Second generation Btk inhibitor (acalabrutinib) in CLL

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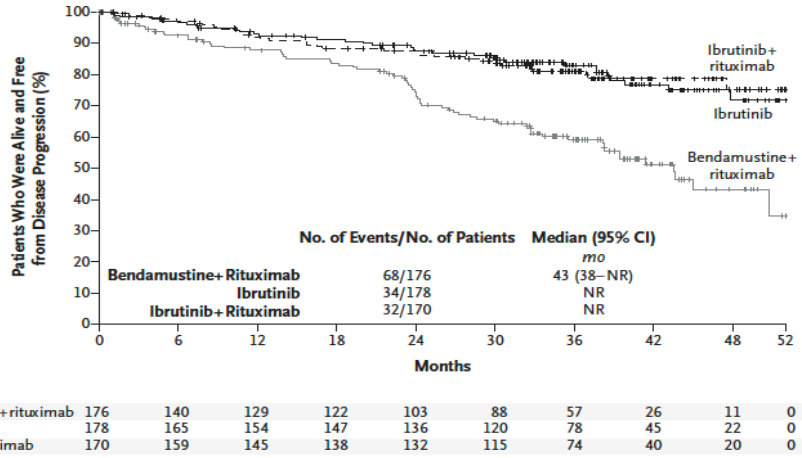
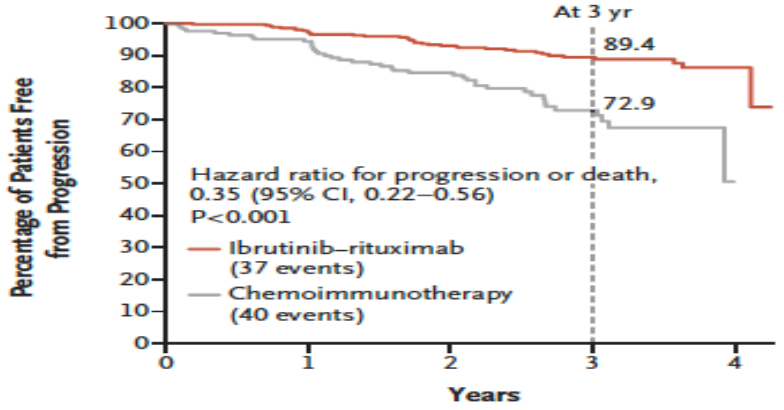
Do we need a second generation Btk inhibitor?

Bendamustine + rituximab vs ibrutinib ± rituximab
(Alliance Intergroup A041202 study)

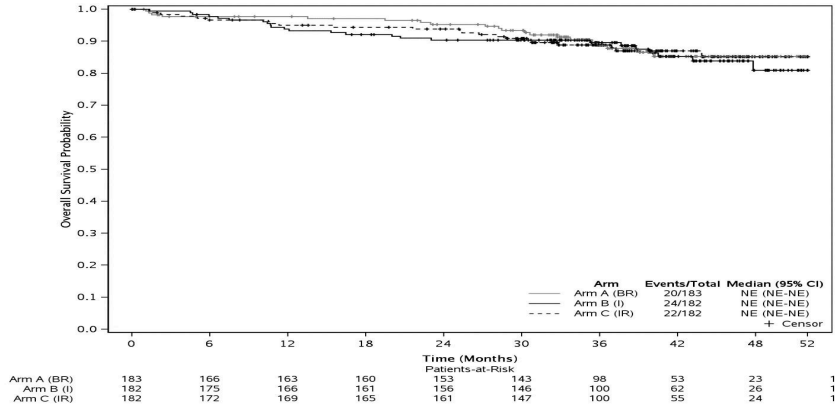
FCR vs ibrutinib+rituximab (ECOG-ACRIN E1912 study)

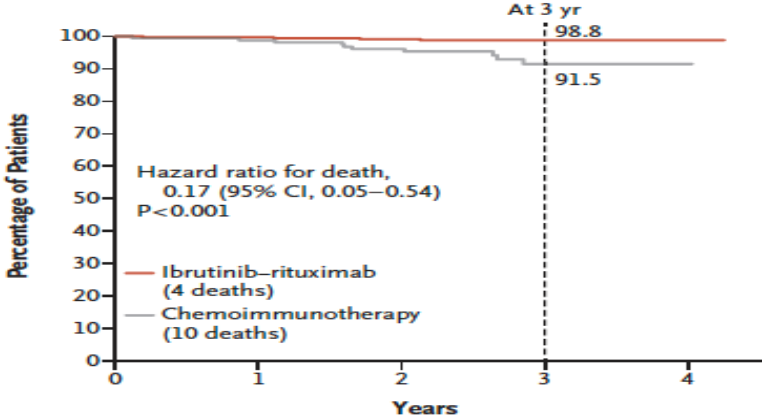
Progression free survival





Overall survival





Woyach *et al.*, N Engl J Med 2018;379:2517-28.

Shanafelt *et al.*, N Engl J Med 2019;381:432-43.

Do we need a second generation Btk inhibitor?

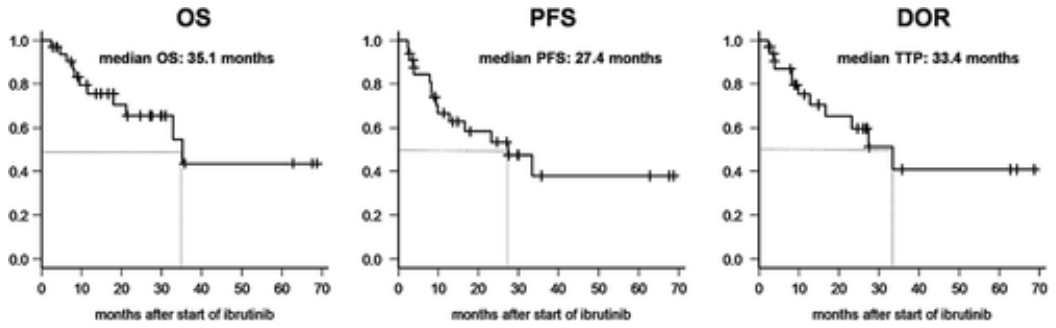
Intolerance – up to 40% of patients stop ibrutinib

Relapsed CLL (Resonate) – 16%
Front-line CLL (Resonate 2) - 21%

Resistance – in relapsed CLL disease progression is frequent

Relapsed CLL (Resonate) – 37%
Front-line CLL (Resonate 2) - 6%

Effectiveness – mantle cell lymphoma



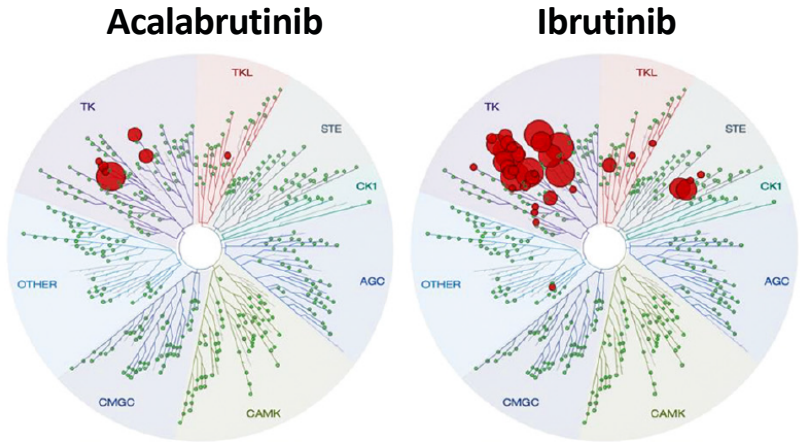
What types of Btk inhibitor?

1. First generation irreversible Btk inhibitor – ibrutinib
2. Second generation irreversible Btk inhibitors
    a) Acalabrutinib
    b) Zanubrutinib
    c) Tirabrutinib
3. Reversible Btk inhibitors
    a) Vecabrutinib
    b) ARQ-531
    c) LOXO-305

Acalabrutinib (ACP-196)

- Acalabrutinib is more selective for BTK with less off-target kinase inhibition compared with ibrutinib in vitro

Kinase Selectivity Profiling at 1 μM



Larger red circles represent stronger inhibition

Kinase Inhibition Average IC_{50} (nM)

Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	126.0	10
ITK	>1000	4.9
BMX	46	0.8
TXK	368	2.0
EGFR	>1000	5.3
ERBB2	~1000	6.4
ERBB4	16	3.4
BLK	>1000	0.1
JAK3	>1000	32

BLK = B lymphocyte kinase; BMX = bone marrow tyrosine kinase gene in chromosome X; BTK = Bruton tyrosine kinase; EGFR = epidermal growth factor receptor; ERBB2 = erb-b2 receptor tyrosine kinase; ERBB4 = erb-b4 receptor tyrosine kinase; IC50 = inhibitory concentration of 50%; ITK = interleukin-2-inducible T-cell kinase; JAK3 = Janus kinase 3; TEC = tyrosine kinase expressed in hepatocellular carcinoma; TXK = T and X cell expressed kinase.

Barf T, et al. *J Pharmacol Exp Ther*. 2017;363(2):240-252.

