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DRUG PROFILE

Acalabrutinib for adults with mantle cell lymphoma

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ABSTRACT

Introduction: Although advances in mantle cell lymphoma (MCL) therapy have improved overall survival (OS), managing relapsed/refractory (R/R) cases remains a great challenge. Bruton tyrosine kinase (BTK) inhibitors have broadened therapeutic options in MCL and became the backbone of second-line strategies.

Areas covered: Ibrutinib, the first-in-class BTK inhibitor registered for MCL therapy, is efficient, with clear benefits of its use. However, ibrutinib-related adverse events due to off-target inhibition of other kinases led to the development of more selective molecules with comparable efficacy and better safety profiles.

Expert commentary: Acalabrutinib, a new BTK inhibitor, currently being evaluated in numerous clinical studies is approved by FDA in relapsing/refractory MCL. Its role will evolve over the next few years. Efficacy and good tolerability of acalabrutinib gives even greater opportunity for potential upfront use and new therapeutic combinations, including monoclonal antibodies, antibody-drug conjugates, immune checkpoint inhibitors, bcl-2 (B-cell lymphoma-2) or IP3K (phosphoinositide 3-kinase) inhibitors.

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Acalabrutinib; adverse events; Bruton tyrosine kinase inhibitors; mantle cell lymphoma

1. Overview of the market

Mantle cell lymphoma (MCL) is an aggressive B-cell non-Hodgkin lymphoma (NHL) and the patients have a poor prognosis. Despite the features of indolent lymphoma at presentation and relatively good initial response to treatment, most patients relapse with lymphoma clone, refractory to subsequent chemotherapy regimens [1]. The better the response to the first-line therapy, the later the relapse, therefore immunochemotherapy followed by consolidation and maintenance strategies remain the current standard of care.

The majority of patients are elderly, with a median age of 68 years. They are usually treated with anthracycline- or bendamustine-based regimens: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or rituximab and bendamustine (BR) [2–4]. Rituximab maintenance proved to increase both progression-free survival (PFS) and overall survival (OS), especially in R-CHOP treated patients. It seemed to be less effective due to adverse reactions after BR induction therapy [4].

In younger, fit patients, intensive front-line immunochemotherapy with rituximab (R) plus high-dose cytarabine (R-HAD) followed by autologous stem-cell transplantation (ASCT) demonstrates a higher response rate, significantly better overall survival and median time to treatment failure [5–8]. The three most commonly used regimens include R-CHOP/R-DHAP [dexamethasone, high-dose cytarabine and cisplatin, based on European Mantle Cell Lymphoma Network (EMCLN) experience] [6]; the R-maxiCHOP/R-HAD protocol, described by the Nordic Lymphoma Group [7,8]; and hyper fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high-dose methotrexate/cytarabine (R-HCVAD/R-MA), developed at the MD Anderson Cancer Center (MDACC) [9]. After the results of the *LyMA* trial, rituximab maintenance is also indicated in all patients who have undergone ASCT [10].

Targeted approaches, like Bruton tyrosine kinase (BTK) inhibitors and immune-modifying drugs (IMIDS), are the backbone of therapy in relapsing/refractory patients. Based on the results of phase 2 clinical trial demonstrating a median PFS of approximately 6 months, the proteasome inhibitor bortezomib received, as first targeted molecule in MCL, the Food and Drug Administration (FDA) approval [11]. A multicenter phase 3 study demonstrated the superiority of temsirolimus compared to investigator's choice, with a median PFS of 4.8 months, leading to its approval by the European Medicine Agency (EMA) [12]. The activity of lenalidomide in patients who progressed on bortezomib-therapy was confirmed in the phase 2 EMERGE trial, with a durable efficacy with overall response rate (ORR) of 28% in a heavily pretreated population, leading to lenalidomide approval by FDA in MCL settings [13]. In the SPRINT trial conducted by the EMCLN, the efficacy of lenalidomide was confirmed with a median PFS of 8.7 months compared to 5.2 months in the control population [14]. Elderly individuals may achieve prolonged responses and good quality of life, while in younger patients, they may be an ideal bridging to allogeneic stem cell transplant.

BTK is a kinase enzyme and a key regulator in the B-cell receptor (BCR) signaling pathway that is critical for the activation, proliferation, and survival of B-cell malignancies [15,16].

