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Acalabrutinib-based regimens in frontline or relapsed/refractory higher-risk CLL: Pooled analysis of 5 clinical trials

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Abstract:
Before targeted therapies, patients with higher-risk chronic lymphocytic leukemia (CLL) defined as del(17p) and/or TP53 mutation (TP53m), unmutated immunoglobulin heavy chain variable region genes (uIGHV), or complex karyotype (CK) had poorer prognosis with chemoimmunotherapy. Bruton tyrosine kinase inhibitors (BTKis) have demonstrated benefit in higher-risk patient populations with CLL in individual trials. To better understand the impact of the second-generation BTKi acalabrutinib, we pooled data from 5 prospective clinical studies of acalabrutinib as monotherapy or in combination with obinutuzumab (ACE-CL-001, ACE-CL-003, ELEVATE-TN, ELEVATE-RR, and ASCEND) in patients with higher-risk CLL in treatment-naive (TN) or relapsed/refractory (R/R) cohorts. A total of 808 patients were included (TN cohort, n = 320; R/R cohort, n = 488). Median follow-up was 59.1 months (TN cohort) and 44.3 months (R/R cohort); 51.3% and 26.8% of TN and R/R patients, respectively, remained on treatment at last follow-up. In the del(17p)/TP53m, uIGHV, and CK subgroups in the TN cohort, median progression-free survival (PFS) and median overall survival (OS) were not reached (NR). In the del(17p)/TP53m, uIGHV, and CK subgroups in the R/R cohort, median PFS was 38.6 months, 46.9 months, and 38.6 months, respectively and median OS was 60.6 months, NR, and NR, respectively. The safety profile of acalabrutinib-based therapy in this population was consistent with the known safety profile of acalabrutinib in a broad CLL population. Our analysis demonstrates long-term benefit of acalabrutinib-based regimens in patients with higher-risk CLL, regardless of line of therapy.

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Data Sharing Statement

Data underlying the findings described in this article may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli can be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

Sequencing data were not deposited into a public database because 1) sequencing was not the primary outcome of the research and 2) the sequencing analyses were conducted as part of the included clinical trials that were previously published (PubMed IDs: 33786588 and 31876911 [ACE-CL-001], 31915195 [ACE-CL-003], 32305093 [ELEVATE-TN], 34310172 [ELEVATE-RR], and 32459600 [ASCEND]).

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KEY POINTS

- Acalabrutinib-based regimens achieve long-term efficacy in patients with higher-risk CLL, across all lines of therapy
- Safety profile of acalabrutinib in patients with higher-risk CLL was similar to the overall safety profile of acalabrutinib

ABSTRACT

Before targeted therapies, patients with higher-risk chronic lymphocytic leukemia (CLL) defined as del(17p) and/or *TP53* mutation (*TP53*m), unmutated immunoglobulin heavy chain variable region genes (uIGHV), or complex karyotype (CK) had poorer prognosis with chemoimmunotherapy. Bruton tyrosine kinase inhibitors (BTKis) have demonstrated benefit in higher-risk patient populations with CLL in individual trials. To better understand the impact of the second-generation BTKi acalabrutinib, we pooled data from 5 prospective clinical studies of acalabrutinib as monotherapy or in combination with obinutuzumab (ACE-CL-001, ACE-CL-003, ELEVATE-TN, ELEVATE-RR, and ASCEND) in patients with higher-risk CLL in treatment-naive (TN) or relapsed/refractory (R/R) cohorts. A total of 808 patients were included (TN cohort, n = 320; R/R cohort, n = 488). Median follow-up was 59.1 months (TN cohort) and 44.3 months (R/R cohort); 51.3% and 26.8% of TN and R/R patients, respectively, remained on treatment at last follow-up. In the del(17p)/*TP53*m, uIGHV, and CK subgroups in the TN cohort, median progression-free survival (PFS) and median overall survival (OS) were not reached (NR). In the del(17p)/*TP53*m, uIGHV, and CK subgroups in the R/R cohort, median PFS was 38.6 months, 46.9 months, and 38.6 months, respectively and median OS was 60.6 months, NR, and NR, respectively. The safety profile of acalabrutinib-based therapy in this population was consistent with the known safety profile of acalabrutinib in a broad CLL population. Our analysis demonstrates long-term benefit of acalabrutinib-based regimens in patients with higher-risk CLL, regardless of line of therapy.

Keywords: Molecular targeted therapy, mutation, tumor suppressor protein p53, immunoglobulin heavy chains, chromosome aberrations

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a heterogenous disease with a highly variable clinical course for which patients with higher-risk genomic aberrations, including del(17p13.1) [del(17p)] and/or *TP53* mutation (*TP53*m), unmutated immunoglobulin heavy chain variable region genes (uIGHV), or complex karyotype (CK), have historically had inferior outcomes.[1] Prior to the development of targeted therapies, patients with higher-risk genomic features had poorer prognosis when treated with standard chemoimmunotherapy.[1] Additionally, fixed-duration treatment with venetoclax and an anti-CD20 antibody has shown shorter responses in patients with del(17p), uIGHV, and/or CK than in patients without those features.[2-5] Targeted agents such as Bruton tyrosine kinase inhibitors (BTKis) administered as continuous therapy have demonstrated benefit in patients with higher-risk CLL and are preferred treatment options in patients with del(17p)/*TP53*m, uIGHV, and/or CK.[6-12]

Acalabrutinib is a second-generation, selective covalent BTKi[13] with demonstrated progression-free survival (PFS) and overall survival (OS) benefits in patients with treatment-naive (TN) and relapsed/refractory (R/R) CLL, including those with higher-risk genomic characteristics.[6-10] Because the numbers of patients with higher-risk CLL in the individual studies of acalabrutinib are relatively small for most higher-risk features, there was a need to collate these data across trials to better understand treatment outcomes. Herein, we conducted a pooled analysis of 5 studies to evaluate the response and long-term efficacy and safety of acalabrutinib-based therapy in both the TN and R/R CLL settings in patients with higher-risk genomic features, including del(17p)/*TP53*m, uIGHV, and CK.

METHODS

Pooled Analysis

The data for this analysis were pooled from 5 clinical studies in patients with CLL with higher-risk genomic features (defined as del(17p)/*TP53*m, uIGHV, or CK [≥ 3 chromosomal abnormalities]; **Table 1**) or without any of the higher-risk features (lower-risk subgroup) treated with acalabrutinib monotherapy or acalabrutinib plus obinutuzumab. The number of patients with CK ≥ 5 abnormalities was too small to analyze and was not included in this analysis. The analysis was conducted separately in patients who had previously untreated CLL (TN cohort) or patients who had received ≥1 prior therapy for CLL (R/R cohort). The TN CLL cohort included data from 3 clinical studies: ACE-CL-001 (TN cohort), ACE-CL-003 (TN cohort [ie, study cohort 2]), and ELEVATE-TN (ACE-CL-007). The R/R CLL cohort included data from 4 clinical studies: ACE-CL-001 (R/R cohort), ACE-CL-003 (R/R cohort [ie, study cohort 1]), ELEVATE-RR (ACE-CL-006), and ASCEND (ACE-CL-309). Detailed methods for each study were previously reported.[6,8,9,14-16] Screening blood samples underwent centralized (except for CL-003) assessment of genomic aberrations with fluorescence in situ hybridization (FISH) and mutational analysis of the IGHV and cellular antigen *TP53* genes by DNA sequencing; for CL-003, FISH, cytogenetics, and IGHV mutational analyses were performed in the Clinical Laboratory Improvement Amendments (CLIA)−certified clinical pathology laboratories at The Ohio State University. FISH probes were used for cytogenetic profiling, and abnormalities in chromosomes 13q, 12, 11q, and 17p were assessed (Vysis CLL FISH Probe Kit; Abbott Molecular). IGHV mutations were

assessed by standard Sanger sequencing using assay sensitivity of 10% and a cutoff of 2%. *TP53* mutations were analyzed by use of the Sanger sequencing methods. CK was defined as having ≥ 3 chromosomal abnormalities with ≥ 1 structural abnormality excluding inversion of chromosome 9. In all of the included studies, acalabrutinib was given as 100 mg twice daily until progressive disease or unacceptable toxicity, with the exception of some patients in ACE-CL-001 and ACE-CL-003 who were initially treated at 200 mg once daily. Patients in ACE-CL-003 and patients in the acalabrutinib plus obinutuzumab arm of ELEVATE-TN also received 6 cycles of obinutuzumab (100 mg on day 1, 900 mg on day 2, and 1000 mg on days 8 and 15 of cycle 2, and 1000 mg on day 1 of cycles 3–7). Although some of these studies had treatment arms other than acalabrutinib monotherapy and acalabrutinib plus obinutuzumab, this analysis pooled data for acalabrutinib monotherapy and acalabrutinib plus obinutuzumab therapy, referred to as acalabrutinib-based treatment.

