Highlights in chronic lymphocytic leukaemia

A. Janssens, MD, PhD

SUMMARY

During the last years several phase III studies comparing targeted agents (alone or in combination) to conventional chemo immunotherapy (CIT) have been published in chronic lymphocytic leukaemia (CLL) and small lymphocytic leukaemia (SLL). EHA 2019 featured several presentations on the most recent progress in this field. A selection of abstracts, as well as their impact on clinical practice, are discussed below.
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CLL14: FIXED-DURATION TREATMENT WITH VENETOCLAX PLUS OBINUTUZUMAB IN PREVIOUSLY UNTREATED CLL

Fischer et al. presented the results of the **CLL 14 trial** as one of the best six abstracts during the Presidential Symposium. This multinational, open-label, phase III trial compared **fixed-duration** targeted **venetoclax (12 cycles) plus obinutuzumab (6 cycles) (VenG) treatment with chlorambucil (12 cycles) plus obinutuzumab (6 cycles) (ClbG)** treatment in previously **untreated CLL** patients (N=432) with comorbidities (CIRS score >6 and/or an estimated creatinine clearance <70 mL/min). Median age, total CIRS score, and CrCl at baseline were 72 years, 8, and 66.4 ml/min respectively. After 29 months median follow-up, superior progression free survival (PFS) (primary endpoint) was observed with VenG *vs.* ClbG (PFS at 2 years VenG *vs.* ClbG, 88% *vs.* 64% (hazard ratio [HR] 0.35, p<0.0001). Minimal residual disease (MRD)-negativity by allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) (key secondary endpoint) was significantly higher with VenG *vs.* ClbG in both peripheral blood (PB) (76% *vs.* 35% [p<0.0001]) and bone marrow (BM) (57% *vs.* 17% [p<0.0001]) 3 months after treatment completion. Landmark analysis for this timepoint by PB MRD status showed that MRD-negativity was associated with longer PFS. MRD-negativity rates were more sustainable with VenG: 81% of VenG *vs.* 27% of ClbG patients were MRD-negative 12 months after treatment completion; MRD-negativity rates by next generation sequencing (NGS) confirmed these results; 78% of VenG *vs.* 34% of ClbG patients had MRD-negative status at $<10^{-4}$, 35% *vs.*, 15% at $\geq 10^{-6}$–$<10^{-5}$ and 31% *vs.* 4% at $<10^{-6}$, respectively.

Fixed-duration VenG (12 months) induced deep, high ($<10^{-4}$ in 1 out of 4 patients and $<10^{-6}$ in 1 out of 3 patients) and long lasting MRD-negativity rates (with a low rate of conversion to MRD-positive status 1 year after treatment) in previously untreated patients with CLL and comorbidities, translating into improved PFS.[1,2]

The CLL14 study also evaluated the prognostic impact of genetic risk factors assessed by fluorescence in situ hybridisation (FISH), immunoglobulin heavy chain variable region mutational status (IGHV) and NGS. None of the parameters impaired overall response rate (ORR) to VenG at treatment completion. For ClbG, the ORR rate was lower in patients with del(17p) (36% *vs.* 73%), del(11q) (58% *vs.* 74%), TP53mut (58% *vs.* 74%), ATMmut (56% *vs.* 75%) and BIRC3mut (33% *vs.* 74%). **Del(17p) was the only genomic abnormality with impact on PFS in ClbG** (HR 4.6, p<0.001) **and VenG** (HR 4.4, p=0.001) (*Figure 1a*). Similarly, *TP53* mutations affected PFS in both treatment arms (ClbG HR 2.7, p=0.001; VenG HR 3.1, p=0.01). However, TP53mut without del(17p) was not associated with shorter PFS. None of the other evaluated factors affected VenG efficacy, while for ClbG del(11q) (HR 2.3, p=0.002), BIRC3 (HR 4.0, p=0.001), NOTCH1 (HR 1.8, p=0.03) and unmutated IGHV (HR 3.4, p<0.001) were adverse factors. In several genetic subgroups, including

Leuven University Hospital, Leuven, Belgium.