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The BTK gene is located on the X chromosome, and its mutation was initially described in X-linked agammaglobulinemia by Ogden Bruton [17,18]. Bruton tyrosine kinase phosphorylation, necessary for its activity, may be prevented by BTK inhibitors [19]. Ibrutinib – the first-in-class, irreversible BTK inhibitor – is an orally bioavailable small-molecule forming a stable covalent bond with cysteine (cys-481). It showed high efficacy in relapsed/refractory (R/R) MCL [20] . In addition to BTK inhibition, ibrutinib targets several other kinases, including interleukin-2-inducible T-cell kinase (ITK), epidermal growth factor receptor (EGFR), T-cell X-chromosome kinase (TXK) and tyrosine kinase expressed in hepatocellular carcinoma (TEC) [19], which may contribute to some of its reported toxicities [21]. To limit off-target kinase inhibition related adverse effects, such as atrial fibrillation, bleeding, rashes, diarrhea, nausea, arthralgia, myalgia, pneumonitis and subdural hematoma [22–25] and improve the safety profile, new BTK inhibitor with enhanced selectivity profile are being investigated. This is a key concept that has contributed to the development of more selective BTK inhibitors. Acalabrutinib is a BTK inhibitor of an enhanced selectivity, extensively studied and already registered by the FDA in relapsing/refractory MCL [26]. Other more selective BTK inhibitors such as zanubrutinib (BGB-3111), tirabrutinib (ONO/GS-4059), vecabrutinib (SNS-062), spebrutinib (CC-292, AVL-292), ARQ-531 and M7583 are also being investigated in the treatment of MCL. Acalabrutinib remains so far the only second-generation BTK inhibitor approved for R/R MCL cases (after at least one prior therapy).

Zanubrutinib (BGB-3111) – a new BTK inhibitor with higher oral bioavailability and better selectivity than ibrutinib for BTK vs. a panel of kinases including ITK [27]. Zanubrutinib inhibits BTK activity and BCR-dependent responses (BTK auto-phosphorylation and downstream PLCγ2 signaling in diffuse large B-cell lymphoma (DLBCL) and MCL cell lines [28]. In addition, its anti-proliferative efficacy and induction of apoptosis in MCL model mouse cells have been demonstrated in lower doses than ibrutinib (2.5 mg/kg twice weekly vs. 50 mg/kg once daily). The initial studies (NCT03189524, NCT03206970) confirmed its good tolerance and clinical activity. Zanubrutinib, being a more selective BTK kinase inhibitor compared to ibrutinib, was only very occasionally responsible for atrial fibrillation or bleeding episodes [29]. The molecule is currently being investigated in phase 3 study in Waldenstrom's macroglobulinemia (WM) (NCT03053440). Results of the phase 2 trial in R/R MCL are expected in late 2019 (NCT03206970).

Tirabrutinib (ONO/GS-4059) – this irreversible molecule with an improved selectivity showed activity in patients with R/R B-cell lymphoma, particularly in CLL (where it confirmed it's efficacy in 92% of the evaluable patients) and activated B cell subtype of diffuse large B cell lymphoma (ABC DLBCL) [27,30].

Vecabrutinib (SNS-062) – a reversible BTK inhibitor with higher exposures and continuous drug level, good oral bioavailability and tolerance in dogs and rats [31]. SNS-062 is being investigated in a phase 1/2 study in B-cell lymphoma (NCT03037645).

Spebrutinib (CC-292, AVL-292) – a covalent, irreversible, orally bioavailable BTK inhibitor with increased specificity for BTK and less inhibition of other kinases, effective in disrupting BCR signaling and inhibiting tumor cells activation, proliferation, and chemotaxis [32,33]. It is able to overcome microenvironment-mediated chemoresistance and normalize immune cell composition. Its activity was confirmed in vitro and in vivo on chronic lymphocytic leukemia (CLL) cells with a promising performance in combination with bendamustine [34].

ARQ-531 – a reversible BTK inhibitor, with proven BCR-induced responses on CLL cells [35] is being investigated in a phase 1 study in hematological malignancies (NCT03162536).

M7583 – a highly selective irreversible molecule binding to BTK. Its safety, pharmacokinetics (PK), pharmacodynamics (PD) and antitumor activity is being investigated in a phase 1/2 study in R/R B-cell malignancies including MCL (NCT02825836) [36].

It is likely that only highly selective first generation and second generation BTK inhibitors will be eventually developed. So far, only acalabrutinib and zanubrutinib were investigated in phase 3 protocols; therefore, they are the most likely candidates.