The institutional review board or independent ethics committees at each participating site approved each study protocol. Each study was conducted according to the principles of the Declaration of Helsinki and International Conference on Harmonisation for Good Clinical Practice. All patients provided written informed consent.

Outcomes

PFS was defined as the time from first dose of study drug (ACE-CL-001 and ACE-CL-003) or from randomization (ELEVATE-TN, ELEVATE-RR, and ASCEND) to documented disease progression, assessed based on International Workshop on

Chronic Lymphocytic Leukemia 2008 criteria,[17] or death from any cause, whichever occurred first. OS was defined as the time from first dose of study drug (ACE-CL-001 and ACE-CL-003) or from randomization (ELEVATE-TN, ELEVATE-RR, and ASCEND) to death due to any cause. Overall response rate (ORR) was defined as the proportion of patients who achieved a complete response (CR), CR with an incomplete blood count recovery, nodular partial response, or partial response (PR); PR with lymphocytosis was not included in the ORR calculation. ORR was reported as best response at any time over the course of the study for each patient. Safety was assessed based on treatment-emergent adverse events (TEAEs).

Statistical Analysis

Analyses of patient demographics, baseline characteristics, and study disposition were reported by TN and R/R cohort for all patients in the higher-risk subgroup and separately by TN and R/R cohort for all patients in the lower-risk subgroup; safety data were reported only for patients in the higher-risk subgroup by TN and R/R cohort.

In the higher-risk subgroup, efficacy analyses for the TN cohort reported data for acalabrutinib monotherapy, acalabrutinib plus obinutuzumab, and/or all acalabrutinib-based treatments combined, while efficacy analyses in the R/R cohort reported data for acalabrutinib monotherapy only. In the lower-risk subgroup, efficacy analyses reported data for acalabrutinib-based treatment combined in the TN cohort and for acalabrutinib monotherapy in the R/R cohort.

In the higher-risk subgroup, investigator-assessed response rates, investigator-assessed PFS, OS, and safety were reported for the TN CLL and R/R CLL cohorts.

PFS and OS outcomes were estimated using the Kaplan–Meier method, and response rates were summarized with corresponding 95% confidence interval (CI) based on Wilson's score.[18] Additional analyses of investigator-assessed response rates, investigator-assessed PFS, and OS were conducted comparing data for the lower-risk subgroup vs the higher-risk subgroup in the TN and R/R cohorts. PFS and OS outcomes were compared between the risk subgroups using hazard ratios (HR) and 95% CI, while response rates were summarized with corresponding 95% CI based on Wilson's score. The Statistical Analysis System Software, version 9.04.01, was used for data analysis.

Retrospective analyses were conducted to evaluate the association of higher-risk genomic features including del(17p)/*TP53*m, uIGHV, and CK with PFS and OS in both the TN and R/R cohorts. First, a univariable analysis was performed with each mutation or co-mutation to assess statistical significance and the predictive ability of each genetic status. Then, a multivariable analysis including all genetic mutation/co-mutations was performed using backward selection method to determine the final model. The univariable and multivariable analyses were performed using Cox proportional-hazards model and the predictive ability of the models was assessed via concordance (C)-index.

RESULTS

Patients

A total of 808 patients with higher-risk CLL (TN cohort, n = 320; R/R cohort, n = 488) were included in the pooled analysis (**Table 2**). In the TN cohort (n = 320), 64 (20%) patients had del(17p)/*TP53*m, 287 (90%) patients had uIGHV, 79 (25%) patients had

CK overall, and 49 (15%) patients had CK without del(17p)/*TP53*m. In the R/R cohort (n = 488), 219 (45%) patients had del(17p)/*TP53*m, 425 (87%) patients had uIGHV, 160 (33%) patients had CK overall, and 69 (14%) patients had CK without del(17p)/*TP53*m. In the higher-risk subgroup, baseline genetic status was generally similar between the TN and R/R cohorts with the exception of relatively lower proportions of patients with del(17p)/*TP53*m and CK overall in the TN cohort compared with the R/R cohort, as expected. Baseline characteristics were generally similar between the higher-risk and lower-risk subgroups in both cohorts, although in the R/R cohort, the median number of prior therapies was higher in the higher-risk subgroup vs the lower-risk subgroup (2 vs 1) (**Supplemental Table 1**).

For the efficacy analyses comparing data for the higher-risk vs lower-risk subgroups, a total of 475 patients were included in the TN cohort (higher-risk subgroup, n = 320; lower-risk subgroup, n = 155) and 554 patients (those treated with acalabrutinib monotherapy only) were included in the R/R cohort (higher-risk subgroup, n = 468; lower-risk subgroup, n = 86).

In the higher-risk subgroup, the median study follow-up duration was 59.1 months in the TN cohort and 44.3 months in the R/R cohort (**Table 3**). The proportion of patients who remained on treatment in the TN and R/R cohort was 51.3% and 26.8%, respectively. Among the patients in the TN cohort, the most common reason for treatment discontinuation was TEAEs (13.8%); 8.1% of patients discontinued due to disease progression. Among the patients in the R/R cohort, the most common reason for treatment discontinuation was disease progression (30.5%); 16.6% of patients discontinued due to TEAEs. In the lower-risk subgroup, the median study follow-up

duration was 61.0 months in the TN cohort and 48.6 months in the R/R cohort, and the most common reason for treatment discontinuation after study termination by sponsor was TEAEs (14.8%) in the TN cohort and TEAEs (19.6%) and disease progression (19.6%) in the R/R cohort (**Supplemental Table 2**).

Efficacy

In the TN cohort, ORR data were generally similar in the overall pooled higher-risk and lower-risk subgroups (95.0% vs 92.3%, respectively; **Supplemental Figure 1A**). Favorable PFS outcomes were observed overall with acalabrutinib monotherapy and acalabrutinib plus obinutuzumab across higher-risk subgroups (**Figure 1A–D**), with no statistically significant difference in PFS between lower-risk vs higher-risk patients (**Supplemental Figure 2A**). There was also no statistically significant difference in PFS between lower-risk patients vs patients with uIGHV, CK, or CK without del(17p)/*TP53*m (**Supplemental Figure 2B**); however, PFS was significantly shorter in patients with del(17p)/*TP53*m vs lower-risk patients. Favorable OS outcomes were also observed overall with acalabrutinib monotherapy and acalabrutinib plus obinutuzumab across higher-risk subgroups (**Figure 2A–C**). Similar to the PFS outcomes, no statistically significant difference in OS was observed between the lower-risk patients vs higher-risk patients or specifically those with del(17p)/*TP53*m (**Supplemental Figures 3A and 3B**, respectively).

