Expert Review of Hematology

ISSN: 1747-4086 (Print) 1747-4094 (Online) Journal homepage: http://www.tandfonline.com/loi/ierr20

Use of acalabrutinib in patients with mantle cell lymphoma

Farrukh T. Awan & Wojciech Jurczak

To cite this article: Farrukh T. Awan & Wojciech Jurczak (2018): Use of acalabrutinib in patients with mantle cell lymphoma, Expert Review of Hematology, DOI: 10.1080/17474086.2018.1473030

To link to this article: https://doi.org/10.1080/17474086.2018.1473030

Accepted author version posted online: 08 May 2018.

Publisher: Taylor & Francis

Journal: *Expert Review of Hematology*

DOI: 10.1080/17474086.2018.1473030

Use of acalabrutinib in patients with mantle cell lymphoma

Farrukh T. Awan,[1] Wojciech Jurczak[2]

1. Department of Internal Medicine, Division of Hematology, The Ohio State University Wexner Medical Center, Columbus, OH, USA;
2. Department of Hematology, Jagiellonian University, Krakow, Poland

Corresponding author:
Farrukh T. Awan, M.D.,
320W 10th Avenue,
Columbus,
OH 43220,
USA.
Email: Farrukh.awan@osumc.edu

Abstract

Introduction: Acalabrutinib, a selective, Bruton tyrosine kinase (BTK) inhibitor, was granted accelerated approval by the FDA on 31 October 2017 for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Areas covered: This narrative review provides an overview of acalabrutinib, its use in clinical practice and potential future developments.

Expert commentary: BTK inhibitors have demonstrated efficacy in patients with relapsed or refractory MCL. To prepare patients for therapy, all preexisting infections should be diagnosed and treated, and infection prophylaxis undertaken. Serious adverse reactions are rare with acalabrutinib; however, patients should be made aware of common adverse events such as headaches, which usually resolve within one month without medical treatment. Interaction with other drugs appears to be less of an issue with acalabrutinib than with ibrutinib; however, patients receiving acalabrutinib therapy must be advised not to take any additional medications without first consulting with their treating physician. A key unmet medical need is treatment options for patients in whom BTK inhibitors are discontinued, because of either intolerance or refractory disease. Patients not tolerating ibrutinib could be switched to acalabrutinib, which has improved selectivity and increased tolerability. First-line treatment with acalabrutinib is being investigated.

Keywords: acalabrutinib; adverse events; B-cell malignancies; Bruton tyrosine kinase inhibitor; efficacy; mantle cell lymphoma

1. Introduction

Mantle cell lymphoma (MCL) is an aggressive B-cell non-Hodgkin lymphoma with a generally poor prognosis [1,2]. Signaling through the B-cell receptor (BCR) drives antigen-dependent B-cell maturation and adaptive immune responses. In MCL, as with other B-cell malignancies, BCR signaling via antigen stimulation or mutation supports survival, proliferation and migration of malignant cells [3-6]. Amplified BCR activity is linked to increased MCL tumor proliferation and identifies patients with MCL with inferior survival, suggesting a link between BCR activation and disease progression [7,8]

Bruton tyrosine kinase (BTK) is a key component of the signalosome that forms as part of the BCR pathway cascade, and is critical for the transduction and amplification of signals from the BCR (Figure 1) [6,9,10]. When antigen binds the membrane immunoglobulin portion of the BCR, the resulting conformational change induces phosphorylation of the immunoreceptor tyrosine-based action motifs, and causing the recruitment of BTK and other signalosome components [6,9,10]. BTK is named after the pediatrician Ogden Bruton, who first described a case of X-linked agammaglobulinemia, a primary immunodeficiency that has since been linked to mutations in the BTK gene [9]. The essential role of BTK in MCL cell activation, proliferation and survival makes its inhibition a compelling therapeutic strategy.

2. Acalabrutinib overview

Acalabrutinib is a highly selective, potent inhibitor of BTK [3,10,11]. Acalabrutinib has a butynamide moiety that covalently binds Cys-481 in the ATP binding pocket of BTK, thereby blocking BCR signaling through BTK [3,12]. The US Food and Drug Administration (FDA) granted accelerated approval to acalabrutinib on October 31, 2017 for the treatment of patients with MCL who have received at least one prior therapy [13,14]. Acalabrutinib is also in clinical development for the treatment of other hematological malignancies, including chronic lymphocytic leukemia (CLL) [3,15], and is included in the US National Comprehensive Cancer Network (NCCN) guidelines as a treatment option for relapsed or refractory CLL [16].

Initial evidence for BTK as a clinically valid target in MCL came from small-molecule BTK inhibitors such as ibrutinib, BGB-3111, M7583 and GS-4059, which bind to the BTK ATP binding pocket, thereby blocking BTK auto-phosphorylation [12]. Given its efficacy in patients with relapsed disease, ibrutinib received accelerated approval by the FDA

in 2013 for patients with MCL who have received at least one prior therapy [17-19]. In Europe, indications for ibrutinib as a single agent include the treatment of adult patients with relapsed or refractory MCL [20]. The SHINE study of ibrutinib in combination with bendamustine and rituximab in patients with newly diagnosed MCL is ongoing (NCT01776840), with primary completion expected in the near future. Resistance to ibrutinib remains a challenge, brought about largely by BTK kinase domain mutations, predominantly Cys-481 substitutions, that are selected for during therapy and that subsequently prevent ibrutinib from binding to BTK [21]. In the pivotal acalabrutinib phase 2 trial in patients with previously-treated CLL, only one patient who progressed on therapy with acalabrutinib had a new Cys-481 mutation at the time of data analysis [3].