2. Introduction to the drug

The best-known, more selective BTK inhibitor is **acalabrutinib (ACP-196)**, a novel molecule, dosed orally 100 mg twice per day, about 12 hours apart, designed to be more potent and selective than ibrutinib and minimize off-target [37]. Key structural components of acalabrutinib include a 2-pyridylbenzamide moiety and the electrophilic 2-butynamide moiety that is involved in covalent and irreversible binding to a cysteine residue (Cys481) in the adenosine triphosphate (ATP) pocket. In contrast to ibrutinib, its butynamide-based binding motif has a reduced intrinsic reactivity and does not inhibit ITK and EGFR kinases, with improved fold selectivity of TEC and TXK inhibition versus BTK compared to ibrutinib. It has, therefore, an improved selectivity and comparable *in vivo* target coverage [21,37,38]. The correlation of biochemical off-target inhibition and its functional consequences in selected cell lines was confirmed for different kinases [21,37,38]. The IC50 value (half maximal inhibitory concentration – the concentration of a drug that is required for 50% inhibition *in vitro*) for acalabrutinib against purified BTK is 5.1 nM compared with 1.5 nM for ibrutinib [37,39]. The degree of inhibition of BCR-induced responses, like phosphorylation BTK and other kinases of ERK (extracellular signal-regulated kinases] pathway is also similar for these molecules in primary CLL cells [39,40]. The data provided from several preclinical studies with animal models of B-cell lymphoma NHL evaluating safety and efficacy moved acalabrutinib into human trials. In a study of the canine model (dogs with confirmed diagnosis of new or relapsed B-cell lymphoma, stage ≥2) acalabrutinib showed biologic activity as a single, oral agent [3/12 have achieved partial remission (PR), 3/12 stable disease (SD), 6/12 progressive disease (PD)] [41]. Acalabrutinib *in vivo* demonstrated its efficacy against NOD scid gamma (NSG) mouse model with xenografts of human CLL cells. It significantly inhibited proliferation of human CLL cells in the mouse spleen at all dose levels and reduced phosphorylation of phospholipase-ɣ2 (PLCɣ2) leading to a transient increase of CLL cell counts in peripheral blood and subsequent reduction of tumor burden [42]. In vivo, in a CLL xenograft model in NSG

mice treated with various doses of acalabrutinib (0.006, 0.06, 0.15, or 0.3 mg/mL) or vehicle alone in the drinking water, acalabrutinib inhibited tumor proliferation as measured by Ki67 expression in CLL cells from the spleen of the mice with a mean decrease in Ki67 of 58%, 70%, and 73% at 0.006 mg/mL, 0.06 mg/mL, and 0.15 mg/mL acalabrutinib, respectively, compared to vehicle [38].

Acalabrutinib was also tested in dose-escalation studies in healthy adult volunteers, to assess safety, PK and PD (ACE-HV -001) [37]. Pharmacokinetic analysis confirmed that plasma concentration of acalabrutinib is more stable and less dependent on meals and lymphoma subtype compared to ibrutinib. In healthy volunteers, acalabrutinib is completely absorbed regardless of the timing of the meals. It achieves the maximum plasma concentration [T_{max}] in 0.5–1.0 hours, and has a short half-life (time required for elimination of 50% of the drug from plasma [T1⁄2] of 0.88–2.1 h) [21,37]. Acalabrutinib 100 mg twice daily in patients with CLL resulted in a maximum plasma concentration [C_{max}] of 827 ng/ml, an area under a plasma concentration/time curve from 0 to 24 h [$AUC_{0-24\ h}$] of 1850 hng/ml and a mean terminal half-life of 1.13 h [21]. Ibrutinib absorption is more sensitive to meals – in CLL patients, differences between fasting and post-meal dosing were substantial in healthy volunteers (average C_{max} of 52 and 120 ng/ml, AUC $_{0\text{-}24\ h}$ 485 and 864 h · ng/ml, and a T 1/2 of 11 and 4.5 h, respectively, [43]). Acalabrutinib reaches a full target occupancy at both 3 and 12 h after a single 100 mg dose, which corelates with nearly complete inhibition of BCR-induced functional B cell response (i.e. CD69 expression) [37]. The short half-life of acalabrutinib lowers the risk of accumulation in the blood. Twice-daily dosing, about 12 hours apart, maintains complete and continuous BTK inhibition across the 24-h dosing interval. Moreover, the twice-daily dosing of 100 mg had led to higher median BTK occupancy comparing to 200 mg once per day, with lower variability compared with once-daily dosing (6.5% vs 16.4%, respectively), maintain adequate high target coverage over each dose interval [37,44].

A greater specificity of acalabrutinib and reduced inhibition of off-target kinases may be related to reduced number of adverse events [37]. Cardiotoxicity, including episodes of atrial fibrillation, are very rarely reported. Furthermore, in an *in vivo* thrombus formation model, blood platelets from patients treated with acalabrutinib had similar reactivity to platelets from healthy volunteers, whereas blood platelets from patients receiving ibrutinib showed diminished aggregation [21,26].