In the R/R cohort, ORR data were also similar in the overall pooled higher-risk and lower-risk subgroups (87.2% vs 84.9%, respectively; **Supplemental Figure 1B**). Favorable PFS outcomes were observed with acalabrutinib monotherapy across higher-

risk subgroups (**Figure 3**), while PFS was significantly shorter in the higher-risk vs lower-risk patients (**Supplemental Figure 2C**). PFS was also significantly shorter in patients with del(17p)/*TP53*m, uIGHV, or CK vs lower-risk patients; however, there was no significant difference in PFS between lower-risk patients vs patients with CK without del(17p)/*TP53*m (**Supplemental Figure 2D**). Favorable OS outcomes were also observed across higher-risk subgroups (**Figure 4**). However, OS was significantly shorter in higher-risk patients and in patients with del(17p)/*TP53*m vs lower-risk patients (**Supplemental Figure 3C and 3D**, respectively).

In patients with del(17p)/*TP53*m, the ORR was 90.6% (CR, 23.4%) in the TN cohort and 86.0% (CR, 5.1%) in the R/R cohort (**Figure 5**). In the TN cohort, the median PFS for patients with del(17p)/*TP53*m was not reached (NR) and the 48-month PFS rate was 76.9%. In the R/R cohort, the median PFS for patients with del(17p)/*TP53*m was 38.6 months and the 36-month PFS rate was 54.4%. PFS was significantly shorter in patients with del(17p)/*TP53*m vs patients without del(17p)/*TP53*m in both the TN and R/R cohorts (**Figure 6A and 6D**, respectively). In the TN cohort, the median OS for patients with del(17p)/*TP53*m was NR and the 48-month OS rate was 88.6%. In the R/R cohort, the median OS for patients with del(17p)/*TP53*m was 60.6 months and the 36-month OS rate was 72.5%. No statistically significant difference in OS was observed in patients with vs without del(17p)/*TP53*m in the TN cohort (**Figure 7A**); however, in the R/R cohort, OS was significantly shorter in patients with del(17p)/*TP53*m vs patients without del(17p)/*TP53*m (**Figure 7D**).

In patients with uIGHV, ORR was 95.8% (CR, 19.9%) in the TN cohort and 87.3% (CR, 7.8%) in the R/R cohort (**Figure 5**). In the TN cohort, the median PFS for

patients with uIGHV was NR and the 48-month PFS rate was 85.6%. In the R/R cohort, the median PFS for patients with uIGHV was 46.9 months and the 36-month PFS rate was 64.6%. No statistically significant difference in PFS was observed in patients with uIGHV vs mIGHV in the TN cohort (**Figure 6B**); however, in the R/R cohort, PFS was significantly shorter in patients with uIGHV vs patients with mIGHV (**Figure 6E**). In the TN cohort, the median OS for patients with uIGHV was NR and the 48-month OS rate was 93.5%. In the R/R cohort, the median OS for patients with uIGHV was NR and the 36-month OS rate was 82.0%. No statistically significant difference in OS was observed in patients with uIGHV vs mIGHV in the TN cohort and R/R cohort (**Figure 7B; Figure 7E**).

In patients with CK, ORR was 91.1% (CR, 19.0%) in the TN cohort and 83.6% (CR, 10.3%) in the R/R cohort (**Figure 5**). In the TN cohort, the median PFS for patients with CK overall was NR and the 48-month PFS rate was 84.1%. Examining data in the subset of patients with CK without del(17p)/*TP53*m, the 48-month PFS rate was 92.7% (**Figure 1D**). In the R/R cohort, the median PFS for patients with CK overall was 38.6 months and the 36-month PFS rate was 55.7% while in the subset of patients with CK without del(17p)/*TP53*m, the 36-month PFS rate was 68.4%. No statistically significant difference in PFS was observed in patients with vs without CK in the TN cohort (**Figure 6C**); however, in the R/R cohort, PFS was significantly shorter in patients with CK vs patients without CK (**Figure 6F**). In the TN cohort, the median OS for patients with CK overall was NR and the 48-month OS rate was 90.6%. In the R/R cohort, the median OS for patients with CK overall was NR and the 36-month OS rate was 77.4%. No statistically significant difference in OS was observed in patients with vs without CK in

the TN cohort (**Figure 7C**); however, in the R/R cohort, OS was significantly shorter in patients with CK vs patients without CK (**Figure 7F**).

A multivariable analysis of TN patients demonstrated that the presence of all 3 genomic features [del(17p)/*TP53*m, uIGHV, and CK combined] was significantly associated with shorter PFS (**Supplemental Table 3**), whereas none of the genomic features were significantly associated with shorter OS (**Supplemental Table 4**). Also, multivariable analysis of R/R patients showed that the presence of both del(17p)/*TP53*m and uIGHV as well as all 3 genomic features [del(17p)/*TP53*m, uIGHV, and CK] was significantly associated with shorter PFS. Similarly, the presence of del(17p)/*TP53*m alone, both del(17p)/*TP53m* and uIGHV, or all 3 genomic features [del(17p)/*TP53*m, uIGHV, and CK] was significantly associated with shorter OS in R/R patients.

Patients with higher-risk CLL in both the TN and R/R cohorts received a median of 1 subsequent line of therapy (**Supplemental Table 5**). The most common subsequent therapy in the TN cohort was chemo- and/or immunotherapy-based treatments (4.7%) followed by targeted therapies (2.8%) and was targeted therapies (14.3%) followed by chemo- and/or immunotherapy-based treatments (7.2%) in the R/R cohort.

Safety

Among the overall population of patients with higher-risk CLL (N = 808), the duration of treatment exposure was 59.3 months in the TN cohort and 39.1 months in the R/R cohort (**Supplemental Table 6**). Of the 808 patients, 568 (70.3%) experienced at least 1 grade ≥ 3 TEAE; the most common grade ≥ 3 TEAEs were neutropenia (19.3%),

pneumonia (9.5%), anemia (8.4%), thrombocytopenia (6.1%), and hypertension (5.4%). TEAEs of any grade that led to treatment discontinuation were reported in 16.5% of patients, most commonly pneumonia and thrombocytopenia, which occurred in 7 (0.9%) and 5 (0.6%) patients, respectively (**Supplemental Table 7**). The most common events of clinical interest were infections (any grade, 78.3%; grade ≥ 3, 28.5%) and neutropenia (any grade, 23.9%; grade ≥ 3, 22.3%), with incidences of any-grade atrial fibrillation/flutter of 7.4% (grade ≥ 3, 2.6%) and any-grade hemorrhage of 45.7% (grade ≥ 3, 4.2%) (**Supplemental Table 8**). The safety profile of acalabrutinib-based treatment in the lower-risk subgroup (data not shown) was similar to that seen in the higher-risk subgroup in both the TN and R/R cohorts.

Deaths were reported in 34 (10.6%) patients in the TN cohort and in 114 (23.4%) patients in the R/R cohort, most commonly due to AEs in both cohorts (19 [5.9%] and 57 [11.7%], respectively; **Supplemental Table 9**). The most common cause of death due to AE per system organ class was infections and infestations in both cohorts (7 [2.2%] and 28 [5.7%], respectively); the most common infection and infestation event was COVID-19 (3 [0.9%]) in the TN cohort and pneumonia (8 [1.6%]) in the R/R cohort (**Supplemental Table 10**). Disease progression was the cause of death in 3 (0.9%) patients in the TN cohort and 33 (6.8%) patients in the R/R cohort; only 1 of these patients (in the R/R cohort) was on active treatment at the time of death. Death due to Richter transformation was uncommon in both cohorts (TN cohort, 1 [0.3%]; R/R cohort, 6 [1.2%]).

