SUPPLEMENTAL INFORMATION TO:

Efficacy and Safety in a 4-Year Follow-Up of the ELEVATE-TN Study Comparing Acalabrutinib With or Without Obinutuzumab Versus Obinutuzumab Plus Chlorambucil in Treatment-Naïve Chronic Lymphocytic Leukemia

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SUPPLEMENTAL TABLES

Supplemental Table 1. Demographics and Baseline Characteristics

| Characteristic | A+O (n=179) | A (n=179) | O+Clb (n=177) |
|---------------|-------------|-----------|---------------|
| Age, median (range), y | 70 (41–88) | 70 (44–87) | 71 (46–91) |
| Male sex | 111 (62.0) | 111 (62.0) | 106 (59.9) |
| ECOG PS score |
| 0–1 | 169 (94.4) | 165 (92.2) | 167 (94.4) |
| 2 | 10 (5.6) | 14 (7.8) | 10 (5.6) |
| Bulky disease ≥5 cm | 46 (25.7) | 68 (38.0) | 54 (30.5) |
| Rai stage |
| III | 47 (26.3)a | 51 (28.5)a | 40 (22.6) |
| IV | 38 (21.2) | 37 (20.7) | 38 (21.5) |
| Cytogenetic subgroup |
| Del(17)(p13.1) | 17 (9.5) | 16 (8.9) | 16 (9.0) |
| Del(17)(p13.1) and/or mutated TP53 | 25 (14.0) | 23 (12.8) | 25 (14.1) |
| Del(11q) | 31 (17.3) | 31 (17.3) | 33 (18.6) |
| Complex karyotypeb | 29 (16.2) | 31 (17.3) | 32 (18.1) |
| Mutated TP53 | 21 (11.7) | 19 (10.6) | 21 (11.9) |
| Unmutated IGHV | 103 (57.5) | 119 (66.5) | 116 (65.5) |

Data are n (%) unless otherwise specified.

aThe proportion of patients with Rai stage III in the A+O and A arms differed from that reported in the primary publication (48 [26.8%] and 50 [27.9%], respectively1) due to lack of database lock at interim analysis and the potential for site-level changes post-interim analysis.

bPatients with ≥3 cytogenetic abnormalities.

A, acalabrutinib; Clb, chlorambucil; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain variable region; O, obinutuzumab.

1. Sharman JP, Egyed M, Jurczak W, Skarbnik A, Pagel JM, Kamdar M, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Lancet 2020; 395: 1278-1291.
## Supplemental Table 2. Patient Disposition and Exposure

| Characteristic                                      | A+O (n=179) | A (n=179) | O+Clb (n=177) |
|-----------------------------------------------------|-------------|-----------|---------------|
| Treated with ≥1 dose of study drug                  | 179 (100.0) | 178 (99.4)| 169 (95.5)    |
| Randomized but not treated                          | 0           | 1 (0.6)  | 8 (4.5)       |
| Treatment status                                    |             |           |               |
| Ongoing                                             | 134 (74.9)  | 124 (69.3)| 0             |
| Completed regimen                                   | NA          | NA        | 137 (77.4)    |
| Discontinued regimen                                | 45 (25.1)   | 55 (30.7) | 40 (22.6)     |
| Death                                               | 2 (1.1)a    | 7 (3.9)b  | 3 (1.7)c      |
| Adverse event                                       | 23 (12.8)   | 22 (12.3) | 26 (14.7)     |
| Lost to follow-up                                   | 0           | 1 (0.6)  | 1 (0.6)       |
| CLL progressive disease                              | 8 (4.5)     | 14 (7.8) | 3 (1.7)       |
| Withdrawal of consent                               | 2 (1.1)     | 2 (1.1)  | 6 (3.4)       |
| Investigator’s discretion                           | 5 (2.8)     | 6 (3.4)  | 0             |
| Other                                               | 5 (2.8)d    | 3 (1.7)e  | 1 (0.6)f      |
| Treatment exposure, median (range), months          | 46.6 (2.3–58.6) | 45.7 (0.3–59.3) | 5.6 (0.9–7.4) |

Data are n (%) unless otherwise specified.

aDue to adverse event (n=2); bDue to adverse event (n=6) and cerebrovascular accident (n=1); cDue to adverse event (n=2) and car accident (n=1); dIncludes patient decision (n=2), treatment interruption due to disease improvement (n=1), treatment interruption >28 days (n=1), and bleeding risk concerns with clopidogrel bisulfate and acetylsalicylic acid concomitant treatment (n=1); eIncludes patient decision (n=1), CML diagnosis (n=1), and drug initially held due to macular edema and new lung cancer growth found at time of restart (n=1); fDid not meet eligibility criteria (post-randomization determination by sponsor; n=1).