3. Clinical efficacy of acalabrutinib

In order to find the optimal acalabrutinib dose and assess safety, efficacy, pharmacokinetics and pharmacodynamics, a phase 1–2 multicenter trial was conducted in CLL, small lymphocytic leukemia (SLL), Richter's transformation, prolymphocytic leukemia (PLL) (ACE-CL-001). In a typical dose-escalation protocol, 61 R/R CLL/SLL patients were evaluated [21]. The acalabrutinib dose, initially increased from 100 to 400 mg daily, was eventually set at 100 mg bidaily, which allows for nearly complete BTK occupancy over 24 hours [21]. In the updated analysis of ACE-CL-001 study, 134 R/R CLL/SLL patients were evaluated; with a median follow-up of 19.8 months acalabrutinib, as a single agent, demonstrated high response rates and durable remissions with ORR rate 93%, including 2% of CR, 83% of PR and 8% of partial remissions with lymphocytosis (PRL) [45]. Response rates were consistent across high-risk subgroups with del 17p (85%), 11q deletion (del 11q) (86%) and unmutated IGHV (88%) [45]. The median PFS was not reached, and the 18-month PFS rate was 88% (95% CI, 81%-93%). With the immature data we have, it is not possible to compare PFS in R/R CLL patients with previous ibrutinib studies; the objective analysis will be possible after obtaining the results from the ACE-CL-006 study (NCT02477696).

BTK inhibitors demonstrate exceptional activity in MCL. The trials conducted in patients with R/R MCL were the first step of ibrutinib and acalabrutinib registration. Both trials: PCYC-1104-CA (NCT01236391) [46] and ACE-LY-004 (NCT02213926) [47] had identical inclusion/exclusion criteria and numbers of participating patients. The subsequent papers [46,47] papers became milestones, setting the new standards of care. Positive results from an open-label phase 2 trial ACE-LY-004 led to accelerated approval by FDA in 2017 [47]. Both studies explored the potential role of monotherapy with BTK inhibitors in MCL, after the failure of the previous 1–5 lines of therapy (Table 1).

(*) ORR defined as the proportion of participants who achieved a best overall response of CR or PR, according to the revised International Working Group Criteria for non-Hodgkin's lymphoma [48] in the PCYC-1104-CA trial and according to the 2014 Lugano classification [49] in the ACE-LY-004 trial

AE – adverse event, ASCT – autologous stem cell transplantation, bd – twice a day, CR – complete remission, DOR – duration of response, ECOG – Eastern Cooperative Oncology Group, MCL – mantle cell lymphoma, MIPI – Mantle Cell Lymphoma International Prognostic Index, ORR – overall response rate, OS – overall survival, qd – once a day, PFS – progression-free survival

The patient cohorts were not entirely comparable – in the ibrutinib trial there were more patients with refractory disease (45% vs. 24%); with intermediate or high MIPI (86% vs. 60%); and treated later in the disease course (median number of previous therapies 3 vs. 2). The adverse prognostic role of high MIPI and refractory disease is well proven. BTK inhibitors are probably more effective if they are used earlier in the course of the disease. In a later subgroup analysis of the PCYC-1104-CA trial [50], patients treated with ibrutinib in the second line had 82% ORR with 27% complete remissions (CR), and median DOR, PFS and OS 16.5, 17.5 and 21.8 months, respectively. Responses in the acalabrutinib trial occurred earlier than in the ibrutinib trial (median time to CR 3.4 vs. 5.5 months) and were possibly deeper (CR 40% vs. 21%); however, they were assessed according to the 2014 Lugano classification, updated Cheson criteria. Positron emission tomography (PET) scan may allow for the earlier CR detection, i.e. in patients with fibrosis, inactive lymph nodes, still assessed as PR in computed tomography (CT); therefore, an objective comparison of treatment effectiveness using two different methods is not possible. Very poor results of patients who became refractory to BTK inhibitors [51] make PFS a good surrogate for OS. The shape of the DOR and PFS curves indicate that the results of the ACE-LY-004 trial are

Table 1. BTK inhibitors monotherapy trials in R/R MCL – differences despite similar inclusion/exclusion criteria.

