

# BTK inhibitors and anti-CD20 monoclonal antibodies for treatment-naïve elderly patients with CLL

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**Abstract:** Older patients account for the majority of patients with chronic lymphocytic leukemia (CLL), and so strategies for managing CLL in this population is of utmost importance. Inhibition of Bruton's tyrosine kinase (BTK) has been a successful therapeutic strategy in CLL, and the first-generation BTK inhibitor ibrutinib has been shown to be superior to standard chemoimmunotherapy in multiple studies specifically targeting older patients. A second-generation BTK inhibitor, acalabrutinib, has also been studied in CLL, and has recently been granted breakthrough designation by the United States Food and Drug Administration. One ongoing question is whether the addition of anti-CD20 monoclonal antibodies improve response or response durability with BTK inhibitors. In this review, we will discuss clinical trials of ibrutinib and acalabrutinib in older patients with CLL, and the possible contributions of anti-CD20 antibodies to these therapies.

**Keywords:** CLL, elderly, ibrutinib, acalabrutinib, zanabrutinib, rituximab, obinutuzumab, ofatumumab

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## Introduction

Chronic lymphocytic leukemia (CLL) is among the most common lymphoid neoplasms in the Western world.<sup>1,2</sup> The incidence was 6.4 cases per 100,000 persons in the United States in 2018,<sup>2</sup> and was estimated to be 4.92 per 100,000/year in Europe from 2000 to 2002.<sup>3</sup> CLL is a disease of the elderly (defined herein as age >65 years), reflected by a median age at diagnosis of approximately 70 years in the United States and an incidence that rises with age.<sup>4,5</sup> Further, many patients are diagnosed with early stage disease, which may not require immediate treatment,<sup>6,7</sup> thus the median age at first treatment is greater than 70 years.

Multivariate analysis has shown age to be an independent prognostic factor in CLL, with age >65 years conferring an increased risk of death compared with those aged 65 years or younger (HR 1.7, 95% CI 1.4–2.1,  $p < 0.0001$ ).<sup>8</sup> Similarly, the 5-year survival of patients with CLL decreases with advancing age relative to age-matched controls in the general population,<sup>4,9</sup> and patients age

>65 years exhibit an excess risk of death from CLL compared with patients aged 55–64.<sup>4</sup> Although relative survival trends have improved in recent decades,<sup>4,9</sup> there remains room for improvement.

The survival differences described above are likely multifactorial in nature. Comorbid medical conditions are common in elderly patients with CLL,<sup>10,11</sup> and comorbid disease may adversely impact treatment<sup>11–13</sup> and overall survival (OS).<sup>13–15</sup> Also, the Rai and Binet staging systems have prognostic value, with higher stage disease portending a poorer prognosis<sup>7,11</sup>; elderly patients present with advanced stage disease more often than their younger counterparts.<sup>7,11</sup>

Other disease-specific factors that negatively impact prognosis include *IGHV* unmutated status and the presence of certain cytogenetic abnormalities (e.g. del11q, del17p, and complex karyotype) and gene mutations (e.g. *BIRC3*, *NOTHC1*, *SF3B1*, and *TP53*).<sup>16–22</sup> Studies assessing the prevalence of these genetic and molecular

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biomarkers in different age groups have conflicting results.<sup>7,11,23,24</sup> However, in a study of 1160 untreated CLL patients, Jeromin and colleagues noted higher mean age in patients with mutations in *TP53* ( $68.7 \pm 10.9$  versus  $65.1 \pm 10.4$ ,  $p = 0.003$ ) compared with patients with wild-type *TP53*,<sup>23</sup> and those with mutated *TP53* had significantly shorter survival (HR 2.21, 95% CI 1.37–3.56,  $p = 0.001$ ). This data was extended by Truger and colleagues,<sup>24</sup> who found an association between increasing age and higher burden of independent adverse prognostic markers (defined as unmutated *IGHV*, *SF3B1* mutation, *TP53* mutation, del11q, or del17p), as well as between higher burden of adverse prognostic markers and shorter OS. Altogether, these data suggest that older patients with CLL have several unique clinicobiologic disease features that may adversely impact the treatment of their disease and the outcomes thereof.

The Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, is one standard of care for the frontline treatment of CLL patients of all ages, including elderly patients with significant comorbidity and those harboring del17p or *TP53* mutation.<sup>25</sup> Despite the clinical successes of ibrutinib, there remains ample opportunity to improve the clinical courses and outcomes of elderly patients with CLL. Below we summarize the clinical experience with ibrutinib in treatment-naïve elderly CLL patients, and discuss emerging data from studies combining ibrutinib and other BTK inhibitors with anti-CD20 monoclonal antibodies that aim to improve upon the success of ibrutinib monotherapy.

### Ibrutinib monotherapy

PCYC 1102 was a two-arm phase Ib/II study of ibrutinib monotherapy, with one arm involving 31 treatment-naïve CLL/small lymphocytic lymphoma (SLL) patients aged 65 or older.<sup>26</sup> The median age for this arm was 71. Also of note, 55% (17/31) of patients had Rai stage III–IV disease, 48% (15/31) had unmutated *IGHV*, 6% (2/31) harbored del17p, and 3% (1/31) harbored del11q. After median follow up of 22.1 months, 29% (9/31) patients required treatment interruption due to grade 3 or greater toxicity, with one patient requiring permanent dose reduction and two patients discontinuing therapy altogether. Diarrhea was the most common adverse event, occurring in 68% (21/31) of patients. One grade

4 event (thrombocytopenia) was reported, and no grade 5 events were reported. With regard to secondary outcome measures of efficacy, at 5 years, 87% of patients achieved an objective response [complete response (CR) + partial response (PR) + PR with lymphocytosis], with 29% achieving CR. Extended follow up of PCYC 1102 revealed an estimated 5-year progression-free survival (PFS) rate for treatment-naïve patients of 92%.<sup>27</sup> Improvements in baseline cytopenias and immunoglobulin deficiencies were noted as well. Taken together, these results suggested that ibrutinib monotherapy was safe and effective in elderly patients with CLL/SLL, and that responses were durable. One important caveat in this trial was that relatively few patients harbored the high-risk cytogenetic features del11q and del17p.

In the follow up from a phase II trial employing ibrutinib monotherapy in patients with CLL, Ahn and colleagues focused on an elderly cohort of 35 patients age 65 years or older.<sup>28</sup> In this cohort, 51.4% of patients (18/35) were treatment-naïve, 74.3% (26/35) had Rai stage III/IV disease, 65.7% (23/35) had *IGHV* unmutated disease, and 8.6% (3/35) harbored *TP53* abnormalities. The primary endpoint was response after 6 cycles of therapy, with safety, tolerability, OS, PFS, and best response assessed as secondary endpoints. Median follow up was 57 months. Following 6 months of ibrutinib therapy, the objective response rate (ORR) in the entire elderly cohort (i.e. treatment-naïve and relapsed/refractory) was 93.9%, with all responses at that time point being PR (72.7%) or PR with lymphocytosis (21.2%). No patients achieved CR after 6 months of therapy. The ORR was noted by authors to be similar in subgroups stratified by treatment history (i.e. treatment-naïve versus relapsed/refractory). After median 57 month follow up, the ORR improved to 97% in the entire elderly cohort, and the depth of response improved to CR 27.3%, PR 66.7%, and PR with lymphocytosis 3%. In terms of survival, no disease progression or death occurred in the treatment-naïve elderly cohort after median 57 months follow up. Safety and tolerability data is reported for this trial, but is not limited to the elderly cohort. In all, 3.5% (3/86) of patients discontinued therapy due to treatment-related adverse events, and 10.5% (9/86) of patients required dose reduction. Notable treatment-emergent grade 3/4 adverse events included neutropenia (38.4%), thrombocytopenia (15.1%), infection (9.3%), atrial fibrillation (5.8%), diarrhea (3.5%), rash (2.3%), and arthritis (2.3%).

