Acalabrutinib Monotherapy in Patients with Waldenström Macroglobulinemia

Brief title: Acalabrutinib Monotherapy in WM

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Research in Context

Evidence before this study Despite recent progress in understanding the pathophysiology of Waldenström macroglobulinemia (WM) and improved treatment options, WM remains an incurable disease with significant morbidity. Bruton tyrosine kinase (BTK) is a validated target based on clinical activity of ibrutinib, an inhibitor of BTK, in WM. BTK may be of increased importance in WM because of the high prevalence of the *MYD88*^{L265P} mutation, which activates NFκB through BTK. Ibrutinib has additional kinase targets beyond BTK, including EGFR, ERBB2, Src, and IL-2 inducible T-cell kinase, which may contribute to adverse events, such as diarrhea, rash, bleeding, and atrial fibrillation. These AEs may lead to discontinuation of an effective treatment and support the development of alternative BTK inhibitors for treatment of WM, to overcome these issues. Acalabrutinib is a BTK inhibitor that is more potent and selective than ibrutinib, as evidenced by kinase selectivity profiling against 395 human kinases. In patients with treatment-naive (TN) and relapsed/refractory (R/R) CLL, acalabrutinib has demonstrated favorable efficacy (ORR including PRL of 93% and 97%, respectively) and acceptable safety. Here we report the results of acalabrutinib treatment in patients with WM.

Added value of this study This is the first clinical analysis of acalabrutinib in patients with WM, expanding existing literature of clinical activity and safety with BTK inhibition in WM by using a highly selective BTK inhibitor.

Implications of all the available evidence Results from this study demonstrate that acalabrutinib is a highly effective BTK inhibitor that yields durable responses with a tolerable safety profile in TN and R/R patients with WM.

Abstract

Background: Acalabrutinib is a highly selective, potent Bruton tyrosine kinase inhibitor. We evaluated the efficacy and safety of acalabrutinib in a phase 2 study of patients with Waldenström macroglobulinemia. ClinicalTrials.gov: NCT02180724

Methods: Treatment-naive (declined or not eligible for chemotherapy) and relapsed/refractory (≥1 prior therapy) patients were enrolled between September 8, 2014 and December 24, 2015. Patients received 100-mg acalabrutinib twice daily in 28-day cycles until progressive disease or toxicity. The primary endpoint was investigator-assessed overall response rate (≥minor response). Secondary endpoints included duration of response, progression-free survival, overall survival, safety, and pharmacokinetics. Pharmacodynamic assessment was an exploratory endpoint.

Findings: Fourteen treatment-naive and 92 relapse/refractory patients (N=106) were treated. With a median follow-up of 27·4 months, the overall and major response rates were 93% and 78%, respectively, for all treated patients. Response rates were influenced by mutation status; ORRs were 94% and 79% for patients with $MYD88^{L265P}$ and $MYD88^{WT}$, respectively. The median duration of response was not reached; 24-month progression-free survival and overall survival rates were 83% and 89%, respectively. Seven (50%) treatment-naive and 69 (75%) relapse/refractory patients remain on treatment. Responses were rapid, with significant reductions in IgM and improvement in serum hemoglobin observed in both cohorts after four weeks of acalabrutinib treatment. Common grade 3/4 adverse events (>5% of patients) were neutropenia (16%) and pneumonia (7%). Grade 3/4 atrial fibrillation and bleeding occurred in 1% and 3% of patients, respectively. Pharmacokinetic parameters were consistent with previous studies, and Bruton tyrosine kinase occupancy was >95% saturated throughout the dosing interval.

Interpretation: Acalabrutinib is highly effective in the treatment of Waldenström macroglobulinemia, with an acceptable safety profile. Although *MYD88* mutational status did influence response, meaningful clinical benefit was demonstrable in $MYD88^{WT}$ patients.

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Introduction

Waldenström macroglobulinemia (WM) is a rare, malignant lymphoproliferative disorder, characterized by lymphoplasmacytic bone marrow infiltration and IgM paraproteinemia and symptoms including anemia and hyperviscosity syndrome.[1] WM may present as extramedullary disease at diagnosis, which is associated with poorer prognosis and later stage disease than disease confined to the bone marrow; lymphadenopathy and organomegaly have been reported in 20-25% of patients with WM.[2] Single-agent rituximab has only modest clinical activity in WM (overall response rate [ORR] up to 60%).[3] Chemoimmunotherapy typically has greater efficacy; however, infectious and hematologic toxicity are of concern.[3]

Bruton tyrosine kinase (BTK) is a critical component of B-cell signaling and is constitutively activated, thus implicated in the pathogenesis of WM.[4-6] This activation of BTK may occur due to an activating somatic mutation of myeloid differentiation factor 88 (*MYD88*),[6] an adaptor protein that mediates Toll-like receptor (TLR) and interleukin-1 receptor (IL1) signaling to regulate diverse immune responses.[7] The *MYD88*^{L265P} mutation has been reported in up to 90% of WM patients and results in downstream activation of NFκB, mediating cell growth and survival.[7] BTK was validated as a target in WM based on clinical activity of the first-in-class BTK inhibitor, ibrutinib. As a monotherapy, ibrutinib is associated with toxicities, such as bleeding, diarrhea, skin rash, and atrial fibrillation, in WM.[8,9] Combining rituximab with ibrutinib may improve efficacy over rituximab monotherapy but is also associated with relatively high rates of toxicities like Grade 3/4 atrial fibrillation, occurring in 12% of patients.[10]

Acalabrutinib is a highly selective, potent, covalent inhibitor of BTK with limited off-target activity that received accelerated FDA approval for the treatment of adult patients with relapsed/refractory (R/R) mantle cell lymphoma (MCL)[11,12] and is also in clinical development for chronic lymphocytic leukemia (CLL) and diffuse large B-cell lymphoma. Acalabrutinib demonstrates minimal effects on EGFR, Tec, Src

family kinases, or interleukin-2 inducible T-cell kinase (ITK) signaling,[13] which may contribute to a potential differentiated profile.

Here, we present results from a phase 2, multicenter, international, open-label study evaluating acalabrutinib monotherapy in treatment-naive (TN) or relapsed/refractory (R/R) patients with WM.

Materials and Methods

Study Design and Participants

This open-label, single-arm, multicenter, phase 2 study (NCT02180724) enrolled patients ≥18 years of age with a confirmed diagnosis of WM requiring treatment. Patients were either R/R (≥1 prior therapy) or TN who declined or were not eligible for chemotherapy. Patients also had an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤2 and serum IgM >upper limit of normal (ULN) or measurable nodal disease (≥1 lymph node ≥2 cm in longest diameter).

Exclusion criteria included prior BTK inhibitor therapy and the presence of significant cardiovascular disease (uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification or QTc >480 ms); patients with prior or concurrent atrial fibrillation could participate. Prior treatment with proton-pump inhibitors (PPIs) was prohibited at study entry; however, patients could be treated with PPIs on study if required. Prior antiplatelet agents and direct-acting oral anticoagulants were permissible. Warfarin or equivalent vitamin K antagonists were prohibited on study.

All patients provided written informed consent. The institutional review board at each participating site approved the study protocol, and the trial is registered at ClinicalTrials.gov (NCT02180724). The study

was conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines.

Endpoints

The primary endpoints were investigator-assessed ORR (best response ≥ minor response [MR]) according to the 6th International Workshop on WM (IWWM) criteria[14] and the modified 3rd IWWM criteria, the former having a more stringent very good partial response (VGPR) category[15] (Appendix Table 1). Secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS), pharmacokinetics (PK), and safety. Pharmacodynamic parameters were exploratory endpoints.

Assessments

Acalabrutinib 100 mg twice daily (BID) or 200 mg once daily (QD) was administered for 28-day cycles until disease progression or an unacceptable toxicity. All patients who received acalabrutinib 200 mg QD (n=6) were switched to 100 mg BID based on efficacy clinical data for CLL patients from ACE-CL-001.[16]

Mutational analysis of *MYD88*^{L265P} was determined by local investigators in 47% (50/106) of patients. *CXCR4* mutation status was not collected in this study.

Adverse events were graded by severity according to the National Cancer Institute Common Toxicity Criteria, version 4.03. After study treatment initiation (Day 1), all patients were evaluated for safety once weekly for the first 4 weeks, every 2 weeks in Cycle 2, monthly thereafter until Cycle 12, and every 3 months after Cycle 12. Bone marrow aspirate and biopsy were conducted at screening and to confirm complete response (CR), as required. Serum immunoglobulins and serum M-protein levels were measured every 4-week cycle up to cycle 6 and every 12 weeks thereafter. Radiologic extramedullary

disease assessments were performed using a computed tomography scan within 30 days before the first dose, every 2 cycles until Cycle 6, every 3 cycles until Cycle 27, and every 6 cycles after Cycle 27.