A, acalabrutinib; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; NA, not applicable; O, obinutuzumab.
### Supplemental Table 3. AEs Over Time (Any Grade) in ≥25% of Patients in Any Treatment Arm

| AE, n (%) | Treatment | ≤1 Year<sup>a</sup> | >1–2 Years<sup>b</sup> | >2–3 Years<sup>c</sup> | >3–4 Years<sup>d</sup> | >4 Years<sup>e</sup> |
|-----------|-----------|---------------------|---------------------|---------------------|---------------------|---------------------|
|           |           | (%)                 | (%)                 | (%)                 | (%)                 | (%)                 |
| Diarrhea  | A+O       | 59 (33.1)           | 27 (16.9)           | 30 (20.0)           | 27 (18.8)           | 12 (15.0)           |
|           | A         | 56 (31.3)           | 26 (16.9)           | 18 (12.3)           | 19 (14.2)           | 10 (13.2)           |
|           | O+Clb<sup>f</sup> | 36 (21.3) | 0                  | 0                  | 0                  | 0                  |
| Headache  | A+O       | 65 (36.5)           | 17 (10.6)           | 17 (11.3)           | 14 (9.7)            | 4 (5.0)             |
|           | A         | 65 (36.3)           | 24 (15.6)           | 23 (15.8)           | 22 (16.4)           | 10 (13.2)           |
|           | O+Clb<sup>f</sup> | 20 (11.8) | 0                  | 0                  | 0                  | 0                  |
| Neutropenia | A+O     | 51 (28.7)           | 18 (11.3)           | 6 (4.0)             | 5 (3.5)             | 1 (1.3)             |
|           | A         | 14 (7.8)            | 8 (5.2)             | 2 (1.4)             | 5 (3.7)             | 1 (1.3)             |
|           | O+Clb<sup>f</sup> | 76 (45.0) | 0                  | 0                  | 0                  | 0                  |
| Fatigue   | A+O       | 47 (26.4)           | 24 (15.0)           | 20 (13.3)           | 17 (11.8)           | 8 (10.0)            |
|           | A         | 27 (15.1)           | 24 (15.6)           | 23 (15.8)           | 19 (14.2)           | 11 (14.5)           |
|           | O+Clb<sup>f</sup> | 30 (17.8) | 0                  | 0                  | 0                  | 0                  |
| Arthralgia | A+O      | 29 (16.3)           | 27 (16.9)           | 26 (17.3)           | 28 (19.4)           | 18 (22.5)           |
|           | A         | 22 (12.3)           | 19 (12.3)           | 13 (8.9)            | 16 (11.9)           | 5 (6.6)             |
|           | O+Clb<sup>f</sup> | 8 (4.7)        | 0                  | 0                  | 0                  | 0                  |
| Cough     | A+O       | 27 (15.2)           | 19 (11.9)           | 18 (12.0)           | 12 (8.3)            | 4 (5.0)             |
|           | A         | 23 (12.8)           | 15 (9.7)            | 16 (11.0)           | 13 (9.7)            | 6 (7.9)             |
|           | O+Clb<sup>f</sup> | 15 (8.9)        | 0                  | 0                  | 0                  | 0                  |
| URTI      | A+O       | 18 (10.1)           | 19 (11.9)           | 21 (14.0)           | 5 (3.5)             | 2 (2.5)             |
|           | A         | 24 (13.4)           | 14 (9.1)            | 15 (10.3)           | 10 (7.5)            | 2 (2.6)             |
|           | O+Clb<sup>f</sup> | 16 (9.5)        | 0                  | 0                  | 0                  | 0                  |
| Nausea    | A+O       | 34 (19.1)           | 16 (10.0)           | 15 (10.0)           | 12 (8.3)            | 5 (6.3)             |
|           | A         | 31 (17.3)           | 15 (9.7)            | 9 (6.2)             | 5 (3.7)             | 3 (3.9)             |
|           | O+Clb<sup>f</sup> | 53 (31.4) | 0                  | 0                  | 0                  | 0                  |
| IRR       | A+O       | 25 (14.0)           | 0                  | 0                  | 0                  | 0                  |
|           | O+Clb<sup>f</sup> | 68 (40.2) | 0                  | 0                  | 0                  | 0                  |
A patient with multiple severity grades for a given AE was counted only once under the maximum severity. Multiple onsets of the same AE within a specific yearly interval were counted once, and the same AE term continuing across several yearly intervals was counted in each of the intervals.