DISCUSSION

In this pooled analysis of clinical trial data in 808 patients with CLL and higher-risk genomic features, PFS and OS rates were high with acalabrutinib-based regimens across higher-risk genomic features in both the TN and R/R cohorts at a median follow-up of nearly 5 and 4 years, respectively. While significantly shorter PFS was only observed in patients with del(17p)/*TP53*m vs without del(17p)/*TP53*m in the TN cohort, findings differed in the R/R cohort where significantly shorter PFS was observed in patients with del(17p)/*TP53*m vs without del(17p)/*TP53*m, with uIGHV vs mIGHV, and with CK vs without CK. This is further supported by the multivariable analysis where the presence of both del(17p)/*TP53*m and uIGHV or all 3 genomic features [del(17p)/*TP53*m, uIGHV, and CK] was significantly associated with shorter PFS in the R/R cohort. While no statistically significant OS difference was observed in patients with vs without each individual genomic feature in the TN cohort, significantly shorter OS was observed in patients with del(17p)/*TP53*m vs without del(17p)/*TP53*m, and with CK vs without CK in the R/R cohort. This is further supported by the multivariable analysis where the presence of del(17p)/*TP53m* alone, both del(17p)/*TP53m* and uIGHV, or all 3 genomic features [del(17p)/*TP53m*, uIGHV, and CK] was significantly associated with shorter OS in the R/R cohort. Therefore, in the R/R cohort, del(17p)/*TP53*m, regardless of other co-mutations, was predictive of OS. This finding, however, was not evident in the TN cohort, indicating that the impact of first-line treatment with acalabrutinib was comparable regardless of higher-risk genomic features. Of note, interpretation of findings from the multivariate analysis is limited due to small sample sizes in some subgroups. The safety profile of acalabrutinib in patients with higher-risk CLL was consistent with the known safety profile of the drug. Although these patients had higher-

risk genomic features, discontinuation rates due to Richter's transformation were low in both the TN (0.3%) and R/R (0.4%) cohorts. At the time of the analysis, more than half of the patients in the TN cohort remained on treatment, with up to 82 months of follow-up in the patient on treatment for the longest duration.

In the TN cohort in the subgroup of 64 patients with del(17p)/*TP53*m treated with acalabrutinib-based therapy, the ORR was 91%, the 24-month PFS and OS rates were 87% and 90%, respectively, and the 48-month PFS and OS rates were 77% and 89%, respectively, at a median follow-up of 59.1 months. These findings are similar to those reported in a pooled analysis of ibrutinib-based treatments in 89 patients with TN CLL and *TP53* aberrations for which ORR was 93% and the 48-month PFS and OS rates were 79% and 88%, respectively, at a median follow-up of 49.8 months.[19] Outcomes reported from the cohort of 110 patients with TN CLL and del(17p) treated with zanubrutinib monotherapy in arm C of the SEQUOIA study also appear to be similar, with estimated 42-month PFS and OS rates of 79% and 90%, respectively, reported at a median follow-up of 47.9 months.[20-22] In contrast to our findings, a long-term follow-up analysis of the Alliance for Clinical Trials in Oncology A041202 study at a median follow-up of 55 months showed no significant difference in PFS between ibrutinib-treated patients with vs without *TP53* abnormalities.[23] However, this could be due to differences in sample size.

In the R/R cohort (median of 2 prior lines of therapy) subgroup of 214 patients with del(17p)/*TP53*m treated with acalabrutinib monotherapy, the ORR was 86%, the 24-month PFS and OS rates were 70% and 81%, respectively, and the 36-month PFS and OS rates were 54% and 73%, respectively, at a median follow-up of 44.3 months in

the overall R/R cohort. By comparison, at a shorter median follow-up of 29.6 months in the head-to-head phase 3 ALPINE study of zanubrutinib vs ibrutinib in patients with R/R CLL (median of 1 prior line of therapy), patients with del(17p) and/or *TP53*m had an ORR of 85% and 24-month PFS rate of 78% with zanubrutinib (n = 75) compared with 71% and 56%, respectively, with ibrutinib (n = 75).[24] Although these analyses all evaluated the efficacy of BTKis in higher-risk CLL, cross-trial comparisons are limited by differences in trial design, time period of study recruitment, heterogeneity in patient populations, and study follow-up duration. Notably, most of the patients in the R/R cohort in this analysis were from the ELEVATE-RR study,[8] which included a more heavily pretreated population than patients from the ALPINE study.[24] The impact of follow-up duration is most important because very few patients with CLL progress before 2 years across all relevant covalent BTKi trials.

The safety profile of acalabrutinib in this analysis was similar to the reported overall safety profile of acalabrutinib, with a relatively low incidence of grade ≥ 3 hypertension (5.4%), any-grade atrial fibrillation/flutter (7.4%), and grade ≥ 3 hemorrhage (4.2%) events observed with long-term follow-up. Discontinuation rates due to TEAEs remained low in both the TN (14%) and R/R (17%) cohorts at median treatment exposure of 59.3 months and 39.1 months, respectively.

With the emergence of BTKis, patients with TN and R/R CLL have several highly effective and well-tolerated treatment options available. Venetoclax plus obinutuzumab is also a highly effective treatment approach in TN CLL. Of note, higher-risk patients with uIGHV and/or *TP53*-aberrant CLL treated with the time-limited venetoclax plus obinutuzumab combination have shorter PFS than patients without higher-risk CLL.[2,3] In

contrast, our analysis has demonstrated that acalabrutinib-based regimens in TN CLL are comparably efficacious in patients with or without higher-risk CLL. The possibility of retreatment with venetoclax plus obinutuzumab for patients who relapse after initially achieving remission with the regimen is a theoretically appealing idea. However, there are currently limited prospective data to understand how effective such a retreatment strategy might be; ongoing studies will hopefully help to address this data gap (eg, NCT04895436). Until such data are available, continuous BTKi-based strategies appear to be the most evidence-based approach for patients with higher-risk CLL.

Some limitations to this retrospective analysis include differences in trial design and pooling data from nonrandomized, single-arm studies, which may introduce selection bias. Despite these limitations, the pooling of 5 clinical studies in both TN and R/R CLL allowed data to be collated from all patients with higher-risk CLL to better understand the impact of acalabrutinib-based treatment. CK defined as ≥ 3 chromosomal abnormalities (with ≥ 1 structural abnormality excluding inversion of chromosome 9) did not appear to be prognostic in patients with TN CLL in this analysis as previously suggested in the era of chemoimmunotherapy,[25] the possibility that poorer outcomes would be seen in patients with CK defined as ≥ 5 abnormalities cannot be excluded, but the number of patients was too small to perform this analysis.

Overall, our results demonstrate the long-term benefit of acalabrutinib-based regimens in patients with CLL and higher-risk genomic features, regardless of line of therapy, with no new safety signals identified in the analysis. Our data continue to support the approach of continuous acalabrutinib as a highly effective and well-tolerated option for treating a broad population of patients with CLL, particularly those with higher-

risk genetic features. However, treatment optimization in patients with del(17p)/*TP53*m is still an urgent unmet need, particularly in the R/R setting.

