635 First-Line Venetoclax Combinations in Fit Patients with CLL: 4-Year Follow-up and NGS-Based MRD Analysis from the Phase 3 GAIA/CLL13 Trial

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Hematology Disease Topics & Pathways:
Research, clinical trials, Lymphoid Leukemias, CLL, Clinical Research, Combination therapy, Diseases, Therapies, Lymphoid Malignancies, Minimal Residual Disease
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Background:

The primary endpoint analysis of the GAIA trial showed superior progression-free survival (PFS) and undetectable MRD (uMRD) rates for venetoclax-obinutuzumab (GV) and GV + ibrutinib (GIV) compared to chemoimmunotherapy (CIT) (Eichhorst et al., NEJM 2023). With additional follow-up, outcomes of the venetoclax (ven)-containing arms were compared and NGS-based MRD results were analyzed.

Methods:

The phase 3 GAIA trial compared 3 different time-limited ven-based combinations against CIT in fit, treatment-naïve patients (pts) with CLL without *TP53* aberrations. Pts were randomized to CIT (FCR ≤65 years; BR >65 years), GV, GIV or ven-rituximab (RV). In addition to MRD by

flow cytometry (FCM), exploratory MRD analyses were performed using the amplicon-based EuroClonality NGS assay. Reported p values have a descriptive character.

Results:

In total 926 pts were randomized (CIT: 229, RV: 237, GV: 229, GIV: 231). After a median observation time of 50.7 months (interquartile range 44.6-57.9), all pts are now off study treatment. PFS continued to be superior for GV and GIV compared to CIT (GV: median not reached [NR] vs 59.4 months; hazard ratio [HR] 0.47 [97.5% CI 0.32-0.69], p<0.001; GIV: NR vs 59.4 months, HR 0.30 [97.5% CI 0.19-0.47], p<0.001, **Figure 1A**). PFS with GV and GIV was also superior compared to RV (GV: NR vs 63.2 months; HR 0.57 [97.5% CI 0.38-0.84], p=0.001; GIV: NR vs 63.2 months, HR 0.38 [97.5% CI 0.24-0.59], p<0.001). PFS between GIV and GV was not significantly different (both NR, HR 0.63 [97.5% CI 0.39-1.02], p>0.025), however, GIV was associated with longer PFS compared to GV in pts with unmutated IGHV (HR 0.58 [95% CI 0.36-0.94]) but not in pts with mutated IGHV (HR 0.87 [95% CI 0.33-2.31]). Estimated 4-year PFS rates were 62.0% (CIT), 70.1% (RV), 81.8% (GV) and 85.5% (GIV). The estimated 4-year rates for time to next treatment were 77.2% (CIT), 86.2% (RV), 90.4% (GV) and 96.0% (GIV). Of the 111 pts with subsequent therapies for CLL-type progression (excluding 12 pts with treatment for Richter's transformation as second line), 60 (54.1%) received BTKi-based therapies, 30 (27.0%) ven-based treatments, 12 (10.8%) ven + BTKi and 5 (5.4%) CIT as second-line treatments. No differences in overall survival were observed between the treatment arms (4-year OS rates, CIT 93.5%; RV 96.2%; GV 95.1%; GIV 95.0%).

In a multivariate analysis, unmutated IGHV (HR 2.86 [95% CI 1.64-5.01], p<0.001) and bulky disease (any lymph node ≥ 5 cm, HR 1.73 [95% CI 1.11-2.69], p=0.016) were independently associated with shorter PFS in the pooled GV/GIV arms.

NGS-based MRD data in PB was available for 816 pts at month 15. Of these, 22.7% (52 pts, CIT), 23.6% (56 pts, RV), 60.3% (138 pts, GV) and 66.2% (153 pts, GIV) achieved uMRD $<10^{-6}$ (uMRD6, **Figure 1B**). In all treatment arms, PFS was shorter in pts with MRD $\geq 10^{-6}$ compared to those with uMRD6 (CIT: HR 9.98 [95% CI 3.64-27.38], RV: HR 6.57 [95% CI 2.72-16.77], GV: HR 3.93 [95% CI 2.18-7.09], GIV: HR 2.10 [95% CI 1.03-4.28]). Pts who achieved uMRD below the conventional cut-off of 10^{-4} by FCM but still had low levels of detectable MRD ($\geq 10^{-6}$ & $<10^{-4}$) by NGS had shorter PFS than pts achieving uMRD6 in the pooled GV/GIV arms (HR 2.18 [95% CI 1.32-3.61], **Figure 1C**). A similar correlation was seen with CIT (HR 4.49 [95% CI 1.53-13.14]) and RV (HR 3.40 [95% CI 1.29-8.98]). In pts with uMRD6 at MO15, clinical response (partial/complete response) did not influence PFS.

