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Acalabrutinib in Waldenström macroglobulinemia yields durable responses with 5 years of follow-up

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Abstract:
Acalabrutinib is a covalent Bruton tyrosine kinase inhibitor. In the phase 2 ACE-WM-001 trial (NCT02180724), at 27.4 months median follow-up, acalabrutinib yielded durable responses in patients with treatment-naive (TN) or relapsed/refractory (R/R) Waldenström macroglobulinemia (WM). We report WM-001 results at 63.7 months median follow-up. Overall, 106 patients (TN, n = 14; R/R, n = 92) were treated; 52.8% discontinued treatment (TN, n = 7; R/R, n = 49), most commonly due to disease progression (19.8%; TN, n = 1; R/R, n = 20) and adverse events (AEs; 17.9%; TN, n = 4; R/R, n = 15). Overall response rates were 92.9% and 94.6%, and major response rates (≥ partial response) were 78.6% and 81.5% in the TN and R/R cohorts, respectively. Median progression-free survival (PFS) was not estimable (NE; 95% CI: 19.3, NE) and 67.5 months (53.3, NE), with estimated 66-month PFS rates of 83.6% (48.0, 95.7) and 52.0% (39.3, 63.2) in the TN and R/R cohorts, respectively. Median duration of response (DOR) was not reached (NR) (11.9 months, NE) and 64.7 months (54.5, NE), with estimated 66-month DOR rates of 90.0% (47.3, 98.5) and 44.8% (27.1, 61.1) in the TN and R/R cohorts, respectively. Median overall survival (OS) was NR in both cohorts; estimated 66-month OS rates were 90.9% (50.8, 98.7) and 71.2% (60.3, 79.6), respectively. Cardiac events of clinical interest occurred in 22 (20.8%) patients. One grade 5 AE (intracranial hematoma) was considered treatment-related. With 5 years of follow-up, efficacy and safety of acalabrutinib in WM were maintained.

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Short title (right running head): Acalabrutinib in Waldenström macroglobulinemia

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Data Sharing Statement

Data underlying the findings described in this manuscript 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/.

KEY POINTS

- Acalabrutinib monotherapy is a highly effective treatment that provides durable responses in patients with TN or R/R WM.
- Long-term acalabrutinib treatment confirms a tolerable safety profile with no new toxicities and a low incidence of cardiovascular events.

ABSTRACT

Acalabrutinib is a covalent Bruton tyrosine kinase inhibitor. In the phase 2 ACE-WM-001 trial (NCT02180724), at 27.4 months median follow-up, acalabrutinib yielded durable responses in patients with treatment-naive (TN) or relapsed/refractory (R/R) Waldenström macroglobulinemia (WM). We report WM-001 results at 63.7 months median follow-up. Overall, 106 patients (TN, n = 14; R/R, n = 92) were treated; 52.8% discontinued treatment (TN, n = 7; R/R, n = 49), most commonly due to disease progression (19.8%; TN, n = 1; R/R, n = 20) and adverse events (AEs; 17.9%; TN, n = 4; R/R, n = 15). Overall response rates were 92.9% and 94.6%, and major response rates (≥ partial response) were 78.6% and 81.5% in the TN and R/R cohorts, respectively. Median progression-free survival (PFS) was not estimable (NE; 95% CI: 19.3, NE) and 67.5 months (53.3, NE), with estimated 66-month PFS rates of 83.6% (48.0, 95.7) and 52.0% (39.3, 63.2) in the TN and R/R cohorts, respectively. Median duration of response (DOR) was not reached (NR) (11.9 months, NE) and 64.7 months (54.5, NE), with estimated 66-month DOR rates of 90.0% (47.3, 98.5) and 44.8% (27.1, 61.1) in the TN and R/R cohorts, respectively. Median overall survival (OS) was NR in both cohorts; estimated 66-month OS rates were 90.9% (50.8, 98.7) and 71.2% (60.3, 79.6), respectively. Cardiac events of clinical interest occurred in 22 (20.8%) patients. One grade 5 AE (intracranial hematoma) was considered treatment-related. With 5 years of follow-up, efficacy and safety of acalabrutinib in WM were maintained.

Keywords: immunoglobulin M, follow-up studies, protein kinase inhibitors, molecular targeted therapy, treatment outcome, clinical trial

INTRODUCTION

Waldenström macroglobulinemia (WM) is a rare B-cell lymphoproliferative disorder characterized by infiltration of the bone marrow and other organs by immunoglobulin M (IgM)-producing clonal lymphoplasmacytic cells.[1,2] Multiple treatments for WM exist; however, due to its low incidence, optimal standards of care are difficult to establish in controlled clinical trials.[1] Treatment options have included alkylating agents, purine analogs, proteasome inhibitors, single-agent rituximab, and rituximab plus chemotherapy, which are associated with significant toxicities, including cytopenias, peripheral neuropathy, infection, treatment-related myeloid neoplasms, and tumor flare reactions.[1,2]

Bruton tyrosine kinase inhibitors (BTKis) are targeted therapies that have demonstrated efficacy and tolerability in patients with treatment-naive (TN) or relapsed/refractory (R/R) WM.[3-5] The first-generation covalent BTKi, ibrutinib, which is approved for the treatment of patients with WM,[6] demonstrated response rates of ≥90% with an estimated 4-year progression-free survival (PFS) rate of 76% in TN WM and a 5-year PFS rate of 54% in R/R WM as monotherapy in phase 2 trials.[7-10] However, ibrutinib has been associated with cardiovascular toxicities.[6] The second-generation covalent BTKi zanubrutinib is also approved for use in this population.[11] In the phase 3, randomized, controlled ASPEN trial in a combined cohort of patients with TN and R/R WM, at a median follow-up of 44.4 months, zanubrutinib demonstrated a higher rate of complete response (CR) plus very good partial response (VGPR) compared with ibrutinib (36.3% vs 25.3%; $P = .07$), with estimated 42-month PFS rates of 78.3% vs 69.7%, respectively ($P = .12$).[5] In addition, compared with ibrutinib, zanubrutinib

demonstrated lower rates of hypertension (14.9% vs 24.5%), atrial fibrillation (6.9% vs 21.4%), and pneumonia (5.0% vs 18.4%); a higher rate of neutropenia (28.7% vs 16.3%); and similar rates of infection (79.2% vs 79.6%).[5] The noncovalent BTKi, pirtobrutinib, is also being investigated in R/R WM.[12,13]