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TABLES

Table 1. Studies included in the pooled analysis of patients in the higher-risk subgroup treated with acalabrutinib-based regimens (N = 808)

				Number of patients treated with A-based regimens (N = 808)		
	Study	**Study description**	**Data cutoff date**	**del(17p)/*TP53*m (n = 283)**	**uIGHV (n = 712)**	**CK‡ (n = 239)**
TN CLL (n = 320)	**ACE-CL-001 TN** cohort NCT02029443	Phase 1/2 A monotherapy in TN CLL/SLL	15 JUL 2021	12	57	12
	ACE-CL-003 TN cohort (cohort 2) NCT02296918	Phase 1b/2 A+O in TN CLL	13 JUN 2021	4	9	8
	ELEVATE-TN CL-007 NCT02475681	Phase 3 A±O vs O+Clb in TN CLL	01 OCT 2021	48	221	59
	Proportion of higher-risk genomic subgroup in TN cohort, n/N (%)*			**64/283 (23)**	**287/712 (40)**	**79/239 (33)**
R/R CLL (n = 488)	**ACE-CL-001 R/R** cohort NCT02029443	Phase 1/2 A monotherapy in R/R CLL/SLL	15 JUL 2021	35	81	20
	ACE-CL-003 R/R cohort† (cohort 1) NCT02296918	Phase 1b/2 A+O in R/R CLL	13 JUN 2021	5	17	14
	ELEVATE-RR CL-006 NCT02477696	Phase 3 A monotherapy vs ibrutinib in R/R CLL	15 SEPT 2020	135	219	123
	ASCEND	Phase 3	03 SEP	44	108	3

	CL-309 NCT02970318	A monotherapy vs IdR/BR in R/R CLL	2021			
	Proportion of higher-risk genomic subgroup in R/R cohort, n/N (%)*			**219/283 (77)**	**425/712 (60)**	**160/239 (67)**

*Genomic categories are not mutually exclusive.

†Data in the R/R cohort of CL-003 were included only in demographics/baseline characteristics, study disposition, and safety analyses (Table 2, Table 3, Supplemental Table 1, Supplemental Table 2); CL-003 data were not included in the R/R efficacy analyses.

‡Complex karyotype was defined as having ≥ 3 chromosomal abnormalities with ≥ 1 structural abnormality excluding inversion of chromosome 9.

A, acalabrutinib; BR, bendamustine plus rituximab; CK, complex karyotype; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; IdR, idelalisib plus rituximab; O, obinutuzumab; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment-naive; uIGHV, unmutated immunoglobulin heavy chain variable region genes.

Table 2. Patient demographics and baseline characteristics among patients with higher-risk CLL

Characteristic	TN CLL (n = 320)	R/R CLL (n = 488)[†]	Total (N = 808)
Age, median (range), y	68 (34−88)	66 (32−89)	67 (32−89)
Male, n (%)	206 (64)	346 (71)	552 (68)
Number of prior therapies, median (range)	0 (0−1)*	2 (1−10)	1 (0−10)
ECOG PS, n (%)			
0−1	301 (94)	451 (92)	752 (93)
≥2	19 (6)	37 (8)	56 (7)
Genetic status[‡], n (%)			
del(17p) and/or *TP53*m	64 (20)	219 (45)	283 (35)
del(17p)/*TP53*m alone[§]	11 (3)	35 (7)	46 (6)
del(17p)/*TP53*m and uIGHV	23 (7)	93 (19)	116 (14)
del(17p)/*TP53*m and CK	9 (3)	14 (3)	23 (3)
del(17p)/*TP53*m with uIGHV and CK	21 (7)	77 (16)	98 (12)
del(17p)/*TP53*m with either uIGHV or CK	53 (17)	184 (38)	237 (29)
uIGHV	287 (90)	425 (87)	712 (88)
uIGHV alone[¶]	207 (65)	200 (41)	407 (50)
uIGHV and CK	36 (11)	55 (11)	91 (11)
uIGHV and del(17p)/*TP53*m	23 (7)	93 (19)	116 (14)
uIGHV with CK and del(17p)/*TP53*m	21 (7)	77 (16)	98 (12)
uIGHV with either CK or del(17p)/*TP53*m	80 (25)	225 (46)	305 (38)
Complex karyotype (≥ 3 chromosomal abnormalities)[‖]	79 (25)	160 (33)	239 (30)
CK alone[§]	13 (4)	14 (3)	27 (3)
CK and uIGHV	36 (11)	55 (11)	91 (11)
CK and del(17p)/*TP53*m	9 (3)	14 (3)	23 (3)
CK with uIGHV and del(17p)/*TP53*m	21 (7)	77 (16)	98 (12)
CK with either uIGHV	66 (21)	146 (30)	212 (26)

or del(17p)/*TP53*m			
Complex karyotype without del(17p) and/or *TP53*m	49 (15)	69 (14)	118 (15)

*One patient in the CL-001 study received an interrupted prior course of treatment.
†R/R dataset includes acalabrutinib plus obinutuzumab data from the CL-003 study in addition to the acalabrutinib monotherapy data from the CL-001, ELEVATE-R/R, and ASCEND studies.
‡Genomic categories are not mutually exclusive.
§Includes patients with mIGHV, which is not considered an unfavorable genetic feature, and excludes the other high-risk genetic features.
¶Includes patients with uIGHV without del(17p)/*TP53*m or CK.
‖Complex karyotype was defined as having ≥ 3 chromosomal abnormalities with ≥ 1 structural abnormality excluding inversion of chromosome 9.
CK, complex karyotype; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; uIGHV, unmutated immunoglobulin heavy chain variable region genes; R/R, relapsed/refractory; TN, treatment-naive; y, years.

Table 3. Patient disposition among patients with higher-risk CLL

Parameter	TN CLL (n = 320)	R/R CLL (n = 488)†	Total (N = 808)
Follow-up, median (range), mo	59.1 (1−82)	44.3 (0−88)	49.1 (0−88)
Patients remaining on treatment, n (%)	164 (51)	131 (27)	295 (37)
Reasons for treatment discontinuation, n (%)			
Progressive disease	26 (8)	149 (31)	175 (22)
Adverse event	44 (14)	81 (17)	125 (15)
Study terminated by sponsor	42 (13)	74 (15)	116 (14)
Death	11 (3)	18 (4)	29 (4)
Lost to follow-up	2 (0.6)	1 (0.2)	3 (0.4)
Richter's transformation	1 (0.3)	2 (0.4)	3 (0.4)
Other*	30 (9)	32 (7)	62 (8)

*Other includes physician decision (TN, n = 11; R/R, n = 15), withdrawal of consent (TN, n = 5; R/R, n = 11), pregnancy (TN, n = 1; R/R, n = 0), and other (TN, n = 13; R/R, n = 6).

†R/R dataset includes acalabrutinib plus obinutuzumab data from the CL-003 study in addition to the acalabrutinib monotherapy data from the CL-001, ELEVATE-R/R, and ASCEND studies.

AE, adverse event; CLL, chronic lymphocytic leukemia; mo, months; R/R, relapsed/refractory; TN, treatment-naive.

FIGURE LEGENDS

Figure 1. PFS in TN CLL with acalabrutinib-based regimens for (A) del(17p)/*TP53m*, (B) uIGHV, (C) CK overall, and (D) CK without del(17p)/*TP53*m. A, acalabrutinib; CK, complex karyotype; CLL, chronic lymphocytic leukemia; O, obinutuzumab; PFS, progression-free survival; TN, treatment-naive; *TP53*m, mutated *TP53*; uIGHV, unmutated immunoglobulin heavy chain variable region genes.

Figure 2. OS in TN CLL with acalabrutinib-based regimens for (A) del(17p)/*TP53*m, (B) uIGHV, or (C) CK. A, acalabrutinib; CK, complex karyotype; CLL, chronic lymphocytic leukemia; O, obinutuzumab; OS, overall survival; TN, treatment-naive; *TP53*m, mutated *TP53*; uIGHV, unmutated immunoglobulin heavy chain variable region genes.

Figure 3. PFS in R/R CLL with acalabrutinib monotherapy for del(17p)/*TP53m*, uIGHV, CK overall, and CK without del(17p)/*TP53*m. CK, complex karyotype; CLL, chronic lymphocytic leukemia; PFS, progression-free survival; R/R, relapsed/refractory; *TP53*m, mutated *TP53*; uIGHV, unmutated immunoglobulin heavy chain variable region genes.

Figure 4. OS in R/R CLL with acalabrutinib monotherapy for del(17p)/*TP53*m, uIGHV, or CK. CK, complex karyotype; CLL, chronic lymphocytic leukemia; OS, overall survival; R/R, relapsed/refractory; *TP53*m, mutated *TP53*; uIGHV, unmutated immunoglobulin heavy chain variable region genes.