For PK assessments, plasma samples were collected at pre-dose, 0·5, 0·75, 1, 2, 4, and 6 hours post-dose on Days 1 and 8. PK parameters were derived from individual plasma acalabrutinib concentration-time profiles by a noncompartmental analysis using Phoenix® WinNonlin® (version 6·4). Pharmacodynamic assessments included BTK occupancy by acalabrutinib in peripheral blood mononuclear cells by an ELISA-based method. Details on pharmacodynamic assessments are in the appendix.

Statistical Analysis

A Simon two-stage design with 76 patients in the R/R cohort provided 90% power to test the null hypothesis that the ORR is ≤35% against the alternative hypothesis that it is ≥55%, with a one-sided significance level of 0·025. No formal statistical tests of hypotheses were performed for the TN cohort. Descriptive statistics (mean, median, standard deviation, minimum, maximum) were used to summarize continuous variables. Numbers and percentages were used to describe categorical variables. Safety and ORR were assessed in all patients who received ≥1 dose of acalabrutinib. DOR, PFS, and OS were assessed in the efficacy-evaluable population, defined as all treated who had ≥1 evaluable response assessment after the first dose of acalabrutinib. Time-to-event endpoints were estimated using the Kaplan–Meier method. Subgroup analyses were performed for patients achieving an overall response using baseline and disease characteristics.

Results

A total of 106 patients with WM (14 TN, 92 R/R) were enrolled from September 8, 2014 through December 24, 2015 at 27 sites in 6 countries (USA, UK, Netherlands, France, Italy, and Greece). Baseline

characteristics are detailed in Table 1. The median age of TN and R/R patients was 73 and 69 years, respectively, with ECOG PS of ≤1 in 12 (86%) TN patients and 88 (96%) R/R patients. Sixty-four percent of TN patients and R/R patients had measurable extramedullary disease. Among R/R patients, the median number of prior therapies was 2 (range 1–7); 41 (45%) had received ≥3 prior therapies. Thirty-three patients (36%) had refractory disease.

Thirty of 106 (28%) patients discontinued acalabrutinib (TN, n=7; 50% of TN patients and R/R, n=23; 25% of R/R patients; Appendix Table 2). For R/R patients, progressive disease (PD) was the most common reason for discontinuation (n=9; 10%]. For TN patients, adverse events were the most common reason for treatment discontinuation (n=3; 21%). For all patients, reasons for discontinuation included adverse events (n=7; 7%), progressive disease (n=9; 8%), investigator decision (n=6; 6%), death (n=4; 4%), withdrawal of consent (n=2; 2%), and initiation of alternative cancer therapy for WM (n=2; 2%). Investigator decision to discontinue treatment was triggered by inadequate response (SD with no response to therapy, n=3); overall clinical decline not related to a specific AE (n=2); and PD without a confirmatory IgM for PD (n=1). Thirteen patients (12%) died while on study (all causes). Four patients (4%) died ≤30 days after the last dose of study drug (due to pneumonia, ischemic heart disease, intracranial hematoma, and carcinomatous peritonitis; n=1 each). Nine patients (9%) died >30 days after the last dose of study drug (chronic inflammatory demyelinating polyneuropathy [n=1], esophageal cancer [n=1], glioblastoma multiforme [n=1], and unknown [n=6; one patient had transformed to DLBCL; median time to death, 128 days [range, 40–414]).

The median duration of follow-up was 27·4 months (range, 4·6–40·7). Investigator-assessed ORRs across two criteria (3rd IWWM criteria and 6th IWWM criteria) were compared to determine the extent to which extramedullary disease (included in later criteria) affected the response rates in the ITT population. The modified 3rd IWWM criteria solely bases response on IgM reduction for partial

response (PR) and VGPR, whereas the 6th IWWM criteria consider lymphadenopathy and organomegaly in determining PR and VGPR (Appendix Table 1); the ORR for the TN and R/R cohorts was 93% and 93%, respectively, with both criteria (Figure 1A). There were minor discrepancies when major response rate (MRR) was assessed across criteria. For TN patients, MRR was 79% with both criteria, whereas MRR for R/R patients was 80% (74/92) with 6th IWWM criteria and 78% (72/92) with the modified 3rd criteria. Differences in VGPR were significant: VGPR was 7% in TN patients and 33% in R/R patients using the modified 3rd criteria and 0% and 9%, respectively, using the 6th IWWM criteria. No CRs were reported in either cohort. ORR using the modified 3rd IWWM criteria was consistent across prespecified subgroups, including patients with age ≥65 years, ≥3 prior therapies, baseline ECOG PS ≥1, low baseline hemoglobin (<110 g/L), and low baseline IgM levels (<4000 mg/dL) (Figure 2).

The influence of *MYD88* mutational status on response and survival outcomes was assessed in a subset of 50 patients (Figure 1B). $MYD88^{L265P}$ mutation was present in 36 patients (72% of those genotyped; R/R, n=34; TN, n=2), and $MYD88^{WT}$ in 14 patients (28%; 13 R/R, 1 TN). The ORR and MRR for $MYD88^{L265P}$ patients were higher than for $MYD88^{WT}$ patients (ORR 94% *vs* 79%; MRR 81% *vs* 64% using 6th IWWM criteria and 78% *vs* 57% using the modified 3rd IWWM criteria, respectively). None of the $MYD88^{WT}$ patients achieved a VGPR; 28% of $MYD88^{L265P}$ patients did.

The kinetics of IgM responses were also evaluated for all patients. The median time to best response was 2·3 months (range, 0·9–23·2) using the 6th IWWM criteria and 4·6 months (range, 0·9–27·6) using the modified 3rd. The rapid reductions in IgM were associated with clinically meaningful improvements in hemoglobin levels (Figure 3). The maximum decline in IgM levels post-baseline was 2375 mg/dL (from a median of 3615 mg/dL at baseline to 700·5 mg/dL post-treatment); the maximum median increase in hemoglobin levels post-baseline was 29 g/L (from 104 g/L to 136 g/L). Similar results were observed in TN patients.

The median duration of response has not been reached for either cohort, with 24-month DOR rates of 90% for TN patients and 82% for R/R patients (Figure 4A). The median PFS and OS were also not reached for either cohort (Figure 4B and C). The 24-month PFS rates for TN and R/R patients were 90% and 81·9%, respectively, and OS rates for TN and R/R patients were 91·7% and 88·9%, respectively. DOR and PFS using the modified 3rd IWWM criteria were consistent with those using the 6th IWWM criteria.

Common adverse events of any grade (N=106) were headache (n=41; 39%), diarrhea (n=35; 33%), contusion (n=31; 29%), dizziness (n=27; 25%), fatigue and nausea (n=24 each; 23% each), upper respiratory tract infection (n=23; 22%), constipation (n=22; 21%), and arthralgia (n=21; 20%; Figure 5). Headaches and diarrhea (39% and 31%, respectively) were mostly grade 1/2. The most common treatment-emergent grade 3/4 adverse events were neutropenia (n=17; 16%), pneumonia (n=7; 7%), and anemia, lower respiratory tract infection, increased alanine aminotransferase, and hyponatremia (n=5 each; 5% each; Appendix Table 3). Of the 11 patients with grade 4 neutropenia, 3 had a history of neutropenia at baseline (moderate and mild), 7 had ≥3 prior therapies, and 6 had acalabrutinib withheld until resolution. Infections occurred in 81 (76%) patients (grade ≥3, n=26; 25%). The most common grade 3/4 infections were pneumonia (n=7; 7%), lower respiratory tract infections (n=5; 5%), and cellulitis (n=3; 3%). One patient admitted for pneumonia on study day 522 tested positive for *Aspergillus* and was treated with an anti-fungal agent, and acalabrutinib was withheld only until resolution. Serious adverse events (SAEs) occurred in 56 (53%) patients. SAEs occurring in ≥3 patients were lower respiratory tract infection (n=7), pneumonia (n=7), pyrexia (n=4), cellulitis (n=3), fall (n=3), and sepsis (n=3). The six grade 5 events during treatment reported (all in 1 patient each) were myocardial ischemia, pneumonia, glioblastoma multiforme, esophageal carcinoma, intracranial hematoma (the patient was taking the anticoagulant apixaban at the time of the event), and malignant ascites (metastatic adenocarcinoma; Appendix Table 3).