There are differences in the selectivity profiles of acalabrutinib and ibrutinib, which can be explained by the different reactivities of their respective BTK binding moieties. Acalabrutinib's butynamide-based binding motif possesses a reduced intrinsic reactivity that minimizes inhibition of off-target kinases, compared with ibrutinib's more reactive acrylamide-based BTK binding motif [12]. In addition to BTK, ibrutinib also irreversibly binds several other kinases, and this additional activity may underlie the overall side-effect profile observed with ibrutinib [19,22-24]. This hypothesis is further supported by the range of side effects reported in ibrutinib clinical studies but that are not typically observed in patients who are BTK-deficient, including rash, diarrhea, blurred vision, atrial fibrillation, arthralgias/myalgias, bruising/ecchymosis and major hemorrhage (including subdural hematomas) [19,22-25].

Acalabrutinib has been developed to minimize off-target activity. Pre-clinical data demonstrate that non-BTK kinases, including epidermal growth factor receptor (EGFR), tyrosine kinase expressed in hepatocellular carcinoma (Tec), interleukin-2 inducible T-cell kinase (Itk) and T cell X chromosome kinase (Txk), which have been associated with adverse effects with ibrutinib, are not functionally inhibited by acalabrutinib (Figure 2) [12]. Tec and some SRC family kinases have a role in the modulation of platelet activation, and the inhibition of these kinases by ibrutinib may contribute to the increased risk of severe bleeding reported in patients treated with ibrutinib [12]. Furthermore, in an *in vivo* thrombus formation model, blood platelets from patients who received acalabrutinib had similar reactivity to platelets from untreated, healthy volunteers, whereas blood platelets from patients receiving ibrutinib showed diminished aggregation [3,11].

The aim to limit off-target kinase inhibition and associated side effects seen with ibrutinib is also guiding the further development of BTK inhibitors such as BGB-3111 and GS-4059, which are in the early stages of clinical development for B-cell malignancies [21].

3. Clinical use of acalabrutinib: dosing and administration

Dosing for acalabrutinib is 100 mg twice daily, about 12 hours apart [13]. In healthy volunteers, complete BTK occupancy was observed at both 3 hours and 12 hours after a single acalabrutinib 100 mg dose, correlating with near-complete inhibition of BCR-induced response for the same time points [12]. In a phase 1/2 study in patients with CLL, individuals treated with acalabrutinib 100 mg twice daily had a median BTK occupancy of 99% at 4 hours post-dose and 97% at trough (pre-dose/12 hours post-dose) at steady-state (treatment day 8) (Figure 3a) [3]. In comparison, in patients receiving acalabrutinib 200 mg once daily, median BTK occupancy at trough (24 hours post-dose) was 92% ($p < 0.01$) (Figure 3b) [26]. In addition to maintaining high target coverage over each dose interval, the twice-daily dosing regimen also led to lower inter-patient variability (6.5%, compared with 16.4% with once-daily dosing), and 95% of patients treated with the twice-daily regimen achieved a BTK occupancy rate of 90% or higher at trough, compared with only 66% of patients treated with the once-daily regimen (Figure 3b) [26]. Patients with MCL and other B-cell malignancies are expected to have increased rates of B-cell proliferation and BTK synthesis that vary across patients. Twice-daily dosing, about 12 hours apart, maintains complete and continuous BTK inhibition across the 24-hour dosing interval, with no increased toxicities from inhibition of other kinases, thus providing improved assurance of clinical effect.

Pharmacokinetic data show that, compared with ibrutinib, acalabrutinib has plasma concentrations that are more stable and less dependent on meals and lymphoma subtype. Acalabrutinib 100 mg twice daily in patients with CLL resulted in a steady state mean maximum plasma concentration (C_{max}) of 827 ng/mL, an area under the plasma concentration–time curve from 0 to 24 hours ($AUC_{0–24\,h}$) of 1850 h·ng/mL and a mean terminal half-life of 0.6 hours [3]. The short half-life of acalabrutinib means that there is no issue around accumulation in blood. For ibrutinib, which is dosed at 560 mg once daily in patients with MCL and 420 mg once daily in patients with CLL [17], exposure was shown to depend on fasting state: administration of 420 mg once daily during fasting versus in close proximity to a meal resulted in a mean C_{max} of 52 and 120 ng/mL, $AUC_{0–24\,h}$ of 485 and 864 h·ng/mL, and terminal half-life of 11 and 4.5 hours, respectively, in patients with CLL [27].

These results suggest that the increased tolerability of acalabrutinib therapy compared with ibrutinib occurs despite a higher drug exposure with acalabrutinib than with ibrutinib, although a definitive comparison of doses cannot be made because of differences in the compounds [3,27].

Co-administration of acalabrutinib with strong CYP3A inhibitors or with proton pump inhibitors should be avoided [13].

4. Published clinical data for acalabrutinib

Positive results from an open-label phase 2 trial in patients with previously-treated MCL (NCT02213926 [ACE-LY-004]; N = 124) led to acalabrutinib being granted Breakthrough Therapy Designation and subsequently accelerated approval by the FDA in August and October 2017, respectively, for patients with previously-treated MCL. In that trial, acalabrutinib 100 mg twice daily achieved an overall response rate (ORR) of 81%, including 40% complete response and 41% partial response, at a median follow-up of 15.2 months [14,28].

Unfortunately, there are currently no data available from any head-to-head studies comparing clinical efficacy of acalabrutinib and ibrutinib, and it is thus not possible to establish a direct comparison between the two treatments. For historical comparison, in a previous phase 2 study of ibrutinib 560 mg daily in patients with relapsed or refractory MCL, ORR was 68% at a median follow-up of 15.3 months [18]. Patients in the ibrutinib trial were more heavily pretreated than those in the acalabrutinib trial (median number of prior therapies: 3 vs 2, respectively), which may explain, in part, the differences in ORR observed in the two trials [14,18].