Figure 5. ORR by higher-risk genomic feature in the (A) TN CLL cohort (acalabrutinib-based regimens) and (B) R/R CLL cohort (acalabrutinib monotherapy). CR includes CRi; PR includes nPR. CI, confidence interval; CK, complex karyotype; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, complete response with incomplete blood count recovery; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naive; *TP53*m, mutated *TP53*; uIGHV, unmutated immunoglobulin heavy chain variable region genes.

Figure 6. PFS in TN CLL with acalabrutinib-based regimens for (A) del(17p)/*TP53m* vs no del(17p)/*TP53m*, (B) uIGHV vs mIGHV, and (C) CK vs no CK and PFS in R/R CLL with acalabrutinib monotherapy for (D) del(17p)/*TP53m* vs no del(17p)/*TP53m*, (E) uIGHV vs mIGHV, and (F) CK vs no CK. CK, complex karyotype; CLL, chronic lymphocytic leukemia; mIGHV, mutated immunoglobulin heavy chain variable region genes; PFS, progression-free survival; R/R, relapsed/refractory; TN, treatment-naive; uIGHV, unmutated immunoglobulin heavy chain variable region genes.

Figure 7. OS in TN CLL with acalabrutinib-based regimens for (A) del(17p)/*TP53m* vs no del(17p)/*TP53m*, (B) uIGHV vs mIGHV, and (C) CK vs no CK and OS in R/R CLL with acalabrutinib monotherapy for (D) del(17p)/*TP53m* vs no del(17p)/*TP53m*, (E) uIGHV vs mIGHV, and (F) CK vs no CK. CK, complex karyotype; CLL, chronic lymphocytic leukemia; mIGHV, mutated immunoglobulin heavy chain

variable region genes; OS, overall survival; R/R, relapsed/refractory; TN, treatment-naive; uIGHV, unmutated immunoglobulin heavy chain variable region genes.

Figure 1ABCD

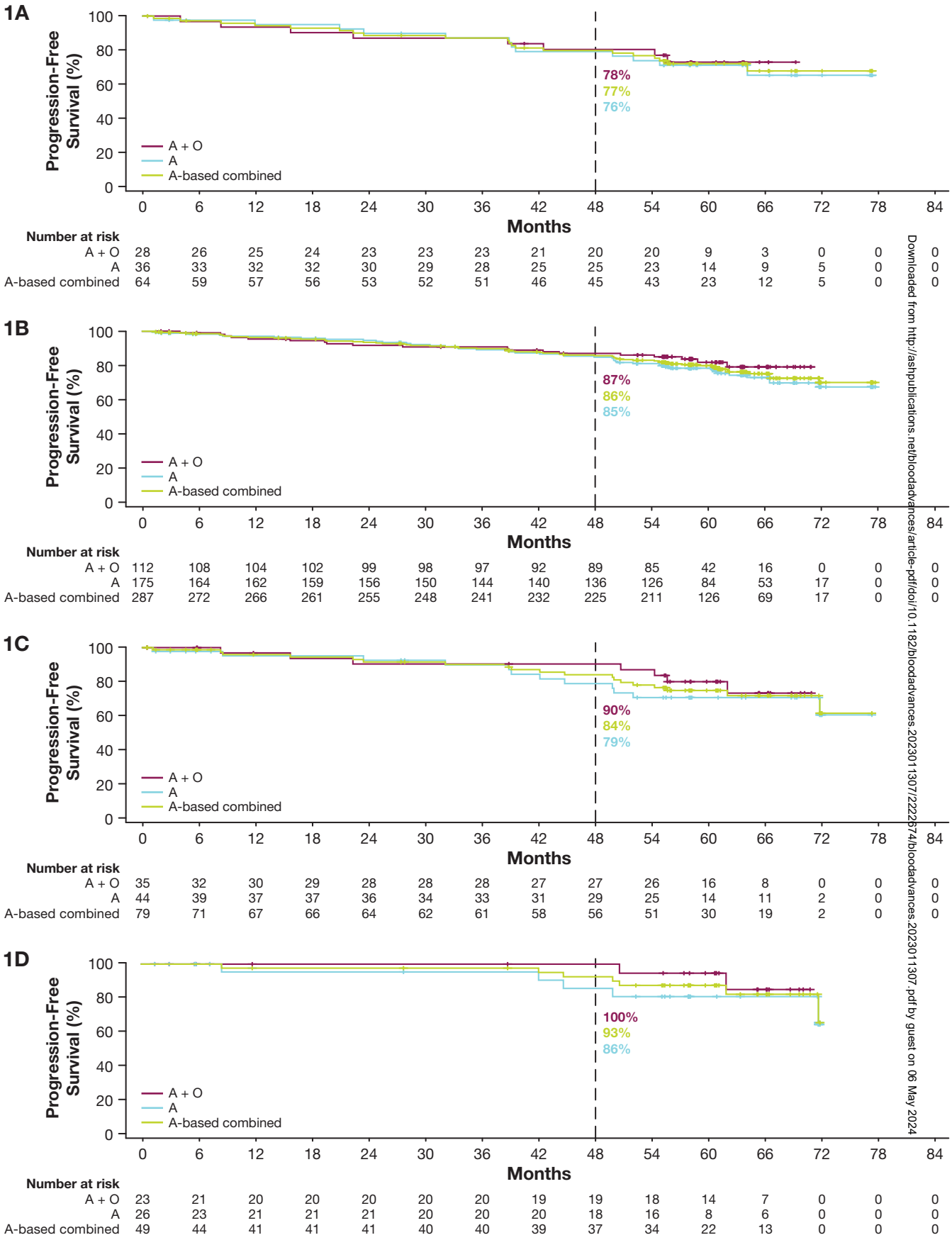
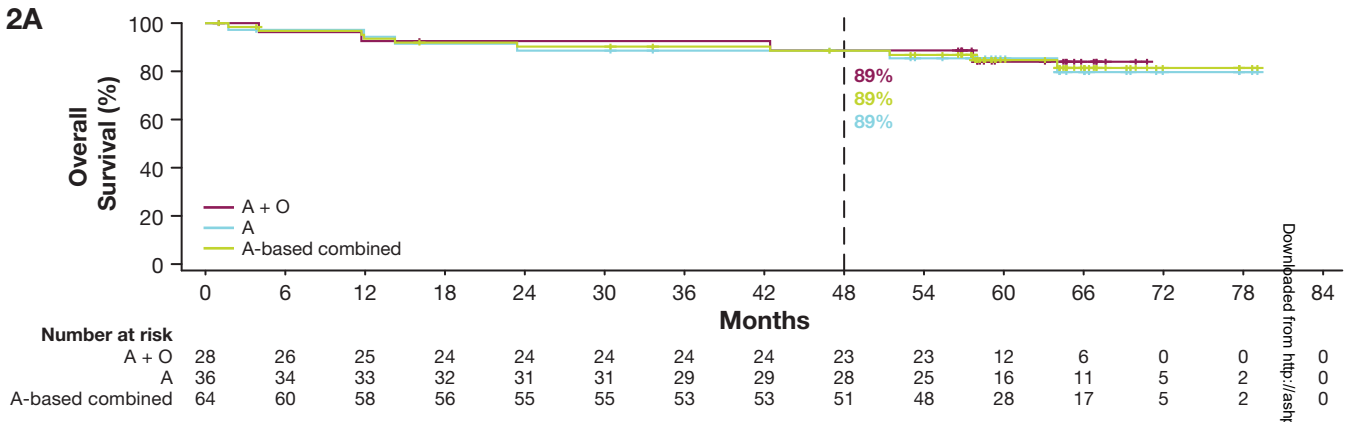
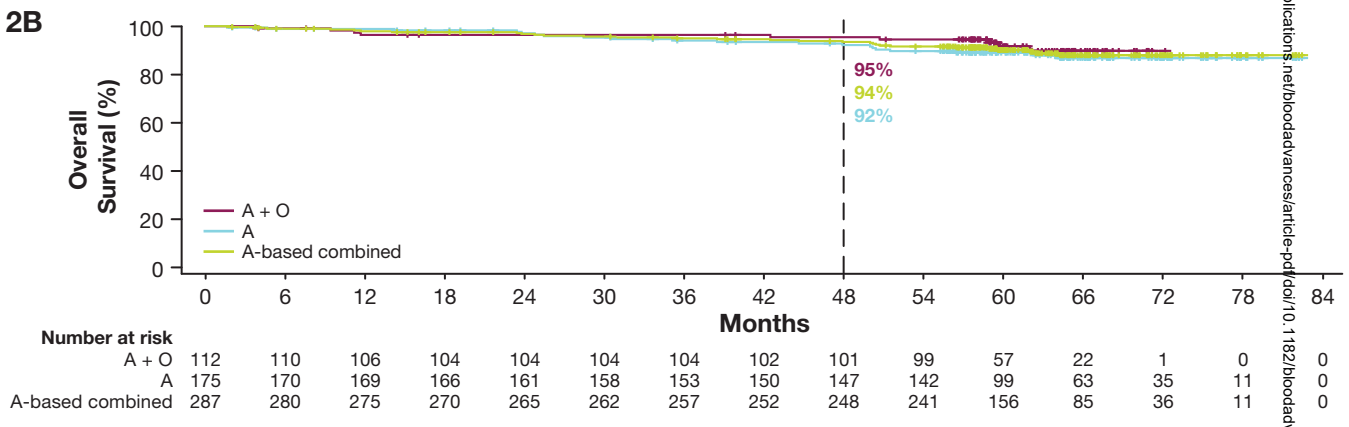