Among adverse events of clinical interest, atrial fibrillation occurred in 5 (5%) patients (TN, n=1; 7% of TN patients and R/R, n=4; 4% of R/R patients) for an incidence rate of 2·3 per 100 patient years (4·0 and 2·0 for TN and R/R patients, respectively). All events were grade 1/2, except for 1 grade 3 event (patient was treated with cardioversion). No patient had a history of atrial fibrillation. All patients with atrial fibrillation had ≥1 risk factor for atrial fibrillation, including age >65 years, hypertension, structural heart disease/arteriosclerotic coronary artery disease (2 patients with prior history), 2nd-degree AV block (1 patient with prior history), and diabetes. Median time to the onset of atrial fibrillation was 391 days (range, 29–820 days). No atrial fibrillation event led to acalabrutinib withholding or discontinuation. Hypertension occurred in 5 (5%) patients, 3 of which were grade 3. All 3 grade 3 hypertension events resolved with or without medication. Bleeding occurred in 61 (58%) patients, most commonly contusion (n=31; 29%), epistaxis (n=12; 11%), increased tendency to bruise (n=11; 10%), petechiae (n=9; 8%), ecchymosis (n=7; 7%, and hematoma (n=6; 6%). Grade 3/4 bleeding events included epistaxis, dysfunctional uterine bleeding, and retinal hemorrhage (n=1 each; 1% each). All grade 3/4 bleeding events were managed with dose delay and resolved.

Serum IgM levels for 52 patients who had ≥7 doses of acalabrutinib withheld were evaluated before and after dose delay. The median serum IgM levels were 1270 mg/dL (range, 69–4490·0 mg/dL) and 1825 mg/dL (range, 373·0–4820·0 mg/dL), respectively. Twenty (38%) of the 52 patients had IgM increases of >5g/L. IgM levels decreased upon the restart of acalabrutinib.

Adverse events leading to discontinuation of acalabrutinib were (n=1 each) acute coronary artery disease, Crohn's disease reactivation, increased transaminases, cold-type hemolytic anemia, glioblastoma multiforme and seizure (both in the same patient), malignant ascites, and metastatic malignant melanoma. Adverse events leading to dose reduction to 100 mg QD occurred in 5 (5%)

patients. Adverse events resulting in dose withholding occurred in 57 (54%) patients. A majority of events (90%) resolved upon dose reduction and dose withholding.

Pharmacokinetic assessments indicated rapid absorption and elimination of acalabrutinib, with minimal potential for accumulation (Figure 6A). Exposure to acalabrutinib PK was similar in TN and R/R patients (Appendix Table 4). At steady-state (Day 8), median BTK occupancy in peripheral blood mononuclear cells with 100 mg BID acalabrutinib was 96% to 98% throughout the dosing interval (Figure 6B). Of the 14 patients evaluated at Day 8, 13 had >90% BTK occupancy at steady-state trough (12 hours post-dose), with low interpatient variability. Functional studies conducted with samples from 17 patients revealed significant inhibition of basal phosphorylated BTK (pBTK) by acalabrutinib at all time points regardless of *MYD88* mutational status (Figure 6C).

Discussion

This phase 2, open-label, single-arm, multicenter study is the first prospective study of acalabrutinib, a highly selective BTK inhibitor, in WM. With an improved understanding of the aberrant signaling in the molecular pathogenesis of WM, BTK inhibitors have demonstrated an increasingly important role in WM treatment. Our results confirm the single-agent clinical activity of acalabrutinib, irrespective of the line of therapy, age, or baseline IgM or hemoglobin levels, for patients with WM.

With a median follow-up of 27·4 months, acalabrutinib was associated with a high ORR (93%), MRR (78%), and VGPR (33%). Efficacy was observed across patients who were TN or R/R after a median of 2 prior therapies and who had not received prior BTK inhibitor therapy. The ORR and MRR were similar when assessed using the modified 3rd IWWM criteria or the 6th IWWM criteria.[14,15]

Acalabrutinib treatment led to rapid reductions in tumor-secreted circulating IgM (maximum decline of 2375 mg/dL for the R/R cohort) as well as improvement in serum hemoglobin (maximum increase of 29 g/L for the R/R cohort), with significant differences after 4 weeks on treatment. These rapid response kinetics in reductions of IgM and serum hemoglobin improvement were sustained and resulted in clinical improvement, as further evidenced by 4 patients discontinuing therapeutic plasmapheresis, and may be a hallmark of BTK inhibition in WM. The difference between the time to best response was longer with the modified 3rd than the 6th IWWM criteria; more patients achieved a VGPR with the 3rd IWWM rather than remaining at a PR, which takes longer to achieve. At 2 years, the estimated PFS rate was 90% in TN patients and 82% in R/R patients. Median DOR, PFS, and OS were not reached. These results are comparable to those reported for ibrutinib with or without rituximab.[10,17]

Previous studies have shown the link between *MYD88*^{L265P} and activation of BTK, suggesting a role for BTK inhibitors. Treon et al. did not demonstrate major responses with ibrutinib in 5 *MYD88*^{WT} patients.[17] Acalabrutinib demonstrated clinical benefit in *MYD88*^{WT} patients, with an MRR of 64%. Although the ORR and MRR were lower in *MYD88*^{WT} patients than in *MYD88*^{L265P} patients (79% and 64% *vs* 94% and 81%, respectively, using 6th IWWM criteria), but given the small sample size, the statistical significance could not be determined. These data are encouraging and suggest that *MYD88*^{WT} patients should not at this time be excluded from further studies. That MYD88 data were available in a subset of patients and the relatively high incidence of *MYD88*^{WT} patients is a potential limitation of this study. It is possible that some *MYD88*^{WT} patients may have harbored *MYD88* mutations other than the *MYD88*^{L265P},[5] however in the iNNOVATE study, meaningful clinical responses (81% ORR and 63% MRR) were documented in *MYD88*^{WT} patients. Furthermore, tumor genotype did not appear to impact survival outcomes.[5,6] The absence of CXCR mutational data is a further limitation of this analysis.

Our pharmacodynamic data support these clinical efficacy results in *MYD88*^{WT} patients. Specifically, we observed a clear reduction of basal pBTK, demonstrating pathway modulation by acalabrutinib. This was observed not only in the *MYD88*^{L265P} population in this analysis, but also in patients with *MYD88*^{WT}, confirming that the *MYD88*^{L265P} mutation is not the only possible mechanism for elevated basal pBTK. Hyperactivity of B cell receptor signaling components in WM patients has been described and is suggested to be caused by high surface IgM expression and low phosphatase activity in WM cells.[4]

The safety profile of acalabrutinib was promising, and adverse events were manageable. Acalabrutinib was well tolerated with a low rate of treatment discontinuation due to adverse events (7%), and 72% of patients remain on treatment after a median follow-up >2 years. Most adverse events were low grade and did not lead to dose modification. Headache and diarrhea were relatively common (in 39% and 33% of patients, respectively) but were low grade; events were manageable with supportive therapy.

In this study, 5% of patients receiving acalabrutinib had atrial fibrillation; all with ≥1 risk factor for atrial fibrillation and no acalabrutinib withholding or discontinuation need. A few cases of hypertension were observed (2 grade 1/2; 3 grade 3). All grade 3 hypertension events resolved with or without medication. Grade 3 bleeding events occurred in 3 patients (3%) with a medical history related to bleeding (dysfunctional uterine bleeding and history of mild thrombocytopenia, epistaxis [patient had a history of bilateral subdural hematoma and epistaxis], and retinal hemorrhage [patient had a history of retinal hemorrhage]). All grade 3 bleeding events resolved with dose delay, and no patient discontinued treatment. The adverse events reported are consistent with the known safety profile of acalabrutinib. [12] For ibrutinib, adverse events, such as atrial fibrillation, hypertension, and major bleeding events, have resulted in treatment discontinuation and are observed at a rate of approximately 5–10%, 5–13%, and 6%, respectively, in patients with WM.[8,9,17] Grade 3/4 atrial fibrillation and hypertension were also

common with ibrutinib and rituximab (12% and 13%, respectively), so therapeutic options with a lower risk of these adverse events would improve on current treatment options.[10]

The pharmacokinetics of acalabrutinib allowed twice-daily dosing with minimal off-target effects, while achieving continuous BTK inhibition over time. Pharmacokinetic parameters were consistent with previously reported studies in CLL and MCL. [12,16]

In summary, acalabrutinib monotherapy achieves robust and durable responses and is well tolerated in TN and R/R patients with WM. Although tumor genotype influences response rates, MRR and clinical benefit are observed in *MYD88*^{WT}patients. Acalabrutinib has an acceptable safety profile, with most adverse events being of low grade and few events requiring dose modification. This study demonstrates the potential for acalabrutinib to improve outcomes for patients with WM.

