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Acalabrutinib in Relapsed or Refractory Mantle Cell Lymphoma: A Single-Arm, Multicenter, Phase 2 Trial

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Research in context

Evidence before this study

Bruton tyrosine kinase (BTK) inhibition with ibrutinib is the current standard of care for patients with relapsed or refractory mantle cell lymphoma (MCL). However, tolerability can be a problem leading to treatment disruption and discontinuation. To better understand the utility and the limitations of ibrutinib treatment in this patient population, we searched PubMed for all clinical trial publications using the search terms "mantle cell lymphoma" AND "ibrutinib" AND ("relapsed" OR "refractory") AND "trial." Existing evidence for the activity of BTK inhibition with ibrutinib in relapsed or refractory MCL includes a single-arm, Phase 2 trial that demonstrated substantial efficacy after a median follow-up of 15.3 months. In that trial, the overall response rate (ORR) was 68%, with 21% of patients achieving a complete response (CR). Additional evidence is provided by a randomized Phase 3 trial in which ibrutinib was shown to be superior to temsirolimus, another agent approved for the treatment of relapsed or refractory MCL. Finally, supportive evidence for the activity of ibrutinib was demonstrated in a Phase 1/1b combination trial with rituximab and bendamustine. Although promising activity has been shown with ibrutinib, it has also been associated with Grade ≥3 toxicities, notably atrial fibrillation, infection, and bleeding, as noted in the prescribing information for ibrutinib. These side effects are not characteristic of germline BTK deficiency, suggesting that the off-target activity of ibrutinib against other kinases may be involved in some of the observed toxicities. Recently, promising activity and tolerability with another BTK inhibitor, acalabrutinib, was demonstrated in patients with relapsed or refractory chronic lymphocytic leukemia. Acalabrutinib is a highly selective, potent BTK inhibitor developed to minimize off-target activity. In vitro studies have

shown that acalabrutinib has more selective BTK inhibition, less off-target kinase activity, and higher in vivo potency than ibrutinib.

Added value of this study

This is the first study evaluating the efficacy and safety of acalabrutinib in mantle cell lymphoma. In this Phase 2, multicenter, open-label study, single-agent acalabrutinib was administered at 100 mg twice-daily to patients with relapsed or refractory MCL. An investigator-assessed ORR of 81% was achieved, with a CR rate at 40%, and responses were durable after a median follow-up of 15.2 months. Compared with previous results in the existing literature, the response rates reported in this study are among the highest rates reported for a single agent in patients with relapsed or refractory MCL. Acalabrutinib also yielded a favorable safety profile, with few Grade ≥3 adverse events and treatment discontinuations due to adverse events. Atrial fibrillation was not observed in this study and the rates of Grade ≥3 infection and hemorrhage were relatively low.

Implications of all the available evidence

The results of the present study suggest that acalabrutinib demonstrates excellent activity in relapsed or refractory MCL. Moreover, acalabrutinib demonstrated a differentiated safety profile compared with that previously reported with BTK inhibition. As such, these data have the potential to change the current practice for relapsed or refractory MCL.

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Abstract

Background

Bruton tyrosine kinase is a clinically validated target in mantle cell lymphoma. Acalabrutinib (ACP-196) is a highly selective, potent Bruton tyrosine kinase inhibitor developed to minimize off-target activity.

Methods

In this open-label, Phase 2 study, oral acalabrutinib was administered at 100 mg twice daily to 124 patients with relapsed/refractory mantle cell lymphoma. The primary endpoint was overall response rate per the Lugano classification. Secondary endpoints included duration of response, progression-free survival, overall survival, safety, pharmacokinetics, and pharmacodynamics.

Findings

The median age was 68 years. Patients received a median of 2 prior therapies (range, 1-5). At a median follow-up of 15·2 months, the overall response rate was 81% with 40% of patients achieving a complete response. The median duration of response, progression-free survival and overall survival were not reached; the 12-month rates were 72%, 67%, and 87%, respectively. The most common adverse events were primarily Grade 1/2 and were headache (38%), diarrhea (31%), fatigue (27%), and myalgia (21%). The most common Grade ≥3 adverse events were neutropenia (10%), anemia (9%), and pneumonia (5%). There were no cases of atrial fibrillation and one case of Grade ≥3 hemorrhage. The median duration of treatment was 13·8 months. Treatment was discontinued in 54 patients (44%), primarily due to progressive disease (31%) and adverse events (6%).