RESONATE 2 was a multicenter, open-label, randomized phase III trial comparing ibrutinib monotherapy with chlorambucil in 269 patients aged 65 or older with treatment-naïve CLL/SLL.<sup>29</sup> Median ages for the ibrutinib and chlorambucil arms were 73 and 72, respectively, and each arm had similar measures of comorbid illness [Cumulative Illness Rating Scale (CIRS) >6, 31%, and 33%]. In terms of disease characteristics, 44% and 47% of patients had Rai stage III–IV disease in the ibrutinib and chlorambucil arms, respectively; 43% and 45% had unmutated *IGHV*; and 21% and 19% harbored del11q. Patients harboring del17p were excluded given the futility of chemotherapy in this subgroup of patients. After a median follow up of 18.4 months, the primary endpoint of median PFS was significantly longer in the ibrutinib arm (not reached *versus* 18.9 months) compared with the chlorambucil arm, translating into a hazard ratio (HR) for progression or death of 0.16 [95% confidence interval (CI) 0.09–0.28;  $p < 0.001$ ]. Importantly, the significant PFS difference was maintained in analyses of high-risk subgroups, including Rai stages III–IV, unmutated *IGHV*, and del11q. In terms of OS, the rate of death was significantly lower in the ibrutinib arm compared with the chlorambucil arm (HR 0.16; 95% CI, 0.05–0.56;  $p = 0.001$ ).<sup>29</sup> Similar to the PCYC 1102 trial,<sup>26</sup> the ORR to ibrutinib in RESONATE 2 was quite high (86% when including PR with lymphocytosis), with most patients achieving PR (77%) and few achieving CR (4%). Ibrutinib was well tolerated, with 9% of patients discontinuing ibrutinib therapy due to adverse events, compared with 23% in the chlorambucil arm. Although this study clearly demonstrated the efficacy of ibrutinib in elderly, treatment-naïve CLL patients, a major criticism has been the choice of therapy in the comparator arm (i.e. chlorambucil) given the proven superiority of combination chlorambucil plus anti-CD20 monoclonal antibodies over chlorambucil alone in this patient population.<sup>30–32</sup>

Extended follow-up studies of RESONATE 2 have since been published,<sup>33,34</sup> and they demonstrated several important features of ibrutinib therapy pertinent to elderly patients. First, responses with ibrutinib were durable (estimated PFS rate of 70% at 60 months in the ibrutinib arm compared with 12% in the chlorambucil arm).<sup>33</sup> Importantly, the trend in PFS benefit was sustained across high-risk subgroups (i.e. Rai stages III–IV, unmutated *IGHV*, and del11q).

Second, the ORR to ibrutinib improved with time (ORR 86% after median follow up of 18.4 months *versus* 92% after median follow up of 60 months).<sup>29,33</sup> Third, the depth of response to ibrutinib improved with time (CR rate 4% after median follow up 18.4 months *versus* 30% after median 60 months).<sup>29,33</sup> Fourth, ibrutinib was generally well tolerated, as supported by the rate of discontinuation due to adverse events of 21% after 60 months of follow up.<sup>33</sup> Finally, the prevalence of adverse events generally improved with time on treatment.<sup>33</sup>

Results of the PCYC112 and RESONATE 2 trials (summarized in Table 1), coupled with studies demonstrating improved clinical outcomes in elderly patients with treatment-naïve disease using chemoimmunotherapy compared with chemotherapy alone,<sup>30,32</sup> prompted trials to evaluate the safety and efficacy of ibrutinib in combination with anti-CD20 monoclonal antibodies.

#### Ibrutinib in combination with anti-CD20 monoclonal antibodies

Two phase III trials have specifically evaluated the efficacy of ibrutinib in combination with anti-CD20 monoclonal antibodies in elderly patients over the age of 65 years with treatment-naïve disease.<sup>35,36</sup> A third trial evaluated ibrutinib in combination with rituximab in CLL patients with high-risk features,<sup>37</sup> but only a fraction of patients were treatment-naïve (27/208, 13%) and not all patients were over the age of 65 (age range 42–83).

