HAEMA 2023; **14**(1-4):16-20

*Review Article*

# Post ASH 2022: Key studies in chronic lymphocytic leukemia (CLL)

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ABSTRACT:

Treatment of CLL (chronic lymphocytic leukemia) has dramatically changed over the last 10 years with the introduction of novel agents. Given the success of these agents in CLL, several ongoing trials are assessing their efficacy and safety in combination, with a tendency to move from continuous treatment to a fixed duration schedule, while others are using measurable residual disease (MRD) to define treatment duration. Despite these advances, new agents are still needed, with either a better safety profile or for the treatment of relapsed/refractory patients. Clinical trial data announced at the 64th ASH annual meeting that we will be presented in greater detail include 1. the outcome results from the CLL13/GAIA trial with regard to genetic markers in the frontline setting 2. the updated results of the uMRD cohort of the CAPTIVATE study, 3. the residual disease kinetics among patients with high-risk features treated with first line fixed duration ibrutinib plus venetoclax who participated in the GLOW study 4. the updated results of the triple combination of acalabrutinib, venetoclax, obinutuzumab (AVO) in previously untreated high-risk CLL patients, 5. the late breaking abstract (LBA)-6 regarding the Alpine trial, where zanubrutinib demonstrated superior PFS compared with ibrutinib in relapsed/refractory (R/R) patients with CLL and 6. data from the extended follow-up of the BRUIN study regarding pirtobrutinib in covalent-BTKi pretreated patients.

**KEY WORDS:** *Acalabrutinib, chronic lymphocytic leukemia, bcl-2 inhibitors, bruton kinase inhibitors, ibrutinib, pirtobrutinib, treatment, venetoclax, zanubrutinib*

## INTRODUCTION

Treatment of CLL (chronic lymphocytic leukemia) has dramatically changed over the last 10 years with the introduction of novel agents targeting the B cell receptor pathway, such as ibrutinib and acalabrutinib and the bcl-2 anti-apoptotic protein such as venetoclax. These agents improved outcomes, both in the frontline and in the relapsed setting including, most importantly patients with high-risk features, such as TP53 aberrations and unmutated immunoglobulin heavy chain (IGHV) gene.[1] Given the success of these agents in CLL, several ongoing trials are assessing their efficacy and safety in combination, with a tendency to move from continuous treatment to a fixed duration schedule, while others are using measurable residual disease (MRD) to define treatment duration. Despite these advances, new agents are still needed with either a better safety profile[2] or for the treatment of relapsed/refractory (R/R) patients.[3]

Clinical trial data announced at the 64th ASH annual meeting that we will be presented in greater detail include 1. the outcome results from the CLL13/GAIA trial with regard to genetic markers in the frontline setting 2. the updated results of the undetectable MRD (uMRD) cohort of the CAPTIVATE study, 3. the residual disease kinetics

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Received 01 May 2023; Accepted 31 May 2023

among patients with high-risk features treated with first line fixed duration ibrutinib plus venetoclax in the GLOW study 4. the updated results of the triple combination of acalabrutinib, venetoclax, obinutuzumab (AVO) in previously untreated high-risk CLL patients, 5. the late breaking abstract (LBA)-6 regarding the Alpine trial, where zanubrutinib demonstrated superior PFS compared to ibrutinib in R/R patients with CLL and 6. data from the extended follow-up of the BRUIN study regarding pirtobrutinib in covalent-BTK inhibitor (BTKi) pretreated

## The CLL13/ GAIA study (NCT02950051)

Genomic aberrations such as IGHV mutational status and TP53 mutations are established prognostic factors in CLL in the chemoimmunotherapy era.[4] The prognostic role of these genetic markers though has not been well established in CLL patients receiving time limited treatment with venetoclax as backbone therapy.[4] The CLL13/ GAIA trial is a randomized phase III study that evaluated the efficacy and safety of three venetoclax plus CD20 antibody-based regimens i.e. rituximab and venetoclax (VenR), obinutuzumab and venetoclax (VenO), ibrutinib, obinutuzumab and venetoclax (IVO), in comparison to standard chemoimmunotherapy (CIT) as a frontline treatment for fit patients with CLL and without TP53 mutation/deletion.[5] The co-primary endpoints of the trial were the rate of uMRD (defined as $<10^{-4}$) by flow cytometry in peripheral blood (PB) at month 15 (VenO vs CIT) and the progression free survival (PFS) for IVO versus CIT.[5] Investigators studied the prognostic role of various genetic markers in patients enrolled in the GAIA study.[4] The incidences of genomic aberrations were for del(11q) 17.5%, for trisomy 12 16.2%, for mono-allelic del(13q) 44.6% and for normal karyotype 21.7%. IGHV was unmutated (U-IGHV) in 55.9% and mutated (M-IGHV) in 41.0% of patients. Subset#2 accounted for 50 patients and was equally distributed among U-IGHV and M-IGHV patients. Regarding the incidence of gene mutations, NOTCH1 (exon 34 and 3'UTR) was present in 20.5% and BRAF/KRAS together in 9.6% of patients.[4]