Interpretation

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Acalabrutinib treatment provided a high rate of durable responses and a favorable safety profile in patients with relapsed/refractory mantle cell lymphoma. These findings suggest an important role for acalabrutinib in the treatment of this disease population.

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Introduction

Mantle cell lymphoma (MCL) is an aggressive B-cell non-Hodgkin lymphoma with a poor prognosis.[1-3] Almost all patients relapse after frontline therapy, and relapsed/refractory (R/R) MCL is incurable.[1,3] B-cell receptor (BCR) signaling is central to the survival and proliferation of malignant B cells, and Bruton tyrosine kinase (BTK), an integral member of the BCR pathway, is a clinically validated target in MCL.[4,5]

In patients with R/R MCL, after a median follow-up time of 15.3 months, treatment with the BTK inhibitor ibrutinib produced an overall response rate (ORR) of 68% (21% complete response [CR]) and a median progression-free survival (PFS) of 13·9 months.[4] However, ibrutinib has been associated with notable Grade ≥3 toxicities, including atrial fibrillation (6%-9% of patients), infection (14%-29%), and bleeding (up to 6%).[6] Since these side effects are not characteristic of germline BTK deficiency,[7,8] the off-target activity of ibrutinib against other kinases, including tyrosine-protein kinase Tec and interleukin-2–inducible T-cell kinase, has been postulated to be involved in these specific toxicities.[9-11]

Acalabrutinib (ACP-196) is a highly selective, potent BTK inhibitor developed to minimize off-target activity.[10] In vitro studies showed that acalabrutinib has more selective BTK inhibition and higher in vivo potency than ibrutinib.[12,13] Acalabrutinib also has rapid oral absorption and a short plasma half-life.[10] Twice-daily dosing maintains complete and continuous BTK inhibition across the 24-hour dosing interval.[10] In patients with relapsed chronic lymphocytic leukemia (CLL), optimal BTK occupancy was observed with 100 mg acalabrutinib twice daily.[10] This dose and schedule demonstrated high response rates, durable remissions, and a favorable safety profile in CLL.

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Based on the promising results with acalabrutinib in relapsed CLL, and given that BTK is an established target in MCL, acalabrutinib administered at 100 mg twice daily was investigated in patients with R/R MCL in the Phase 2 ACE-LY-004 study (NCT02213926).

Methods

Study Design

In this Phase 2, single-arm, multicenter, open-label study, patients were enrolled at 40 sites across nine countries. Acalabrutinib was administered orally at 100 mg twice daily in 28-day cycles until progressive disease (PD) or unacceptable toxicity. Dose modification guidelines (Supplementary Table S1) were defined in the study protocol. The institutional review board at each site approved the protocol. The study was conducted according to the principles of the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice.

Patients

Eligible patients had confirmed MCL with translocation t(11;14)(q13;q32) and/or overexpressed cyclin D1, and measurable disease (≥ one lesion measuring ≥2 cm in the longest diameter). Patients had relapsed after, or were refractory to, one to five prior therapies. Refractory disease was defined as achieving less than partial response (PR) with the most recent treatment before study entry. Other eligibility criteria included age ≥18 years, Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2. Exclusion criteria included absolute neutrophil count $<0{\cdot}75\times10^9$/L or platelet count $<50\times10^9$/L (or $<0{\cdot}50\times10^9$/L or $<30\times10^9$/L, respectively, for patients with bone marrow involvement), and creatinine level >2·5× the upper limit of normal. Patients with significant cardiovascular disease (uncontrolled/symptomatic arrhythmias, congestive heart

failure or myocardial infarction) within six months of screening, any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval >480 ms were excluded. Concomitant treatment with warfarin or equivalent vitamin K antagonists was prohibited. Patients previously treated with BCR inhibitors (BTK, PI3K or SYK inhibitors) or BCL-2 inhibitors were excluded. All patients provided written informed consent.