In the recently published phase III A041202 study,<sup>36</sup> 524 patients aged 65 or older with previously untreated CLL were randomized to receive either bendamustine plus rituximab (BR), ibrutinib plus rituximab (IR), or ibrutinib alone. Both the bendamustine and rituximab components were administered for six cycles, while ibrutinib was administered in typical fashion until disease progression or unacceptable toxicity. The median age of the enrolled cohort was 71 years. In this trial, 6% of patients harbored del17p, 10% mutated *TP53*, 19% del11q, 29% complex karyotype, and 61% unmutated *IGHV* gene (of note, only 360/524 patients underwent testing for *IGHV* mutation status). These cytogenetic and molecular abnormalities were similarly represented in each treatment cohort, with the exception of complex karyotype, which was represented

more heavily in the IR cohort. In terms of efficacy, the ibrutinib and IR regimens achieved higher ORR, but lower CR rate compared with BR (ORR 94%, 93%, and 81%, respectively; CR rate 7%, 12%, and 26%). These findings are consistent with previously published data.<sup>29,38</sup> Like ORR, PFS favored the ibrutinib-containing regimens. After median follow up of 38 months, the estimated 2-year PFS rates were 74% for BR, 88% for IR, and 87% for ibrutinib alone. There was no significant difference among the three treatment groups with regard to OS, but the crossover design and relatively short follow up may confound interpretation of this outcome measure. Perhaps the most important finding, though, was that rituximab provided no clear benefit when added to ibrutinib, as response rates and PFS with IR were essentially identical to that of ibrutinib monotherapy. In terms of safety, the rates of hematologic and nonhematologic adverse events were similar to prior studies,<sup>26,29,38</sup> and the addition of rituximab to ibrutinib proved no more toxic or intolerable than ibrutinib alone.

The iLLUMINATE trial was a phase III study involving 229 patients aged 65 years or older (or younger than age 65 with CIRS >6, creatinine clearance <70, del17p, or mutated *TP53*) who were randomized to receive chlorambucil plus obinutuzumab (CO) or ibrutinib plus obinutuzumab (IO) as first-line treatment for CLL/SLL.<sup>35</sup> The median ages were 70 and 72 for the IO and CO arms, respectively; patients under the age of 65 comprised 21% and 19% of patients in each arm. Also of note, 65% of patients in each treatment arm had high-risk disease features, defined as the presence of del11q, del17p, mutated *TP53*, or unmutated *IGHV*. The primary endpoint was PFS as determined by independent review committee, and, to this end, the combination of ibrutinib and obinutuzumab proved superior. After median follow up of 31.3 months, median PFS was not reached in the IO group and was 19 months in the CO group. Estimated 30-month PFS rates were 79% and 31%. Interestingly, in a subgroup analysis of only those patients with high-risk disease features, median PFS was not reached in the IO arm, and was 14.7 months in the CO group. Median OS was not reached in either treatment group, possibly related to the cross-over design, with 40% of patients in the CO arm going on to receive ibrutinib. With regard to response rates and depth of response, IO again proved superior. More

specifically, the ORR was 88% with IO and 73% with CO, with corresponding CR rates of 19% and 8%. In this study, minimal residual disease (MRD) was assessed in the peripheral blood or bone marrow by flow cytometry, and was defined as <1 CLL cell per 10,000 leukocytes. Overall, rates of MRD-negativity in the peripheral blood or bone marrow were 35% and 25% in the IO and CO treatment arms, respectively. In the subset of patients with high-risk disease features, MRD-negativity rates in the peripheral blood or bone marrow were 27% (IO) and 15% (CO). In sum, these results indicate that elderly patients and those with high-risk disease features are more likely to respond, achieve CR and MRD-negativity, and live free of disease progression when treated with IO compared with CO. However, when framing the results of this trial, it is important to note an apparent incongruity in the PFS results obtained with CO in the iLLUMINATE and CLL11 trials: median PFS 19 months in iLLUMINATE *versus* 26.7 months in CLL11.<sup>30</sup> These differences were attributed to differences in methods of disease monitoring and discrepant numbers of patients with high-risk disease features.<sup>35</sup>

The combination of ibrutinib and obinutuzumab in the iLLUMINATE trial was reasonably well tolerated, with only 9% of patients discontinuing ibrutinib due to treatment-related adverse events over a median 29.3 months of treatment. Another 4% of patients in the IO arm discontinued obinutuzumab due to treatment-related adverse events. Dose reductions due to adverse events were required in 15% of patients receiving IO. In general, the safety profile for the IO combination was similar to prior trials of these agents used as monotherapy.<sup>39</sup> Grade 3 or 4 adverse events occurred in 68% of patients treated with IO, with neutropenia (18%), thrombocytopenia (15%), pneumonia (6%), and atrial fibrillation (5%) being the most common. Serious, or grade 3 or greater, obinutuzumab-related infusion reactions occurred in 3% of patients. Deaths due to adverse events occurred in 9% of patients in the IO arm.