Clinical data have been reported for acalabrutinib in patients with CLL. In a phase 1/2 clinical study that also included individuals with Richter syndrome or prolymphocytic leukemia (ACE-CL-001; estimated total N = 286) [3,4,29], acalabrutinib monotherapy (100–400 mg once daily in the dose-escalation part of the study, and 100 mg twice daily thereafter) provided effective treatment for patients with relapsed CLL (n = 60 evaluable), with an ORR of 95% at a median follow-up of 14.3 months [3]. In the 18 patients with del(17)(p13.1), the ORR was 100%. In patients with treatment-naïve CLL enrolled in ACE-CL-001 (n = 72 evaluable), acalabrutinib achieved an ORR of 96% at a median follow-up of 10.5 months [4]. Acalabrutinib was well tolerated even in those patients with CLL enrolled in ACE-CL-001 who were ibrutinib intolerant (n = 33) [29]. Only 36% of patients experienced a recurrence of

a prior ibrutinib-related adverse event, most of which were decreased or the same severity as the original event, and no patients discontinued acalabrutinib because of a recurrent adverse event. The activity of acalabrutinib in ibrutinib-intolerant patients was promising, with an ORR of 79%.

5. Acalabrutinib clinical development

In total, 13 clinical trials of acalabrutinib for the treatment of MCL and chronic lymphocytic leukemia (CLL) are underway or complete (Table 1). The dose escalation and pharmacokinetic characteristics of acalabrutinib were assessed in two trials initiated in 2014 (NCT02029443, NCT02157324). Acalabrutinib as monotherapy was examined in patients with relapsed or refractory MCL in ACE-LY-004 (NCT02213926) [14]. Two subsequent trials (NCT02717624, NCT02972840) are assessing acalabrutinib in combination with bendamustine plus rituximab in patients with treatment-naïve, relapsed or refractory MCL. Several trials are assessing acalabrutinib as monotherapy or combination therapy in different patient populations with CLL (Table 1).

Although necessary for registration, trials conducted as part of acalabrutinib clinical development will not be able to compare directly the efficacy and safety of acalabrutinib over other BTK inhibitors, such as ibrutinib, or inositol-trisphosphate 3-kinase (PI3K) inhibitors, such as idelalisib. To address this question, a phase 3 non-inferiority trial directly comparing acalabrutinib with ibrutinib has been initiated for patients with relapsed or refractory CLL and presence of del(11q) and/or del(17p) (NCT02477696; estimated N = 500).

6. Adverse event monitoring and management

BTK inhibitors offer advantages over other therapeutic options in terms of their overall adverse event profiles. For acalabrutinib in MCL, the most common adverse events in the ACE-LY-004 trial (median follow-up: 15.2 months) were headache (38% [≥ grade 3: 2%]), diarrhea (31% [≥ grade 3: 3%]), fatigue (27% [≥ grade 3: 1%]) and myalgia (21% [≥ grade 3: 1%]) [14,28]. For historical comparison, in the phase 2 study of ibrutinib 560 mg daily in patients with relapsed or refractory MCL (median follow-up: 15.3 months) the most common adverse events were diarrhea (50% [≥ grade 3: 6%]), fatigue (41% [≥ grade 3: 5%]), nausea (31% [≥ grade 3: 0%]) and peripheral edema (28% [≥ grade 3: 2%])[18].

Most side effects both with acalabrutinib and with ibrutinib are grade 1/2, including diarrhea and upper respiratory tract infections, which frequently resolve over time during treatment continuation. There are some differences between acalabrutinib and ibrutinib in terms of adverse event profiles: most notably, atrial fibrillation and grade 3 or higher bleeding events are seen more commonly with ibrutinib, and headache has been reported more commonly with acalabrutinib [3,4,29]. No cases of atrial fibrillation and one case of bleeding of grade 3 or higher were reported in the ACE-LY-004 trial [14,28]. No cases of atrial fibrillation or major haemorrhage have been reported to date in the relapsed and treatment-naïve CLL cohorts in the ACE-CL-001 trial; two patients in the ibrutinib-intolerant cohort experienced atrial fibrillation deemed not related to study treatment [3,4,29]. In a pooled analysis of acalabrutinib safety data from seven clinical trials in hematological malignancies, atrial fibrillation of any grade was reported in 2.3% of patients, with most events occurring in patients with known risk factors [30]. Grade 3 or higher hemorrhage, serious adverse event and/or any grade or seriousness of central nervous system hemorrhage was reported in 2.5% of patients [30]. In comparison, 5% of patients with relapsed CLL treated with ibrutinib experienced grade 3 or higher bleeding events [19], while 6% of patients with previously untreated CLL experienced atrial fibrillation and 4% experienced major hemorrhage [31]. With longer follow-up (median: 26.7 months), half of all patients with MCL treated with ibrutinib experienced bleeding events (≥ grade 3: 6%) and 11% experienced atrial fibrillation (≥ grade 3: 6%) [25,32]. A pooled analysis of ibrutinib clinical trial data showed multiple atrial fibrillation events to be more common with ibrutinib than with comparator therapy; most events developed de novo in patients without a history of atrial fibrillation [33]. Longer follow-up with acalabrutinib is needed to understand if and how the rates of atrial fibrillation and bleeding evolve.

Patients receiving BTK inhibitor therapy should be monitored for signs of bleeding and the benefit–risk of withholding treatment in the days around any planned surgery should be considered. Patients should also be monitored for atrial fibrillation and managed as appropriate. Hypertension is relatively common, and patients receiving BTK inhibitor therapy should be monitored and, if necessary, treated for hypertension.