Acalabrutinib is a second-generation, covalent BTKi approved for the treatment of mantle cell lymphoma and chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma. In the head-to-head ELEVATE-RR trial of patients with R/R CLL, acalabrutinib demonstrated comparable efficacy to ibrutinib and an improved tolerability and cardiovascular safety profile, with statistically significant reductions in the rates of atrial fibrillation and hypertension.[14,15]

Acalabrutinib has demonstrated activity in the treatment of TN and R/R WM. In the phase 2 ACE-WM-001 trial (NCT02180724), with median follow-up of 27.4 months, acalabrutinib monotherapy yielded high overall response rates (ORRs) of 93% in both patients with TN WM (n = 14) and R/R WM (n = 92) with a well-tolerated toxicity profile.[3] Here, we present the final safety and efficacy results from the ACE-WM-001 trial with a median follow-up of 63.7 months.

METHODS

Study design and participants

ACE-WM-001 was a phase 2, open-label, multicenter, single-arm study conducted at 27 study sites in 6 countries. Study details, including detailed inclusion and exclusion criteria and patient demographics, were previously published.[3] Briefly, eligible patients were adults aged 18 years or older with a confirmed diagnosis of WM requiring

treatment, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or less, and serum IgM greater than the upper limit of normal or measurable nodal WM involvement (≥1 lymph node ≥2 cm in longest diameter). Patients with R/R WM had received at least 1 prior therapy and patients with TN WM had either declined chemoimmunotherapy or could not receive it due to comorbidities. Key exclusion criteria included prior exposure to a BTKi, significant cardiovascular disease (including 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 corrected QT interval >480 msec), or requirement of treatment with vitamin K antagonists or proton-pump inhibitors.

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

Procedures

Patients were initially randomized to acalabrutinib capsules 100 mg twice daily (BID) or 200 mg once daily (QD), informed by phase 1/2 CLL safety, pharmacokinetic, and pharmacodynamic data. Subsequently, all patients were switched to acalabrutinib 100 mg BID, which was administered in 28-day cycles until disease progression or unacceptable toxicity, based on safety, activity, and target occupancy findings from the phase 1/2 CLL study.[16] Dose delays were permitted for any unmanageable, potentially

study drug−related grade ≥3 toxicity or any clinically important event considered appropriate by the investigator and approved by the medical monitor (eg, invasive procedure/surgery). Following a third occurrence of grade 3 or 4 study drug−related toxicity, a dose modification to 100 mg QD was permitted. Treatment was discontinued if study drug−related toxicity persisted for more than 28 days or following a fourth occurrence.

Outcomes and Assessments

Efficacy parameters were based on investigator assessment per the modified 3rd International Workshop on WM (IWWM)[17] and the 6th IWWM criteria[18]; the modified 3rd IWWM criteria defined categorical responses based on total serum IgM quantitation, whereas the 6th IWWM criteria defined categorical responses based on either IgM M protein quantitation by densitometry or by total serum IgM quantitation by nephelometry as well as assessment of extramedullary disease (**Supplemental Table 1**).[17,18] The modified 3rd IWWM criteria were prioritized to facilitate comparisons with other studies; detailed results per the 6th IWWM criteria are reported in the Supplement. The primary endpoint was investigator-assessed ORR by these criteria, defined as a minor response or better. Because the modified 3rd IWWM criteria did not define a category for very good partial response (VGPR), ACE-WM-001 prospectively prespecified VGPR as ≥90% serum reduction in IgM level from baseline without meeting CR requirements, which is also included in the 6th IWWM criteria.

Key secondary endpoints included investigator-assessed duration of response (DOR), PFS, and overall survival (OS). DOR was defined as the time from initial

response (minor response or better) to disease progression or death. PFS was defined as the interval from the start of therapy to disease progression or death. OS was measured from the start of therapy to the date of death and was not censored for treatment discontinuation. Adverse events (AE) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Statistical analysis

The safety and efficacy analyses included all enrolled patients who received at least 1 dose of study drug. The data cutoff for this analysis was March 31, 2021. The Kaplan-Meier method was used to estimate time-to-event endpoints. The exact binomial test was used to determine 95% confidence intervals (CI).

RESULTS

Patients

A total of 106 patients (TN, n = 14; R/R, n = 92) with WM were enrolled and received acalabrutinib treatment. After enrollment began, a March 2015 protocol amendment discontinued the 200 mg QD dose based on updated safety, efficacy, and BTK occupancy data,[3] with 100 mg BID used thereafter. The 6 patients (n = 1 TN; n = 5 R/R) who were enrolled under the original study design and received 200 mg QD were switched to 100 mg BID. For these 6 patients, the median duration of exposure to 200 mg QD was 6.9 months (range, 1.8–13.8) and the median duration of exposure to 100 mg BID was 65.1 months (range, 7.4–68.8). Among the patients who only received 100 mg BID in the TN (n = 13) and R/R (n = 87) cohorts, the median duration of exposure

was 60.9 months (range, 3.8–68.1) and 60.5 months (range, 2.8–78.3), respectively, and the median relative dose intensity was 91.8% (range, 58.6–99.8) and 98.0% (range, 49.9–104.0), respectively.

At screening, the median age of enrolled patients was 69 years (range, 39–90), 68.9% of patients were male, 94.3% of patients had an ECOG PS of 0 or 1, and the median IgM serum concentration was 3615.0 mg/dL (**Table 1**). The median length of follow-up was 63.7 months (range, 4.6–78.3), and 47.2% of patients were still receiving acalabrutinib at the time of data cutoff (**Table 2**). The most common reasons for treatment discontinuation were disease progression (TN, 7.1%; R/R, 21.7%) and AEs (TN, 28.6%; R/R, 16.3%).

