Acalabrutinib monotherapy in patients with Waldenström macroglobulinemia: a single-arm, multicentre, phase 2 study


Summary

Background Chemoimmunotherapy is typically the standard of care for patients with Waldenström macroglobulinemia; however, infectious and hematologic toxic effects are problematic. Acalabrutinib is a selective, potent Bruton tyrosine-kinase inhibitor. The aim of this trial was to evaluate the activity and safety of acalabrutinib in patients with Waldenström macroglobulinemia.

Methods This single-arm, multicentre, phase 2 trial was done in 19 European academic centres in France, Italy, Greece, the Netherlands, and the UK, and eight academic centres in the USA. Eligible patients were 18 years or older, and had treatment naive (declined or not eligible for chemoimmunotherapy) or relapsed or refractory (at least one previous therapy) Waldenström macroglobulinemia that required treatment, an Eastern Cooperative Oncology Group performance status of 2 or less, and received no previous Bruton tyrosine-kinase inhibitor therapy. Patients received 100 mg oral acalabrutinib twice per day in 28-day cycles until disease progression or unacceptable toxicity. The primary endpoint was investigator-assessed overall response (at least a minor response) according to the 6th International Workshop for Waldenström Macroglobulinemia (IWWM) and the modified 3rd IWWM workshop criteria. The primary outcome and safety were assessed in all patients who received at least one dose of treatment. This study is registered with ClinicalTrials.gov, number NCT02180724, and is ongoing, but no longer enrolling.

Findings Between Sept 8, 2014, and Dec 24, 2015, 122 patients were assessed for eligibility, of which 106 (87%) patients were given acalabrutinib (14 were treatment naive and 92 had relapsed or refractory disease). With a median follow-up of 27·4 months (IQR 26·0–29·7), 13 (93% [95% CI 66–100]) of 14 treatment naive patients achieved an overall response and 86 (93% [86–98]) of 92 relapsed or refractory patients achieved both the modified 3rd and 6th IWWM criteria. Seven (50%) of 14 treatment naive patients and 23 (25%) of 92 relapsed or refractory patients discontinued treatment on study. Grade 3–4 adverse events occurring in more than 5% of patients were lower respiratory tract infection (17 [16%] of 106 patients) and pneumonia (7 [7%]). Grade 3–4 atrial fibrillation occurred in one (1%) patient and grade 3–4 bleeding occurred in three (3%) patients. The most common serious adverse events were lower respiratory tract infection (n=7 [7%]), pneumonia (n=7 [7%]), pyrexia (n=4 [4%]), cellulitis (n=3 [3%]), fall (n=3 [3%]), and sepsis (n=3 [3%]). Pneumonia (n=5 [5%]) and lower respiratory tract infection (n=4 [4%]) were considered treatment related. One treatment-related death was reported (intracranial hematoma).

Interpretation This study provides evidence that acalabrutinib is active as single-agent therapy with a manageable safety profile in patients with treatment-naive, or relapse or refractory Waldenström macroglobulinemia. Further studies are needed to establish its efficacy against current standard treatments and to investigate whether outcomes can be improved with combination therapies.

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Introduction Waldenström macroglobulinemia is a rare, lymphoproliferative disorder characterised by lymphoplasmacytic bone marrow infiltration and immunoglobulin M (IgM) paraproteinemia; clinical features include anemia, constitutional symptoms, hyperviscosity syndrome, and peripheral neuropathy. Chemoimmunotherapy with rituximab in combinations with alkylators (bendamustine and bortezomib) is the typical standard of care of these patients; however, infectious and hematologic toxic effects are concerning.
target in Waldenström macroglobulinemia based on activity of the Bruton tyrosine-kinase inhibitor ibrutinib. Ibrutinib is effective in patients with relapsed or refractory Waldenström macroglobulinemia, but is associated with toxic effects such as bleeding, diarrhea, skin rash, and atrial fibrillation (grade ≥2, 5–10%). Combining rituximab with ibrutinib might improve activity over rituximab monotherapy (overall response of 92% after a median follow-up of 26–5 months) but is also associated with toxic effects (eg, grade 3–4 atrial fibrillation in 12% of patients). Acalabrutinib is a highly selective, covalent Bruton tyrosine-kinase inhibitor that received accelerated approval by the US Food and Drug Administration for the treatment of adult patients with relapsed or refractory mantle cell lymphoma, and is also in clinical development for chronic lymphocytic leukemia and diffuse large B-cell lymphoma. Acalabrutinib shows little effect on EGFR, Tec, Src family kinases, or interleukin 2–inducible T-cell kinase, which could contribute to adverse events, such as diarrhea, rash, bleeding, and atrial fibrillation. These adverse events could lead to discontinuation of an effective treatment and support the development of alternative Bruton tyrosine-kinase inhibitors for the treatment of Waldenström macroglobulinemia to overcome these issues. Acalabrutinib is a Bruton tyrosine-kinase inhibitor that is more potent and selective than ibrutinib, as indicated by kinase selectivity profiling against 395 human kinases. In patients with treatment naive and relapsed or refractory chronic lymphocytic leukemia, acalabrutinib has shown efficacy and acceptable safety. Here we report the activity and safety results of acalabrutinib treatment in patients with Waldenström macroglobulinemia.