Headache is one of the most commonly reported adverse events with acalabrutinib, with the majority of patients experiencing it as a grade 1/2 event [3,4,14,28,30]. In most patients receiving acalabrutinib therapy, headache was transient (first 2–3 weeks only), did not recur and was self-limiting, responding well to over-the-counter medications such as acetaminophen or caffeinated drinks.

Serum immunoglobulins, which may have a protective effect against infections, remained relatively stable in patients with CLL treated with acalabrutinib as well as in patients with MCL treated with ibrutinib, although slightly raised post-baseline levels of immunoglobulin A were observed in some ibrutinib-treated patients with CLL [3,19,32]. Cases of fungal infection, in particular with aspergillosis, have been described early on after starting ibrutinib therapy [34]. In the pooled analysis of acalabrutinib clinical trial safety data in hematological malignancies (N = 610), four cases of opportunistic fungal infection were reported [30]. The rate of thrombocytopenia of grade 3 or higher was 8% with acalabrutinib monotherapy in a pooled analysis of clinical trial data from 612 patients with hematological malignancies [13]. Rates of at-least grade 3 thrombocytopenia reported for patients with B-cell malignancies treated with ibrutinib monotherapy were in the range of 5–17% [17].

7. Conclusion

BTK inhibitors are approved for the treatment of adult patients with relapsed or refractory MCL and are regarded as a current standard of care. Safer, more selective medications such as acalabrutinib may potentially increase response rates and other important clinical outcomes. Further data and investigation are, however, required to support this point. Improved tolerability could result in improved adherence, better efficacy and lower incidence of resistance.

8. Expert commentary

BTK inhibitors have demonstrated efficacy in patients with relapsed or refractory MCL, with high rates of complete remission, and reasonable rates of progression-free and overall survival. However, they do not offer a cure and thus need to be taken chronically, with discontinuation resulting in disease relapse. Preventing development of resistance remains an unmet medical need.

BTK inhibitors are potent drugs that impair B cell immunity. It is, therefore, crucial to prepare patients for therapy by diagnosing and treating all preexisting infections, and to consider infection prophylaxis based on medical history and local preferences. Serious adverse reactions are rare with acalabrutinib; however, it is important to ensure that patients are aware of common adverse events such as headaches, which usually resolve within one month without any medical treatment. Interaction with other drugs is less of an issue with acalabrutinib than with ibrutinib; however, patients receiving acalabrutinib therapy must be

cautioned not to take any additional medications without first consulting with their treating physician. Patients should also be counseled about the importance of treatment adherence.

Regarding future research goals, the primary aim of most industry-sponsored trials is registration of the new agents, while identifying their optimal use in clinical practice is usually left to international working groups or other non-commercial organizations. We still do not know the optimal way to use BTK inhibitors. Present trial designs are to add ibrutinib or acalabrutinib to existing chemotherapy protocols, such as bendamustine plus rituximab, although we do not know whether cytostatic agents are at all necessary, and whether or not anti-CD20 antibodies or BCL2 inhibitors will potentiate the effects of BTK inhibitor therapy. The abundance of new drugs means that there are now even more potentially effective therapeutic combinations. Checking all possible synergistic combinations is simply not feasible. Studying combinations with immunomodifying drugs such as lenalidomide or anti-PD1 therapeutics is an interesting area of research.

9. Five-year view

Targeted therapy is regarded as standard of care in relapsed or refractory MCL and is recommended in the 2017 ESMO guidelines [35]. Ibrutinib induces responses in a higher proportion of patients than lenalidomide (complete response and partial response – ibrutinib: 21% and 47%, respectively; lenalidomide: 5% and 35%, respectively); however, these are not durable with either treatment, with median progression-free survival being 13.6 months and 8.7 months, respectively [18,32,36]. In patients responding to ibrutinib and lenalidomide, the median duration of response is similar – 17.5 months and 16 months, respectively – indicating a prolonged immunomodulatory effect.

The biggest unmet medical need is treatment options for patients in whom BTK inhibitors need to be discontinued, either because of intolerance or because of refractory disease. Despite the initial success of ibrutinib as monotherapy for relapsed or refractory MCL, with a response rate of 68% in the phase 2 study [18], primary or acquired ibrutinib resistance remains a challenge [37]. Patients with MCL who progress following treatment with ibrutinib experience de novo resistance, and incomplete and short responses to salvage therapies [38]. Patients refractory to ibrutinib have a poor prognosis, with an average overall survival of 2.9 months [39]. Twelve-month overall survival was 87% with acalabrutinib in the ACE-LY-004 trial [14,28], but nevertheless we think it appears doubtful that patients with ibrutinib-refractory MCL would respond to acalabrutinib. Other targeted small molecules

may in future provide treatment options for patients responding to neither ibrutinib nor acalabrutinib. A trial investigating first-line treatment with acalabrutinib, designed similarly to SHINE, is ongoing, but we do not yet know the SHINE trial results or if bendamustine is at all necessary in this setting. Even though improved progression-free survival is to be expected with first-line acalabrutinib, we think it unlikely that patients with MCL would be cured with this approach, and once their disease becomes refractory, we are back to the unmet medical need.

In terms of interesting areas of research, in our opinion a potential future option could be for patients responding to BTK inhibitors to undergo allogeneic stem cell transplant. Performing the procedures in patients with complete response would allow for a good efficacy of transplants, with reduced intensity conditioning. BTK inhibitors may also serve as a bridge-to-transplant in the allogeneic hematopoetic cell transplant setting [40,41]. Additionally, one may speculate about the feasibility of restarting BTK inhibitor therapy after the engraftment, with the purpose of keeping the disease in remission before the transplant is fully immunologically competent to take over. Using this approach, we have treated a couple of patients with CLL at the Jagiellonian University Department of Haematology, and they are doing well.