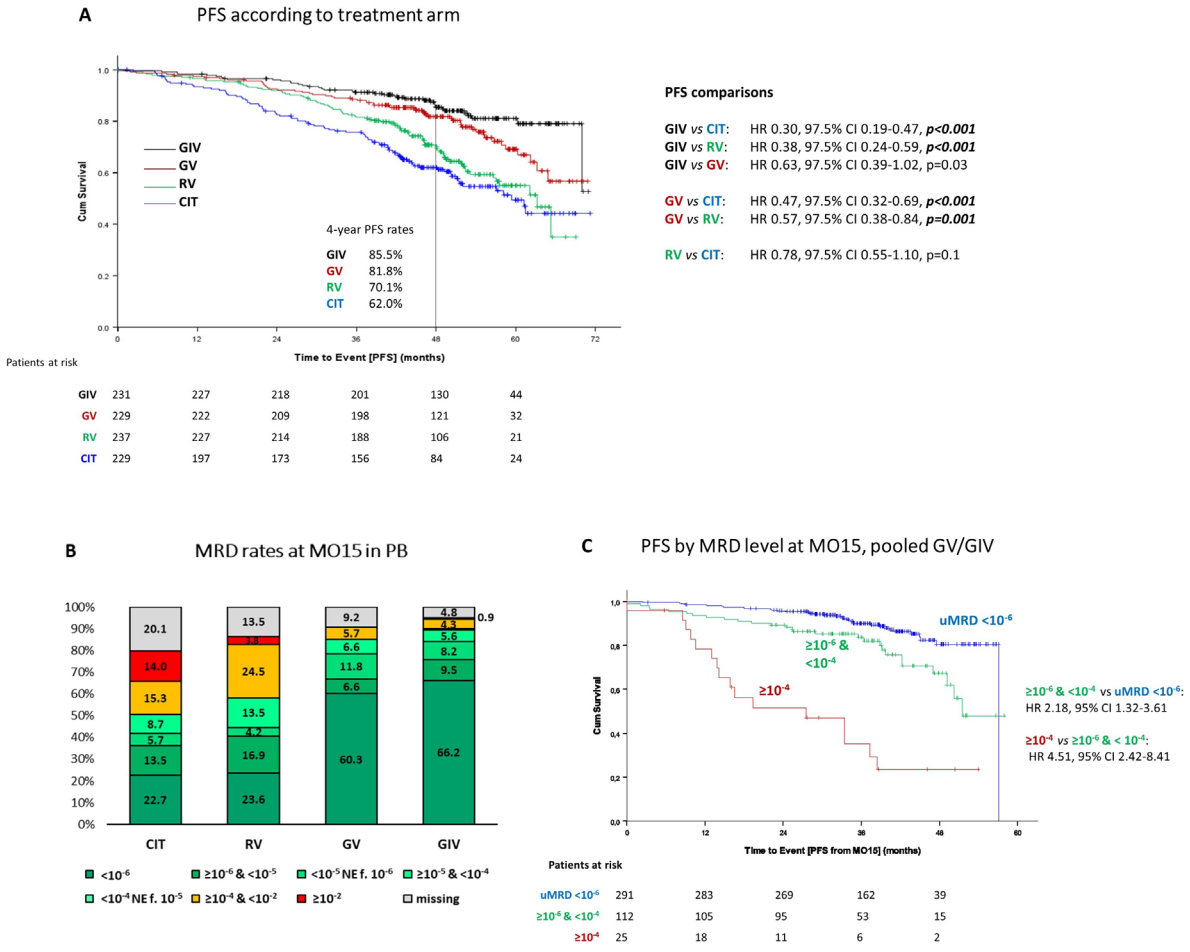
Grade ≥3 infections were highest in GIV and CIT (CIT: 45 pts [20.8%], RV: 27 [11.4%], GV: 34 [14.9%], GIV: 51 [22.1%]) and cardiac disorders most frequent with GIV (CIT: 14 pts [6.5%], RV: 19 [8.0%], GV: 18 [7.9%], GIV: 41 [17.7%]). Fatal adverse events occurred in 16 (7.4%, CIT), 8

(3.4%, RV), 9 (3.9%, GV) and 11 (4.8%, GIV) pts. The rate of second primary malignancies was higher with CIT (4.19/1000 patient-months) compared to RV (2.34), GV (2.39) and GIV (2.88). When excluding non-melanoma skin cancer, the incidence rates were 2.21 (CIT) 1.21 (RV), 1.16 (GV) and 2.36 (GIV).

Conclusions:

With more than 4 years of follow-up, GV and GIV show superior PFS compared to CIT and RV. Pts with unmutated IGHV have longer PFS with GIV compared to GV. A majority of pts treated with time-limited GV or GIV (60.3% and 66.2%) achieves uMRD6 at MO15. NGS-based MRD assessment identifies pts with very long PFS and appears to improve prognostication in pts with uMRD $<10^{-4}$ by conventional FCM. Unmutated IGHV and bulky disease were independently associated with shorter PFS in pooled GV/GIV.

Figure 1



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