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AUTHORSHIP CONTRIBUTIONS

RO, HMC, SR, SD, TA, ST, SI, TAS, BC, DG: Manuscript writing and approval

FF, PLZ: Data collection, data interpretation, manuscript writing and approval

MJK, RI: Study design, data collection, data interpretation, manuscript writing and approval

JK: Accrual of patients onto the clinical trial, manuscript development and editing, and approval of final manuscript

MM, HW: Data collection, manuscript writing and approval

OT: Manuscript writing and approval, Patients' recruitment and care, national coordination on behalf of the Lysa Group

DYC, SKL, PP, HW: Manuscript writing and approval, Data analysis, Data interpretation

DM: Manuscript writing and approval, literature search, provided Fig 6C, data analysis and interpretation

RF: Manuscript writing and approval, data collection, data analysis, data interpretation

MF: literature search, data interpretation, data analysis, manuscript writing and approval

AH: Manuscript writing and approval, study design and implementation

EK: Data analysis and interpretation, manuscript writing and approval

DECLARATION OF INTERESTS

FF reports personal fees from Roche, personal fees and non-financial support from AbbVie, outside the submitted work.

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MM reports other from Servier, grants from Celgene, other from Jansen Cilag, other from Takeda, outside the submitted work.

HW reports other from Acerta Pharma, from null, during the conduct of the study.

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RI reports other from Acerta Pharma, during the conduct of the study; in addition, RI has a patent for BTK inhibitors pending.

DM is a current employee of Acerta Pharma and has equity ownership in Acerta Pharma.

PP reports other from Acerta Pharma, during the conduct of the study; other from Acerta Pharma, other from AstraZeneca, outside the submitted work.

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SR reports grants and personal fees from Janssen, outside the submitted work.

BC reports other from Acerta/Astra-Zeneca, other from Abbvie, other from TG Therapeutics, other from Karyopharm, other from Bayer, other from Roche-Genentech, other from Astellas, other from Pharmacyclics, grants from Acerta/Astra-Zeneca, grants from Abbvie, grants from TG Therapeutics, grants

MF reports other from AstraZeneca, during the conduct of the study.

AH reports other from Acerta Pharma, during the conduct of the study.

HW reports other from Acerta Pharma, outside the submitted work.

ROLE OF THE FUNDING SOURCE

The study was sponsored by Acerta Pharma, a member of the AstraZeneca Group. The study protocol and statistical analysis plan were designed by the academic authors together with the sponsor, Acerta Pharma, a member of the AstraZeneca Group. The investigators and their research teams collected all data; the data were verified by the sponsor and compiled for analysis. Statistical analyses were performed by the biometrics group at Acerta. All authors had full access to the data and analyses used in this manuscript. The corresponding author wrote the first draft; subsequent drafts were prepared by all authors with editorial assistance from Shala Thomas, PhD. All authors reviewed the manuscript, decided to submit for publication, and vouch for the accuracy and completeness of the data reported and for adherence to the study protocol.

Data Sharing Statement

Whether data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to others **- Yes**

What data will be made available (deidentified participant data, participant data with identifiers, data dictionary, or other specified data set) - **Deidentified participant data**

Whether additional, related documents will be available (eg, study protocol, statistical analysis plan, informed consent form) - **Study protocol, clinical report package**

When these data will be available (beginning and end date, or "with publication", as applicable) - **The timelines vary per study request and can take up to a year upon full submission of the request for analysis, decision, de-identification, and sharing of the requested data or documents.**

Where the data will be made available (including complete URLs or email addresses if relevant) - **https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure**

By what access criteria data will be shared (including with whom, for what types of analyses, by what mechanism – eg, with or without investigator support, after approval of a proposal, with a signed data access agreement – or any additional restrictions) - **AstraZeneca Group of Companies Data Request Portal (leveraging our existing Trial Transparency System) allows researchers to submit a request to access de-identified patient level data and/or anonymized clinical study reports. In the case of sharing de-identified patient level data, the full dataset may not be shared in view of the following:**

- **Clinical consent for some countries prohibits secondary use of the data**
- **Patients may withdraw their consent for participation in the trial at any point**
- **Less than three quasi identifiers are shared per patient**

- **Other aspects might also be taken into consideration to protect patient privacy (eg, review of rare clinical events where information is aggregated to a higher-level before sharing)**

References

1. Network. NCC. Waldenstrom Macroglobulinemia (Version 2.2019). https://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf.

2. Cao X, Ye Q, Orlowski RZ, et al. Waldenstrom macroglobulinemia with extramedullary involvement at initial diagnosis portends a poorer prognosis. *J Hematol Oncol* 2015; **8**: 74.

3. Leblond V, Kastritis E, Advani R, et al. Treatment recommendations from the Eighth International Workshop on Waldenstrom's Macroglobulinemia. *Blood* 2016; **128**(10): 1321-8.

4. Argyropoulos KV, Vogel R, Ziegler C, et al. Clonal B cells in Waldenstrom's macroglobulinemia exhibit functional features of chronic active B-cell receptor signaling. *Leukemia* 2016; **30**(5): 1116-25.

5. Treon SP, Cao Y, Xu L, Yang G, Liu X, Hunter ZR. Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia. *Blood* 2014; **123**(18): 2791-6.

6. Yang G, Zhou Y, Liu X, et al. A mutation in MYD88 (L265P) supports the survival of lymphoplasmacytic cells by activation of Bruton tyrosine kinase in Waldenstrom macroglobulinemia. *Blood* 2013; **122**(7): 1222-32.

7. Hunter ZR, Xu L, Yang G, et al. The genomic landscape of Waldenstrom macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. *Blood* 2014; **123**(11): 1637-46.

8. Treon SP, Gustine J, Meid K, et al. Ibrutinib monotherapy in symptomatic, treatment-naive patients with Waldenstrom Macroglobulinemia. *J Clin Oncol* 2018; **36**(27): 2755-61.

9. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenstrom's macroglobulinemia. *N Engl J Med* 2015; **372**(15): 1430-40.

10. Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 trial of ibrutinib plus rituximab in Waldenstrom's Macroglobulinemia. *N Engl J Med* 2018; **378**(25): 2399-410.

11. AstraZeneca. CALQUENCE: package insert. 2017.

12. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. *Lancet* 2018; **391**(10121): 659-67.

13. Barf T, Covey T, Izumi R, et al. Acalabrutinib (ACP-196): A covalent Bruton tyrosine kinase inhibitor with a differentiated selectivity and in vivo potency profile. *J Pharmacol Exp Ther* 2017; **363**(2): 240-52.

14. Owen RG, Kyle RA, Stone MJ, et al. Response assessment in Waldenstrom macroglobulinaemia: update from the VIth International Workshop. *Br J Haematol* 2013; **160**(2): 171-6.

15. Kimby E, Treon SP, Anagnostopoulos A, et al. Update on recommendations for assessing response from the Third International Workshop on Waldenstrom's Macroglobulinemia. *Clin Lymphoma Myeloma* 2006; **6**(5): 380-3.

16. Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. *N Engl J Med* 2016; **374**(4): 323-32.

17. Treon SP, Meid K, Gustine J, et al. Long-term follow-up of previously treated patients who received ibrutinib for symptomatic Waldenstrom's Macroglobulinemia: Update of pivotal clinical trial. *Blood* 2017; **130**(Suppl 1): 2766.

Table 1. Patient demographics and baseline characteristics

Characteristic	TN (n=14)	R/R (n=92)
Median age (range), years	73 (48–86)	69 (39–90)
Male sex, n (%)	10 (71)	63 (68)
ECOG PS ≤1, n (%)	12 (86)	88 (96)
Median time since initial WM diagnosis (range), years	0·4 (0·04–5·8)	6·1 (0·2–25·4)
Bone marrow involvement, n (%)	14 (100)	89 (97)[a]
Extramedullary disease, n (%)	9 (64)	59 (64)
Lymphadenopathy ≥1·5 cm	7 (78)	50 (85)
Splenomegaly ≥13 cm	4 (44)	26 (44)
Median serum IgM (range), mg/dL	4615 (633–7530)	3565 (291–9740)
≥4000 mg/dL, n (%)	9 (64)	37 (40)
Median absolute neutrophil count (range), cells $\times 10^9$/L	3·2 (0·4–7·6)	2·9 (0·6–9·2)
Median hemoglobin (range), g/dL	9·8 (6·2–14·1)	10·6 (6·0–15·4)
<11 g/dL, n (%)	11 (79)	53 (58)
<10 g/dL, n (%)	9 (64)	35 (38)
Median hematocrit (range), %	30 (19–41)	33 (19–46)
Median platelets (range), cells/mm^3	187,000 (36,000–364,000)	203,000 (20,000–526,000)
<100,000 cells/mm^3, n (%)	2 (14)	11 (12)
Prior therapies		
Median number of prior therapies (range)	-	2 (1–7)
≥3 prior therapies, n (%)	-	41 (45)

Refractory disease[b], n (%)	-	33 (36)
Anti-CD20 therapy (single agent or part of a regimen)	-	81 (88)
Cyclophosphamide-based regimen	-	32 (35)
Chlorambucil-based regimen	-	29 (32)
Proteasome inhibitor-based regimen	-	28 (30)
Purine analogue ± rituximab	-	21 (23)
Bendamustine ± rituximab	-	18 (20)
CHOP/CVP/COP ± rituximab	-	18 (20)
Purine analogue + cyclophosphamide ± rituximab	-	15 (16)
Other[c]	-	22 (24)

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; COP/CVP = cyclophosphamide, vincristine, and prednisone; DHAP = cisplatin, cytosine arabinoside, and dexamethasone; ECOG PS = Eastern Cooperative Oncology Group performance status; ESHAP = etoposide, cytarabine, cisplatinum, methylprednisolone; Ig = immunoglobulin; ImiD = immunomodulatory imide drugs; R/R = relapsed/refractory; TN = treatment naïve; WM = Waldenström macroglobulinemia.