Methods

Study design and participants
In this single-arm, multicentre, phase 2 study, we enrolled patients aged 18 years or older with a diagnosis of Waldenström macroglobulinemia requiring treatment, based on the investigator’s assessment at eight US centres and 19 European centres in France, Italy, Greece, the Netherlands, and the UK (appendix p 2). Eligible patients had relapsed or refractory disease (received at least one previous therapy) or were treatment naive who declined or had comorbidities that would preclude treatment with chemotherapy, such as symptomatic hyper-viscosity with IgM 5000 mg/dL or higher, or disease-related neuropathy. Eligible patients also had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or less, absolute neutrophil count greater than 0·75×10⁹ cells per L (>0·50×10⁹ cells per L for patients with bone marrow involvement) or platelet count greater than 50×10⁹ cells per L (>30×10⁹ cells per L for patients with bone marrow involvement), creatinine less than 2·5 times the institutional upper limit of normal (ULN), total bilirubin less than 2·5 times ULN, or aspartate aminotransferase and alanine aminotransferase less than 3·0 times ULN and serum IgM greater than the ULN, or measurable nodal disease (at least one lymph node ≥2 cm diameter).

Exclusion criteria included previous Bruton tyrosine-kinase inhibitor therapy and relevant cardiovascular disease (uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening; any class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification; or QTc >480 ms); patients with previous or concurrent atrial fibrillation could participate. Patients with comorbidities, including organ system dysfunction or uncontrolled active systemic infection, could participate if the investigator believed that the patient would benefit from the intervention and the risk would be outweighed by the benefit.
were excluded. Previous treatment with proton-pump inhibitors was prohibited at study entry; however, patients could be treated with proton-pump inhibitors on study if required. Previous antithrombotic 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. The study was done according to the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. The protocol is included in the appendix (pp 15–63).

Procedures

Six patients received oral acalabrutinib 200 mg once per day. Based on safety, activity, and occupancy data in patients with chronic lymphocytic leukaemia, a protocol amendment was made as of March 15, 2015, and the six patients on 200 mg once per day were switched to 100 mg twice per day for the remainder of the study. All subsequent patients received 100 mg twice per day. All patients received treatment for 28 days and until disease progression or unacceptable toxic effects. Dose delays were allowed for any unmanageable, potentially study termination drug-related grade 3–4 toxic effects until recovery for up to 28 consecutive days. For persistent study drug-related grade 3–4 toxic effects (3rd occurrence), dose modifications (100 mg twice per day to 100 mg once per day) were allowed. Patients were removed from study for withdrawal of consent, termination of the study, lost to follow-up, or death.

Bone marrow biopsy and aspiration were done at screening and to confirm complete response. Response was assessed according to the 6th International Workshop on Waldenström macroglobulinemia (IWWM) criteria and the modified 3rd IWWM criteria, the former having a more stringent very good partial response category (appendix p 10). Pathologic bone marrow assessment was done centrally. Serum immunoglobulins and serum M-protein were measured every cycle to cycle 6 and every 12 weeks thereafter. Radiologic extramedullary disease assessments were done by computed tomography within 30 days before the first dose, every two cycles until cycle 6, every three cycles until cycle 27, and then every six cycles.

The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 version 3.0 was used to assess health-related quality of life. At each assessment in cycle 2, 4, 6, and 9, and then every three cycles until cycle 48, absolute scores and changes from baseline were calculated for each subscale, including core and overall total score.

Adverse events were graded by severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. After day 1, all patients were evaluated for safety once per week for the first 4 weeks, every 2 weeks in cycle 2, monthly thereafter until cycle 12, and every 3 months after cycle 12. Serious adverse events were considered those which resulted in death, or persistent or substantial disability or incapacity, was considered life-threatening or a significant medical event by the investigator, or required prolonged inpatient hospitalisation.