Assessments

The primary endpoint was ORR, defined as the proportion of patients achieving either a PR or a CR at any time during the treatment period based on investigator assessment according to the 2014 Lugano classification.[14] Secondary endpoints included investigator-assessed duration of response (DOR), PFS, overall survival (OS), safety, pharmacokinetics, and pharmacodynamics. Independent Review Committee (IRC)-assessed ORR, DOR, and PFS using the Lugano classification were secondary endpoints. IRC-assessed ORR, DOR, and PFS based on criteria established by the International Harmonization Project in 2007 were exploratory endpoints.[15]

Disease assessments included physical examinations, bone marrow assessments, and image evaluations. These included computed tomographic (CT) scans with contrast performed at the end of Cycles 2, 4, and 6 and every three cycles thereafter, and positron-emission tomographic (PET)/CT scans performed at the end of Cycles 2 and 6 and as clinically indicated or to confirm a CR. A bone marrow aspirate/biopsy was required to confirm a CR for patients with bone marrow disease involvement at baseline. Gastrointestinal (GI) endoscopy was required to confirm a CR for patients with a history of GI involvement as documented by the investigator at baseline. An independent central review vendor also evaluated responses based on CT and PET scans, bone marrow–biopsy specimens, endoscopy results, and clinical data.

Safety assessments included the frequency and severity of adverse events (AEs), clinical

laboratory tests (hematology, clinical chemistry, and urinalysis), vital sign measurements, physical examinations, and ECOG PS. AE severity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4·03. Pharmacokinetic and pharmacodynamic testing was conducted in Cycles 1 and 2 (Supplementary Methods).

Statistical Analysis

The planned sample size was 117 patients. The original protocol consisted of two parallel cohorts (bortezomib-naive and bortezomib-exposed) using a Simon's two-stage design.[16] An interim futility analysis was conducted using the stopping rules for Simon's two-stage design. Based on this analysis, enrollment to both cohorts could continue without interruption.

Results from the Phase 2 study of ibrutinib in R/R MCL indicated that prior bortezomib exposure does not influence response to BTK inhibitor therapy[4]; therefore, the cohorts were merged. The original planned sample size was retained to obtain adequate safety and exposure data.

The final analysis was planned to occur approximately 14 months after the last patient was enrolled. Efficacy and safety analyses included all patients receiving ≥ one dose of acalabrutinib. The same analysis methods for investigator-assessed ORR were applied to IRC-assessed ORR. DOR, PFS and OS were estimated using the Kaplan-Meier method. Noncompartmental analysis was used to characterize pharmacokinetic parameters, and pretreatment and post-treatment pharmacodynamic variables were compared using paired t-tests.

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 a professional medical writer paid by the sponsor. 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.

Results

Patients

From March 12, 2015, through January 5, 2016, 124 patients with R/R MCL were enrolled and treated. Patient baseline characteristics are provided in Table 1. The median age was 68 years (range 42-90 years) with 65% of patients aged ≥65 years. At baseline, 75% had Ann Arbor stage IV disease and 73% of patients had extranodal disease; the most common extranodal sites were bone marrow (51%), GI tract (10%), and lung (10%). The simplified Mantle Cell Lymphoma International Prognostic Index scores at baseline were intermediate and high in 44% and 17% of patients, respectively. The median number of prior therapies was 2 (range 1-5); 23% received ≥3 prior therapies, and 24% were refractory to the most recent treatment. Prior treatment with bortezomib/carfilzomib or lenalidomide was reported in 19% and 7% of patients, respectively. Eighteen percent of patients had undergone high-dose chemotherapy with stem cell transplantation. At a median follow-up of 15.2 months (range 0·3-23·7 months), 70 patients (56%) were receiving treatment and 54 patients (44%) had discontinued. The median relative dose intensity was 98·5%. The reasons for treatment discontinuation were PD in 39 patients (31%) and

AEs in 7 patients (6%; Supplementary Table S2), initiation of subsequent anticancer therapy in five patients, all of whom received a stem cell transplant (4%), and lost to follow-up, patient withdrawal, and patient decision to stop treatment in one patient each (1%).

Pharmacokinetics and Pharmacodynamics

Pharmacokinetic parameters were evaluated on Days 1 and 8 at different timepoints following dosing (Figure 1A and Supplementary Table S3). Overall, acalabrutinib pharmacokinetic parameters indicated relatively rapid absorption and elimination, with low potential for accumulation.

Binding of acalabrutinib to BTK (target occupancy) was measured in peripheral blood (Figure 1B). Acalabrutinib administered at 100 mg twice daily resulted in a median BTK occupancy of 99% four hours after dosing (Days 1 and 8), and 95%-97% at the drug trough timepoints (before next dose) on Days 8, 28, and 56. After 28 days of treatment, plasma levels decreased for TNF alpha, CXCL13 (both $p<0{\cdot}001$), and other cytokines involved in inflammation and cell trafficking (Supplementary Figure S1). An increase in CD3+CD8+ T cells ($p<0{\cdot}05$) from baseline was observed on Cycle 2 Day 28 (Supplementary Figure S2).

