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- A 4-year update analysis from the phase 3 ELEVATE-TN study was performed to assess long-term efficacy and safety of acalabrutinib (A) ± obinutuzumab (O) compared with O + chlorambucil (Clb) in patients with treatment-naïve (TN) chronic lymphocytic leukemia (CLL)

- With longer term follow-up at 46.9 months (~4 years [range, 0.0–59.4 months]), the efficacy and safety of A+O and A was maintained relative to O+C1b
  - Median PFS was significantly longer for A-containing arms (not reached [NR] vs O+C1b [27.8 months]);

- With longer term follow-up at 46.9 months (range, 0.0–59.4 months), the efficacy and safety of A+O and A was maintained relative to O+Clb
  - Median PFS was significantly longer for A-containing arms (not reached [NR] vs O+Clb [27.8 months]):
    - A+O vs O+Clb: HR 0.10 (95% CI: 0.07, 0.17)
    - A vs O+Clb: HR 0.19 (95% CI: 0.13, 0.28)
  - Estimated PFS rates at 48 months trended in favor of A+O over A (87% vs 78%, respectively)
  - PFS findings were consistent across high-risk genetic subgroups
  - For OS, fewer deaths occurred in patients who received A+O vs O+Clb; however, statistical significance was not reached
- Safety of A+O and A was consistent with interim findings, including low incidences of cardiovascular events (atrial fibrillation and hypertension), and low rates of treatment discontinuation, despite longer treatment exposure
  - Despite the higher CR rate, grade ≥3 infections occurred at a higher incidence with A+O (24%) compared with A alone (16%)

- In conclusion, A ± O demonstrates durable disease control, tolerability, and flexibility to tailor treatment as a monotherapy or combination therapy in TN CLL patients



Chemoimmunotherapy has historically been the standard of care for chronic lymphocytic leukemia, or CLL, which is a type of cancer that develops from B cells in the blood. Acalabrutinib is a targeted therapy that acts by inhibiting the activity of a protein called Bruton tyrosine kinase, or BTK, which plays a key role in CLL. Obinutuzumab is an antibody that targets CD20, a marker that is expressed on B cells which can be targeted for treatment. ELEVATE-TN is a phase 3 study that has previously shown significantly better results for acalabrutinib with or without obinutuzumab (chemotherapy-free regimens) compared with obinutuzumab plus chlorambucil (a chemoimmunotherapy regimen) in patients with previously untreated CLL after 28.3 months. Here, we report the long-term results from this study after 4 years of follow-up.



Assessments measuring how well patients' disease responded to treatment (efficacy) and what toxicities patients experienced (safety) were collected and compared between the treatment groups, focusing on comparison of the acalabrutinib treatment arms versus the chemoimmunotherapy arm.



At 4 years of follow-up, treatment with acalabrutinib, either with or without obinutuzumab, continued to show improved progression-free survival over the chemoimmunotherapy regimen, which aligns with earlier results from this study. Acalabrutinib plus obinutuzumab showed a trend towards improved overall survival compared with obinutuzumab plus chlorambucil. Safety of acalabrutinib, both alone and in combination with obinutuzumab, was maintained despite longer time on treatment.

These results show that acalabrutinib either alone or in combination with obinutuzumab maintains its efficacy and safety long-term in patients with previously untreated CLL.



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- BTK is essential for B cell receptor signaling and plays a critical role in CLL tumor cell migration, adhesion, proliferation, and survival<sup>1-3</sup>

- Acalabrutinib is a next-generation, potent, highly selective BTK inhibitor Food and Drug Administration-approved for the treatment of CLL/small lymphocytic lymphoma and previously treated mantle cell lymphoma<sup>4,7</sup>

- Early results from the pivotal phase 3 ELEVATE-TN study at a median follow-up of 28.3 months demonstrated superior efficacy of A ± O compared with O + Clb with an acceptable tolerability profile in patients with TN CLL<sup>7</sup>

- Results from a 4-year update of ELEVATE-TN are reported here

- A total of 535 patients (A+O, n=179; A, n=179; O+Clb, n=177) were randomized (Supplemental Table 1)