Kinase inhibition by ibrutinib (RPKM)

Max	50-100%	10-50%	<10%

	Btk	EGFR	ERBB2	ITK	JAK3	BLK	TXK	TEC	BMX
lymph node	25.215	0.96	1.984	23.878	18.238	18.903	5.67	1.401	0.653
spleen	18.354	2.399	3.303	8.016	10.946	13.722	3.293	0.714	0.46
bone marrow	10.689	0.011	0.399	3.903	6.022	1.255	1.151	2.419	2.391
appendix	16.713	2.086	5.688	14.742	19.489	6.903	3.135	1.068	1.054
colon	2.73	6.6	23.463	1.357	1.211	0.614	0.452	0.651	1.609
duodenum	1.996	2.264	25.114	1.192	1.286	0.251	0.38	0.613	1.853
esophagus	1.706	12.244	28.242	1.258	0.539	0.196	0.362	1.448	1.139
small intestine	2.78	2.882	25.254	2.673	1.668	0.558	0.64	0.729	2.083
stomach	2.949	3.675	18.99	2.186	2.055	1.454	0.35	0.522	0.305
gall bladder	4.215	5.19	13.767	4.246	2.691	0.459	0.709	0.578	1.417
urinary bladder	6.332	5.419	18.075	3.533	3.739	1.69	1.284	0.486	1.292
heart	0.536	1.638	13.89	0.247	0.306	0.103	0.097	0.385	1.729
skin	1.161	15.598	30.178	0.303	0.557	0.023	0.651	1.339	0.124
brain	1.391	7.382	3.469	0.166	0.765	0.035	0.038	0.063	0.077
endometrium	1.139	6.099	9.462	0.959	0.907	0.014	0.396	0.512	0.624
fat	0.928	11.438	4.586	0.254	0.509	0.034	0.154	0.203	1.546
kidney	0.347	5.822	34.694	0.212	0.456	0.014	0.335	0.529	0.107
liver	0.897	8.657	8.136	0.508	0.404	0.106	0.229	0.633	0.141
lung	6.878	7.609	19.713	3.135	1.845	0.253	0.749	0.938	0.875
placenta	2.691	36.612	12.284	0.281	2.747	0.087	1.188	0.542	2.234
adrenal	1.428	4.387	2.204	0.549	0.538	0.051	0.236	0.912	0.156
ovary	0.267	7.517	10.64	0.292	3.829	0.027	0.041	0.187	0.255
pancreas	0.134	1.916	3.119	0.099	0.151	0.02	0.031	0.06	0.11
prostate	0.788	6.146	21.356	0.543	0.941	0.198	0.139	0.354	0.274
salivary gland	0.592	4.088	11.97	0.365	0.647	0.24	0.186	0.402	0.086
testis	1.025	2.779	5.871	0.598	1.598	0.117	0.477	0.882	0.162
thyroid	0.47	12.717	18.11	0.463	0.328	0.076	0.186	0.682	0.439

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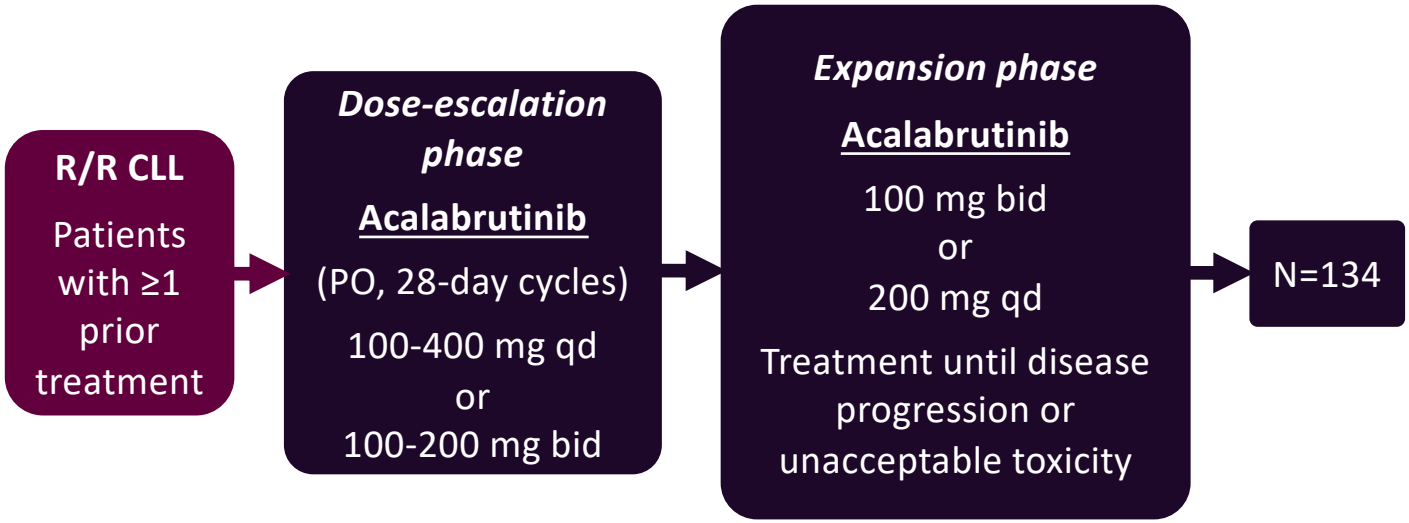
ACE-CL-001: Acalabrutinib Monotherapy in R/R CLL

Enrollment: 3 February 2014 to 26 November 2015



Primary endpoints:
- Safety

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

Ad hoc endpoint:
- Time to response

All patients were switched to 100 mg BID

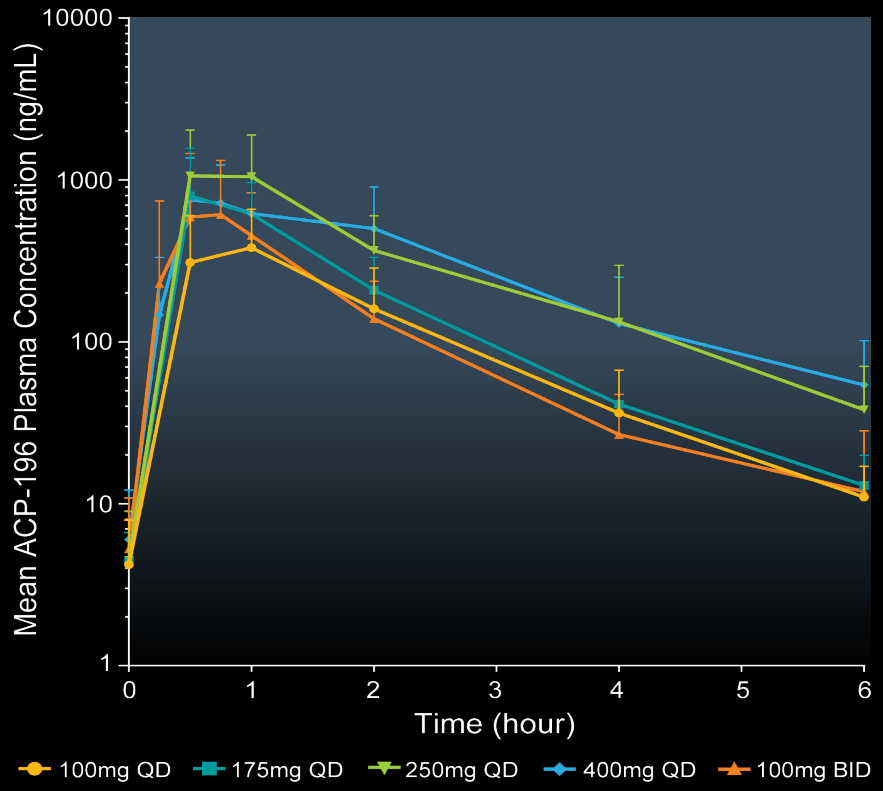
Data cutoff: 3 April 2017

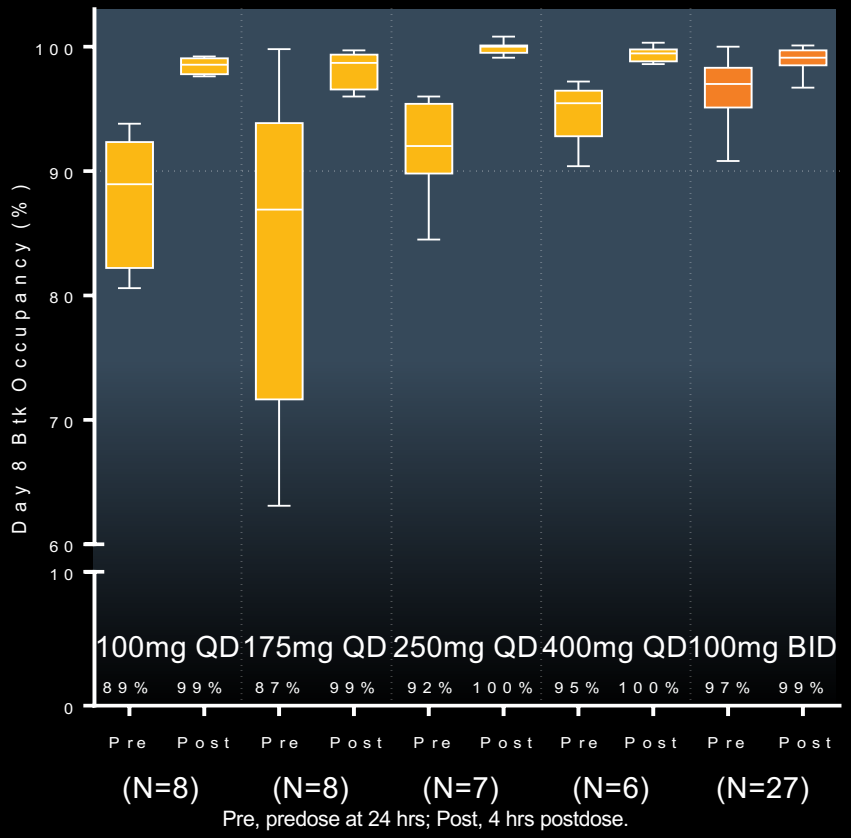
bid = twice daily; CLL = chronic lymphocytic leukemia; bid = twice daily; DOR = duration of response; IWCLL = International Workshop on Chronic Lymphocytic Leukemia; ORR = overall response rate; PFS = progression-free survival; po = orally; qd = once daily; R/R = relapsed/refractory.