Efficacy

According to the modified 3rd IWWM criteria, the ORR was 92.9% (95% CI, 66.1–99.8) for patients in the TN cohort and 94.6% (95% CI, 87.8–98.2) for patients in the R/R cohort, and the major response rate (defined as a partial response or better) was 78.6% (95% CI, 49.2–95.3) and 81.5% (95% CI, 72.1–88.9), respectively (**Table 3**). The ORR was consistent across prespecified subgroups including patient age (<65 or ≥65 years), baseline ECOG PS (0 or ≥1), baseline hemoglobin level (<110 g/L or ≥110 g/L), baseline IgM level (<4000 mg/dL or ≥4000 mg/dL), and number of prior regimens for patients in the R/R cohort (1−3 or >3) (**Supplemental Figure 1**). Rapid reductions in serum IgM levels were observed with acalabrutinib treatment in both the TN (**Figure 1A**) and R/R (**Figure 1B**) cohorts; a median change from baseline of −2030 (range, –8906.0 to 1800.0) mg/dL in IgM was observed. Consistent with early target

engagement, most patients achieved their best response within the first 6 months; median time to best response for the TN and R/R cohorts was 4.9 months (range, 1.0–16.6) and 5.6 months (range, 0.9–66.5), respectively. Notably, responses continued to deepen beyond the initial IgM decline in a subset of patients, with incremental improvements observed over the first 18–24 months, after which response depth generally plateaued, reflected by the progressive downward trajectories in IgM and the distribution of time to best response extending into later time windows, particularly in patients with R/R disease. The maximum percentage decrease in each patient's IgM from baseline to nadir is shown in **Figure 2**; the median (range) and mean (standard deviation) maximum percentage decrease in IgM levels were −82.9% (−98.9%–0.8%) and –75.1% (22.9), respectively. The median (range) times to minimum post-baseline IgM were 840 (113, 1927) and 984.5 (28, 2353) days for the TN and R/R cohorts, respectively.

Response outcomes were generally similar when assessed using the 6th IWWM criteria (**Supplemental Table 2**). The CR plus VGPR rate was 7.1% for patients in the TN cohort and 27.2% for patients in the R/R cohort, and the median time to best response was 4.9 months (range, 1.8–22.1) and 4.6 months (range, 0.9–66.5), respectively.

According to the modified 3rd IWWM criteria, median PFS was not reached (NR; 95% CI, 19.3–not estimable [NE]) for patients with TN WM and was 67.5 months (95% CI, 53.3–NE) for patients with R/R WM (**Figure 3A**). The estimated 66-month PFS rates were 83.6% and 52.0% for the TN and R/R cohorts, respectively. In the R/R cohort, the estimated 60-month PFS rates were 71.4% and 63.6% among patients who achieved

best overall responses of CR/VGPR and PR, respectively (**Supplemental Figure 2**). Median DOR was NR (95% CI, 11.9–NE) for patients with TN WM and was 64.7 months (95% CI, 54.5–NE) for patients with R/R WM (**Figure 3B**). The estimated 66-month DOR rates were 90.0% and 44.8% for the TN and R/R cohorts, respectively. Similar PFS and DOR outcomes were reported using the 6th IWWM criteria (**Supplemental Figure 3**). Median OS was NR in both cohorts (95% CI, NE–NE; **Figure 3C**). The estimated 66-month OS rates were 90.9% and 71.2% for the TN and R/R cohorts, respectively.

Safety

The most common any-grade treatment-emergent AEs are summarized in **Table 4**. Grade 3 or 4 TEAEs occurred in 62.3% of patients overall, most commonly (in ≥5% of patients) neutropenia (17.0%), pneumonia (9.4%), lower respiratory tract infection (6.6%), and anemia (5.7%).

Serious TEAEs were reported in 68 (64.2%) patients overall, most commonly (in ≥3% of patients) pneumonia (n = 11, 10.4%), lower respiratory tract infection (n = 10, 9.4%), pyrexia (n = 5, 4.7%), cellulitis (n = 4, 3.8%), hip fracture (n = 4, 3.8%), sepsis (n = 4, 3.8%), and urinary tract infection (n = 4, 3.8%).

Overall, TEAEs led to treatment discontinuation in 28.6% of patients in the TN cohort and 17.4% of patients in the R/R cohort (**Table 5**). Those with TEAEs that led to treatment discontinuation since the previous report[3] included 1 patient in the TN cohort who discontinued due to myocardial ischemia and 10 patients in the R/R cohort who discontinued due to cardiac arrest, cardiac failure, myocardial infarction, esophageal

stenosis, mouth ulceration, central nervous system lymphoma, intracranial hematoma, intracranial mass, liver metastasis (unknown origin), and bronchiectasis (n = 1 each). The TEAEs leading to acalabrutinib discontinuation since the last report that were considered related to treatment by the investigator were mouth ulceration, bronchiectasis, and intracranial hematoma.

Acalabrutinib was withheld for 7 or more days for any reason in 67 (63.2%) patients overall. TEAEs led to dose withholdings in 66 (62.3%) patients; TEAEs leading to dose withholdings in ≥5% of patients included neutropenia (n = 9, 8.5%), pneumonia (n = 9, 8.5%), pyrexia (n = 7, 6.6%), and skin lesion (n = 6, 5.7%). Acalabrutinib dose reductions occurred in 26 (24.5%) patients overall. TEAEs led to dose reductions in 10 (9.4%) patients and included alanine aminotransferase increased and aspartate aminotransferase increased (n = 2, 1.9%; both occurred in 2 separate patients), hip fracture (n = 1, 0.9%), and disease progression (n = 1, 0.9%). Other reasons for dose reductions included patient error (n = 15), other non-procedure (n = 4), investigator decision (n = 2), other procedure (n = 1), and unknown (n = 1).

Grade 5 TEAEs were reported in 12 (11.3%) patients including COVID-19 infection, COVID-19 pneumonia, cardiac arrest, central nervous system lymphoma, glioblastoma multiforme, intracranial hematoma, intracranial mass, malignant ascites, multiple organ dysfunction syndrome, myocardial ischemia, esophageal carcinoma, and pneumonia (n = 1 each). Intracranial hematoma was the only grade 5 TEAE considered treatment-related by the study investigator. Of the two grade 5 cardiac TEAEs, the patient with cardiac arrest had no prior cardiac history, whereas the patient with myocardial ischemia had extensive pre-existing cardiac disease.