No genetic subgroup was associated with uMRD. CIT led to a significantly lower uMRD rate in U-IGHV patients than in M-IGHV (42.0% vs. 66.3%, p<0.01) and in del(11q) patients than in del(13q) (39.0% vs. 58.4%, p=0.04) while mutated MYD88 was associated with a higher uMRD rate (92.3% vs 50.2%, p=0.02).[4]

In multivariable analysis including all clinical, laboratory and genetic markers significantly associated with PFS, treatment with VenO and IVO were independent favorable factors (HR 0.42 and 0.33, respectively, both p<0.01), while U-IGHV (HR 2.43, p<0.01) and mutated NOTCH1 (HR 1.46, p=0.03) were confirmed to be independent unfavorable prognostic factors. When CIT only patients were included in the multivariate analysis, del11q (HR 1.89, p=0.03), U-IGHV (HR 3.08, p<0.01) and mutated NOTCH1 (HR 2.12, p=0.01) were found to be unfavorable prognostic markers in terms of PFS. In the multivariate analysis for VenR/VenO/IVO patients, adverse prognostic markers were U-IGHV (HR 1.85, p<0.01), mutations in NOTCH1 (HR 1.54,p<0.01) and BRAF/RAS (HR 1.87, p<0.01).[4]

These early results from the GAIA study show an association of gene mutations with lower uMRD rates and shorter PFS after CIT and venetoclax-based regimens.[4] Interestingly, IGHV and NOTCH1 mutational status retain their prognostic role in both treatment types. These results warrant further examination in larger series and validation in independent cohorts to clarify the prognostic and predictive role of these genomic aberrations.

## The CAPTIVATE trial (NCT02910583)

CAPTIVATE is a multicenter, randomized phase II trial with two different cohorts an MRD cohort[6] and a fixed duration cohort[7] in previously untreated CLL patients <70 years of age and with ECOG performance status 0-1 requiring therapy. In the MRD cohort, participants received a lead-in phase of three cycles of ibrutinib 420 mg/daily and then 12 cycles of combined ibrutinib 420 mg/daily plus venetoclax 400 mg/daily following a ramp-up dosing. Patients with confirmed uMRD were randomly double-blind assigned 1:1 to placebo or ibrutinib; patients without confirmed uMRD (uMRD not confirmed) were randomly assigned 1:1 to open-label ibrutinib or ibrutinib plus venetoclax. Primary endpoint was 1-year disease-free survival (DFS) rate with placebo versus ibrutinib in the confirmed uMRD population.[6] DFS was defined as the time from randomization to MRD relapse, progression of disease per investigator assessment or death, whichever occurred sooner. One-year DFS rate was not statistically different between placebo and ibrutinib in the confirmed uMRD population.[6]

At the 64th ASH annual meeting and exhibition, Allan and colleagues presented an update of the MRD cohort, for patients with confirmed uMRD after a median follow up of 56 months.[8] The 3-year DFS was 93% for the ibrutinib arm versus 85% for the placebo arm, with no statistical difference (p=0.1621). The 3-year DFS in patients with del(17p), TP53 mutations or complex karyotype were similar to the overall population.[8] At 4 years post randomization, there was no significant difference in PFS or OS rates between the two arms. In particular, the 4-year PFS rates were 95% with ibrutinib, and 88% with placebo, whereas the 4-year OS rates were 98% with ibrutinib and 100% with placebo. The MRD negativity rate dropped

from 100% at the time of randomization to 75% on the ibrutinib arm and 74% on the placebo arm at 3 years post randomization. Overall, though there was no difference in the MRD negativity rate between the two arms.

