Acalabrutinib Monotherapy in Patients With Relapsed/Refractory Mantle Cell Lymphoma: Final Results From a Phase 2 Study

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Objective

- Final results and median OS data from the ACE-LY-004 study of acalabrutinib in patients with R/R MCL are reported

Conclusions

- Long-term 38.1-month median follow-up of the R/R MCL patients in this study confirmed that acalabrutinib is highly active, with a median time on treatment of 17.5 months
  - High response rates observed (ORR=81%; CR=48%)
  - Median DOR: 28.6 months
  - Median PFS: 22.0 months
  - Median OS: 59.2 months
    - Median OS was 55.9 months in patients with ≥2 prior cancer therapies, and was not reached in patients with 1 prior cancer therapy
- With the 38.1-month follow-up, no new safety signals were observed
- The LY-004 final results support the use of acalabrutinib in patients with R/R MCL

Introduction

- Mantle cell lymphoma (MCL) is an aggressive, rare, B-cell non-Hodgkin lymphoma with a poor prognosis; nearly all patients relapse and require additional lines of therapy[1-5]
- Bruton tyrosine kinase (BTK) inhibition is an effective therapy for many B-cell malignancies, including MCL[5-10]
- Acalabrutinib is a next-generation, potent, highly selective BTK inhibitor that is approved for the treatment of patients with relapsed/refractory (R/R) MCL based on response rates reported previously in this trial (ACE-LY-004; NCT02213926)[10,11]
- In a long-term analysis at 38.1 months' follow-up, safety and efficacy of acalabrutinib were maintained and median overall survival (OS) had not yet been reached[12]
- We now report the final OS results of this study along with summaries of response and safety data in patients with R/R MCL treated with acalabrutinib 100 mg twice daily

Methods

- ACE-LY-004 is an open-label, multicenter, phase 2 study of acalabrutinib in patients with MCL
- Key inclusion criteria:
  - Age ≥18 years
  - Confirmed MCL with chromosomal translocation t(11;14)(q13;q32) and/or overexpression of cyclin D1
  - Relapsed or refractory to at least 1 but no more than 5 prior treatments for MCL
    - No prior BTK/BCL-2 inhibitor exposure
  - Measurable nodal disease (≥1 lesion measuring ≥2.0 cm in the longest dimension and ≥1.0 cm perpendicularly)
  - Eastern Cooperative Oncology Group performance status (ECOG PS) score ≤2
- Primary endpoint was investigator-assessed overall response rate (ORR), defined as the proportion of patients who achieved partial response (PR) or better according to the Lugano classification for non-Hodgkin lymphoma[13]
- Secondary endpoints included:
  - Investigator-assessed duration of response (DOR), progression-free survival (PFS), and OS
  - Safety

Poster

Supplementary material

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Results

Patients and Exposure

- The cut-off date for these data was December 4, 2020, with a median follow-up of 38.1 months and median treatment exposure of 17.5 months (range: 0.1–65.3; **Supplemental Table 1**)
- A total of 124 patients were enrolled and patient characteristics were as previously reported[10] (**Table 1**)
- 18 patients remained on treatment as of the data cut-off
- Patient disposition is shown in **Supplemental Table 1**
  - Median dose intensity for all patients was 99%

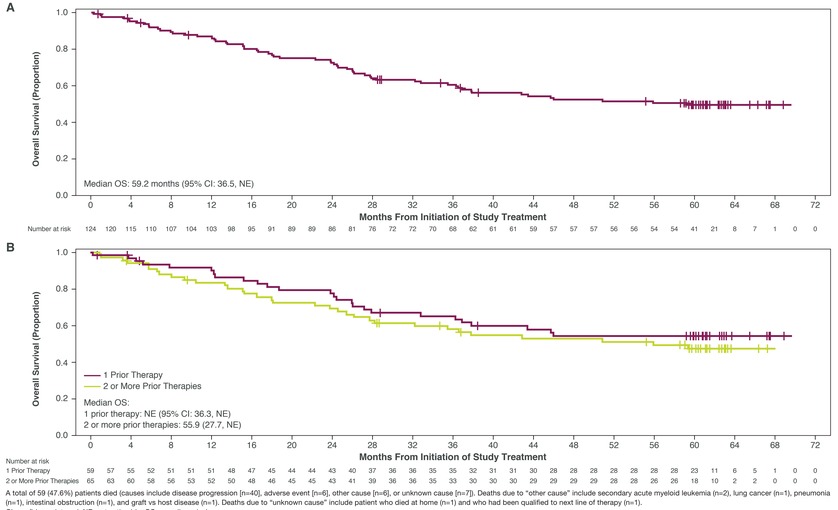
Table 1. Demographics and Baseline Characteristics

