Abstract 2158

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ASCEND Phase 3 Study of Acalabrutinib vs Investigator's Choice of Rituximab Plus Idelalisib or Bendamustine in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia

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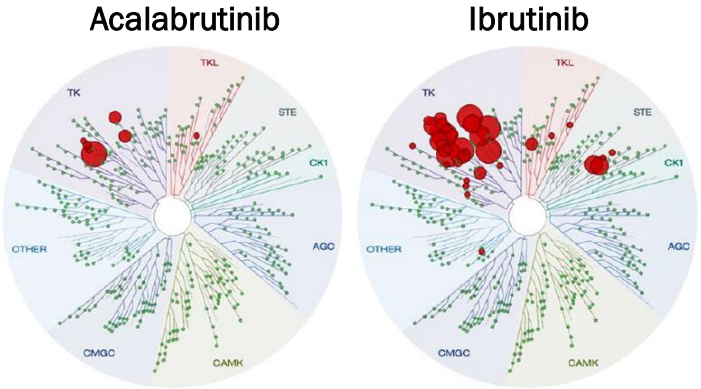
Background

- This randomized, global, multicenter, open-label Phase 3 study evaluated the efficacy and safety of acalabrutinib monotherapy vs investigator choice therapy in R/R CLL
- Bendamustine plus rituximab (BR) and the PI3K inhibitor idelalisib plus rituximab (IdR) are standard therapies for relapsed/refractory (R/R) CLL[1-4]
- For BR, overall response rate (ORR) is 45% to 68% and median progression-free survival (PFS) is 14 to 17 months[5,6]; for IdR, ORR is 84% and median PFS is 19 months[7]
- Acalabrutinib is more selective for Bruton tyrosine kinase (BTK), with less off-target kinase inhibition compared with ibrutinib in vitro[8]

Kinase Selectivity Profiling at 1 μM



Larger red circles represent stronger inhibition

CLL = chronic lymphocytic leukemia; PI3K = phosphinositide 3-kinase; R/R = relapsed/refractory.

1. Eichhorst B, et al. *Ann Oncol.* 2015;26(suppl 5):v78-84. 2. NCCN Clinical Practice Guidelines in Oncology: Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia, version 4.2019. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Accessed June 11, 2019. 3. Fischer K, et al. *J Clin Oncol.* 2011;29(26):3559-66. 4. Furman RR, et al. *N Engl J Med.* 2014;370(11):997-1007. 5. Seymour JF, et al. *N Engl J Med*. 378(12):1107-1120. 6. Zelenetz AD, et al. *Lancet Oncol.* 2017;18(3):297-311. 7. Sharman JP, et al. *J Clin Oncol.* 2019;37(16):1392-1402. 8. Barf T, et al. *J Pharmacol Exp Ther.* 2017;363(2):240-252.

ASCEND Study Design (ACE-CL-309)

Relapsed/Refractory CLL (N= 310)

Stratification:

del(17p), y vs n

ECOG PS 0-1 vs 2

1-3 vs ≥4 prior therapies

RANDOMIZE

1:1

Acalabrutinib

100 mg PO BID

Idelalisib plus Rituximab (IdR)

Idelalisib 150 mg PO BID + rituximab[a]

- or -

Bendamustine plus Rituximab (BR)

Bendamustine 70 mg/m^2 IV[b] + rituximab[c]

Primary endpoint:

- PFS (assessed by IRC)

Key secondary endpoints:

- ORR (assessed by IRC and investigator)
- Duration of response
- PFS (assessed by investigator)
- OS

***Crossover** from IdR/BR arm allowed after confirmed disease progression*

- 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.

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.