**Median study follow-up:** 46.9 months (range, 0.0–59.4 months)

- **Treatment still ongoing:** 74.9% (A+O) and 69.3% (A)
- **Overall treatment discontinuation rates:** 25.1% (A+O), 30.7% (A), and 22.6% (O+Clb)
  - Most common reasons: AEs (12.8%, 12.3%, 14.7%, respectively), and progressive disease (4.5%, 7.8%, 1.7%)

- Median treatment exposure:** 46.6 months (A+O), 45.7 months (A), and 5.6 months (O+CIb)

-  A total of 69 patients crossed over from O+Clb to A alone

**A.**

Progression-Free Survival (%)

Number at risk

| Months | 0   | 3   | 6   | 9   | 12  | 15  | 18  | 21  | 24  | 27  | 30  | 33  | 36  | 39  | 42  | 45 | 48 | 51 | 54 | 57 | 59 |
|--------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|
| A+O    | 179 | 176 | 171 | 168 | 164 | 163 | 160 | 157 | 156 | 155 | 153 | 152 | 150 | 141 | 132 | 85 | 59 | 33 | 12 | 2  | 0  |
| A      | 179 | 167 | 163 | 158 | 156 | 155 | 153 | 150 | 149 | 146 | 142 | 141 | 136 | 130 | 123 | 79 | 61 | 35 | 16 | 4  | 0  |
| O+CbIb | 177 | 163 | 156 | 153 | 139 | 125 | 110 | 100 | 86  | 82  | 67  | 66  | 55  | 48  | 42  | 22 | 13 | 6  | 2  | 1  | 0  |

**A+O vs O+CbIb**  
HR\* (95% CI): 0.10 (0.07, 0.17)  
 $P < 0.0001^b$

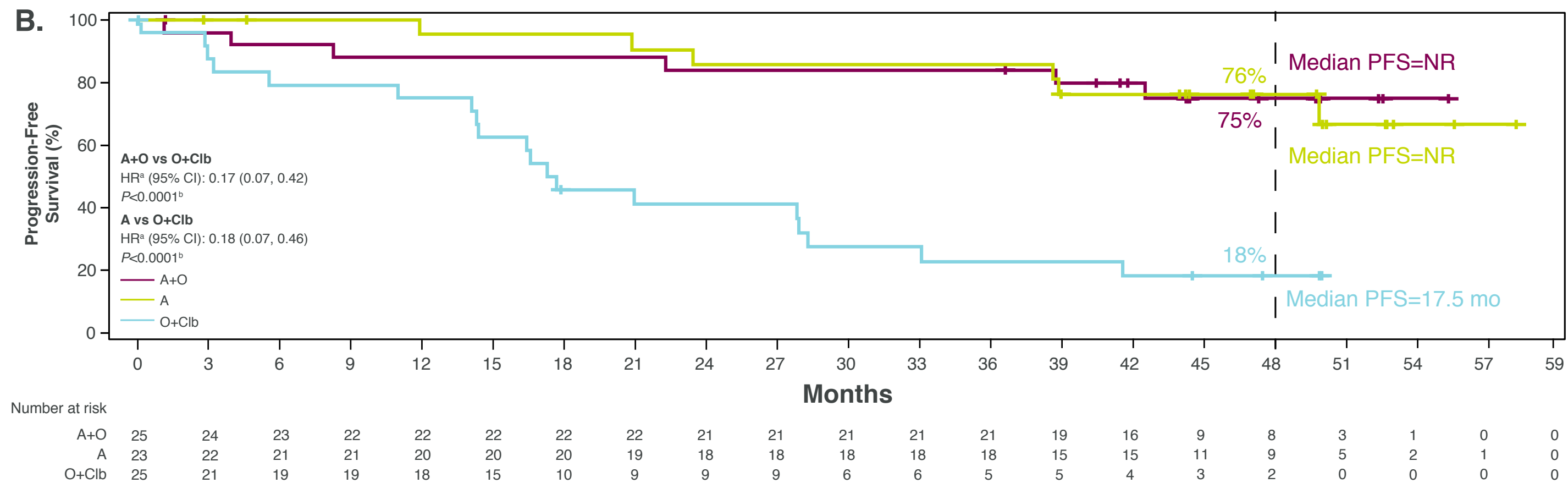
**A vs O+CbIb**  
HR\* (95% CI): 0.19 (0.13, 0.28)  
 $P < 0.0001^b$