The studies described above (summarized in Table 1), serve to demonstrate the superior PFS benefit of ibrutinib-containing regimens over two chemoimmunotherapy regimens in routine use in elderly patients with CLL. However, the addition of rituximab to ibrutinib has thus far not provided added benefit in terms of response rates

or survival. Further, while acknowledging the limitations of cross-trial comparisons, the outcomes achieved with combination obinutuzumab and ibrutinib seem similar to results with ibrutinib monotherapy.<sup>29,35,36</sup> Of course, longer-term follow up will be needed to discern if there is any benefit in combining ibrutinib with an anti-CD20 monoclonal antibody.

As we await such follow up, it is worth discussing existing data that might explain the apparent lack of added benefit when anti-CD20-directed agents are combined with ibrutinib. Anti-CD20 antibodies like rituximab and obinutuzumab are known to exert their anti-tumor effects through multiple immune-mediated mechanisms, including complement-dependent cytotoxicity (CDC), antibody-dependent phagocytosis, antibody-dependent cellular cytotoxicity (ADCC), and direct cell death.<sup>40–42</sup> In an autologous CLL model [i.e. natural killer (NK) cells and CLL cells derived from the same patient], Kohrt and colleagues showed that ibrutinib antagonizes NK cell-mediated and rituximab-dependent cellular cytotoxicity.<sup>43</sup> The antagonistic effect of ibrutinib was postulated to result from inhibition of a non-BTK target, specifically interleukin-2 inducible tyrosine kinase (ITK), given the known role of ITK in NK cell effector function.<sup>44</sup> Other studies have confirmed the findings of ibrutinib-impaired ADCC and NK cell degranulation,<sup>45,46</sup> and have gone on to show that ibrutinib additionally impairs rituximab-, and obinutuzumab-dependent phagocytosis.<sup>45–48</sup> Also, ibrutinib has been shown to downregulate CD20 expression on target CLL cells, and thereby negatively impact ofatumumab-mediated CDC.<sup>49,50</sup> Thus, ibrutinib seems to antagonize the anti-tumor effects of anti-CD20 antibodies by several mechanisms, which may help to explain why clinical outcomes with ibrutinib plus an anti-CD20 antibody seem roughly equivalent to ibrutinib alone. Importantly, if, as the data suggest, the antagonistic effects of ibrutinib are partly mediated by inhibition of non-BTK targets, then a more specific BTK inhibitor might be expected to yield better clinical outcomes when paired with an anti-CD20 antibody.

### **Acalabrutinib: existing data and future directions**

Acalabrutinib (ACP-196) is a second-generation, irreversible BTK inhibitor that is similar to ibrutinib in several respects. More specifically, both

acalabrutinib and ibrutinib are oral drugs that covalently bind to cysteine 481 in the ATP binding pocket of BTK, and exhibit half maximal inhibitory concentrations (IC<sub>50</sub>) in the low nanomolar range (IC<sub>50</sub> 5.1 nM and 1.5 nM for acalabrutinib and ibrutinib, respectively).<sup>51</sup> However, one important difference between acalabrutinib and ibrutinib is selectivity. As discussed above, ibrutinib is known to antagonize NK cell-mediated and anti-CD20 antibody-dependent ADCC due to its off-target inhibition of ITK. Preclinical studies have demonstrated that acalabrutinib inhibits ITK far less potently than ibrutinib, with an ITK IC<sub>50</sub> of >1000 nM for acalabrutinib compared with 4.9 nM for ibrutinib.<sup>51</sup> Further, several groups have demonstrated that acalabrutinib does not antagonize rituximab- or obinutuzumab-dependent NK cell-mediated ADCC,<sup>52,53</sup> nor does it impair rituximab- or obinutuzumab-dependent phagocytosis.<sup>46,48</sup> In light of these preclinical data, the hope is that acalabrutinib and anti-CD20 monoclonal antibodies can be combined to improve clinical outcomes through additive or synergistic effects.