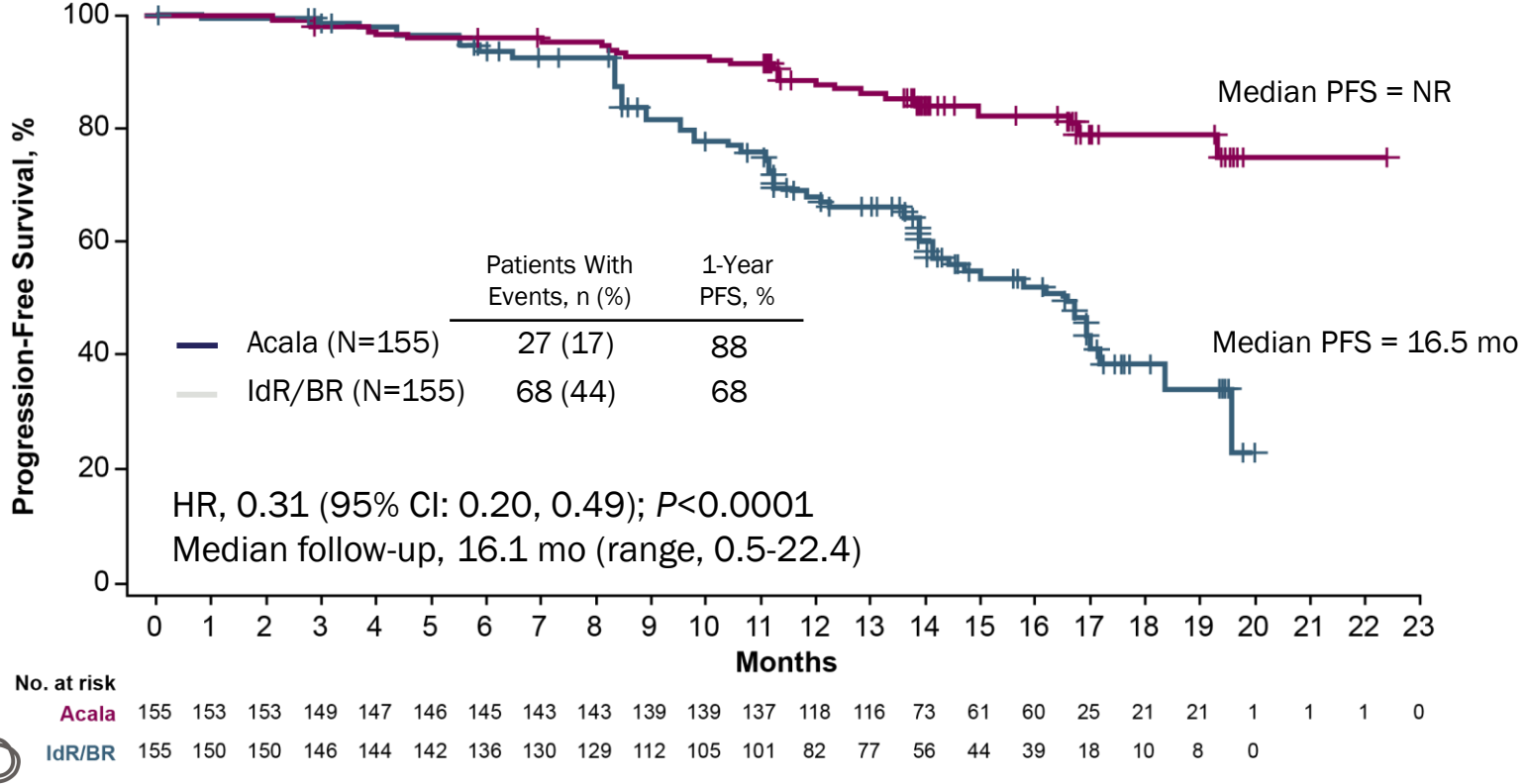
[b]Bendamustine retreatment was allowed if the prior response to bendamustine lasted >24 months.

[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.