Plasma samples were obtained before treatment and at 0–5, 0–75, 1, 2, 4, and 6 h after dose on days 1 and 8. Pharmacokinetic parameters were derived from individual plasma acalabrutinib concentration–time profiles by a noncompartmental analysis using Phoenix WinNonlin (version 6.4). Bruton tyrosine-kinase occupancy by acalabrutinib was assessed in peripheral blood mononuclear cells by an ELISA-based method (appendix p 3). Absolute counts of T, B, and natural killer cells were assessed in peripheral blood from patients treated with acalabrutinib who had assessments at baseline and the respective visit. Cells were measured by flow cytometry.

The presence of MYD88L265F was established by local investigators in 50 (47%) of 106 of patients. Methods were at the discretion of local laboratories and included next-generation sequencing, Sanger sequencing, multiplex ligation-dependent probe amplification, high-resolution melting, and allele specific PCR. CXCR4 mutation status was not recorded.

Figure 1: Trial profile

*Two additional patients discontinued due to intestinal mass and oesophageal carcinoma (one each). The reasons for discontinuation were updated to disease progression (intestinal mass) and initiation of alternative cancer therapy (oesophageal carcinoma).
Outcomes

The primary endpoints were the proportion of patients achieving an investigator-assessed overall response (at least a minor response) according to the 6th International Workshop for Waldenström Macroglobulinemia (IWWM) and the modified 3rd IWWM workshop criteria.14,15

Secondary endpoints included duration of response (time from initial response at or less than minor response to progressive disease or death from any cause), progression-free survival (time from the start of acalabrutinib to the first documented progressive disease or death from any cause), overall survival (time from the start of acalabrutinib until death from any cause), the effect of acalabrutinib on peripheral T, B, and NK cell counts and serum immunoglobulin levels, pharmacokinetics, quality of life, and safety. Pharmacodynamic parameters (BTK occupancy and biological markers of B-cell function) were exploratory endpoints.

Statistical analysis

A Simon two-stage design with a cohort of 76 patients with relapsed or refractory disease provided 90% power to test the null hypothesis (an overall response of ≤35%) against the alternative hypothesis (overall response ≥55%), with a one-sided significance of 0.025. The threshold was chosen based on previous experience with rituximab and ibrutinib in patients with Waldenström macroglobulinemia.16,17

The data cutoff for the analyses presented was Feb 13, 2018. Overall response, progression-free survival, overall survival, and safety were assessed in all patients who received at least one dose of acalabrutinib. Duration of response was assessed in the activity-evaluable population, defined as treated patients who had at least one evaluable response assessment after the first dose of acalabrutinib. Time-to-event endpoints were estimated using the Kaplan–Meier method. 95% CIs were calculated using exact binomial test.

Quality of life data are presented as changes from baseline in median Global Health Status Scores with acalabrutinib treatment. We tabulated the pharmacokinetic parameters and used descriptive statistics to summarise them. For median haemoglobin and IgM analysis, we assessed baseline median values for all patients and the median of the maximum increase at the time of best response for all patients. Details of methods for exploratory analysis of pharmacodynamic parameters are in the appendix (pp 3–4). For each pharmacodynamic variable, we summarised the change from baseline to each assessment. As appropriate, the on-treatment values were compared with the pretreatment baseline values using paired t tests.

Prespecified subgroup analyses were done using baseline and disease characteristics (age [≤65 or ≥65 years], ECOG performance status [0 or ≥1], baseline haemoglobin and IgM levels, disease status [treatment-naive or previously treated], number of previous regimens received [1–3 or >3], and mutational status [MYD88WT or MYD88L265P]) in patients who had an overall response. Descriptive statistics were used to summarise data where appropriate.