	PCYC-1104-CA (NCT01236391)	ACE-LY-004 (NCT02213926)
Study Name	Safety and Efficacy of PCI-32765 in Participants with Relapsed/Refractory MCL	An Open-label, Phase 2 Study of ACP-196 in Subjects with MCL
Study Timeline (Start – primary completion date)	February 2011 – January 2014	March 2015 – February 2017
Inclusion Criteria:		
• Men and women ≥18 years of age.		
• Pathologically confirmed MCL, with documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1 and measurable disease on cross-sectional imaging that is ≥2 cm in the longest diameter and measurable in two perpendicular dimensions.		
• Relapsed/refractory after at least 1, but no more than 5, prior treatment regimens for MCL		
• Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.		
Dose	Ibrutinib – 560 mg daily (qd)	Acalabrutinib – 100 mg twice a day (bd)
Number of patients, median age	115, median age 68	124, median age 68
Number of previous therapies	**3 (1–5)**	**2 (1–5)**
Previous ASCT	11%	18%
% of patients with intermediate-risk or high-risk according to MIPI	86%	60%
Refractory disease	45%	24%
Bulk > 5 and > 10 cm	39% and 8% respectively	37% and 8% respectively
Primary endpoint – ORR (*):	ORR – 68% CR – 21% PR – 47%	ORR – 81% CR – 40% PR – 41%
Median time to initial response (months)	1.9 (range 1.4–13.7)	1.9 (range 1.5–4.4)
Median time to CR (months)	5.5 (range 1.7–24.7)	3.4 (range 1.9–5.5)
Duration of Response (DOR)	median – 17.5 months	72% at 12 months
Progression Free Survival (PFS)	median – 13.9 months	67% at 12 months
Overall Survival (OS)	58% at 18 months	87 at 12 months
Hematological AE: any grade/3–4 grade (%):	17/16	14/14
Neutropenia	11/10	15/11
Anemia	13/11	<5%
Thrombocytopenia		
Most Common AE any grade/grade 3–4 (%):	0	38/2
Headache	53/6	31/3
Diarrhea	49/5	27/1
Fatigue	17/0	21/1
Myalgia	33/1	18/1
Nausea		
AE of special interest any grade/grade 3–4 (%)	7/6	7/6
Pneumonia	7/6	0/0
Atrial fibrillation	41/6	31/1
Bleeding events		
Patients discontinuing therapy due to AE (%)	11	6

probably superior, however even that does not allow to conclude that acalabrutinib is a better drug, as the comparison was not a direct one, and patient cohorts were in some respects different.

Acalabrutinib safety and efficacy as monotherapy or in combination therapy has been investigated in patients with hematological malignancies (Table 2).

ABC – activated B-cell, CLL-chronic lymphocytic leukemia; DLBCL – diffuse large B-cell lymphoma, FL – follicular lymphoma, HL-Hodgkin lymphoma; MALT – mucosa-associated lymphois tissue, MCL-mantle cell lymphoma; MM-multiple myeloma; MZL – marginal zone lymphoma, NHL-non-Hodgkin lymphoma; PLL-prolymphocytic leukemia; RS-Richter syndrome; SLL-small lymphocytic lymphoma; WM, Waldenström's macroglobulinemia.

Currently, there are many ongoing preclinical studies evaluating the combinations of acalabrutinib with other drugs: chemoimmunotherapy (BR), phosphoinositide-3 kinase (PI3K) inhibitor ACP-319 [52,53], B-cell lymphoma 2 (BCL-2) inhibitors [54]. In clinical studies, the combination of acalabrutinib with programmed cell death protein 1 (PD-1) inhibitors (checkpoint inhibitors) is also investigated in solid tumors [55] and with venetoclax and obinutuzumab in treatment-naive CLL patients (the phase-II trial, NCT03580928). Combining ibrutinib with venetoclax in 24 MCL patients in phase 2 trial resulted in over 60% potentially durable complete responses with confirmed ongoing responses at 15 months in 78% of the patients [56]; ibrutinib in combination with venetoclax is currently evaluated in phase III study initiated in R/R MCL (NCT03112174), where patients are randomized to ibrutinib alone or in combination with venetoclax.

Developing even more efficient regimens containing acalabrutinib may be particularly useful as bridging to allogeneic stem-cell transplant in younger patients with R/R MCL.

Whether BTK inhibitors will have any role in the first-line therapy of MCL remains an unanswered question. Although it is nearly certain that adding them to immunochemotherapy regimens will increase the response rate and prolong PFS, the fate of the patients, once they become refractory, would be probably bad. Therefore, to prolong OS, one would most likely need the first-line BTK-inhibitor-containing regimen to be better than two lines of therapy: the current first-line standard of care and subsequent BTK inhibitor monotherapy. The first attempt was done with ibrutinib (SHINE trial, NCT01776840), where 523 elderly patients, not eligible for intensive therapy, were randomized to BR + rituximab maintenance vs. BR-ibrutinib + rituximab-ibrutinib maintenance. The recruitment was completed over 3 years ago, but the analysis has been

Table 2. Clinical trials of acalabrutinib for hematological malignancies.