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

ACE-CL-001 (Part 1): Pharmacokinetics/Pharmacodynamics

1 hour half-life; Rapid oral absorption; Full Btk occupancy





Pre, predose at 24 hrs; Post, 4 hrs postdose.

Byrd *et al*. ASH 2015: Abstract #831

ACE-CL-001: Baseline Patient Characteristics

Characteristic	N=134
Median age, y (range)	66 (42-85)
Male sex, n (%)	99 (74)
ECOG performance status ≤1, n (%)	130 (97)
Bulky disease ≥5 cm, n (%)	52 (39)
β2-microglobulin >3.5 mg/L , n/N (%)	76/101 (75)
Median number of prior therapies (range)	2 (1-13)
Histology, n (%)	
CLL	132 (99)
SLL	2 (1)
Genomic status, n/N (%)	
Del(17p)	27/116 (23)
Del(11q)	21/116 (18)
Unmutated IGHV status	81/111 (73)
Complex karyotype (≥3 abnormalities)	29/71 (41)

CLL = chronic lymphocytic leukemia; ECOG = Eastern Cooperative Oncology Group; IGHV = immunoglobulin variable region heavy chain; SLL = small lymphocytic leukemia.

Byrd JC, et al. ASH 2017

ACE-CL-001: Patient Disposition

- Most patients (78%) are still on treatment after a median of 24.5 months

Disposition, n (%)	N=134
Median follow-up, months (range)	24.5 (0.6-37.4)
On treatment	105 (78)
Patients with treatment discontinuation	29 (22)
Reason patient discontinued treatment	
Adverse event[a]	12 (9)
Progressive disease	10 (7)
Death	2 (1)
Progressive disease	1 (1)
Unknown[b]	1 (1)
Withdrawal by patient	3 (2)
Physician decision[c]	2 (1)

[a]Adverse events leading to discontinuation included congestive cardiac failure (n=1), pneumonia (n=3), autoimmune hemolytic anemia (n=1), abdominal pain (n=1), diarrhea (n=1), neutropenia and thrombocytopenia (n=1), dyspnea (n=1), thrombocytopenia (n=1), anemia and neutropenia (n=1), and atrial fibrillation (n=1; discontinued on 23rd day of study).
[b]Cause of death might possibly be community acquired pneumonia but unknown as contact was lost with the patient before death.
[c]Due to lack of response and physician preference.

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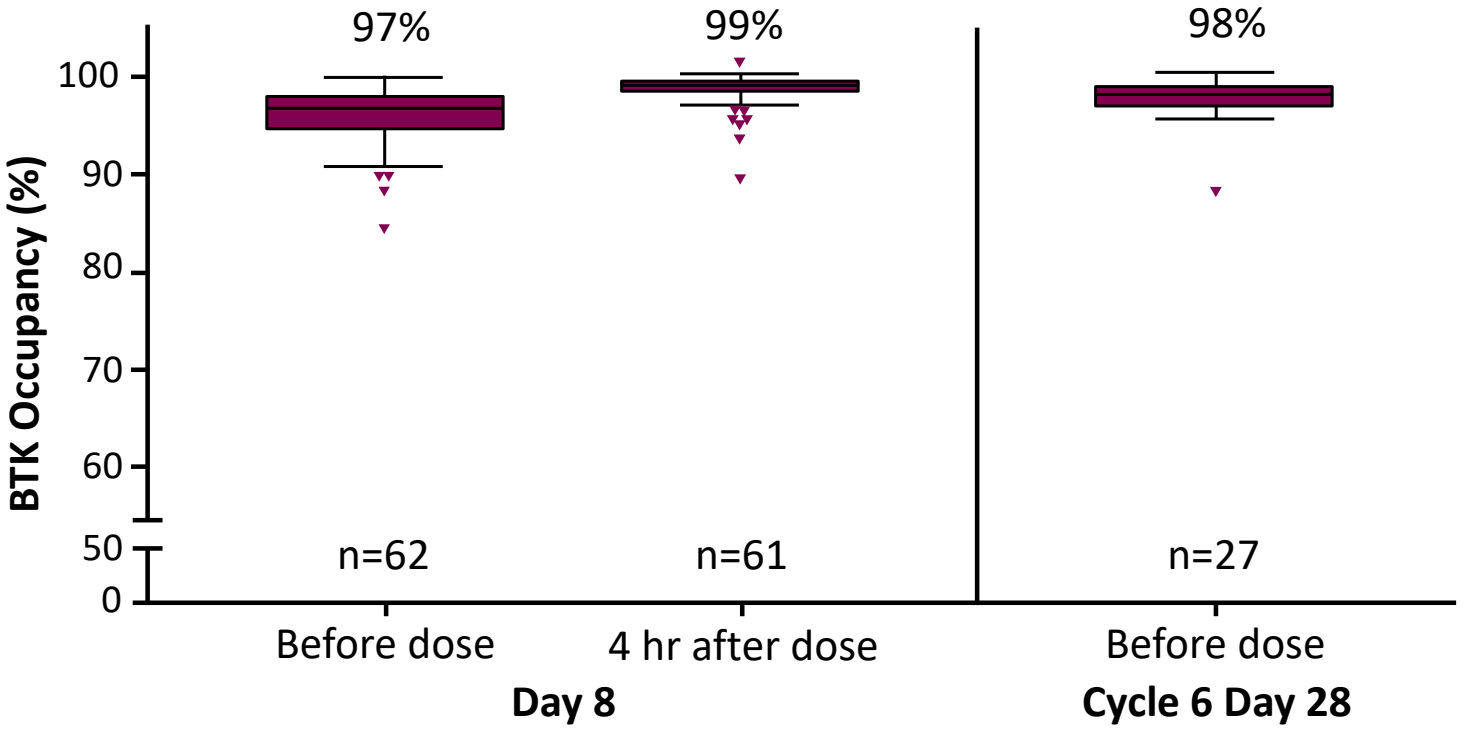
ACE-CL-001: Pharmacodynamics

- At steady-state, acalabrutinib dosed at 100 mg bid resulted in a median BTK occupancy of 99% 4 hours postdose and 97%-98% before next dose



bid = twice daily; BTK = Bruton tyrosine kinase.

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ACE-CL-001: Investigator-Assessed Response to Acalabrutinib

- ORR was high, including in patients with high-risk CLL

	N=134[a]
ORR (CR + PR), % (95% CI)[b]	87 (80, 92)
ORR + PRL, % (95% CI)[b]	93 (88, 97)
Best Response, n (%)	
CR[c]	4 (3)
PR	112 (84)
PRL	9 (7)
SD	3 (2)
PD	1 (1)
Unknown/NA[d]	5 (4)
ORR by high-risk subgroup (CR + PR), n/n, % (95% CI)[b]	
del(17p)	24/27, 89 (71, 98)
del(11q)	19/21, 90 (70, 99)
Unmutated IGHV	73/81, 90 (82, 96)
Complex karyotype (≥3 abnormalities)	23/29, 79 (60, 92)