10. Key issues

- Mantle cell lymphoma (MCL) is an aggressive B-cell non-Hodgkin lymphoma with a generally poor prognosis
- The Bruton tyrosine kinase (BTK) inhibitor acalabrutinib is approved for the treatment of patients with previously treated MCL and is also in clinical development for the treatment of other hematological malignancies, including chronic lymphocytic leukemia.
- The biggest unmet medical need is treatment options for patients in whom BTK inhibitors need to be discontinued, either because of intolerance or because of refractory disease.
- Acalabrutinib is a highly selective, potent Bruton tyrosine kinase inhibitor with minimal off-target activity that is approved for the treatment of patients with previously treated MCL and is also in clinical development for the treatment of other hematological malignancies, including chronic lymphocytic leukemia (CLL).
- Side effects are mostly of grade 1/2, including headache and diarrhea, which frequently resolve over time during treatment continuation.

Funding

This work was supported by AstraZeneca (Wilmington, DE, USA).

Declaration of interest

FT Awan has served in an advisory role for Pharmacyclics, Gilead, Abbvie and has received research funding from Pharmacyclics and Innate Pharma. W Jurczak has received grants from Acerta, Janssen, Merck, Gilead, TG Therapeutics, Sandoz, Pfizer and Takeda. Anja Becher, PhD, of Oxford PharmaGenesis, Oxford, UK, provided medical writing support, which was in accordance with Good Publication Practice (GPP3) guidelines and funded by AstraZeneca (Wilmington, DE, USA). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as:

** of interest*

*** of considerable interest*

1. Cheah CY, Seymour JF, Wang ML. Mantle cell lymphoma. J Clin Oncol. 2016;34:1256–1269.
2. Hoster E, Klapper W, Hermine O *et al.* Confirmation of the mantle-cell lymphoma International Prognostic Index in randomized trials of the European Mantle-Cell Lymphoma Network. J Clin Oncol. 2014;32:1338–1346.
3. Byrd JC, Harrington B, O'Brien S *et al.* Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016;374:323–332.

   ****A pivotal trial of acalabrutinib in patients with CLL.**
4. Byrd JC, Jones JA, Furman RR *et al.* Acalabrutinib, a second generation Bruton tyrosine kinase (Btk) inhibitor, in previously untreated chronic lymphocytic leukemia (CLL). J Clin Oncol. 2016;34 (suppl; abstr 7521)
5. Slupsky JR. Does B cell receptor signaling in chronic lymphocytic leukaemia cells differ from that in other B cell types? Scientifica (Cairo). 2014;2014:208928.
6. Woyach JA, Johnson AJ, Byrd JC. The B-cell receptor signaling pathway as a therapeutic target in CLL. Blood. 2012;120:1175–1184.
7. Cinar M, Hamedani F, Mo Z, Cinar B, Amin HM, Alkan S. Bruton tyrosine kinase is commonly overexpressed in mantle cell lymphoma and its attenuation by ibrutinib induces apoptosis. Leuk Res. 2013;37:1271–1277.
8. Saba NS, Liu D, Herman SE *et al.* Pathogenic role of B-cell receptor signaling and canonical NF-kappaB activation in mantle cell lymphoma. Blood. 2016;128:82–92.
9. Ponader S, Burger JA. Bruton's tyrosine kinase: from X-linked agammaglobulinemia toward targeted therapy for B-cell malignancies. J Clin Oncol. 2014;32:1830–1839.
10. Smith CI. From identification of the BTK kinase to effective management of leukemia. Oncogene. 2017;36:2045–2053.
11. Wu J, Zhang M, Liu D. Acalabrutinib (ACP-196): a selective second-generation BTK inhibitor. J Hematol Oncol. 2016;9:21.
12. Barf T, Covey T, Izumi R *et al.* Acalabrutinib (ACP-196): a covalent Bruton tyrosine kinase (BTK) inhibitor with a differentiated selectivity and in vivo potency profile. J Pharmacol Exp Ther. 2017;[Epub ahead of print]

13. AstraZeneca Pharmaceuticals LP. Calquence (acalabrutinib) prescribing information. Available at: https://www.calquence.com. Accessed 3 Nov 2017.
14. Wang M, Rule S, Zinzani PL *et al.* Acalabrutinib in relapsed or refractory mantle cell lymphoma: a single-arm, multicenter, phase 2 trial. 2018;391:659–667.

****A pivotal trial of acalabrutinib in patients with MCL.**

15. Byrd JC, Wierda WG, Schuh A *et al.* Acalabrutinib monotherapy in patients with relapsed/refractory chronic lymphocytic leukemia: updated results from the phase 1/2 ACE-CL-001 study. Blood. 2017;130:498 (abstract).
16. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: chronic lymphocytic leukemia/small lymphocytic lymphoma. NCCN Evidence Blocks Version 5.2018. Available at NCCN.org. Accessed 10 April 2018
17. Pharmacyclics & Janssens Biotech. Imbruvica (ibrutinib) prescribing information. Available at: https://www.janssenmd.com/pdf/imbruvica/imbruvica_pi.pdf. Accessed 11 Sep 2017.
18. Wang ML, Rule S, Martin P *et al.* Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013;369:507–516.

****A pivotal trial of ibrutinib in patients with MCL.**

19. Byrd JC, Furman RR, Coutre SE *et al.* Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013;369:32–42.

****A pivotal trial of ibrutinib in patients with CLL.**

20. electronic Medicines Compendium (eMC). Imbruvica 140 mg hard capsules. Last updated on eMC 30 Aug 2017. Available at: https://www.medicines.org.uk/emc/medicine/29383. Accessed 11 Sep 2017.
21. Wu J, Liu C, Tsui ST, Liu D. Second-generation inhibitors of Bruton tyrosine kinase. J Hematol Oncol. 2016;9:80.
22. Byrd JC, Brown JR, O'Brien S *et al.* Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371:213–223.
23. O'Brien S, Furman RR, Coutre SE *et al.* Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial. Lancet Oncol. 2014;15:48–58.
24. O'Brien S, Jones JA, Coutre SE *et al.* Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. Lancet Oncol. 2016;17:1409–1418.