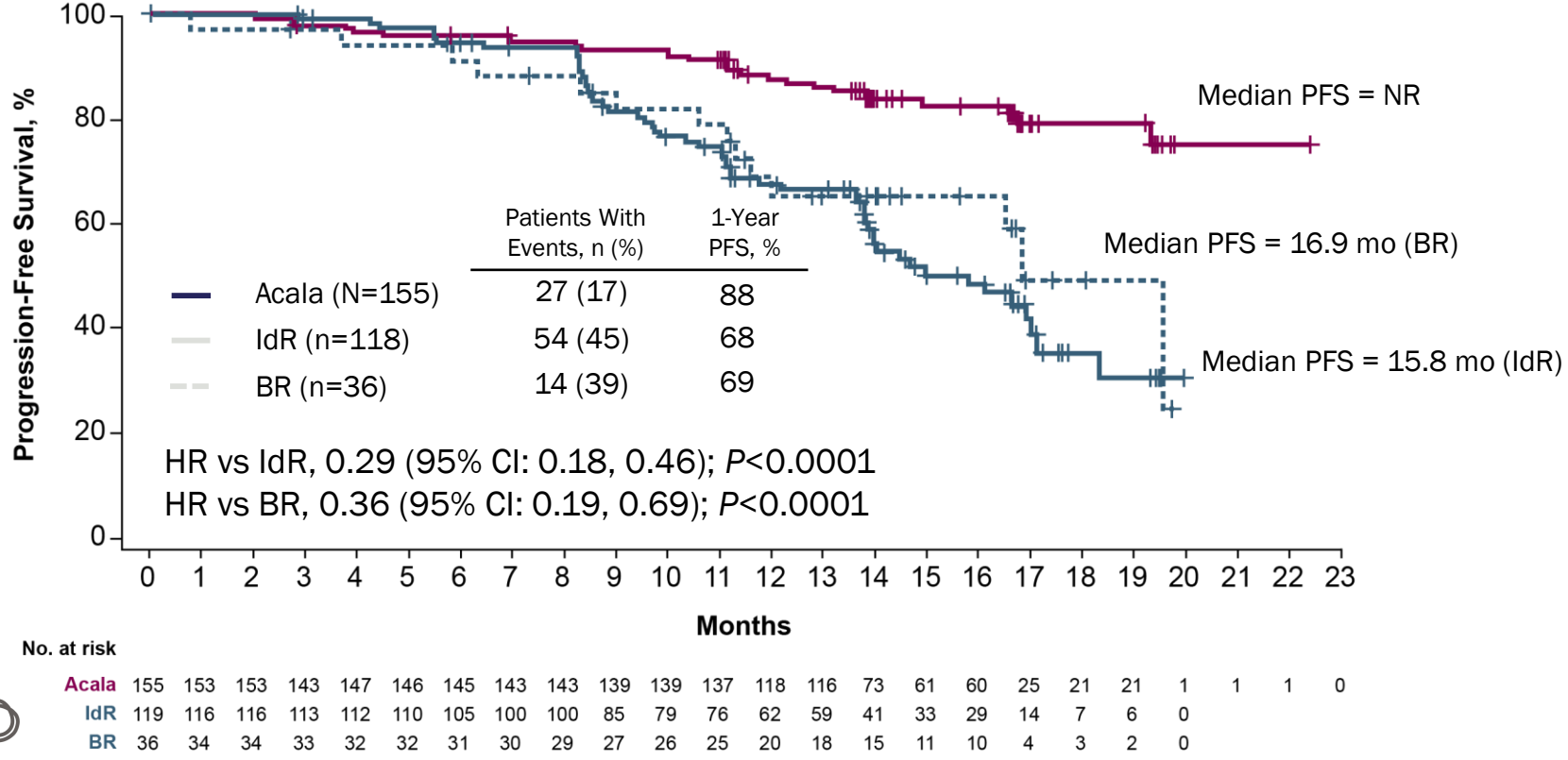
BR = bendamustine plus rituximab; IdR = idelalisib plus rituximab; IGHV = immunoglobulin heavy-chain variable region gene.