**A+O vs A**  
HR\* (95% CI): 0.56 (0.32, 0.95)  
 $P = 0.0296^c$

87% Median PFS=NR

78% Median PFS=NR

25% Median PFS=27.8 mo

<sup>a</sup>Hazard ratio was based on unstratified Cox-Proportional-Hazards model; <sup>b</sup>P-value was based on unstratified log-rank test

- Key inclusion criteria:
  - Age  $\geq 65$  years, or  $>18$  to  $<65$  years with comorbidities (defined below)
    - Creatinine clearance 30–69 mL/min (by Cockcroft-Gault equation)
    - Cumulative Illness Rating Scale-Geriatric (CIRS-G) score  $>6$
  - Untreated CLL
    - Requiring treatment per iwCLL 2008 criteria<sup>8</sup>
  - ECOG PS score  $\leq 2$
  - Adequate hematologic, hepatic, and renal function
- Key exclusion criteria:
  - Significant cardiovascular disease
    - Uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTC  $>480$  msec at screening

**TN CLL (N=535)**

**Stratification**

- del(17p), y vs n
- ECOG PS 0-1 vs 2
- Geographic region (N America, W Europe, or other)

**RANDOMIZE 1:1**

- Acalabrutinib\* + Obinutuzumab\* (A+O)**
- Acalabrutinib\* monotherapy (A)**
- Obinutuzumab\* + Chlorambucil\* (O+Cib)**

*Crossover from O+Cib to A was allowed after IRC-confirmed progression*

**Primary endpoint**

- PFS (IRC-assessed): A+O vs O+Cib

**Secondary/other endpoints**

- PFS (IRC-assessed): A vs O+Cib
- PFS (INV-assessed)
- ORR (IRC- and INV-assessed)
- Time to next treatment
- OS
- uMRD
- Safety

**Note: After interim analysis,\* PFS assessments were by investigator only**

NCCT02475681.  
Data cutoff: September 11, 2020.  
\*Continued until disease progression or unacceptable toxicity at 100 mg PO BID. \*Treatments were fixed duration and administered for 6 cycles.

| Treatment Group | n   | CR (%) | PR (%) | ORR (%) | SD (%) | PD (%) |
|-----------------|-----|--------|--------|---------|--------|--------|
| A+O             | 179 | 65.9   | 0.6    | 66.5    | 30.7   | 2.2    |
| A               | 179 | 81.0   | 1.7    | 82.7    | 11.2   | 3.9    |
| O+Cb            | 177 | 69.5   | 9.0    | 78.5    | 13.0   | 1.7    |

ORR, 96.1% (95% CI: 92.1, 98.1;  $P < 0.0001$ )

ORR, 89.9% (95% CI: 84.7, 93.5;  $P = 0.035$ )

ORR, 82.5% (95% CI: 76.2, 87.4)

\*Based on Cochran-Mantel-Haenszel test with adjustment for 17p deletion status (yes vs no) vs O+Cb. †Includes CR and CRI. ‡Includes PR, nPR, and PRL.

**A+O vs O+Clb**  
HR\* (95% CI): 0.50 (0.25, 1.02)  
P=0.0604

**A vs O+Clb**  
HR\* (95% CI): 0.95 (0.52, 1.74)  
P=0.9164

Median OS=NR  
88%  
88%  
88%

Number at risk

| Months | 0   | 3   | 6   | 9   | 12  | 15  | 18  | 21  | 24  | 27  | 30  | 33  | 36  | 39  | 42  | 45  | 48 | 51 | 54 | 57 | 60 |
|--------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|----|
| A+O    | 179 | 176 | 176 | 173 | 170 | 168 | 167 | 165 | 164 | 164 | 163 | 162 | 161 | 161 | 156 | 132 | 83 | 54 | 30 | 7  | 0  |
| A      | 179 | 178 | 175 | 172 | 170 | 168 | 167 | 163 | 159 | 157 | 156 | 155 | 154 | 151 | 145 | 126 | 80 | 53 | 28 | 9  | 0  |
| O+Clb  | 177 | 170 | 166 | 163 | 163 | 160 | 158 | 154 | 150 | 149 | 146 | 142 | 140 | 139 | 137 | 120 | 79 | 51 | 23 | 5  | 0  |

\*Hazard ratio was based on stratified Cox-Proportional-Hazards model (stratified by del[17p] status).