Please send all correspondence to: A. Janssens, MD, PhD, Department of Development and Regeneration, Leuven University Hospital, Herestraat 49, 3000 Leuven, Belgium, Tel: +32 (0)16 346862, E-mail: ann.janssens@uzleuven.be

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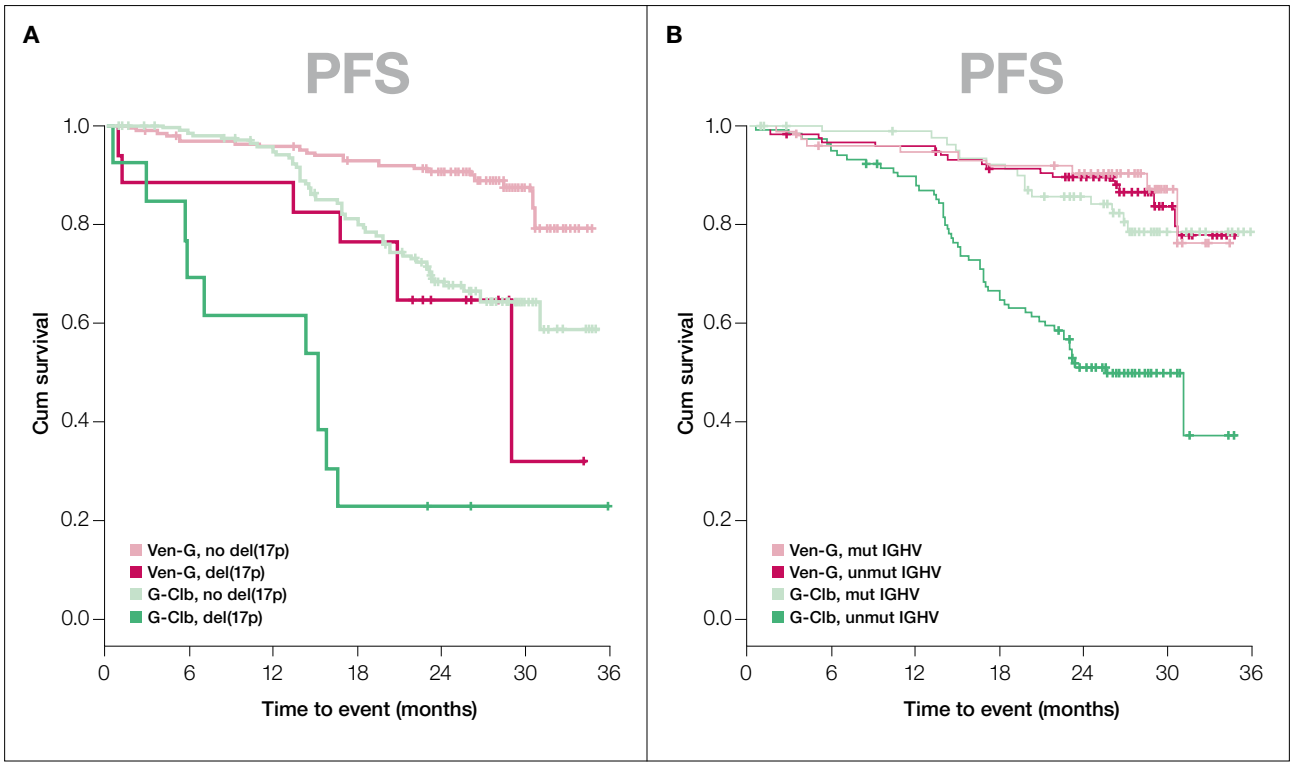

FIGURE 1. Progression-Free Survival in the CLL14 study.[3]

del(17p), del(11q), TP53mut, NOTCH1mut, SF3B1mut and ATMmut, VenG was superior to ClbG in PFS. Regarding IGHV, **patients with unmutated status had a significant PFS benefit from VenG** in comparison to ClbG (IGHVunmut HR 0.2, p<0.001; IGHVmut HR 0.6, p=0.29) (*Figure 1b*). Multivariable testing for interaction between treatment and IGHV mutational status was significant (p=0.03), indicating unmutated IGHV as a predictive factor for increased benefit from VenG. **Overall survival (OS) was lower with del(17p) in both treatment arms** (ClbG: HR 11.0, p<0.001; VenG: HR 3.4, p=0.03) and with TP53mut, BRAFmut and IGHVunmut in the ClbG arm (HR 5.5, p=0.002; HR 6.6, p<0.01; HR 5.4, p=0.03), while none of the other factors were significantly associated with overall survival.