[a]The remaining n=3 patients were indeterminant.

[b]Defined as best overall response rate of stable disease or progressive disease.

[c] Includes plasmapheresis (n=7), other chemotherapy regimens not listed (n=6), DHAP/ESHAP ± rituximab (n=4), corticosteroids alone (n=3), IMiD alone (n=3), IMiD + cyclophosphamide-based regimen (n=2), and proteasome inhibitor + cyclophosphamide-based regimen (n=1).

Figure legends

Figure 1. Overall response rates by patient population and by *MYD88* mutational (*MYD88*^{L265}) status. ORR were assessed in all patients who received ≥1 dose of acalabrutinib (A), and for the MYD88 subanalysis, in the 50 patients where the mutational status was determined by local investigators (B). Abbreviations: CR = complete response; IWWM = International Workshop on Waldenström Macroglobulinemia; MR = minor response; MRR = major response rate (≥PR); ORR = overall response rate (≥ MR); PR = partial response; R/R = relapsed/refractory; TN = treatment-naive; VGPR = very good partial response. [a] ORR or MRR may not equal MRR + MR or PR + VGPR + CR, respectively, as shown due to rounding.

Figure 2. Overall response rate by subgroup (Modified 3rd IWWM criteria). Forest plot containing overall response rate analyzed by subgroups according to baseline demographic and clinical characteristics, with 95% confidence interval. Abbreviations: ECOG = Eastern Cooperative Oncology Group; Ig = immunoglobulin; ORR = overall response rate.

Figure 3. Change in median hemoglobin levels and median IgM levels with acalabrutinib treatment. (A) relapsed/refractory and (B) treatment-naive patients**.** Abbreviations: BID = twice daily; BTK = Bruton tyrosine kinase; D = day; post = 4 hours post-dose; pre = pre-dose; PK = pharmacokinetics; R/R relapsed/refractory; TN = treatment-naive.

Figure 4. Duration of response and survival outcomes (Modified 3rd IWWM criteria). (A) Duration of response, (B) Progression-free survival, (C) Overall survival**.** Investigator-assessed DOR, PFS, and OS using the Modified 3rd IWWM Criteria are shown. Also included are estimated 24-month DOR, PFS, and OS rates. DOR, PFS, and OS were assessed in the efficacy-evaluable population, defined as all treated who had ≥1 evaluable response assessment after the first dose of acalabrutinib. Abbreviations: DOR =

duration of response; IWWM = International Workshop on Waldenström Macroglobulinemia; OS = overall survival; PFS = progression-free survival; R/R = relapsed/refractory; TN = treatment-naïve.

Figure 5. Common adverse events in ≥15% of all patients. Adverse events reported for the 106 patients in the safety population evaluated. All adverse events are listed as Medical Dictionary for Regulatory Activities preferred terms. Abbreviations: LRTI = lower respiratory tract infection; URTI = upper respiratory tract infection.

Figure 6. Pharmacokinetics and pharmacodynamics of acalabrutinib in WM. (A) Pharmacokinetics of acalabrutinib. Plasma concentration of acalabrutinib in samples collected on Day 1 and Day 8 post-dose; (B) BTK occupancy by covalent acalabrutinib. BTK occupancy at indicated timepoints relative to first dose of acalabrutinib. Red horizontal lines represent the median (96–98% BTK occupancy at any timepoint post first dose); (C) BTK pathway modulation in MYD88 mutant and WT WM patients. Percent change in basal phosphorylated BTK at indicated timepoints relative to first dose of acalabrutinib by MYD88 status Statistical analysis represents the comparison of each timepoint to baseline. **p<0.01. ***p<0.001. ****p<0.0001. Abbreviations: BID = twice daily; BTK = Bruton tyrosine kinase; pBTK = phosphorylated BTK; D = day; post = 4 hours post-dose; pre = pre-dose; PK = pharmacokinetics; R/R relapsed/refractory; TN = treatment-naïve.

Figure 1.

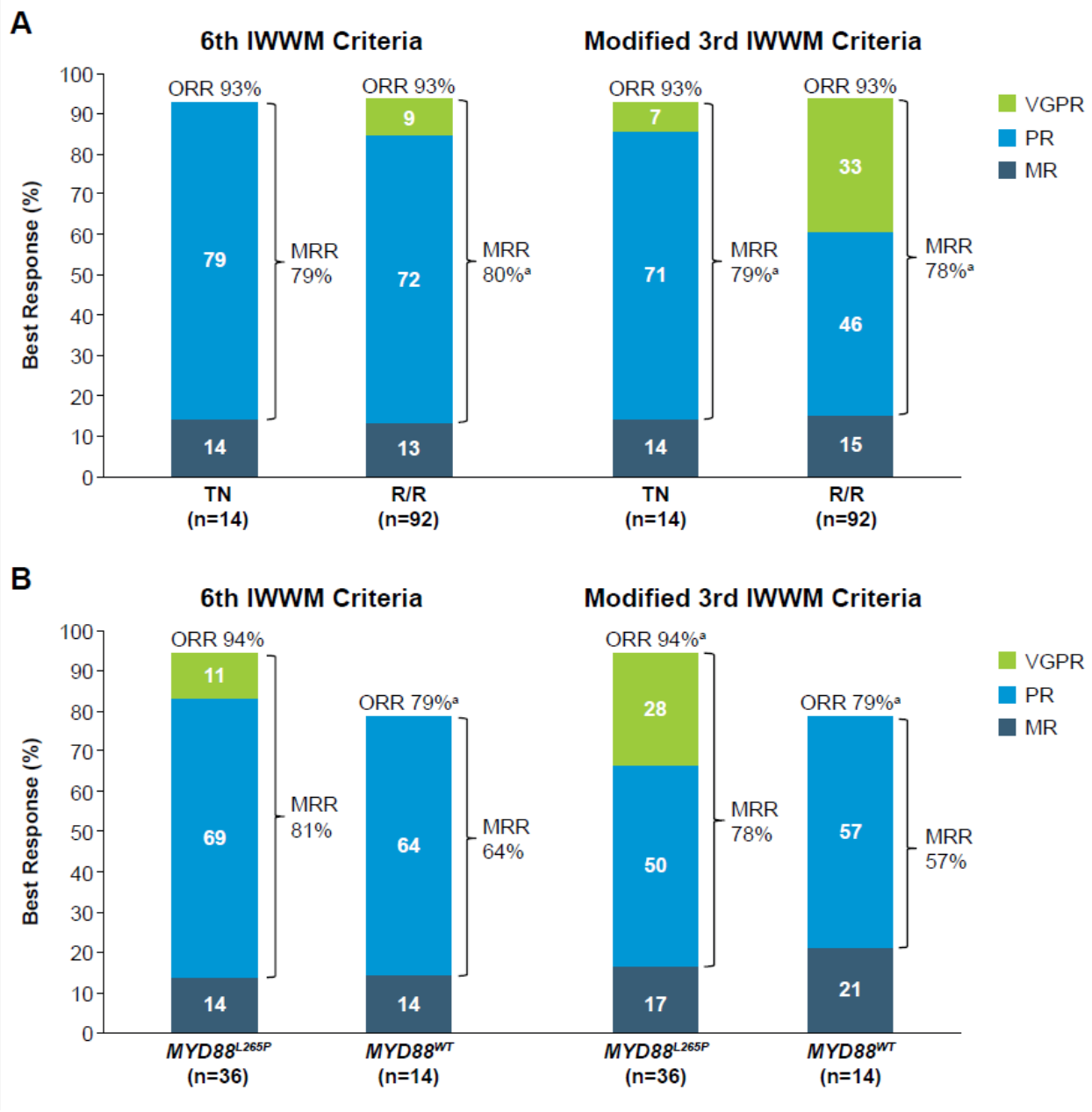

A
6th IWWM Criteria
Modified 3rd IWWM Criteria
Best Response (%)
ORR 93%
ORR 93%
ORR 93%
ORR 93%
79
14
MRR 79%
9
72
13
MRR 80%a
7
71
14
MRR 79%a
33
46
15
MRR 78%a
TN (n=14)
R/R (n=92)
TN (n=14)
R/R (n=92)
VGPR
PR
MR
B
6th IWWM Criteria
Modified 3rd IWWM Criteria
Best Response (%)
ORR 94%
ORR 79%a
ORR 94%a
ORR 79%a
11
69
14
MRR 81%
64
14
MRR 64%
28
50
17
MRR 78%
57
21
MRR 57%
MYD88L265P (n=36)
MYD88WT (n=14)
MYD88L265P (n=36)
MYD88WT (n=14)
VGPR
PR
MR

Figure 2.