### Baseline characteristics

<table>
<thead>
<tr>
<th>Treatment naive (n=14)</th>
<th>Relapsed or refractory (n=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>73 (48–86)</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>10 (71%)</td>
</tr>
<tr>
<td><strong>Female sex</strong></td>
<td>4 (29%)</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>12 (86%)</td>
</tr>
<tr>
<td>0</td>
<td>3 (21%)</td>
</tr>
<tr>
<td>1</td>
<td>9 (64%)</td>
</tr>
<tr>
<td>2</td>
<td>2 (14%)</td>
</tr>
<tr>
<td><strong>Median time since initial Waldenstrom macroglobulinemia diagnosis (range), years</strong></td>
<td>0 4 (0–5–5)</td>
</tr>
<tr>
<td><strong>Bone marrow involvement</strong></td>
<td>14 (100%)</td>
</tr>
<tr>
<td><strong>Extramedullary disease</strong></td>
<td>9 (64%)</td>
</tr>
<tr>
<td><strong>Lymphadenopathy ≥1.5 cm</strong></td>
<td>7 (58%)</td>
</tr>
<tr>
<td><strong>Splenomegaly ≥13 cm</strong></td>
<td>4 (44%)</td>
</tr>
<tr>
<td><strong>Median serum IgM (range), mg/dL</strong></td>
<td>4615 (633–7530)</td>
</tr>
<tr>
<td><strong>Median serum Ig4000 mg/dL, (range), g/dL</strong></td>
<td>9 (64%)</td>
</tr>
<tr>
<td><strong>Median absolute neutrophil count (range), cells × 10⁹/L</strong></td>
<td>3 (2–4)</td>
</tr>
<tr>
<td><strong>Haemoglobin</strong></td>
<td></td>
</tr>
<tr>
<td>Median (range), g/dL</td>
<td>10.6 (6.0–15.4)</td>
</tr>
<tr>
<td>≤1 g/dL</td>
<td>11 (79%)</td>
</tr>
<tr>
<td>&gt;1 g/dL</td>
<td>9 (64%)</td>
</tr>
<tr>
<td><strong>Median haematocrit (range), %</strong></td>
<td>31 (39–41)</td>
</tr>
<tr>
<td><strong>Median platelets (range), cells per μL</strong></td>
<td>187 000 (36 000–364 000)</td>
</tr>
<tr>
<td>&lt;100 000 cells per μL</td>
<td>2 (14%)</td>
</tr>
</tbody>
</table>

Previous therapies

| **Median time to last treatment, months (range)** | 162 (0–03–89 6) |
| **Median number of previous therapies (range)** | 2 (1–7) |
| **≥3 previous therapies** | 41 (45%) |
| **Refractory disease** | 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 with or without rituximab** | 21 (23%) |
| **Bendamustine with or without rituximab** | 18 (20%) |
| **CHOP/CVP/COP with or without rituximab** | 18 (20%) |
| **Purine analogue plus cyclophosphamide with or without rituximab** | 15 (16%) |
| **Other** | 22 (24%) |

Data are n (%) unless otherwise specified. 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, and methylprednisolone. Ig = immunoglobulin. IMD = immunomodulatory side drugs. * The remaining three patients were of indeterminant status. † Extramedullary disease was defined as lymphadenopathy (≥1.5 cm) and splenomegaly (an enlarged spleen of any size) present at baseline. ‡ Defined as best overall response rate of stable disease or progressive disease. § 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).

Table 1: Baseline characteristics
One interim analysis for futility for overall response was planned and done once the initial 28 patients enrolled had 8 weeks of evaluable activity data.

We used SAS version 9.4 for analysis. This study is registered with ClinicalTrials.gov, number NCT02180724.

Role of the funding source
The sponsor of the study had a role in the study design, data collection, analysis, and interpretation. All authors had full access to the data, reviewed the manuscript, decided to submit for publication, and vouch for the accuracy and completeness of the data reported and for adherence to the protocol. The corresponding author, with the aid of a medical communications agency, had the final responsibility to submit for publication.

Results
Between Sept 8, 2014 and Dec 24, 2015, 122 patients with Waldenström macroglobulinemia were assessed for eligibility. 16 patients were excluded (12 did not meet inclusion criteria or met exclusion criteria, and four withdrew consent). 106 patients (14 treatment naive, 92 relapsed or refractory) were enrolled (figure 1; appendix p 2). Baseline characteristics are shown in table 1. Median number of previous therapies for relapsed or refractory patients was two (range 1–7), with 41 (45%) of 92 patients having had received at least three previous therapies; 33 (36%) had refractory disease. The median time from last treatment to the first dose of acalabrutinib was 16–2 months (IQR 2–6–29–9). 13 (12%) of 106 patients received previous single-agent rituximab. 12 patients were not managed according to protocol due to the following protocol violations: two did not consent during the patient’s next consecutive visit with protocol following protocol violations: two did not consent during the patient’s next consecutive visit with protocol amendment 6.0, eight had serious adverse events not reported within 24 h, one achieved the endpoint out of statistical window, and one had uncompleted safety assessments.