In summary, the prognostic value of genomic aberrations, IGHV and gene mutations were confirmed for ClbG, while with VenG only del(17p) and TP53mut were associated with shorter PFS and only del(17p) with shorter OS. Unmutated IGHV was identified as a predictive factor characterizing a group of patients with particular benefit from VenG.[3]

Complex karyotype (CKT) (metaphase spreads after IL-2/CpG-stimulation), defined as presence of ≥3 chromosomal aberrations, is associated with poor prognosis in CLL. In the same **CLL14 trial**, the prognostic role of CKT was investigated. CKT was found in 17% and 15% of VenG and ClbG patients, respectively. Del(17p)/TP53mut was detected in 33% and 31% of VenG and ClbG CKT patients. In the VenG arm, ORR was 82% in CKT and 87% in non-CKT patients; the MRD negativity rate 3 months after treatment completion did not differ between groups in PB and BM. No difference in PFS or OS was observed between CKT and non-CKT patients. For ClbG, ORR was 50% in CKT and 78% in non-CKT patients; the MRD negativity rate was lower in CKT *vs.* non-CKT patients, both in PB (20% *vs.* 40%, respectively) and BM (0% *vs.* 22%, respectively). Median PFS was 19 months in ClbG CKT patients and not reached (NR) in non-CKT patients (HR 2.790, p<0.001). Likewise, OS was significantly shorter in CKT *vs.* non-CKT patients (median NR, HR 3.736, p=0.006). In CKT patients, presence of del(17p)/TP53mut did not significantly alter PFS compared with patients without del(17p)/TP53mut in the VenG or ClbG groups. While CKT correlates well with CLL-international prognostic index (IPI) high/very high risk, 2 out of 3 of these patients do not show TP53 aberrations. ***Presence of CKT in patients treated with ClbG is associated with shorter PFS and OS, including patients without TP53 aberrations. In contrast, VenG is able to overcome the adverse risk associated with CKT.*** These findings support the clinical importance of chromosome analysis before choosing frontline therapy, and underline the particular value of VenG in CLL CKT patients.[4]