Events of clinical interest (ECIs; any grade, grade 3–4) included atrial fibrillation/flutter (11.3%, 1.9%), bleeding events (62.3%, 5.7%), and hypertension (6.6%, 3.8%) (**Table 6; Supplemental Table 3**). Among the 8 patients with grade 3–4 cardiac events, 6 patients (one each with atrial fibrillation, cardiac failure congestive, coronary artery disease, cardiac failure, right ventricular failure, and nodal arrhythmia [all grade 3]) had a prior history of cardiac disease. Two patients had possible cardiac risk factors but no documented cardiac history (one with grade 4 myocardial infarction had an abnormal screening ECG; one with grade 4 acute coronary syndrome had a prior mild pulmonary embolism). Cumulative incidence rates, measuring time to first event and counting patients only once, were used to describe cardiac events, neutropenia, infections, bleeding events, headache, diarrhea, and arthralgia/myalgia. Atrial fibrillation and hypertension had low cumulative incidence rates over time (**Figure 4**). The cumulative incidence rates of any-grade and grade ≥3 neutropenia remained low and consistent over time (**Supplemental Figure 4A**). The cumulative incidence rate of any-grade infections had the greatest increase in the first 6 months of treatment and eventually plateaued; these events comprised mostly low-grade events (**Supplemental Figure 4A**). The majority of bleeding events were first reported in the first 6 months of treatment (**Supplemental Figure 4B**). The cumulative incidence rates of any-grade headache, diarrhea, and arthralgia/myalgia showed an initial increase and then remained consistent over time (**Supplemental Figure 4C**).

DISCUSSION

The final results of this phase 2 study confirm that acalabrutinib monotherapy achieved high overall and major response rates for patients with TN and R/R WM that were maintained over a median follow-up of 63.7 months. The TN cohort showed particularly favorable outcomes, with median DOR, PFS, and OS not reached and plateaus achieved on the corresponding Kaplan-Meier curves; the 66-month rate estimates were greater than 80% for PFS and greater than 90% for DOR and OS at a median follow-up of 66 months. Acalabrutinib also demonstrated substantial PFS benefit in patients with R/R WM who had CR/VGPR with an estimated 60-month PFS rate of 71.4%. Acalabrutinib monotherapy continued to be well tolerated, with no new toxicities and few drug-related treatment discontinuations seen with long-term treatment in patients with WM, both of which are necessary to achieve long-term disease control in chronic disease.

The results presented here are consistent with long-term data from phase 3 studies of other BTKis in patients with TN or R/R WM.[19,20] The final analysis of the iNNOVATE study in a subgroup of patients with rituximab-refractory WM treated with ibrutinib monotherapy reported an ORR of 87%, an estimated 60-month PFS rate of 40%, and an estimated 60-month OS rate of 73% with approximately 5 years of follow-up.[19] Patients who were either TN or R/R but not refractory to rituximab in the iNNOVATE trial received ibrutinib combination therapy with rituximab, which yielded an ORR of 92%, an estimated 54-month PFS rate of 68%, and an estimated 54-month OS rate of 86% with a median follow-up of approximately 4 years.[20] In the phase 3, randomized, controlled ASPEN trial in patients with WM at a median follow-up of 44.4 months, zanubrutinib and ibrutinib demonstrated a similar rate of major response per 6th

IWWM criteria (81.4% and 79.8%, respectively)[5] compared with acalabrutinib (combined: 83.0% [TN, 78.6%; R/R, 83.7%]) in the present study. Additionally, the estimated 42-month PFS rate for zanubrutinib (78.3%) and ibrutinib (69.7%) was comparable to the estimated 48-month PFS rate for acalabrutinib (64.8% [TN, 83.6%; R/R 62.7%]).

Efficacy data separated by TN and R/R cohorts of patients with WM treated with zanubrutinib monotherapy are available from the previously reported first-in-human phase 1/2 study, although the long-term follow-up in that study was shorter than in the present study (2.5 years vs 5.5 years).[21] In that study, ORR and 24-month PFS and OS estimates in patients with TN WM treated with zanubrutinib were 100%, 92%, and 100%, respectively,[21] which are consistent with the ORR and estimated 24-month PFS and OS rates reported in the 2-year WM-001 update for the TN cohort (93%, 90%, and 92%, respectively),[3] as well as the ORR and estimated 66-month PFS and OS rates reported in the present update (93%, 84%, and 91%). In the R/R WM cohort of the phase 1/2 study of zanubrutinib monotherapy, estimated 36-month PFS and OS rates of 76% and 80% were reported,[21] which are comparable to the estimated 24-month PFS and OS rates for the R/R WM cohort in the previous report of this study (82% and 89%, respectively)[3] and generally align with the ORR and estimated 66-month PFS and OS rates reported herein with considerably longer follow-up (95%, 52%, and 71%, respectively).

In this long-term follow-up of the WM-001 study, AEs were consistent with the previously reported primary analysis, with low rates of atrial fibrillation/flutter and hypertension seen over time, with a plateau on the cumulative incidence curves.[3] Rates

of any-grade atrial fibrillation/flutter with acalabrutinib were 11.3% in the current analysis (vs 4.7% in the previous report of this study),[3] lower than those reported for ibrutinib (23.5%) and closer to zanubrutinib (7.9%) in the ASPEN study, despite longer treatment exposure here (42 and 43 months for ibrutinib and zanubrutinib, respectively, in ASPEN vs >60 months in the present study).[5] Additionally, any-grade hypertension with acalabrutinib was low (6.6%) compared with ibrutinib (25.5%) and zanubrutinib (14.9%) in ASPEN.[5] Cross-trial AE comparisons are limited by differences in follow-up (63.7 months here vs 44.4 months in ASPEN) and the absence of derived exposure-adjusted incidence rates in this trial. The longer follow-up may have also contributed to differences in treatment discontinuation due to AEs (acalabrutinib, 18.9%; ibrutinib, 20.4%; zanubrutinib, 8.9%) and in the incidence of grade 5 AEs (acalabrutinib, 11.3%; ibrutinib 5.1%; zanubrutinib, 3.0%).[5] Furthermore, the cumulative incidence curve for bleeding events, measuring time to first bleed event, demonstrates a plateau after 6 months, suggesting that perhaps only a subgroup of patients is at risk for bleeding events or there is a physiologic adaptation occurring after 6 months that enables improved hemostasis.