IRC-Assessed PFS Superior for Acalabrutinib vs IdR/BR



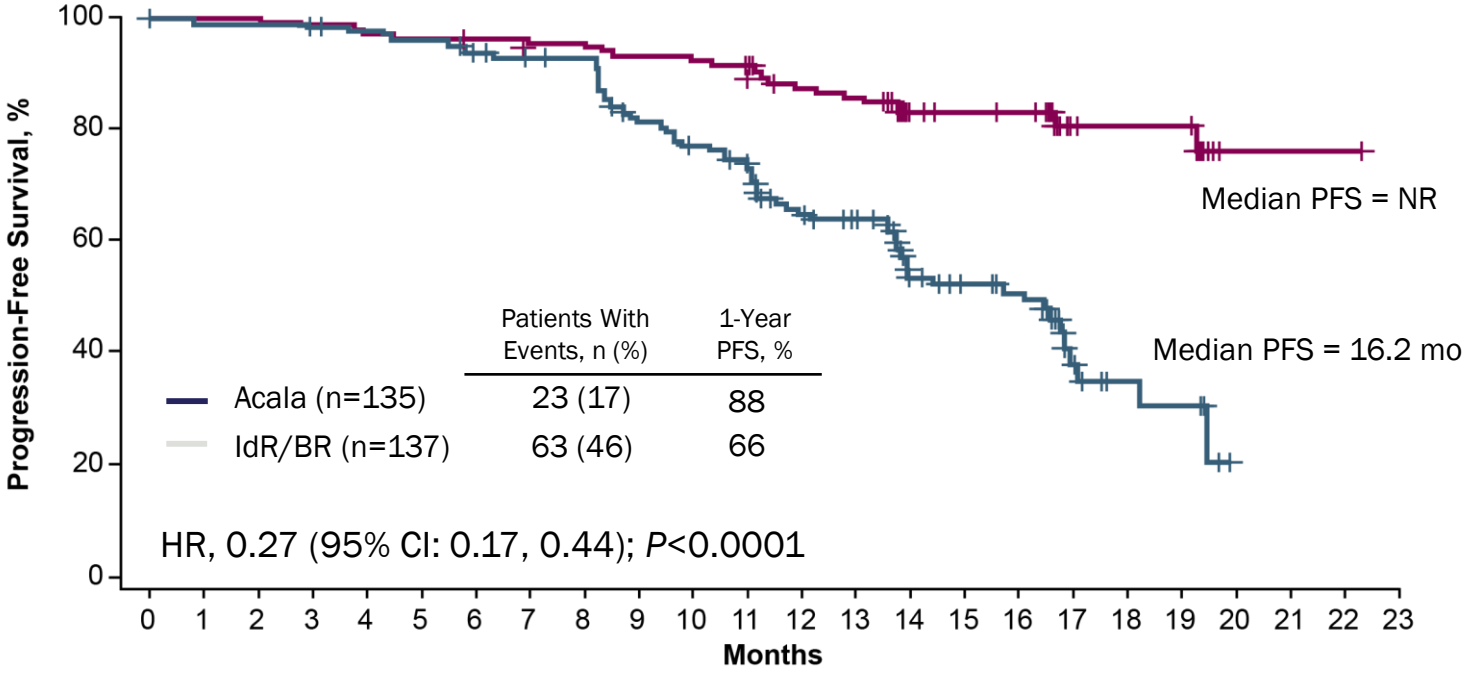
Acala = acalabrutinib; BR = bendamustine plus rituximab; HR = hazard ratio; IdR = idelalisib plus rituximab; IRC = independent review committee; NR = not reached; PFS = progression-free survival.

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.

IRC-Assessed PFS in Patients With High-Risk Cytogenetic Features[a]



No. at risk

Acala	135	133	133	130	128	127	126	125	125	122	122	120	102	100	62	54	53	23	19	19	1	1	1	0
IdR/BR	137	132	132	128	126	124	119	114	113	98	91	87	70	65	46	38	34	14	8	7	0			

[a]Including del(17p), *TP53* mutation, del(11q), or unmutated IGHV.