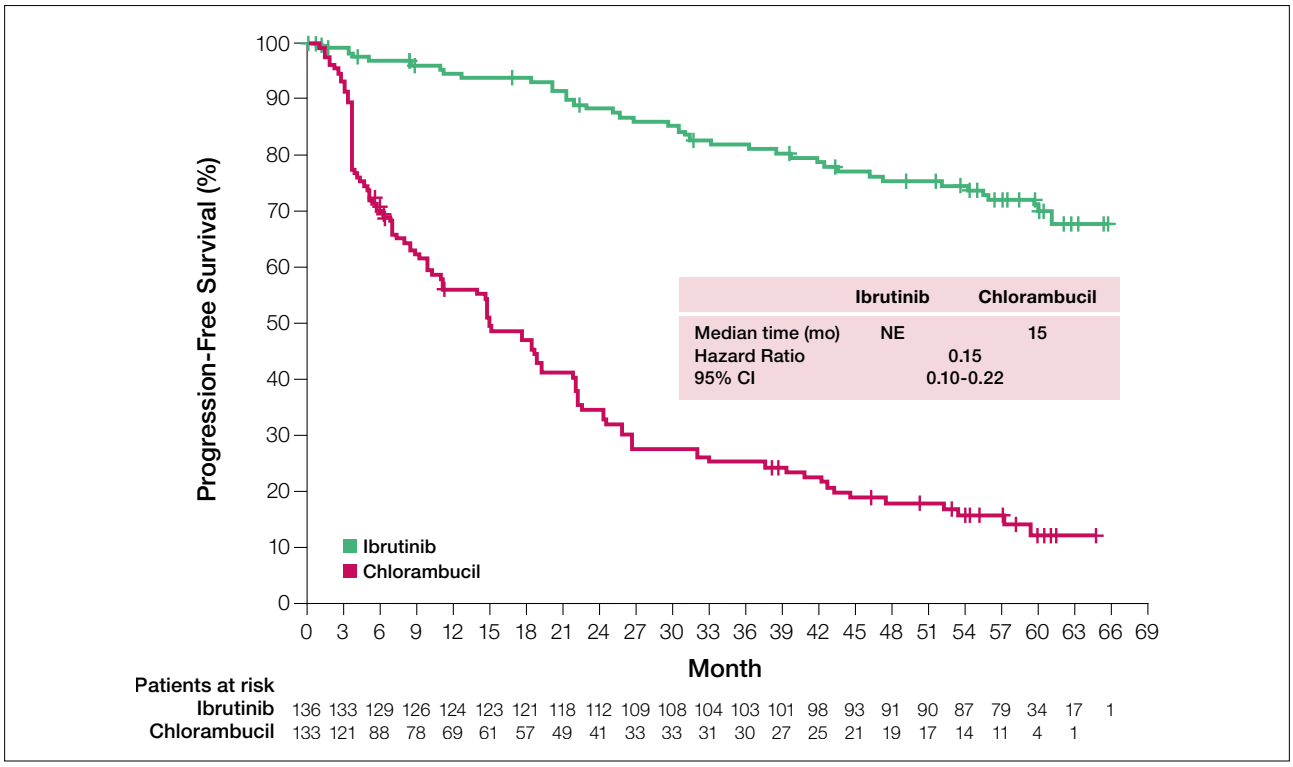

FIGURE 2. Progression-Free Survival with single-agent ibrutinib versus chlorambucil in first-line CLL/SLL.[5]

5-YEAR FOLLOW-UP DATA OF THE PHASE III RESONATE-2 TRIAL EVALUATING FIRST-LINE IBRUTINIB IN CLL

Tedeschi et al. reported the **long-term efficacy and safety data** over a median follow up of 5 years of the **RESONATE-2 trial**. This phase III study compared the efficacy and safety of **first-line ibrutinib** (420 mg once daily continuously until disease progression or unacceptable toxicity) ***vs.* Clb** (0.5–0.8 mg/kg for up to 12 cycles) in patients ≥65 years old with previously untreated CLL/SLL without del(17p) (N=269). PFS estimates at 60 months were 70% for ibrutinib *vs.* 12% for Clb (*Figure 2*). Ibrutinib also resulted in improved OS *vs.* Clb; 83% *vs.* 68% at 60 months, respectively, even with 57% of patients crossing over from Clb to ibrutinib after progression. Ibrutinib improved PFS compared to Clb in patients with unmutated IGHV (HR 0.11) and in patients with del(11q) (HR 0.03). As a composite, patients with high-risk genomics (unmutated IGHV, del(11q), and/or TP53 mutation) had superior outcomes with ibrutinib compared with Chl (PFS: HR 0.08; OS: HR 0.37). The most common grade ≥3 adverse events (AEs) included neutropenia (13%), pneumonia (12%), hypertension (8%), anaemia (7%), hyponatremia (6%), atrial fibrillation (5%), and cataract (5%); rates of most events decreased over time. Dose reductions due to AEs decreased over time. Patients responded to subsequent CLL therapies, including CIT and alternate kinase inhibitors following ibrutinib discontinuation. Ibrutinib benefit continues in 58% of patients who remained on therapy.

Single-agent ibrutinib had sustained PFS and OS benefit, including for patients with high-risk genomic features, in the longest follow-up to date from a phase III study of first-line BTK-directed therapy. ***Responses to ibrutinib improved over time*** with nearly three-fold more patients achieving CR/CRi with long term follow up. ***With up to 66 months follow up, more than half of patients remain on long-term continuous ibrutinib treatment. No new safety signals emerged.***[5]

