)
≥10 cm	7 (16)	5 (24)
Prior therapies, median (range)	4 (1 – 12)†	3 (1 – 11)†
Prior ibrutinib, n (%)	43 (100)	5 (24)
Months on ibrutinib, median (range)	17 (1 – 56)	6 (2 – 11)
Refractory, n (%)	39 (91)	2 (10)
Prior idelalisib, n (%)	4 (9)	21 (100)
Months on idelalisib, median (range)	10 (2 – 31)	8 (1 – 27)
Refractory, n (%)	2 (5)	14 (67)

*Site reported data.
†2 received only frontline ibrutinib; 2 received only frontline idelalisib.

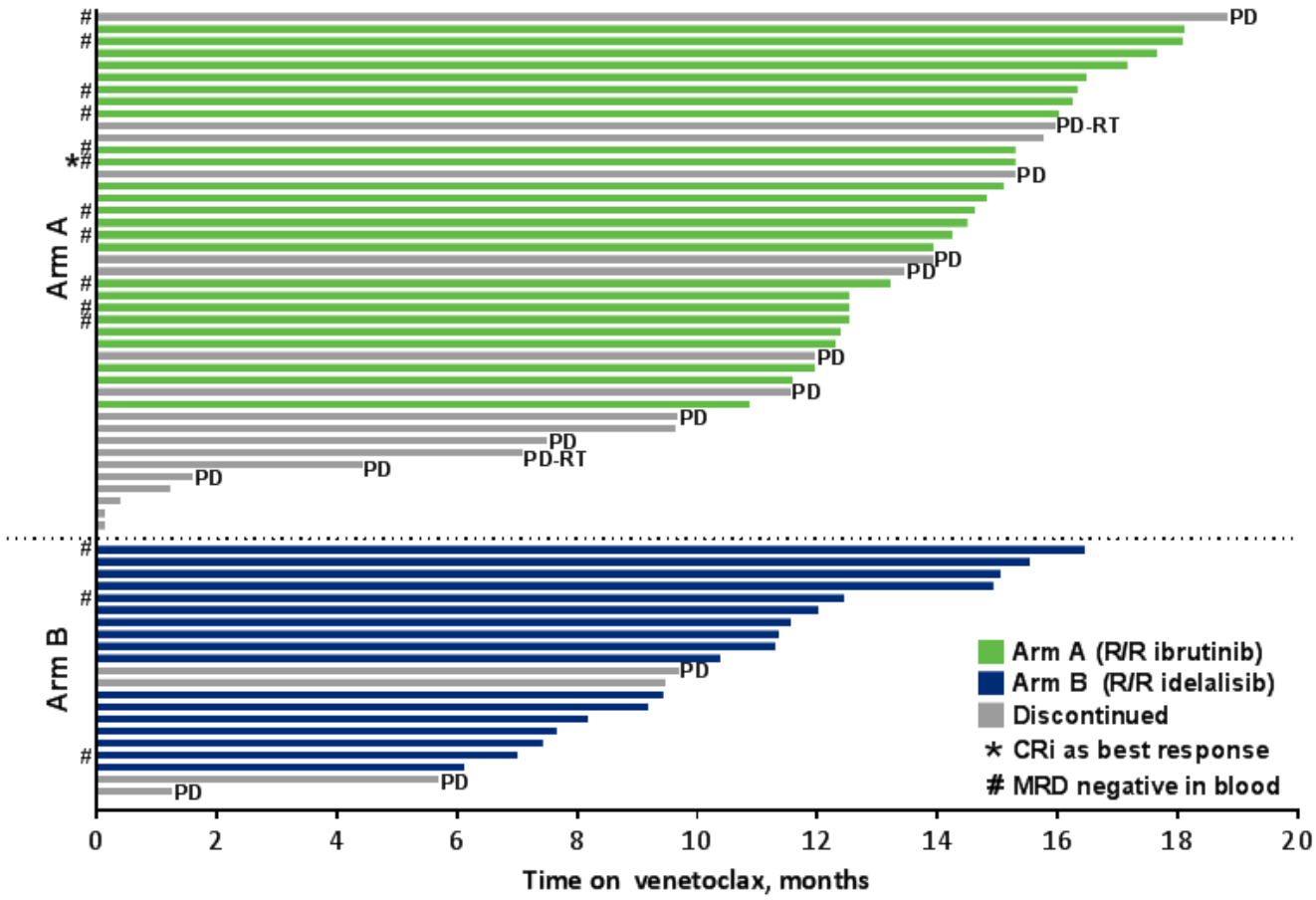
Efficacy

	Arm A n=43		Arm B n=21	
Best response, n (%)	Assessed by		Assessed by	
	IRC	Investigator	IRC	Investigator
ORR	30 (70)	29 (67)	13 (62)	12 (57)
CR/CRi	0/1 (2)	2 (5)/1 (2)	0/0	2 (10)/1 (5)
nPR	0	2 (5)	0	0
PR	29 (67)	24 (56)	13 (62)	9 (43)
Non-responder*	13 (30)	14 (23)	8 (38)	9 (43)
SD	–	9 (21)	–	8 (38)
PD	–	1† (2)	–	1† (5)
D/C‡	–	4 (9)	–	0

*Non-responder category for IRC includes both SD or PD, which were not identified as separate categories per IRC.
†CLL progression and discontinued due to progression.
‡D/C, patient discontinued the study prior to assessment.