\[\text{a} \text{A+O (n=178), A (n=179), O+Clb (n=169); b} \text{A+O (n=160), A (n=154), O+Clb (n=0); c} \text{A+O (n=150), A (n=146), O+Clb (n=0); d} \text{A+O (n=144), A (n=134), O+Clb (n=0); e} \text{A+O (n=80), A (n=76), O+Clb (n=0); f} \text{O+Clb treatment was for fixed duration of 6 cycles.}\]

A, acalabrutinib; AE, adverse event; Clb, chlorambucil; IRR, infusion-related reaction; O, obinutuzumab; URTI, upper respiratory tract infection.
**Supplemental Table 4.** Incidence and Time to Onset of AEs (Any Grade) Leading to Acalabrutinib Discontinuation

| Time to onset of AE leading to discontinuation, months | A+O (n=178) | A (n=179) |
|-------------------------------------------------------|-------------|-----------|
| Mean (SD)                                             | 16.9 (14.7) | 16.3 (18.3) |
| Median (range)                                        | 9.6 (1.7–44.8) | 8.6 (0.2–57.4) |
| Time to onset of AE leading to discontinuation         |             |           |
| <3 months                                             | 3 (1.7)     | 8 (4.5)   |
| 3–6 months                                            | 5 (2.8)     | 1 (0.6)   |
| 6–9 months                                            | 4 (2.2)     | 4 (2.2)   |
| 9–12 months                                           | 1 (0.6)     | 2 (1.1)   |
| 12–24 months                                          | 3 (1.7)     | 2 (1.1)   |
| 24–36 months                                          | 4 (2.2)     | 3 (1.7)   |
| 36–48 months                                          | 4 (2.2)     | 2 (1.1)   |
| >48 months                                            | 0           | 2 (1.1)   |
| AE leading to treatment discontinuation               |             |           |
| Abdominal distension                                  | 1 (0.6)     | 0         |
| Acute kidney injury                                   | 1 (0.6)     | 0         |
| Acute myeloid leukemia                                 | 0           | 1 (0.6)   |
| Acute myocardial infarction                           | 0           | 1 (0.6)   |
| Condition                                      | Value | Reference Value |
|------------------------------------------------|-------|-----------------|
| Bladder neoplasm                               | 1 (0.6) | 0               |
| Brain injury                                   | 0     | 1 (0.6)         |
| Brain neoplasm                                 | 0     | 1 (0.6)         |
| Bronchopulmonary aspergillosis                 | 0     | 1 (0.6)         |
| Cardiac failure                                | 0     | 1 (0.6)         |
| Cardiac tamponade                              | 0     | 1 (0.6)         |
| Chronic myeloid leukemia                       | 0     | 1 (0.6)         |
| Chronic obstructive pulmonary disease          | 1 (0.6) | 0               |
| Coronary artery stenosis                       | 0     | 1 (0.6)         |
| Delirium                                       | 0     | 1 (0.6)         |
| Disseminated cryptococcosis                    | 0     | 1 (0.6)         |
| Fatigue                                       | 1 (0.6) | 1 (0.6)         |
| Febrile neutropenia                            | 1 (0.6) | 0               |
| Gastrointestinal hemorrhage                    | 1 (0.6) | 0               |
| Glioblastoma                                   | 0     | 1 (0.6)         |
| Hematuria                                      | 0     | 1 (0.6)         |
| Hemophagocytic lymphohistiocytosis             | 0     | 1 (0.6)         |
| Hepatitis B reactivation                       | 2 (1.1) | 0               |
| Ischemic stroke                                | 1 (0.6) | 0               |
| Lung disorder                                  | 0     | 1 (0.6)         |
| Malaise                                        | 0     | 1 (0.6)         |
| Metastases to bone                             | 1 (0.6) | 0               |
| Condition                              | Acalabrutinib | Obinutuzumab |
|----------------------------------------|---------------|--------------|
| Myocardial infarction                  | 1 (0.6)       | 0            |
| Myositis                               | 0             | 1 (0.6)      |
| Nausea                                 | 0             | 1 (0.6)      |
| Odynophagia                            | 0             | 1 (0.6)      |
| Pericardial effusion                   | 1 (0.6)       | 0            |
| Pneumonia bacterial                    | 0             | 1 (0.6)      |
| Progressive multifocal leukoencephalopathy | 1 (0.6)     | 0            |
| Pulmonary fibrosis                     | 0             | 1 (0.6)      |
| Pyrexia                                | 1 (0.6)       | 0            |
| Rash                                   | 1 (0.6)       | 0            |
| Rectal adenocarcinoma                  | 1 (0.6)       | 0            |
| Road traffic accident                  | 1 (0.6)       | 0            |
| Sepsis                                 | 2 (1.1)       | 1 (0.6)      |
| Squamous cell carcinoma                | 2 (1.1)       | 0            |
| Thrombocytopenia                       | 0             | 2 (1.1)      |
| Thyroid cancer                         | 1 (0.6)       | 0            |
| Transient ischemic attack              | 1 (0.6)       | 0            |
| Vomiting                               | 0             | 1 (0.6)      |
| Weight increased                       | 1 (0.6)       | 0            |

