A Randomized Phase III Study of Venetoclax-Based Time-Limited Combination Treatments (RVe, GVe, GIVe) Vs Standard Chemoimmunotherapy (CIT: FCR/BR) in Frontline Chronic Lymphocytic Leukemia (CLL) of Fit Patients: First Co-Primary Endpoint Analysis of the International Intergroup GAIA (CLL13) Trial

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Background:

For fit CLL patients (pts), continuous BTK inhibitor treatment is replacing CIT as standard of care in frontline setting, particularly in pts with unfavorable prognostic factors. The time limited combinations venetoclax plus obinutuzumab (GVe) and venetoclax plus rituximab (RVe) have produced high rates of undetectable minimal residual disease (uMRD), which strongly associates with long progression-free survival (PFS) both in frontline and relapsed setting. For frontline therapy GVe is approved in this setting based on data from the CLL14 trial in an unfit population. However, data from a fit cohort are not yet available. The GAIA (CLL13) trial evaluated the efficacy and safety of three Ven+CD20 antibody-based regimens in comparison to CIT as a frontline treatment for fit pts with CLL and without TP53 mutation/deletion.

Methods:

Treatment-naïve fit (CIRS ≤6, normal creatinine clearance with ≥ 70ml/min) CLL pts requiring therapy were eligible. Based on known poor response to CIT, pts with TP53 aberrations were excluded. Pts were randomized in a 1:1:1:1 ratio to receive six courses of CIT (FCR for pt ≤65 years: fludarabine 25 mg/m² d1-3, cyclophosphamide 250 mg/m² d1-3, rituximab 375 mg/m² d1 cycle 1 and 500 mg/m² d1 cycle 2-6; BR for pt >65 years: bendamustine 90mg/m² d1-2, rituximab) or one of three venetoclax (V) combinations (standard ramp-up from cycle 1 d22, 400 mg/d cycle 2-12): V and rituximab (375/500mg/m² d1 cycle 1-6) [RVe], V and obinutuzumab (1000 mg d1, 8, 15 cycle 1 and d1 cycle 2-6) [GVe], or V, obinutuzumab and ibrutinib (420 mg/d cycle 1-12, if MRD-detectable continued until cycle 36) [GIVe] .

Pts were stratified according to country, Binet stage and age (≤ 65/> 65 years). The co-primary endpoints of the trial are (1) the rate of uMRD (<10-4) by flow in peripheral blood (PB) at month 15 (MO15, GVe vs CIT) and (2) PFS (GIVe vs CIT), each with a significance level of 2.5%. The co-primary endpoint PFS will be analyzed within a pre-planned interim analysis as soon as 138 (65%) PFS events will have been reported in the GIVe and CIT arm. The co-primary endpoint analysis of uMRD per protocol was performed after the last MO15 MRD sample had been collected. In addition, comparisons regarding uMRD for all study arms were performed using a pre-specified hierarchical test sequence. Bone marrow (BM) was evaluated 3 months after end of treatment (MO9 for CIT, MO15 for all others arms) in pts with clinical CR. Key secondary endpoints as investigator-assessed responses according to iwCLL 2008 guidelines and safety were analyzed.

Results:

A total of 926 pts (CIT: 229 (150 FCR, 79 BR), RVe: 237, GVe: 229, GIVe: 231) with a median age of 61 years (range 27-84) were accrued between 12/2016 and 09/2019. The majority of pts were in advanced Binet stage (B: 37.8%, C: 35.6%) and unmutated IGHV status was present in 56%. Fourteen pts did not receive study treatment (13 FCR, 1 GVe) and were not included in the safety population. The data cut for the first co-primary endpoint analysis was February 28, 2021. The median observation time was 27.9 months.

The co-primary endpoint uMRD in PB at MO15 was met as the rate of uMRD in ITT population was significantly higher in GVe compared to CIT: 86.5% (97.5% CI 80.6-91.1) vs 52.0% (CI 44.4-59.5; p<0.0001), respectively. GIVe also showed a superior uMRD rate of 92.2% (CI 87.3-95.7) compared to CIT (p<0.0001), while RVe (57.0%, CI 49.5-64.2) did not (p=0.317) (Figure 1A). Corresponding BM uMRD rates in ITT population were 37.1% (CIT), 43.0% (RVe), 72.5% (GVe) and 77.9% (GIVe), respectively. MO15 overall response rates and complete response rates (CRR) are shown in Figure 1B.

The most common grade 3-5 treatment-emergent AE were neutropenia (50.5% of all pts), thrombocytopenia (12.2%), tumor lysis syndrome (7.5%), infusion-related reaction (7.2%), febrile neutropenia (6.5%) and pneumonia (5.3%)). Atrial fibrillation and bleeding events occurred more frequently in GIVe while infusion-related reactions were most common in the GVe arm (Table 1). The absolute numbers of second malignancies were 33, 19, 22 and 21 for CIT, RVe, GVe and GIVe. Fatal AEs occurred in 5, 7, 6 and 9 of the patients.

Conclusions:

The time-limited therapies of GVe and GIVe provided superior uMRD rates in PB at MO 15 compared to CIT. In addition, uMRD rates in BM and CRR were higher in GVe and GIVe in particular than in CIT. All arms showed a good safety profile in this fit pt population.