Figure 2ABC





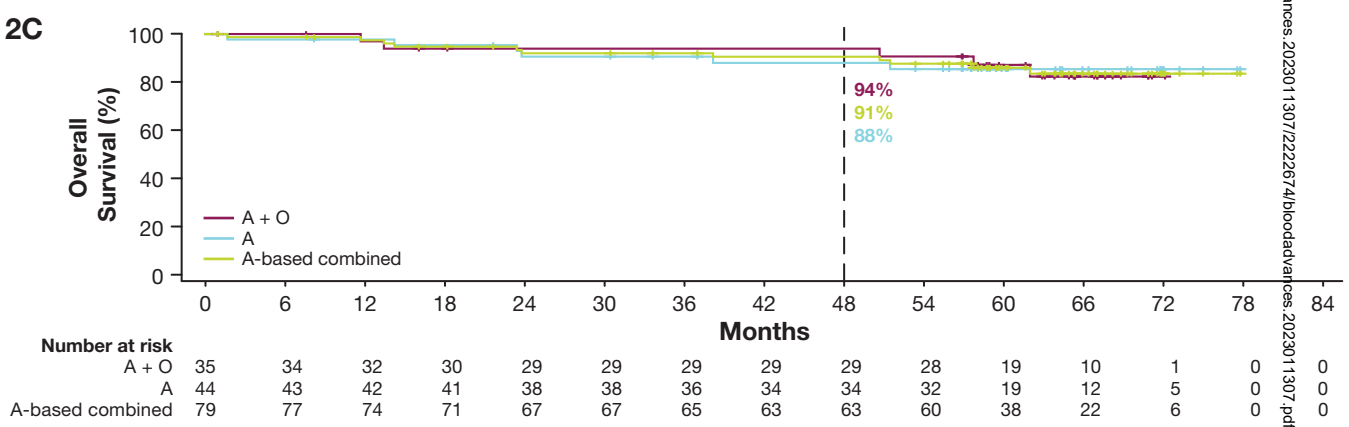


Figure 3

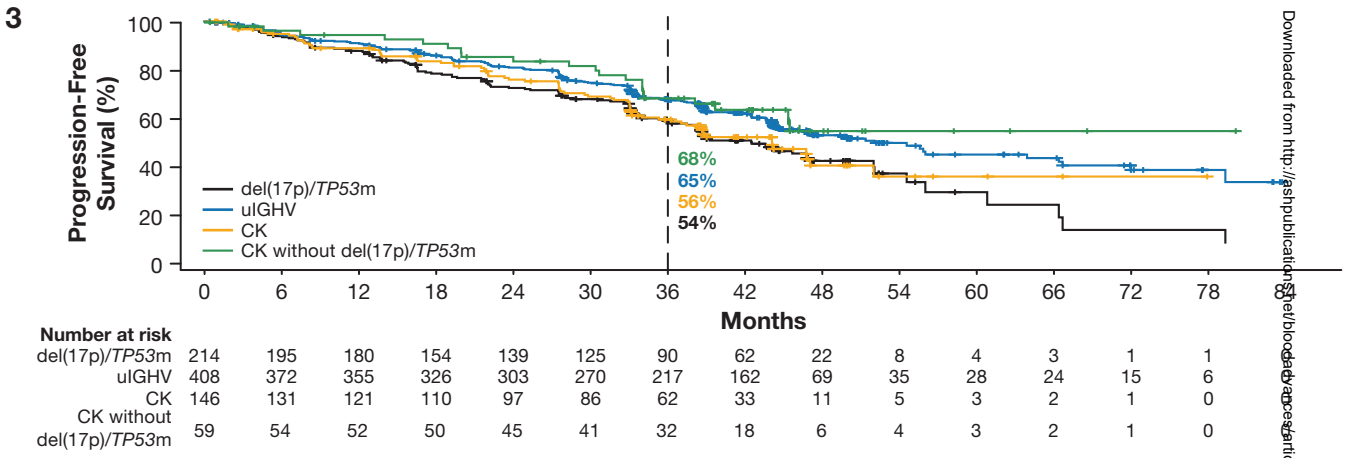


Figure 4

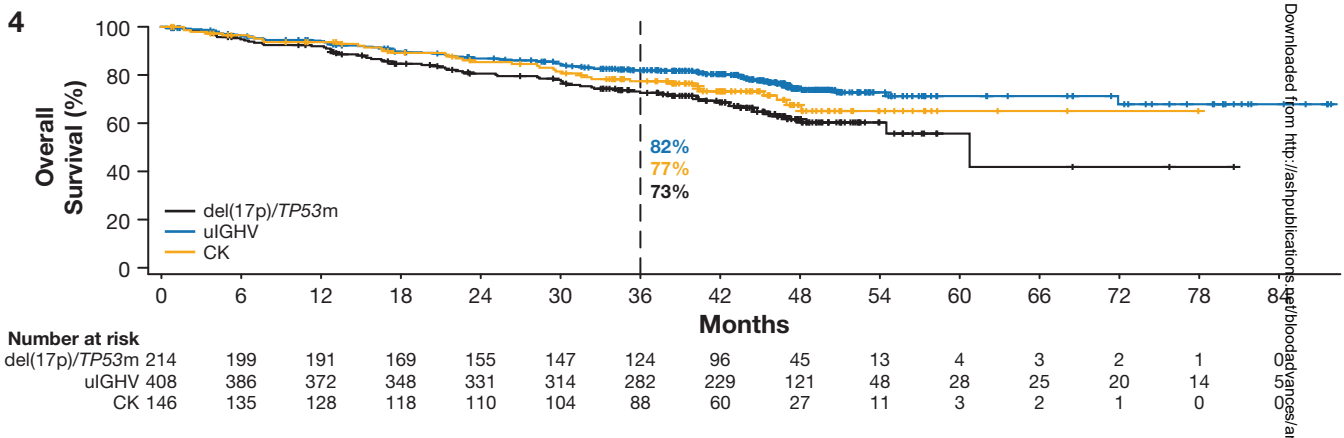