At data cutoff (Feb 13, 2018), the median duration of follow-up was 27.4 months (IQR 26.0–29.7). An overall response was reported in 13 (93% [95% CI 66–100]) of 14 treatment-naive patients and 86 (93% [86–98]) of 92 relapsed or refractory patients, per both the modified 3rd and 6th IWWM criteria (figure 2A). Major response, defined as a response greater than or equal to a partial response, was recorded in 11 (79% [95% CI 49–95]) of treatment-naive patients and 72 (78% [68–86]) of relapsed or refractory patients, per the modified 3rd IWWM criteria. An overall response was achieved consistently across prespecified subgroups, including patients 65 years or older, patients with at least three previous therapies, patients with a baseline ECOG PS of at least 1, patients with low baseline haemoglobin (<110 g/L), and patients with low baseline IgM (<4000 mg/dL; figure 3).

Response by MYD88 mutational status was assessed in 50 patients who were genotyped (figure 2B): the MYD88* mutation was present in 36 (72%) patients (34 relapsed or refractory, two treatment naive), and MYD88** in 14 (28%) patients (13 relapsed or refractory, one treatment naive). Overall response was reported in 34 (94%) of 36 MYD88* patients and 11 (79%) of 14 MYD88** patients, per both criteria. Major response was reported in 28 (78% [95% CI 61–90]) of 36 MYD88* patients versus eight (57% [29–82]) of 14 MYD88** patients, per the modified 3rd IWWM criteria; no MYD88** patient had a very good partial response, whereas ten (28%) of 36 MYD88* patients did.

Figure 2: Overall response by disease and MYD88 mutational status
Assessed in all patients who received at least one dose of acalabrutinib (A) and in the 50 patients for whom the mutational status was determined by local investigators (B). IWWM=International Workshop on Waldenström Macroglobulinemia. Overall response might not equal the addition of responses because of rounding. Error bars denote 95% CIs for overall response.

Table 1. Median number of previous therapies for relapsed or refractory patients, per both the modified 3rd IWWM criteria (34 relapsed or refractory, two treatment naive), and MYD88** in 14 (28%) patients (13 relapsed or refractory, one treatment naive). Overall response was reported in 34 (94%) of 36 MYD88* patients and 11 (79%) of 14 MYD88** patients, per both criteria. Major response was reported in 28 (78% [95% CI 61–90]) of 36 MYD88* patients versus eight (57% [29–82]) of 14 MYD88** patients, per the modified 3rd IWWM criteria; no MYD88** patient had a very good partial response, whereas ten (28%) of 36 MYD88* patients did.
The median time to best response was 4.6 months (IQR 1.9–9.2). The kinetics of IgM responses were evaluated in all patients; five patients had IgM greater than 7000 mg/dL at baseline. Rapid reductions in IgM were associated with clinically meaningful improvements in haemoglobin in relapsed or refractory patients (appendix p 5). The median decline in IgM at time of best response was 2126 mg/dL (IQR 960–3160), or a 57% reduction (50–72); the maximum median increase in haemoglobin at time of best response was 1200 mg/dL (500–2300), or 12% increase (4–24). Similar results were observed in treatment naive patients (appendix p 5).

No clinically significant changes in T cell (CD3+, CD4+, CD8+), B cell (CD19+), or natural killer cell numbers were observed from baseline in relapsed refractory or treatment naive patients (appendix p 6).

Median duration of response has not been reached in either cohort (n=99), with a 24-month duration of response of 90% (95% CI 47–99) for treatment naive patients and 82% (47–99) for relapsed or refractory patients (figure 4A). The median progression-free survival and overall survival were also not reached in either cohort (figures 4B, 4C); 19 patients had progression-free survival events (one treatment naive, 18 relapsed or refractory) and 12 patients died (all relapsed or refractory patients). The 24-month progression-free survival was 90% (95% CI 47–99) in treatment naive and 82% (72–89) in relapsed or refractory patients; overall survival was 92% (54–99) in treatment-naive patients and 89% (80–94) in relapsed or refractory patients. Patients treated with acalabrutinib also showed a general improvement in EORTC QLQ-30 scores at the end of treatment compared with baseline (appendix p 8).

30 (28%) of 106 patients discontinued acalabrutinib during the study period (7 [50%] of 14 treatment naive patients and 23 [25%] of 92 relapsed or refractory patients; figure 1). 13 (12%) of the 106 patients died during the study (all causes); four (4%) died 30 days or less after the last dose of acalabrutinib (one pneumonia, one ischemic heart disease, one intracranial haematomata, and one carcinomatous peritonitis), and nine (9%) died more than 30 days after last dose of treatment (one chronic inflammatory demyelinating polyneuropathy, one oesophageal cancer, one glioabloma multiforme, and six unknown [one patient transformed to DLBCL, which could be the cause of death; median time to death 128 days, range 40–414]). Of the patients who discontinued acalabrutinib, 17 (one treatment naive, 16 relapsed or refractory) received subsequent therapy, most commonly bendamustine-rituximab (five patients; appendix p 12).