There were low numbers of additional treatment discontinuations due to AEs since the last report (n = 11),[3] and only 3 of the additional AEs leading to treatment discontinuation were considered to be related to treatment. Overall, only 7 patients discontinued treatment due to AEs considered related to treatment. Given the risk of IgM rebound after BTKi discontinuation, even in patients on prolonged treatment, minimizing BTKi discontinuation is important,[8,22-24] underscoring the value of sustained BTKi treatment. In this follow-up, acalabrutinib produced a rapid IgM reduction early in

treatment, coinciding with timing of best response for most patients, and this reduction was sustained throughout treatment. This early IgM decline, together with favorable responses, may reduce the likelihood of treatment discontinuation. Overall, the AEs were consistent with the known safety profile of acalabrutinib, supporting the tolerability of long-term acalabrutinib therapy in patients with WM.

Limitations of this study include the small size of the TN cohort, which constrains comparisons with other BTKi monotherapy trials for TN WM and warrants cautious interpretation. This phase 2 study also lacks an internal control; thus, all cross-study comparisons (eg, with ibrutinib and zanubrutinib) are indirect and subject to differences in baseline risk, eligibility criteria, and follow-up; therefore our conclusions focus on within-study efficacy and safety. Risk stratification was limited to age, ECOG PS, number of prior regimens, and baseline hemoglobin/IgM; no central genomic testing (*MYD88*, *CXCR4,* or *TP53*) was performed, limiting genotype-specific inference and cross-trial comparability. Findings should therefore be considered genotype-agnostic and hypothesis-generating. At trial inception, the relevance of *MYD88* or *TP53* mutations to WM outcomes was not yet established. Previous studies of ibrutinib in WM demonstrated that patients with wild-type *MYD88* or *TP53* mutation had lower response rates and inferior survival outcomes compared with patients with *MYD88* mutations or wild-type *TP53*.[9,25] In contrast, zanubrutinib yielded clinically meaningful responses in patients with wild-type *MYD88* or *TP53*-mutated WM.[21,25] The efficacy of acalabrutinib in combination with bendamustine and rituximab is being studied in the frontline WM setting in patients with wild-type *MYD88* or *TP53* mutation in the BRAWM trial; initial results have shown high CR/VGPR rates.[26]

In conclusion, the final results of this phase 2 study demonstrate durable responses and tolerable safety for patients with TN or R/R WM following long-term treatment with acalabrutinib monotherapy. With >5 years of follow-up, acalabrutinib treatment in WM was highly effective with no new toxicities and a low incidence of cardiovascular events. These data support the central role and benefit of BTKis, such as acalabrutinib, in the management of patients with WM, especially those with R/R disease. Outcomes of patients with TN WM warrant further study, particularly in the real-world setting.

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TABLES

Table 1. Baseline characteristics

Characteristic	TN (n = 14)	R/R (n = 92)
Age, median (range), y	72.5 (48.0–86.0)	69.0 (39.0–90.0)
Male sex	10 (71.4)	63 (68.5)
ECOG PS ≤1	12 (85.7)	88 (95.6)
Time since WM diagnosis, median (range), y	0.4 (0.04–5.77)	6.1 (0.16–25.4)
Bone marrow involvement	14 (100)	89 (96.7)
Extramedullary disease	9 (64.3)	59 (64.1)
Lymphadenopathy ≥1.5 cm	7 (50.0)	50 (54.3)
Splenomegaly ≥13 cm	4 (28.6)	26 (28.3)
Serum IgM, median (range), mg/dL	4615.0 (633.0–7530.0)	3565.0 (291.0–9740.0)
Number of prior therapies, median (range)	NA	2 (1–7)
≥3 prior therapies	NA	41 (44.6)
Prior therapies (in ≥15% of R/R patients)		
Anti-CD20 therapy	NA	80 (87.0)
Cyclophosphamide-based regimen	NA	32 (34.8)
Chlorambucil-based regimen	NA	29 (31.5)
Proteosome inhibitor–based regimen	NA	28 (30.4)
Purine analogue ± rituximab therapy	NA	21 (22.8)
Bendamustine ± rituximab therapy	NA	18 (19.6)
CHOP/CVP/COP ± rituximab therapy	NA	18 (19.6)
Purine analogue + cyclophosphamide ± rituximab therapy	NA	15 (16.3)
Refractory to last therapy	NA	33 (35.9)

Data are n (%) unless otherwise specified.
CHOP, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone/prednisolone; COP, cyclophosphamide, oncovin, and prednisone/prednisolone; CVP, cyclophosphamide, vincristine, and prednisone/prednisolone; ECOG PS, Eastern Cooperative Oncology Group performance status; IgM, Immunoglobulin M; NA, not applicable; R/R, relapsed/refractory; TN, treatment-naive; WM, Waldenström macroglobulinemia; y, years.

Table 2. Patient disposition

Characteristic	TN (n = 14)	R/R (n = 92)
Study follow-up, median (range), mo	66.0 (7.7–68.1)	63.6 (4.6–78.3)
Remaining on acalabrutinib	7 (50.0)	43 (46.7)
Reason for discontinuation of acalabrutinib		
Adverse event*	4 (28.6)[†]	15 (16.3)[‡]
Disease progression	1 (7.1)	20 (21.7)
Withdrawal of consent	1 (7.1)	1 (1.1)
Investigator's discretion[§]	1 (7.1)	6 (6.5)
Started alternative cancer therapy	0	3 (3.3)[‖]
Death	0	4 (4.3)[#]

Data are n (%) unless otherwise specified.
*Data for reason for treatment discontinuations due to adverse events were captured from the treatment termination case report form.
[†]Included 1 patient with a grade 5 AE (myocardial ischemia).
[‡]Included 7 patients with grade 5 AEs (multiple organ dysfunction syndrome, malignant ascites, central nervous system lymphoma, cardiac arrest, glioblastoma multiforme, intracranial mass, and intracranial hematoma).
[§]These reasons included inadequate response to treatment (n = 1) in the TN cohort and no response to treatment (n = 3), neutropenia and thrombocytopenia (n = 1), temporary delay leading to no continuation of dosing (n = 1), and problems communicating due to hearing difficulties (n = 1) in the R/R cohort.
[‖]Included 1 patient with a grade 5 AE (esophageal cancer).
[#]Included 3 patients with grade 5 AEs during the treatment-emergent period (pneumonia, COVID-19 pneumonia, and COVID-19) and 1 patient with a grade 5 AE after the treatment-emergent period (chronic inflammatory demyelinating polyradiculoneuropathy occurring 45 days after last study dose).
AE, adverse event; R/R, relapsed/refractory; TN, treatment-naive.