	All Patients (N=124)
Age, median (range), y	68 (42–90)
Male, n (%)	99 (80)
ECOG PS ≤1, n (%)	115 (93)
Bulky lymph nodes, n (%)	
≥5 cm	46 (37)
≥10 cm	10 (8)
Extranodal involvement, n (%)	89 (72)
Ann Arbor stage IV disease, n (%)	93 (75)
Simplified MIPI score, n (%)[a]	
Low risk (0–3)	48 (39)
Intermediate risk (4–5)	54 (44)
High-risk (6–11)	21 (17)
Number of prior systemic regimens, median (range)	2 (1–5)
Refractory disease, n (%)[b]	30 (24)
Blastoid/pleomorphic MCL, n (%)[10]	26 (21)
Ki-67 proliferation index, n (%)[10]	
<50%	64 (52)
≥50%	32 (26)
Missing	28 (22)

[a]Derived using the factors of age, ECOG PS score, lactate dehydrogenase level, and white cell count, with score range depending on the range of these factors.
[b]Defined as a lack of at least partial response to last therapy before study entry.
ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MIPI, Mantle cell lymphoma International Prognostic Index; y, years.

Efficacy

Figure 1. A: Overall Survival; B: Overall Survival by Line of Therapy



A total of 59 (47.6%) patients died (causes include disease progression [n=40], adverse event [n=6], other cause [n=6], or unknown cause [n=7]). Deaths due to "other cause" include secondary acute myeloid leukemia (n=2), lung cancer (n=1), pneumonia (n=1), intestinal obstruction (n=1), and graft vs host disease (n=1). Deaths due to "unknown cause" include patient who died at home (n=1) and who had been qualified to next line of therapy (n=1).
CI, confidence interval; NE, not estimable; OS, overall survival.

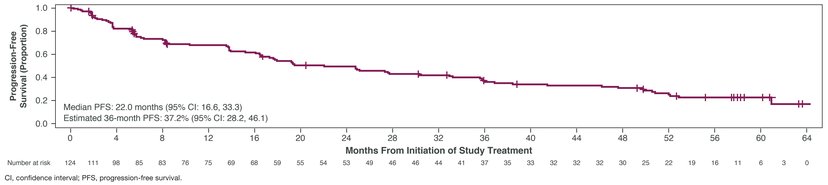
- ORR (complete response [CR] and partial response [PR]) and CR rate were 81% and 48% (**Supplemental Table 2**)
- ORR was not statistically different in patients who had 1, 2, or ≥3 prior therapies (83.1%, 86.5%, and 71.4%, respectively; **Supplemental Figure 1**)
- Median OS was reached at 59.2 months (95% CI: 36.5, not evaluable; **Figure 1A**)
  - Median OS was consistent in different subgroups, including by line of therapy (1 or ≥2; **Table 2** and **Figure 1B**)
  - Cause of death is shown in **Supplemental Table 3**
- Median DOR and median PFS remained unchanged since the previous report at 38.1 months of follow-up (29 months and 22 months; **Supplemental Figure 2A** and **Figure 2**)[12]

Table 2. Overall Survival by Subgroup

OS	Subgroup	
	1 prior cancer therapy (n=59)	≥2 prior cancer therapies (n=65)
Median OS[a], months (95% CI)	NE (36.3, NE)	55.9 (27.7, NE)
60-month OS rate, % (95% CI)	53.1 (39.2, 65.2)	46.1 (33.1, 58.1)
	Ki-67 index ≤50 (n=70)	Ki-67 index >50% (n=26)
Median OS[a], months (95% CI)	NE (36.5, NE)	22.3 (12.1, NE)
60-month OS rate, % (95% CI)	56.0 (43.1, 67.0)	33.5 (16.0, 52.0)
	Complete response (n=59)	Partial response (n=42)
Median OS[a], months (95% CI)	NE (NE, NE)	37.8 (24.4, NE)
60-month OS rate, % (95% CI)	70.7 (57.2, 80.7)	34.7 (19.6, 50.4)
	Subsequent anti-cancer therapy (n=70)	No subsequent anti-cancer therapy (n=54)
Median OS[a], months (95% CI)	40.3 (27.2, NE)	NE (50.8, NE)
60-month OS rate, % (95% CI)	42.9 (31.2, 54.0)	59.9 (44.2, 72.5)

[a]Survival is calculated as the number of months from the first dose date to the date of death or censoring.
CI, confidence interval; NE, not evaluable; OS, overall survival.