Study ID	Agent	Condition	Phase
PHASE 1–2			
NCT02029443 (ACE-CL-001)	Acalabrutinib	R/R or treatment- naïve CLL, SLL, PLL, RS	1
NCT02112526 (ACE-LY-002)	Acalabrutinib	R/R de novo ABC DLBCL	1
NCT02296918 (ACE-CL-003)	Acalabrutinib +obinutuzumab	R/R or treatment- naïve CLL, SLL, PLL	1b
NCT02717624 (ACE-LY-106)	Acalabrutinib+bendamustine+ rituximab	R/R or treatment- naïve MCL	1
NCT03527147 (PRISM)	Acalabrutinib + AZD9150 vs acalabrutinib + AZD6738	R/R DLBCL	1
NCT02157324 (ACE-CL-002)	Acalabrutinib + ACP-319	R/R CLL	1/2
NCT02328014 (ACE-LY-001)	Acalabrutinib + ACP-319	Treatment-naïve and R/R B-cell malignancies	1/2
NCT02362035 (ACE-LY-005)	Acalabrutinib+pembrolizumab	NHL, MM, HL, CLL, RS, WM	1/2
NCT03328273 (ACE-CL-110)	AZD6738 vs acalabrutinib+ AZD6738	R/R CLL	1/2
NCT02180711 (ACE-LY-003)	Acalabrutinib vs acalabrutinib+rituximab	Treatment-naive or R/R FL, MALT, MZL	1/2
NCT03571308 ACCEPT	RCHOP + acalabrutinib	Tretament-naive DLBCL	1b/2
NCT02213926 (ACE-LY-004)	Acalabrutinib	R/R MCL	2
NCT02717611 (ACE-CL-208)	Acalabrutinib	R/R CLL (ibrutinib intolerant)	2
NCT02337829 (15-H-0016)	Acalabrutinib	R/R or treatment- naïve del(17p) CLL, SLL	2
NCT03580928	Acalabrutinib+venetoclax+obinutuzumab	Treatment-naïve CLL	2
NCT02180724 (ACE-WM-001)	Acalabrutinib	Treatment-naive or R/R WM	2
PHASE 3			
NCT02477696 (ACE-CL-006)	Acalabrutinib vs Ibrutiib	R/R CLL	3
NCT02475681 (ACE-CL-007)	Obinutuzumab + chlorambucil versus Acalabrutinib + obinutuzumab versus Acalabrutinib	Treatment- naïve CLL	3
NCT02972840 (ACE-LY-308)	Bendamustine+ rituximab vs acalabrutinib+ bendamustine+ rituximab	Treatment- naïve MCL	3
NCT02970318 (ACE-CL-309)	Acalabrutinib vs investigator's choice of idelalisib+ rituximab or bendamustine+ rituximab	R/R CLL	3

postponed, as there are not enough events reported yet. This may paradoxically be good news for BTK inhibitors, as the smaller-than-estimated number of events may be due to the exceptional results of ibrutinib-treated patients. An identical randomized trial (ACE-LY-308, NCT02972840) is currently ongoing with acalabrutinib. The preliminary results of the phase 2 protocol (ACE-LY-106, NCT02717624) will be presented at the ASH 2018 annual conference. In the younger population, where intermediate-dose cytarabine and consolidation with high-dose therapy supported by stem-cell transplant is the current standard, the potential role of ibrutinib is being investigated in the EMCLN TRIANGLE trial (NCT02858258). The original idea to include ibrutinib throughout the whole induction regimen had to be altered due to cytopenias after ibrutinib-R-DHAP therapy – in the current version of the protocol, it is given intermittently, only with R-CHOP.

4. Post-marketing surveillance

An effective treatment for R/R MCL is a real unmet medical need. The major drawback of BTK trials in R/R MCL is the difficulty in finding a good comparator for the phase 3 trials, due to the lack of therapies regarded as a standard of care in this clinical situation. Ibrutinib efficacy was confirmed in a randomized comparison to temsirolimus [57]. The difference was so striking (median PFS 14.6 vs. 6.2 months) that it made any further BTK inhibitor comparisons with temsirolimus unethical. In the lenalidomide registration trial in R/R MCL, it's efficacy was compared with the investigator's choice [14].