The most common adverse events of any grade were headache, diarrhoea, contusion, dizziness, fatigue, nausea, upper respiratory tract infection, constipation, and arthralgia (table 2). Headaches (41 [39%] of 106) and diarrhoea (33 [31%]) were mostly grade 1–2. The most common serious adverse events were pneumonia (seven [7%]), sepsis (seven [7%]), lower respiratory tract infection (five [5%]), pneumonia (seven [7%]), and pyrexia (four [5%]; table 2). Of the 11 patients with grade 4 neutropenia, three had a history of neutropenia (moderate or mild), seven had at least three previous therapies, and six had acalabrutinib withheld until resolution. Infections occurred in 81 (76%) of 106 patients (grade 3, 26 [25%]). The most common grade 3–4 infections were pneumonia (seven [7%]), lower respiratory tract infections (five [5%]), and cellulitis (three [3%]). One patient admitted for pneumonia (study day 522) tested positive for Aspergillus and was treated with an antifungal agent; acalabrutinib was withheld only until resolution.

Serious adverse events occurred in 56 (53%) of 106 patients. Serious adverse events occurring in at least three of the 106 patients were lower respiratory tract infection (n=7), pneumonia (n=7), pyrexia (n=4), cellulitis (n=3), fall (n=3), and sepsis (n=3). Of these most common serious adverse events, pneumonia (n=5) and...
**Number at risk**

- **Relapsed or refractory**
  - Treatment naive: 13 (0)
  - Relapsed or refractory: 86 (0)

- **Treatment naive**
  - Relapsed or refractory: 14 (0)
  - Treatment naive: 13 (0)

**Duration of response (%)**

- **Treatment naive**
  - Relapsed or refractory: 90·0% (47·3–98·5)

**Progression-free survival (%)**

- **Treatment naive**
  - Relapsed or refractory: 90·0% (47·3–98·5)

**Overall survival (%)**

- **Treatment naive**
  - Relapsed or refractory: 91·7% (53·9–98·8)
lower respiratory tract infection (n=4) were considered treatment related. The six reported fatal events (grade 5) during treatment (one patient each) were myocardial ischemia, pneumonia, glioblastoma multiforme, oesophageal carcinoma, intracranial haematoma (the patient had relapsed or refractory disease and was taking the anticoagulant apixaban at the time of the event; acalabrutinib was withheld at onset, and death occurred 21 days after the last treatment), and malignant ascites (metastatic adenocarcinoma). The intracranial haematoma was the only death considered treatment-related.

Atrial fibrillation occurred in five (5%) of 106 patients (one [7%] of 14 treatment naive patients and four [4%] of 92 relapsed or refractory patients). All events were grade 1–2, except for one (1%) grade 3 event (patient was treated with cardioversion). None of these patients had a history of atrial fibrillation, but they had at least one risk factor for atrial fibrillation, including age older than 65 years, hypertension, structural heart disease or arteriosclerotic coronary artery disease (two patients with history), second-degree AV block (one patient with history), and diabetes. Median time to the onset of atrial fibrillation was 391 days (range 29–820). No atrial fibrillation event led to acalabrutinib withholding or discontinuation. Four patients (all with relapsed or refractory disease) had atrial fibrillation before the study started, which did not worsen on study. Hypertension occurred in five (5%) patients, three events of which were grade 3. Bleeding occurred in 61 (58%) of 106 patients—most commonly contusion (31 [29%] of 106), epistaxis (12 [11%]), increased tendency to bruise (11 [10%], petechiae (nine [8%]), ecchymosis (seven [7%]), and haematoma (six [6%]). Grade 3–4 bleeding events included epistaxis (one [1%]), dysfunctional uterine bleeding (one [1%], and retinal haemorrhage (one [1%]). All grade 3–4 bleeding events were managed with dose delay and resolved.

Acalabrutinib was withheld for at least 7 days for 53 patients because of adverse events (31 [58%] of 53), procedures (16 [30%]), nonprocedures (13 [25%], including the inability to determine compliance, unreturned pill diary, and missed doses), investigator decision (4 [8%]), and patient error (3 [6%]). Serum IgM was evaluated before dose delay for 52 patients and after dose delay for 51 patients; median serum IgM was 1305 mg/dL (range 69–4490) and 1880 mg/dL (373–4820), respectively, 11 (21%) of 53 patients had IgM increases of more than 500 mg/dL during dose hold.