Figure 2. Progression-Free Survival



CI, confidence interval; PFS, progression-free survival.

Safety

- The adverse event (AE) profile remained consistent with the known acalabrutinib safety profile (**Table 3**)
- Selected AEs of clinical interest:
  - Atrial fibrillation (any grade, n=3 [2.4%]; grade 3/4, n=0)
  - Hypertension (any grade, n=5 [4.0%]; grade 3/4, n=2 [1.6%])
  - Hemorrhage (any grade, n=46 [37.1%]; grade 3/4, n=5 [4.0%])
  - Infections (any grade, n=84 [67.7%]; grade 3/4, n=21 [16.9%])
- Dose reductions occurred in 13 (10.5%) patients, with 3 (2.4%) due to AEs
- Treatment-emergent AEs (TEAEs) led to study treatment discontinuation in 15 (12.1%) patients

Table 3. Most Common AEs (Reported in ≥10% of Patients)

	All Patients (N=124)				
AE Preferred Term, n (%)	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Headache	48 (39)	30 (24)	16 (13)	2 (2)	0
Diarrhea	47 (38)	25 (20)	17 (14)	5 (4)	0
Fatigue	37 (30)	26 (21)	8 (6)	2 (2)	0
Cough	29 (23)	24 (19)	5 (4)	0	0
Myalgia	27 (22)	19 (15)	6 (5)	2 (2)	0
Nausea	27 (22)	14 (11)	11 (9)	2 (2)	0
Asthenia	22 (18)	15 (12)	5 (4)	2 (2)	0
Constipation	20 (16)	15 (12)	5 (4)	0	0
URTI	20 (16)	4 (3)	14 (11)	2 (2)	0
Dyspnea	19 (15)	13 (10)	3 (2)	2 (2)	1 (0.8)
Pyrexia	19 (15)	13 (10)	6 (5)	0	0
Vomiting	19 (15)	10 (8)	6 (5)	3 (2)	0
Anemia	18 (15)	1 (0.8)	3 (2)	12 (10)	2 (2)
Dizziness	18 (15)	15 (12)	3 (2)	0	0
Rash	18 (15)	9 (7)	7 (6)	2 (2)	0
Contusion	16 (13)	14 (11)	2 (2)	0	0
Sinusitis	16 (13)	4 (3)	12 (10)	0	0
Abdominal pain	15 (12)	5 (4)	8 (6)	2 (2)	0
Pneumonia	15 (12)	1 (0.8)	5 (4)	9 (7)	0
Back pain	14 (11)	11 (9)	3 (2)	0	0
Neutropenia	14 (11)	0	0	7 (6)	7 (6)
Arthralgia	13 (10)	7 (6)	6 (5)	0	0

No grade 5 events were reported after using 10% cutoff.
AE, adverse event; URTI, upper respiratory tract infection.

References

1. Swerdlow SH, et al. *Blood*. 2016;127:2375-90. **2.** Vose JM. *Am J Hematol*. 2017;92:806-13. **3.** Jain P, Wang M. *Am J Hematol*. 2019;94:710-25. **4.** Wang M, et al. *Lancet*. 2018;391:659-67. **5.** Owen C, et al. *Curr Oncol*. 2019;26:e53-60. **6.** Byrd JC, et al. *Blood*. 2020;135:1204-13. **7.** Sherman JP, et al. *Lancet*. 2020;396:1278-91. **8.** Owen RG, et al. *Lancet Haematol*. 2020;7:e112-21. **9.** Wang ML, et al. *N Engl J Med*. 2013;369:507-16. **10.** Wang M, et al. *Leukemia*. 2019;33:2762-6. **11.** Calquence Prescribing Information. AstraZeneca. 11/2019. **12.** Wang M, et al. *Blood*. 2020;136(Suppl 1):38-9.

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