Acala = acalabrutinib; BR = bendamustine plus rituximab; HR = hazard ratio; IdR = idelalisib plus rituximab; IGHV = immunoglobulin heavy-chain variable region gene; IRC = independent review committee; NR = not reached; PFS = progression-free survival.

IRC-Assessed PFS Benefit With Acalabrutinib Consistent Across Subgroups

Subgroup	No. of Events/ No. of Patients		Hazard Ratio (95% CI)
	Acala	IdR/BR	
Overall	27/155	68/155	0.30 (0.19, 0.48)
Age group			
<65 years	7/58	27/57	0.20 (0.09, 0.46)
≥65 years	20/97	41/98	0.40 (0.23, 0.68)
Sex			
Male	22/108	45/100	0.34 (0.20, 0.57)
Female	5/47	23/55	0.21 (0.08, 0.57)
ECOG at randomizaton			
0 or 1	24/137	60/135	0.30 (0.18, 0.48)
2	3/18	8/20	0.36 (0.10, 1.37)
Rai stage at screening			
Stage 0-II	16/90	35/90	0.36 (0.20, 0.66)
Stage III-IV	11/65	33/64	0.24 (0.12, 0.47)
Bulky disease			
<5 cm	14/79	28/80	0.36 (0.19, 0.69)
≥5 cm	13/76	40/75	0.26 (0.14, 0.49)
No. of prior therapies			
1-3	21/139	59/138	0.27 (0.16, 0.44)
≥4	6/16	9/17	0.64 (0.23, 1.80)
Presence of del(17p)			
Yes	4/28	12/26	0.21 (0.07, 0.68)
No	23/127	56/129	0.33 (0.21, 0.54)
***TP53* mutation**			
Yes	8/39	20/34	0.24 (0.11, 0.56)
No	19/113	48/119	0.33 (0.20, 0.57)
IGHV			
Mutated	5/33	10/26	0.32 (0.11, 0.94)
Unmutated	22/118	56/125	0.32 (0.19, 0.52)
Complex karyotype			
Yes	12/50	24/46	0.32 (0.16, 0.63)
No	12/97	40/92	0.23 (0.12, 0.44)