Efficacy

A reduction in lymphadenopathy was observed in 94% of patients (Figure 2A). Investigator-assessed ORR was 81%, with 40% of patients achieving a CR (Figure 2B). Efficacy was further evaluated by an IRC which showed an ORR of 80% with a 40% CR rate. High concordance was observed between investigator- and IRC-assessed ORR and CR (91% and 94%), respectively. A response to treatment occurred in 78% of patients with lymph nodes ≥5 cm in diameter (Figure 3 and Supplementary Figure S3). ORR was consistent across prespecified subgroups, though CR

rates were lower in patients with Ann Arbor Stage IV disease (29%), bone marrow involvement (14%), and extranodal disease (28%; Figure 3 and Supplementary Figure S4). Patients enrolled in the United States compared with those outside of the United States had higher CR rates (56% vs 30%), which may be due to fewer patients in the United States with bone marrow involvement (27% vs 63%). Among responders, 92% responded by the first assessment (end of Cycle 2); time to response ranged 1·5-4·4 months.

Median DOR, PFS, and OS have not been reached based on investigator assessment (Figures 2C-E). At 12 months, the estimated DOR rate was 72% (95% CI: 62%, 80%) and the estimated PFS rate was 67% (95% CI: 58%, 75%). The estimated 12-month OS rate was 87% (95% CI: 79%, 92%).

Safety

The AEs observed were mostly Grade 1/2. The most common AEs of any grade were headache (38%), diarrhea (31%), fatigue (27%), and myalgia (21%; Table 2). Headache events were mostly Grade 1 (30/47 patients [64%]); median time to onset was five days and most patients (77%) experienced only one event. Headache led to withholding of study treatment in <2% of patients; none discontinued due to headache. Grade ≥3 AEs were infrequent and included primarily neutropenia (10%), anemia (9%), and pneumonia (5%). Serious AEs were reported in 48 patients (39%; Supplementary Table S4). Serious AEs were considered treatment-related in 10% of patients; none were reported in > one patient.

Selected AEs reported with ibrutinib treatment were reviewed to assess potential BTK inhibitor class effects.[4] In this study, there were no cases of atrial fibrillation; 3 (2%) Grade 3/4 cardiac AEs were reported in one patient each and were Grade 3 acute coronary syndrome (considered treatment-related), Grade 3 acute myocardial infarction, and Grade 4 cardiorespiratory arrest (both

not treatment-related; Supplementary Table S5). Infections occurred in 53% of patients; 40% had Grade 1/2 infections (Supplementary Table S6). Bleeding events, the most frequent of which were contusion and petechiae, occurred in 31% of patients and were all Grade 1/2 except for one Grade 3 GI hemorrhage (1%) in a patient with a history of GI ulcer (Supplementary Table S7). One patient had Grade 3 hypertension (not treatment-related). Seven patients (6%) discontinued treatment due to AEs (Supplementary Table S2). AEs leading to discontinuation occurred in one patient each: aortic stenosis, diffuse large B-cell lymphoma, blood blister and petechiae (both in one patient with Grade 3 acute coronary syndrome treated with clopidogrel), dyspnea and leukostasis syndrome (both in one patient), noncardiac chest pain, pulmonary fibrosis, and thrombocytopenia.

Of the 27 deaths, most (n=22) were due to PD; five patients (4%) died within 30 days of receiving the last dose of acalabrutinib (all due to PD). One death was due Grade 5 aortic stenosis in a patient with a history of aortic stenosis (not considered treatment-related). Two deaths were reported as due to "other" reasons, which included secondary acute myeloid leukemia and intestinal obstruction caused by complications after removal of a colorectal tumor and stroma, both occurring >60 days after the last dose of acalabrutinib. Two deaths were reported as unknown at the time of data cutoff; both occurred >100 days after the last dose of acalabrutinib.

Lymphocytosis

Lymphocytosis occurred in 38/123 patients (31%; 95% CI: 23%, 40%). Median time to first post-baseline absolute lymphocyte count meeting the lymphocytosis criteria was 1.1 weeks (range 0·7-47·9 weeks) (Supplementary Methods and Supplementary Figure S5). Lymphocytosis resolved for 30/38 patients (79%). Median duration of lymphocytosis was 5.6 weeks (range 0·1-59·0 weeks).