NOVEL TREATMENT OPTIONS FOR PATIENTS WITH RELAPSED/ REFRACTORY CLL

Novel treatment options for patients with relapsed/refractory (R/R) CLL are either based on continuous treatment (e.g. the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib) or fixed duration treatment regardless of the level of response (*e.g.* the Bcl-2 inhibitor venetoclax+rituximab (R)). The aim of the VISION / HOVON 141 study is to evaluate feasibility of MRD-guided treatment cessation and re-initiation in patients with R/R CLL (N=230) after induction treatment with venetoclax+ibrutinib. Patients are treated with ibrutinib monotherapy (420 mg daily) for two months. In cycle 3 venetoclax is ramped up weekly to the final dosage

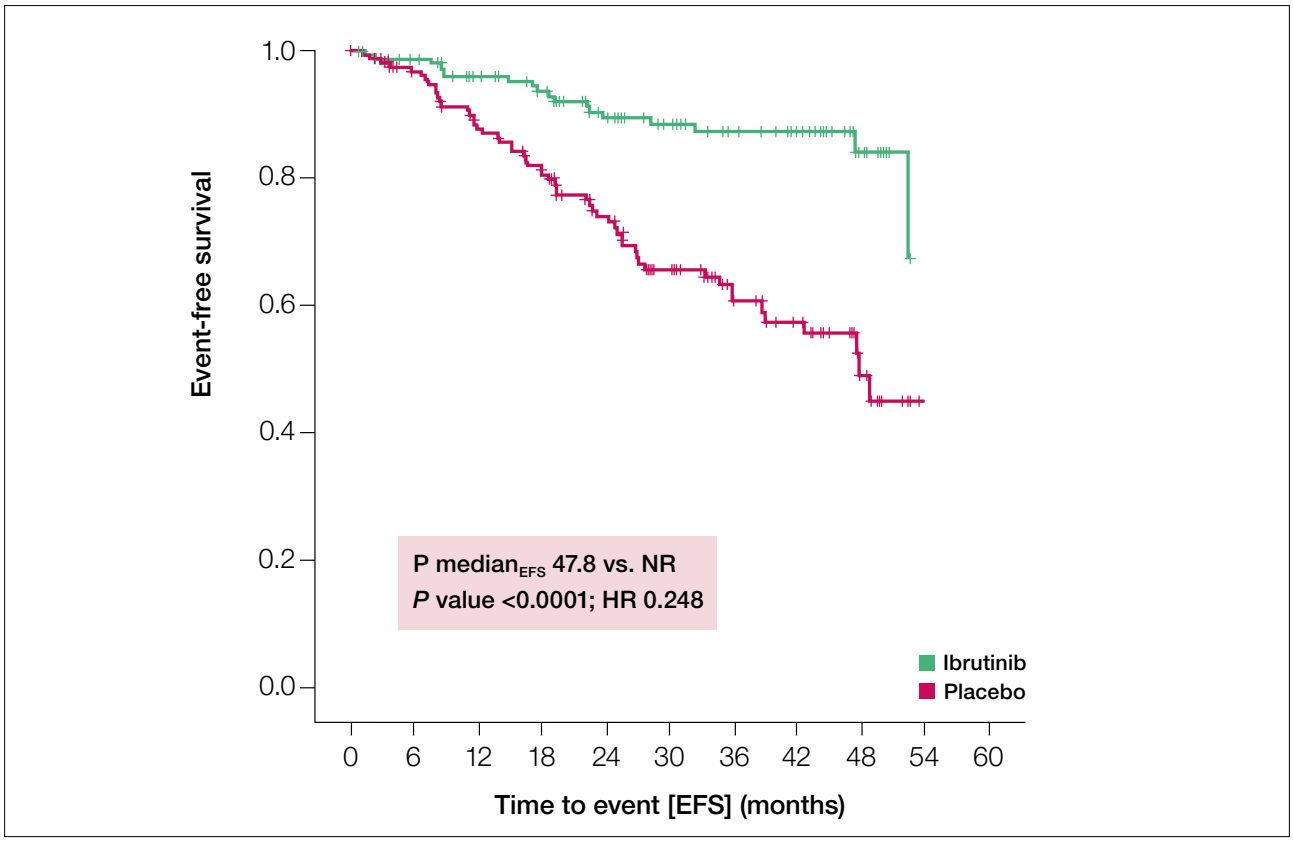

FIGURE 3. Event-free survival (intent to treat population) of the CLL12 trial.[8]

of 400 mg daily from start of cycle 4. Combination of venetoclax+ibrutinib is given for a total of 15 cycles; patients achieving undetectable MRD on PB and BM (by central flow cytometry, $<10^{-4}$ level) are randomized thereafter 1:2 between maintenance ibrutinib or observation (stopping therapy).