Current Status

- Median time on study (range): Arm A, 13 months (0.1–18); Arm B, 9 months (1.3–16)

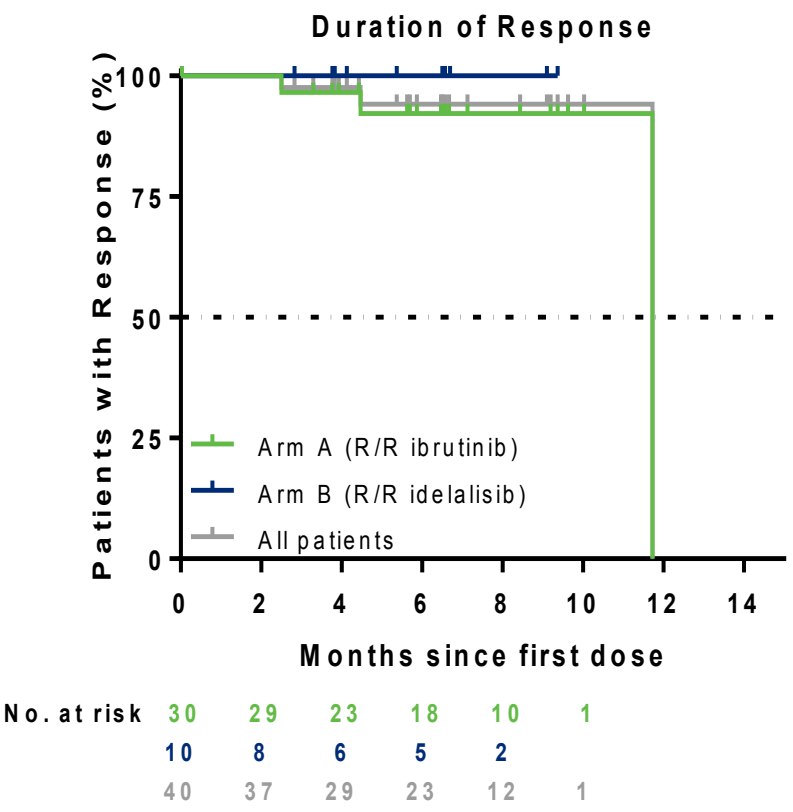


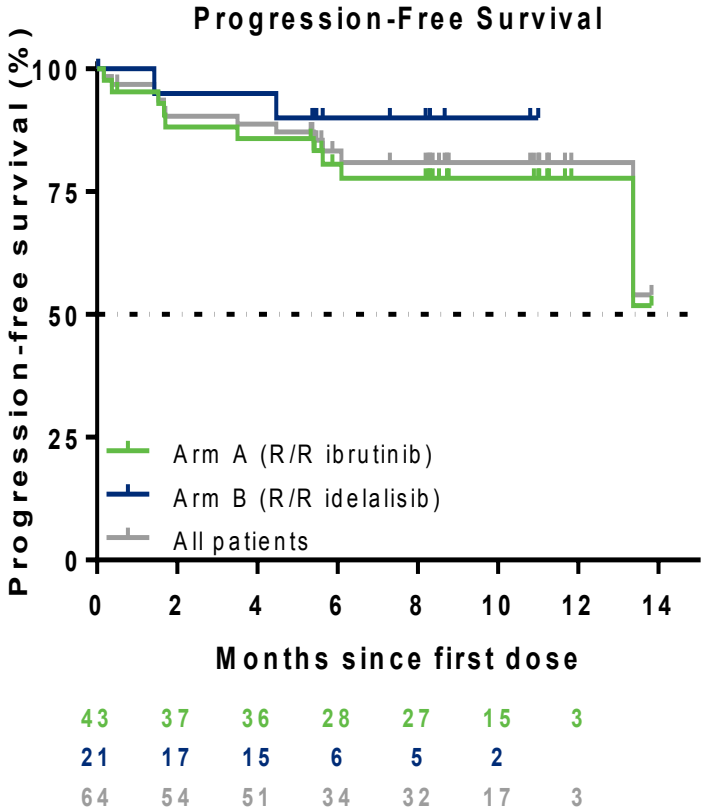
Data as of 10June2016

PD, progressive disease. PD-RT, progressive disease due to Richter's transformation.
Early discontinuations were due to AEs (n=3) and withdrawn consent (n=1).