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Discussion

R/R MCL remains incurable with standard therapy. Approved agents include bortezomib (ORR, 32%; CR, 8%),[17] lenalidomide (ORR, 28%; CR, 7%),[18] and ibrutinib (ORR, 68%; CR, 21%).[4] Allogenic transplantation may offer long-term remissions to some patients, but is limited by treatment-related morbidity and the difficulty of finding a suitable donor.[2] In this study in R/R MCL, single-agent acalabrutinib achieved a high ORR of 81% with a CR rate at 40%, and these responses were durable after a median follow-up of 15·2 months. In addition, ORR was consistent across all prespecified subgroups analyzed, including subgroups with different number of prior regimens. Although ORR was consistent with the overall population, CR rates were lower in patients with extranodal or bone marrow involvement. The 2014 Lugano Classification[14] response criteria which expanded and standardized the interpretation of PET-CT scans to improve response evaluation were used in this study and reflect the current standard of care in MCL. Based on the criteria established by the International Harmonization Project in 2007, an ORR of 68% and a 21% CR rate were previously reported with ibrutinib in R/R MCL.[4,15] In this study, response was also assessed by an IRC using this criteria as an exploratory endpoint, resulting in an ORR of 75% and a 30% CR rate (Supplementary Table S8).

Acalabrutinib yielded a favorable safety profile in patients with R/R MCL, with few Grade ≥3 AEs and treatment discontinuations due to AEs. Previous studies with ibrutinib reported Grade ≥3 atrial fibrillation (6-9% of patients), infection (14-29%), and bleeding (up to 6%).[6] Although randomized studies are necessary to understand the differences in safety profiles between acalabrutinib and ibrutinib, atrial fibrillation was not observed in this study and the rates of Grade ≥3 infection (13%) and hemorrhage (1%) were low. Although headache was common, only two patients (2%)

experienced Grade 3 headache. Headaches tended to occur early in treatment and without reoccurrence, and no patient discontinued due to headache. Overall, treatment with acalabrutinib demonstrated a favorable benefit-risk profile and represents a promising treatment option for patients with R/R MCL.

The higher selectivity of acalabrutinib to BTK potentially results in less off-target activity and thus an improved tolerability profile, even with twice-daily dosing.[13] More frequent dosing may contribute to improved efficacy with covalent inhibitors: since covalent binding leads to permanent BTK inactivation, the duration of the pharmacodynamic effect is a function of BTK de novo synthesis rate, which may be faster in malignant cells.[13] Indeed, twice-daily dosing of acalabrutinib resulted in complete and continuous inhibition of BTK signaling over 24 hours in patients with R/R MCL, and in patients with CLL.[10]

Given the single arm nature of this study, comparisons with the safety and efficacy reported in the single arm ibrutinib study are limited.[4] The patient population enrolled in each trial differed; the ibrutinib study enrolled subjects that may be considered more heavily pretreated with a median number of three prior therapies (compared with two in the current study) and only 14% of subjects had a low risk simplified MIPI score (compared with 39%). Because BTK is a validated target in MCL, physicians may have been more willing to enroll less advanced patients into the current trial, rather than choosing approved therapies or stem cell transplant. Longer follow-up will add more certainty to the response duration and the toxicity profile. Finally, we are planning to collect data on Ki67 expression, and blastoid and pleomorphic histologic variants, and correlation with efficacy may provide further information on the usefulness of this agent in patient subsets.

In conclusion, this Phase 2 study in R/R MCL demonstrated that twice-daily acalabrutinib monotherapy resulted in a high ORR and CR rate, with responses that were durable and clinically

meaningful. An alternative BTK inhibitor with greater target selectivity and potency, compelling efficacy, and a differentiated safety profile provides an attractive new therapeutic option for patients with R/R MCL.[13] As such, these data have the potential to change the current practice for R/R MCL. Further studies of acalabrutinib are underway, including an ongoing global, Phase 3, double-blind, randomized trial of bendamustine and rituximab with acalabrutinib versus placebo in first-line treatment of MCL.