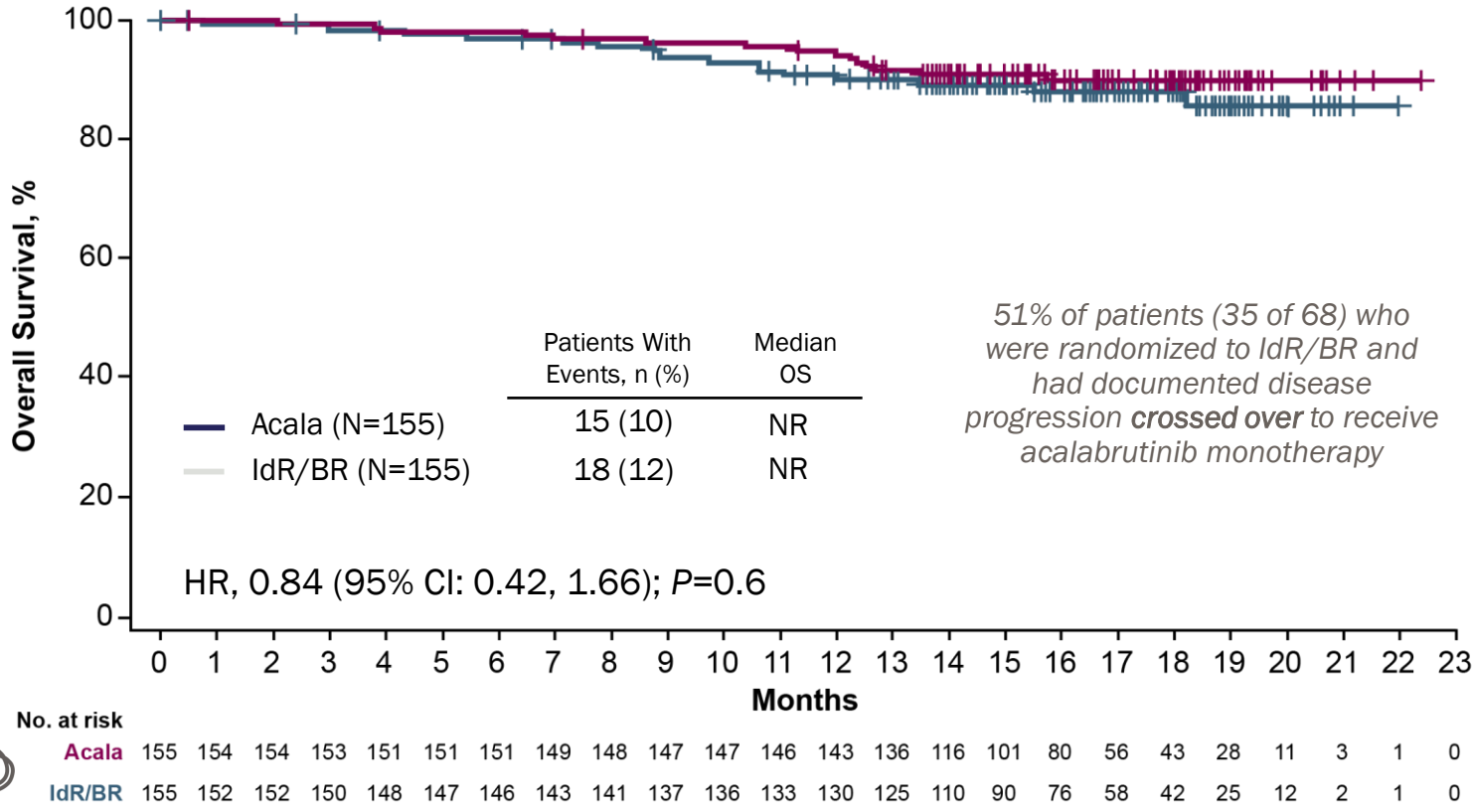
Acala = acalabrutinib; BR = bendamustine plus rituximab; ECOG = Eastern Cooperative Oncology Group; IdR = idelalisib plus rituximab; IGHV = immunoglobulin heavy-chain variable region gene; IRC = independent review committee; PFS = progression-free survival.

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.

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*

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

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.

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.

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.

Grade ≥3 AEs and SAEs in ≥5% of Patients in Any Group

Grade ≥3 AEs, n (%)	Acalabrutinib n=154	IdR n=118	BR n=35
Any	76 (49)	106 (90)	17 (49)
Neutropenia	24 (16)	47 (40)	11 (31)
Anemia	18 (12)	8 (7)	3 (9)
Pneumonia	8 (5)	10 (8)	1 (3)
Diarrhea	2 (1)	28 (24)	0
Thrombocytopenia	6 (4)	9 (8)	1 (3)
ALT increased	2 (1)	10 (8)	1 (3)
Neutrophil count decreased	2 (1)	9 (8)	1 (3)
Pyrexia	1 (1)	8 (7)	1 (3)
AST increased	1 (1)	6 (5)	1 (3)
Transaminases increased	0	6 (5)	0
Constipation	0	0	2 (6)

SAEs, n (%)	Acalabrutinib n=154	IdR n=118	BR n=35
Any	44 (29)	66 (56)	9 (26)
Pneumonia	8 (5)	10 (8)	1 (3)
Diarrhea	1 (1)	16 (14)	0
Pyrexia	1 (1)	8 (7)	1 (3)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BR = bendamustine plus rituximab; IdR = idelalisib plus rituximab; SAE = serious AE.

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.

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 an option in the future treatment paradigm

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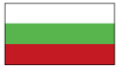

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