Figure 5AB

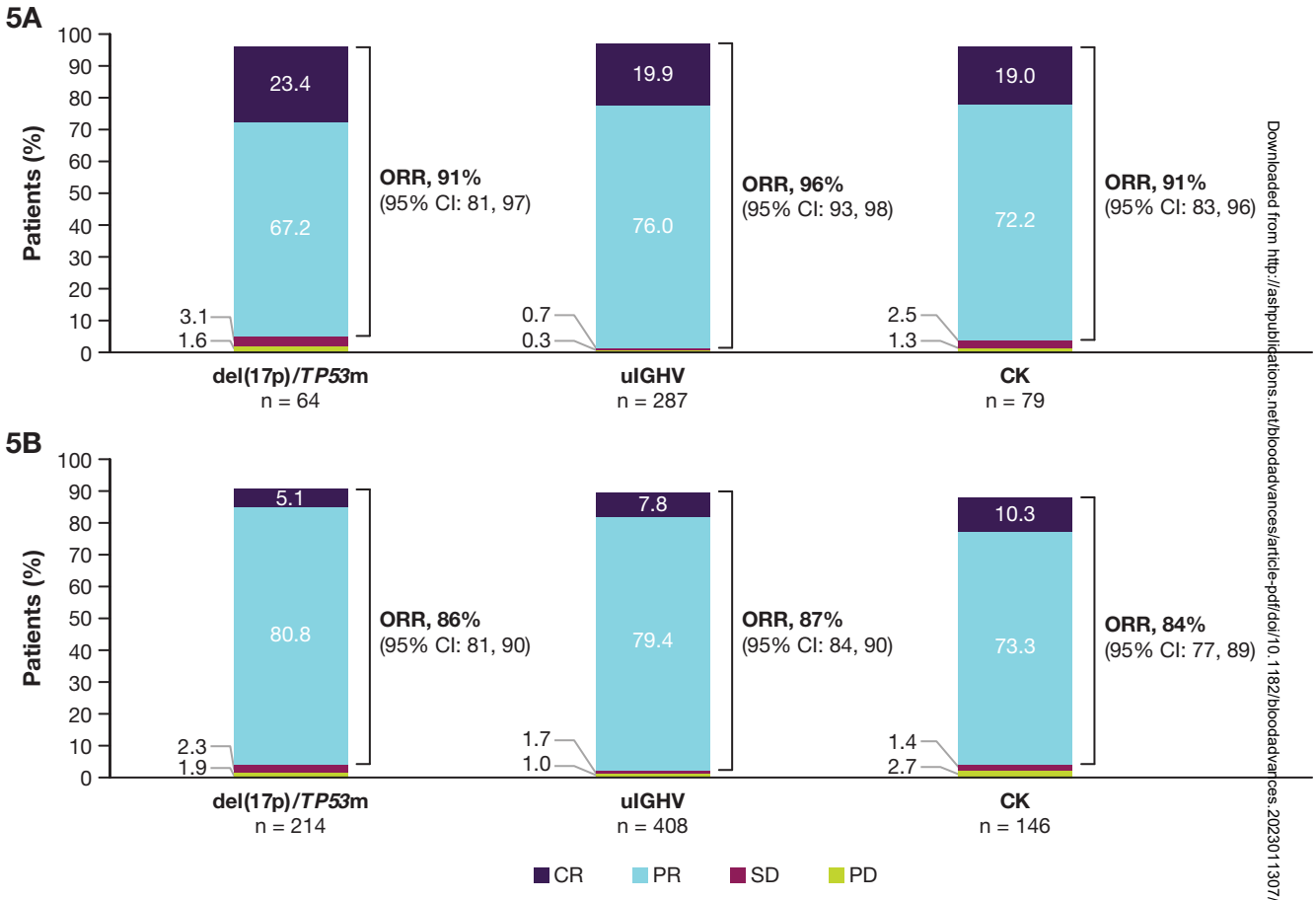


Figure 6ABCDEF

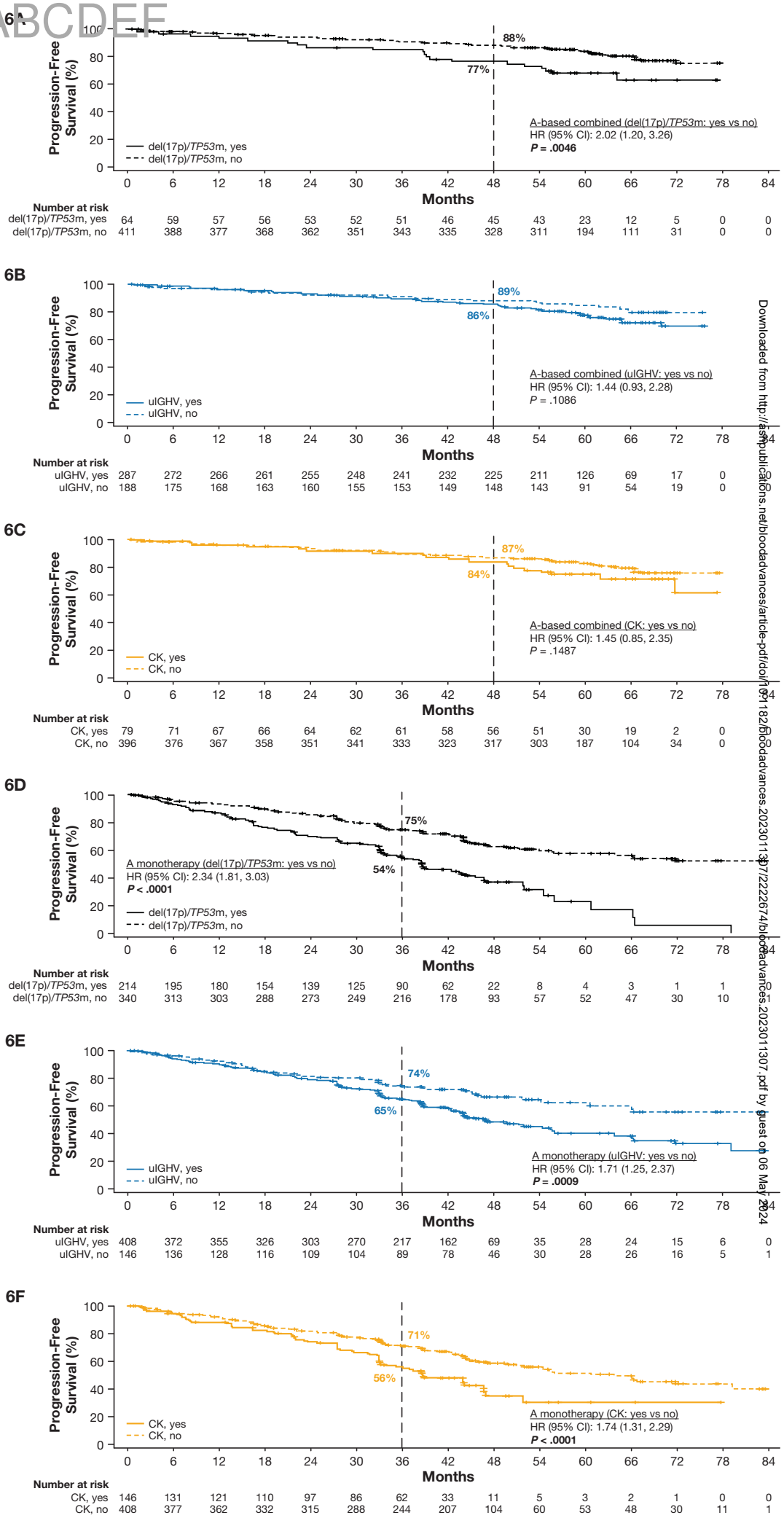


Figure 7ABCDEF