In acalabrutinib accelerated registration, FDA underlined the necessity of a long time analysis of safety issues and adverse reactions. Acalabrutinib is more potent *in vivo* than ibrutinib with fewer off-target effects. The first encouraging safety profile of acalabrutinib was reported after updated analysis of ACE-CL-001 study assessing 134 patients with R/R CLL, with headache, diarrhea, upper respiratory tract infection and fatigue being the most common adverse events [45]. There were no episodes of major hemorrhages and only 3% atrial fibrillation (2% grade≥3) [45], regarded in ibrutinib patients as AEs of special interest. In a comparable ibrutinib CLL trial AEs were more common [23]. Although patients with significant cardiovascular diseases or electrocardiogram abnormalities were excluded from both trials, after

a relatively short follow-up period of 9.4 months, episodes of AF were observed in 5% of the ibrutinib treated patients (10/195), including 6 (3%) with grade ≥3 [23]. Similarly, in treatment-naive CLL patients with no significant cardiovascular disease, AF episodes were not recorded during acalabrutinib treatment [58], while 6% (8/136) receiving ibrutinib developed AF at the median follow-up time of 17.4 months [59]. No major hemorrhages (CTCAE 3–4) have been reported during acalabrutinib therapy in both described studies, except one episode of bleeding from gastric ulcer related to concomitant aspirin usage [21,58]. In ibrutinib trials, 1–5% of the patients, have experienced grade 3 or higher bleeding complications [23,59]. In 33 CLL/SLL patients who discontinued ibrutinib due to drug-related AEs, no serious bleeding episodes were reported after switching to acalabrutinib therapy, even in the six patients who had CTCAE 3–4 hemorrhagic complications while on ibrutinib [60]. These data are in line with higher *in vivo* selectivity of acalabrutinib for inhibiting BTK with no inhibition of platelet activity.

In CLL studies diarrhea and fatigue have been more often reported during ibrutinib [22,23,61] than acalabrutinib treatment [21,58]. Headache is the only common adverse reaction literally characteristic for acalabrutinib (42–43%) [21,58]; all other AEs are less common and less severe (Table 1). Most of the headaches were of mild severity, CTCAE grade 1–2 and occurred only during the first weeks of therapy, resolving over time, not causing treatment discontinuation [21,58]. Safety analysis comparison of acalabrutinib and ibrutinib in R/R MCL is summarized in Table 1. The most common (≥20%) AEs in the Wang et al. analysis were headache (38%), diarrhea (31%), fatigue (27%) and myalgia (21%) with no major hemorrhages nor AF.

The incidence of infections in patients treated with BTK inhibitors is increased, due to the underlying lymphoproliferative disease and effective elimination of B lymphocytes. In the ibrutinib MCL trial, upper respiratory tract infections were observed in 25/111 (23%) of patients and the most common serious infection of grade 3–5 was pneumonia recorded in 6% of the patients [39]. During acalabrutinib treatment in R/R MCL patients, pneumonia occurred in 7/124 (6%) of patients, but only in grade 2–3 [40]. The longer follow-up will provide more information about the safety profile of acalabrutinib in MCL settings.

Comparing the two registered BTK inhibitors, one should finally raise the question of adverse events, particularly those leading to therapy discontinuation. Acalabrutinib was less frequently discontinued due to its AEs. Although the difference between the two MCL trials seems small (6 vs. 11%), in a recent meta-analysis [62], discontinuation of ibrutinib was reported to be 12%, with a further 6% of the necessary dose reductions. In a long time, real-life experience Ibrutinib was discontinued due to toxicity even in 21% of the patients [63]. Long term analysis of acalabrutinib is lacking, although the discontinuation rate is supposed to be much smaller. The causes of discontinuation, outcomes of patients who discontinued acalabrutinib, and the genomic landscape are rare reported. In the analysis of 28 R/R MCL, after the median duration of treatment with acalabrutinib of 6.5 months, 15 patients discontinued the treatment (3/15 due to intolerance of the drug, 12/15 due to progression) [64]. Compared to tumors at baseline, ATM was mutated at a higher frequency in samples at progression compared to baseline (67% vs 50%, respectively); mutation of CARD11, NLRC5, and β2M were detected only at progression [64]. The non-BTK mutations may be associated with acalabrutinib resistance and disease progressions and there is an urgent need to further evaluation in a larger group of patients [64].

5. Regulatory affairs

Acalabrutinib (Calaquence) got the accelerated FDA approval in October 2017, based on the positive results of ACE-LY-004 study [47], as a single agent for relapsed or refractory MCL. FDA required to conduct a study to characterize the long-term safety of acalabrutinib monotherapy. An additional trial addressing the question of the appropriate dose and drug pharmacokinetics in patients with severe hepatic impairment is also planned. Additionally, Acerta Pharma B.V. will have to submit interim and complete final reports showing long-term safety with a minimum of 24 months of follow-up from study ACE-LY-004 in patients with mantle cell lymphoma.

EMA chose not to register acalabrutinib based on the clinical data gathered until now.