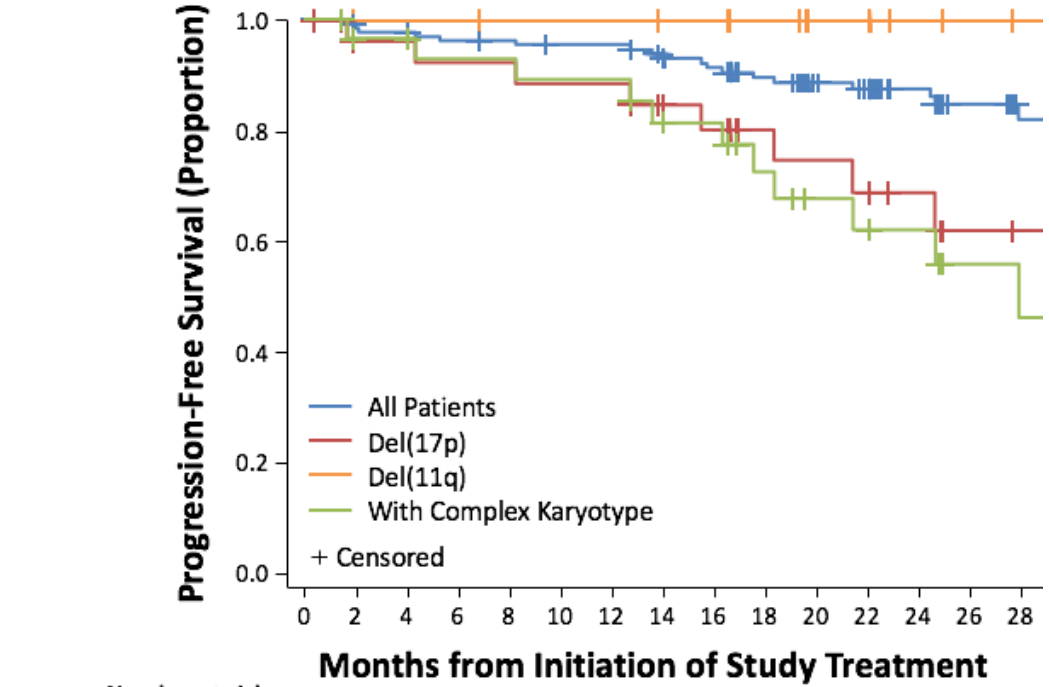
[a]Data reported in patients who received ≥1 dose of study drug. [b]95% exact binomial confidence interval. [c]Three cases were MRD-positive CRs. [d]These patients had no postbaseline tumor assessment.

Byrd JC, et al. ASH 2017

ACE-CL-001: Time-to-Event Outcomes

- Median PFS in the overall population was not rea
- Median TTR (≥ PR) was 5.3 months (95% CI: 1.7, 2
  and median DOR was not reached

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



Number at risk

All Patients	134	129	127	124	123	121	121	114	111	98	83	78	64	46	30
Del(17p)	27	25	25	24	24	23	23	19	18	14	13	12	10	6	5
Del(11q)	21	20	20	20	19	19	19	18	18	16	12	12	9	7	5
With Complex Karyotype	29	27	27	25	25	24	24	20	20	15	12	11	10	6	5

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

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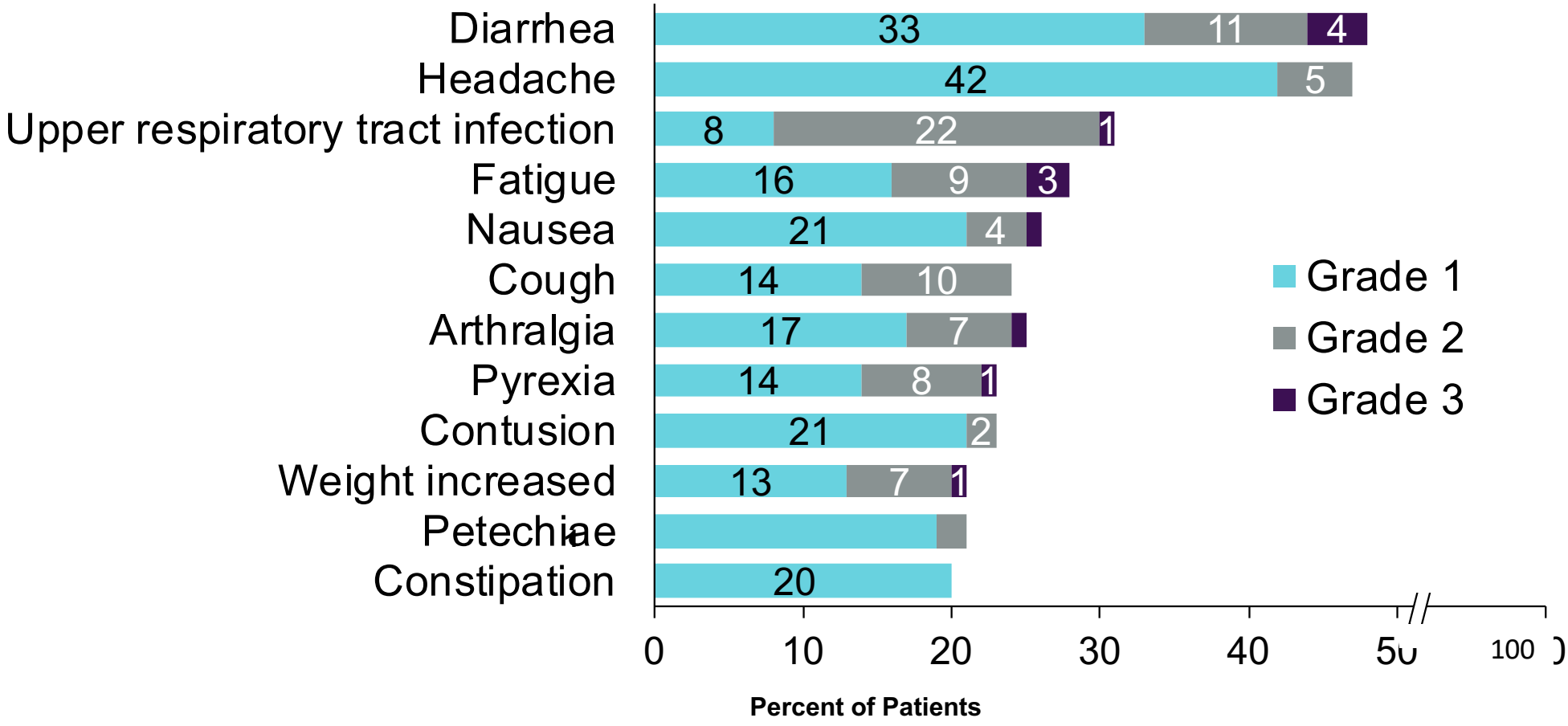
ACE-CL-001: Common Adverse Events (≥20% Patients)



Byrd JC, et al. ASH 2017

ACE-CL-001: Safety

- Grade ≥3 AEs occurred in 74 patients (55%)
  - Grade ≥3 AEs occurring in ≥5% of patients were neutropenia (12%) and pneumonia (11%)
- One case of grade ≥3 bleeding occurred (epistaxis)
- Other AEs of interest (any grade/grade ≥3) included hypertension (13%/4%) and atrial fibrillation or atrial flutter (3%/1%)
- Seven patients experienced Grade 5 AEs: pneumonia (n=4), candida sepsis (n=1), congestive cardiac failure (n=1), and plasmablastic lymphoma (n=1)
- The most common AEs leading to discontinuation were pneumonia (n=3), anemia, neutropenia, and thrombocytopenia (n=2 each)
- Richter transformation occurred in 4 patients (3%)

AE = adverse event.

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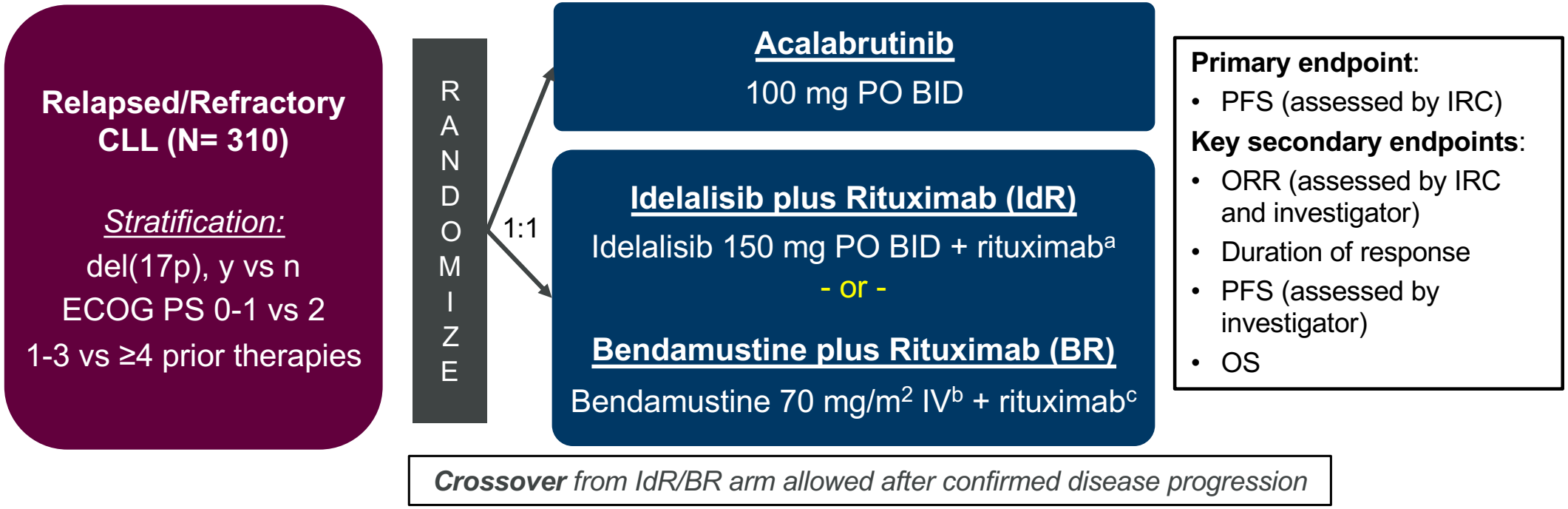
ACE-CL-001: Conclusions

- Acalabrutinib monotherapy in patients with R/R CLL/SLL resulted in an overall ORR of 87% (≥ PR) and 93% (≥ PRL)
  - High response rates were also observed in patients with high-risk disease
- With a median follow-up of 24.5 months, median PFS was not reached, including in patients with del(17p)(p13.1) and del(11q)(q22.3)
  - 18-month DOR rate was 88% with similar findings in high-risk CLL
- Reported AEs with acalabrutinib indicated a tolerable safety profile, including a relatively low rate of Grade ≥3 bleeding and cardiac events
- Treatment with acalabrutinib is being investigated in patients with TN (ACE-CL-007 [NCT02475681] and R/R CLL (ACE-CL-006 [NCT02477696] and ACE-CL-309 [NCT02970318]) in 3 ongoing Phase 3 studies

AE = adverse event; CLL = chronic lymphocytic leukemia; DOR = duration of response; ORR = overall response rate; PFS = progression-free survival; R/R = relapsed/refractory; SLL = small lymphocytic leukemia; TN = treatment naive.