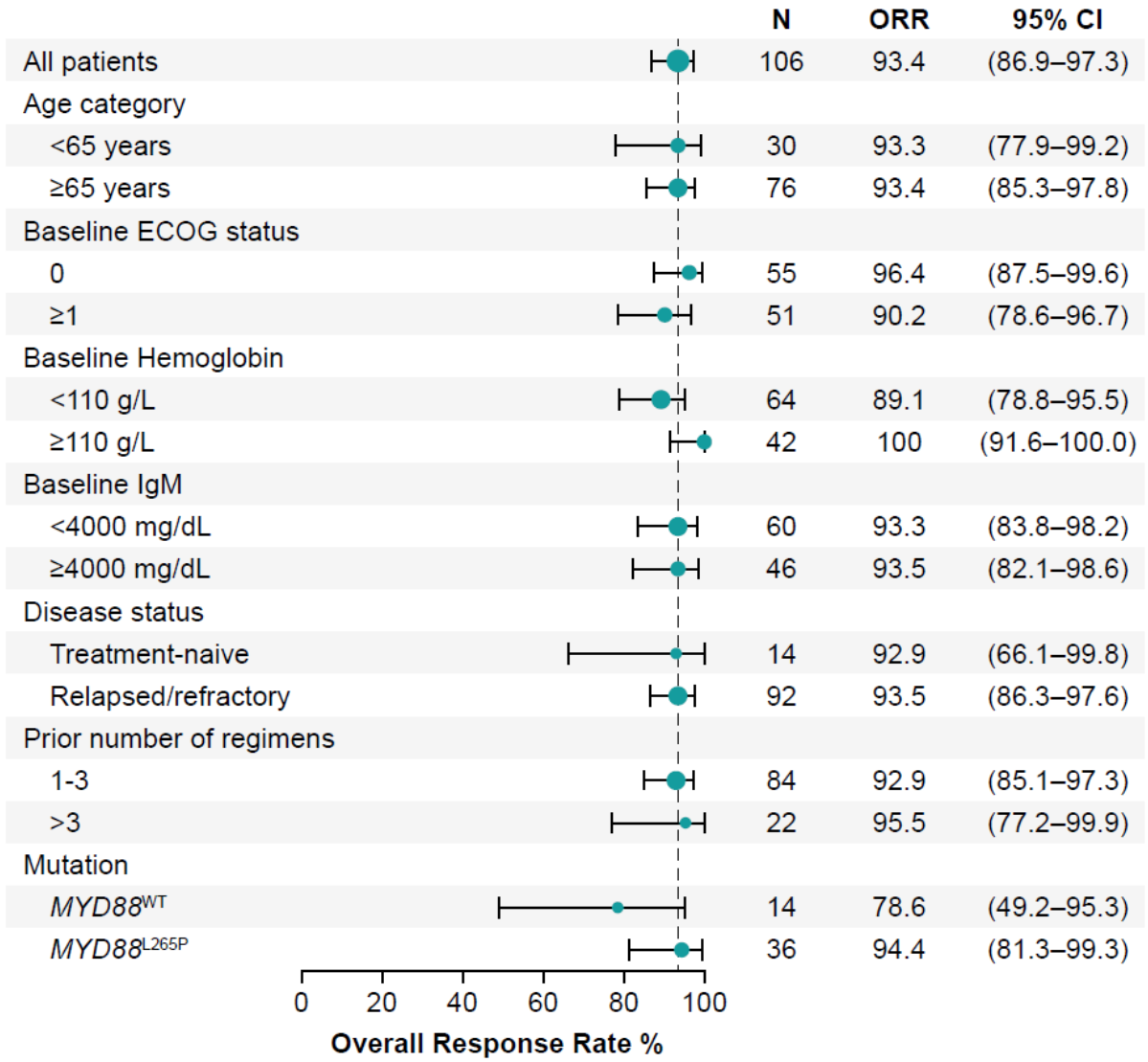

N
ORR
95% CI
All patients
106
93.4
(86.9–97.3)
Age category
<65 years
30
93.3
(77.9–99.2)
≥65 years
76
93.4
(85.3–97.8)
Baseline ECOG status
0
55
96.4
(87.5–99.6)
≥1
51
90.2
(78.6–96.7)
Baseline Hemoglobin
<110 g/L
64
89.1
(78.8–95.5)
≥110 g/L
42
100
(91.6–100.0)
Baseline IgM
<4000 mg/dL
60
93.3
(83.8–98.2)
≥4000 mg/dL
46
93.5
(82.1–98.6)
Disease status
Treatment-naive
14
92.9
(66.1–99.8)
Relapsed/refractory
92
93.5
(86.3–97.6)
Prior number of regimens
1-3
84
92.9
(85.1–97.3)
>3
22
95.5
(77.2–99.9)
Mutation
MYD88WT
14
78.6
(49.2–95.3)
MYD88L265P
36
94.4
(81.3–99.3)
0
20
40
60
80
100
Overall Response Rate %

Figure 3.