25. Wiczer TE, Levine LB, Brumbaugh J *et al.* Cumulative incidence, risk factors, and management of atrial fibrillation in patients receiving ibrutinib. Blood Adv. 2017;1:1739–1748.
26. Covey T, Gulrajani M, Cheung J *et al.* Pharmacodynamic evaluation of acalabrutinib in relapsed/refractory and treatment-naive patients with chronic lymphocytic leukemia (CLL) in the phase 1/2 ACE-CL-001 study. Blood. 2017;130:1741 (abstract).
27. de Jong J, Sukbuntherng J, Skee D *et al.* The effect of food on the pharmacokinetics of oral ibrutinib in healthy participants and patients with chronic lymphocytic leukemia. Cancer Chemother Pharmacol. 2015;75:907–916.
28. Wang M, Rule S, Zinzani PL *et al.* Efficacy and safety of acalabrutinib monotherapy in patients (pts) with relapsed/refractory mantle cell lymphoma (R/R MCL) in the phase 2 ACE-LY-004 study. Blood. 2017;130:155 (abstract).
29. Awan FT, Schuh A, Brown JR *et al.* Acalabrutinib monotherapy in patients with ibrutinib intolerance: results from the phase 1/2 ACE-CL-001 clinical study. Blood. 2016;128:638 (abstract).
30. Byrd JC, Owen R, O'Brien SM *et al.* Pooled analysis of safety data from clinical trials evaluating acalabrutinib monotherapy in hematologic malignancies. Blood. 2017;130:4326 (abstract).
31. Burger JA, Tedeschi A, Barr PM *et al.* Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med. 2015;373:2425–2437.
32. Wang ML, Blum KA, Martin P *et al.* Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. Blood. 2015;126:739–745.
33. Brown JR, Moslehi J, S OB *et al.* Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. Haematologica. 2017;102:1796–1805.
34. Ghez D, Calleja A, Protin C *et al.* Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib. Blood. 2018 [Epub ahead of print]
35. Dreyling M, Campo E, Hermine O *et al.* Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28:iv62–iv71.
36. Trneny M, Lamy T, Walewski J *et al.* Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial. Lancet Oncol. 2016;17:319–331.

37. Chiron D, Di Liberto M, Martin P *et al.* Cell-cycle reprogramming for PI3K inhibition overrides a relapse-specific C481S BTK mutation revealed by longitudinal functional genomics in mantle cell lymphoma. Cancer Discov. 2014;4:1022–1035.
38. Cheah CY, Chihara D, Romaguera JE *et al.* Patients with mantle cell lymphoma failing ibrutinib are unlikely to respond to salvage chemotherapy and have poor outcomes. Ann Oncol. 2015;26:1175–1179.
39. Martin P, Maddocks K, Leonard JP *et al.* Postibrutinib outcomes in patients with mantle cell lymphoma. Blood. 2016;127:1559–1563.
40. Bouabdallah K, Tabrizi R, Vigouroux S, Clement L, Dilhuydy MS, Milpied N. Successful bridge with Ibrutinib monotherapy to allogeneic stem cell transplant in relapsed mantle-cell lymphoma: P626. Bone Marrow Transplant. 2017;52:S454 (abstract).
41. Grillo G, Zucchetti E, Zilioli VR *et al.* Ibrutinib as bridge therapy to allogeneic stem cell transplantation in refractory mantle cell lymphoma (MCL): a case report: P106. Bone Marrow Transplant. 2017;52:S169 (abstract).

Table 1. Ongoing clinical trials of acalabrutinib in MCL and CLL.

Study ID	Condition	Intervention	Phase	Primary efficacy endpoint(s)	N	Completion[a]
NCT02213926 (ACE-LY-004)	R/R MCL	Acalabrutinib	2	PFS; timeframe: ≥ 1 year	124	Mar. 2017[b]
NCT02717624 (ACE-LY-106)	R/R or treatment-naïve MCL	Acalabrutinib+ bendamustine+ rituximab	1	N with TEAEs; timeframe: to last dose	48[c]	Feb. 2021
NCT02972840 (ACE-LY-308)	Treatment-naïve MCL	Bendamustine+ rituximab vs acalabrutinib+ bendamustine+ rituximab	3	PFS; timeframe: 48 months	546[c]	Oct. 2022
NCT02157324 (ACE-CL-002)	R/R CLL	Acalabrutinib vs ACP-319 vs acalabrutinib+ ACP-319	1	Pharmacokinetics, change in exposure	12	Sep. 2018
NCT02296918 (ACE-CL-003)	R/R or treatment-naïve CLL, SLL, PLL	Acalabrutinib+ obinutuzumab	1b	ORR; timeframe: 12 months	45	Nov. 2018
NCT02029443 (ACE-CL-001)	R/R or treatment-naïve CLL, SLL, RS, PLL	Acalabrutinib	1/2	Maximum tolerated dose	286[c]	Jan. 2019
NCT03328273 (ACE-CL-110)	R/R CLL	AZD6738 and acalabrutinib+ AZD6738	1/2	Maximum tolerated dose	62[c]	Apr. 2020
NCT02362035 (ACE-LY-005)	NHL, MM, HL, CLL, RS, WM[d]	Acalabrutinib+ pembrolizumab	1/2	N with TEAEs; timeframe: 104 weeks	159	Apr. 2021
NCT02717611 (ACE-CL-208)	R/R CLL (ibrutinib intolerant)	Acalabrutinib	2	ORR; timeframe: up to 36 months	60	Feb. 2020
NCT02337829 (15-H-0016)	R/R or treatment-naïve del(17p) CLL, SLL	Acalabrutinib	2	ORR; timeframe: 6 months	48[c]	Dec. 2017
NCT02477696 (ACE-CL-006)	R/R CLL	Acalabrutinib vs ibrutinib	3	PFS; timeframe: 36 months	500[c]	Jun. 2019
NCT02475681 (ACE-CL-007)	Treatment-naïve CLL	Obinutuzumab+ chlorambucil vs acalabrutinib+ obinutuzumab vs acalabrutinib	3	PFS; timeframe: 49 months	535	Dec. 2019
NCT02970318 (ACE-CL-309)	R/R CLL	Acalabrutinib vs investigator's choice of idelalisib+ rituximab or bendamustine+ rituximab	3	PFS; timeframe: 48 months	306[c]	Jan. 2020

CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; ORR, overall response rate; PFS, progression-free survival; PLL, prolymphocytic leukemia; R/R, relapsed or refractory; RS, Richter syndrome; SLL, small lymphocytic lymphoma; TEAE, treatment-emergent adverse event; WM, Waldenström macroglobulinemia.

[a]Estimated primary completion date as reported on ClinicalTrials.gov.
[b]Estimated final study completion date is January 2018.
[c]N is for estimated enrolment.
[d]Any other therapy for the treatment of cancer needed to be completed ≥ 4 weeks before the start of the study therapy.

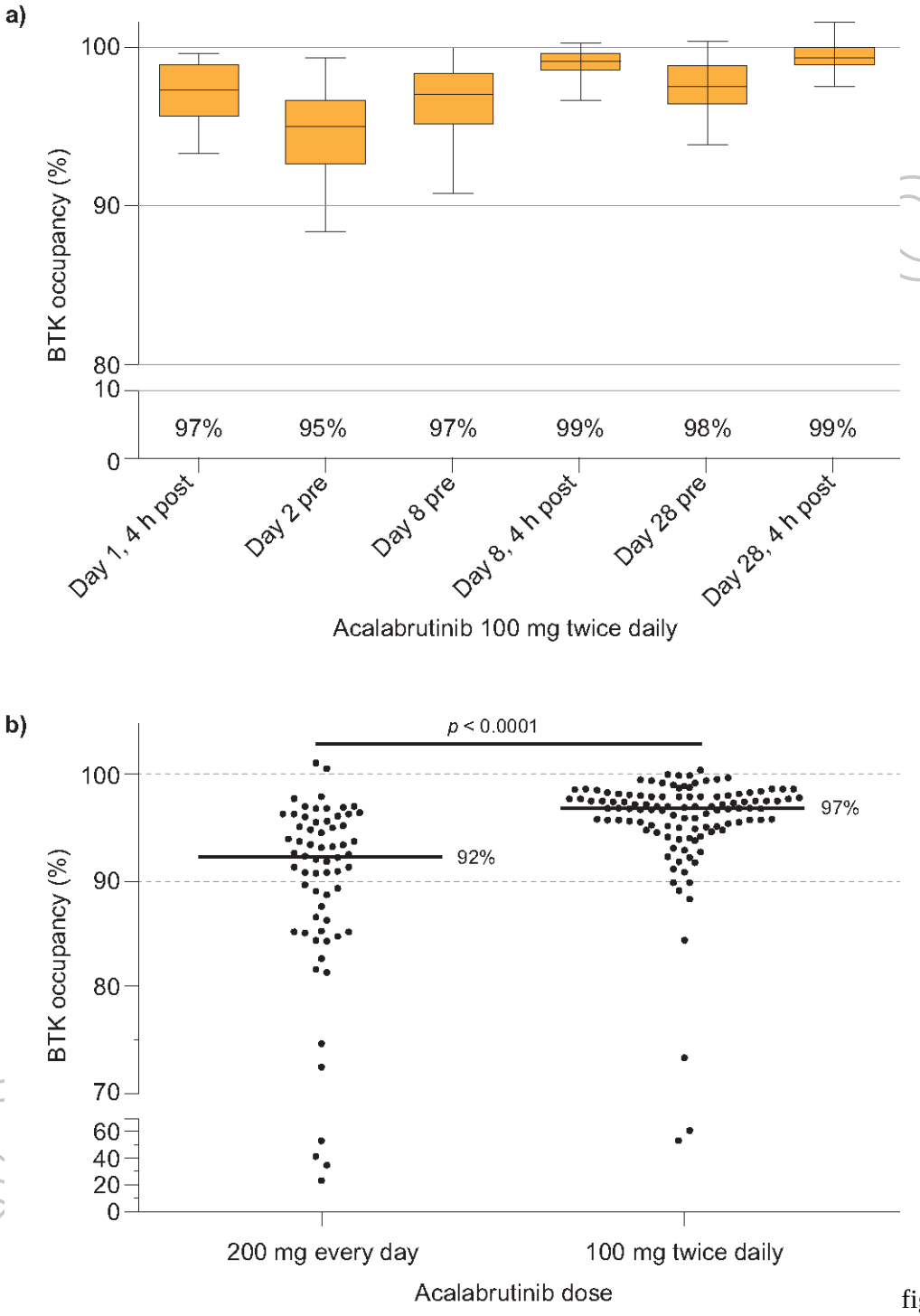
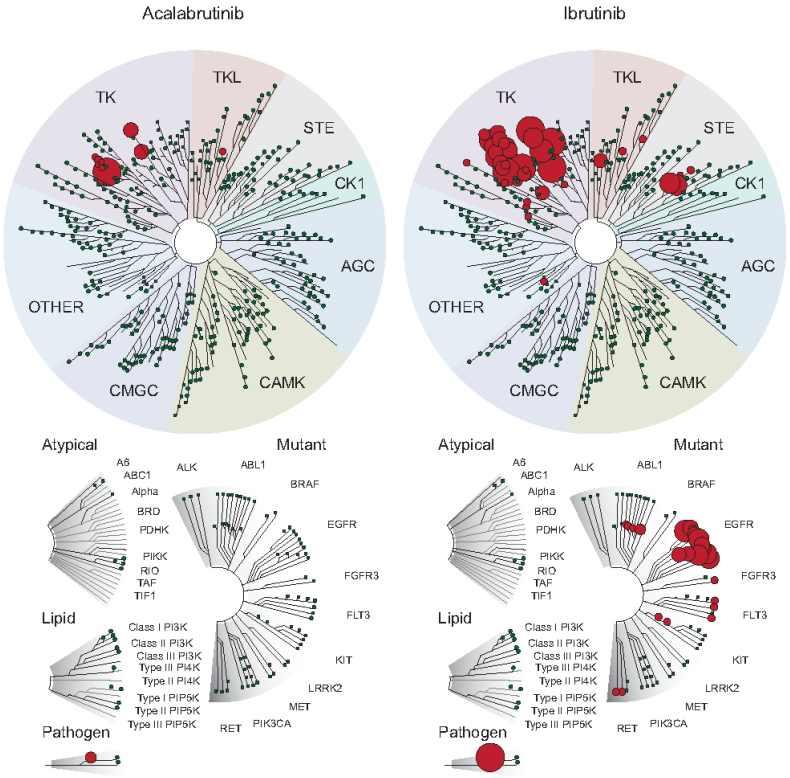