|                                  | A+O (n=178) |                       | A (n=179)  |                       | O+Clb (n=169) |          |
|----------------------------------|-------------|-----------------------|------------|-----------------------|---------------|----------|
|                                  | Any Grade   | Grade ≥3              | Any Grade  | Grade ≥3              | Any Grade     | Grade ≥3 |
| Cardiac events <sup>a</sup>      | 37 (20.8)   | 14 (7.9) <sup>b</sup> | 34 (19.0)  | 15 (8.4) <sup>b</sup> | 13 (7.7)      | 3 (1.8)  |
| Atrial fibrillation              | 7 (3.9)     | 1 (0.6)               | 11 (6.1)   | 2 (1.1)               | 1 (0.6)       | 0        |
| Bleeding                         | 84 (47.2)   | 5 (2.8)               | 75 (41.9)  | 5 (2.8)               | 20 (11.8)     | 0        |
| Major bleeding <sup>d</sup>      | 7 (3.9)     | 5 (2.8)               | 7 (3.9)    | 5 (2.8)               | 2 (1.2)       | 0        |
| Hypertension                     | 14 (7.9)    | 6 (3.4)               | 13 (7.3)   | 5 (2.8)               | 7 (4.1)       | 6 (3.6)  |
| Infections                       | 134 (75.3)  | 42 (23.6)             | 132 (73.7) | 29 (16.2)             | 75 (44.4)     | 14 (8.3) |
| SPMs                             | 28 (15.7)   | 13 (7.3)              | 24 (13.4)  | 5 (2.8)               | 7 (4.1)       | 3 (1.8)  |
| SPMs excluding non-melanoma skin | 15 (8.4)    | 10 (5.6)              | 11 (6.1)   | 4 (2.2)               | 3 (1.8)       | 2 (1.2)  |

Data are n (%) unless otherwise specified. Median duration of exposure was 46.6 months for A+O, 45.7 months for A and 5.6 months for O+O. b. Cardiac events that occurred in  $\geq 1$  patient (any grade; other than atrial fibrillation) in any group included angina pectoris, palpitations, arrhythmogenic block complete, myocardial ischemia, tachycardia, bradycardia, cardiac failure, left ventricular failure, myocardial infarction, pericardial effusion, acute myocardial infarction, and supraventricular tachycardia. c. Cardiac events (grade  $\geq 3$ ) that occurred in  $\geq 1$  patient (other than atrial fibrillation) include arrhythmogenic block complete (n=3), angina pectoris (n=2), myocardial ischemia (n=2), and myocardial infarction (n=2). d. Cardiac events (grade  $\geq 3$ ) that occurred in  $\geq 1$  patient (other than atrial fibrillation) include acute myocardial infarction (n=3), cardiac failure (n=2), and myocardial infarction (n=2). e. Defined as any serious or grade  $\geq 3$  hemorrhagic event, or any grade hemorrhagic event in the central nervous system.

- Most common AEs (**Supplemental Table 3**) were generally unchanged from the interim report
  - Most AEs in the A-containing arms occurred predominantly during the first year of treatment (**Supplemental Figure 2**)
- AEs that occurred more frequently in A+O and A vs O+Clb included headache, diarrhea, fatigue, arthralgia, cough, and URTI
- AEs that occurred more frequently with O+Clb included neutropenia, nausea, and infusion-related reaction
- Overall, events of clinical interest, including CV events, were similar in both A-containing arms (**Table 1**) and consistent with previous interim analysis results
  - Cumulative incidence curves for select AEs are shown in **Supplemental Figure 3**

[illegible]

- Vitale C, Burger JA. *Expert Opin Pharmacother*. 2016;17:1077-89.
- Lougaris V, et al. *J Allergy Clin Immunol*. 2014;133:1644-50.e4.
- de Gorter DJ, et al. *Immunity*. 2007;26:93-104.
- Calquence [package insert]. AstraZeneca Pharmaceuticals; 2019.
- Project Orbis: FDA approves acalabrutinib for CLL and SLL. <https://www.fda.gov/drugs/resources-information-approved-drugs/project-orbis-fda-approves-acalabrutinib-lls>. Accessed March 31, 2021.
- Sharma J, et al. *Lancet*. 2020;395:1278-91.

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