Efficacy Per Independent Review

- Median DoR, PFS, and OS had not been reached after 11.8 months of follow up
- Estimated 12 month PFS for all patients: 80% (95% CI: 67%, 89%)

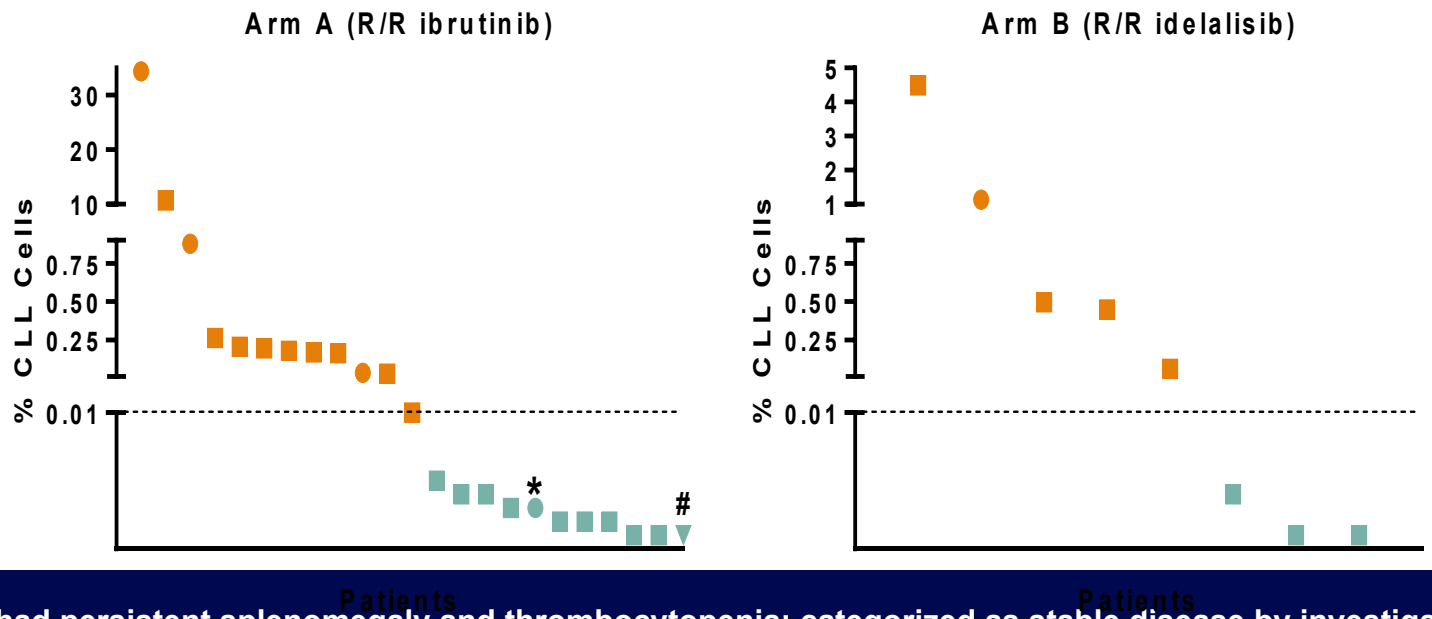




Data as of 10June2016

Minimal Residual Disease in Peripheral Blood

MRD-positive MRD-negative ▼ CRi ■ PR ● Non-responder by IRC



*Patient had persistent splenomegaly and thrombocytopenia; categorized as stable disease by investigator.
#Also had confirmed bone marrow MRD-negative assessment.

- 14/31 (45%) patient samples have demonstrated MRD-negative peripheral blood between Weeks 24 – 48
- 5 patients demonstrating sustained MRD negative status in blood had subsequent marrow evaluations; 1 patient was MRD negative in bone marrow

Data as of 10June2016

Safety

Event, n (%)	All Patients N=64
Any grade AE	**64 (100)**
Common all-grade AEs (≥20% patients)	
Neutropenia	37 (58)
Thrombocytopenia	28 (44)
Diarrhea	27 (42)
Nausea	26 (41)
Anemia	23 (36)
Fatigue	20 (31)
Decreased WBC	14 (22)
Hyperphosphatemia	14 (22)

Event, n (%)	All Patients N=64
Grade 3/4 AEs	**53 (83)**
Common grade 3/4 AEs (≥10% patients)	
Neutropenia	29 (45)
Thrombocytopenia	18 (28)
Anemia	14 (22)
Decreased WBC	8 (13)
Febrile neutropenia	7 (11)
Pneumonia	7 (11)
Serious AEs	**34 (53)**
Febrile neutropenia	6 (9)
Pneumonia	5 (8)
Multi-organ failure	2 (3)
Septic shock	2 (3)
Increased potassium	2 (3)

- **No clinical TLS was observed; 1 patient with high tumor burden met Howard criteria for laboratory TLS**

Data as of 10June2016

Venetoclax followed by Ibrutinib

- Six of 8 patients with progressive CLL/SLL on venetoclax were treated with ibrutinib as their first postprogression therapy
- Five achieved a PR
- 3 remain alive on therapy at last follow-up (6, 13, and 16 months)
- 3 died, 2 of toxicity and 1 of PD

Anderson et al. Blood. 2017 June 22;129(25):3362-3370