Clinical trials investigating acalabrutinib, alone and in combination with other agents, for the treatment of CLL are currently underway. To this end, Byrd and colleagues published preliminary results of a phase I/II trial (NCT02029443) evaluating acalabrutinib given in two dose schedules [100 mg twice daily (BID) and 200 mg once daily (QD)] in patients with previously untreated CLL.<sup>54</sup> At time of publication, 74 patients had been treated, and 72 were evaluable for response. Median age of the treated cohort was 64 (range: 48–85) years. After median time on study of 11 (range: 1–15) months, 97% (72/74) of patients remained on acalabrutinib. In terms of adverse events, few recurrent grade 3–4 events were reported, with only syncope and hypertension occurring in more than one patient (syncope, *n* = 2; hypertension, *n* = 2). One grade 5 event (pneumonia) occurred. Acalabrutinib demonstrated good clinical activity, with an ORR of 96% [PR = 86%, PR with lymphocytosis = 10%, standard deviation (SD) = 4%]. No patients had achieved CR at time of publication. Details regarding adverse event and response rates in patients age 65 or older are not yet available.

Additionally, Woyach and colleagues presented preliminary results from a phase Ib/II trial of acalabrutinib in combination with obinutuzumab

in patients with treatment-naïve ( $n = 19$ ) or relapsed/refractory ( $n = 26$ ) CLL.<sup>55</sup> Obinutuzumab was administered every 28 days for six cycles starting with Cycle 2, and all patients ultimately received acalabrutinib 100 mg QD until progressive disease or unacceptable toxicity. The median age was 61 (range = 42–76) years. After median follow up of 36 (treatment-naïve) and 39 (relapsed/refractory) months, the most commonly encountered grade 3–4 adverse events were decreased neutrophil count (24%), syncope (11%), decreased platelet count (9%), increased weight (9%), and cellulitis (9%). Two (4%) grade 3 bleeding events and 1 (2%) grade 3 atrial fibrillation event were reported. In the treatment-naïve cohort, the ORR was 95% (CR = 32%, PR = 63%), and bone marrow MRD-negativity rate was 26% as measured on Cycle 12 Day 1. Median duration of response and PFS were not reached. Data pertaining specifically to elderly patients were not reported.

Finally, results of a phase III trial (NCT02475681) were recently reported, comparing the safety and efficacy acalabrutinib alone (A) or in combination with obinutuzumab (AO) to chlorambucil in combination with obinutuzumab (CO) in treatment-naïve CLL patients age 65 years or older (or younger than age 65 with CIRS >6 or creatinine clearance <70). A total of 535 patients were randomized (1:1:1) to the three treatment arms. The median age of the entire study cohort was 70 years (range, 41–91). The primary outcome measure was PFS, with additional secondary outcome measures of ORR, OS, and safety. After median follow up of 28 months, median PFS was significantly longer in the A and AO arms (medians not reached) compared with the CO arm (22.6 months). Median OS was not reached in any treatment arm. When compared with CO, the AO regimen reduced the risk of progression or death by 90% (HR 0.10, 95% CI 0.06–0.18,  $p < 0.0001$ ). The ORR in each treatment arm was 85% for A, 94% for AO, and 79% for CO, with the difference between the AO and CO treatment arms deemed statistically significant ( $p < 0.0001$ ). In terms of safety, grade >3 adverse events occurred in 50%, 70%, and 70% of patients in the A, AO, and CO arms, respectively. Infusion reactions occurred in 13% of patients in the AO arm and 40% of patients in the CO arm. Rates of any grade atrial fibrillation (4%/3%/1%), grade >3 bleeding (2%/2%/0%), and grade >3 hypertension (2%/3%/3%) were

similar across the A/AO/CO treatment arms, while any grade bleeding was more common in the acalabrutinib-containing arms (39%/43%/12%). Adverse events led to treatment discontinuation in 9% of patients treated with A, 14% treated with AO, and 11% treated with CO. Final analysis of this study, with more mature survival, response, and safety data, is eagerly awaited. It will be interesting to see if the combination of acalabrutinib and obinutuzumab yields the best outcome, especially given the *in vitro* results described above suggesting little-to-no antagonistic effect of acalabrutinib on anti-CD20 antibody-dependent immune-mediated processes.<sup>46,48,52,53</sup>