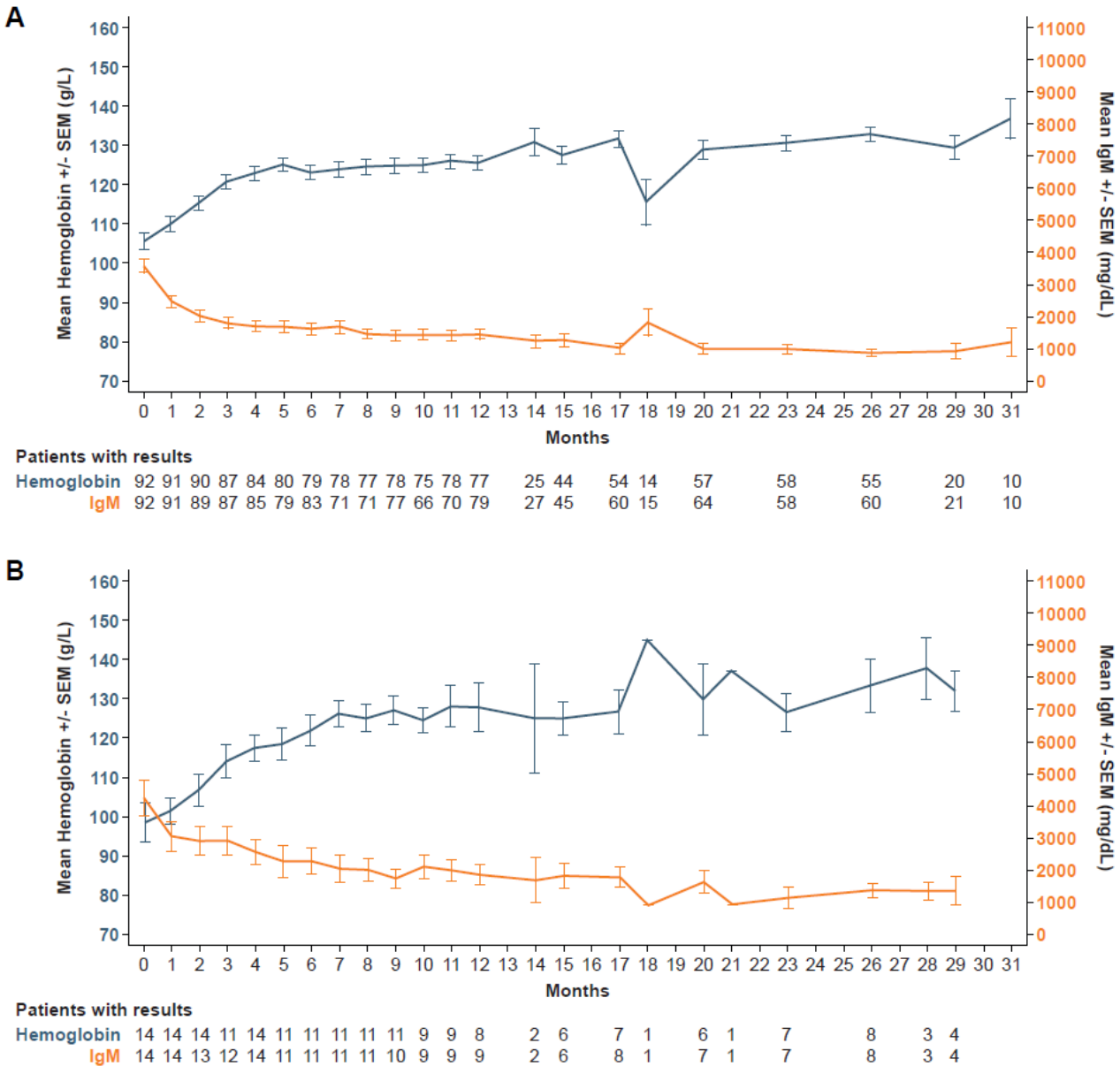
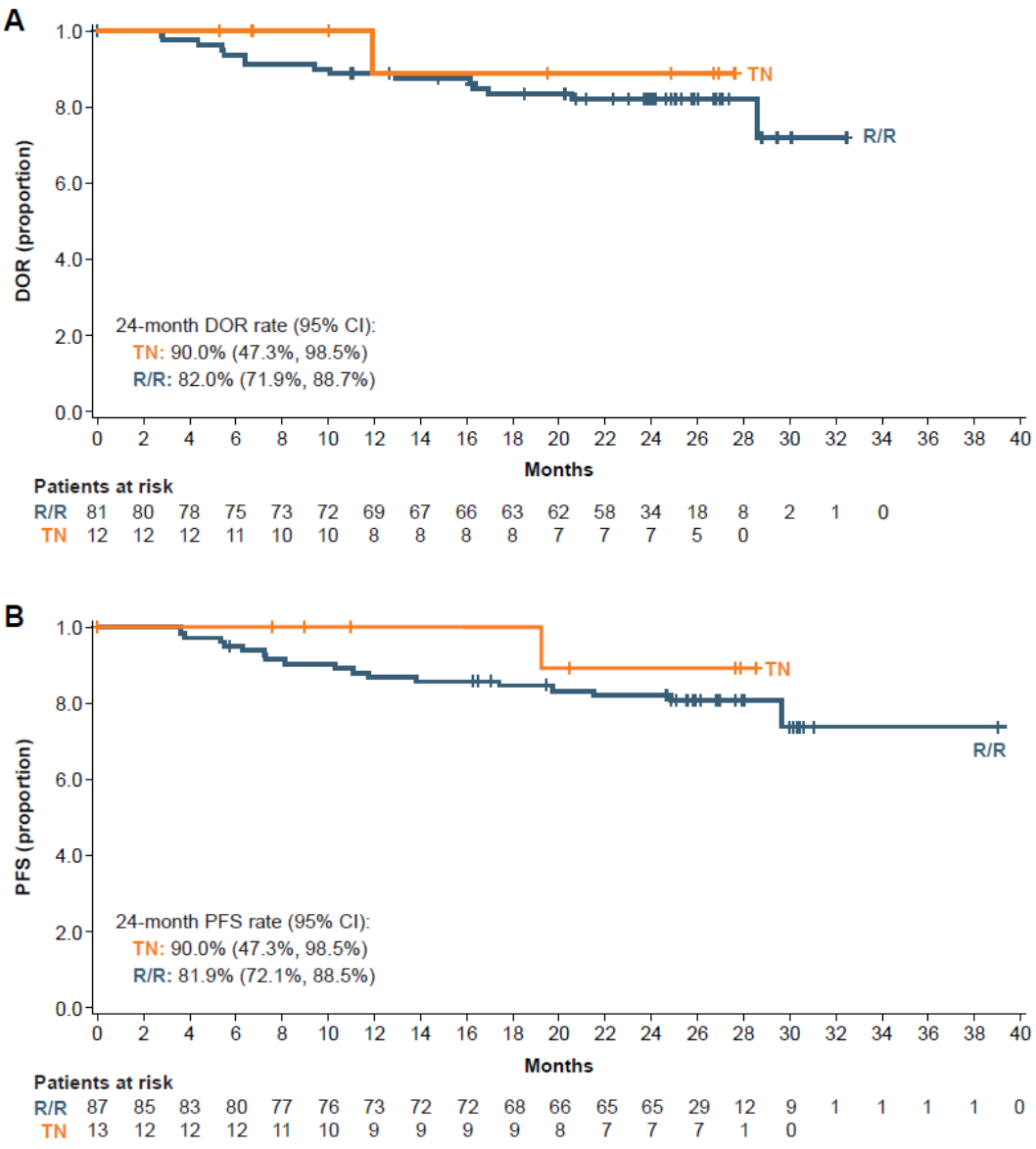

A
Mean Hemoglobin +/- SEM (g/L)
Mean IgM +/- SEM (mg/dL)
Months
Patients with results
Hemoglobin 92 91 90 87 84 80 79 78 77 78 75 78 77 25 44 54 14 57 58 55 20 10
IgM 92 91 89 87 85 79 83 71 71 77 66 70 79 27 45 60 15 64 58 60 21 10
B
Mean Hemoglobin +/- SEM (g/L)
Mean IgM +/- SEM (mg/dL)
Months
Patients with results
Hemoglobin 14 14 14 11 14 11 11 11 11 11 9 9 8 2 6 7 1 6 1 7 8 3 4
IgM 14 14 13 12 14 11 11 11 11 10 9 9 9 2 6 8 1 7 1 7 8 3 4

Figure 4.


A
DOR (proportion)
1.0
8.0
6.0
4.0
2.0
0.0
TN
R/R
24-month DOR rate (95% CI):
TN: 90.0% (47.3%, 98.5%)
R/R: 82.0% (71.9%, 88.7%)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
Months
Patients at risk
R/R 81 80 78 75 73 72 69 67 66 63 62 58 34 18 8 2 1 0
TN 12 12 12 11 10 10 8 8 8 8 7 7 7 5 0
B
PFS (proportion)
1.0
8.0
6.0
4.0
2.0
0.0
TN
R/R
24-month PFS rate (95% CI):
TN: 90.0% (47.3%, 98.5%)
R/R: 81.9% (72.1%, 88.5%)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
Months
Patients at risk
R/R 87 85 83 80 77 76 73 72 72 68 66 65 65 29 12 9 1 1 1 1 0
TN 13 12 12 12 11 10 9 9 9 9 8 7 7 7 1 0

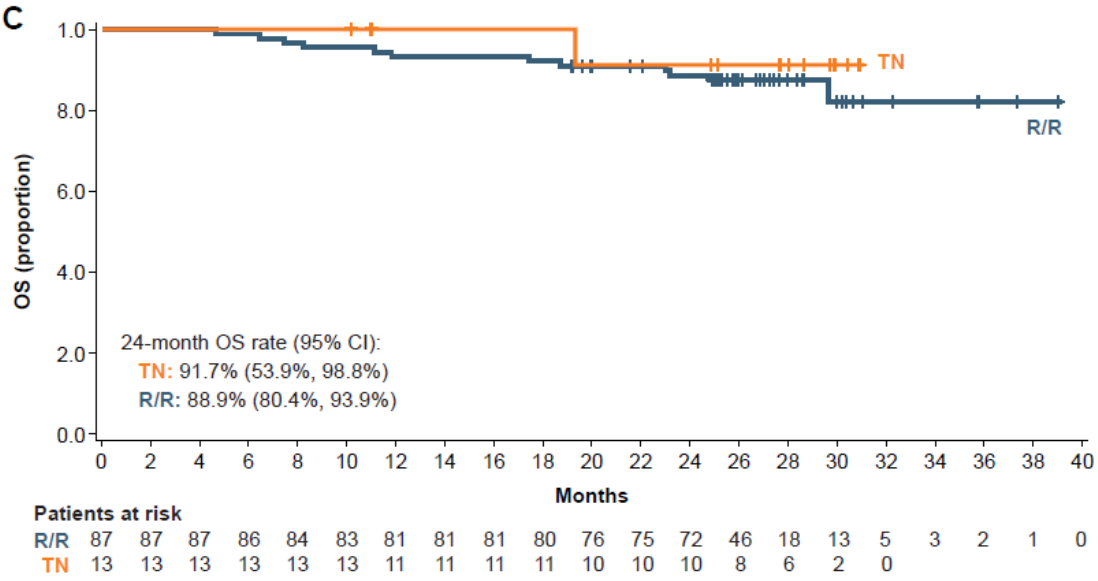

C
OS (proportion)
1.0
8.0
6.0
4.0
2.0
0.0
TN
R/R
24-month OS rate (95% CI):
TN: 91.7% (53.9%, 98.8%)
R/R: 88.9% (80.4%, 93.9%)
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
Months
Patients at risk
R/R 87 87 87 86 84 83 81 81 81 80 76 75 72 46 18 13 5 3 2 1 0
TN 13 13 13 13 13 13 11 11 11 11 10 10 10 8 6 2 0

Figure 5.