Byrd JC, et al. ASH 2017

ASCEND Study Design (ACE-CL-309)



- Interim analysis was planned after occurrence of ~79 PFS events (2/3 of primary event goal)

[a]First dose at 375 mg/m^2, subsequent doses (up to 8) at 500 mg/m^2 every 2 wk for 4 infusions, then every 4 wk for 3 infusions.
[b]On day 1 and day 2 of each cycle.
[c]First dose at 375 mg/m^2, subsequent doses at 500 mg/m^2 on day 1 of each cycle for up to 6 cycles.
BID = twice daily; CLL = chronic lymphocytic leukemia; ECOG PS = Eastern Cooperative Oncology Group performance status; IRC = independent review committee; IV = intravenous; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PO = orally.

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Patient Demographics and Baseline Characteristics

Characteristic	Acalabrutinib N=155	IdR/BR N=155
Age, median (range), y	68 (32-89)	67 (34-90)
Bulky disease ≥5 cm, n (%)	76 (49)	75 (48)
Rai stage III-IV, n (%)[a]	65 (42)	64 (41)
No. prior therapies, median (range)	1 (1-8)	2 (1-10)
1	82 (53)	67 (43)
2	40 (26)	46 (30)
3	17 (11)	24 (15)
≥4	16 (10)	18 (12)
Prior therapy type, n (%)		
Purine analogues	109 (70)	104 (67)
Alkylators other than bendamustine	133 (89)	131 (85)
Bendamustine[b]	47 (30)	48 (31)
Anti-CD20 monoclonal antibodies	130 (84)	119 (77)
Stem cell transplantation	1 (1)	1 (1)
Cytogenetic status, n/n (%)		
del(17p)	28/155 (18)	21/154 (14)
del(11q)	39/155 (25)	44/154 (29)
Unmutated IGHV[c]	118/154 (77)	125/153 (82)
Complex karyotype[d]	50/154 (32)	46/153 (30)

[a]Derived based on data collected at screening.
[b]Bendamustine retreatment was allowed if the prior response to bendamustine lasted >24 months.
[c]1 patient in the acalabrutinib arm and 2 patients in the IdR/BR arm had missing data; 3 and 2 patients, respectively, were not evaluable.
[d]1 patient in the acalabrutinib arm and 2 patients in the IdR/BR arm had missing data; 7 and 15 patients, respectively, were not evaluable.
BR = bendamustine plus rituximab; IdR = idelalisib plus rituximab; IGHV = immunoglobulin heavy-chain variable region gene.

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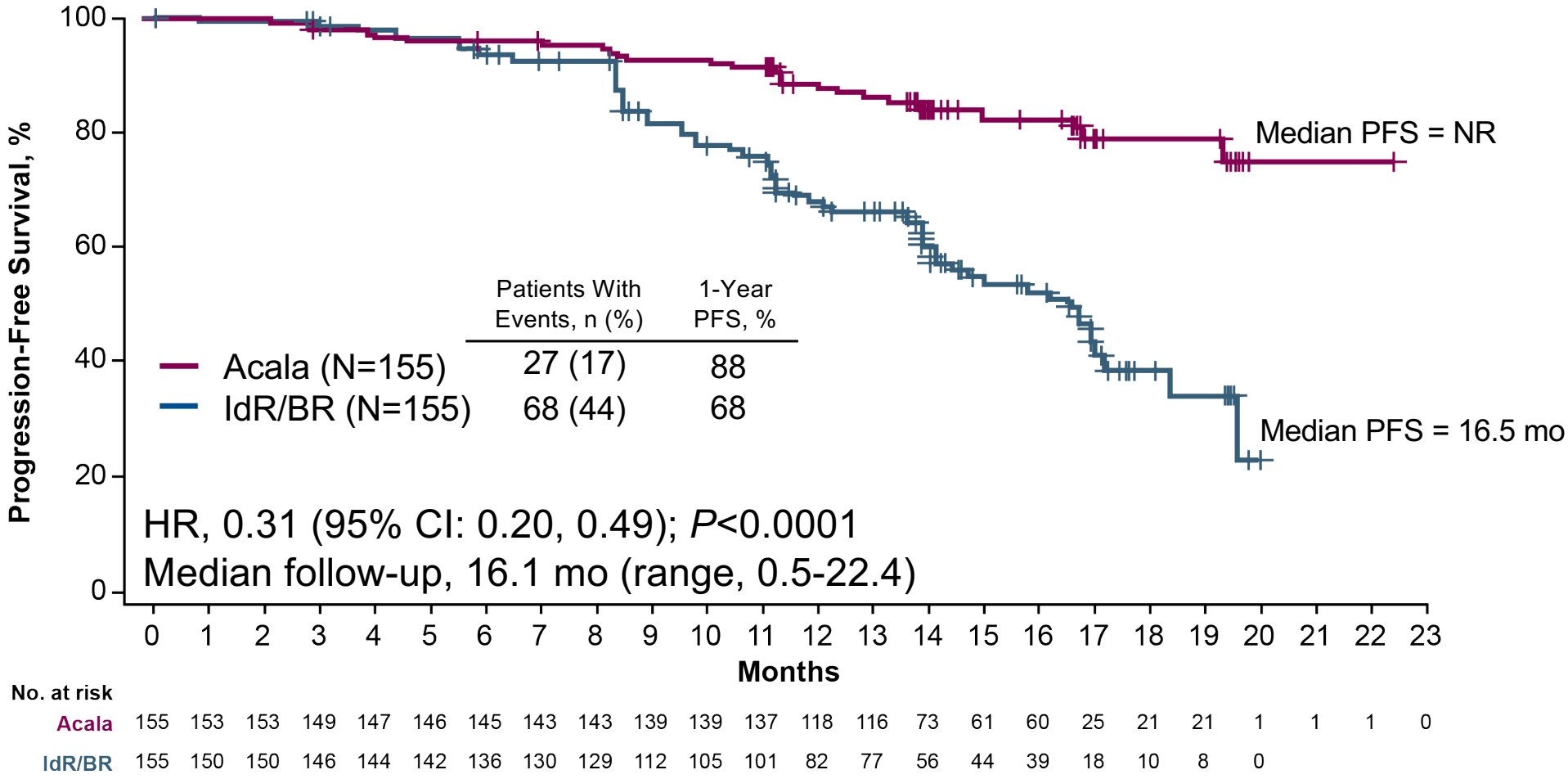
IRC-Assessed PFS Superior for Acalabrutinib vs IdR/BR



Acala = acalabrutinib; BR = bendamustine plus rituximab; HR = hazard ratio; IdR = idelalisib plus rituximab; IRC = independent review committee; NR = not reached; PFS = progression-free survival.