These results support the benefit of fixed duration therapy of I+V in patients with confirmed MRD, since continued treatment with ibrutinib did not add any more benefit with regards to DFS, PFS and OS.[8]

## The GLOW Study (NCT03462719)

The GLOW study is a phase 3 trial evaluating the efficacy and safety of ibrutinib plus venetoclax in untreated CLL patients, who were either over 65 years of age or <65 years old, but with CIRS (Cumulative Illness Rating Scale) score greater than 6 or creatinine clearance of less than 70 ml/min. Patients with TP53 mutations or del(17p) were excluded. Patients were randomized 1:1 to receive I+V (3 cycles ibrutinib lead-in, then 12 cycles I+V) or chlorambucil-obinutuzumab (Clb+O, 6 cycles). The primary endpoint was PFS as assessed by an independent review committee (IRC).[9] The study enrolled 211 patients and results with a median follow up of 27.7 months were published revealing a significantly longer PFS for I+V than for Clb+O (HR 0.216; p<0.001). This PFS improvement was noted across all pre-defined subgroups. Updated results were present at the 64th ASH annual meeting and exhibition after a median follow up of 46 months. The combination of I+V reduced the risk of progression or death by 79% versus the control arm with an estimated 3.5 year PFS of 74.6% for I+V and 24.8% for Clb+O.

Regarding the MRD kinetics, PB uMRD was attained early during treatment with I+V and declined by 17% over 2 years. At 3 months after end of treatment (EOT +3), the proportion of patients who received I+V who achieved uMRD in bone marrow (BM) was 51.9% while in the Clb+O arm was 17.1%. Notably, 40% of patients retained uMRD 2 years post treatment, including >25% with deeper uMRD responses of $<10^{-5}$. The PFS though was better sustained with I+V versus Clb+O regardless of the MRD status at the EOT +3.

Unmutated IGHV and TP53 mutations are negative prognostic and predictive factors for both CIT and venetoclax plus anti-CD20 regimens for CLL.[10] For this reason, Niemann et al investigated MRD kinetics and outcomes of I+V in the GLOW study in these subgroup of patients.[10] Noteworthy, uIGHV CLL patients in the I+V arm achieved earlier and higher rates of uMRD rates compared to mIGHV CLL patients. Specifically, uMRD rates after 6 cycles of combination treatment and at EOT+3 were 52.2% and 59.7% respectively in uIGHV patients and 31.3% and 40.6% respectively in mIGHV patients. However, uMRD was better sustained post-treatment in patients with mIGHV patients.

At 42 months 87.5% of patients in the I+V arm were alive versus 77.6% in the Clb+O (HR 0.487, p=0.0205). Most deaths in the Clb+O occurred while off treatment. More infection-related deaths were seen in the Clb+O arm.[10]

In summary, in the GLOW study 75% of previously untreated older patients or with comorbidities were alive and progression free at 3.5 years with this all-oral, fixed-duration regimen of I+V. This is the first fixed duration combination to demonstrate an OS advantage in previously untreated CLL patients (HR 0.487) versus CIT.[10] It should also be noted that outcomes depended more on the IGVH mutational status and not on MRD negativity, challenging the use of MRD as surrogate marker of PFS in this therapeutic setting.

## The AVO trial

The "AVO" trial is an investigator initiated open-label, single-arm, phase 2 study, evaluating the combination of acalabrutinib, obinutuzumab and venetoclax in treatment naive patients with CLL, enriched for high-risk features. The study initially included treatment naïve patients with any genetic profile (cohort 1, n=37 patients), followed by a multi-center expansion cohort, that included only patients with mutations or deletions of TP53 (cohort 2, n=31 patients).

Treatment was given every 28 days and started with the administration of acalabrutinib, at 100 mg twice daily. Obinutuzumab was added in cycle 2 and given for six cycles (100 mg on cycle 2 day 1, 900 mg on day 2, 1000 mg on day 8, and 1000 mg on day 15 and on day 1 of cycles 3-7), while venetoclax was added in cycle 4, once daily, with dose ramp-up from 20 mg up to a final dose of 400 mg thereafter.

The primary endpoint was complete remission (CR) with uMRD (defined as $<10^{-4}$ as measured by four-color flow cytometry) in the BM, at cycle 16 day 1 (C16D1). If the patient had CR and uMRD at C16D1, therapy could be discontinued. All other patients continued AV through cycle 24 with the option to discontinue if they achieved BM uMRD.

At the 64$^{th}$ ASH annual meeting and exposition, results from 68 patients enrolled (cohort 1 all comers n=37, cohort 2 TP53-aberrant patients n=31) were presented with a median follow up of 35 months. AVO achieved high rates of clinical response and undetectable MRD at cycle 16 in cohort 1, since 43% (24/56) of all patients were in CR and 86% (48/56) had BM uMRD at C16. Patients with TP53 aberrations achieved similar results with 52% (15/29) achieving CR and 83% (24/29) achieving BM uMRD at Cycle 16. No difference in response or MRD based on

IGHV mutational status was noted. At a median follow-up of 35 months, responses are durable with a 93% PFS. This triplet therapy also had a good safety profile. Dose reduction was needed in 14 patients (21%). Most common hematological toxicities were neutropenia (75%, grade 3-4 37%) and thrombocytopenia (78%, grade 3-4 28%). Most common non hematological toxicity was headache (78%, mainly grade 1 and 2) and fatigue (76%, grade 3 1%). Atrial fibrillation (AF) was noted in only 3%.