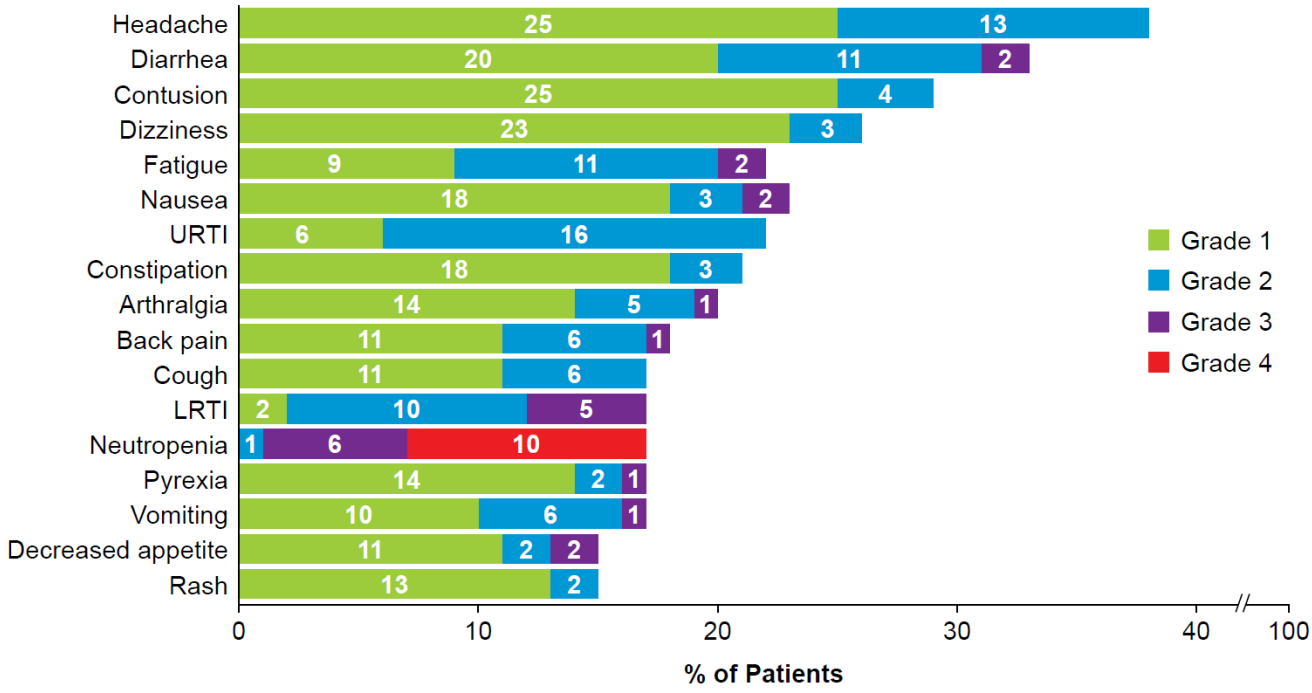
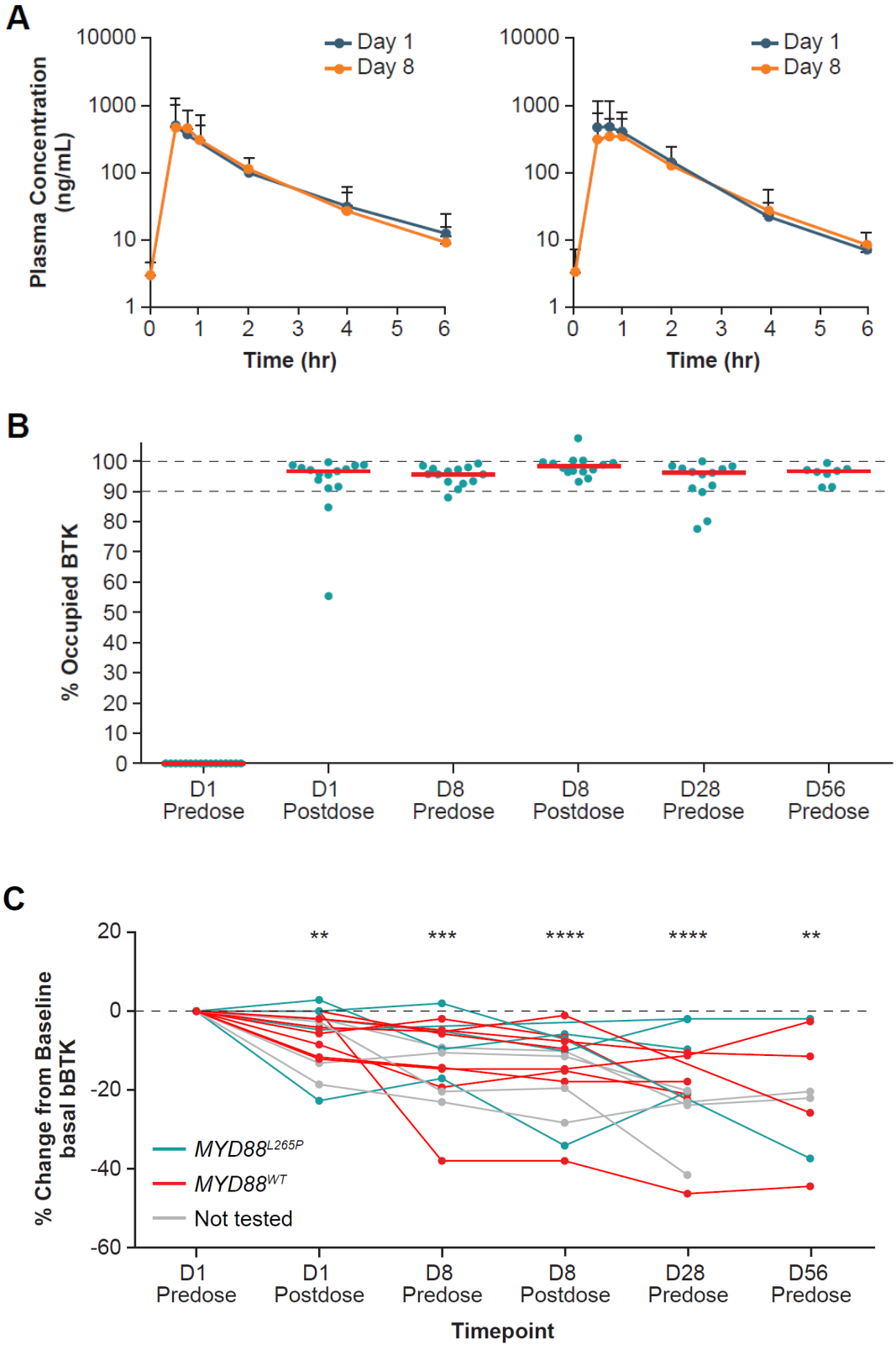

Headache
Diarrhea
Contusion
Dizziness
Fatigue
Nausea
URTI
Constipation
Arthralgia
Back pain
Cough
LRTI
Neutropenia
Pyrexia
Vomiting
Decreased appetite
Rash
25
13
20
11
2
25
4
23
3
9
11
2
18
3
2
6
16
18
3
14
5
1
11
6
1
11
6
2
10
5
1
6
10
14
2
1
10
6
1
11
2
2
13
2
0
10
20
30
40
100
% of Patients
Grade 1
Grade 2
Grade 3
Grade 4

Figure 6.


A
Plasma Concentration (ng/mL)
10000
1000
100
10
1
Day 1
Day 8
0 1 2 3 4 5 6
Time (hr)
B
% Occupied BTK
100
90
80
70
60
50
40
30
20
10
0
D1 Predose
D1 Postdose
D8 Predose
D8 Postdose
D28 Predose
D56 Predose
C
% Change from Baseline basal bBTK
20
0
-20
-40
-60
**
***
****
****
**
MYD88L265P
MYD88WT
Not tested
D1 Predose
D1 Postdose
D8 Predose
D8 Postdose
D28 Predose
D56 Predose
Timepoint