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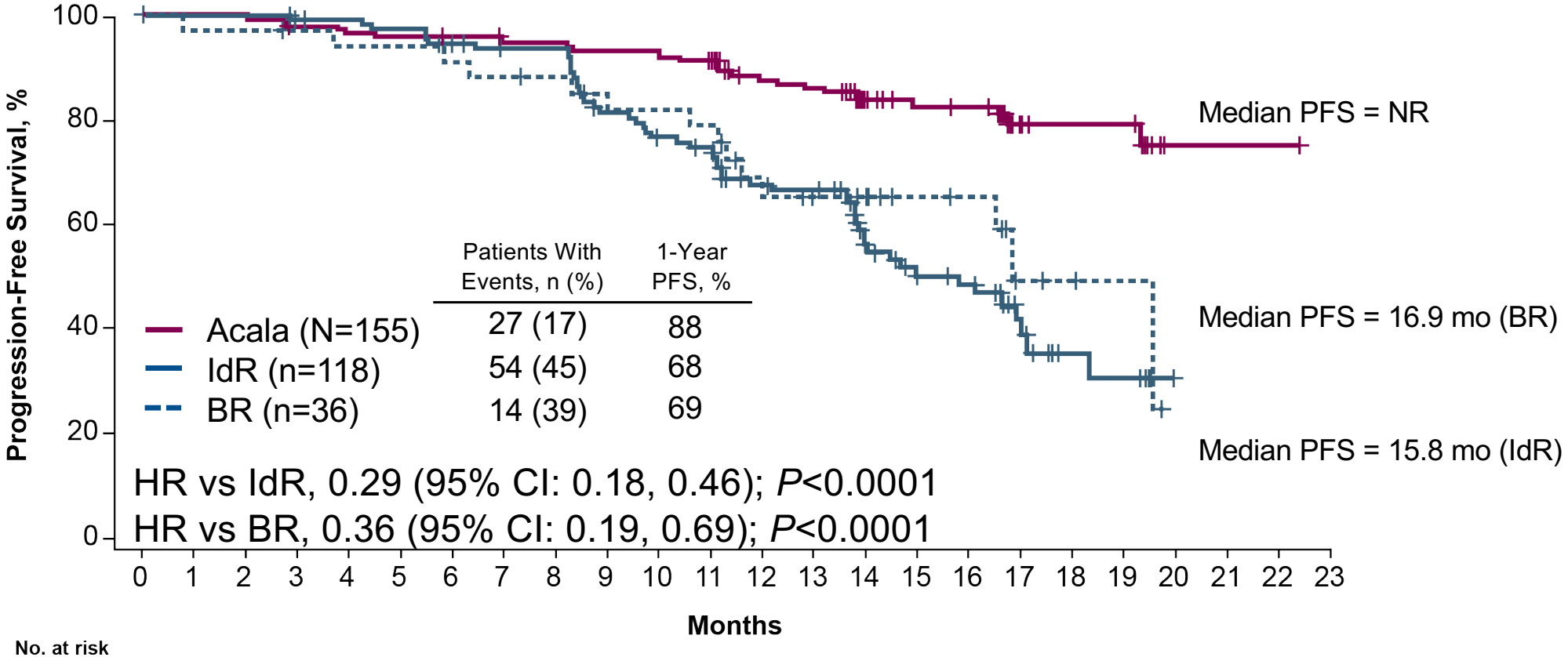
IRC-Assessed PFS Superior for Acalabrutinib vs IdR or BR



No. at risk

Acala	155	153	153	143	147	146	145	143	143	139	139	137	118	116	73	61	60	25	21	21	1	1	1	0
IdR	119	116	116	113	112	110	105	100	100	85	79	76	62	59	41	33	29	14	7	6	0			
BR	36	34	34	33	32	32	31	30	29	27	26	25	20	18	15	11	10	4	3	2	0			

Acala = acalabrutinib; BR = bendamustine plus rituximab; HR = hazard ratio; IdR = idelalisib plus rituximab; IRC = independent review committee; NR = not reached; PFS = progression-free survival.

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IRC-Assessed Response for Acalabrutinib and IdR/BR

Response	Acalabrutinib N=155	IdR/BR N=155	Comparison
ORR (CR + CRi + nPR + PR), % (95% CI)	81 (74, 87)	76 (68, 82)	*P*=0.22
ORR (CR + CRi + nPR + PR + PRL), % (95% CI)	88 (82, 93)	77 (70, 83)	*P*=0.01
Best response, n (%)			
CR	0	2 (1)	
PR	126 (81)	115 (74)	
PRL	11 (7)	3 (2)	
SD	9 (6)	12 (8)	
PD	2 (1)	1 (1)	
Unknown	7 (5)	22 (14)	
DOR, median (95% CI), mo	NR (NR-NR)	13.6 (11.9-NR)	HR, 0.33 (0.19-0.59) *P*<0.0001
12-mo DOR rate, % (95% CI)	85 (76, 91)	60 (48, 69)	

BR = bendamustine plus rituximab; CR = complete response; CRi = complete response with incomplete bone marrow recovery; DOR = duration of response; HR = hazard ratio; IdR = idelalisib plus rituximab; IRC = independent review committee; nPR = nodal partial response; NR = not reached; ORR = overall response rate; PD = progressive disease; PR = partial response; PRL = partial response with lymphocytosis; SD = stable disease.

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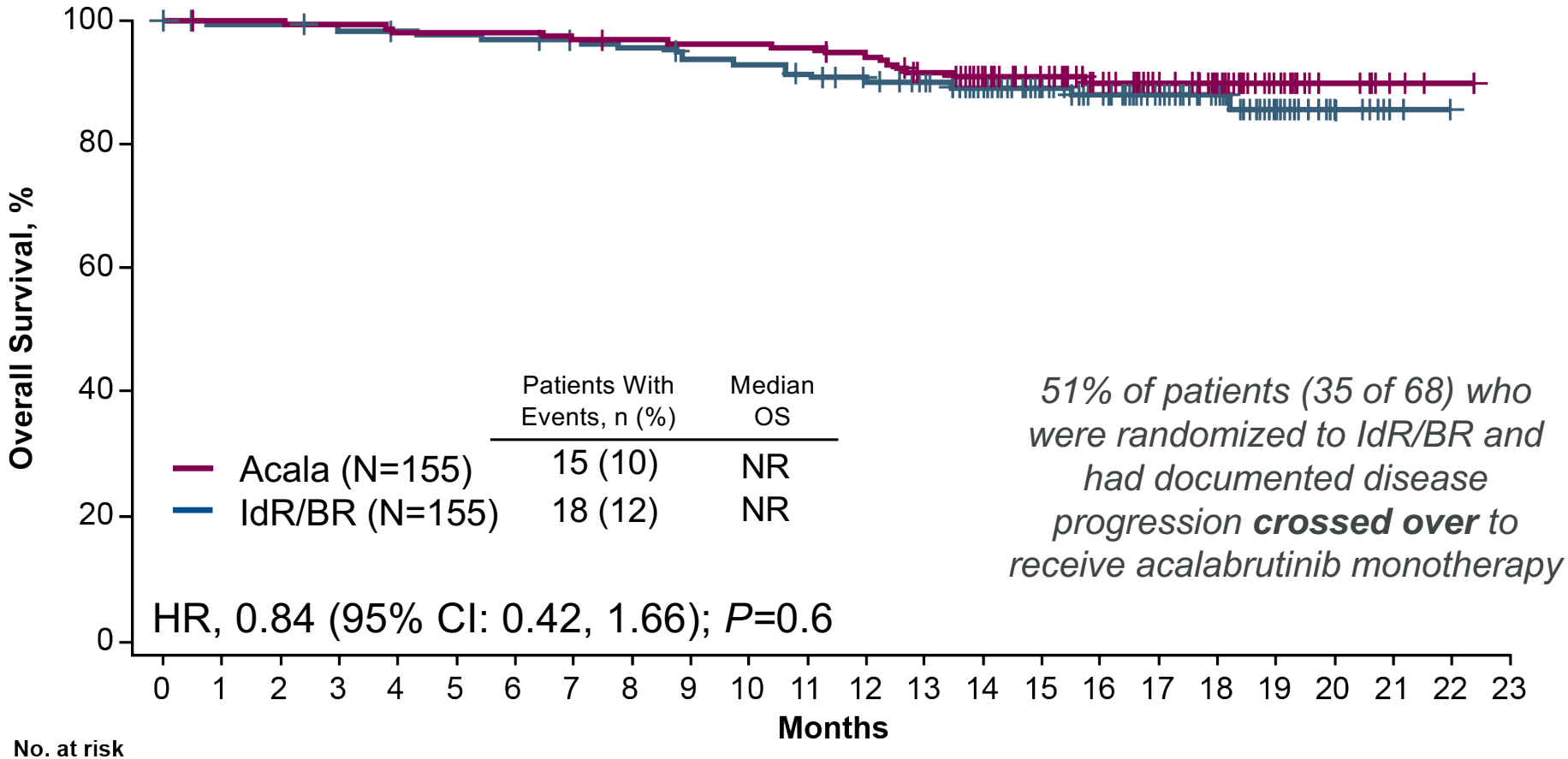
Overall Survival (Median Follow-Up, 16.1 Months)



*51% of patients (35 of 68) who were randomized to IdR/BR and had documented disease progression **crossed over** to receive acalabrutinib monotherapy*

No. at risk																								
Acala	155	154	154	153	151	151	151	149	148	147	147	146	143	136	116	101	80	56	43	28	11	3	1	0
IdR/BR	155	152	152	150	148	147	146	143	141	137	136	133	130	125	110	90	76	58	42	25	12	2	1	0

Acala = acalabrutinib; BR = bendamustine plus rituximab; HR = hazard ratio; IdR = idelalisib plus rituximab; NR = not reached; OS = overall survival.

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Patient Disposition and Exposure[a]

	Acalabrutinib n=154	IdR n=118	BR n=35
Received ≥6 IV treatment cycles, n (%)	NA	92 (78)	28 (80)
Relative dose intensity (range), %	99.5 (52.5-100.0)	91.2 (46.6-100.0)[b]	96.4 (14.5-102.5)[c]
Treatment exposure (range), mo	15.7 (1.1-22.4)	11.5 (0.1-21.1)[b]	–
Discontinued treatment, n (%)			
Adverse event	17 (11)[d]	58 (49)[b]	6 (17)[e]
Disease progression	10 (6)	11 (9)[b]	1 (3)
Death	1 (1)	0[b]	0
Completed treatment	NA	NA[b]	28 (80)
Other	2 (1)	7 (6)[b]	0

- Richter transformation occurred in 4 patients (3%) in the acalabrutinib arm and 5 (3%) in the IdR/BR arm (IdR, n=4; BR, n=1)

[a]3 randomized patients who were not dosed are not included in this table.