Table 3. Response to acalabrutinib using the modified 3rd IWWM criteria

Characteristic	Modified 3rd IWWM Criteria	
	TN (n=14)	R/R (n=92)
ORR (≥ mr), n (%)	13 (92.9)	87 (94.6)
95% CI	(66.1–99.8)	(87.8–98.2)
MRR (≥ PR), n (%)	11 (78.6)	75 (81.5)
95% CI	(49.2–95.3)	(72.1–88.9)
Best response, n (%)		
CR*	0	2 (2. 2)
VGPR	1 (7.1)	38 (41.3)
PR	10 (71.4)	35 (38.0)
mr	2 (14.3)	12 (13.0)
SD	0	4 (4.3)
Time to initial response, median (range), mo	1.0 (0.9−7.4)	1.0 (0.9−39.6)

Data are n (%) unless otherwise specified.
*CR confirmed as immunofixation negative per IWWM criteria (**Supplemental Table 1**).
CI, confidence interval; CR, complete response; IWWM, International Workshop on Waldenström's Macroglobulinemia; mo, months; mr, minor response; MRR, major response rate; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naive; VGPR, very good partial response.

Table 4. Treatment exposure and most common AEs (≥25% of patients [any grade] or ≥5% [grade ≥3] overall)

	TN (n = 14)		R/R (n = 92)		Total (N = 106)	
Treatment exposure, median (range), mo	42.4 (3.8–68.1)		60.8 (2.8–78.3)		60.8 (2.8–78.3)	
Relative dose intensity, median (range), %	92.6 (58.6–99.8)		97.7 (49.9–104.0)		97.5 (49.9–104.0)	
AE, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Patients with ≥1 AE	14 (100.0)	11 (78.6)	92 (100.0)	67 (72.8)	106 (100.0)	78 (73.6)
Diarrhea	6 (42.9)	0	35 (38.0)	2 (2.2)	41 (38.7)	2 (1.9)
Headache	5 (35.7)	0	39 (42.4)	0	44 (41.5)	0
Arthralgia	5 (35.7)	0	29 (31.5)	1 (1.1)	34 (32.1)	1 (0.9)
Dizziness	5 (35.7)	0	23 (25.0)	0	28 (26.4)	0
Nausea	5 (35.7)	0	21 (22.8)	2 (2.2)	26 (24.5)	2 (1.9)
Upper respiratory tract infection	4 (28.6)	0	27 (29.3)	1 (1.1)	31 (29.2)	2 (1.9)
Constipation	4 (28.6)	0	23 (25.0)	0	27 (25.5)	0
Fatigue	3 (21.4)	0	29 (31.5)	2 (2.2)	32 (30.2)	2 (1.9)
Contusion	3 (21.4)	0	27 (29.3)	0	30 (28.3)	0
Cough	3 (21.4)	0	24 (26.1)	2 (2.2)	27 (25.5)	2 (1.9)
Pneumonia	1 (7.1)	0	14 (15.2)	11 (12.0)	15 (14.2)	11 (10.4)
Lower respiratory tract infection	0	0	25 (27.2)	7 (7.6)	25 (23.6)	7 (6.6)
Neutropenia	0	0	20 (21.7)	18 (19.6)	20 (18.9)	18 (17.0)
Anemia	0	0	11 (12.0)	6 (6.5)	11 (10.4)	6 (5.7)

AE, adverse event; mo, month; R/R, relapsed/refractory; TN, treatment-naive.

Table 5. AEs leading to treatment discontinuation

AEs leading to treatment discontinuation,* n (%)	TN (n = 14)	R/R (n = 92)	Total (N = 106)
Any AE leading to treatment discontinuation	4 (28.6)	16 (17.4)	20 (18.9)
Blood and lymphatic system disorders			
Cold type hemolytic anemia	0	1 (1.1)	1 (0.9)
Cardiac disorders			
Coronary artery disease	1 (7.1)	0	1 (0.9)
Cardiac arrest	0	1 (1.1)	1 (0.9)
Cardiac failure	0	1 (1.1)	1 (0.9)
Myocardial infarction	0	1 (1.1)	1 (0.9)
Myocardial ischemia	1 (7.1)	0	1 (0.9)
Gastrointestinal disorders			
Crohn's disease	1 (7.1)	0	1 (0.9)
Esophageal stenosis	0	1 (1.1)	1 (0.9)
Intestinal mass	0	1 (1.1)	1 (0.9)
Mouth ulceration	0	1 (1.1)	1 (0.9)
Investigations			
Transaminases increased	1 (7.1)	0	1 (0.9)
Neoplasms benign, malignant, and unspecified			
Central nervous system lymphoma	0	1 (1.1)	1 (0.9)
Esophageal carcinoma	0	1 (1.1)	1 (0.9)
Glioblastoma multiforme	0	1 (1.1)†	1 (0.9)
Malignant ascites	0	1 (1.1)	1 (0.9)
Metastases to liver	0	1 (1.1)	1 (0.9)
Metastatic malignant melanoma	0	1 (1.1)	1 (0.9)
Nervous system disorders			
Intracranial hematoma	0	1 (1.1)	1 (0.9)
Intracranial mass	0	1 (1.1)	1 (0.9)
Seizure	0	1 (1.1)†	1 (0.9)
Respiratory, thoracic and mediastinal disorders			

Bronchiectasis	0	1 (1.1)	1 (0.9)

*Data for AEs leading to treatment discontinuation were captured from the AE case report form. AEs were coded using MedDRA Version 24.0. A patient was counted only once for each preferred term.
†Glioblastoma multiforme and seizure occurred in the same patient.
AE, adverse event; R/R, relapsed/refractory; TN, treatment-naive.