Adverse events leading to discontinuation of acalabrutinib occurred in seven (7%) of the 106 patients; events (one each) were acute coronary artery disease, Crohn disease reactivation, increased aminotransferase, cold-type haemolytic anaemia, glioblastoma multiforme and seizure (in the same patient), malignant ascites, and metastatic malignant melanoma. Two additional patients discontinued due to intestinal mass and oesophageal carcinoma (one each). The reasons for discontinuation were updated to disease progression (intestinal mass) and initiation of...
alternative cancer therapy (oesophageal carcinoma). The treatment discontinuations because of coronary artery disease, cold-type haemolytic anaemia, Crohn disease, and increased amino transferase were considered treatment-related. Adverse events leading to dose reduction to 100 mg once per day occurred in five (5%) of the 106 patients. Adverse events resulting in dose withholding occurred in 57 (54%) of the 106 patients. Most events resolved on dose reduction and dose withholding (data not shown).

Regarding pharmacokinetics, rapid absorption and elimination of acalabrutinib was observed, with minimal potential for accumulation (appendix p 9). Acalabrutinib exposure was similar in treatment naive and relapsed or refractory patients (appendix p 13). At steady state (day 8), the median Bruton tyrosine kinase occupancy in peripheral blood mononuclear cells with 100 mg twice per day acalabrutinib ranged from 96% to 98% throughout the dosing interval (appendix p 9). Of the 14 patients evaluated at steady state, 13 had more than 90% Bruton tyrosine kinase occupancy at trough (12 h after dose), with low interpatient variability. Significant inhibition of basal phosphorylated Bruton tyrosine-kinase by acalabrutinib was observed at all timepoints (n=17; appendix p 9).

Discussion
This phase 2, single-arm, multicentre study is, to our knowledge, the first prospective study of acalabrutinib in patients with Waldenström macroglobulinemia, and the largest prospective study in these patients to date. As understanding of the aberrant signalling in Waldenström macroglobulinemia has improved, Bruton tyrosine kinase inhibitors have shown an increasingly important role in Waldenström macroglobulinemia treatment. With a median follow-up of over 2 years, acalabrutinib was associated with a high overall response per the modified 3rd IWWM criteria, similar for relapsed or refractory (93% [95% CI 86–98]) and treatment naive patients (93% [66–100]). Our results provide evidence of the single-agent activity of acalabrutinib, irrespective of the line of therapy, age, or baseline IgM or haemoglobin concentrations.

The responses observed for acalabrutinib are consistent with those reported for ibrutinib monotherapy in relapsed or refractory patients (overall response 91% [95% CI 80–96] per the 3rd IWWM criteria; n=63) and treatment naive patients (overall response 100% [95% CI not reported] per the 6th IWWM criteria; n=30) with similar follow-up times. Median duration of response, progression-free survival, and overall survival for acalabrutinib were not reached, but seemed similar to those reported for ibrutinib with or without rituximab. The quality of life improvement suggested with acalabrutinib further contributes to its treatment value in patients with Waldenström macroglobulinemia.

Clinically meaningful responses were also documented for patients with MYD88WT. These data contrast with those of ibrutinib; Treon and colleagues did not report major responses in five patients with MYD88WT. These apparent differences are difficult to explain given that a study has suggested that MYD88WT disease is associated with NFKB activating mutations downstream of Bruton tyrosine-kinase.

Discussion
These data are, however, encouraging and merit further study. In the iNNOVATE study, meaningful clinical responses (overall response 81% [95% CI not reported]; major response 63% [95% CI not reported]) were documented in MYD88WT patients, but it is unclear whether this reflects the additive effect of rituximab or the nonstandard genomic profiling method used. Similarly, it is noteworthy that major responses (including very good partial response) have been reported with zanubrutinib.

The adverse events reported are consistent with the known safety profile of acalabrutinib, with low atrial fibrillation, hypertension, and grade 3–4 bleeding. For ibrutinib, adverse events grade 2 or higher resulted in treatment discontinuation, and are observed at a rate of approximately 5–10% for atrial fibrillation, 5–13% for hypertension, and 6% for major bleeding events in patients with Waldenström macroglobulinemia. Grade 3–4 atrial fibrillation (12%) and hypertension (13%) were also common with ibrutinib and rituximab, so therapeutic options with a lower risk of one or more of these adverse events would improve clinical outcomes.