Overall, this study provided the foundation for an MRD-guided, time-limited approach with the AVO triplet to be used in TP53 aberrant. A+V combination is currently under investigation with or without obinutuzumab in the phase 3 ACE-CL-311/Amplify trial (NCT03836261) versus CIT in non high- risk previously untreated CLL patients.

### The ALPINE trial

ALPINE is a multicenter, randomized, open-label, phase 3 trial of zanubrutinib versus ibrutinib in R/R CLL patients. This study compared the efficacy, safety and side-effect profile of zanubrutinib with those of ibrutinib. The primary endpoint was the investigator-assessed overall response rate (ORR) and key secondary endpoints were PFS and the incidence of AF or flutter.

The trial was originally designed to include 400 patients and the primary endpoint of ORR to be determined by IRC. However, the protocol of the study was later modified to include 600 participants and the primary endpoint to be assessed by the investigators of the trial. Patients (n=652) were enrolled and randomized in a 1:1 manner to receive zanubrutinib 160 mg twice daily (n=327) and ibrutinib 420 mg once daily (n=325), until disease progression, unacceptable toxicity, treatment consent withdrawal or study termination. The preplanned interim analysis was scheduled approximately 12 months after the first 415 patients were enrolled. At 15 months of median follow up ORR was significantly higher with zanubrutinib versus ibrutinib (78.3% versus 62.5%; $p < 0.001$).[11]

At the latest 64th ASH annual meeting after a median follow-up of 29.6 months ORR was 86.2% for zanubrutinib versus 75.7% for ibrutinib (p=0.007). In addition, the secondary endpoints of the trial were presented. In particular, it was presented[12] and later published[2] that zanubrutinib demonstrates superior PFS compared to Ibrutinib (79.5% versus 67.3%, HR 0.65, p=0.0024). It should be noted that in the RESONATE trial PFS at 24 months was 74% for ibrutinib.[13] PFS as assessed by an independent review committee in patients with TP53 aberrations was at 24 months 77.6% for zanubrutinib versus 55.7% for ibrutinib (HR 0.52, p=0.0134).

In terms of safety, the rate of adverse events was similar in both arms. Lower rate of grade ≥ 3 and serious adverse events (SAEs) and fewer AEs leading to treatment discontinuation and dose reduction were noted in the zanubrutinib arm. Moreover, cardiac adverse events and AF/flutter were lower with zanubrutinib, suggesting that this second-generation BTK inhibitor has favorable cardiac profile.

To sum up, these data suggest that zanubrutinib yields a better ORR than ibrutinib, with a better safety profile especially in terms of cardiotoxicity and a PFS benefit, including patients with TP53 aberrations.

### The BRUIN study

Pirtobrutinib, is a highly selective, non-covalent BTKi that inhibits both well type and C481 – mutant BTK with a favorable pharmacology, that enables continuous BTK inhibition. BRUIN is multicenter study for patients with previously untreated B-cell malignancies including CLL/SLL. Key endpoints included ORR, PFS and safety. Among the 276 pts with CLL/SLL who had received a prior BTKi, the majority (75%) discontinued prior BTKi therapy due to disease progression. In this difficult to treat population, ORR including partial response (PR) with lymphocytosis was 74%, being mostly PR (64%). Most common AEs were fatigue (26%) and diarrhea (20%). Only 2% discontinued due to treatment-related AE.[3]

## CONCLUSIONS

The management of CLL has changed dramatically over the last decades with the development of novel drugs. Several clinical trials are currently testing not only new drugs, but also new combinations, new sequences along with time-limited approaches. As patients with CLL live longer and more are being treated with both a BTKi and a bcl-2 inhibitor, double refractory patients will soon be a major problem and therefore there is an emerging unmet medical need for these patients. Non-covalent BTKi, such as pirtobrutinib and approaches such as CAR T cell therapy show promising efficacy results and are eagerly awaited to reach our therapeutic quiver. Till, then it is our privilege and responsibility as physicians to undertake clinical trials to accelerate progress.

***Conflict of Interest:*** E.H. has received honoraria from Abbvie, Janssen-Cilag and Astra Zeneca, E.K. has received honoraria from Abbvie, E.A no conflict of interest

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