Declaration of interests

Dr. Casasnovas reports grants, personal fees and non-financial support from Roche, Gilead, and Takeda, personal fees and non-financial support from Bristol Myers Squibb, MSD, and Celgene, personal fees from Abbvie, outside the submitted work. Dr. Covey reports other from Acerta Pharma during the conduct of the study. Dr. Davies reports grants from Acerta Pharma during the conduct of the study, grants, personal fees and non-financial support from F Hoffmann-La Roche, Celgene, Takeda Pharma, Gilead Sciences, personal fees and non-financial support from CTI, grants from Bayer and GSK, grants and personal fees from Janssen, Pfizer, and Karyopharma, personal fees and non-financial support from Mundipharma, personal fees from Kite Pharma, outside the submitted work. Dr. Dupuis reports personal fees from Abbvie and Roche, outside the submitted work. Dr. Goy reports non-financial support from Celgene, Genentech, Pharmacyclics/J&J during the conduct of the study, and personal fees from Celgene, Pharmacyclics/J&J, Acerta, and Takeda outside the submitted work. Dr. Hamdy reports other from Acerta Pharma during the conduct of the study and other from Acerta Pharma outside the submitted work, and a patent issued by Acerta Pharma. Dr. Izumi reports other from Acerta Pharma outside the submitted work, and a patent for acalabrutinib pending. Dr. Jacobsen reports personal fees

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Tables

Table 1. Patient Demographic and Baseline Characteristics

	All treated patients N=124
Age (years)	68 (42-90)
≥65	80 (65%)
Male sex	99 (80%)
ECOG PS	
0	71 (57%)
1	44 (35%)
2[a]	9 (7%)
Simplified MIPI score	
Low risk (0-3)	48 (39%)
Intermediate risk (4-5)	54 (44%)
High risk (6-11)	21 (17%)
Missing	1 (1%)
Tumor bulk	
≥5 cm	46 (37%)
≥10 cm	10 (8%)
Extranodal disease	90 (73%)
Bone marrow	63 (51%)
Gastrointestinal	13 (10%)
Lung	12 (10%)

Ann Arbor Stage IV disease	93 (75%)
Number of prior therapies	2 (1-5)
Refractory disease[b]	30 (24%)
Previous therapy	
Rituximab[c]	118 (95%)
CHOP[c]	64 (52%)
Bendamustine and rituximab-based regimen	27 (22%)
Hyper-CVAD	26 (21%)
Bortezomib/carfilzomib	24 (19%)
Stem-cell transplant	22 (18%)
Lenalidomide	9 (7%)

Data are median (range) or n (%). CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone. CVAD=cyclophosphamide, vincristine, doxorubicin and dexamethasone. ECOG PS=Eastern Cooperative Oncology Group performance status. MIPI=Mantle Cell Lymphoma International Prognostic Index. [a]One patient had an ECOG PS of 3. [b]Refractory disease was defined as a lack of at least a PR to the last therapy before study entry.[4] [c]Alone or as part of a combination regimen.

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Table 2. Adverse Events

	All treated patients (N=124)					
Adverse event	All grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5[a]
Most common events[b]						
Headache	47 (38%)	30 (24%)	15 (12%)	2 (2%)	0	0
Diarrhea	38 (31%)	21 (17%)	13 (10%)	4 (3%)	0	0
Fatigue	34 (27%)[c]	24 (19%)	8 (6%)	1 (1%)	0	0
Myalgia	26 (21%)	19 (15%)	6 (5%)	1 (1%)	0	0
Cough	24 (19%)	21 (17%)	3 (2%)	0	0	0
Nausea	22 (18%)	12 (10%)	9 (7%)	1 (1%)	0	0
Pyrexia	19 (15%)	14 (11%)	5 (4%)	0	0	0
Most common Grade ≥3 events[d]						
Anemia	15 (12%)	1 (1%)	3 (2%)	10 (8%)	1 (1%)	0
Neutropenia	13 (10%)	0	0	6 (5%)	7 (6%)	0
Pneumonia	7 (6%)	0	1 (1%)	6 (5%)	0	0

Data are n (%). [a]Only 1 Grade 5 event (aortic stenosis) was reported. [b]Reported in ≥15% of all treated patients. [c]Includes 1 case of fatigue without grading. [d]Reported in ≥5% of all treated patients.

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Figure legends

Figure 1. Pharmacokinetics and Pharmacodynamics of Acalabrutinib in Mantle Cell Lymphoma. Panel A shows mean acalabrutinib plasma concentrations over time on Day 1 and Day 8 following a 100-mg dose. Panel B shows Bruton tyrosine kinase (BTK) occupancy on Day 1, and predose and postdose during steady-state.