Additional limitations of this study include it being a small, single arm study, and the absence of quantitative bone marrow burden assessments and assessments of the proportion of eligible patients who declined chemotherapy versus those who were ineligible, and lack of data on response to previous therapies.

In summary, we report that acalabrutinib monotherapy shows durable responses and manageable toxicity in treatment naive and relapsed or refractory patients with Waldenström macroglobulinemia. Clinical benefit was also noted in some patients with MYD88WT although additional substantiation is required. Single-agent acalabrutinib represents a valid treatment option for patients with relapsed or refractory disease; however, further studies are needed to establish whether outcomes can be improved with combination strategies. Randomised trials versus rituximab-based chemotherapy are warranted in the upfront setting to determine its efficacy.

Contributors
RGO, HM, SR, SD, TA-S, SKT, SI, BDC, FF, PLZ, MJK, RI, MCM, HW, OT, D-YC, SKL, PP, RRF, DM, MMF, EK, AH, and DG wrote and approved the manuscript. MJK, RI, FF, PLZ, MCM, HW, and RRF collected data. MJK, RI, FF, D-YC, SKI, PP, HW, RRF, DM, MMF, EK, and...
Articles

PLZ interpreted the data. D-YC, SKL, PP, HW, RRF, DM, MMF, and EK analysed the data. MJK and RI designed the study. AH was responsible for study design and implementation. JK was responsible for accrual of patients into the clinical trial, manuscript development and editing, and approval of the final manuscript. OT was responsible for patients’ recruitment and care, and national coordination on behalf of the Lysa Group. DM and MMF did the literature search. DM provided figure S1C.

Declaration of interests

FF reports personal fees from Roche and personal fees and nonfinancial support from AbbVie, outside the submitted work. MJK reports research support from Celgene, Takada, and Roche and travel grants, honoraria, or advisory boards from Novartis, Kite/Gilead, Roche, BMS, MSD, Amgen, Janssen/Cilag, and Celgene. PLZ reports grants from Roche, Celgene, MSD, Verastem, [J], and Servier, outside the submitted work. MCM reports other from Servier, grants from Celgene, other from Janssen Cilag, and other from Takeda, outside the submitted work. HW reports other from Acerta Pharma during the study. DG reports personal fees from Genentech/Roche, outside the submitted work. OT reports personal fees from Janssen, personal fees from Gilead, grants and personal fees from Amgen, personal fees from Celgene, and personal fees from AbbVie, outside the submitted work. RI reports other from Acerta Pharma, during the study; in addition, RI has a patent personal fees from AbbVie, outside the submitted work. MJK reports research support from Celgene, Takada, and Roche and travel grants, honoraria, or advisory boards from Novartis, Kite/Gilead, Roche, BMS, MSD, Amgen, Janssen/Cilag, and Celgene. PLZ reports grants from Roche, Celgene, MSD, Verastem, [J], and Servier, outside the submitted work. MCM reports other from Servier, grants from Celgene, other from Janssen Cilag, and other from Takeda, outside the submitted work. HW reports other from Acerta Pharma during the study. DG reports personal fees from Genentech/Roche, outside the submitted work. OT reports personal fees from Janssen, personal fees from Gilead, grants and personal fees from Amgen, personal fees from Celgene, and personal fees from AbbVie, outside the submitted work. RI reports other from Acerta Pharma, during the study; in addition, RI has a patent pending for bruton tyrosine-kinase inhibitors. DM is an employee of Acerta Pharma and has equity ownership in Acerta Pharma. PP reports other from Acerta Pharma, during the study; other from Acerta Pharma; and other from AstraZeneca, outside the submitted work. SKL reports personal fees from Acerta Pharma, during the study. RRF reports grants and personal fees from Acerta, personal fees from AbbVie, personal fees from Gilead, personal fees from Genentech, personal fees from Incyte, personal fees from Janssen, personal fees from Loxo Oncology, personal fees from Pharmacyclics, personal fees from Sunesis, personal fees from TG Therapeutics, and personal fees from Verastem, outside the submitted work. EK reports grants and personal fees from Amgen, personal fees from Genesis Pharma, grants and personal fees from Janssen, and personal fees from Takeda, during the study. RGO reports personal fees from Celgene, personal fees from Janssen, and personal fees from Pharmacyclics during the study. SR reports grants and personal fees from Janssen, personal fees from the Eighth International Workshop on Waldenstrom’s Macroglobulinemia: update of pivotal clinical trial. [J Haematol 2013; 160: 171–76.