[b]Idelalisib only or [c]bendamustine only.

[d]Events (n=1 each): abdominal pain, alanine aminotransferase increased, bladder transitional cell carcinoma, brain neoplasm, malignant brain neoplasm, congestive cardiac failure, cerebral ischemia, cytopenia, headache, hepatitis B, immune thrombocytopenic purpura, malignant lung neoplasm, peritonitis, prostate cancer, respiratory tract infection, and squamous cell carcinoma of the skin.

[e]2 patients completed B but discontinued R due to adverse events.

BR = bendamustine plus rituximab; IdR = idelalisib plus rituximab; IV = intravenous; NA = not applicable.

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Safety Overview[a]

AE Type, n (%)	Acalabrutinib n=154	IdR n=118	BR n=35
Patients with ≥1 AE (all grades)	144 (94)	117 (99)	28 (80)
Serious AEs	44 (29)	66 (56)	9 (26)
Grade 3 or 4 AEs	70 (45)	101 (86)	15 (43)
Grade 5 AEs	6 (4)[b]	5 (4)[c]	2 (6)[d]

[a]The AE reporting period was longer with acalabrutinib than IdR/BR; reporting, irrespective of seriousness, ends 30 days after the last dose of study drug(s) or at documented disease progression, whichever is longer.

[b]Acalabrutinib: brain neoplasm, cachexia, cerebral ischemia, malignant lung neoplasm, neuroendocrine carcinoma, and sepsis (n=1 each).

[c]IdR: chronic cardiac failure, cardiopulmonary failure, interstitial lung disease, myocardial infarction, and pseudomonal pneumonia (n=1 each).

[d]BR: acute cardiac failure and gastric neoplasm (n=1 each).

AE = adverse event; BR = bendamustine plus rituximab; IdR = idelalisib plus rituximab.

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Most Common AEs in ≥15% of Patients in Any Cohort

	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)

AE = adverse event; BR = bendamustine plus rituximab; IdR = idelalisib plus rituximab; IRR = infusion-related reaction; NA = not applicable.

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Events of Clinical Interest for Acalabrutinib

	Acalabrutinib n=154		IdR n=118		BR n=35	
AEs, n (%)	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Atrial fibrillation	8 (5)	2 (1)	4 (3)	1 (1)	1 (3)	1 (3)
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)

[a]Includes Grade 3 gastrointestinal hemorrhage (n=2) and Grade 4 immune thrombocytopenic purpura (n=1).
[b]Includes Grade 4 immune thrombocytopenic purpura (n=1), Grade 3 hematuria (n=1), and Grade 3 gastrointestinal hemorrhage.
[c]Includes Grade 3 anemia and Grade 3 tumor hemorrhage, both in a single patient.
[d]Squamous cell carcinoma (n=3 patients); squamous cell carcinoma of the lip, metastatic squamous cell carcinoma, malignant melanoma and malignant brain neoplasm (n=1 patient); and malignant lung neoplasm, bladder transitional cell carcinoma, neuroendocrine carcinoma, prostate cancer (n=1 patient each).
BR = bendamustine plus rituximab; IdR = idelalisib plus rituximab; NMSC = nonmelanoma skin cancer; SPM = second primary malignancy.

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Conclusions

- In the **ASCEND** study:
  - Acalabrutinib monotherapy was superior to IdR/BR in prolonging IRC-assessed PFS in patients with R/R CLL
    - PFS improvement was observed across subgroups, including high-risk features
    - Responses to acalabrutinib were durable
  - Acalabrutinib monotherapy had a more tolerable safety profile than IdR/BR
- The Phase 3 ELEVATE-TN study investigating acalabrutinib–obinutuzumab and acalabrutinib monotherapy as first-line therapy compared with obinutuzumab–chlorambucil (NCT02475681) has met the primary endpoint of IRC-assessed PFS
- Acalabrutinib has demonstrated efficacy in previously untreated and R/R CLL and may be considered as a option in the future treatment paradigm

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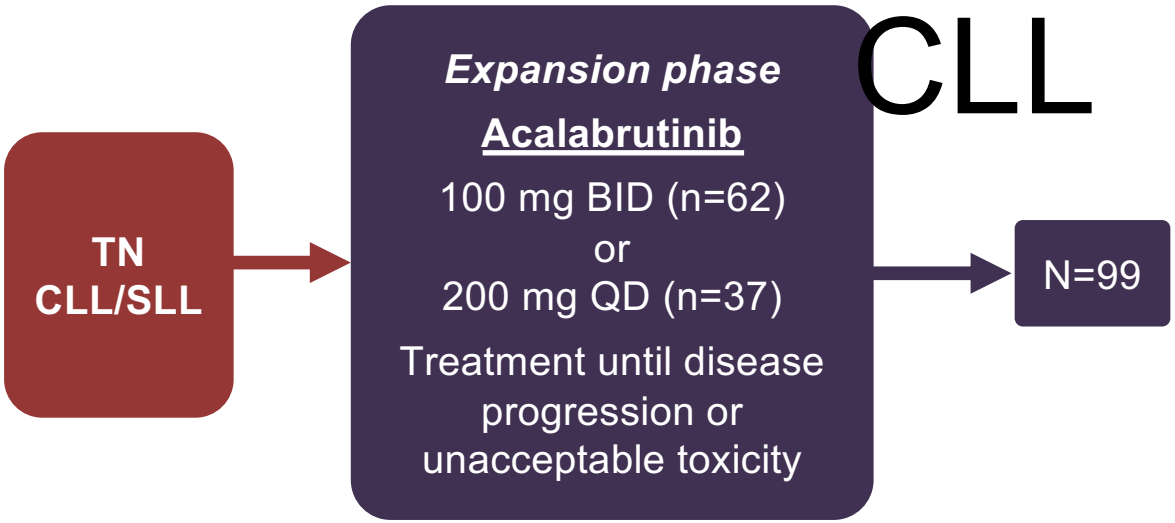
ACE-CL-001: Acalabrutinib Monotherapy in Treatment-naive CLL

- Enrollment: September 9, 2014 to July 30, 2015
- Data cutoff: September 1, 2018



All patients were switched to 100 mg BID[a]

Primary endpoints:
- Safety

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

Exploratory endpoints:
- Time to response
- EFS
- BTK drug occupancy, changes in T/NK/monocyte cell counts

[a] Under Amendment 6 (1 May 2015) of the protocol, patients in Cohort 7 were switched to 100 mg BID.

1. Hallek M, et al. *Blood.* 2008;111(12):5446-5456. 2. Cheson BD, et al. *J Clin Oncol.* 2012(23);30:2820-2822.

BID = twice daily; BTK = Bruton tyrosine kinase; CLL = chronic lymphocytic leukemia; DOR = duration of response; EFS = event-free survival; IWCLL = International Workshop on CLL; NK = natural killer; ORR = overall response rate; PFS = progression-free survival; QD = once daily; SLL = small lymphocytic leukemia; TN = treatment-naive.

Patient Demographics and Baseline Characteristics

Characteristics	N=99
Age, median (range), y	64 (33-85)
Male sex, n (%)	66 (67)
ECOG PS ≤1, n (%)	99 (100)
Bulky lymph nodes ≥5 cm, n (%)	46 (46)
Rai stage III-IV, n (%)	47 (47)
β_2-Microglobulin >3.5 mg/L, n/N (%)	72/93 (77)
Histology, n (%)	
CLL	98 (99)
SLL	1 (1)
Genomic status, n/N (%)	
Unmutated *IGHV*	57/92 (62)
Del(17p)	9/91 (10)
TP53 mutation	10/66 (15)
NOTCH1 mutation	10/66 (15)
Complex karyotype	12/60 (20)