This pre-planned interim analysis showed that ***treatment with ibrutinib and venetoclax in the setting of R/R CLL shows a favourable benefit-risk profile and a complete remission (CR) in 61% of patients after 9 cycles of treatment with an increasing uMRD rate to 52% after one year of treatment. The data safety monitoring board recommends continuing of the study.***[6]

The ongoing phase I/II **TRANSCEND CLL 004 study** assesses the safety, pharmacokinetics and efficacy of lisocabtagene maraleucel (liso-cel, JCAR017), an investigational, anti-CD19 chimeric antigen receptor (CAR) T cell product administered as a defined composition of CD4+/CD8+ CAR T cells. **Eligible CLL/SLL patients had received ≥2 prior lines of therapy (including BTK inhibitors)**, and had an ECOG ≤1. After 3 days of lymph depleting chemotherapy, patients received liso-cel infusion at either dose level one (50×10^6) or dose level two (100×10^6) total CAR T cells. 16 patients received liso-cel: N=6 in dose level one and N=10 in dose level two. Of the patients, 75% had high-risk features (TP53 mutation, complex karyotype, or del(17p)); 100% had received prior ibrutinib and 50% had received prior venetoclax. Median number of prior lines of therapy was 4.5 (range 2-11). There was one dose-limiting toxicity of grade 4 hypertension at dose level two. The most common grade 3/4 AEs were thrombocytopenia (75%), anaemia (69%), neutropenia (63%) and leukopenia (56%). One patient had grade 3 cytokine release syndrome (CRS); 3 patients had grade 3 neurological events (NE). **Best ORR was 87%** (13/15 patients). Seven patients (47%) achieved CR with/without complete blood count recovery (CR/CRi). ORR at 6 months was 83% (5/6). **Undetectable MRD** (uMRD) in blood (flow cytometry in blood (sensitivity, 10^{-4}) was achieved in 10/15 patients **(67%) by day 30**, and in BM (NGS (sensitivity, 10^{-6}) in 7/8 patients (88%). MRD-negative CRs were seen in patients who had failed both ibrutinib and venetoclax. Median (range) time to peak blood CAR+ T cell level was 16 (4-30) days.

In this study of heavily pre-treated patients with standard- and high-risk CLL/SLL and previous ibrutinib treatment, liso-cel-related toxicities (i.e. CRS and NE) were manageable. Patients rapidly achieved CR/CRi and uMRD. The phase II component of the study is currently enrolling patients for treatment at dose level two.[7]

KEY MESSAGES FOR CLINICAL PRACTICE

1. While waiting on the OS analysis of the CLL12 trial, a 'watch and wait' strategy is still recommended in asymptomatic early stage CLL, even with high risk of progression.
2. In the longest follow-up to date from a phase III study of first-line BTK-directed therapy responses to ibrutinib improved over time and more than half of patients remain on long-term continuous ibrutinib treatment (66 months follow up).
3. 12 months of fixed-duration VenG induced deep and long lasting MRD-negativity rates in a high number of comorbid treatment naïve CLL patients translating into improved PFS compared to ClbG treatment. VenG is able to overcome the adverse risk associated with most genomic aberrations and mutations (except del(17p) and TP53mut), and with unmutated IGIV and CKT. Long term follow up will learn more on long-term efficacy.
4. Acalabrutinib monotherapy significantly improved PFS with a more tolerable safety profile compared with IdR/BR in patients with R/R CLL. This is the first trial where a BTK and a PI3K delta inhibitor were compared head to head.
5. Liso-cel could induce CR and uMRD in heavily pre-treated CLL/SLL patients with manageable CRS and NE toxicities.