6. Conclusions

Acalabrutinib has a response rate in R/R MCL of 80%, with half of that percentage being CRs. The median duration of response has not yet been achieved. Acalabrutinib, being a highly selective BTK inhibitor, has a favorable toxicity profile compared to ibrutinib, with literally no cardiac toxicity or atrial fibrillation reported in clinical trials so far [47]. It is an attractive alternative for all R/R MCL patients and a necessity for those where ibrutinib is discontinued due to adverse reactions. Overcoming the BTK inhibitor resistance, due to, i.e. Cys481 mutations, remains the future challenge, which should be addressed by the second generation of BTK inhibitors.

7. Expert commentary

Despite the improvement in the results of survival rates MCL, relapsed/refractory disease remains a challenge. BTK inhibitors are the current standard of care. The majority of patients with MCL are elderly; therefore, intensive treatment in R/R disease, including RIC allo-SCT consolidation is rarely an option. Ibrutinib side effects due to off-target kinase inhibition led to the development of the second generation, more selective BTK inhibitors, to improve safety and tolerability. Preliminary acalabrutinib clinical data, its favorable pharmacokinetic/pharmacodynamic profile and decreased discontinuation rates, allow speculating on increased efficiency of more selective BTK inhibitors. Acalabrutinib allows treating patients, where ibrutinib had to be discontinued due to its adverse effects. Particularly promising is the reduced prevalence of AF and bleeding episodes, important in older patients with preexisting cardiovascular comorbidities. Combinations of acalabrutinib with other drugs in MCL, to further increase its efficacy and overcome emerging resistance is being investigated.

8. Five-year view

The eventual role of BTK inhibitors in MCL therapy is not yet established. Although results of several important clinical trials should be announced in the next 2–3 years, it may not change the current standard of care. The question about bringing BTK inhibitors into the first line setting may remain unanswered. Even if the 'SHINE' trial (NCT01776840) is positive, proving PFS benefit of elderly patients treated with BR + ibrutinib, it may not change the routine clinical practice. The lack of effective regimens in patients developing resistance to BTK inhibitors may mean that only prolonging OS would be regarded important.

Exceptionally good results of elderly patients treated at MDACC with chemotherapy-free regimen (rituximab – ibrutinib), with 100% RR, raise the question of its role in the first line setting. In United Kingdom the randomized comparison of rituximab-CHEMO (bendamustine or CHOP) with rituximab-ibrutinib is ongoing. The role of ASCT is challenged in EMCLN 'Triangle' trial, performed in younger, fit patients.

None of the BTK inhibitor-containing regimens proved to be curative in MCL so far. Combination with venetoclax, a drug inhibiting bcl-2 is currently compared to ibrutinib monotherapy, in a randomized, phase 3 protocol (NCT03112174).

Introducing BTK inhibitors in MCL therapy changed the standard of care and prolonged OS. Resistance to chemotherapy develops relatively early in the disease course, making it a true unmet medical need. It is a fascinating, dynamically evolving area of research.

Key issues

- Mantle cell lymphoma (MCL) is an aggressive B-cell non-Hodgkin lymphoma (NHL) and the patients have a poor prognosis. Although advances in upfront aggressive therapy have improved overall survival (OS), particularly in younger patients, managing relapsed/refractory (R/R) cases remains a great challenge.
- Bruton tyrosine kinase (BTK) inhibitors have broadened therapeutic options in MCL and became the backbone of second-line strategies.
- Ibrutinib – the first-in-class, irreversible, orally bioavailable small-molecule BTK inhibitor – showed high efficacy in relapsed/refractory (R/R) MCL. In addition to BTK inhibition, ibrutinib targets several other kinases, which may contribute to some of its reported toxicities. To limit off-target kinase inhibition with side effects such as atrial fibrillation, bleeding, rashes, diarrhea, nausea, arthralgia, myalgia, pneumonitis, and subdural hematoma and improve the safety profile, new, second-generation BTK inhibitors are being investigated.
- The best-known selective BTK inhibitor is acalabrutinib (ACP-196), a novel molecule, dosed orally 100 mg twice per day, about 12 hours apart, designed to be more potent and selective than ibrutinib and minimize off-target activity and adverse events. Cardiotoxicity, including episodes of atrial fibrillation, are very rarely reported.
- The results of trials with acalabrutinib suggest potential superiority of acalabrutinib versus ibrutinib in a safety profile, as for efficacy no head-to-head comparison data are yet available, however, the ACE-CL-006 study in R/R CLL patients, completed recruitment in 2017.
- Acalabrutinib got the accelerated FDA approval in October 2017, based on the positive results of ACE-LY-004 study, as a single agent for relapsed or refractory MCL.

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