Table 6. Key events of clinical interest

ECI, n (%)	TN (n = 14)		R/R (n = 92)		Total (N = 106)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Cardiac events	3 (21.4)	2 (14.3)	19 (20.7)	6 (6.5)	22 (20.8)	8 (7.5)
Atrial fibrillation/ flutter	1 (7.1)	0	11 (12.0)	2 (2.2)	12 (11.3)	2 (1.9)
Bleeding	10 (71.4)	0	56 (60.9)	6 (6.5)	66 (62.3)	6 (5.7)
Major bleeding	0	0	9 (9.8)	6 (6.5)	9 (8.5)	6 (5.7)
Hypertension	0	0	7 (7.6)	4 (4.3)	7 (6.6)	4 (3.8)
Infections	8 (57.1)	2 (14.3)	79 (85.9)	30 (32.6)	87 (82.1)	32 (30.2)
SPMs	1 (7.1)	0	17 (18.5)	7 (7.6)	18 (17.0)	7 (6.6)
SPMs excluding non-melanoma skin	1 (7.1)	0	11 (12.0)	6 (6.5)	12 (11.3)	6 (5.7)

ECI, event of clinical interest; R/R, relapsed/refractory; SPM, second primary malignancy; TN, treatment-naive.

FIGURE LEGENDS

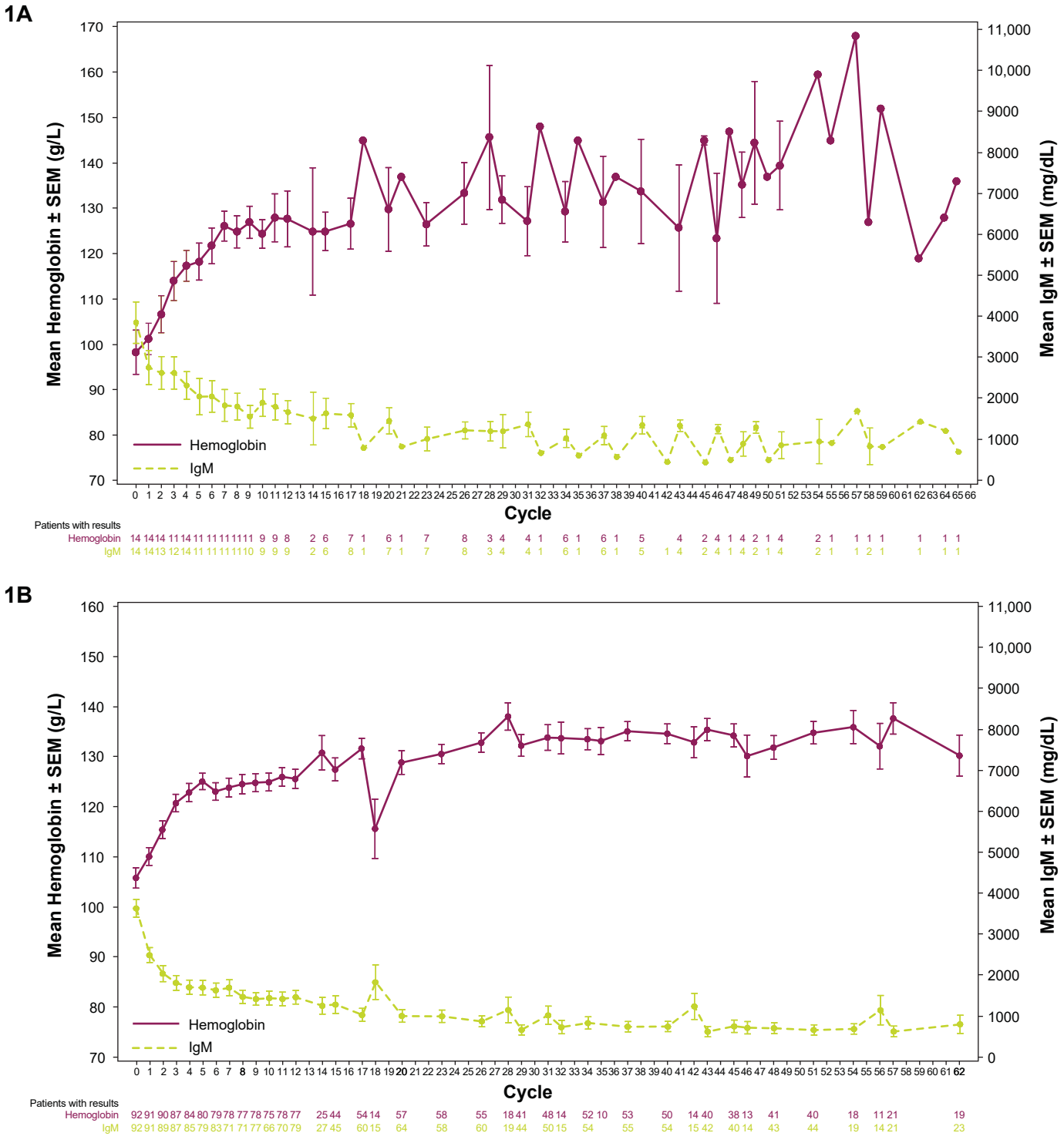
Figure 1. Mean change in hemoglobin and IgM over time. Patients with TN WM (A) and R/R WM (B) are shown. IgM, immunoglobulin M; SEM, standard error of the mean.

Figure 2. Maximum IgM percentage improvement in all patients. All 106 treated subjects with baseline IgM higher than the upper limit of normal of 230 mg/dL and with non-missing percentage change from baseline were included. The dark blue bars indicate patients in the TN cohort (median [range]: –74.7% [–98.8%, –27.4%]); burgundy bars indicate patients in the R/R cohort (–84.2% [–98.9%, 0.8%]). *Patient had disease progression prior to achieving best IgM response. IgM, immunoglobulin M; IWWM, International Workshop on Waldenström's Macroglobulinemia; mr, minor response; PR, partial response; R/R, relapsed/refractory; TN, treatment-naive; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

Figure 3. Efficacy results. (A) Progression-free survival (PFS), (B) duration of response (DOR), and (C) overall survival (OS) are shown. [a]DOR and PFS per modified 3rd IWWM criteria. CI, confidence interval; IWWM, International Workshop on Waldenström's Macroglobulinemia; NR, not reached; R/R, relapsed/refractory; TN, treatment-naive.