Figure 2. Efficacy of Acalabrutinib in Mantle Cell Lymphoma. Tumor burden was defined as the sum of the product of diameters (SPD) of all target lesions at baseline. Panel A depicts the maximum change from baseline in the SPD for all treated patients with baseline and ≥1 postbaseline lesion measurement. Panel B shows the overall response rate and best response according to the Lugano Classification[14] based on assessment by the investigator (primary endpoint) and an Independent Review Committee (secondary endpoint). Patients without postbaseline disease assessment were not evaluable. Panel C shows the Kaplan-Meier curve for duration of response in patients with a complete response versus those with a partial response. Panels D and E show the Kaplan-Meier curves for progression-free survival (D) and overall survival (E). CR=complete response. DOR=duration of response. IRC=Independent Review Committee. NE=not evaluable. NR=not reached. ORR=overall response rate. OS=overall survival. PD=progressive disease. PFS=progression-free survival. PR=partial response. SD=stable disease.

Figure 3. Subgroup Analysis of Overall Response Rate. Forest plot containing overall response rate analyzed by prespecified subgroups according to baseline demographic and clinical characteristics. The 95% confidence interval was based on exact binomial distribution. Abbreviations: ECOG PS=Eastern Cooperative Oncology Group Performance Status. MIPI=Mantle Cell Lymphoma International Prognostic Index. ORR=overall response rate. US=United States.