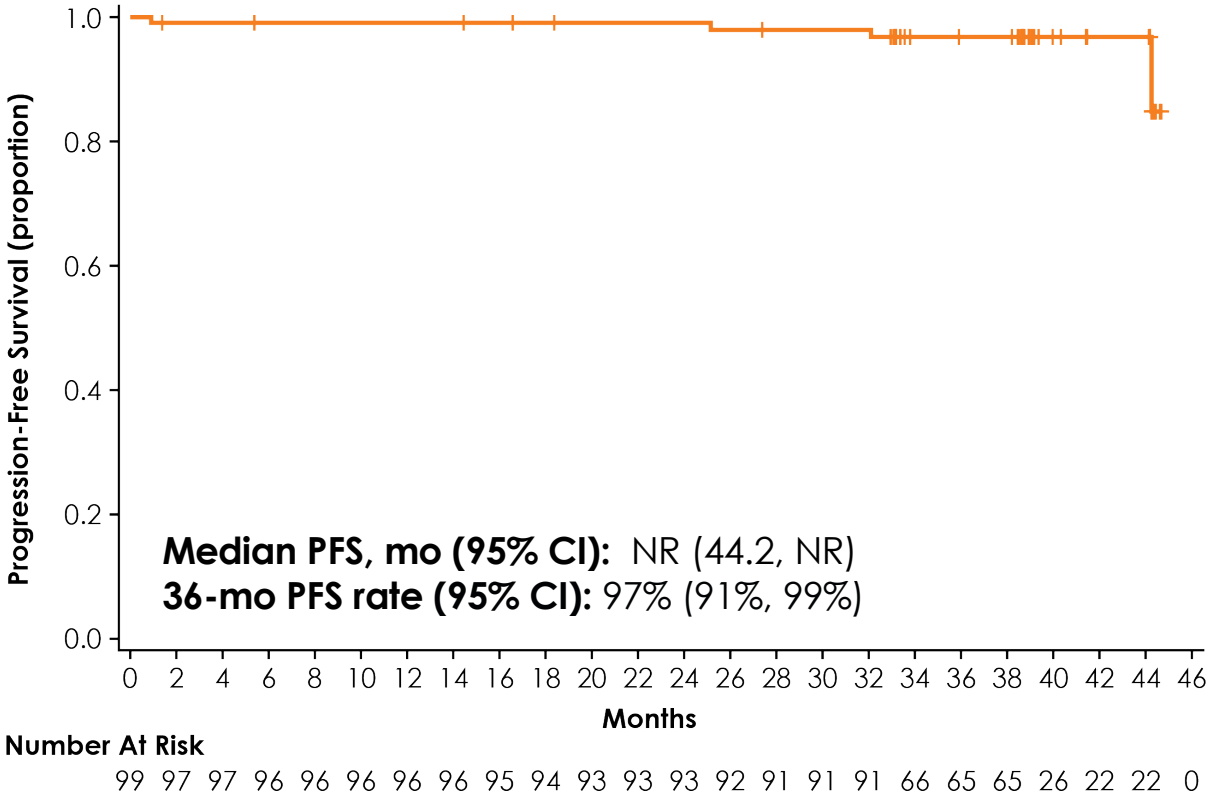
CLL = chronic lymphocytic leukemia; ECOG PS = Eastern Cooperative Oncology Group performance status; *IGHV* = immunoglobulin heavy-chain variable region.

Key AEs of Clinical Interest

- Atrial fibrillation (all grades) occurred in 6 patients (6%)
  - The overall atrial fibrillation incidence rate was 2.7 per 100 person-years
  - Two Grade 3 AEs occurred (2%; 1 AE on day 1213 and 1 AE on day 8); there were no Grade 4 AEs
  - No patients discontinued acalabrutinib due to atrial fibrillation
- Hypertension (all grades) occurred in 17 patients (17%)[a]
  - Seven AEs (7%) were Grade 3; there were no Grade 4 AEs
  - Acalabrutinib was withheld for 1 dose for 1 patient while the patient received emergency care
  - No patients discontinued acalabrutinib due to hypertension
- Bleeding events (all grades) occurred in 63 patients (64%)
  - The most common bleeding events (>15%) were contusion (39%), petechiae (18%), and ecchymosis (16%)
  - Three Grade 3 AEs occurred (3%; hematuria, intracranial hemorrhage, UGIH); there were no Grade 4 AEs
  - Acalabrutinib was withheld for 2 patients (5 days and 13 days).
  - No patient discontinued acalabrutinib due to bleeding events

Byrd, ASH 2018

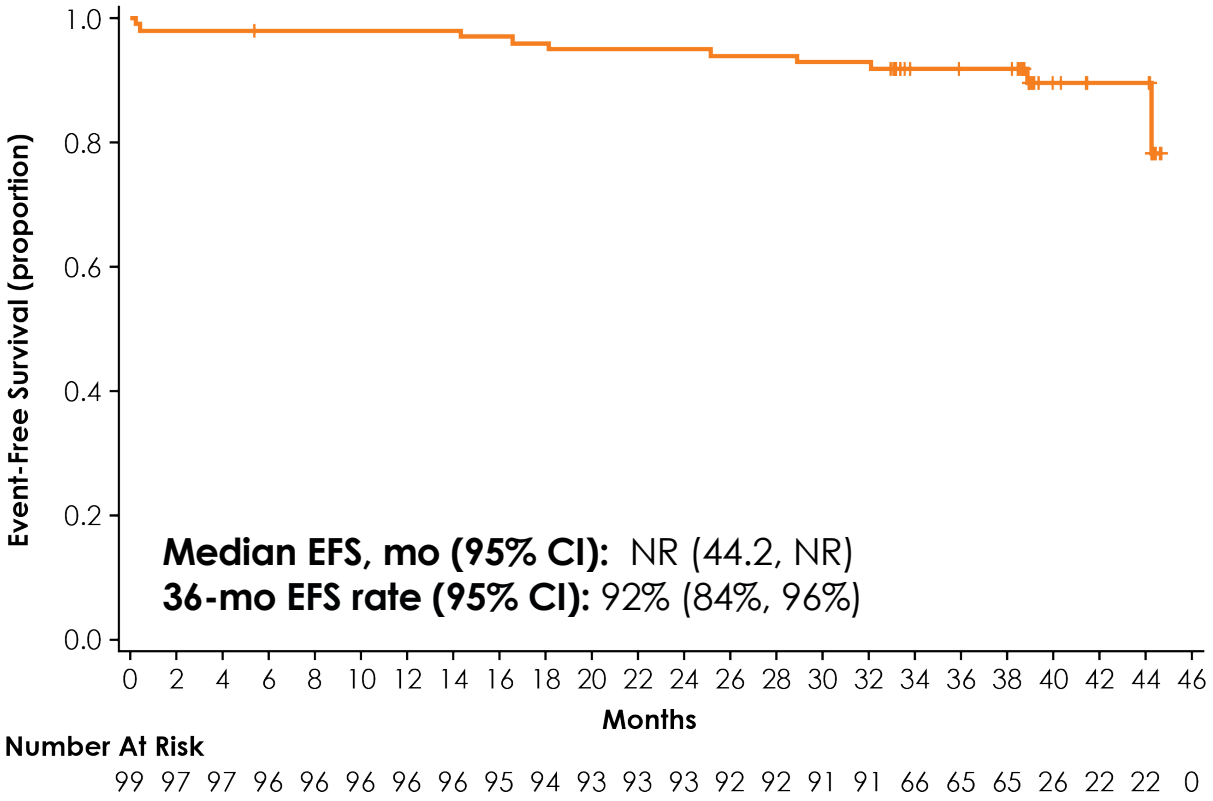
Progression-Free Survival



PFS = progression-free survival.

3

Event-Free Survival[a]



[a] Defined as progression, death, discontinuation due to AE, or start of new anticancer therapy.
AE = adverse event; EFS = event-free survival.

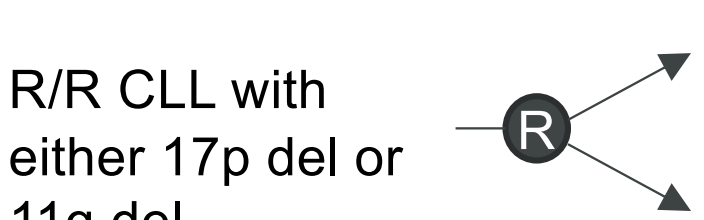
Conclusions

- In patients with TN CLL, acalabrutinib monotherapy continues to demonstrate a favorable safety profile
  - No new safety signals with additional follow-up and additional patients enrolled
  - Low rate of treatment discontinuation due to AEs or progression
  - Low rates of Grade 3/4 atrial fibrillation, hypertension, and bleeding events
- Acalabrutinib monotherapy produced high response rates that appear durable
  - ORR of 97% for all patients and 100% for patients with high-risk features
  - Median time on study of 42 months; median DOR and median PFS not reached
- Acalabrutinib is being further investigated in patients with TN CLL in an ongoing Phase 3 study (ACE-CL-007 [NCT02475681])

AE = adverse event; CLL = chronic lymphocytic lymphoma; DOR = duration of response; EFS = event-free survival; ORR = overall response rate; PFS = progression-free survival; TN = treatment-naive.

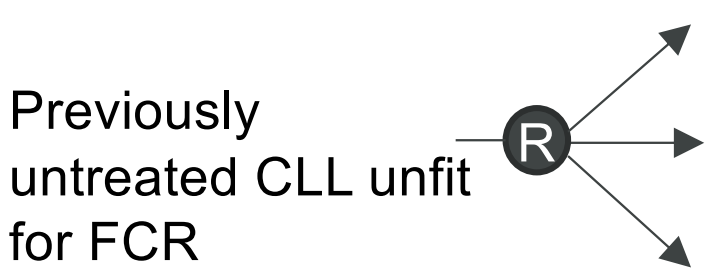
Phase IIII trials of acalabrutinib in CLL

ACE-CL-006 elevate in relapsed refractory CLL



Enrollment: n=533
Recruitment closed 31/10/17
Awaiting primary end-point

ACE-CL-007 elevate in treatment naïve CLL



Enrollment: n=535
6/6/19 – press release of primary end-point

- Rationale for next generation to improve tolerance and to overcome resistance
- Acalabrutinib:
  - effective compared to CIT and idelalisib+rituximab
  - well tolerated but as yet no direct comparison with ibrutinib
  - Patients experiencing GI side-effects or arthralgia with ibrutinib appear to tolerate acalabrutinib better
- Next generation Btk inhibitors:
  - Irreversible inhibitors
  - Reversible inhibitors