fig 3



Kinase	IC_{50} (nM)	
	Acalabrutinib	Ibrutinib
BTK	5.1 ± 1.0 (n = 4)	1.5 ± 0.2 (n = 4)
BMX*	46 ± 12 (n = 3)	0.8 ± 0.1 (n = 3)
ITK*	> 1000 (n = 4)	4.9 ± 1.2 (n = 4)
TEC*	93 ± 35 (n = 2)	7.0 ± 2.5 (n = 2)
TXK*	368 ± 141 (n = 3)	2.0 ± 0.3 (n = 3)
EGFR*	> 1000 (n = 3)	5.3 ± 1.3 (n = 3)
ERBB2*	~1000 (n = 3)	6.4 ± 1.8 (n = 3)
ERBB4*	16 ± 5 (n = 3)	3.4 ± 1.3 (n = 3)
JAK3*	> 1000 (n = 3)	32 ± 15 (n = 3)
BLK*	> 1000 (n = 3)	0.1 ± 0.0 (n = 3)
FGR	> 1000 (n = 2)	3.3 ± 1.1 (n = 2)
FYN	> 1000 (n = 2)	29 ± 0 (n = 2)
HCK	> 1000 (n = 2)	29 ± 0 (n = 2)
LCK	> 1000 (n = 2)	6.3 ± 1.3 (n = 2)
LYN	> 1000 (n = 2)	20 ± 1 (n = 2)
SRC	> 1000 (n = 2)	19 ± 1 (n = 2)
YES1	> 1000 (n = 2)	4.1 ± 0.2 (n = 2)

Fig 2

Fig 2

fig

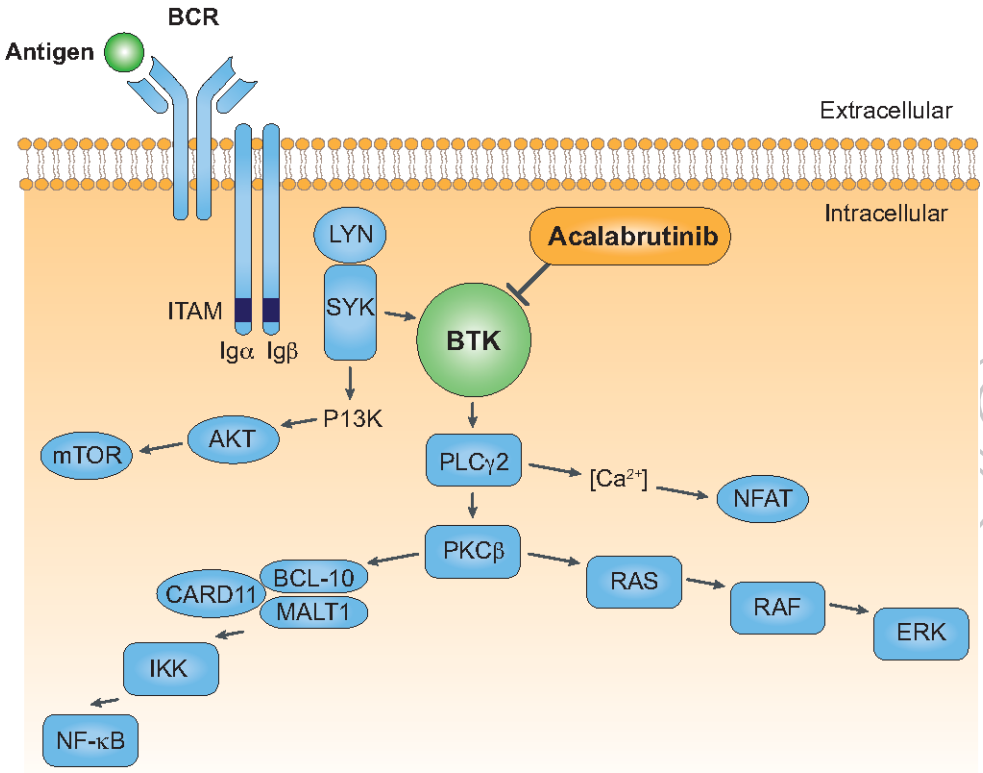


fig 1