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Figure 1

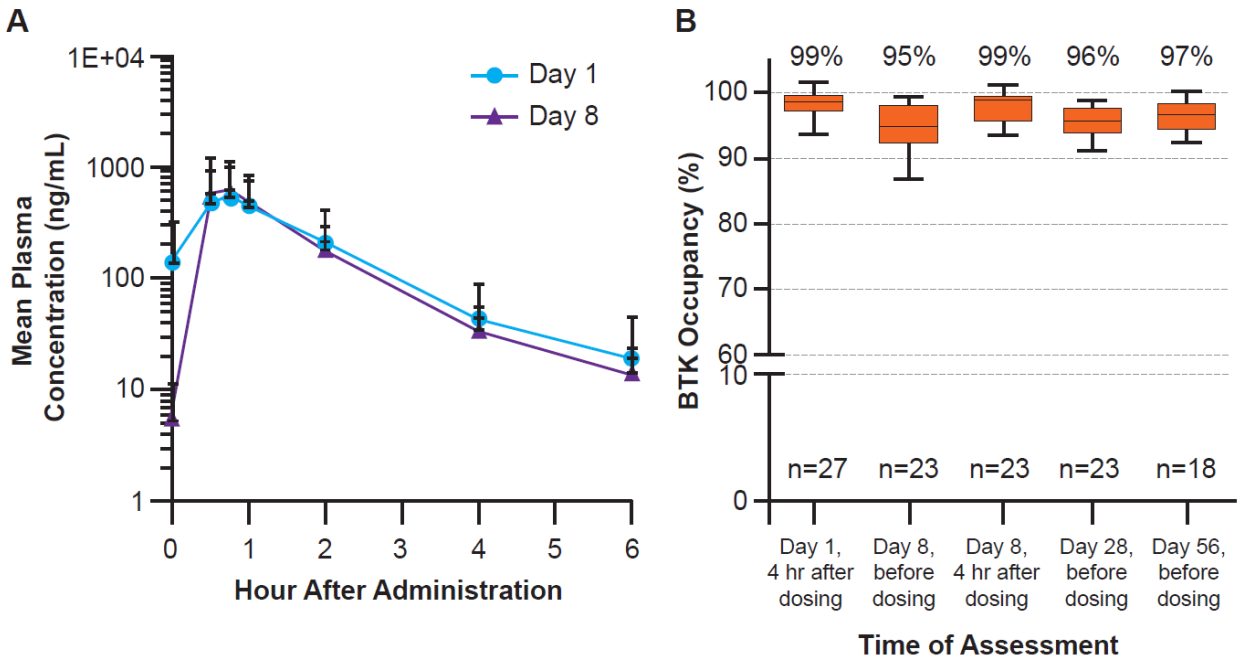

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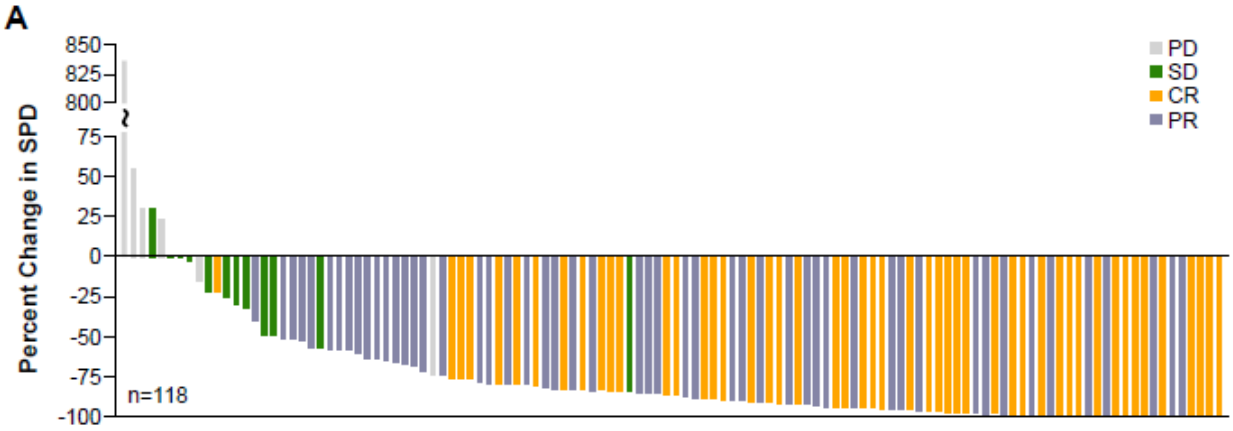
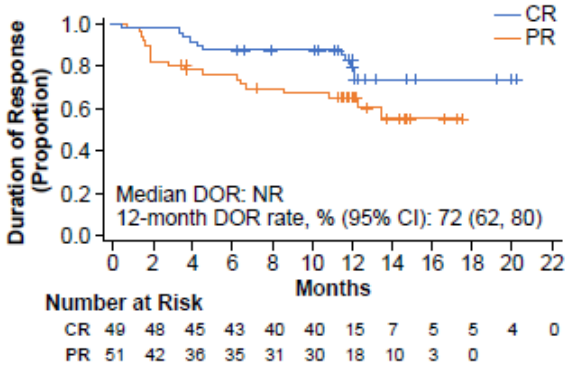
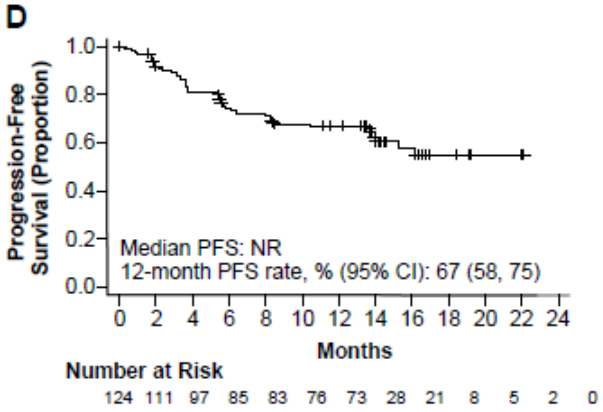
Figure 2



B

	N=124	
	Investigator assessed n (%); 95% CI	IRC assessed n (%); 95% CI
ORR (CR + PR)	100 (81); 73, 87	99 (80); 72, 87
Best response		
CR	49 (40); 31, 49	49 (40); 31, 49
PR	51 (41); 32, 50	50 (40); 32, 50
SD	11 (9); 5, 15	9 (7); 3, 13
PD	10 (8); 4, 14	11 (9); 5, 15
NE[a]	3 (2); 1, 7	5 (4); 1, 9





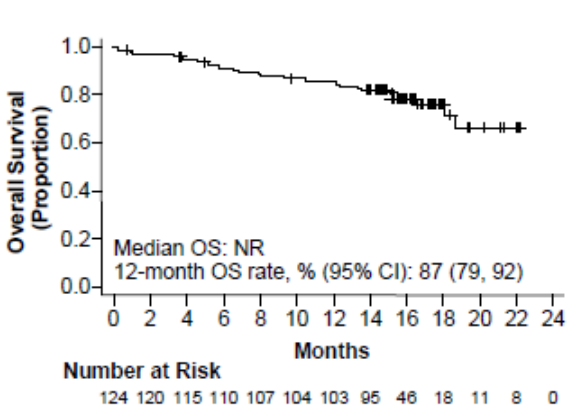


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Figure 3