IBRUTINIB FOR ASYMPTOMATIC, BINET A, TREATMENT-NAÏVE CLL PATIENTS WITH INTERMEDIATE, HIGH OR VERY HIGH RISK OF PROGRESSION

Two of the six late breaking abstracts were also related to CLL. So far, treatment of asymptomatic, early stage CLL patients has not been proven beneficial. The **CLL12 trial** is a placebo-controlled, double-blinded phase III trial where **ibrutinib** (N=182) or placebo (N=181) is tested in **asymptomatic, Binet A, treatment-naïve CLL patients with intermediate, high or very high risk of progression**. Patients with low risk (N=152) were allocated to an observational arm and were not included in primary endpoint analysis. At median observation time of 31 months, event free survival (EFS) was not reached in the ibrutinib arm and was 47.8 months in the placebo arm (HR 0.25, p<0.0001) (*Figure 3*). Similarly, PFS was not reached for ibrutinib and was 14.8 months with placebo (HR 0.18). Time to next treatment (TTNT) was longer in the ibrutinib arm (HR 0.21). There was no significant difference in all-grade (grade ≥3) AEs occurring in 82.2% (43.3%) of patients in the ibrutinib group and in 84.8% (38.7%) in the placebo group. Most common serious AEs (N=126) were infections (11.4 *vs.* 11.8%), neoplasms (5.9 *vs.* 10.7%) and cardiac disorders (8.6 *vs.* 6.7%) for patients of the ibrutinib and placebo group, respectively. The results of this study allow to conclude that ***ibrutinib significantly improves EFS, PFS and TTNT in patients with asymptomatic treatment-naïve early stage CLL when compared to placebo***. There were no significant differences in AEs between both study arms.[8]

ACALABRUTINIB FOR R/R CLL

In the **ASCEND trial**, a randomized, global, multicentre, open-label phase III study, the efficacy and safety of **acalabrutinib** monotherapy (100 mg oral twice daily (BID)) was evaluated *vs.* **investigator choice of Idelalisib (Id)-R** (150 mg oral BID in combination with up to 8 intravenous (IV) infusions of R [375 or 500 mg/m^2]) **or Bendamustine-R** (70 mg/m^2 IV day 1 and 2 of each cycle combined with R [375 or 500 mg/m2 IV] on day 1 of each 28-days cycle for up to 6 cycles) **in R/R CLL**. Patients with confirmed progression on IdR/BR could cross over to receive acalabrutinib monotherapy. Secondary endpoints included OS, IRC-assessed ORR and safety. 310 patients were randomized to acalabrutinib (N=155) or IdR/BR (N=155 [IdR, N=119; BR, N=36]); median age was 67 years (range, 32-90); 16% had del(17p); 27% had del(11q); 42% had Rai stage III/IV CLL. Median number of prior therapies was 1 (range 1-8) for acalabrutinib and 2 (1-10) for IdR/BR. Discontinuation due to AEs occurred in 11% of patients on acalabrutinib *vs.* 49% Id, 12% R in IdR, 11% B and 17% R in BR. At a median follow-up of 16.1 months, acalabrutinib significantly prolonged independent review committee (IRC)-assessed PFS (primary endpoint) *vs.* IdR/BR (median NR *vs.* 16.5 months;

HR 0.31, p<0.0001); PFS rates at 12 months were 88% with acalabrutinib and 68% with IdR/BR. PFS improvement with acalabrutinib (*vs.* IdR/BR) was seen across subgroups including del(17p), *TP53* mutation and Rai stage. 12-month OS rates (secondary endpoint) were 94% and 91% (with 15 and 18 deaths) for acalabrutinib and IdR/BR, respectively. 23% of patients randomized to IdR/BR crossed over to receive subsequent acalabrutinib monotherapy. AEs of interest were atrial fibrillation (5.2% of patients on acalabrutinib *vs.* 3.3% on IdR/BR), bleeding AEs (26% *vs.* 7.2%; including major haemorrhage [1.9% *vs.* 2.6%]), grade ≥3 infections (15% *vs.* 24%), and second primary malignancies (excluding non-melanoma skin cancer; 6.5% *vs.* 2.6%).

Acalabrutinib monotherapy significantly improved PFS with a more tolerable safety profile compared with IdR/BR in patients with R/R CLL.[9]

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