Figure 4. Cumulative incidence rate for any-grade atrial fibrillation and hypertension.

Figure 1AB



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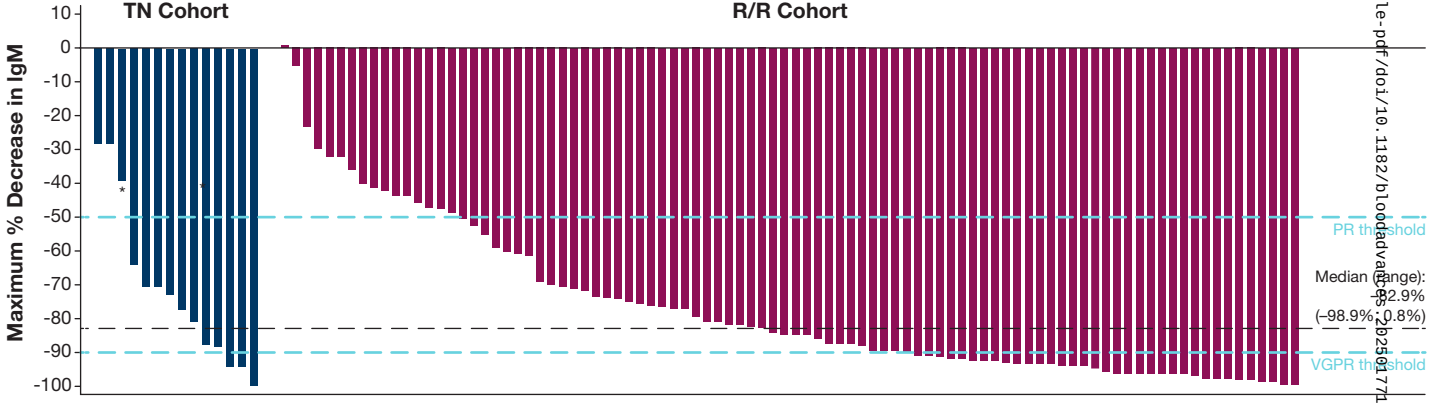

Figure 3ABC

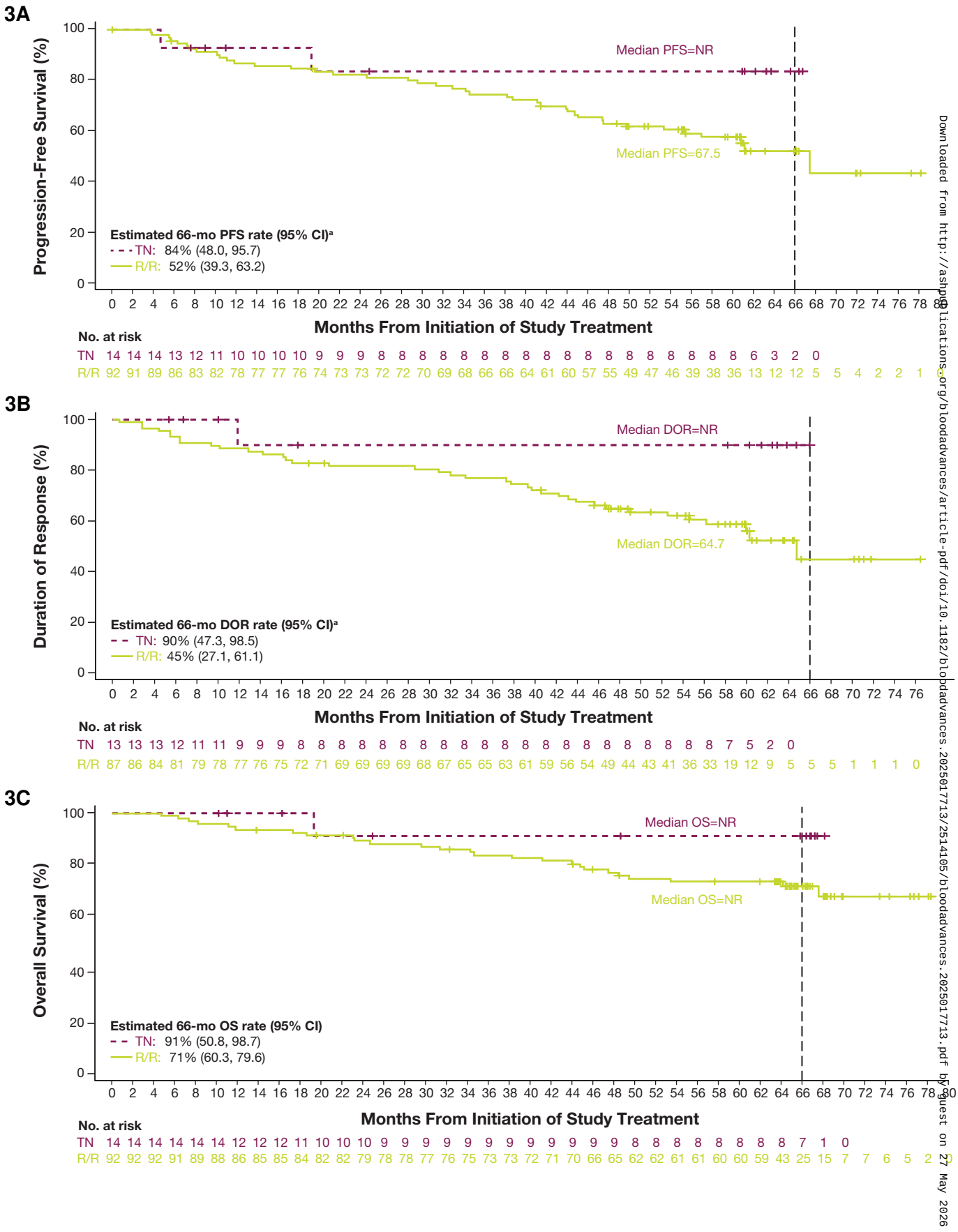

Figure 4