### Zanubrutinib: existing data and future directions

Zanubrutinib (BGB-3111) is an orally bioavailable, second-generation, irreversible BTK inhibitor with an IC<sub>50</sub> similar to that of ibrutinib.<sup>56</sup> With regard to ITK, zanubrutinib is more selective, with an IC<sub>50</sub> of 56 nM compared with 3 nM for ibrutinib.<sup>56</sup> *In vitro*, zanubrutinib was shown to inhibit rituximab-dependent and NK-cell mediated target cell lysis significantly less potently than ibrutinib.<sup>57</sup> This finding may have implications for combination therapy with zanubrutinib and anti-CD20 monoclonal antibodies. As it stands, zanubrutinib has demonstrated single agent safety and efficacy in B-cell malignancies including CLL in an early phase clinical trial.<sup>58</sup> Although there are no ongoing studies specifically focused on treatment-naïve CLL patients age 65 years or older, two ongoing studies (NCT03336333 and NCT02569476) are open to this patient population. In NCT03336333, a phase III trial, previously untreated patients with CLL are randomized to receive either zanubrutinib or BR. This trial does not include a treatment arm with zanubrutinib plus anti-CD20 monoclonal antibody. In NCT02569476, a phase Ib study, patients with B-cell malignancies will be treated with the combination zanubrutinib and obinutuzumab. Results from these studies are eagerly awaited.

### Conclusion

CLL is a heterogeneous disease of the elderly. Numerous studies have aimed to determine the safest and most effective treatment for this unique patient population. The PCYC 1102 and RESONATE 2 trials helped to establish ibrutinib

**Table 1.** Summary of clinical trials evaluating ibrutinib +/- anti-CD20 monoclonal antibodies in treatment-naïve older patients with CLL.

Trial	Treatment arms	Number of patients	Median age (range)	Median follow up (months)	ORR (CR + Cri+ PR)	PFS rate	Grade $\geq$ 3 AE
PCYC 1102 <sup>26,27</sup>	Ibrutinib	31	71 (65–84)	5 years	87% (including PR-L)	92% at 5 years	37%
RESONATE 2 <sup>29,33,34</sup>	Chlorambucil	133	72 (65–90)	18.4	35%	34% at 24 months; median 15 months	52%
	Ibrutinib	136	73 (65–89)	18.4	92% (including PR-L)	89% at 24 months	52%
A041202 <sup>36</sup>	Bendamustine + Rituximab	183	70 (65–86)	38	81%	74% at 24 months	Hematologic 61%, nonhematologic 63%
	Ibrutinib	182	71 (65–89)	38	94%	87% at 24 months	Hematologic 41%, nonhematologic 74%
	Ibrutinib + Rituximab	182	71 (65–86)	38	93%	88% at 24 months	Hematologic 39%, nonhematologic 74%
iLLUMINATE <sup>35</sup>	Chlorambucil + Obinutuzumab	116	72 (66–77)	31.3	73%	31% at 30 months	70%
	Ibrutinib + Obinutuzumab	113	70 (66–75)	31.3	88%	79% at 30 months	68%

AE, adverse event; CLL, chronic lymphocytic leukemia; CR, complete response; ORR, objective response rate; PFS, progression-free survival; PR, partial response; PR-L, partial response with lymphocytosis.

monotherapy as the current standard of care for frontline therapy in elderly patients, including those with high-risk disease features. Despite the safety and efficacy of ibrutinib, there is a concerted effort to improve outcomes for elderly patients with CLL by combining BTK inhibitors with other agents, like anti-CD20 monoclonal antibodies. However, existing studies of ibrutinib in combination with rituximab or obinutuzumab do not seem to demonstrate improvement in clinical endpoints compared ibrutinib monotherapy. The lack of added benefit with combination therapy may be related to ibrutinib-specific antagonism of anti-CD20 monoclonal antibodies. Looking ahead, ongoing studies with the second-generation BTK inhibitors, such as acalabrutinib and zanubrutinib, alone, and in combination with anti-CD20 monoclonal antibodies, are eagerly awaited, and may yet change the frontline treatment paradigm for elderly patients with CLL.

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