Data are n (%) unless otherwise specified.

A, acalabrutinib; AE, adverse event; O, obinutuzumab; SD, standard deviation.
SUPPLEMENTAL FIGURES

Supplemental Figure 1. Investigator-Assessed Progression-Free Survival by Del(17)(p13.1)

\[\text{Hazard ratio was based on unstratified Cox-Proportional-Hazards model.}\]
\[\text{P-value was based on unstratified log-rank test.}\]
\[\text{A, acalabrutinib; CI, confidence interval; Clb, chlorambucil; HR, hazard ratio; NR, not reached; O, obinutuzumab; PFS, progression-free survival; w/o, without.}\]
Supplemental Figure 2. Overall Survival

Note: In the O+Clb arm, 103 patients had disease progression, among whom 69 crossed over to the acalabrutinib arm and 34 did not.

\(^a\)Hazard ratio was based on stratified Cox-Proportional-Hazards model, stratified by del(17)(p13.1) status. \(^b\)P-value was based on stratified log-rank test.

A, acalabrutinib; CI, confidence interval; Clb, chlorambucil; HR, hazard ratio; NR, not reached; O, obinutuzumab; OS, overall survival.
Supplemental Figure 3. Investigator-assessed ORR (A) and MRD\(^a\) status (B)
ORR is defined as achieving CR, CRi, nPR, or PR per the investigator or IRC assessment per iwCLL 2008 criteria at or before initiation of subsequent anticancer therapy. Peripheral blood testing to assess MRD occurred for patients with bone marrow-confirmed CR. Peripheral blood MRD status based on last two timepoints (most recent MRD assessments available by the data cutoff) in patients with CR/CRi.

\(^a\)MRD was defined as the proportion of patients with <1 CLL cell in 10,000 leukocytes (<10\(^a\)).

\(^b\)Based on Cochran-Mantel-Haenszel test with adjustment for 17p deletion status (yes vs no) vs O+Clb.

\(^c\)Includes CR and CRi.

\(^d\)Includes PR, nPR, and PRL.

A, acalabrutinib; CI, confidence interval; Clb, chlorambucil; CR, complete response; Cri, complete response with incomplete hematologic recovery; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRD, minimal residual disease; NE, not evaluable; nPR, nodular partial remission; O, obinutuzumab; ORR, overall response rate; PD, progressive disease; PR, partial remission; SD, stable disease; uMRD, undetectable minimal residual disease.
**Supplemental Figure 4.** Cumulative Incidence Over Time for Any-Grade Events of Atrial Fibrillation (A) and Hypertension (B)

Treatment-emergent AEs during the randomization period only are included. O+Clb patients are censored at the last dose date of O+Clb +30, the start of new anticancer therapy, or the first dose date of crossover to A monotherapy -1, whichever came first.

A, acalabrutinib; AE, adverse event; Clb, chlorambucil; O, obinutuzumab.